Cystic Fibrosis Trust

Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis

Fifth edition

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Uniting for a life unlimited

Members of the Working Group

Editorial board

Catherine Brown, Cystic Fibrosis Specialist Physiotherapist, West Midlands Adult CF Centre, University Hospitals Birmingham, Birmingham

Elaine Edwards, Clinical Specialist Physiotherapist, Leeds Children's Hospital, Leeds Teaching Hospital Trust, Leeds

Alison Gates, Lead Specialist Physiotherapist, Oxford Adult CF Centre, Oxford

Nicola Mills, Physiotherapist Advance Practitioner, University Hospitals of Leicester NHS Trust, Leicester

Gemma Stanford, Clinical Specialist Physiotherapist in Adult Cystic Fibrosis, Royal Brompton Hospital Adult CF Centre, Royal Brompton Hospital, Guys and St Thomas's NHS Foundation Trust, London

Harriet Wood, Adult Cystic Fibrosis Physiotherapist, Liverpool Heart and Chest Hospital, Liverpool

Contributors

Afrasiab Ahmad, Royal Brompton Hospital, Guys and St Thomas's NHS Foundation Trust, London, (section 12.2)

Carolyn Aitken-Arbuckle, Royal Hospital for Children and Young People, Edinburgh (section 4.2)

Lauren Alexander, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast (section 11, good practice point consensus)

Mel Archer, Children's and Specialist Services, Shropshire Community NHS Trust, Shrewsbury (section 15)

Christine Blackburn, Leeds Children's hospital, Leeds Teaching Hospital Trust, Leeds (sections 6.3, 6.4, good practice point consensus)

Marie Bolton, Nottingham Children's Hospital, Nottingham (sections 2, 3, good practice point consensus)

Victoria Bright, University Hospital Southampton NHS Foundation Trust, Southampton (section 11)

Catherine Brown, West Midlands Adult CF Centre, University Hospitals Birmingham, Birmingham (section 17)

Helen Brown, Royal Papworth Hospital, Cambridge (section 16, good practice point consensus)

Laura Bundy, University Hospital Southampton NHS Foundation Trust, Southampton (section 12.9)

Victoria Carrolan, Heartlands Hospital, Birmingham (sections 6.3, 6.4)

Heather Carter, All Wales Adult Cystic Fibrosis Centre, University Hospital Llandough, Cardiff (good practice point consensus)

Sarah Caunter, All Wales Adult Cystic Fibrosis Centre, University Hospital Llandough, Cardiff (sections 6.1, 6.2, 6.7, 8, 12.1, good practice point consensus)

Jocelyn Choyce, Birmingham Heartlands Hospital, Birmingham (section 12.9, good practice point consensus)

Louise Collins, University Hospital Limerick, Limerick, Ireland (section 12.8, good practice point consensus)

Tracey Daniels, York Hull Adult Cystic Fibrosis Centre, York and Scarborough Teaching Hospitals, York (sections 2, 8, 15)

Hannah Day, Sheffield Children's Hospital, Sheffield (sections 6.3, 6.9, good practice point consensus)

Harriet Day, Oxford University Hospitals NHS Foundation Trust, Oxford (section 12.2, good practice point consensus)

Emma Dixon, Royal Brompton Hospital, Guys and St Thomas's NHS Foundation Trust, London (sections 3, 12.1, 14)

Helen Douglas, Brunel University of London, UK (sections 4.3, 5, good practice point consensus)

Elaine Edwards, Leeds Children's Hospital, Leeds Teaching Hospital Trust, Leeds (section 14, good practice point consensus)

Jayne Faulkner, Oxford University Hospitals NHS Foundation Trust, Oxford (section 4.2)

Rachael Fleming, Newcastle Hospitals NHS Foundation Trust, Newcastle (good practice point consensus)

Helen Forbes, Basingstoke and North Hampshire Hospitals, Basingstoke (sections 6.3, 6.4)

Catherine Fordyce, Manchester University NHS Foundation Trust, Manchester (section 13.2)

Kath France, York Hull Cystic Fibrosis Centre, York (section 7)

Alison Gates, Oxford Adult CF Centre, Oxford (sections 2, 12.4, 12.5, good practice point consensus)

Penny Galey, Norfolk and Norwich University Hospital, Norfolk (sections 6.8, 10, 12.6, good practice point consensus)

Georgie Goodwin, Royal Victoria Infirmary, Newcastle upon Tyne (section 12.9, good practice point consensus)

Stephanie Graham, Great North Children's Hospital, Newcastle Upon Tyne Hospitals Trust, Newcastle (sections 3, 6.5, 6.6)

Nuala Harnett, Great North Children's Hospital Newcastle Upon Tyne (sections 3, 6.5, 6.6, good practice point consensus)

Jayne Johnson, New Cross Hospital, Wolverhampton (good practice point consensus)

Zoe Johnstone, Royal Hospital for Children and Young People, Edinburgh (section 17)

Enfys Jones, University Hospitals of Leicester, Leicester (good practice point consensus)

Victoria Kendall, Manchester University NHS Foundation Trust, Manchester (section 12.1, good practice point consensus)

Hannah Langman, Manchester University NHS Foundation Trust, Manchester (section 12.1)

Katherine Lavery, Adult CF Service, Belfast Trust, Belfast (section 7)

Aoibheann Leeney, St. Vincent's University Hospital, Dublin (good practice point consensus)

Kieran Lock, Addenbrooke's Hospital, Cambridge (good practice point consensus)

Margaret MacLeod, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen (section 9)

Rachel McDowell, University of Bath, Bath (good practice point consensus)

Gillian Middleton, NHS Lanarkshire, Scotland (good practice point consensus)

Alice Midwinter, Oxford Adult CF Centre, Oxford (section 12.9)

Alexandra Milner, Royal Papworth Hospital, Cambridge (sections 6.1, 6.2, 6.7, 12.6)

Nicola Mills, University Hospitals of Leicester NHS Trust, Leicester (good practice point consensus)

Janet Mitchell, Manchester University NHS Foundation Trust, Manchester (section 2, good practice point consensus)

Hannah Morgan, Cardiff University Hospitals NHS Trust, Cardiff (good practice point consensus)

Lisa Morrison, West of Scotland Adult CF Centre, Queen Elizabeth University Hospital, Glasgow (sections 4.1, 4.3, 16, good practice point consensus)

Lisa Murphy, Northern Ireland Regional Adult CF Unit, Belfast (good practice point consensus)

Ciara O'Connor, St. Vincent's University Hospital, Dublin (section 12.6, good practice point consensus)

Maria Oldfield, Manchester University NHS Foundation Trust, Manchester (section 12.1)

Madeline Pilbury, Stockport NHS Foundation Trust, Stockport (good practice point consensus)

Kim Palmer, Chesterfield Royal Hospital, Chesterfield (section 6.4)

Suzanne Palmer, Queen Elizabeth University Hospital, Glasgow (sections 4.2, 9)

Rakhee Patel, Adult CF Service, University Hospital Southampton NHS Trust, Southampton (section 7)

Nicole Petch, Manchester University NHS Foundation Trust, Manchester (section 12.7)

Caroline Ramtohul, Bradford Teaching Hospitals NHS Foundation Trust, Bradford (good practice point consensus)

Clare Reilly, National Adult Cystic Fibrosis Unit, St Vincent's University Hospital, Dublin (section 12.3, good practice point consensus)

Zoe Saynor, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton (sections 4.3, 5)

Emily Scott, University of Liverpool, Liverpool (good practice point consensus)

Emily Smith, Manchester University NHS Foundation Trust, Manchester (good practice point consensus)

Gemma Stanford, Adult CF Centre, Royal Brompton Hospital, Guys and St Thomas's NHS Foundation Trust, London (sections 4.1, 6.8, 10, 12)

Julia Taylor, Manchester University NHS Foundation Trust, Manchester (section 11)

Jo-Dee Tame, Cardiff University and Noah's Arc Children's Hospital for Wales, Cardiff (section 4.2)

Lucy Wadsworth, Manchester University NHS Foundation Trust, Manchester (good practice point consensus)

Adam Walsh, Alder Hey Children's Hospital, Liverpool (sections 13.1, good practice point consensus)

Louise Warnock, Oxford Adult CF Centre, Oxford (sections 12.4, 12.5, good practice point consensus)

Pip White, Professional Advisor, Chartered Society of Physiotherapy (section 17)

Anne Whiting, Sailsbury Foundation NHS Trust, Sailsbury (good practice point consensus)

Harbinder Sunsoa, West Midlands Adult CF Centre, Birmingham (section 5.4.5)

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Contents

1. Foreword

1.1 Document development

This document is the update of the 2020 version and is comprehensive support document for physiotherapists working in CF care. It is endorsed by the Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF) and Cystic Fibrosis Trust. It covers the physiotherapy care and management of infants, children and adults with CF.

New sections in this edition include the use of Simeox®, cystic fibrosis screen positive inconclusive diagnosis (CFSPID), and CFTR-related disorder.

Contributions to this document are from professionals working in the specialist field of CF, as well as the invaluable input of other health professionals. We have consulted in areas where additional expertise is pivotal. This document has been developed independently of any funding bodies.

1.2 How to use this document

This standard aims to:

- be a useful tool and comprehensive reference document for all physiotherapists and clinicians involved in the delivery of care to people with CF
- be used as a reference document for people with CF and their families and carers
- support physiotherapists to develop local guidelines tailored to their specific needs and circumstances in caring for people with CF.

Good clinical practice points highlight areas of experienced clinical practice that are relevant to clinicians, but that do not currently have substantive evidence to support them.

There are a number of appendices, which have been compiled by the authors and are currently in use in clinical practice.

1.3 Review of the document

The content of this standard has been reviewed by relevant experts and has undergone peer review.

During the update, consideration has been made within each section on the impact of CFTR modulators. As we continue to navigate a new era of CF care and with the wider implementation and further development of modulator therapies, many aspects of care are likely to change with increasing regularity and it is anticipated that this will be a 'live' document, with relevant changes made to each section as they are needed.

1.4 Grading scheme for recommendations

Evidence used to support the recommendations made in this standard has been graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

GRADE gives health professionals a useful tool in making clear, pragmatic interpretations of strong versus weak recommendations. **As few areas of physiotherapy management in CF have sufficient and robust evidence, it is of paramount importance to inform health professionals about:**

- the quality of the evidence (QoE) (high, moderate, low or very low)
- which outcomes are critical
- the overall strength of the recommendation (strong or weak) to better inform their clinical reasoning and decision process.

Although recommendations overall may be graded as 'strong' (with a strong degree of confidence that the desirable effects outweigh the undesirable), the quality of the evidence may be moderate or low, due to the methodological issues within the studies available.

Where there is no evidence to either support or refute practice, no recommendation is made. Additionally, there is an occasional requirement for further research into specific fields of physiotherapeutic management of CF and these points have been highlighted by the authors of the relevant sections.

1.5 Good Practice Point methodology

In areas where robust evidence is lacking, but clinical consensus is essential for best practice, Good Practice Points (GPPs) were developed. These points represent expert-informed recommendations derived from the collective clinical experience of chapter authors.

To ensure widespread clinical consensus and validity among ACPCF members, a rigorous survey process was implemented. GPPs were

disseminated via four sequential weekly surveys. This staggered approach was designed to minimise clinician time commitment and mitigate survey fatigue.

ACPCF members were asked to evaluate each GPP using a four-point Likert scale: "Agree," "Partially Agree," "Disagree," or "Unable to Say." The "Unable to Say" option was provided to accommodate members who felt they lacked sufficient clinical expertise or experience to offer a meaningful contribution.

For GPPs receiving a "Partially Agree" response, members were prompted to provide detailed comments. These comments were instrumental in allowing the editors to refine and adapt the GPPs, aiming to achieve a minimum of 80% overall agreement.

1.5.1 Criteria for acceptance and revision (excluding "Unable to Say" responses)

- **Acceptance:** GPPs achieving 80% or more agreement were automatically accepted for inclusion in the standards.
- **Rejection:** GPPs receiving more than 20% disagreement.
- **Revision:** GPPs falling within the range of less than 80% agreement but less than 20% disagreement underwent revision. These GPPs were meticulously edited and adjusted based on the comments provided by members who selected "Partially Agree".

This systematic approach, focusing on the opinions of members who provided substantive feedback, ensured that all included GPPs reflect a high level of clinical consensus and are grounded in the practical experience of ACPCF members, thereby enhancing the quality and applicability of the standards.

1.6 Supporting documents

These standards have been developed in association with the following documents:

NHS England Specialised Services Clinical Reference Group for Cystic Fibrosis

NHS England

- Clinical Commissioning Policy: Levofloxacin nebuliser solution for chronic Pseudomonas lung infection in cystic fibrosis (adults), 2018.
- NHS England National Service Specification – Cystic Fibrosis children, 2018.
- Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis, 2014.
- Clinical Guidelines: Care of Children with Cystic Fibrosis, 2023.

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- Standards for the clinical care of children and adults with cystic fibrosis in the UK, 2024.
- Pseudomonas aeruginosa infection in people with cystic fibrosis. Suggestions for prevention and infection control, 2004.
- Methicillin-resistant Staphylococcus aureus (MRSA), 2008.
- The Burkholderia cepacia complex. Suggestions for Prevention and Infection Control, 2004.
- Laboratory Standards for Processing Microbiology Samples from People with Cystic Fibrosis, 2022.
- Mycobacterium abscessus: Recommendations for infection prevention and control, 2018.
- Standards for the nursing management of cystic fibrosis, 2025.
- Nutritional Management of Cystic Fibrosis, 2016.
- Pharmacy standards in cystic fibrosis care in the UK, 2022.
- Management of cystic fibrosis diabetes, 2022.

European CF Society

- European Cystic Fibrosis bone mineralisation standards, 2011.
- European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre, 2014.
- European Cystic Fibrosis Society Standards of Care: Best Practice guidelines, 2014.
- European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis, 2014.
- Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients, 2011.
- Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease, 2011.
- End of life care for patients with cystic fibrosis, 2011.
- New clinical diagnostic procedures for cystic fibrosis in Europe, 2011.

- Chronic Pseudomonas aeruginosa infection definition: EuroCareCF Working Group report, 2011.
- Pulmonary exacerbation: Towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials, 2011.
- Travelling with cystic fibrosis: Recommendations for patients and care team members, 2010.
- Guidelines for the management of pregnancy in women with cystic fibrosis, 2008.

ACPCF

- Clinical Guidance for the Physiotherapy Management of Screened Infants with Cystic Fibrosis, 2020.

British Thoracic Society

- Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient (Section 3 – Cystic Fibrosis), 2009.

Chartered Society of Physiotherapy

- Quality Assurance Standards for Physiotherapy Service Delivery, 2013.
- Code of Members Professional Values and Behaviour, 2019.

NICE

- Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis [TA276], 2013.
- Mannitol dry powder for inhalation for treating cystic fibrosis [TA266], 2012.
- Cystic fibrosis: diagnosis and management [NG78], 2017.
- Cystic fibrosis: Quality standard [QS168], 2018.

2. Physiotherapy National Standards of Care for people with Cystic Fibrosis (2026)

The majority of people with CF in the UK receive all or some of their care from a Specialist CF Centre. In some circumstances, particularly in the care of children, care arrangements between a Specialist CF Centre and network clinics have been developed.

A safe and effective Specialist CF service requires a team with appropriate levels of experience, knowledge and skill.

The main principles are set out under the following sections:

See reference list for supporting documents.[1-17]

2.1 Staffing

People with CF will be cared for by physiotherapists with an appropriate level of expertise in the physiotherapy management of CF. Continuity of care is known to improve health outcomes and patient satisfaction.

Physiotherapy teams must be suitably staffed to meet the complex needs of people with CF. There should be adequate time, knowledge, and skill within the team for delivery of specialist physiotherapy care, leadership, education, and research. During workforce planning, careful consideration should be given to the emerging needs of people with CF. The provision of development opportunities is important for succession planning and supports the continuation of care into the future.

2.1.1 Recommended qualified physiotherapy staffing levels

Workforce planning must evolve to meet the changing needs of people with CF. Local models of care should consider patient choice, differences in population needs, and service delivery arrangements.

The staffing table shows suggested whole-time equivalent (WTE) of qualified physiotherapists for a five-day physiotherapy service and the overall MDT WTE. It is recommended that this table should be used flexibly to meet the needs of the population.

Table 1: Physiotherapy staffing levels – adapted from the Standards for the clinical care of children and adults with cystic fibrosis in the UK, 2024.

	MDT	Registered Physiotherapists
WTE for 200 adults with CF	18.5	4.0
WTE for 100 children with CF	9.25	2.0

In Ireland the recommended physiotherapy staffing is 2.0 WTE for 50 adults or children with CF as per National Clinical Programme for CF's 'A Model of Care for Ireland', 2019.

Physiotherapy staffing will include an appropriate skill mix to maintain experience in managing complex and evolving needs of people with CF. CF time should be protected and staff should not routinely be required to cross-cover other departments or specialities during CF time.

The mechanism for weekend, on-call and seven-day provision will not impinge on the weekday staffing levels. Refer to guidance within the Chartered Society of Physiotherapy (CSP) Dealing with change at work.[5]

2.1.2 CF Specialist Centres

Principle CF Physiotherapist

Physiotherapy care at a CF Specialist Centre must be led by a Principal CF Physiotherapist or a Consultant Physiotherapist (Band 8). Job titles may vary to reflect local workforce terminology.

The roles, responsibilities and characteristics for a Principal CF Physiotherapist should include:

- Responsibility for the co-ordination of a specialist physiotherapy service within a regional CF Centre.
- Demonstration of highly developed knowledge acquired through specialist training and experience to Master's level or equivalent.

- Maintenance of CF-specific continuing professional development (CPD) including annual attendance at national and international conferences.
- CF-specific clinical auditing, quality improvement and research.
- Delivery of CF specialist clinical education at graduate and post-graduate level.
- Demonstrations of up-to-date knowledge of current CF research and involvement in local research activity where appropriate.

Advanced or Highly Specialist CF Physiotherapist

The Principal CF Physiotherapist post must be supported by Advanced or Highly Specialist CF Physiotherapist post(s) (band 7 or above). The number of Advanced CF Physiotherapist posts will depend on the size of the Centre and the local scope of practice of the posts.

The roles, responsibilities and characteristics of an Advanced CF Physiotherapist should include:

- Taking a lead role in the organisation and delivery of physiotherapy care for people with CF.
- Demonstration of specialist knowledge and skills acquired through Specialist post-graduate courses, CPD and experience.
- Maintenance of CF-specific CDP including annual attendance at national and international Conferences.
- Teaching and supervisions of specialist and less experienced Physiotherapists.

The complexity of the caseload requires robust cross cover arrangements between the Principal CF Physiotherapist and the Advanced CF Physiotherapist posts.

In addition to these posts, MDTs in large and/or complex Specialist CF Centres benefit from the strategic leadership and expertise provided by a Consultant Nurse or a Consultant Allied Health Professional post.

Recruitment to these pivotal physiotherapy posts will be undertaken in collaboration with the Clinical Director of the CF Centre.

Specialist Physiotherapist

Experienced Physiotherapists developing clinical expertise in the physiotherapy management of CF, in either a static or wider rotational post (band 6), or community staff who treat individuals with CF as part of a mixed caseload are well placed to deliver specialist CF care when supported and supervised by Advanced CF Physiotherapists.

The roles, responsibilities and characteristics of Specialist Physiotherapists should include:

- Management of own specialist caseload that includes a significant proportion of care for people with CF.
- Specialist expertise acquired through degree and supplemented by specialist post-graduate training and experience.
- Supervision of less experienced physiotherapists, assistants and students.
- Maintenance of own competencies and skills through CPD relevant to CF practice.

Physiotherapist

Newly qualified and less experienced physiotherapists traditionally gain experience of a broad range of clinical areas in rotational posts (band 5). Rotations are usually short in duration and provide a foundation for the physiotherapist's professional career.

The roles and responsibilities of a Physiotherapist should include:

- Assessment and treatment of own caseload of patients, within scope of practice, as directed by Advanced CF Physiotherapist.
- Regular supervision and specialist advice from more experienced Specialist Physiotherapist
- Development of competencies and skills through preceptorship (where applicable), regular education and training, and use of competency frameworks.

Physiotherapy Support Worker

A physiotherapy support worker is a non-registered practitioner who undertakes delegated work in pursuit of physiotherapy interventions.[7] Support workers make a valuable contribution to physiotherapy services enhancing patient outcomes, patient experience and service efficiency.[7] Support workers may work exclusively with the physiotherapy team or have a muti-professional role. Scope of practice and level of support worker will depend on the needs of the service. The registered physiotherapist retains overall responsibility for patient care.

Services that employ Physiotherapy Support Workers should:

- ensure that safe and effective delegation processes are in place in line with Health and Care Professions council (HCPC) standards, by adhering to local policies and implementing the principles outlined in optimising capability in the physiotherapy support worker workforce[7]

- implement a process to develop the support workers knowledge, skills and behaviors to enable them to work at the top of their scope of practice. The **Allied Health Professions' Support Worker Competency, Education, and Career Development Framework** provides comprehensive guidance on this process[9]
- ensure that appropriate supervision is in place.[8]

Links with other professions

People with CF benefit from MDT support due to the complex and systemic nature of CF. Other healthcare professional roles such as Exercise Practitioners, Physiologists and Occupational Therapists will often work closely alongside the physiotherapy team. However, these roles are distinct and separate to the CF physiotherapy team.

Other physiotherapists may also be employed in other roles within the wider MDT, for example research or quality improvement. Similarly, these staff members should not be counted in the CF physiotherapy team.

2.1.3 Network Clinics

Care at each clinic visit, during inpatient stay and ongoing care must be either delivered by, or directly supervised by, an Advanced Physiotherapist (Band 7). The Advanced Physiotherapist must have strong links and regular two-way communication with the Principal CF Physiotherapist at the Specialist CF Centre.

Where care is provided by other Specialist Physiotherapists (Band 6 or above), these should be static posts to ensure continuity of care and maintenance of specialist skills.

Patients must be reviewed collaboratively between the Specialist Centre Physiotherapist and Network Clinic Physiotherapist at least biannually.

Where clinical posts are shared with other services, there must be strategies in place to ensure that the demands from other services do not result in a disproportionate amount of time spent providing care to the non-CF case load.

All physiotherapists who are permanently part of teams providing care for people with CF must:

- have access to training and continuing professional development opportunities in CF
- follow the Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis Fifth Edition.
- access peer support locally, for example via Physiotherapists at the Specialist Centre, and nationally from the membership of the ACPCF specialist interest group.

2.2 Service provision

Individuals with CF will have access to ongoing supportive physiotherapy at all stages of their life, in a range of different care settings. Clinical assessment and interventions will be provided by physiotherapists with the appropriate level of expertise required to meet the individual's clinical need. This will be directed by the Principal CF Physiotherapist in partnership with an Advanced CF Physiotherapist to ensure oversight and continuity of right care.

2.2.1 Outpatients

All individuals with CF will receive the following care:

- They will be seen by a Specialist Physiotherapist at each clinic visit. Clinic physiotherapy provision will be supervised, and long-term plans directed by an Advanced or Principal CF Physiotherapist.
- They will see the Principal CF Physiotherapist (or Advanced Physiotherapist if there is no Principal Physiotherapist) at least once a year and more frequently if required.
- They will have open access to Specialist physiotherapy support between clinic visits when needed, such as during a course of antibiotics, after a change of technique or if any concerns arise.
- Appropriate facilities and technology (including remote monitoring) will be in place to provide this intervention either face to face or via virtual clinics. This should be based on clinical need, alongside consideration of easy and convenient access to care. For more details, see the **Standards for the clinical care of children and adults with cystic fibrosis in the UK, 2024**.[16]
- Specialist physiotherapy should be available to provide the necessary education and support with the set-up and use of remote technology, with processes in place to ensure appropriate monitoring and response to captured clinical data.

2.2.2 Annual review

NICE quality standard QS168[18] requires members of the CF MDT to meet annually to review assessment results and treatment for all people with CF. Disease progress must be reviewed and care adjusted as needed to prevent or limit symptoms, complications and disease progression.

To fulfil this requirement, the following conditions will be met within physiotherapy teams:

- The physiotherapy annual review will be carried out by the Principal CF Physiotherapist or an Advanced CF Physiotherapist. The Principal CF Physiotherapist will provide regular clinical supervision to the Advanced CF Physiotherapists undertaking annual review assessments and plans.
- There will be sufficient time allocated at annual review to address:
  - Airway clearance
  - Exercise plans (including exercise testing)
  - Inhalation therapies (and associated devices)
  - Musculoskeletal (MSK) issues and posture
  - Continence issues
  - Gastro-oesophageal and sinus disease
- Consideration should be given to obtaining induced sputum samples in non-sputum producing patients.
- There will be treatment and referral pathways in place for management of MSK, continence or sinus issues should they arise.
- An individualised, goal-orientated physiotherapy plan will be developed in partnership with the person with CF (and carers if appropriate) and communicated to the physiotherapy and multidisciplinary team.
- There will be processes in place for submission of accurate physiotherapy-related data for national registry and care quality dashboard, subject to patient consent and national requirements.

2.2.3 Inpatients

There will be adequate staffing and an appropriate skill mix to ensure that the following conditions are met:

- Inpatient care packages are delivered by a team led by an Advanced CF Physiotherapist, with oversight and expert intervention easily available from a Principal CF Physiotherapist.
- All individuals with CF admitted to hospital for inpatient care will have access to physiotherapy assessment and treatment. There will be an initial assessment and regular review of patient progress by an Advanced CF Physiotherapist.
- People with CF who are admitted to hospital will be offered physiotherapy optimisation and a minimum of twice-daily treatment, more regularly if required (unless an alternative regimen is agreed by the person/carer and the Advanced CF Physiotherapist).
- Individuals with CF and/or their carers will not be expected to provide their own inpatient physiotherapy because of shortfalls in physiotherapy staffing levels.
- Individuals with CF admitted for inpatient care will have opportunities to carry out targeted daily exercise.
- Physiotherapy to support airway clearance will be available at weekends as with weekdays. It will be delivered by physiotherapists trained and competent in CF physiotherapy provision.
- An emergency on-call physiotherapy service will be available to inpatients with CF during out of hours if required.

2.2.4 Community

Home care physiotherapy will be provided where appropriate by an Advanced CF Physiotherapist at times of particular need, for example:

- At diagnosis.
- To provide school visits on starting primary or secondary school if required.
- When additional support is required to implement changes to a treatment plan, such as airway clearance modifications, new inhaled therapy regimens, and new exercise programmes.
- To support with delivery of exercise programmes where additional assistance may be required, such as prehab, accessing community gyms, and change in health status.
- To support during the peri-natal period.
- To support adherence with complex treatment regimens.
- To assist the provision of palliative care at home.
- To resolve complex oxygen or non-invasive ventilation issues.
- Where optimisation of physiotherapy is required during home IV treatment.

2.2.5 Specific life stages

Individuals with CF may require additional support throughout or at certain life stages. Physiotherapy staff should be appropriately trained, with processes and patient pathways in place to ensure timely access to correct information and additional support when required.

2.2.5.1 New diagnosis

- All newly diagnosed people with CF (either through newborn screening or diagnosis later in life) will see a Principal CF Physiotherapist or an Advanced CF Physiotherapist.

- Care may be provided jointly by the Principal CF Physiotherapist and the Advanced CF Physiotherapist, but there will be regular communication and a clear management plan with oversight and input from the Principal CF Physiotherapist.
- For infants, refer to management of screened infants with CF (**section 3**) and the CFSPID (**section 13.1**).
- For late diagnosis, following assessment, a physiotherapy management plan will be advised appropriate to symptoms.
- Frequency of input from the physiotherapy team will be tailored to the individual, but frequent assessment and advice will be required in the months following diagnosis. If required access to physiotherapy may be weekly in the months following diagnosis.

2.2.5.2 Transition

NICE guideline NG43[15] recommendations should be followed when supporting a young person when transitioning from paediatric to adult services.

Alongside the overarching principles outlined within these recommendations, the following should also be met:

- All young people with CF transitioning from paediatric to adult CF care will have appropriate input from the relevant adult, paediatric and Network physiotherapy services throughout the transition process, utilising a coordinated and documented transition program such as Ready Steady Go and Hello.
- Processes will be in place to allow ongoing communication between the relevant physiotherapy services during transition to optimise the support provided to the individual and their family.
- The Principal or Advanced CF Physiotherapist will carry out the initial physiotherapy consultation on transition to adult services. An individualised physiotherapy plan, which considers both physical and emotional aspects of care, will be developed in partnership with, and communicated to, the person/carer and the receiving physiotherapist and MDT.

2.2.5.3 Surgery

- All people with CF undergoing surgical procedures, for instance port or PEG insertion should have access to specialist physiotherapy to optimise respiratory status and physical fitness pre-operatively and provide appropriate support in the post-operative period.
- Disease severity, type of surgery and any likely associated risks should be considered when considering modification of physiotherapy treatment plans.

2.2.5.4 Pregnancy and parenthood

- There should be regular specialist physiotherapy support throughout pregnancy, post-partum and in early parenthood for modification and optimisation of airway clearance, exercise programmes, inhaled therapies and screening for MSK and continence issues, with appropriate referral pathways in place.
- All pregnant mothers with CF will have an assessment by the Advanced or Principal Physiotherapist during hospital admissions or when changes to inhaled treatments or airway clearance techniques are required.

2.2.5.5 Transplantation and post-transplant care

- There will be appropriate specialist physiotherapy support leading up to transplantation for the optimisation of airway clearance, inhalation therapies, exercise, oxygenation and ventilation needs. Where appropriate, complementary therapies may be considered for symptom relief.
- There will be communication between the physiotherapy team at the individual's CF Centre and the transplant centre with a clear physiotherapy management plan.
- There will be appropriate Specialist physiotherapy support following transplantation, with exercise programmes and inhalation therapies. Additional input should be provided as required, such as for optimisation of airway clearance or sinus management.

2.2.5.6 Growing older with CF

- There will be appropriate specialist physiotherapy support for the older person with CF. Physiotherapy provision should consider age-related changes and complications, with appropriate modification to airway clearance, exercise programmes and inhaled therapies to ensure both physical and emotional needs are met.
- Physiotherapists should ensure appropriate support for complex age-related complications (such as MSK, cardiovascular, frailty, discharge planning) either through extending scope or ensuring patient pathways are in place to access an appropriate non-CF specialist physiotherapy service.

2.2.5.7 End-of-life and palliative care

- There will be appropriate Specialist physiotherapy input throughout the stages of end-of-life care, with oversight and expertise provided from both the Principal and Advanced CF Physiotherapists to support individuals with symptom relief through optimisation of airway clearance, oxygenation and ventilation as required.
- Complimentary therapies may be considered for pain relief, breathlessness and anxiety management.

2.2.6 Intervention

All individuals with CF will have regular physiotherapy assessment and monitoring of treatment , at a frequency based on their individual needs. Any alterations to medication regimens or treatment plans should be discussed with the Principal or Advanced CF Physiotherapist.

All individuals will receive the necessary education and support, with age-appropriate verbal and written instruction. A structured adherence program will be available to support individuals with changes to treatment regimes.

Physiotherapists are routinely involved in range of areas of CF care. **Further detail is provided in sections 3–17 of these, including:**

- Physical activity and exercise, including exercise testing
- Airway clearance techniques
- Sinus disease
- Inhalation therapies
- Oxygen therapy
- Non-invasive ventilation (NIV)
- MSK and postural management
- Pelvic health

2.3 Facilities

People with CF will have access to age-appropriate facilities for their physiotherapy care as inpatients and outpatients.

- Facilities will recognise the need for privacy and dignity when carrying out airway clearance and exercise. This should include single rooms for airway clearance and ensuite facilities where possible.
- Adequate facilities for exercise will be available to people with CF as inpatients, such as a gym with an adequate range of exercise equipment and sufficient space and facilities for aerobic exercise and exercise testing to be carried out.
- Facilities for physiotherapy treatment must allow teams to follow national and local infection control policies.

2.4 Equipment

All people with CF will be provided with appropriate respiratory and exercise equipment and will be trained in its use and maintenance.

- There must be written protocols regarding the use of the equipment used by people with CF.
- People with CF will be provided with the respiratory equipment they require for use at home, for instance to nebulise medication, for airway clearance, for oxygen delivery and humidification. Access to inhaled therapies will be in accordance with the NHS England policy or the policy of their devolved nation.
- People with CF and their carers will be trained in the use of equipment supplied for home use.
- Advice including written instructions regarding the use and maintenance of equipment provided for home use (including cleaning, disinfection and sterilisation and servicing as applicable) will be provided to all people with CF and their carers, and will be in line with manufacturers' guidance.
- All equipment used by people in hospital will be serviced and maintained (including cleaning, disinfection and sterilisation as applicable) according to manufacturer's instructions and/ or national and local policies.
- There must be a clear and adequate budget available for the provision of respiratory equipment, including advanced, fast and efficient nebuliser devices such as vibrating mesh technology (VMT) nebulisers in accordance with the summary of product characteristics (SPC) for the medications being delivered. Replacement of consumables will be made at the recommended intervals. There will be clear responsibility as to who holds this budget.

2.5 Clinical standards

Physiotherapy clinical care will be based on the best evidence available:

- NHSE (or equivalent for devolved nations), NICE, HCPC, ACPCF, CF Trust guidelines, quality

standards, protocols, toolkits and consensus documents will be followed.

- All physiotherapy staff caring for people with CF should have knowledge of and know how and when to access all the relevant guidelines and guidance papers listed within these standards.
- All physiotherapy staff caring for people with CF will be expected to access these standards during their induction period and identify areas for training and development.
- There must be evidence that the physiotherapy service provided for individuals with CF is regularly evaluated through clinical audit and quality assurance programmes.

2.6 Infection control

All physiotherapists working with people with CF will consider issues of hygiene and the prevention of cross-infection.

- All staff will have knowledge of and work to:
  - Local infection control policies, which should make specific reference to physiotherapy management in different settings.
  - CF Trust guidelines relating to prevention and infection control with *Burkholderia cepacia complex*, *Pseudomonas aeruginosa*, *Mycobacterium abscessus* and MRSA in people with CF.[10,12,13,17]
- All people with CF will have their own home respiratory equipment, such as airway clearance devices, nebuliser devices and consumables, oxygen equipment and NIV.
- Some respiratory equipment, such as intermittent positive pressure breathing (IPPB), high frequency chest wall oscillation (HFCWO), high flow nasal oxygen (HFNO), ultrasonic nebulisers, cough assist and NIV devices may be used by more than one person in the hospital setting. Local standard operating procedures relating to minimisation of cross-infection between people with CF will be in place for these devices.
- Physiotherapists will have access to records of individual microbiological status and be able to identify people at high risk of cross-infection.
- There will be rigid adherence to infection control policies when carrying out airway clearance, exercise, nebulisation and spirometry.
- All staff will take all reasonable precautions to reduce the risk of cross-infection in accordance with local policy. This will include:
  - Rigorous handwashing.
  - Decontamination of pulse oximeters, stethoscopes and exercise equipment between use by people with CF.
  - Wearing of aprons and gloves for airway clearance.
  - Careful handling of respiratory secretions (sputum pots should be covered and disposed of at least daily and soiled tissues disposed of immediately).
- All staff members should be aware of the physiotherapy guidance around infection control and methods of decontamination of equipment found in these standards.

2.7 Professional development and training

Physiotherapists caring for people with CF have a professional responsibility to keep up to date with current CF research and to continually update their skills and knowledge to provide the best possible clinical care.

All physiotherapists providing care to people with CF must adhere to the following requirements:

- Ensure that they meet:
  - **HCPC standards of conduct, performance and ethics**
  - **HCPC standards of proficiency**
  - **HCPC standards of continuing professional development (CPD)**
- Ensure they maintain their CPD in general respiratory care and ensure they have adequate clinical skills to follow these standards.
- Have an annual appraisal and be able to provide evidence of meeting professional development plans.
- Where appropriate submit research, case reports or quality improvement work to national and international conferences.
- Seek feedback from people with CF using the physiotherapy services, to ensure that they continue to meet their needs, and use feedback to help direct future service improvements.
- Demonstrate a commitment to ongoing CPD, demonstrated by membership of the ACPCF specialist interest group, as well as attendance at local or regional CF study events, and relevant national and international conferences.

3. Management of screened infants with cystic fibrosis

3.1 Introduction

Babies born with CF have essentially normal lungs but within various timescales develop chronic respiratory disease. Since the introduction of newborn screening (NBS) throughout the UK, babies are diagnosed with CF soon after birth, often before they develop any symptoms or lung pathology. Additionally, a new group of patients has emerged named 'cystic fibrosis screen positive inconclusive diagnosis' (CFSPID). This refers to children who have either a normal sweat test in the presence of two mutations, at least one of which is of uncertain significance (Group A) or a borderline sweat test in the presence of zero or one mutation (Group B).[19] Please see **section 13.1** for more details regarding this cohort.

The majority of newborn-screened infants present to CF Centres with no signs or symptoms of disease. The importance of early intervention is well recognised and most CF Centres have adopted a policy of close monitoring and aggressive treatment of early lung disease.[20,21] A significant number of children with CF now have normal lung function well into early adulthood even though they are very likely to have underlying lung pathology.[22]

The advent of NBS raised questions about the role of traditional, routine airway clearance in asymptomatic babies. While specialist physiotherapists agreed unanimously that physiotherapy interventions were appropriate once respiratory symptoms were apparent, the place of routine daily airway clearance prior to this was less clear.[23,24] It was also recognised that while infants may be asymptomatic at diagnosis, over time they will swing along a spectrum of being asymptomatic at times and symptomatic at others.

The ideal solution would have been to undertake a prospective randomised controlled trial (RCT) comparing twice-daily routine airway clearance with a regimen of close monitoring and airway clearance as required. As this proved not to be a possibility, a Delphi consensus was undertaken by the ACPCF amongst specialist physiotherapists in the UK, in order to formulate guidelines for the management of infants with CF diagnosed by NBS.[25] Consensus was reached on the majority of statements and although most physiotherapists agreed that routine twice-daily airway clearance was no longer needed, it was not possible to reach a full consensus. A later amendment included the individualisation of treatment interventions.

Physiotherapists have a duty to provide safe and effective care and daily treatment regimens need to be tailored to individual needs, lifestyle and symptoms, particularly as long-term routine airway clearance is a substantial burden for patients and families.[26]

Arguments for starting airway clearance early in symptom free infants are three-fold. Firstly, there is good evidence that early lung disease precedes the development of overt symptoms in children with CF.[20,27–35] Secondly, anatomical and physiological differences, which result from immaturity of the respiratory system, in combination with CF, mean infants with CF are more vulnerable than older children with CF to respiratory complications and infection. Finally, establishing daily routines early in a life-long illness may help with acceptance of the need for treatment and adherence for both the child and family. It may also enable parents to build and maintain their competency in airway clearance techniques (ACTs).[36,37] Conversely, the presence of bacterial infection and raised inflammatory markers reported from broncho-alveolar lavage fluid (BALF) is not always associated with excessive sputum production or symptoms that respond to airway clearance. There is no physiological argument or scientific proof that physiotherapy is helpful in alleviating the inflammatory process within the airways. It is well known that adherence to routine therapy in chronic disease poses a significant problem and that when the benefit of a treatment is not immediately apparent, adherence is often poorest.[38–41]

In summary there is no absolute clear approach to the physiotherapy management of infants with CF who are symptom-free. This was reinforced by the European Cystic Fibrosis Society (ECFS) neonatal screening group who developed a consensus on the management of NBS infants.[42] **They stated that:**

- infants must receive care by a CF specialist physiotherapist
- techniques to facilitate airway clearance should be undertaken on a regular basis
- debate exists as to the best strategy in managing asymptomatic infants; physiotherapy should be completed more frequently in the symptomatic infant.

With the introduction of CFTR modulators physiotherapy management may change in the future; however currently there is no evidence, in this cohort, to support change in practice.

3.2 Literature review

3.2.1 Early detection of lung changes

There is clear evidence that the lungs of babies with CF show physiological changes correlating with reduced airway function such as thickened airway walls, narrowed airway lumens and air trapping from an early age,[33,43] in the absence of overt clinical symptoms or objective findings on examination. Investigative techniques including high-resolution CT bronchoalveolar lavage (BAL), infant lung function and lung clearance index (LCI) serve to confirm this.

Mott et al and the Australian respiratory early surveillance team (AREST CF) carried out a retrospective analysis of repeat CT scans on 143 children, ranging from two months to 6.5 years in a NBS programme to investigate if early structural lung disease persists and progresses over one year.[44] Bronchiectasis was detected in 75%, either on the initial or subsequent scan. It persisted in 74% of those detected in the initial scan. Progression over time was evident in 63% of subsequent scans, compared to initial scans. Air trapping was seen in 88% of scans. This persisted at the second scan in 81%, and progression over time was evident in 46%. Radiological progression of both bronchiectasis and air trapping was associated with severe genotype, worsening neutrophilic inflammation and pulmonary infection. Ranganathan et al conducted a review of early CF lung disease and documented that bronchiectasis was present in asymptomatic infants with CF.[35] Free neutrophil elastase activity on BAL was present in 30% of infants with CF and was a predictor of bronchiectasis by the age of three years with air trapping identified as an additional risk factor. Bronchiectasis was found in 30–40% of three-to-four-year-olds and increased to 80% by the age of five, despite normal lung function parameters.

As part of the AREST group, Esther et al (2019)[45] found abnormal mucus accumulation in CF BALF, associated with increased mucin and inflammatory marker expression, despite low bacterial infection. In a small study, DeBoer et al (2021)[46] identified increased simulated airway resistance in 18 infants with CF compared to the seven controls, which may be related to early airway inflammation. Another study[47] found that early viral infections, most commonly rhinovirus, were associated with later greater neutrophilic inflammation and classic CF bacterial pathogens on BAL in 70 NBS infants.

A UK study looking at NBS infants at one year of age[48] found that lung and airway damage was much milder than previously reported, and that associations between inflammation, abnormal physiology and structural changes are present but weak when comparing BALF, LCI and CT results from 65 infants. Aurora et al[49] continued this study, following up with the same cohort between two years and pre-school age, concluding that future lung function decline is related to minor abnormalities of CT and LCI in infancy. This may focus CF management on these individuals and suggests it is important not to dismiss minor changes on CT in the infant years.

Conversely, the AREST group (Carzino et al, 2020)[50] published data the same year pairing BAL samples with CT scans at age three months, 12 months and annually until age six. They detected pro-inflammatory markers in 53% of BAL samples, and this was associated with increased risk of both air trapping and bronchiectasis on CT scan. Despite this, there was disparity between sites of isolation of pro-inflammatory microbes and the anatomical site of early bronchiectasis, highlighting the potential un-coupling of early inflammation from infection and bronchiectasis. As both groups of authors suggest, longer term follow-up is warranted to understand this fully.

LCI is a measure of ventilation inhomogeneity derived from a multiple breath washout (MBW) technique. Its clinical usefulness in early lung disease detection has meant its use has surged over the last 20 years, particularly in children, where more sensitive objective measures are required.[51] The repeatability of LCI in individuals with CF has been confirmed and a review relating to NBS and early lung function outcomes concluded that LCI is more effective than FEV_1 at detecting early lung disease and is better correlated with structural change on chest CT in children with CF than FEV_1 z score.[52,53]

Kieninger et al[54] provided the first evidence that abnormal lung function exists as early as eight weeks of age in more than 40% of infants with CF, measured by LCI and functional residual capacity (FRC), independent of clinical symptoms. Ah-Fong Hoo et al and the London CF Collaboration group found elevated LCI and decreased $FEV_{0.5}$ in 35% of the 71 infants with CF under their care, and concluded that despite protocol driven treatment from Specialist Centres, abnormal lung function occurred in the absence of respiratory symptoms.[55] Conversely, Davies et al tracked infant lung function over the first two years of life and found that changes were mild and transient.[56]

Korton et al[57] carried out a prospective assessment of the number and severity of respiratory symptoms in the first year of life in infants with CF and healthy controls, and association with infant lung function. There was no significant difference between the two groups in terms of respiratory symptoms or duration of symptoms. No linear association was found between frequency of respiratory symptoms and LCI, indicating that

early lung disease may not be captured by clinical presentation.

Several studies have aimed to identify factors measured in infancy that could predict lung function abnormality at pre-school age.[48,49,58] Isolation of a significant pathogen, most commonly *P. aeruginosa* was found to be the most significant univariate predictor of pre-school LCI and ventilation distribution efficiency (VDE).

3.2.2 Adherence

There is little evidence regarding adherence to airway clearance in infants and young children with CF, and the argument for establishing a daily routine to optimise adherence is not proven.

Jakobsen and a team at Aarhus University Hospital in Denmark report obtaining high adherence to positive expiratory pressure (PEP) treatment in around 100 babies with CF over a six-week period.

However, non-adherence to treatment regimes in chronic disease has been reported to be as high as 50%.[38,39,41] Time-consuming interventions which have no obvious immediate benefit, and those interventions which cause disruption to lifestyle are associated with poorer rates of adherence.[39–41] It has also been suggested that insistence on routine daily treatment may even reduce adherence during the adolescent years when the need for treatment may become greater.[59]

Andrews et al[60] undertook semi-structured interviews and analysed daily diaries from 13 parents of one-to-two-year-olds with CF. Themes included parents feeling pressure, doubt and guilt about the responsibility of performing chest physiotherapy, but that performing chest physiotherapy was also perceived as a positive experience and opportunity to impact the health of their child. The interviews suggest we should be aware of these parental perceptions and experiences and use this to enhance the personalisation of physiotherapy programs with minimal burden.

3.2.3 Physiotherapy intervention

There is clear evidence to suggest early lung disease is present even in the absence of symptoms and it is widely accepted that early management of lung disease is essential. However, the early pathophysiological changes are often inflammatory in nature and not always associated with symptoms that respond to airway clearance. Conversely, if infection with likely sputum production is part of the early pathological picture then early institution of airway clearance would appear sensible.

Physiotherapy encompasses education, formal airway clearance, inhalation therapy, physical activity and structured exercise and it is the role of the specialist CF physiotherapist to closely monitor and develop individualised programmes for each infant accordingly. There is very little evidence in the current literature that addresses these specific issues in babies with CF, but some small studies are relevant.

Button et al demonstrated increased gastro-oesophageal reflux in physiotherapy regimens which used postural drainage (PD) incorporating a head down tilt when compared with regimens which used modified PD omitting any head down tilt.[61,62] Long-term follow-up of these infants also reported fewer respiratory complications in the group receiving modified PD. Despite weaknesses in these studies, in particular the small subject numbers, the potentially detrimental effects of PD they raised have led many to recommend that the head-down-tipped position should no longer be used during airway clearance for infants with CF. A recent Cochrane review identified that the majority of reflux episodes reached the upper oesophagus and should make therapists carefully consider their treatment strategy.[63]

The immediate effects of a single session of four modes of treatment (inhaled salbutamol, inhaled N-acetylcysteine, chest physiotherapy; or a combination of all three) on lung function in 19 infants during the first year of life were assessed by Maayan et al.[64] The regimens were applied in a randomised fashion. No significant changes in lung volumes, measured by infant whole body plethysmography were reported in individual groups but there was a small improvement with the combined treatment group when compared with inhalation therapy or chest physiotherapy alone.

A recent Cochrane systematic review of conventional chest physiotherapy (PD, percussion, vibration, huffing and coughing) compared to other airway clearance techniques included studies that enrolled newborn babies, and concluded that there remains no conclusive evidence to suggest that conventional chest physiotherapy has any advantage over other ACTs.[65]

Constantini et al compared the long-term efficacy of PEP mask versus PD and percussion in infants with CF.[66] There was no difference in deterioration on chest radiograph or days per year of antibiotics over a one year period. The authors concluded that PEP was safe to use in early childhood and equally effective as PD and percussion, although patients and parents preferred PEP. Kiernan et al, in a small clinical audit of 21 babies with CF reviewed manometer pressures reached during PEP clinical review sessions, concluding that the UK Standards

recommendation of 10–20 cm H_20 were not achieved in this cohort.[67] Sharp et al carried out a retrospective audit to compare PD and percussion with infant PEP and autogenic drainage (AD) in newborn screened infants.[68] They demonstrated a significant reduction in respiratory exacerbations requiring admission during the first year of life in the PEP group (mean 0.71) compared to PD and percussion (mean 1.66). A recent review by Dixon (2024), investigating current infant PEP practice in the UK, utilising a digital questionnaire and ACPCF database, confirmed that practices are varied. Responses were from Specialist Centres (64%; 18/28) and Network or local hospitals. Infant PEP was used in 88% of Centres, confirming it as an established ACT for this cohort albeit with little evidence.[69]

A systematic review of AD and assisted AD was undertaken. However, due to lack of paediatric specific RCTs, small sample sizes and unclear risk of bias, it was not possible to determine the efficacy and/or safety.[70] The effects of assisted AD, combined or not with bouncing on gastro-oesophageal reflux in infants, was investigated by Lievens et al.[71] The study included 105 infants referred to confirm a clinically suspected diagnosis of gastro-oesophageal reflux, who were then allocated to a single 20-minute treatment of either assisted AD or assisted AD with bouncing on a gym ball. Results showed that assisted AD, whether combined with bouncing or not, did not cause an increase in reflux episodes in infants under the age of one year.

Byrne et al offered a more individualised approach to physiotherapy management following the introduction of the NBS programme, including 25 babies over a three-year period. Daily airway clearance was no longer advocated as standard;[72] parents were taught ACTs, advised about respiratory symptoms and when to initiate treatment. Eighteen families followed the new protocol; the remaining either had persistent respiratory symptoms or social issues necessitating the need for routine airway clearance from the outset. There were 11 hospital admissions, 10 for respiratory causes. Five infants changed from intermittent to routine ACTs due to isolation of *P. aeruginosa*. The remaining children continued into early childhood without the burden of daily treatment.

In 2013, Cystic Fibrosis Trust undertook a survey to identify the types of physiotherapy taught and practised in the UK infant population.[73] Results were collated from 17 paediatric Specialist Centres and 40 parents of babies with CF. The results showed a shift away from a rigid regime for families with more flexibility and individual assessment.

In 2018 the ACPCF decided to review current practise nationally for infants aged 0–3 years with CF and CFSPID. Two 10-question SurveyMonkey® questionnaires including a mixture of multiple choice and open questions were sent out via email to ACPCF members and direct emails to paediatric UK Centre leads from the ACPCF national database.[74]

In total, 39 responses were received for the CF questionnaire, 25 from Specialist Centres, 13 from Network Clinics and one unknown. The majority (62%) of infants had an initial physiotherapy review within one week of diagnosis and all infants within three weeks. Frequency of review varied from weekly to monthly in the early stages, extending to monthly during the first year, with 26% of Centres reporting that they offered home visits to support this. All Centres taught ACTs; the most frequent techniques taught were PEP mask (34%) and percussion (31%). Other techniques mentioned included AD, vibrations, exercise, modified PD, Bubble PEP (when old enough), gym ball bouncing, and blowing games. The majority of respondents chose more than one ACT.

Various factors were reported to influence advice given on type, duration and frequency of airway clearance, the most prevalent being respiratory symptoms (37%). Other factors included parent and carer ability to carry out assessment and/or treatment, routine treatment to facilitate adherence, genetic mutation and/or sweat test result, comorbidities such as abdominal surgery, clotting, physiological principles, chest X-ray changes, microbiology, age, led by Specialist Centre, evidence, and older CF sibling status. If infants became in-patients they received daily input. Some respondents specifically described advising once-a-day airway clearance increasing to twice a day with symptoms or when unwell.

Types of exercise recommended by Centres included general developmental activity, gym ball exercises, tummy time, swimming, active play, baby group and gym classes, arm and leg exercises, floor play, activity encouraged as a family, baby massage, yoga, anything the child enjoys.

Parents and carers were advised to monitor respiratory signs and symptoms. The phrase 'look, listen and feel' was often referred to. Half of the Centres reported providing parents with a specific assessment tool, of which almost half of these used the ACPCF assessment tool. The Great Ormond Street Hospital (GOSH) infant leaflet was also used. Most respondents reported that nebulised mucolytics would be considered but are not used routinely. Since then, the ACPCF have also developed an infant leaflet.

Overall, key recommendations from the Delphi consensus regarding assessment, treatment, activity and exercise for infants with CF are being followed.[25]

3.2.4 Good practice points

- All infants with a confirmed diagnosis of CF must receive care from a CF specialist physiotherapist or a local team who liaise with the Specialist Centre.
- Infants should be reviewed on a regular basis. An easily accessible physiotherapy service for assessment, advice and support is essential.
- All parents and carers should be taught to assess signs and symptoms, using a structured respiratory assessment tool as appropriate.
- Even if the baby is asymptomatic, all parents and carers should be taught to assess symptoms, in addition to being taught an appropriate airway clearance technique to use when assessment indicates.
- The initiation of airway clearance should be determined by the physiotherapist on an individual basis. Asymptomatic babies may not require daily airway clearance but it may be suitable in some instances, for example for some families who feel or seem unable to confidently assess their child's chest. Airway clearance should be more frequent in the symptomatic infant.
- When airway clearance is required, parents and carers should be told the types and frequency of treatment needed, based on clinical status. Families and carers should be fully involved in this decision process.
- Modified PD positions are considered more appropriate than a head down tilt, with regards to both their efficacy in infants with relatively few secretions and the potential for exacerbating gastro-oesophageal reflux.
- The beneficial effects of exercise are well documented. Advice regarding positioning, movement and exercise programmes should begin from diagnosis.
- Direct contact numbers for the CF physiotherapy team should be available to the parents and carers, the wider MDT, primary care and Network Clinic teams as appropriate.

3.2.5 Research recommendations

- Long-term comparison of routine airway clearance versus symptom driven airway clearance in infants with CF.
- Evaluation of parental perceptions of performing airway clearance for infants with CF.
- Long-term evaluation of need for airway clearance in infants taking CFTR modulators.

4. Outcome measures

Outcome measures are used for a variety of reasons, including:

- to assess the impact of the disease on daily function
- to assist in clinical decision-making
- assess the efficacy and effectiveness of treatment interventions within clinical practice and research
- to assess the costs and benefits of a service
- potentially to commission funding for a service.

An outcome measure should be assessed for important clinimetric properties such as validity, reliability and responsiveness to treatment. Outcome measures relevant to physiotherapy are restricted by their complexity and feasibility. Feasibility is multifaceted and refers to financial, practical and ethical considerations, as well as patient and assessor acceptability and ease of use in the clinical setting. For instance, high-resolution CT scans and radioisotope aerosol labelling carry risk to the patient; LCI is not yet used clinically but primarily in the research setting.

For the purpose of this document, we have concentrated on outcome measures that could potentially be used to evaluate physiotherapy interventions.

4.1 Outcome measures for airway clearance

ACTs are recommended for many people with CF as part of their CF management. There are many different ACTs and physiotherapists need to collaborate with their patients to identify a suitable regime. Assessment of the efficacy of ACTs needs to consider the individual; a measure assessing amount of sputum cleared, for example, will not be useful in a non-productive patient. Likewise, a patient with severe CF lung disease may not be able to complete a lengthy or effortful breathing test such as a MBW or spirometry.

There are several papers illustrating the methodological and ethical issues in assessing ACTs,[75–77] and currently there is a debate about what makes a sensitive, responsive, and clinically valid outcome measure when evaluating them. Most outcome measures used to assess ACTs have no agreed minimal clinically important difference (MCID), which can make interpretation of effect difficult.

Historically, in clinical trials of ACT, outcome measures of convenience are often used as they are easy to measure and are valid and reliable for other aspects of CF.[78] The most common outcomes used in CF ACT trials are sputum weight and FEV_1.[78,79] While these are both readily accessible and easy to use within a clinical or research setting, several papers have questioned their validity and responsiveness when used to assess ACT effect.[75–77,80–84]

The era of CFTR modulator medications brings an additional challenge to the assessment of ACTs, as clinicians and people with CF are considering the necessity of ACTs in light of a frequently improved health status post-modulators. There is now a need for outcomes which can assess not only the effect of completing ACTs, but also the effect of not completing ACTs. Additionally, many people taking CFTR modulator medications produce very little sputum which makes sputum weight an obsolete outcome.

When considering efficacy of ACT, we have seen that improved quality of ACT performance can positively impact outcome measures such as lung function.[85] For an ACT to be effective and demonstrate improvement in clinically relevant outcome measures, the quality of the ACT delivery needs to be firmly established. Furthermore, integrated digital technologies within ACT devices, such as pressure and breath duration measurement mechanisms as identified by Filipow et al and Raywood et al,[86,87] can, through feedback, positively impact on the quality of treatment completed. Using these opportunities to observe real-time changes in the delivery of ACT, the physiotherapist can optimise treatment and enhance efficacy, potentially reducing burden of care, with quality over quantity being the key determinant.[85]

Many systematic reviews recognise a variety of outcome measures, while suggesting that further work is required to identify the most appropriate outcome measures for use in airway clearance interventions.[78,79,81,88–97] Future work needs to focus on clinimetric properties alongside patient preference and acceptability for use across the spectrum of CF. Importantly, the outcome measures used must be meaningful to both patients and clinicians, with an understanding of what a change means,[98] identifying an MCID for each outcome measure can help with this interpretability.

4.1.1 Sputum

It has been suggested that amount of sputum cleared is not specific to airway clearance or alveolar recruitment, not sensitive to small changes and has limited repeatability as it is subject, at times, to the preference of the person as to whether or not to expectorate.[81,82] Sputum also could be swallowed, cleared following, rather than during an ACT session, or contaminated by saliva, all which can result in over- or under-estimations of ACT effect. A recent RCT investigating outcome measures for ACT effect for a single session of ACT suggested that sputum weight was responsive to the effects of ACT,[84] whereas a 2021 metanalysis of previous ACT studies of varying length concluded that sputum weight was not sensitive to the effects of ACT, indicating sputum weight is not useful as a longer-term outcome measure. Collection of sputum on a long-term basis is also likely to be impractical so sputum volume or weight may only helpful when evaluating short-term ACT effect in an appropriate individual who is productive of sputum. If used, strict controls on the methodology should be adopted such as use of graduated sputum containers for volume or calibrated scales for weight, to ensure accuracy.

4.1.2 FEV_1

FEV_1 is the most common spirometric measure used to assess ACT effect and is well understood by patients and clinicians making it an outcome which will likely be utilised for the foreseeable future. However, it does have limitations: it can be difficult to demonstrate a change in FEV_1 as it is effort dependent[99] and it may not be sensitive enough to detect small but clinically significant changes as those over a session of ACT or in patients with mild disease.[77,80,81,100,101] Furthermore, the nature of completing a forced expiratory manoeuvre, such as FEV_1 may create an airway reaction, influencing the ability to use it as a measure to assess the effect of airway clearance, with no recognised best time point for performing spirometry after airway clearance.[102] Two recent analyses of FEV_1 as an outcome measure for ACT have concluded that it is not sensitive to the effects of ACT.[78,79] Thus, although spirometry could be used[103] to monitor response to treatments when performed with a standardised technique, it is not recommended specifically to assess ACT effect. It would be best used in conjunction with other outcomes.

4.1.3 Novel outcome measures

Some studies investigating ACT effect have been published recently using other outcome measures such as the lung clearance index (LCI) derived from the MBW test,[104–108] electrical impedance tomography (EIT),[109–111] radioaerosol techniques,[112–114] hyperpolarised gas MRI,[115] ventilatory dynamics ascertained through cardiopulmonary exercise testing (CPET),[116] and impulse oscillometry (IOS).[117–119] The responsiveness of these novel outcome measures to ACT effect seems to be variable. While they offer insight into the effect of ACT, there is no definitive answer to which is best for assessing ACT.

In terms of short-term assessment of ACT effect, Stanford et al assessed LCI, EIT, IOS for responsiveness to a single session of ACT and found none of them to be responsive to ACT effect, and thus suggested they should not be used to assess short-term ACT.[84] Changes in LCI and some spirometric parameters[120,121] have been reported in recent studies investigating ACT interventions over periods of one month to two years, and thus may be worth consideration in future longer-term research investigation. Additionally, MRI using hyperpolarised gases has potential for future use, having shown ability to detect change after interventions such as exercise testing[122] and antibiotic therapy.[123]

While some of the newer outcome measures, such as LCI, have been shown to have good clinimetric properties for use assessing other aspects of CF (reliability, validity, responsiveness, and sensitivity),[124,125] evidence for the clinimetric properties of outcome measures to specifically assess airway clearance effect is lacking.[126] Importantly for clinical practice, many of the emerging outcomes involve expensive equipment, specialist training and/or lengthy test procedures which may not be acceptable or suitable for everyone with CF. More research into the specific clinimetrics of these outcome measures for ACT assessment is needed before adoption in clinical practice.

4.1.4 Number of exacerbations

Several studies have used the number of exacerbations over a set time period as an outcome measure; a large and robust multicentre trial reported this to be a valuable measure when comparing physiotherapeutic interventions.[127] However, in a complex disease such as CF, other changes in treatment which are difficult to control for (not limited to ACTs) may affect outcomes during such a time period and need to be carefully considered when reporting changes. Additionally, in the CFTR modulator era, many people with CF are experiencing fewer exacerbations[128,129] or exacerbations which can be harder to detect both for individuals and clinical teams. These changes in exacerbations may make this outcome more difficult to use in the future.

4.1.5 Patient-reported outcomes

Patient reported outcome measures (PROMs) can be easy to use and can help gather important insights into patient views of interventions. Patient preference is key to a successful ACT regime and may be the most meaningful outcome to patients. While currently there is not a specific validated PROM to assess ACT effect, many studies have used visual analogue scales (VAS) to assess change before and after ACT, and these can be helpful in clinical and research contexts. Other PROMs could be used to assess effect of ACTs – for example, a recent publication used analysis of results from six single case reports of the Cystic Fibrosis Questionnaire – Revised (CFQR) to link completion of an ACT to clinically meaningful changes in health-related quality of life (QoL).[130] Despite the very small participant numbers, this does raise the possibility of using QoL as an outcome for ACT effect.

4.1.6 Recommendations

- Physiotherapists should use the best clinically applicable outcome measures to assess the efficacy of airway clearance techniques on an individual basis, taking into account limitations of each outcome measure *(QoE – high)*.
- Outcome measures used to assess short-term effects of ACTs:
  - Sputum volume, weight, colour, ease of expectoration in individuals who are productive of sputum.
  - PROMs such as VAS scales or preference.
  - Other physiological tests or spirometry have not been shown to be sensitive to the short-term effects of ACTs and are not recommended to be used in this context.
- Outcome measures used to assess the longer-term effects of ACTs:
  - Healthcare utilisation, such as time to next exacerbation.
  - PROMs such as VAS scales or preference.
  - Physiological assessments such as LCI, IOS, or hyperpolarised gas MRI and changes in QoL measures could be considered but have not at present been fully assessed for use in this context *(QoE – moderate)*.
  - Spirometry could be used, when performed with a standardised technique, to monitor long-term response to ACTs, although its sensitivity limitations means it would be best used in conjunction with other outcomes *(QoE – moderate)*.
- The quality of ACTs may be assessed through measures of digital feedback *(QoE – moderate)*.

4.1.7 Good practice points

- Factors influencing the choice of outcome measure for airway clearance need to be assessed prior to selection of an outcome measure to use. These include:
  - clinimetric properties of the test
  - clinical relevance to the individual
  - practical ability to complete the outcome measure selected
  - context of use, such as ease of use in day-to-day practice or clinical trial.
- Outcome measures can be administered by trained individuals. However, the interpretation of the results requires the expertise of professionals specifically skilled and trained in that area, and this may be a different person than the one who administered the test.
- Evaluation of the clinimetric properties of alternative outcome measures such as LCI, IOS and hyperpolarised gas MRI for the specific context of ACT assessment is required before adoption into research or clinical practice.
- Outcome measures used, and the meaning of their results, should be fully explained to the individual completing the tests when used in clinical and research settings.

4.1.8 Research recommendations

- Clinimetric analysis of outcome measures to identify the most appropriate short and long-term outcome measures to assess the efficacy of ACTs.

4.2 Induced sputum

This section discusses the use of hypertonic sodium chloride specifically to induce sputum. All references in this section to induced sputum are referring to sputum samples obtained in this way.

Sputum collection is essential to detect changes in pathogens and guide the management of respiratory disease. It may be one of the most valuable methods for monitoring disease activity, as lung function and imaging may be insensitive,

especially in the case of younger children.[131,132] Small studies suggest spontaneously expectorated samples are representative of lower airway secretions.[133] However, there are many people with CF, particularly children, and those taking highly effective CFTR modulators, who are unable to spontaneously produce a valid sample.

BAL is often considered the "gold standard" for obtaining sputum to identify microbial and inflammatory changes in the airways. However, this technique is expensive, invasive, risky and requires sedation; it is also potentially limited to certain areas of the lungs.[131,132,134–136]

It has been shown that sputum induction provides an equivocal sample to a two lobe BAL, but is cheaper, easier to perform, non-invasive and reproducible.[134,137,138] In some cases, induced sputum sampling has been shown to elicit superior samples to those obtained by BAL.[132,136,137,139–141] Induced sputum has been found to produce a more representative sample of the bronchial tree than spontaneously expectorated sputum.[141–144]

Sputum induction has been demonstrated to be safe for use with young children in a large number of papers, demonstrating that it is well-tolerated and that there were no adverse events.[131,134,135,138,145,146] Some studies have included children as young as one month old with a high percentage of success.[131,132,138,147] It has not been found to promote significant inflammatory changes in the airways.[132,135] Sputum induction, with or without suction combined, has been demonstrated to have a statistically significantly higher microbial content than cough swabs when compared directly.[132,138]

There is variable success with sputum induction using hypertonic sodium chloride in the clinical setting. To date there has not been a universally agreed procedure for sputum induction.[141] The ECFS Clinical Trial Network has created four Standard Operational Procedures (SOPs) specifically for young and older children and adults with CF,[148–151] for those able to expectorate and patients who are unable to expectorate. These were created specifically for clinical trials but can be adapted for use in the general clinical setting, considering each patient individually and using clinical reasoning.[148–151]

Precautions and contraindications to this technique are similar to those in the TB sputum induction guidelines.[148–152] Consideration should be given to the fact that sputum induction may cause bronchoconstriction and excessive coughing and should not be carried out in people with CF where this could be harmful.[152]

Frequency of sputum induction should be individualised following discussion with the MDT, considering the patient's presentation, microbiology, staff availability and facilities.

The various components of induced sputum will be discussed individually.

4.2.1 Technique considerations

Oral hygiene

It is considered good practice to avoid eating for one hour prior to procedure, rinse out the mouth with water and/or brush teeth to minimise any potential contaminants.[133,142,152–156]

Short-acting bronchodilator prior to induced sputum

A number of studies used a short-acting bronchodilator prior to commencing induced sputum.[131–134,139,141,143,145,146,157] However, some studies did not pre-dose with a bronchodilator considering that they can have a paradoxical effect and increase airway instability.[135] There was no significant fall in FEV_1 in either of these groups.[135,157]

Nebuliser device

It has been suggested that a number of nebuliser-related variables can affect the success of the procedure, such as the nebuliser device, the size of the aerosol particles generated and rate of aerosol generation. However, when nebuliser devices were directly compared this was not substantiated.[155,158] Most studies reviewed used ultrasonic nebulisers for the technique. Other studies used VMT or conventional jet nebulisers without adversely affecting the samples obtained. A mouthpiece should be used unless the patient is unable to.[152,153,159,160]

Hypertonic sodium chloride concentration

There are no valid direct comparisons of the concentration of hypertonic sodium chloride used for sputum induction. Due to the irritant nature of hypertonic sodium chloride, studies have suggested that higher concentrations may be more effective but have a higher risk of bronchospasm.[135,161] Bronchospasm was reversible with use of a short-acting bronchodilator.

It is unclear whether duration of nebulised hypertonic sodium chloride affects the success of a sample.[162] The ECFS Clinical Trial Network SOPs for clinical trials state different durations depending on whether the patient can expectorate or not, and their age.[148–151] For example, four sets of three-minute cycles of nebulised hypertonic sodium chloride for expectorating older children and adults compared with 10-minute continuous nebulisation for the three other groups (non-expectorating older children and adults, and young children whether able to expectorate or not).

It is important to note that these were developed for clinical trials and therefore clinicians may use their clinical reasoning to provide individualised approaches to achieve the best sample in clinical practice. Studies looking at the effect of mucociliary clearance in relation to concentration of hypertonic sodium chloride in CF found that higher concentrations (7% and 12%) significantly improved mucociliary clearance.[157] If an individual with CF is at risk of bronchoconstriction, it is recommended to start at a lower concentration (3%) and gradually increase it until a sample is obtained.[153]

Monitoring

Monitoring should be performed for the entire sputum induction procedure.[148–151] Most studies have performed spirometry to monitor for changes in FEV_1 during induced sputum[138,143,145,163] and the ECFS Clinical Trial Network SOP advises the procedure can continue for as long as FEV_1 is over 80% of baseline. Observing the patient for adverse effects, continual SpO_2 monitoring, and auscultation are considered adequate.[148–151]

A short-acting bronchodilator to reverse any clinical signs of bronchoconstriction should be prescribed and available.[131,132,134,160] Continual monitoring should be used if baseline SpO_2 is less than 95% or the individual with CF is prescribed O_2.[148–151] The clinician should know the patient's usual target saturation range and consider, as appropriate, supplementary oxygen if the SpO_2 is less than 90%.[148–151,154] Induced sputum should be stopped if SpO_2 falls less than 90% and the individual is showing signs of bronchoconstriction.[133,161] An SOP for a rescue protocol is available and can be adopted and adapted if required in agreement with the MDT and physiotherapy team.[148–151]

Airway clearance techniques

There are currently no published studies looking at the direct effect of using different ACTs in combination with nebulised hypertonic sodium chloride to induce sputum. One study suggested that induced samples are only obtained from the central airways,[142] however the induced sputum method in this study did not include ACT, only cough. Other studies have found evidence of sputum from the peripheral airways and alveolar space,[136,138,139,141,162] which may suggest that samples from the periphery may be easier to yield if ACTs are employed in combination with sputum induction. The choice of ACT used could affect this.

It may be beneficial to encourage the patient to do a combination of tidal breathing and deep breaths while taking the hypertonic sodium chloride via the nebulizer.[148–151]

Suction and cough swabs post-induced sputum procedure

Sputum induction samples have been found to be positive for almost three times the number of pathogens compared with pre-induced sputum cough swabs.[138]

To gain an effective sample in the non-expectorating patient, performing oropharyngeal suction[154] or a cough swab can be considered following a sputum induction procedure. If oropharangeal suction is deemed appropriate, the procedure should be discussed in full with the individual with CF or their parents and carers.[148–151] No significant difference in culture yield has been observed between post-induced sputum samples collected by nasopharyngeal suction, voluntary expectoration or oropharyngeal suction.[147]

Oropharyngeal cough swabs post sputum induction procedure were previously found to be effective in obtaining valuable samples.[160] However, cough swabs could potentially provide false negative results and cannot accurately assess for fungal or mycobacterial infections and should not be used for this purpose.[132,146,147]

Pain and discomfort

There is evidence to show that induced sputum is well-tolerated in children.[138] However, these procedures can be distressing for patients. A study looking at pain associated with sputum sampling methods found that patients can experience mild to moderate pain with cough swabs and induced sputum.[144] The risk of adverse effects is likely to be reduced if correct procedure is followed and if the clinician has adequate training in techniques.

Infection control

Induced sputum is considered an aerosol-generating procedure – physiotherapists must ensure that locally agreed PPE guidance is followed. There have not been any studies that specifically looked at infection risk with CF during sputum induction. There is no mention of infection control precautions detailed in the studies reviewed and there is continued debate as to whether use of nebulisers and chest physiotherapy are aerosol-generating procedures.[164] A study looking at *P. aeruginosa* in cough aerosol reported that it remained viable in the air in 78% of patients after 45 minutes.[165]

Local aerosol-generating procedure guidance should be followed during sputum induction.

Sputum induction for alcohol and acid-fast bacilli (AAFB) testing

Currently we are unaware of the transmissibility of bacteria such as *M. abscessus*,[166] how long the aerosol remains viable and how far it travels. It is suggested that the treatment room be left empty for as long as possible following a procedure, in concordance with local infection control policies and dependent on air exchanges per hour. Ideally the procedure would take place in a negative pressure room.[146]

Sputum induction is carried out when clinically indicated or to obtain an AAFB sample to assess for mycobacteria. There is some evidence to suggest the routine inclusion of sputum induction and AAFB sampling at annual review can detect non-tuberculous mycobacteria (NTM) sooner than clinical signs and may help to allow appropriate cohort segregation and improve infection control.[146,167]

4.2.2 Recommendations

- Induced sputum should be performed at least once a year in people with CF who cannot expectorate sputum, even if they are asymptomatic *(QoE – moderate)*.
- Monitoring during the induced sputum procedure should be continuous *(QoE – moderate)*.
- Stop induced sputum procedure if there is subjective or objective wheeze, if SpO_2 falls below 90% or if FEV_1 falls more than 20% (if using spirometry) *(QoE – low)*.
- Unless safely performed within the 12 months prior, induced sputum will be performed in a clinical area with resuscitation equipment available *(QoE – moderate)*.
- Perform induced sputum in a room with the door closed where the air from the room is exhausted to the external environment, unless a well-maintained HEPA filtration unit is in place *(QoE – moderate)*.
- Avoid anyone entering the room for one to two hours after induced sputum procedure, depending on the frequency of air exchanges *(QoE – moderate)*.
- Perform induced sputum procedure in line with local infection control and prevention guidelines *(QoE – low)*.

4.2.3 Good practice points

- If there are signs of clinical deterioration, consider the use of induced sputum in place of cough swabs for pathogen surveillance in people with CF who are unable to produce a spontaneous sputum sample.
- Recognising that induced sputum may be distressing for some individuals with CF, use available strategies, such as distraction techniques or alternative methods, to minimise discomfort, where practically feasible.
- To minimise sample contamination during induced sputum, people with CF should be instructed to brush teeth with a new toothbrush and water, rinse mouth with water and avoid eating one hour prior to procedure, where practically feasible.
- To mitigate potential bronchoconstriction during hypertonic sodium chloride sputum induction, especially in people with CF with a history of adverse reactions to inhaled medications or those new to the procedure, prescription and use of a short-acting bronchodilator prior to the procedure should be considered. Clinical judgement and individual patient evaluation are essential.
- Consider an ultrasonic nebuliser for sputum induction if available, taking into consideration infection control policies.
- Use a low output device such as a jet nebuliser for sputum induction if high output devices are not tolerated or not available. Currently there is no evidence to support one device over another and no evidence evaluating VMT nebulisers for sputum induction.
- Use a higher hypertonic sodium chloride concentration (7%), if able, for induced sputum to optimise mucociliary clearance.
- Consider starting with a lower concentration of hypertonic sodium chloride (3%) if the patient is at known risk of bronchospasm.
- When multiple sputum samples are produced during induction, prioritise processing later samples where feasible as they may contain a higher concentration of relevant pathogens. This could include collecting all samples produced in one to two containers to be sent for processing.
- Oropharyngeal cough swab can also be considered if expectorated sputum or

suction is not possible – however, it is recognised that cough swabs may not provide as representative a sample.

- A rescue short acting bronchodilator should be prescribed and available prior to the procedure in case the patient shows signs of bronchospasm following inhalations.

4.2.4 Research recommendations

- Given the recognised research priority in CF of the best way to diagnose lung infections in the era of CFTR modulator therapies with reduced sputum, there is a need for further research looking at induced sputum.
- With the changing landscape of CF care, with some patients attending less frequent hospital reviews, home induced sputum is a pertinent area for investigation. Future research should consider the effect on pathogen yield of time of day of sample collection, early morning salivary samples, induced sputum performed at home and postage of induced sputum samples.
- The combination of ACT and/or exercise with nebulised hypertonic sodium chloride should be investigated for optimal induced sputum procedure.

4.3 Exercise Testing

This section provides a contemporary overview of best practice recommendations for exercise testing for people with CF. Several key articles have been published providing expert consensus on exercise testing practices in CF, with a recent update from the ECFS Exercise Working Group now including guidance and standard operating procedures for test selection, test conduct and test reporting for a range of recommended tests with good clinimetric properties when used in CF.[168] We recommend these accompany the guidelines presented here.[168–172] Recommendations for the assessment of habitual physical activity and sedentary behaviours are also provided.

4.3.1 Reasons for exercise testing

Regular exercise testing is recommended as part of routine assessment for all people with CF aged over 10 years.[168,173,174] A range of validated tests, which can provide insight into aerobic fitness, strength, and other components of fitness are available and should be used where possible.

The choice of test depends on the reason for testing (test indication) and clinical characteristics of the individual, such as age, lung disease severity and comorbidities. Importantly, there is no one size-fits-all approach when performing exercise testing in CF.[168] It is essential to define the test indication and intended use of the test information, since this will guide what exercise testing data is needed. **Test indications include:**[168]

- General assessment of functional exercise capacity and muscle function.
- Monitoring disease progression.
- Screening for exercise-induced risks such as hypoxaemia and arrhythmias.
- Assessment for lung transplantation.
- Evaluation of therapeutic interventions.
- Assessment of baseline exercise performance before physical activity promotion and/or an exercise training programme.

Depending on the type of test and, in particular, the measurements obtained during testing, dynamic endpoints, such as exercise capacity, can provide valuable insights into the integrated functioning of multiple organ systems (cardiovascular, MSK, respiratory). These modalities provide a more comprehensive understanding of an individual's health status.[168] This information cannot be obtained from more static methods such as monitoring lung function, radiological investigations or measures of nutritional status that are routinely used in clinical practice.

Over the shorter-term, exercise testing can help assess changes in clinical status, such that tests identifying poor exercise capacity for the degree of lung function deficit warrant prompt attention and act as an early warning of clinical deterioration. Exercise testing can assist with transplant stratification,[169,175] and, for this reason, at least annual exercise testing is recommended for all patients by the CF Trust and ECFS.[16,174]

Much focus has been on the evaluation of aerobic fitness, since several studies have demonstrated that better aerobic fitness measured by peak oxygen uptake (VO_{2peak}) is associated with greater 7–12-year survival in people with CF.[176–178] However, more simple outcome measures that do not require sophisticated assessments, such as peak work rate (W_{peak}), have also been shown to be promising prognostic markers of lung transplantation and death in advanced CF lung disease.[169]

It is important to remember the wealth of information an exercise test provides, offering not only an indication of an individual's function, but also the mechanisms responsible for any

impairment to this (see figure in Appendix Ia). This information can also help us understand responses to treatment such as CFTR modulator therapies.

Furthermore, exercise testing can be a motivational experience for people with CF, who may feel that participating in exercise testing demonstrates their ability to exercise at a higher intensity than anticipated, thus freeing them from personal uncertainty and/or parental fears regarding future activities. This is becoming more apparent following implementation of CFTR modulators.

Exercise test results can also facilitate exercise programmes tailored to the needs of each individual, involving improving fitness, or maintenance in those with significant ventilatory limitation but good fitness levels[171] (see example Case Study in Appendix Ib).

4.3.2 Starting exercise testing

Annual exercise testing as a minimum is recommended for all people with CF over 10 years, although the age at which routine and regular exercise testing begins depends on the type of exercise testing undertaken, as well as the physical and mental development of the individual. CPET is recommended from 10 years of age.[174]

Those using a cycle ergometer must meet the minimum height requirement (usually 128 cm), and must maintain a standard pedal speed, which may preclude some children. However, paediatric cycle ergometers are available and technically acceptable tests can be achieved in younger children. Testing in the early years provides a prime opportunity to familiarise children with exercise testing equipment and protocols and encourage exercise participation. Where CPET is not feasible in the early years, younger children (six years or younger) should be tested using validated field-based tests such as the 25-level modified shuttle test (MST-25).[168]

4.3.3 Frequency of exercise testing

Exercise testing before and after significant change or intervention is recommended, for example before and after a new treatment or exercise programme.[179] In addition, exercise testing plays a vital role in pre-transplant assessment, with both field tests and laboratory based CPET being validated for this purpose.[175]

A case study example, presented in Appendix Ib, (represented with permission from Urquhart & Saynor [2018]),[171] highlights the need for intervention and subsequent evaluation of the response to exercise testing.

4.3.4 Preparing for an exercise test

People with CF should:

- avoid strenuous exercise for 24 hours before CPET, or two hours before a field test.
- refrain from eating for at least two hours before CPET, or one hour before a field test
- take their usual pre-exercise bronchodilator dose at least 10 minutes before the test if applicable.

Additional preparation for those with CF diabetes (CFD)[180–182]

Exercise testing, although not often prolonged, is usually strenuous and therefore a risk factor for hypoglycaemia in people with CFD. When testing those who are prescribed insulin or some oral hypoglycaemic agents, ensure that:

- no more than three hours have elapsed since the preceding meal and that the meal contained adequate carbohydrate
- the individual with CF is adequately hydrated
- appropriate snacks and fast-acting glucose are on hand during and after the exercise test if required to correct hypoglycaemia
- insulin is not injected in areas likely to be heavily involved in the exercise such as the thighs and gluteals, where possible
- blood glucose levels are monitored and recorded before and after the exercise test, taking any necessary steps to avoid hypoglycaemia (delayed hypoglycaemia can occur up to 24–36 hours post-exercise so monitoring should continue as such – recording and sharing exercise blood glucose data can aid the patient with ongoing self-management)
- blood glucose is 4 mmol/L or higher prior to exercise testing and a 10 g snack such as a biscuit or banana is offered if blood sugar is below 7 mmol/L
- salt supplementation is considered.

Field tests with audio instructions

- Pre-recorded audio instructions should be played prior to the test.
- For shuttle testing, to help the participant establish the first very slow speed of walking, the operator can walk alongside for the first shuttle.

4.3.5 Choosing an exercise test

CF-specific recommendations are available for standardised functional and laboratory-based exercise tests.[168,174] The most recent European consensus statement on exercise testing in CF,

endorsed by the European Respiratory Society (ERS),[174] recommends CPET as the test of choice for routine monitoring and assessment of exercise-related symptoms for people with CF. However, other standardised tests can be useful to assess aerobic fitness, integrated exercise performance or muscle strength – all of which are important considerations in CF.

The ECFS Exercise Working Group and ACPCF specialist interest group has therefore developed expert opinion-based clinical practice guidance,[168] along with test instructions, for a selection of commonly used, valid tests which have documented clinimetric properties for people with CF.

A small selection of exercise tests, performed consistently and to a high standard, are recommended alongside known guidance for CPET.[168,170] Importantly, these standards also highlight previously used tests that are no longer suggested for people with CF and areas where research is necessary.

When conducting exercise tests, it is important to use age-appropriate subjective measures of perceived effort and breathlessness. The Dalhousie pictorial scale has been demonstrated to be valuable in measuring both perceived exertion and dyspnoea in people CF of all ages and is strongly associated with ventilation and work intensity in both children and adults.[183]

For each of the selected tests, test instructions and templates for test reporting, a summary of their respective clinimetric properties and a decision-making algorithm (figures 1 and 2) have been provided in Saynor et al, 2023.[168]

4.3.5.1 CPET

CPET is a fully integrated, objective assessment of the efficiency and performance of the cardiovascular, respiratory and MSK systems through the spectrum of exercise intensities. It remains the first-choice test of aerobic exercise performance for people with CF. CPET offers thorough assessment of fitness levels and exercise-limiting factors as well as identifying potential risks and exercise-related symptoms, whilst opening up avenues for exercise counselling and individualised training programmes.[174]

A number of documents are available to aid clinical teams working with people with CF and other chronic respiratory disease with test conduct[170,184] (including criteria for acceptance of maximal test) and reporting[168,170] Cycle ergometer tests are recommended over treadmill-based tests for people with CF, and CPET protocols can include linear ramp or stepwise minute-by-minute increments.[170,174] Supramaximal (S_{max}) verification testing has been suggested as a useful tool as a way of testing the validity of the maximal CPET data.[185–188] However, at present, S_{max} remains a research tool in CF.

CPET-measured peak pulmonary oxygen uptake ($\dot{V}O_{2peak}$) remains the gold standard measurement of aerobic fitness due to its high prognostic utility.[169,174,176–178,189] Several other CPET-derived outcome measures also have high prognostic utility and enable evaluation of exercise limitation, such as $\dot{V}O_2$ at the ventilatory anaerobic threshold (AT), peak minute ventilation ($\dot{V}_{Epeak}$), peak power output (W_{peak}), change in transcutaneous arterial oxygen saturation (ΔSpO_2), time to exhaustion, and perceptions of effort and dyspnoea.[169,176] Peak exercise data should be reported as 30 second averages for the interval, with $\dot{V}O_{2peak}$ taken as the highest 10–15 second oxygen uptake values. This standardisation will reduce variability in reporting between Centres and enable between-study comparison of data.

A range of reference values are available to aid interpretation of CPET data:[190–192]

- An abnormally low exercise capacity is defined as $\dot{V}O_{2peak}$ less than 80% predicted. The next challenge is to identify whether reduced $\dot{V}O_{2peak}$ may be due to cardiovascular and/or peripheral muscle disease, or as is more likely in more severe CF, the result of deconditioning and/or ventilatory limitation. A schematic overview of how to determine exercise function or cause of any dysfunction in individuals with CF is presented in **Appendix Ia**.[193]
- The normal mechanism for exercise termination in a healthy individual is cardiac limitation, with HR_{peak} being attained (no cardiac reserve) and minute ventilation ($\dot{V}_E$) falling short of estimated maximal voluntary ventilation (MVV) – exercise $\dot{V}_E$ less than 85% MVV.[174]
- The physiology in children differs from adults, and expected HR_{peak} falls with age, whilst children with CF often achieve a HR_{max} over 200 bpm during CPET.
- AT onset provides a submaximal indicator of an individual's aerobic fitness. Deconditioning results in an early onset AT, indicative of reduced efficiency to transfer and utilise O_2 at the muscular level. An AT occurring at less than 50% predicted $\dot{V}O_{2peak}$ (in the absence of cardiac disease or muscle abnormalities) is likely to be associated with deconditioning and can be improved with training.

If treadmill CPET is the only option then the modified Bruce protocol is recommended for testing in CF,[174] although it should be noted that this does not allow for a linear increase of work

rate, as a ramp or minute-by-minute increment. Predictive equations enable estimation of $\dot{V}O_{2peak}$ from treadmill test acquired data.[174]

Regardless of modality and protocol, the patient should be encouraged to rest for a brief period with CPET equipment in place before starting exercise.[170] This enables familiarisation with test equipment and for the tester to measure resting SpO_2, arterial blood sampling (if indicated), ECG, blood pressure, $\dot{V}_E$ and gas exchange variables. Resting respiratory exchange ratio (RER) values can aid with the identification of anticipatory hyperventilation which can occur when testing equipment is in place.

4.3.5.2 Aerobic exercise testing on ergometer without gas exchange measures

Whilst CPET remains the gold standard test to assess aerobic fitness in CF,[174] in situations where breath-by-breath gas analysis is not possible then cycle ergometer W_{peak} testing (linear ramp or minute-by-minute increments) is a useful alternative with high prognostic value.[168,169,176] Physiological measurements can be collected, such as HR and SpO_2, as well as perceptions of effort and breathlessness.[174] It is not possible to measure power output with a treadmill test, therefore if CPET is not available then cycle ergometry peak power output (W_{peak}) testing should be considered as the best alternative.

4.3.5.3 Suggested functional exercise tests considered suitable for people with CF

The value of alternative exercise tests (field and localised peripheral muscle function tests) for people with CF should not be discounted. The utility of and information provided by some of these tests are different to CPET. A combination of tests is ideal, including a test for aerobic fitness along with tests of functional performance and peripheral muscle function. However, in situations where only a single test is possible, priority should be given to testing aerobic fitness in an appropriate way.

4.3.5.4 Field tests of aerobic capacity

In situations where CPET and ergometer testing without gas exchange measures are not possible, a field test of aerobic capacity should be considered. There are a number of tests available including incremental shuttle tests, submaximal treadmill tests, walking tests and step tests. Appropriately designed incremental field tests should continue beyond a physiologically feasible level of exercise, enabling subjects to exercise to volitional fatigue. Standard operating procedures for these tests are available.[168,174]

These tests are often more practical in the clinic setting, as they require less equipment, are portable, low cost, quick and easy to set up and report, and can be useful in assessing exercise tolerance, functional exercise capacity, and guiding exercise prescription. However, it should be noted that not all individuals will achieve maximal exercise even with incremental tests.[168,194,195] Moreover, field tests give only limited information about exercise capacity, reasons for exercise limitations, and potential exercise-associated adverse reactions.[194] There is also no clear way to establish whether a maximal effort has been given due to the limited outcome measures collected.

4.3.5.5 6-minute walk test (6MWT)

The 6MWT is a self-paced functional exercise test. The individual walks up and down a 30 m corridor aiming to cover as much distance as possible in six minutes. This self-paced, and therefore non-incremental test is recommended for use with those people with CF who have advanced lung disease (FEV_1 less than 40% predicted) to assess for need for supplemental oxygen or transplant referral.[196] An adequate pulse oximeter signal is required throughout test.

Achieving less than 400m during the 6MWT indicates a need for transplant referral regardless of FEV_1.[196] However, it has been suggested that less than 475m is a value predictive of death or lung transplant.[197] The studies reporting these thresholds were conducted prior to the introduction of CFTR modulator therapies, therefore further work is needed to re-evaluate the prognostic value of the 6MWT in people with CF.[168]

Technical standards and test instructions and reporting templates are available.[168,198] If conducting this test, it should be noted that there is a learning effect and therefore two tests should be undertaken (at least 30 minutes apart and with HR and SpO_2 returned to baseline before the second test) on the first experience.[199]

4.3.5.6 Shuttle tests

Shuttle tests require the individual to walk then run (shuttle) back and forth around two distance markers placed at measured intervals. The external pacing (bleep) indicates the speed required as the individual should complete the shuttle at the time of the subsequent bleep. The test is incremental, thus bleeps become quicker every minute, indicating an increase in walk/run speed is required.

Tests should have the range to take people with CF to maximal exercise and a test is complete when the individual reports that they are unable to continue or if they fail to reach the distance marker by the bleep on two consecutive shuttles. Therefore, shuttle tests provide more useful

information (with HR and SpO_2 and perceived dyspnoea and effort measured) about maximal exercise capacity[200] than is possible with 6MWT, especially for those with mild or moderate lung disease.[201] A correlation (r=0.79) between distance achieved during shuttle test and $\dot{V}O_{2peak}$ has been observed,[202] although it is important to remember that it is not possible to identify which physiological factors are limiting aerobic capacity if not directly measured with CPET.

Whilst there are a number of shuttle tests available, the 10m 25-level modified shuttle test (MST-25) has good test-retest reliability,[203] is practical in the clinical setting and has enough levels to be potentially maximal for all individuals with CF with no ceiling effect.[204] Thus, it is a valuable tool for assessing fitness and prescribing exercise when CPET is not possible. Furthermore, an MCID of ~97m has been reported for children and young people with mild-moderate CF,[205] although this was using the 15-level version (MST-15) before it was extended to MST-25.

A number of reference equations have been proposed for MST distance predictions for children and young people[206–208] and adults.[209,210] However, reference equations are limited by the characteristics of the sample used during development and there is a lack of global, validated reference equations for MST-25.[211] Further research is needed to understand the clinimetric properties of the MST-25 and to develop global, validated reference equations.

4.3.5.7 Alternative forms of exercise testing

Alternative components of fitness can be measured and may prove useful in exercise counselling and in the management of muscular and postural issues in CF. These include assessment of muscular strength and endurance,[212] flexibility and core strength and stability. Other forms of exercise testing assessing short-term muscle performance such as the Wingate Test and isokinetic testing have been used for scientific purposes but rarely in a clinical setting.

4.3.5.8 Integrated test of aerobic capacity and muscle strength

Sit-to-stand (STS) tests assess various factors affecting functional capacity, such as strength, endurance, coordination, balance and postural control, and therefore integrate aerobic and strength measurements. The one minute STS test (1-min STS) is frequently used in respiratory disease, including CF, and has evidence of good clinimetric properties[213–216] with moderate-to-strong correlations with $\dot{V}O_{2peak}$ and W_{peak},[217,218] quadriceps muscle strength[215,217,218] and key prognostic indicators in people with CF.[176]

It measures the maximum number of times an individual can perform STS from a chair in one minute. The MCID has been reported to be five repetitions in adults with CF.[218] As with the 6MWT, this self-paced test has a learning effect therefore two tests should be completed on the first occasion.[213,218,219] Currently, there is limited evidence to guide how much recovery time is needed between tests to ensure performance is not compromised, though it has been suggested that around 30 minutes should allow for sufficient recovery.[168]

The 1-min STS test is practical in the clinical setting due to its short duration and minimal equipment and space requirements. However, it must be noted that it does not measure maximal exercise capacity, rather assesses functional exercise performance, thus acting as a useful guide for exercise prescription, a screening tool for oxygen desaturation,[217,220] or for interim functional assessment during telerehabilitation.[215]

4.3.5.9 Tests of localised peripheral muscle function

Skeletal muscle dysfunction is common in people with CF,[221] even in those with mild lung disease, and can result in increased fatigability and reduced physical activity participation, reduced endurance and strength (in adults and children with CF)[221] and be associated with poor clinical outcomes.[222] This may further exacerbate exercise intolerance and reduce health-related QoL, thus increasing risks of hospitalisation and poorer survival.

Peripheral muscle testing in CF should be considered for clinical and research purposes, notably for early detection and monitoring of limb muscle abnormalities, to design and evaluate targeted therapies.

The 1-min STS test provides some insight into muscle strength. However, specific and detailed assessment of peripheral muscle strength may be important for elements of clinical practice, such as developing a strength training programme[168] and assessing change in the increasingly overweight population of people with CF, where loss of fat-free mass may be concealed by a higher body mass index.[222] Furthermore, recognising changes in muscle strength and body composition may go some way to contributing to the understanding of response to CFTR modulator therapies. Saynor et al (2023) provide detailed test instructions in the online supplement to their guidance and standard operating procedures paper.

Handgrip dynamometry measures the maximum force that an individual can achieve on a dynamometer using forearm muscles, thus is a quick and easy-to-administer measure of distal upper-limb muscle strength. Handgrip strength

has been used as a simple indicator of nutritional status as well as an of gauge of global muscle strength in both adults and children with CF.[223–230] The ESPEN-ESPGHAN-ECFS guideline on nutrition care for cystic fibrosis recommends that serial hand grip strength measurements can be considered in adults and children ≥6 years with CF as it may help detect early changes in muscle function and therefore can function as an indicator of nutritional status.[231]

However, preserved handgrip strength does not necessarily indicate global normal skeletal muscle strength, especially as lower-limb muscle strength tends to be more affected in CF than upper-limb muscle strength.[232] Quadriceps strength can be measured relatively easily by a chair with a fixed strain gauge,[233,234] and endurance and fatigability can be assessed with the addition of real-time visual feedback.[235]

4.3.5.10 Respiratory muscle function testing

Assessment of respiratory muscle function should also be considered. Respiratory muscle performance in CF can be a key determinant of aerobic fitness.[236] Impairment of inspiratory and expiratory respiratory muscles is a common clinical finding in people with primary lung disease. It is unclear whether people with CF exhibit respiratory muscle dysfunction or preserved respiratory muscle function.[237,238] However, respiratory muscle function is influenced by a variety of factors including hyperinflation, nutritional status,[238] systemic corticosteroid use, *P. aeruginosa* colonisation, inactivity, and chronic inflammation.[237] Multiple CF-related comorbidities, including thoracic kyphosis and postural abnormalities, may also create a restrictive lung dysfunction that elevates the demand imposed on the respiratory pump.[239–241] Individuals with CF commonly exhibit an imbalance between the ventilatory load and the capacity of the respiratory muscles, which can cause inefficient breathing patterns[242] and may contribute to exercise intolerance.

4.3.6 Exercise testing outcome measures and reporting

There are several outcome measures that should be used for exercise testing, dependent on the exercise test chosen and the equipment available. Some are specific to the test, such as work rate in watts and $\dot{V}O_{2peak}$ for CPET, and distance covered and shuttles completed for field tests, but several key measures should be obtained across all tests protocols:

- **Objective measurement of HR and SpO_2 will be measured before, during and after an exercise test, and during recovery, as a minimum.** Monitoring should be continuous and recorded if equipment allows, to facilitate a more thorough assessment. If an individual does desaturate during exercise, the corresponding intensity of exercise (HR, work rate, effort rating) can then be used to guide 'safe zones' within their exercise prescription.
- **Subjective measures of perceived exertion, breathlessness or fatigue should also be used to assess symptoms.** Numerous pictorial scales are now available to assist in the collection of this type of information (such as OMNI[243] and Dalhousie[183,244,245]). Refer to the statement on exercise testing for further details.[170]

The following statement by the ERS is recommended before exercise testing to ensure more standardised instruction and collection of subjective data:

"During every stage of exercise, we are going to ask you about the intensity of your breathlessness and leg discomfort at that point in time. As you should avoid speaking during the test, you will use a finger of your hand to point which number between 0 and 10 best reflects the intensity of each of these sensations".

The reporting of findings and outcomes of exercise tests should be standardised. **A guidance document with a template for reporting CPET results[176] lists the following components for an exercise test report:**

- Basic information on the patient
- Technical report
- Response to exercise:
  - aerobic/anaerobic performance
  - cardiovascular response
  - ventilatory response
  - gas exchange response
  - metabolic response
- Report summary

Refer to Radtke et al. (2019)[170] for more details on each of these sections and to obtain the template, which is also included in **Appendix Id**.

A review by Urquhart and Vendruscolo (2017) offers advice on how to interpret and use CPET outcome measures to guide exercise counselling in children with CF.[246] Saynor et al (2023)[168] also provides standard operating procedures and reporting templates for the non-CPET exercise tests recommended for people with CF.

4.3.7 The future of exercise testing

New tests continue to be developed. For example, the Alfred step test,[247] an incremental step test developed specifically with and for people with CF, is being used in a number of clinics, and further work is ongoing to establish clinimetric properties. Standard operating procedures and clinimetric properties must be established and reported for all new and existing exercise tests for people with CF to ensure correct data interpretation.

4.3.8 Assessment of habitual physical activity and sedentary behaviour

Assessment of the habitual physical activity behaviours of people with CF is an important consideration, taking into account the amount and intensity of activity, as well as time spend being sedentary. A survey exploring perceptions of physical activity monitoring among children and young people with CF and their CF teams reported that teams recognised the potential benefits of the devices in clinical practice.[248] However, physical activity assessment is not commonplace or consistent in clinical practice. This section aims to summarise some of the assessment methods available to guide the incorporation of physical activity assessment in the clinical setting. The reader should also make use of several key articles published on this topic[193,249,250] as well as the European expert position statement on the assessment of physical activity in people with CF.[251]

Motion sensors, activity questionnaires and diaries are all useful to gauge an individuals' general physical activity behaviours and, as with exercise testing, the purpose of data collection will guide the choice of tool used. The range of tools also differ in terms of cost and ease of use. The current recommendation from the European position statement is that activity monitors offer a comprehensive assessment of physical activity and should, as a minimum, report on dimensions of physical activity including energy expenditure, step count and time spent in different intensities and sedentary time.[251] Data suggest that people with CF enjoy wearing monitoring devices and wrist-worn devices and devices providing feedback were the preferred choice.[248] ActiGraph is one such option.

Sophisticated activity monitoring can eliminate the subjective evaluation of activity; however, it is more technical and costly to offer in most clinical settings.

Simple pedometers may offer an inexpensive method of obtaining a measurement of physical activity, and there is some evidence for supporting their use in CF.[193] Commercially available fitness watches have been used in a number of research studies, but further research is needed in this area.

Questionnaires provide an appreciation of an individual's perception of their physical activity[250] but not data reflecting symptoms whilst active. It may however be useful as a screening tool to guide further discussion about exercise patterns, goal setting and subsequent exercise prescription. It should be noted that questionnaires depend on patient recall and are subjective so should be used with caution. Although there is insufficient data to recommend the use of one diary over another, the Habitual Activity Estimation Scale (HAES) has the most data demonstrating reliability and validity and can be used to assess activities of varying intensity.[248]

The increase in use of commercially available activity monitors offers an opportunity to measure the physical activity patterns of individuals longitudinally[248] which can also act as a useful focus for physical activity counselling.

4.3.9 Summary

Exercise testing is a standard of care and at least annual interval testing should be undertaken, to provide an accurate dynamic assessment of physical function that may not be detected by other assessments such as pulmonary function.

Traditional testing of lung health using spirometry tells us how much and how fast air exits the lungs, whereas exercise testing measures the efficiency and performance of these lungs in combination with cardiovascular, pulmonary and MSK systems during exercise. Exercise testing provides precise information that is of prognostic importance, as well as allowing us to further understand individual pathophysiology of exercise limitation and individually tailor exercise programmes for people with CF. Assessment of habitual physical activity and sedentary time should also be considered where possible, to provide a more comprehensive insight into an individual's activity and fitness.

4.3.10 Recommendations

- Exercise testing is recommended as part of the routine assessment of people with CF at least annually *(QoE – high)*.
- Exercise testing is recommended to assess for changes in overall management, such as examining efficacy of interventions, pre- and post-admission, or modifying exercise prescription *(QoE – high)*.
- Exercise testing is essential to monitor response to exercise training, to assess fitness, and to allow safe and effective exercise prescription *(QoE – high)*.
- Exercise testing is recommended in people with CF aged 10 years and older but can be started at

a younger age to aid familiarisation in later years *(QoE – moderate)*.

- Regular standardised exercise testing, as per the guidance of the ECFS Exercise Working Group and PhySIIG, should guide the advice and support given by the CF team.
- Emergency procedures will be accessible during all exercise testing *(QoE – moderate).*
- Contraindications to testing will be assessed before each testing session *(QoE – high)*.
- Exercise test-specific standardised objective measurements should be recorded as appropriate and as a minimum HR, SpO_2 and indicators of effort and breathlessness should be performed before, during and after testing *(QoE – moderate)*.
- Other measures of fitness (such as strength and flexibility) and physical activity may be appropriate but should be assessed on an individual basis and follow recommended guidelines *(QoE – low)*.

Tests of aerobic fitness

- CPET is the gold standard test recommended for the evaluation of aerobic exercise performance in people with CF *(QoE – moderate)*
- If a metabolic cart is not available or assessment of pulmonary gas exchange and ventilation is not possible due to pathogens, teams should consider undertaking a cycle-ergometer peak power (W_{peak}) test, with measures of heart rate, oxygen saturation, perceived exertion and breathlessness *(QoE – moderate)*.
- The 6MWT is preferable for use in people with advanced CF lung disease or as part of lung transplant assessment, but its use as an annual test cannot be recommended *(QoE – moderate)*.
- The MST-25 can be considered for the assessment of aerobic fitness when CPET is not available. This test is suggested for use in all people with CF, particularly those who are fitter and for whom the MST-15 would elicit submaximal responses at test completion, due to ceiling effects. Other shuttle tests available with 20m tracks tests are often not practical *(QoE – moderate)*.
- The 3-minute step test is not recommended for use as a measure of functional exercise capacity. *(QoE – moderate)*

Integrated tests of functional performance and tests of peripheral muscle strength

- Tests such as the 1-min STS test may prove useful measures *(QoE – moderate)*.
- The 1-min STS test offers a safe, feasible functional performance test. It should be noted that this test is measuring integrated exercise performance rather than assessing maximal exercise capacity and can offer additional complementary information to an aerobic exercise test *(QoE – moderate)*.
- Peripheral muscle testing allows the determination of skeletal muscle strength. Research is urgently needed to inform the choice and clinical usefulness of these tests *(QoE – moderate)*.

4.3.11 Good practice points

- Exercise testing should be offered to people with CF when indicated by their individual needs and preferences, to evaluate physical function and fitness levels and allow for individual exercise prescription.
- CPET with measures of pulmonary gas exchange and ventilation should be offered based on clinical need and resource availability to provide a valuable assessment of functional capacity.
- Where possible, assessments of additional components of fitness such as muscle strength, should be considered based on clinical need.
- People with CF should be assessed during a period where there is no evidence of pulmonary exacerbation prior to annual assessment of exercise testing to ensure accurate and useful results.
- Age-appropriate subjective measures of perceived exertion, breathlessness or fatigue should be used to assess symptoms during exercise tests and to guide intensity of exercise training.
- Where possible, information obtained from exercise testing should be used to help guide more individualised exercise prescription.
- Where possible, exercise testing should be considered as an assessment tool to monitor other clinical interventions, such as new medications or an exercise training programme.

5. Physical activity and exercise

The importance of exercise in maintaining a healthy lifestyle is well-recognised in both health and disease. Being physically active provides a number of physical and psychosocial health benefits, including contributing towards maintaining a healthy weight, reducing the risk of many non-communicable diseases and supporting good mental health. These are all becoming more relevant as people with CF are living longer, in part as a result of CFTR modulator therapies.

This section will provide a contemporary overview of the best practice recommendations for exercise counselling for people with CF, as well as the evidence that underpins its use, which may facilitate patient-education regarding the importance of exercise. Several key articles have been published to provide evidence-based guidelines for physical activity and exercise prescription for people with CF.[172,252–254]

In line with the published expert guidelines for people with CF,[254] the following definitions apply for this document:

Habitual physical activity – bodily movement produced regularly by the contraction of skeletal muscles that result in a substantial increase over resting energy expenditure.

Exercise – planned, structured, and repetitive bodily movement performed to improve or maintain one or more components of physical fitness.

Sport – an activity involving physical exertion and skill in which an individual or team competes against another.

5.1 Exercise limitation in CF

In the era of increased life expectancy and new treatments, people with CF may have similar or greater exercise capacity than their healthy peers. However, a large number of individuals are not only affected by decreased cardiorespiratory (aerobic) fitness, but also decreased muscle strength and endurance. Furthermore, posture issues and flexibility commonly affect people with CF.[255,256]

Several factors may contribute to reduced fitness in CF. Ventilatory limitation is often not observed during exercise in young children and adolescents who are physically active with good lung function, even at maximal limits. However, as lung disease severity progresses, ventilatory limitation during exercise is common. These individuals may present with increased lung dead space that worsens with lung disease severity, and which can be increased during exercise,[257] requiring a higher minute ventilation.[171] Additionally, airway obstruction may be present due to mucus within the airways with or without airway hyper-reactivity, requiring greater inspiratory airflows generated with greater respiratory muscle effort to achieve similar ventilation.

In contrast to healthy individuals who have significant ventilatory reserve at maximal exercise, people with CF may have an exercise ventilation that reaches or exceeds their predicted maximum.[258] In short, those with more severe CF may have higher metabolic demands during exercise due to an increased work of breathing, as well as a higher ventilatory rate, due to increasing physiological dead space. Such factors, coupled with an inability to increase minute ventilation during exercise due to lung disease, contribute to ventilatory limitation being the principal factor determining exercise capacity in these individuals.

There are non-pulmonary consequences of CF that may also affect exercise capacity. Peripheral muscle weakness is common in people with CF, particularly in the lower limbs[259–261] and can have a significant impact on exercise tolerance and the capacity to undertake activities of daily living.[232,262] However, physical activity alone cannot explain these changes.[232] Other structural and functional changes in skeletal muscle are evident in people with CF,[260,262–265] for which several contributing factors have been proposed. CFTR is expressed in skeletal muscle cells[264] and lack of CFTR in skeletal muscle has been shown to predispose mice with CF to muscle wasting and diaphragm muscle pump failure.[266] Reduced antioxidant capacity, due to increased systemic inflammation and/or oxidative damage, may also lower mitochondrial efficiency.[267]

CFTR is also expressed in human vasculature and vascular endothelial dysfunction is associated with a poorer VO_{2max} in young people with CF.[268,269] Additionally, there is evidence of heart involvement in children and adults with CF,[270] which may be related to dysfunctional CFTR.[271]

5.2 Changing landscape

With CFTR modulators now being available for most people with CF in the UK, the landscape of CF is changing rapidly. Many individuals with CF benefiting from CFTR modulators are experiencing a reduction in symptom burden, exercise limitation and, for some, self-selected treatment burden.

There has been an associated increase in fat mass, but the impact on exercise capacity is unclear.

Increasingly, different methods to measure body composition are being used in clinical practice to measure fat-free mass and fat mass which provide a more accurate measure of nutritional status than the traditionally used measures like weight and BMI.[231] This is evolving dietetic practice and not available routinely in all centres but can be used to direct targeted exercise programmes and monitor sequential change.

With or without body composition, there is likely value in the CF physiotherapist joint working with CF dietician to deliver targeted coordinated exercise and diet advice, where the specialist CF dietitian can give individualised nutritional advice on appropriate diet for type and intensity of exercise. This may include advice on carbohydrate, protein and fluid intake alongside appropriate timing before and after exercis e.

Those benefiting from CFTR modulators can experience the long-term health benefits of being physically fit and active, including helping to maintain a healthy weight, and preventing or minimising the impact of many non-communicable diseases. Those not able to benefit from CFTR modulators can continue to experience the known benefits of physical activity and exercise in CF, including maintaining health and function, slowing the progression of lung disease and prolonging survival.

5.3 Evidence for recommendations

In 2022 a systematic review[252] concluded that physical activity interventions probably have a positive effect on exercise capacity,[253] but little or no effect on lung function and health-related quality of life. However, the evidence for this was of lower quality highlighting the need for more research studies, with improved designs and conducted over longer duration.

Evidence from smaller studies has demonstrated both physical activity and exercise to be beneficial for people with CF, with high physical activity levels associated with improved aerobic fitness[272] – an important prognostic indicator.[176–178,189,273] Being more active is associated with improved pulmonary function,[272] glycaemic control[274] and bone mineral density.[275,276] Structured exercise training has also been shown to slow the typical decline in lung function,[277] or even result in an improvement in lung function in some cases.[278,279] There is also evidence that appropriate exercise training can improve exercise capacity,[279] quality of life[280,281] and mucociliary clearance.[282]

It is currently considered part of standard CF care to encourage a physically active lifestyle[172,252–254,283,284] and physical activity and exercise should be part of the routine management for people with CF at any age. Regular advice and education on frequency, intensity, duration and type of activity should be initiated from diagnosis in order to ensure fitness levels are maintained. This should, where possible, be informed by exercise testing (see section 4.3 for more details).

5.4 Potential exercise-related risks

Exercise appears to be relatively safe for most people with CF, with adverse events such as cardiac arrhythmias, pneumothorax, and hypoglycaemia associated with exercise occurring in less than 1% of around 1,000 from a survey of 37 CF Centres.[285] However, contraindications to exercise do exist and may be absolute or relative, and are more common in people with CF with more advanced disease and additional complications and comorbidities such as CFD and CF liver disease (enlargement of liver and/or spleen).

Exercise type is an important consideration, with the following documented to present specific risks:

- Exercise at high-altitude may increase the risk of desaturation and right heart failure.[286,287]
- Diving may increase the risk of pneumothorax especially in patients with more severe disease.[286]
- Contact and combat sports should be avoided in people with CF with advanced lung disease, liver disease, a portacath, and those at risk of fractures, for example due to low bone density.[288]

5.4.1 Oxygen desaturation

People with CF with more severe disease may be at increased risk of exercise-induced oxygen desaturation and may require assessment for supplementary oxygen to ensure saturation levels are maintained above 90% during exercise.[289,290] This will improve performance and recovery and help prevent the development of pulmonary hypertension and/or cor pulmonale. Whilst there is limited evidence of safety and efficacy of NIV during exercise, two small studies suggested that the use of NIV during exercise may result in improved ventilation and oxygenation in people with CF, although impact on duration of exercise was varied.[291,292]

5.4.2 Resistance training in young people

Despite concern regarding resistance training for young people, there is limited evidence on the incidence of injuries during strength training in children and adolescents. Rather, as outlined in the International Position Statement on Youth Resistance Training,[293] there is a compelling body of scientific evidence to support participation in appropriately designed youth resistance training programmes that are supervised and instructed by qualified professionals.

Resistance training prescription should be based according to training age, motor skill competency, technical proficiency and existing strength levels, and the biological age and psychosocial maturity level of the young person should be considered.[293] In line with international guidelines, youth resistance training should focus on developing the technical skill and competency to perform a variety of resistance training exercises at an appropriate intensity and volume, while providing young people with the chance to engage in programmes that are safe, effective and enjoyable.[293] Given the increased risk of osteopenia or osteoporosis in people with CF, the fracture history should be determined in each individual.

5.4.3 Renal considerations

Care must also be taken with the use of muscle-building protein supplements, as the renal handling capabilities for these may be altered in CF. Furthermore, these renal handling capabilities may be challenged at times iatrogenically by the use of nephrotoxic drugs.

Creatine is one of the most popular nutritional ergogenic aids for athletes, which has consistently been shown to increase intramuscular creatine concentrations, which can improve exercise performance (particularly during high-intensity exercise) improve training adaptations, and aid post-exercise recovery. However, in the CF population, creatine may also pose renal-related risks when taken alongside of intravenous aminoglycosides, with anecdotal cases of acute renal failure reported.

5.4.4 Sodium deficiency

It is well known that people with CF are at an increased risk of sodium deficiency. Increased sweat production and salt losses may increase the risk of dehydration and hyponatraemia, particularly during prolonged exercise or in warm conditions. Low salt levels may also reduce thirst perception and reduce fluid intake during exercise. Since dehydration can cause tiredness, headaches, dizziness, muscle weakness and may contribute to thicker sputum making airway clearance more difficult, education on this topic is important before an individual with CF begins or changes an exercise programme.

Pre-exercise assessments of hydration status such as urine colour charts should also be considered to help plan activity fluid and salt intakes. There is a lack of evidence available to guide individual sodium requirements for people with CF and no exercise-specific recommendations, however this should be discussed with the dietician where possible. Individual needs may vary and should at present be guided by signs and symptoms of sodium depletion, dietary intake, exercise level and individual sweat rate.[180] Little is known regarding how CFTR modulator therapy may alter the sweat and thermoregulatory responses of people with CF and further research is needed in this area. Salt supplementation may be considered.

5.4.5 Hypoglycaemia and CFD

Hypoglycaemia during exercise is a recognised risk for individuals with CFD, particularly in combination with insufficient caloric or carbohydrate intake. Education delivered by the CF MDT is essential.

Where feasible, self-monitoring of blood glucose should be encouraged alongside appropriate adjustment of caloric and carbohydrate intake based on the planned activity.

In accordance with the CF Trust Management of CFD guidelines ,[182] the following should be considered for individuals who are prescribed insulin or oral hypoglycaemic agents:

- Liaise with CF Diabetes team to provide tailored advice and support to optimise safe exercise participation.
- Ensure that no more than three hours have elapsed since the previous meal and that meal contained adequate carbohydrate.
- Maintain adequate hydration before, during, and after exercise.
- Ensure appropriate snacks and fast-acting carbohydrate are readily available during and after exercise to treat hypoglycaemia if required.
- Where possible avoid injecting insulin in areas heavily involved in the exercise, such as the thighs and gluteal muscles.
- Blood glucose levels should be checked and recorded before, during, and after exercise, with appropriate action taken to prevent hypoglycaemia.

- Be aware that delayed hypoglycaemia may occur up to 24–36 hours post-exercise, and continued monitoring during this period is advised.
- Sharing and reviewing exercise-related glucose data can support ongoing self-management.
- Blood glucose should be ≥4.0mmol/L before undertaking intense exercise.
- If pre-exercise blood glucose is <7.0mmol/L, a 10g carbohydrate snack (such as a banana or biscuit) is recommended prior to starting activity.

5.5 Exercise Training recommendations

Every person with CF should have access to individually tailored exercise programmes that are frequently re-evaluated. Advice and counselling should be developed with the individual and be directed by exercise capacity testing (see **section 4.3**), physical activity monitoring and appropriate physical activity counselling. The guidelines below aim to offer a general practical guide to exercise training recommendations for people with CF, however those with more specific sport and exercise goals should seek more individual input.

Table 2.

Type of activity	1–6 years	7–12 years	13–19 years	> 19 years
Habitual PA	60 mins/day 180 mins/day in a variety of different developmentally appropriate activities	60 mins/day Variety of activities enjoyed, preferably as a family	60 mins/day Variety of activities enjoyed, especially with family and friends	150 mins (preferably 300)/ week Variety of activities of choice
Aerobic exercise	No formal program recommended, but should perform full-body activities that increase breathlessness and heart rate	30–60 mins MVPA/day (at least 70% HR_{max}) Especially if using for airway clearance (must also huff/cough)	30–60 mins MVPA/day (at least 70% HR_{max}) Especially if using for airway clearance (must also huff/cough)	30–60 mins MVPA/day (at least 70% HR_{max}) Especially if using for airway clearance (must also huff/cough)

Table 2. continued

Type of activity	1–6 years	7–12 years	13–19 years	> 19 years
Resistance training	No formal program recommended, but should perform activities using bodyweight to develop strength (e.g. calisthenics) 2–3 times/week	Exercise with own body weight aimed at strengthening muscles and bones (e.g. calisthenics) most days If interested, begin formal weight training under good supervision, focusing on learning good technique first (2 times/week)	Formal RT 2–3 session/week per muscle group 1–3 sets 8–12 reps 70–85% 1-RM Incorporate limb and trunk muscles	Formal RT 2–3 session/week per muscle group 1–3 sets 8–12 reps 70–85% 1-RM Incorporate limb and trunk muscles
Other outcomes	Encourage normal motor development, including agility, balance and coordination	Encourage normal motor development, including agility, balance and coordination	Encourage muscle activities to help prevent or minimise postural control	Adapt for disease-related complications (e.g., CFD, low bone density)

Adapted from Swisher et al[254] and incorporating WHO physical activity guidelines as referenced in Southern et al.[172] HR_{max}, maximum heart rate; MVPA, moderate-to-vigorous physical activity; RT, resistance training; 1-RM, one repetition maximum.

5.6 Other types of exercise

5.6.1 Yoga

Yoga is an ancient mind-body practice which has its origins in the Indus Valley. The physical practice of yoga (known as Hatha yoga) is only one element, but it is what is commonly recognised as yoga in the West and therefore what is discussed here. Yoga combines breathing exercises (pranayama), physical postures (asanas), and relaxation and mindfulness techniques.

Although there is a growing body of evidence for yoga in the non-CF population there have only been three pilot studies undertaken in CF. Two of these pilot studies have been presented in abstract form have shown that yoga is safe and tolerated in adolescents and young people with CF,[294] and can lead to improvements in posture, chest wall excursion, lower extremity muscle performance and self-perceptions of body weight.[295] The final study was published and showed yoga reduced immediate anxiety and joint pain in people with CF between the ages of seven and 20 years.[296]

Some physiotherapists in the UK are integrating yoga into their clinical practice and report benefits including improvements in:

- low back pain
- thoracic kyphosis
- stress incontinence
- ease of airway clearance
- body image
- body awareness
- breath awareness
- cardiovascular fitness
- anxiety
- sleep
- disease mastery.

There are a wide range of different types of yoga practices including Anusara, Ashtanga, Bikram, Iyenga, Jivamukti, Kundalini, Restorative, Vinyasa and Yin yoga. Practices vary in sequencing, asanas, use of props, the duration of how long poses are held for, the temperature of the room and philosophical focus.

5.6.2 Pilates

Pilates is a series of carefully controlled movements that aim to strengthen the body in an even way, with particular emphasis on strengthening the core muscles and using controlled breathing in time with the exercises. Pilates exercises can be performed in a 1:1 or group environment and are done on a mat or using special equipment, such as blocks and supports.

The suggested benefits of Pilates include improved body awareness, postural alignment, tone, strength and flexibility. The main principle of Pilates (building core strength) has been used in conventional physiotherapy for decades and many physiotherapists currently use Pilates-based exercises in their own clinical practice alongside other techniques for the treatment of low back pain and neurological conditions.

Upon review of the literature there are no research trials which solely evaluate the benefits Pilates for people with CF. However, in 2016, nine out of the 39 CF Centres who responded to the complimentary therapy questionnaire reported that they use Pilates in their clinical practice and find it beneficial for posture, fitness, MSK pain relief, airway clearance, breathing control and relaxation. In 2019 a qualitative study of UK CF MDTs regarding the promotion of physical activity for adolescence with CF noted Pilates was an example of exercise used in this group.[297] However, no further recommendations were given.

5.6.3 Tai chi

Tai chi is a Chinese form of meditative movement which combines slow, choreographed movements with deep breathing and mindfulness. Research suggests tai chi can improve physical and emotional wellbeing for various chronic conditions including arthritis, low bone density, heart disease, hypertension and sleep problems. Benefits include increased muscle strength, improved flexibility, pain and balance, and mild aerobic benefits depending on the speed and size of the movements.

Two studies have been conducted in the CF population to date.[298,299] The initial study by Lorenc was a small sample pilot feasibility study with seven people with CF which showed no adverse effects and suggested that tai chi may reduce CF treatment impact, improve respiratory symptoms, self-efficacy and sleep.[298] The second was the follow-up to Lorenc's study, and was a randomised comparative effectiveness trial. Twenty-six adults and fourteen children with CF participated in eight tai chi lessons over a three-month period, either via videoconferencing or face-to-face. Tai chi was found to be safe and well-tolerated. It was feasible to deliver individual lessons via videoconferencing and it appeared to improve self-reported symptoms such as sleep, day and night-time, stomach ache and breathing.[299]

5.7 Recommendations

5.7.1 Physical activity

- Young children with CF should perform regular, developmentally-appropriate physical activity for at least 60 minutes per day *(QoE – high)*.
- Older children and adolescents with CF should perform at least 60 minutes of moderate-to-vigorous physical activity per day *(QoE – high)*.
- Adults with CF should perform 150–300 minutes (2.5–5 hours) or more of moderate-to-vigorous physical activity per week and should seek to include a mix of aerobic and resistance training *(QoE – high)*.
- Those who are inactive or limited in their physical capacity should be encouraged to accumulate 10-minute bouts of physical activity throughout the day *(QoE – moderate)*.
- All individuals with CF should be encouraged to reduce sedentary time *(QoE – high)*.
- Pre-school aged children should reduce screen time to a maximum of one hour per day *(QoE – high)*.

5.7.2 Aerobic exercise

- Young children with CF should perform regular, developmentally appropriate physical activity for at least 60 minutes per day *(QoE – high)*.
- Children and adolescents with CF should perform 30–60 minutes, three times per week or more of aerobic exercise at an intensity of at least 70% maximum heart rate to improve fitness – this can also help to meet daily physical activity targets *(QoE – moderate)*.
- Adults with CF should perform 30–60 minutes, three times per week or more of aerobic exercise at an intensity of at least 70% maximum heart rate) to improve fitness – this can also help to meet daily physical activity targets *(QoE – moderate)*.
- Patients should be educated regarding the clinical importance of high aerobic fitness levels *(QoE – moderate)*.
- Patients should be educated on the difference between moderate and vigorous intensity physical activity and aerobic exercise and on the use of subjective measures of exertion, for example validated scales to assess exertion and/or breathless *(QoE – low)*.

5.7.3 Exercise intensity definitions

Moderate-intensity physical activity definitions

- The individual is exercising at 40–59% of their peak aerobic capacity ($\dot{V}O_{2peak}$) as measured during CPET *(QoE – moderate)*.
- The individual is exercising at a self-reported perceived exertion rating of 11–13, as measured on the Borg perceived exertion scale (a valid 15 item scale [range 6–20] for exercise prescription; see **Appendix Ie**) *(QoE – low)*.
- The individual is exercising at a rating of perceived breathlessness between 3–4 as measured using the modified Borg breathlessness scale (range 0–10; see **Appendix Ie**) *(QoE – low)*.

Vigorous-intensity physical activity definitions

- The individual is exercising at 60–85% of their $\dot{V}O_{2peak}$ as measured during CPET *(QoE – moderate)*.
- The individual is exercising at a self-reported perceived exertion rating of 14–16, as measured on the Borg perceived exertion scale (see **Appendix Ie**) *(QoE – low)*.
- The individual is exercising at a rating of perceived breathlessness of 5–6 as measured using the modified Borg breathlessness scale (range 0–10; see **Appendix Ie**) *(QoE – low)*.

5.7.4 Resistance exercise

- Adults with CF should undertake resistance exercise as a complement to and not a replacement for cardiorespiratory (aerobic) exercise *(QoE – moderate)*.
- Adults should be advised to undertake resistance exercise on two or more non–consecutive days of the week *(QoE – low)*.
- Weight training should be regarded as the preferred mode of resistance exercise to optimise the health benefits and monitor progression. Alternative modes of resistance training may be considered such as using body weight, resistance bands, free weights, medicine balls or weight machines *(QoE – low)*.
- Resistance training should incorporate both upper and lower limb exercises that target the major muscle groups *(QoE – moderate)*.
- To improve muscular strength a load should be selected that equates to 70–85% of the person's 1-RM (1–3 sets, 8–12 reps for each exercise). To improve muscular endurance a load should be selected that equates to less than 70% of the patients 1-RM and more repetitions performed *(QoE – moderate)*.

- In the absence of the person's 1-RM, a resistance (weight) should be selected that brings about local muscular fatigue after the desired number of repetitions for each exercise *(QoE – low)*.
- Respiratory muscle training may be considered *(QoE – low)*.

5.7.5 General exercise recommendations

- Individuals with CF should be made aware of any increased medical risks associated with specific exercise or sporting activities *(QoE – moderate)*.
- Specific types of strength training (such as power lifting, body-building and maximal lifts) should be avoided until physical and skeletal maturity *(QoE – moderate)*.
- Specific guidance should be given on fluid-replacement and dietary or insulin requirements when appropriate *(QoE – moderate)*.
- People with CF who exhibit desaturation will be assessed for supplementary oxygen during exercise *(QoE – moderate)*.
- High-intensity interval training may be considered in people with CF who have achieved the recommended amount of physical activity for more than six months *(QoE – moderate)*.
- All individuals with CF who have expressed a desire to become more physically active should be offered support and advice *(QoE – low)*.
- Adults with CF may benefit from incorporating activities to maintain and/or improve posture and flexibility on most days of the week *(QoE – low)*.

5.8 Good practice points

- Physical activity and exercise should be part of the routine management for people with CF at any age for health and a good quality of life.
- People with CF should be made aware of the health benefits of a physically active lifestyle and the physiological principles that underpin exercise training.
- A recommended exercise programme should be offered to all people with CF who request one
- Recommended exercise programmes must consider:
  - motivations and goal
  - current level of physical activity and ability
  - health status
  - circumstance
  - preferences
  - barriers to being physically active.
- People with CF should be advised to minimise the time spent inactive for extended periods of time, particularly during periods of clinical stability.
- A structured exercise programme will be offered to patients who have MSK disorders that are likely to benefit from exercise training.
- Alternative exercise options such as pilates, yoga and tai chi can be considered for people with CF and may provide exercise options throughout the spectrum of CF. Qualified instructors are recommended who will be able to adapt the class to an individual's needs.

6. Airway clearance techniques

6.1 Introduction

Airway clearance techniques (ACTs) aim to optimise mucociliary clearance of viscous secretions to prevent or reduce distal airway obstruction. These interventions are considered a mainstay of treatment for people with CF and have been considered essential for all, ideally starting from diagnosis. However, the advent of CFTR modulators has seen a significant reduction in sputum production for those who are currently eligible and able to tolerate, with some people with CF questioning the need to continue ACT,[300] whilst others and their caregivers consider ACT important to maintaining their health despite new therapies.[301]

Current research on the effectiveness of CFTR modulators is based on use alongside traditional interventions such as ACT, and the long-term effects of these medications are unknown. Additionally, as there is a paucity of reliable research on the effectiveness of ACT within this demographic, due to the complexities of physiotherapy design protocols,[92] it would therefore be unwise at this current time to alter ACT practise without robust evidence to support this, especially in those with established airway disease.

Priority research questions have been identified by the James Lind Alliance for people with CF and include how to simplify treatment burden, identifying which therapies are effective in delaying and preventing progression of lung disease in early life, and whether exercise is an effective replacement for traditional ACT. As further unequivocal evidence is required it is important that physiotherapists continue to empower people with CF to monitor their symptoms and adjust interventions as symptoms fluctuate.

Adherence to airway clearance tends to be lower when people with CF have a negative association with their treatment, such as high burden, which is then associated with poorer outcomes. Regular follow-up, including revision of an individual's knowledge and technique will help ensure appropriate decision-making is made collaboratively by the physiotherapist and person with CF in response to their changing needs. Additionally, the awareness of need to complete ACT may have changed for those on modulator therapy and retraining on self- assessment of need for ACT is likely to be required. This could take the form of utilising home spirometry or the 'exploratory' or extended forced expiratory technique (FET) prior to or following formal ACT or exercise to determine whether to initiate or continue with prescribed clearance routines.

Since available evidence does not favour any single treatment technique it is important that individual preference should be highly regarded when deciding which treatment option to choose.[302] Importantly, a Cochrane review showed that people with CF preferred self-administered ACTs that facilitate independence.[65] Additionally, treatment plans need to take into consideration the person's age, the physiological effects of the intervention, individual preference and perceived burden of treatment.

Whilst treatment options are both discussed here and often researched individually, combining different treatments can sometimes make airway clearance more effective and improve adherence.[303] It has been suggested that effective airway clearance has two components: a method to ventilate behind obstructed lung units and, secondly, an expiratory airflow of greater than 30–60L/min with a peak expiratory flow to peak inspiratory flow of ratio of 1:4.[304] Additionally, to optimise the effects of ACT airways should be hydrated and dilated prior to initiation through appropriate methods and medication.

6.1.1 Research recommendations

- Safe and effective titration of ACTs with the use of CFTR modulator therapy population.
- Development of outcome measures which support titration of ACTs, especially within populations with poor lung function and established bronchiectasis.
- Further understanding of the changing attitudes of people with CF towards ACT so that physiotherapy services can remain dynamic and meet the needs of an ever-diverse population.

6.2 The Active Cycle of Breathing Technique

The Active Cycle of Breathing Techniques (ACBT) consists of three components:

1. Breathing control

In the initial stage of ACBT, the individual performs tidal breathing (gentle relaxed breathing) using the lower chest with a slower flow, but at their own respiratory rate.[305]

Relaxing the shoulders and upper chest muscles encourages diaphragmatic breathing. Inspiration is ideally through the nose.[306] Breathing control is incorporated to allow rest periods and prevent bronchoconstriction between the more active parts of ACBT.[307]

2. Thoracic expansion exercises (TEEs)

TEEs are deep active inspirations to full capacity with a passive unforced expiration, repeated to a maximum of four breaths at a time.[307] A three-second hold at full inspiration keeping the airway/glottis open should be encouraged. This allows improved ventilation to all areas before then passively breathing out.

Increasing the lung volume above tidal breathing reduces collateral ventilatory resistance, allowing air to flow behind secretions aiding their mobilisation, while forces exerted between adjacent alveoli also aid lung re-expansion.[308]

If secretions still need to be mobilised after thoracic expansion exercises, a further set of these deep breaths can be repeated after a period of breathing control before the FET. No more than four TEEs are recommended prior to breathing control to prevent patient fatigue and hyperventilation.[309]

3. Forced expiration technique (FET)

The FET, also known as a 'huff' is an active forced expiration completed with a rounded mouth shape and open glottis, which is repeated once or twice with breathing control in-between.[307] This can be done at various lung volumes to help with expectoration with minimal effortful coughing,[310] starting with a mid-to-low-lung volume breath mobilising peripheral secretions, then a high- to-mid-lung volume breath to move more proximal secretions.

FET has been reported in the literature as "probably the most effective part of chest physiotherapy"[311] and is now often independently incorporated into other airway clearance techniques or exercise regimes to ensure effective secretion clearance.[112,127,312–314]

ACBT can be adapted in terms of session length and position according to individual need, but each component of the cycle should be clearly defined. It is considered a simple technique which, once learnt, is not dependent on a device or on carer assistance, which minimises treatment burden[308] whilst promoting independence. This can be introduced as huffing games with children from around two years old[305] and full ACBT can be taught to people with CF from as young as four years of age,[312] depending upon the individual.

Although current evidence does not show that the effects of ACBT are enhanced by the addition of devices such as PEP,[315] the Flutter®,[313,316] or high frequency chest wall oscillation (HFCWO) the vest,[313] it is possible to combine ACBT with adjuncts, PD, or manual techniques which may suit individual preference and should be considered.[93,317,318] In severe infections or end stage disease, ACBT can be combined with NIV or other positive pressure support with setting modification to support deep and tidal breathing.[304,305] ACBT can also be utilised with the necessary advice, supervision and monitoring following haemoptysis or pneumothorax once the individual is medically stable.

6.2.1 Research

Current literature includes both short and long-term studies with a recent Cochrane review concluding that there was insufficient evidence to support or reject the use of ACBT over any other airway clearance technique.[76,90,302] ACBT was comparable with other airway clearance techniques in terms of individual preference, pulmonary function, quality of life, exercise tolerance, oxygen saturations and occurrence of infective exacerbations[90] and has been found to not increase hypoxeamia[93] or air flow obstruction.[319] Further long-term evidence is required to assess ACBT in terms of PROMs and objective effect, especially with the introduction of CFTR modulator therapy.[80,90,305]

6.2.2 Recommendations

- ACBT should be considered when recommending an airway clearance technique for all people with CF if they are able to follow instructions *(QoE – low)*.
- FET should be incorporated into airway clearance and exercise regimes to enhance airway clearance *(QoE – moderate)*.

6.2.3 Good practice points

- The use of ACBT should be adapted to the individual in terms of number of sets of each component completed and the length of breathing control rest periods and should therefore be reviewed regularly.
- ACBT can be tailored to individual needs and disease stage and used from early childhood onwards.
- ACBT can be taught to promote independence with airway clearance and may be considered less burdensome by some individuals, depending on their circumstances and preferences.

- Combining ACBT with other adjuncts, taking into consideration patient disease severity, preferences, lifestyle, treatment burden, individual tailoring and effectiveness of treatment combinations can be advantageous.

6.3 Autogenic drainage

Autogenic drainage (AD) is a controlled breathing technique, which aims to mobilise secretions from the peripheral airways into the central airways to aid expectoration and airway clearance. AD can be performed in any position to assist regional ventilation. A person's preferred posture and position for performing AD should be optimised and supported.

6.3.1 Diagnostic breath

At the start of a cycle of AD it is recommended to clear the nose to enable nose-breathing, particularly on inspiration.[305] The person with CF is then instructed to complete a 'diagnostic breath' consisting of a slow full inspiration followed by a full expiration. Inspiration should ideally be through the nose, using the diaphragm and lower chest, followed by a three second inspiratory pause at the top of inspiration, keeping the glottis open. Expiration, ideally through the mouth, should be active, achieving the highest possible expiratory flow without causing airway compression or bronchoconstriction.[312]

Feedback from this diagnostic breath, in terms of audible crepitations, tactile fremitus and proprioceptive sensations for the participant, should then be used to target the next phase of the AD cycle[305] or to indicate the continuation of ACT if combining with other interventions. Crepitations or fremitus detected at the start of the diagnostic breath out is said to represent secretions in the central airways, while crepitations or fremitus detected towards full exhalation are said to represent secretions in the peripheral airways.

6.3.2 Tidal volume breaths

The main part of the AD cycle consists of tidal volume-sized breathing, carried out at differing lung volumes (low, mid, or high), aiming to maximise expiratory flow at that generation of the bronchial tree to mobilise secretions from those parts of the airways.[320] At all lung volumes inspiratory flow rates are encouraged to be slow, quiet and gentle while expiratory flow should be as high as possible while avoiding airway closure.[312,321]

Depending upon where secretions were detected in the diagnostic breath, the participant will start their breathing at that level to further mobilise secretions from that area, for example crepitations heard at low lung volumes will lead to the participant exhaling fully to focus on 'unsticking' secretions from the peripheral airways. Mid-lung volume breathing can then be used to 'collect' secretions moved to the middle airways before high-lung volume breathing (full inspirations) works to 'evacuate' secretions from the proximal central airways to the upper airway and mouth.

Once secretions have been mobilised to the highest level they can be cleared with FET and coughing. Ideally the AD cycles would be repeated until the participants airways feel as clear as possible,[305,312] until fatigue prevents the completion of a good technique or as the individual's need defines.

It is possible to combine AD with adjuncts such as PEP or NIV (in end-stage disease or severe infections) to support the needs of the individual. Additionally, a recent small study has reported good outcomes from AD combined with the novel therapy Simeox® singularly, or more beneficially with a strap. While this may be beneficial to some individuals, the physiological basis of AD should be considered, and settings adapted as required. It is possible to utilise AD following haemoptysis or pneumothorax once the individual is medically stable and with the necessary advice, supervision and monitoring.

6.3.3 Assisted autogenic drainage (AAD)

It has been reported that children over the age of eight can be taught AD.[70] However, the individual should be assessed in terms of maturity and readiness to learn as some children may not have the focus and concentration required.[305,321] It is also possible to use the principles of AD with younger children or patients who are unable to complete independent techniques.[322] This is often called assisted AD or AAD.[323,324]

Breaths at differing lung volumes can be achieved by applying gentle manual pressure to the chest during inspiration; in expiration the breathing motion of the individual is followed.[305,324] As with AD, feedback from audible crepitations or airway closure alongside tactile fremitus is important to target therapy.[36,305] The abdominal wall should be stabilised during AAD to avoid paradoxical movements.[305] Clearance is completed with a spontaneous cough.[305]

AAD is often combined with therapeutic exercise such as bouncing on an exercise ball.[305,324] Trials investigating AAD and AAD with bouncing and

concluded they did not induce gastro-oesophageal reflux in infants under one year old[322] and even showed a decrease in reflux within this age group.[71]

6.3.4 Research and evidence

A 2019 Cochrane review of AD suggests that while it can be considered an effective ACT which supports self-management and is comparable to other interventions, it is challenging to learn and requires individual effort and commitment. Therefore, consideration should be given to the age of the individual and whether this is being supervised or regularly reviewed by a physiotherapist.[325]

Most of the research into AD has compared its efficacy with other airway clearance techniques such as ACBT, oscillating PEP (OPEP), PEP and high pressure PEP. A 2017 Cochrane review reported there were no statistically significant differences between AD and other airway clearance techniques in respect to changes in outcome measures such as FEV_1, QoL, sputum weight, hospital admissions and intravenous antibiotic use.[326] Two short-term studies have also suggested that performing AD led to fewer episodes of oxygen desaturation.[327] One study reported patient preference for AD over PD and percussion[76], however another concluded that AD did not affect the rheology of sputum, and so may not be an optimal ACT for people with viscous secretions.[328] Additionally, a further trial suggested AD may be a preferable technique for individuals exhibiting airway hyperreactivity.[327]

A single session of AD has been shown to decrease peripheral resistance, except in distal airways[119] more specifically within children with CF with moderate-to-severe bronchial congestion when supervised by a physiotherapist.[325] Another study has compared the effect of a single session of AD to period of rest in a small sample of CF patients. They reported a small statistical improvement in spirometry and a moderate improvement in global airway inspiratory resistance as measured by the forced oscillation technique, although distal airway resistance was unchanged.[119]

More recently a study has reported improved therapeutic effects of AD when combined with the novel therapy Simeox® and an AD belt (a supportive belt worn around the lower part of the thorax during AD) simultaneously versus AD alone, reporting improvements in spirometry, saturation and patient comfort which could lead to improved adherence. However, the limitations of this are availability and cost of the Simeox® device, as well as the improvements being found to be greater within paediatric population under 10.5 years of age.[329] See **section 6.9** for more information on Simeox®.

It can therefore be concluded that the use of AD will be heavily person-dependent, and further evidence is required for the short-term and long-term effects of AD, AAD and the additional benefits of AD combined with adjuncts. Such studies should aim to utilise more robust outcome measures, including PROMs, in both adult and paediatric populations.[70,325,327]

6.3.5 Recommendations

- AD should be considered when choosing an airway clearance technique for people with CF who are able to follow instructions (caution should be taken with children under the age of eight) *(QoE – low)*.
- There is evidence to suggest that AD is as effective as other airway clearance techniques *(QoE – low)*.
- Consider AD in individuals with airway hyper-reactivity *(QoE – very low)*.
- Regular assessment of AD should be completed to ensure effectiveness of technique *(QoE – very low)*.
- The physiological principles of AD should be considered when combining AD with adjuncts or positive pressure support *(QoE – very low)*.

6.3.6 Good practice points

- AD should be taught by a trained physiotherapist who can adapt the technique to the individual's needs.
- AD can be considered for use as an independent ACT at all stages of lung disease. Any person with CF performing AD should be assessed for their ability to complete the different lung volumes required without shortness of breath.
- AD or AAD where appropriate, can be considered as an ACT, tailored to individual needs and development stage.
- AD may be helpful in treating individuals with reactive or hypersensitive airways.
- AD has minimal contraindications for use and should be considered when selecting independent ACTs.
- Combining AD with adjuncts such as PEP, NIV or Simeox® and AD belt can be helpful for patients who need extra support. Physiotherapists should ensure the physiological principles of AD are complemented by adding the adjunct and assessing the combination's effect.

6.4 Positive expiratory pressure (PEP)

The use of resistance when breathing out creates a positive expiratory pressure (PEP), which can be used to enhance the mobilisation of bronchopulmonary secretions. PEP breathing generates a temporary increase in FRC by breathing through a closed system, increasing interdependence between alveoli, facilitating collateral ventilation and therefore recruiting previously obstructed airways. It is useful in those with unstable airways, as it evens out ventilation and splints the airways avoiding collapse.[330] The peak expiratory flow rate/peak inspiratory flow rate (PEFR/PIFR) ratio with PEP is 0.47, so periods of PEP breathing are frequently combined with AD, the FET and cough to facilitate airway clearance.[330,331]

6.4.1 Low pressure PEP

Clinically, low pressure PEP is the most used form of PEP and may be applied via a mouthpiece or mask. it is usually in the sitting position[331] but may also be performed in positions that increase ventilation such as supine or side lying.[305] Breathing through the device should be at tidal volume with only slightly active expiration (not prolonged or forced).[332] A manometer should be inserted between the expiratory valve and the resistor to measure mid-expiratory pressure to allow selection of the appropriate level of expiratory resistance.[333] The appropriate resistance is one which achieves a stable mid-expiratory pressure of 10–20cm H_2O.[88,332] Each cycle should be 12–15 breaths to maintain FRC.[330] The developers of PEP recommend using PEP with a mask to avoid leaks via the upper airways and mouth; using a mouthpiece does not increase FRC.[88]

Several short-term and long-term (over one year) studies have compared low pressure PEP with other methods of airway clearance.[65,80,91,112,127,331,334–338] A systematic review of PEP in CF reported that in short or long-term studies no significant difference had been demonstrated between PEP and other ACTs with reference to pulmonary function, exercise capacity or QoL.[81,88,90,92,116,304,339] Longer-term studies comparing PEP with other ACTs show equivocal or conflicting results in terms of FEV_1.[86,88,91,92,116] A significant reduction in respiratory exacerbations requiring antibiotics was demonstrated in those who used PEP compared to HFCWO over a one-year period.[88,127,304] One study demonstrated that whole lung mucociliary clearance was greater when using PEP compared to treadmill exercise, but there was no difference in peripheral lung clearance between the two interventions.[112,304] Another study in children showed that airway clearance with PEP and AD prior to exercise led to improved ventilatory dynamics.[116] A systematic review showed larger sputum weight with PEP and FET compared to control but no change in mucus transport rate.[81]

A systematic review by Cochrane in 2023[65] found that individuals prefer self-administered ACT such as PEP and OPEP and supported the benefits of independence with ACT using the PEP device. Preference for PEP has been reported in several studies,[66,304,331,335,337] although the quality of many of these studies is reported as low.[116]

6.4.2 High pressure PEP

High pressure PEP involves forced expiratory manoeuvres against resistance, creating a high expiratory pressure, increasing FRC and end expiratory flow.[340] The same mask for low pressure PEP is used with a different manometer equipped to measure higher pressures (typically 40–100cm H_2O).[90,305]

The individual takes 8–10 breaths at moderate tidal volume while sitting, then inhales to total lung capacity before performing a forced expiratory manoeuvre against the resistance to residual volume. This normally results in them coughing from low lung volumes and expectorating secretions. This is repeated until the cough is dry and no more secretions are produced.[305,341]

The appropriate resistance is calculated by connecting the outlet of the PEP mask to a spirometer and should be routinely assessed at clinics or more frequently on initiation of the technique. The individual should perform forced expiratory manoeuvres through different sized resistors where the resistor is chosen based on the maximal expiratory flow through all lung units which is demonstrated by interpretation of the flow-volume curve.[305]

A short-term study found high pressure PEP yielded greater sputum volume when compared to AD. Improved lung function parameters were also found but did not exceed those achieved after AD and were associated with significantly lower sputum yield in those with airway hyperactivity, leading the authors to conclude that high pressure PEP may induce bronchoconstriction and should be preceded by the use of a bronchodilator, or that another available airway clearance technique such as AD should be considered.[327,342] A long-term study concluded high pressure PEP resulted in improved lung function and greater sputum yield, as well as decreased airway instability and hyperinflation when compared to conventional physiotherapy.[343] There have been no recent studies conducted in this area.

Pryor and Prasad advise this technique takes a considerable amount of effort and therefore would not be suitable for someone who tires easily.[341]

6.4.3 Infant PEP (iPEP)

The use of PEP has also been investigated in infants and is reported to be as effective as PD and percussion.[66] This technique uses a soft face mask which is placed on the baby's face and gives a small amount of back pressure to the airways when the baby breathes out, helping to open the airways and clear any mucus. There is no specific guidance to resistor selection when using PEP with babies; the assumption is that appropriate resistance is one which achieves an approximate mid-expiratory pressure of 10–20cm H_2O when a manometer is situated within the circuit.[88,332] A study conducted in 2020 reviewed PEP pressures achieved by a wide range of babies and children under the age of four in a CF clinic and found the mean pressure achieved was only 3.74cm and pressures above 10cm were not achieved in any of the babies or children.[67] This is backed up by a recent study in 2024 which concludes that 'iPEP is a well-established ACT for infants but since there is little consensus regarding technique, this remains individual to the individual and their team'.[69]

6.4.4 Bubble positive expiratory pressure

A bubble PEP circuit can be made up from a plastic bottle, tubing and water. The bottle is filled to 10–20cm in depth. The tubing is placed into the water and as the individual breathes out against the resistance of the water, PEP is produced. Breathing out against the resistance of the water should be interspersed with FET and cough to encourage the clearance of secretions. The inner diameter of the tube should be 8mm to ensure the PEP threshold is the same as the water column pressure.[344]

There appears to be limited research on bubble PEP available. One study showed that some bubble PEP devices did not reach the recommended pressure of 10cm H_2O and none reached 20cm H_2O.[345]

6.4.5 Recommendations

- PEP should be considered when recommending an ACT for all people with CF *(QoE – low)*.
- There is insufficient evidence to support or refute the use of high-pressure PEP in CF *(QoE – low)*.

6.4.6 Good practice points

- PEP has not been proven to be any more or less effective overall than other ACTs.
- The level of the expiratory resistor used should be regularly re-assessed and may need to be changed with alterations in clinical status.
- Appropriate cleaning regimens of PEP devices as per manufacturer guidelines should be recommended.
- If used, treatment with high pressure PEP must be assessed regularly, by a physiotherapist skilled in the technique, due to the high pressures used (40–100cm H_2O).

6.4.7 Research recommendations

- Safe and effective iPEP technique needs to be established.

6.5 Oscillatory positive expiratory pressure (OPEP)

OPEP devices produce intra-thoracic oscillations by creating variable oral resistances that alter expiratory airflow. This generates controlled oscillating positive expiratory pressure, which mobilises respiratory secretions.[89] Exhalation through these devices also generates repeated accelerations of expiratory airflow, both this and the oscillations have been shown to result in improved sputum clearance.[330,346,347]

Oscillations or interruptions during expiratory airflow are considered to mechanically reduce the viscoelasticity of sputum and enhance mucociliary clearance.[330] The intermittent increases in endobronchial pressure reduce airway collapse during exhalation, increasing the likelihood of clearing mucus from the tracheobronchial tract.[89,315,347]

Devices used for OPEP:

- **Flutter®**
  - A small plastic device containing a large ball bearing, which repeatedly interrupts the outward flow of air.[347,348]
  - A three-second breath hold can help ventilate behind obstructed areas of the lung.[346]
  - PEFR of 68L/minute.
  - PEFR/PIFR ratio of 1.15.

- Oscillates at 15–29Hz.
- PEP of 5–19cm H_2O.[346]
- The position of the device can be altered to change the amount of vibration felt within the chest, tilting upwards to generate a higher frequency or downwards to generate a lower frequency.[88]

- **Pari OPEP®**
  - A similar device to the flutter working with the same principle of providing resistance to expiratory flow with a metal ball bearing, helping splint airways open.
  - Produces oscillations by vibrating at a frequency equal to 15Hz.
  - The position of the device can be altered to change the amount of vibration felt within the chest, tilting upwards to generate a higher frequency or downwards to generate a lower frequency.[88]

- **Acapella®**
  - A flow-operated oscillatory PEP device, which uses a counterweighted plug and magnet to generate the oscillatory resistance.[349]
  - It ventilates behind obstructed lung areas by collateral ventilation.[346]
  - Different acapella® systems are available for a variety of PEP needs:
    - Acapella® DH (green) – short-term use
    - Acapella® DM (blue) – short-term use; can be used for patients unable to sustain expiratory flow greater than 15L/min
    - Acapella® choice – long-term use
    - Acapella® duet – long-term use; built-in nebuliser port.[350]
  - PEFR of 34L/minute.
  - PEFR/PIFR ratio of 0.64.
  - Oscillates at 13–30Hz.
  - PEP of 6–21cm H_2O.[346]

- **Cornet®**
  - A horn-shaped tube housing a rubber inner tube.
  - The degree of rotation of this inner tube reflects the resistance generated.
  - As the individual exhales through the horn the inner tube unfurls generating a rhythmic bending and unbending of the inner tube within the horn throughout the expiration phase.[349]

- **Aerobika®**
  - A flow-operated OPEP device, which uses a one-way valve to generate the oscillatory resistance.[351]
  - The Aerobika® may also be used simultaneously with nebulised aerosol drug delivery.

- **Quake®**
  - This device oscillates a column of air in both inspiratory and expiratory phases of respiration.
  - It does not rely on an oscillating valve like the Flutter® and Acapella®, as it uses a manually turned cylinder that fits within another cylinder. Airflow occurs only when slots within the two cylinders line up. Therefore, the airflow is interrupted at regular intervals as the user turns the crank.
  - The rate at which the device is cranked will determine the frequency of the flow interruption. Since the resulting vibration is not determined by the users' rate of flow, the Quake® theoretically may be more helpful for people with severe obstructive lung disease who are unable to generate high PEFRs.[351]

Numerous systematic reviews of OPEP devices in CF report no clear evidence that they were more or less effective than other forms of airway clearance and no evidence that one device was superior to another.[88–90,304,352] When oscillations are combined with dornase alfa, there is a significant reduction in sputum rigidity and cough clearance index.[346] One study comparing four OPEP devices in a simulated CF model found that each device functioned differently as more than one repetition of a series of exhalations are performed.[351] They found that the Aerobika® provided the most consistent pressure amplitude across resistance settings and produced the highest mean pressure amplitude at medium and high resistance.[353] More recently another study comparing 10 different OPEP devices concluded that 'significant functional differences' exist between OPEP devices making it difficult to translate improved patient outcomes between devices.[354]

In one RCT, the Flutter® was shown to favourably alter respiratory flow bias compared to treadmill exercise.[282] Morrison and Innes also found some small but significant changes in sputum volume and weight and frequency of exacerbations, but these results were not wholly in favour of OPEP devices.[351]

There is a lack of evidence evaluating OPEP since the introduction of CFTR modulator therapy. Going forward as CF may present in a different

way, clinicians will have to continue to use their clinical judgement and education of people with CF on how to monitor for symptoms and alter their treatment regimens to reflect this.

6.5.1 Recommendations

- Consider oscillatory devices when recommending an appropriate ACT for a person with CF *(QoE – low)*.

6.5.2 Good practice points

- OPEP has not been proven to be more or less effective overall than other ACTs. There is no evidence that one device is superior to another.
- People with CF must be instructed in appropriate cleaning regimens of OPEP devices as per manufacturer guidelines.

6.6 Extra-thoracic oscillations – high frequency chest wall oscillation (HFCWO) vest

Extra-thoracic oscillations are generated by forces external to the respiratory system, for example HFCWO. HFCWO consists of an air-pulse generator connected to an inflatable jacket (or vest) that fits over the chest.[355] Air pulses are transmitted to the vest, creating oscillations to the chest wall of 5–25Hz. Physiologically, HFCWO enhances mucociliary transport by creating a cough-like expiratory flow bias that shears mucus from the airway walls,[127] with the associated vibrations altering the rheological properties of mucus by decreasing the viscoelasticity and potentially rehydrating mucus.[356] The HFCWO compressor can be decontaminated after use as per local infection prevention and control guidelines. The vest component is single patient use and must not be used for any other person.

Evidence for the use of the HFCWO in CF is variable when considering sputum clearance measured by wet or dry sputum weight. No consistent statistical difference between HFCWO and other ACTs have been demonstrated.[313,335,357–363] When respiratory function is the primary outcome, there is no evidence to suggest that HFCWO is superior to other ACTs.[313,351,357,358,364–368] One study demonstrated significant desaturation using HFCWO compared to PEP in people with moderate-to-severe disease and recommended oxygen saturation monitoring.[364] There is strong evidence illustrating an increase in pulmonary exacerbations and shorter time to next exacerbation when using HFCWO compared to PEP over a sustained period of time.[127]

The HFCWO device does not provide any PEP,[369] therefore in order to ventilate behind secretions it has been advised that HFCWO should be combined with either deep inspiratory manoeuvres, three second breath hold, or a PEP device to achieve optimal outcomes.[356] A short-term improvement in LCI was demonstrated following 30 minutes of HFCWO compared to control of no chest physiotherapy. However, this supposed treatment effect was heterogeneous and not clinically relevant for the majority of the cohort.[105]

HFCWO during Nebulisation does not affect peripheral drug deposition.[368] Augmented ventilation was demonstrated in 15 people with CF following a single session of HFCWO, as assessed by a lower end-tidal CO_2 compared to no treatment.[356] Assessment of people with CF with mild lung disease found small but significant improvements in spirometry measurements but unchanged mucous plugging on Xe MRI.[370]

Mobile HFCWO units are now available and effects are comparable with standard non-mobile units in terms of sputum volume and weight.[371] No changes in lung function were demonstrated following a single treatment session with either unit. It was hypothesised that the mobility offered may help people with CF with adherence but this has not been proven.

Adherence to HFCWO has been measured using a novel electronic device, recording daily timing and duration of use. Adherence was 82% in children, 69% in adolescents and 56% in adults. As prescribed therapy time increased, adherence decreased. Assistance with starting therapy was associated with significantly higher adherence.[372] Convenience, efficacy and comfort were the comparisons evaluated for patient satisfaction and again results were variable. In some studies, people with CF preferred the flexibility of alternative devices but others preferred HFCWO.[127,313,356–358,360–362,373] Individual preference must be considered when formulating an airway clearance programme and consideration of the impact a given device may have on a person with CF at particular stages of their life, especially on adherence.[369]

6.6.1 Recommendations

- ACTs such as PEP and OPEP should be considered before HFCWO for people with CF *(QoE – low)*.
- The cost of the HFCWO may be prohibitive, especially in view of the lack of evidence of superiority over other ACTs *(QoE – high)*.

- Oxygen saturations should be monitored for people with CF with moderate-to-severe disease using HFCWO *(QoE – low)*.

6.6.2 Good practice points

- HFCWO should be considered when a person with CF is unable to carry out other ACTs for reasons such as autistic spectrum disorder, learning difficulties or due to the severity of their CF.
- HFCWO may be considered as an adjunct to other ACTs such as ACBT, PEP, where resources allow and individual preferences are taken into account.

6.6.3 Research recommendation

- Evaluation of effectiveness of airway clearance devices alone compared to airway clearance devices supplemented by HFCWO.

6.7 Intrapulmonary percussive ventilation (IPV)

Intrapulmonary percussive ventilation (IPV) is a mechanical airway clearance device that combines internal thoracic percussion and inspiratory pressure through rapid mini bursts of air superimposed onto a spontaneous breathing pattern. This causes airway pressures to oscillate between 5 and 35cm H_2O and the airway walls to vibrate in synchrony with these oscillations.[305] Expiration against the percussive element of the device leads to the maintenance of positive pressure within the airways.[373] IPV can be delivered either via a mouthpiece or mask.

The proposed methods of action include:

- maintenance of small airway patency, ventilation and prevention of airway closure and atelectasis
- enhanced movement of secretions
- improved distribution of nebulised medications.

A number of studies have investigated the use of IPV in CF, but the evidence is limited and is often focused on people with CF with only mild or moderate disease severity.[361,374,375]

A comparative study of IPV and conventional chest physiotherapy reported no differences between the techniques in terms of pulmonary function and expectorated sputum.[369,375–377] A single intervention study compared IPV with conventional chest physiotherapy and the Flutter® in a randomised cross-over design concluding that IPV and the Flutter® were equivalent to conventional chest physiotherapy in terms of sputum cleared or change in pulmonary function measures from baseline.[374] Both studies included stable children and adults but the sample sizes were small and only short-term effects of the interventions were studied. Similar findings have been found in stable people with CF in the outpatient setting.[378]

A single case presentation of a young person with advanced CF disease demonstrated the use of IPV during an exacerbation and displayed improvements in lung function, reduction in mucus plugging on CT scan and with continued use at home, a reduced requirement for future hospitalisation and requirements of IV antibiotics. It was also said to improve tolerance of inhaled mucolytics.[379] Conversely one longer-term study compared IPV to CPT over a six-month period and found no significant difference in hospitalisations or use of oral and IV antibiotic use.[378] All individuals with CF who used IPV for the duration of the study reported they would continue with the device if given the opportunity.

A short-term randomised cross-over study compared the efficiency of IPV with conventional chest physiotherapy and high frequency chest wall compression (HFCWC).[361] All three treatment regimens had similar short-term efficacy in terms of sputum clearance with no positive or negative preference for comfort or convenience.

A Cochrane review concluded that there was uncertainty as to whether conventional chest physiotherapy improves lung function compared to IPV due to very low-certainty evidence. There was no difference in results for number of days in hospital for an exacerbation, number of hospital admissions and number of days of IV antibiotics when comparing physiotherapy modalities.[65]

Whilst IPV manufacturers claim improved distribution of nebulised medications there are studies which report that, in healthy adults, IPV produced lower lung deposition of radiolabelled aerosol and had more inter-individual variability than a jet nebuliser.[380,381]

It is advised that the circuit is dissembled and thoroughly cleaned and disinfected every 48 hours. There are disposable single patient circuits available, and the non-disposable parts must be ethylene oxide sterilised, pasteurised, or autoclaved between patients.

Portable IPV units are available with single patient consumables, and instructions for on re-use to avoid stringent cleaning processes for use at home.

6.7.1 Recommendation

- Consider IPV when recommending an ACT for adults with mild to moderate CF *(QoE – very low)*.

6.7.2 Good practice points

- IPV is a costly airway clearance device that requires ongoing purchase of consumables such as tubing, filters and interfaces and servicing of the device is recommended at regular intervals. As a result, these devices are not considered a convenient long-term airway clearance strategy, and this should be taken into account when considering this device.
- IPV could be considered when other ACTs have proved unsuccessful or if fatigue is a problem for a person with CF with advanced or complex airway disease, presence of thick, tenacious secretions or for areas of unresolved consolidation despite conventional management.
- Consider combining or alternating IPV with other ACTs to maximise effectiveness such as ACBT, modified PD or AD.
- When using IPV, consider also using the device for the inhalation of mucoactive drugs such as hypertonic sodium chloride to combine effect or improve tolerance.
- IPV settings should be tailored to the individual depending on clinical presentation and tolerance. Consider starting on low pressures for comfort and build up as tolerated until chest wall movement can be felt at the base of the thorax. Start with a high oscillating frequency (high cycles per minute) to break down mucus and shear secretions from the airway walls, then change to a low frequency (low cycles per minute) as the treatment progresses to promote migration of secretions centrally and enhance alveolar ventilation.
- Contraindications to IPV include untreated pneumothorax, haemoptysis, rib fractures, and active tuberculosis infection.

6.7.3 Research recommendations

- Effectiveness of portable units compared to hospital IPV devices.
- PROMs using IPV.

6.8 Postural drainage (PD) and manual techniques

PD with the addition of manual techniques, sometimes called conventional chest physiotherapy, was the first ACT recommended for people with CF and continues to be used by some individuals,[305] usually in combination with other ACT such as ACBT or PEP.

6.8.1 Postural drainage (PD)

PD involves an individual taking certain positions to drain different sections of the lungs, with 12 specific positions identified.[382] The positions use the effect of gravity to enhance mucociliary action, moving peripheral secretions to the more central airways for easier clearance.[382,383] PD has been shown to improve regional ventilation[312] and can be a helpful adjunct to airway clearance in situations of lung abscesses or localised pathology. PD is a passive technique, reliant solely on gravity and regional ventilation changes from altered position. The addition of breathing exercises, huffing, and coughing is key to utilising PD effectively.

While traditional PD positions include a head-down tip to enhance drainage from the lower lobes,[382] more recent research highlights that tipped postures can aggravate gastro-oesophageal reflux and lead to a risk of aspiration.[61] Modified PD positions are now used with no head-down tip to limit this risk. Though limited, the evidence for modified PD has shown equal efficacy to traditional PD positions, fewer risks of long-term respiratory complications and less episodes of dyspnoea.[63,384]

6.8.2 Manual techniques

Percussion or clapping and expiratory vibrations or shaking over the chest wall can be added to PD to enhance the clearance of secretions.[305,312,346] Percussion consists of rhythmical clapping on the chest wall with a cupped hand, usually during deep breathing;[346] this can be completed by the individual or by a helper. Vibrations and shaking both involve oscillations of the chest wall in an inwards direction during expiration from a maximal inspiration, shaking being a larger movement, while vibrations involve a finer oscillatory motion.[346]

The exact physiological mechanism of manual techniques has not been ascertained.[346] Murray likened it to a ketchup bottle[385] – by applying force to the outside of the bottle (like the chest wall), it encourages the ketchup (the secretions) to be moved up the bottle to be expelled. This theory would also be enhanced by tipping the bottle (as with PD). It has also been suggested

that percussion generates differing airflows which create shearing forces within the airways beneath the percussed section, loosening secretions and enhancing mucociliary clearance.[346,386]

Combining modified PD and manual techniques can take away an individual's independence with airway clearance, while being burdensome on helpers to complete. Self-percussion is possible but often distracts from the more principal element of breathing exercises; different physiotherapy techniques should be discussed with medically well or minimally productive people with CF.

However, those with end-stage lung disease or severe infective exacerbations may find modified PD with or without manual techniques helpful in combination with ventilatory support such as NIV, as this may help mobilise secretions while reducing individual effort. This technique is used by physiotherapists during acute exacerbations requiring inpatient admissions. Modified PD and manual techniques can also be considered for use with individuals who cannot actively participate in self-administered ACTs and time should be given to effectively teach care givers.

6.8.3 Research evidence for PD and manual techniques

The addition of percussion to PD has been shown to enhance the removal of secretions in a small sample of patients who had copious secretions.[387] Vibrations have been shown to significantly increase PEFRs over relaxed expiration,[388] and there is some evidence that high frequency oscillations can decrease the viscoelastic properties of mucus and enhance mucociliary clearance.[312,389] The addition of PD and percussion to the FET has been shown to slow the annual rate of decline in lung function compared to FET only or no completed airway clearance.[390,391]

The literature highlights some potential detrimental effects of traditional PD and percussion, including hypoxic episodes, bronchospasm, and increased gastro-oesophageal reflux.[392–394] Care needs to be taken when treating people with raised intracranial pressures, cardiac rhythm changes, newborns and immature infants.[346]

6.8.4 Recommendations

- Consider modified PD and percussion as an adjunct to other ACTs for people with CF with copious secretions *(QoE – very low)*.
- Consider modified PD and percussion as an adjunct to other ACTs for people with CF with lung abscesses or specific regional pathology *(QoE – very low)*.
- Consider modified PD and percussion as an adjunct to other ACTs for people with CF who are unable to complete effective self-administered ACTs either due to age, cognition, severity of disease or fatigue *(QoE – very low)*.

6.8.5 Good practice points

- When utilising PD, modified positions which avoid a head down tilt are recommended, especially for infants and those with identified gastro-oesophageal reflux. People with CF opting to use head-down positions for airway clearance should be offered further education and an effective alternative.
- Modified PD should be combined with an ACT to enhance ventilation and expiratory flow.
- Modified PD can be considered for people with CF who, due to their age or disease progression, cannot be as independent or active a participant in their usual airway clearance regimen.
- Modified PD can be considered for people with CF with lung abscesses or specific regional pathology.

6.9 Intermittent positive pressure breathing (IPPB)

Traditional IPPB equipment (commonly referred to as the 'Bird') is now no longer manufactured, which will make traditional IPPB obsolete as a treatment option in the near future. This guideline is intended to inform practice for Centres which currently have access to traditional IPPB equipment and to offer insight into newer forms of IPPB equipment.

IPPB is an established technique in physiotherapy airway clearance clinical practice.[395] Its clinical use through the Bird, was first described in the late 1940s. As time progresses, although IPPB specific devices will not be as widely available, the principles of treatment can be transferred and used with other devices. For example, cough assist machines or NIVs can help with some elements of support, such as inspiratory effort management. There are also new machines being developed that may have effects similar to those of IPPB, such as the Alpha 300 (available through Air Liquide Healthcare) and the IPPB mode of the NIPPY Clearway 2 (available through Breas), although currently evidence for the use of these machines in CF is limited.

IPPB is used in spontaneously breathing patients and involves patient-triggered delivery of positive airway pressure during inspiration, usually with a mouthpiece. Airway pressure then returns to atmospheric pressure during expiration. Flow rate can be adjusted for comfort, which may vary throughout active and rest phases of an airway clearance session. It is possible to attach a positive end expiratory pressure (PEEP) valve or OPEP device to the expiratory port of the traditional IPPB circuit to deliver additional PEP or OPEP effects.

IPPB requires either compressed oxygen or air as a driving gas making it a treatment unsuitable for home use. Careful consideration needs to be given to the most appropriate driving gas selection particularly in people with CF with established chronic hypercapnic respiratory failure, given that the lowest oxygen concentration possible is approximately 45%.[396] NIV support may be a better option for these patients, allowing longer duration of pressure support if clinically indicated, and more precise titration of any additional oxygen requirement.

The dry compressed driving gas must be humidified via a nebuliser in the circuit. Clinical practice guidelines acknowledge that there is no evidence demonstrating superiority of IPPB to delivered bronchodilators over metered dose inhalers (MDI) or conventional jet nebuliser systems. However, when all other validated systems have failed, IPPB delivery in individual patients may be carefully considered.[397]

IPPB has been reported to increase tidal volumes and therefore minute ventilation, and to reduce work of breathing. Expert patient assessment and instruction is required to ensure that the positive pressure is delivered to a relaxed patient who is not fighting the IPPB machine. Circuits are intended for single patient use and must be disposed of after the individual has discontinued this treatment. All non-disposable parts of the equipment must be appropriately decontaminated in line with manufacturer's instructions and local infection control policy.[397] Contraindications for the use of positive pressure, such as haemoptysis and pneumothoraxes, apply to the use of IPPB.

Gates et al conducted a retrospective study of the use of IPPB in adults with CF who were admitted due to acute exacerbation over a period of five months.[398] Out of the 39 patients that were admitted, 12 received IPPB in combination with AD. For some patients PEP and OPEP devices were also combined with IPPB. The indications for use were impaired sputum clearance, increased work of breathing and lobar collapse. Whilst this study recognises the need for further prospective studies it highlights this as a potential technique that may be useful for acute exacerbation management.

When considering newer systems, a conference abstract by Brown et al reports a comparison of the Breas NIPPY Clearway 2 to traditional IPPB in ten adults with CF admitted for management of a pulmonary exacerbation. No difference in the volume sputum expectorated was observed, with IPPB marginally preferred with the Clearway 2 requiring higher flow rate settings. The authors concluded the NIPPY Clearway 2 was a potential alternative to traditional IPPB.[399]

6.9.1 Recommendations

- The NIPPY Clearway 2 can be considered for use as an alternative IPPB device for people with CF *(QoE – very low)*.

6.9.2 Good practice points

- Due to the lack of published clinical trials investigating IPPB use in CF, the clinical decision-making of the physiotherapist must be informed by the pathophysiology, the clinical status and an in-depth knowledge of the advantages and disadvantage of the available equipment and operator competence.[395]
- IPPB and circuit cleaning and appropriate decontamination must be done in conjunction with national and local infection control policies.
- Use 0.9% saline to provide humidity to the IPPB driving gas. Hypertonic sodium chloride can be used if additional mucolytic effect is required.
- An OPEP device or PEEP valve may be added on to the expiratory port in the traditional IPPB circuit, which may enhance mucociliary clearance.
- Alternative devices which deliver IPPB can be considered, although further investigation into their efficacy is required.

6.10 Simeox®

The Simeox® device delivers targeted pneumatic vibratory stimulation to the bronchial tree during relaxed exhalation. This stimulation involves a series of intermittent negative pressure pulses at either 6 or 12Hz. These pulses generate shearing forces on mucus, facilitating its liquification, while suction forces help to remove it. As a result, mucus is mobilised in the distal airways and transported to more proximal airways to facilitate expectoration.[120,400,401]

The proposed methods of action of the Simeox® device include:

- liquefying airway mucus to facilitate expectoration
- mobilisation of mucus from distal airway areas
- prevention of airway collapse during drainage.

The Simeox® user manual specifies no absolute contraindications for use however, it highlights undrained pneumothorax, massive haemoptysis, and unstable cardiovascular pathologies as relative contraindications, necessitating additional discussion with a HCP before initiation or continuation of use.[401] Although these contraindications have not been extensively explored in current literature, they may present an alternative ACT for people with CF when other adjuncts are unsuitable due to contraindications.

Several studies have looked at the effect of the Simeox® device on children and adults with CF, however the evidence is limited due to small sample sizes a varied use of outcome measures and some studies being performed during exacerbation and some when individuals were stable. Additionally, the available studies either did not report or utilised differing intervention cycles, providing inconsistent evidence for how and when best to use the device with people with CF.

The studies do however provide good safety data for the use of Simeox® in CF. Many report patient preference and improved QoL on CFQ-R questionnaire and show evidence to support patient choice with treatment in relation to improved adherence.

6.10.1 Adults

Trials focusing on use within adult populations including people with CF and non-CF respiratory conditions reported high adherence (80.9%), improved QoL and high satisfaction scores (9/10, on a 10-point visual analogue scale) including preference for use over traditional ACT (73%). No significant improvements were found in respiratory function, but a trend towards increased sputum expectoration during first use of the device were reported (41.1 ± 22.1g versus 27.5 ± 15.6g). Importantly, no adverse effects were reported during these studies and one study showed feasibility for considering use of Simeox® for people with CF opting to be monitored virtually by health care professionals.[402,403]

6.10.2 Paediatrics

Studies within paediatric populations reported improved patient comfort, QoL, preference (73%) and respiratory parameters versus traditional ACT. Positive effect has also been reported with Simeox® when combined with other ACTs (AD with AD belt and Simeox® or alongside traditional ACT).[329] The limited data suggested that participants younger than 10.5 years benefited more optimally compared to older participants, with an FEV_1 gain of 8%. As seen within adult studies no adverse effects were reported.[120,400,404,405]

6.10.3 Recommendations

- Simeox® is deemed a safe adjunct to traditional ACT for both children and adults with CF. It has demonstrated stability or improvements in lung function, health-related QoL, and patient comfort and preference. However, current literature suggests a preference for its use within younger cohorts *(QoE – moderate)*.
- Virtual follow-up of Simeox® usage is likely to be effective when conducted by a physiotherapist. This approach can ensure proper adherence, address any concerns, and optimise therapy outcomes remotely *(QoE – low)*.
- Since an increase in sputum weight was observed after the first use of Simeox®, it could be considered for induced sputum protocols. This suggests that Simeox® may have a role in facilitating sputum clearance, which could be particularly relevant in research or clinical settings where induced sputum collection is necessary for diagnostic or therapeutic purposes *(QoE – low)*.
- Simeox® may be useful if offered as an alternative to an individual's usual adjunct during exacerbation to offer them variety in treatment options and potentially improve adherence to treatment *(QoE – moderate)*.

6.10.4 Good practice points

- Centres should have **online training** from the Simeox® rep to explain technique and how to best teach people with CF, particularly children.
- Whilst literature may not yet provide clear guidance on which people with CF may benefit most from its use, individual preference is likely to be a significant factor in decision-making. Assessing these practical aspects can help healthcare providers determine the feasibility of integrating Simeox® into care plans.

6.10.5 Research recommendations

- Development of robust multicentre protocols, clearly outlining device usage parameters and encompassing non-stable participants. Given the current unavailability and cost constraints of the device within the UK, there is a crucial need for the publication and sharing of case reports. These reports should comprehensively detail participant selection criteria, common indications, and preferred settings in both paediatric and adult Centres. Such transparency may facilitate funding procurement for these devices, enabling their adoption for home use if they prove preferable to other forms of ACT.
- Production of case study publications detailing device usage in the presence of both absolute and relative contraindications could provide valuable insights. These publications would offer reassurance to people with CF and their CF teams by helping to determine the benefits and risks of device use.

7. Sinus disease

The most common upper-airway disorder in people with CF is chronic rhinosinusitis (CRS), developing secondary to mucus hyper-viscosity and impaired mucociliary clearance.[406] Decreased mucosal secretions, thickening of mucus and impaired mucociliary clearance are responsible for local inflammation and increased risk of bacterial infection.[407]

The unified airway concept is a framework for the understanding and management of the upper and lower airways as one integrated physiological unit. The sinonasal and bronchopulmonary systems have an interdependent physiological function, and inflammatory conditions that impact one system tend to impact the other similarly.[408] Infections often originate in the paranasal sinuses and can be responsible for temporary or chronic lung infections in people with CF.[409]

The prevalence of sinonasal complications in people with CF has gradually increased as CF life expectancy increases, which may influence pulmonary exacerbations and have a negative effect on QoL.[410] There is still a substantial variation in the prevalence and reporting of symptoms with CRS. Radiological evidence suggests that every person with CF has CRS but only 37.3% of patients report sinus symptoms, suggesting symptoms are significantly under-reported.[406,411–413] This may be because these symptoms are present early in life and children adapt to them.[414] In children with CF, data suggests that CRS begins very early, with average age at onset of 5.4 years old, and then rapidly reaches its maximum state at the average age of 6.9 years old.[407]

It has been identified that people with CF with high-risk genotypes (Class I to III mutations) have more severe sinonasal symptoms than those with lower risk genotype (Class IV and V).[415,416] Homozygous F508del is associated with more severe CRS, presence of nasal polyps and a higher need for endoscopic surgery.[406] Individuals who are carriers for one defective CFTR gene may be more predisposed to developing CRS; a recent case report suggested that people with severe CRS with a single CFTR mutation and intermediate sweat chloride value (excluding CF), should be sent for further extensive CFTR genotyping to look for rare genes.[417]

7.1 Signs, symptoms, and investigations

7.1.1 Diagnosis

CRS is defined as inflammation of the nose and paranasal sinuses persisting for more than 12 weeks with one or more of the following:

- Nasal blockage.
- Nasal discharge.
- Decreased sense of smell.
- Facial pain or pressure.[418]

There is no universally accepted set of diagnostic criteria for CRS in people with CF. However, commonly used criteria involve assessing both objective imaging findings and subjective symptom assessment.[419] Nasal endoscopy is the best diagnostic method for rhinosinusitis with nasal polyps in children.[414]

Anatomically, people with CF often have hypoplastic sinuses, independent of previous surgery. A study on adults with CF demonstrated that 66% of the frontal sinuses were either aplastic or hypoplastic.[409] People with more severe extra-pulmonary manifestations of CF may also be at increased risk of CRS that requires endoscopic surgery.[420]

Nasal polyposis in people with CF becomes more common as children age with a prevalence of up to 50% in adolescents.[409] CFDM is associated with nasal polyposis recurrence.[421]

7.1.2 Objective measures

Most people with CF have characteristic CT findings from early childhood.[409] A poor correlation has been found between patient-reported symptom scores and the severity of disease assessed by CT scans suggesting that CT scan findings should not be relied upon as the main objective measure, as they do not accurately reflect an individual's symptom burden.[422]

Several studies show that CRS has a negative impact on life productivity, pulmonary health, and sense of smell, indicating a negative influence of CRS on overall wellbeing.[421]

The Sinus and Nasal Quality of Life Survey (SN-5) (**Appendix IIa**) is the only validated symptom questionnaire for children ages 2–12. Parents complete the SN-5 for their children.[409,423] Multiple studies support the use of the validated SNOT-22 (**Appendix IIb**) as a tool to identify sinus disease

in adults with CF. This tool assesses severity, outcomes following treatment, and prompts referrals to ENT colleagues.[424–427]

7.1.3 Microbiology

There is a complex relationship between the microbiology of nasal and lung cultures in children with recent evidence suggesting a low to moderate concordance.[428] Given the discrepancy between sinus and pulmonary cultures, upper respiratory cultures should not act as a surrogate for lower airway cultures in young children.[429] It has been suggested that concordance between the microbiology of nasal and lung cultures increases with age, however. Nasal sinuses may act as bacterial reservoirs, potentially transmitting pathogenic microorganisms to the lower airways.[430]

Research has indicated that children with CF with no symptoms have paranasal sinus infections, demonstrating the importance of monitoring and managing CF in children, whether or not they exhibit symptoms. Consequently, it may be wise to routinely monitor paranasal sinuses for all children with CF, involving the collection of samples during each outpatient clinic visit (**Appendix IIc**).[431,432] A protocol for collecting a nasal rinse sample is also described by Mainz et al.[430]

It has been reported that 80% of people with CF tested positive for at least one bacterial species in nasal lavage, with *Staphylococcus aureus* being the most prevalent.[428] Gene sequencing identified *P. aeruginosa*) and *S. aureus* as abundant in CRS, with other bacteria present (including *Haemophilus influenza*, *Achromobacter*, *Burkholderia*, and *Streptococcus*).[433] Younger individuals had greater bacterial diversity and tended to grow *S. aureus* and *H. influenza* with a transition to *P. aeruginosa* with increasing age.[24]

Positive fungal sinus cultures were found in 21% of children undergoing sinus surgery.[434] It has been suggested that children with CF and children with nasal polyps have more frequent positive fungal cultures than children without nasal polyps having sinus surgery.

7.2 Management

CRS in CF is challenging to treat due to factors like increased mucus viscosity, chronic infections, and distinctive pathogens. A major goal in the treatment of CF is to prevent or delay chronic lung infections including bacterial colonisation of the lung from the sinuses.

Despite lack of high-level evidence, it remains clear that people with CF require specialised management of their sinus disease to both prevent CRS progression and improve pulmonary outcomes. While there are no 'gold standards' in the treatment of CF-related sinus disease, it often includes combination therapy including medication (**Appendix IId**), nasal irrigation and endoscopic sinus surgery.

7.2.1 Sinonasal washout

Sinonasal washout, also called nasal irrigation and sinus rinsing, aids the clearance of secretions, increases efficacy of topical medications and provides symptom relief.[406] Washout alone, or with other adjunctive measures, may improve QoL, decrease symptoms, and decrease medication use, particularly in people with frequent sinusitis.[435] Although various methods exist, the squeeze bottle and neti pot seem to provide the best delivery to the paranasal sinuses.[436] Nasal irrigation can be performed using either a homemade saltwater solution or a solution made with sachets bought from a pharmacy.

In studies comparing the use of isotonic saline and hypertonic sodium chloride solutions, isotonic solutions are preferred due to fewer adverse events, with supporting evidence for 0.9% saline solution.[406,437]

7.2.2 Sinus nebuliser therapy

Sinonasal inhalation of vibrating aerosols is a recognised method of delivering mucolytics and antibiotics directly to the paranasal sinuses.

Evidence supports the use of a sinus-specific nebuliser such as PARI SINUS over a standard nebuliser. The PARI SINUS device delivers topical nebulised solution particles to the nasal cavity through vibrating aerosol inhalation.[411,438] Nebulisation with the PARI SINUS nebuliser aims to reduce pathogen colonisation and is well-tolerated.[439]

Several studies have investigated the effects of mucolytics. Some have compared the effectiveness of 0.9% saline with 6% hypertonic sodium chloride and found improvements in SNOT-22 results in both groups, with no significantly better results from 6% hypertonic sodium chloride than 0.9% sodium chloride.[440]

Nebulisation of 2.5mg dornase alfa (Pulmozyme®) via the PARI SINUS has been shown to positively affect both symptoms and QoL in comparison to isotonic saline.[406,438]

Evidence suggests tobramycin via the PARI SINUS or colistin via irrigation may be effective at reducing *P. aeruginosa* infection.[441,442]

7.2.3 Medication

Topical steroids are effective and can be used safely with minimal systemic effects.[411] They can be delivered as a nasal spray or drops and are frequently recommended to help reduce symptoms and improve QoL.[411,443] The correct positions for nasal spray and nasal drop delivery, outlined in Appendices IIe and IIf, are recommended to enhance effective application of treatment. The MYGIND position with the head over edge of a bed to enhance gravity is used for nasal drop delivery[406] (**Appendix IIf**).

7.2.4 Other non-surgical treatment options

There are a number of other treatments suggested for symptomatic relief of CRS, including:

- dry-needling
- myofascial release
- sinus massage
- ultrasound
- OPEP (RC-Cornet), and auto-inflation devices (Otovent).

The evidence for these treatments is limited and further research is required.

7.2.5 Surgery

Surgical intervention such as endoscopic sinus surgery (ESS) should be reserved for people with persistent symptoms despite maximal medical therapy.[438] Recent evidence supports ESS followed by intensive post-operative medical therapy, but overall high-level evidence is lacking.

Several studies have evaluated the effect of sinus surgery on pulmonary function with divergent conclusions. Sinus surgery is recommended for people with CF without chronic lung infection or with a transplanted lung to eradicate Gram-negative bacteria in the paranasal sinuses, thereby avoiding or preventing re-colonisation of the lungs.[409]

7.2.6 CFTR modulator therapy

The literature on CFTR modulators has suggested that objective and subjective improvements are observed in CF sinus disease with the use of elexacaftor/tezacaftor/ivacaftor (Kaftrio®). These include improvements in bacterial cultures, endoscopic appearances, imaging, symptoms, and QoL.[413,444–446]

Endoscopic findings have improved in both children and adults with Kaftrio®, observed after a nine-month period. Changes included resolution of crusting, and a resolution or decrease in size of polyps.[447] Lack of Kaftrio® is associated with people pursuing endoscopic sinus surgery.[448]

CT scan changes observed after Kaftrio® include improvements in opacification, mucosal thickening, and radiologic scoring systems (Lund-Mackay and Sheikh-Lind).[413,447,449–452] CRS-MRI scores also improved with Kaftrio®, thought to be due to a reduction in mucopyoceles in the sinuses.[453,454] One study reported a potential for structural reversibility, and another that lumacaftor/ivacaftor (Orkambi®) may prevent an increase in paranasal abnormalities in pre-school children.[453,454]

SNOT-22 scores improve relative to baseline as soon as seven days after commencement of Kaftrio® in both adolescents and adults with CF and remain improved above the MCID for up to two years in adults.[447,449] In one study, median SNOT-22 scores were 36.5 pre-therapy, and 20 after six months of modulator therapy.[455] SN-5 scores show a similar improvement, with average scores improving from 13.67 to 7.67, after an average of 249 days.[456] Improved SNOT-22 scores have been correlated with improved CT scan scores.[452] Some studies report a plateau in the improvement of symptoms, with one suggesting the plateau occurs as early as 28 days after starting modulator therapy.[447,449]

QoL measured by the five-dimensional EuroQoL questionnaire improves in adults with CF after commencing Kaftrio®, which translated to an improved health utility value or overall health status.[449,451] The improvement in health utility value remained above the MCID for up to two years.[449] Overall productivity improved by 22% after two years of Kaftrio®.[449]

Studies found that Kaftrio® reduces bacterial colonisation for *P. aeruginosa* and methicillin-resistant *S. aureus* in oropharyngeal samples, and a reduction in sino-pulmonary related infection visits and antibiotic therapy over a 15-week period.[128,451]

Investigation into the long-term benefits of CFTR modulator therapy in CF is still ongoing. The evidence for the use of Kaftrio® in CF sinus disease is promising, but most of the studies have been observational.

As the life expectancy and prevalence of CRS continues to increase in CF, optimal management should consist of MDTs that are familiar with CF-related sinus disease.[457]

7.3 Recommendations

- Consider using the SNOT-22 outcome measure as a quick, inexpensive and validated questionnaire for assessing and monitoring CRS in adults with CF *(QoE – moderate)*.
- Consider using the SN-5 outcome measure as a quick, safe, and reliable qualitative survey for assessing and monitoring sinonasal symptoms in children with CF *(QoE – low to moderate)*.
- Consider regular nasal sampling to detect sinus infection at an early stage as an important step towards eradication *(QoE – moderate to low)*.
- Consider referral for nasal endoscopy for the best method for the diagnosis of CRS with nasal polyps in people with CF *(QoE – moderate to high)*.
- Consider sinonasal inhalation of dornase alfa to help improve sinonasal symptoms *(QoE – high)*.
- Consider sinonasal inhalation of antibiotics such as tobramycin to reduce bacterial colonisation, reduce exacerbations and relieve symptoms *(QoE – low)*.
- Consider using sinonasal saline washout to improve symptoms and QoL *(QoE – moderate)*.
- Consider using topical steroids for symptom relief *(QoE – low)*.

7.4 Good practice points

- People with CF should be screened for symptoms of CRS at least annually or more frequently if symptoms persist or as an outcome following treatment.
- Physiotherapists should be aware of sinonasal nebuliser equipment to be able to offer the most appropriate delivery system.
- Physiotherapists should understand nasal inhalation devices and have an awareness of how to administer them correctly.
- Physiotherapists should be aware of existing treatment regimens and enable individual choice to optimise adherence to treatment.
- Tailored adjunctive treatments, including dry needling, myofascial release, sinus massage, ultrasound, OPEP (RC-Cornet), and auto-inflation devices (Otovent), may be integrated into care plans when appropriate resources and expertise are available, aiming to improve specific sinus symptoms and overall wellbeing.
- Independent prescribers should consider adding medication for CRS to their core formulary.
- Symptoms of CRS should be monitored before and after CFTR modulator therapy.
- Recognise that CRS remains very sensitive to medical and surgical treatment during childhood.

7.5 Research recommendations

- The prevalence of methicillin-resistant *S. aureus* in sinus cultures of children with CF has increased over time and warrants further investigation.[429]
- Further research is required to determine if frequent positive fungal cultures in children with nasal polyps represent colonisation or contribute to the inflammatory environment of the airways.[409]
- Further research is needed to establish the potential benefits of tobramycin via the PARI SINUS or colistin via irrigation in reducing *P. aeruginosa* infection.
- The evidence for alternative treatments such as dry-needling, myofascial release, sinus massage, ultrasound, OPEP, and auto inflation devices in the symptomatic relief of CRS is limited and further research is required.
- More high-quality research is required to enhance the body of evidence for the use of CFTR modulator therapy in people with CF with CRS.

8. Inhalation therapy

Delivering medication via the inhalers and nebulisers has potential advantages:

- Medication is delivered straight to the target area of the lungs.
- A higher concentration is achieved at the site of action.
- There is less systemic exposure when compared to oral or intravenous treatment.[458,459]

Some medications are only available in inhaled form, while for others inhaling the medication may be safer, more acceptable and more practical to deliver than other modes of delivery. There is growing evidence that the direct targeting of some therapies to the site of action may be more effective.[459] A wide range of medications may be delivered by the inhaled route and various inhaler and nebuliser devices are available to do this.[460] **Appendix IIIh** gives the details of commonly used inhaled medication in CF.

Managing the practicalities of inhaled therapy such as the choice of medication, drug response assessment (see **Appendix IIIa** and **IIIb**), device selection, device provision, education and monitoring is frequently done by physiotherapists.[461,462] This is logical given the timing needs of some medications around airway clearance and that many inhalation devices require breathing pattern and cough suppression training. With the advent of independent and supplementary prescribing for physiotherapists, prescriptions for inhaled medication are often completed and monitored by the physiotherapist.[462]

There has long been consensus and guidance in the use of inhaled therapy for people with CF,[18,463–472] for example inhaled therapy for eradication or long-term suppression of *P. aeruginosa*. However, the introduction of CFTR modulators has created some uncertainty about the use of inhaled medication in the management for this group of people. Clinicians should be aware that research is ongoing and it is important that we carefully identify the characteristics of participants in research studies to ensure the results are transferred appropriately to clinical practice. These results will impact commissioning, guidance and formularies, making it imperative that the most up-to-date documents are referred to when treatment decisions are made.

8.1 Medication

There are documents and online advice which guides the use of inhaled therapy for people with CF[18,463–472] and other local and regional policies. Before CFTR modulators, it was accepted that there was good evidence that inhaled therapies were both clinically and cost-effective.[18,463] Research is underway in those prescribed CFTR modulators to ascertain new best management approaches.[473–476]

There is little guidance about the use of bronchodilators or inhaled corticosteroids for people with CF. Cochrane reviews suggest that short acting bronchodilators may be beneficial in individuals with demonstrable bronchodilator responsiveness or bronchial hyper-responsiveness,[469] but that there is poor evidence for the use of long-acting beta$_2$ agonists or long-acting muscarinic antagonist bronchodilators for people with CF.[470] The withdrawal of inhaled steroids evaluation study by Balfour-Lynn et al suggests that inhaled corticosteroids are best reserved for people with an additional diagnosis of asthma.[471]

Historically there has been clear guidance around the use of mucolytics and hyperosmolar agents.[18,463,465,466,472] People with CF who have clinical evidence of lung disease should be prescribed dornase alfa as the first choice of mucoactive agent.[18,463,466] If clinical evaluation or lung function testing indicates an inadequate response to dornase alfa, combining with or changing to hypertonic sodium chloride is recommended.[466]

NICE recommends mannitol dry powder for inhalation as an option for adults with CF who fulfil all of the following criteria:

- Unable to use dornase alfa because of ineligibility, intolerance or inadequate response.
- Lung function rapidly declining (FEV_1 decline greater than 2% annually).
- Other osmotic agents are not considered appropriate.[465]

It may also be considered for children and young people who cannot use dornase alfa and hypertonic sodium chloride because of ineligibility, intolerance or inadequate response.[465] Additionally, there is good evidence for the use of hypertonic sodium chloride for sputum induction and/or improving the quality of airway sampling.[138]

The evidence for these current recommendations was completed before CFTR modulator availability. Studies are underway to identify the effects of rationalising mucoactive therapies in people prescribed CFTR modulators.[473–476] These studies take different approaches and focus on different populations of people with CF. One study, SIMPLIFY, has completed and published. The results suggest that dornase alfa or hypertonic sodium chloride may be withdrawn without meaningful short-term clinical deterioration for people taking Kaftrio® with well-preserved lung function.[474] Average FEV_1 for participants was 96.9% predicted.[474] Care should be taken when applying these results in clinical practice. Clinicians may wish to take an individualised approach while research continues for those prescribed CFTR modulators.

CFTR modulators have had a limited impact on the prescribing of inhaled antimicrobial regimens.[477] People should be prescribed inhaled antibiotics for the eradication of *P. aeruginosa*;[463,466] those with chronic *P. aeruginosa* infection should have sustained treatment with an inhaled antibiotic.[18,463,466] For people who have chronic *B. cepacia* complex infection and declining pulmonary status, sustained treatment with an inhaled antibiotic should be considered to suppress the infection.[18,463,466] Inhaled antibiotic therapy is also recommended within certain treatment regimens for NTM[478]. The FORMaT study is currently underway to compare different treatment regimens for eradication in *M. abscessus*.[479]

There is no clear guidance about continuing or discontinuing inhaled antibiotics while the person is on IV antibiotics. There is some evidence for the use of inhaled antibiotics alongside an IV antibiotic for acute exacerbations.[480]

For specific recommendations see the appropriate clinical commissioning policy, local formulary and guidelines for your area and relevant CF Trust guideline.

8.2 Bronchodilator trials

It is recommended that spirometry is used to assess the initial response to bronchodilators,[469] with regular reassessment to ensure this response is maintained.[481] **Timings and suggested significance of FEV_1 change of post-dose spirometry depends on the medication given:[482]**

- An increase of 15% in FEV_1 or $FEF_{25–75}$ 15 minutes following inhalation of a $beta_2$ agonist.
- An increase of 15% in FEV_1 or $FEF_{25–75}$ 30 minutes after an anticholinergic agent.

The approved bronchodilator trial protocol is outlined in the Association for Respiratory Technology and Physiology guidance.[103]

8.3 Drug response assessment (DRA)

Inhaled antibiotics, dornase alfa and hyperosmolar agents such as mannitol dry powder for inhalation and hypertonic sodium chloride may cause bronchoconstriction.[483,484] The SPC of many of the commonly used inhaled antibiotics and mannitol dry powder for inhalation specify the need for a DRA.[485–494] Although this is not stated for dornase alfa,[495] there are case reports of bronchoconstriction and the NHSE inhaled commissioning policy advises a DRA.[466] The need for a DRA is also not stated for inhaled levofloxacin although bronchoconstriction is listed as an uncommon side effect.[496] As hypertonic sodium chloride is classified as a medical device and not a medication, there is no SPC but there is evidence of the potential for bronchoconstriction so a DRA is recommended.[497]

The SPC for Bronchitol[485] provides clear methodology for completing an initiation dose assessment to ensure safe and effective administration of a test dose. For all other medication a decrease of more than 10–15% FEV_1 or $FEF_{25–75}$ following inhalation defines significant bronchoconstriction.[18,460,461] Should this occur, a further test dose with pre-medication of a bronchodilator is advisable.[18,460,461,485–494,498] Appendices III a, b and d describe and provide a template and competencies for the DRA procedure.

There is the potential for bronchial hyper-reactivity to inhaled medication once long-term treatment is established. Processes should be in place to ensure ongoing monitoring for subjective and/or objective bronchoconstriction to inhaled medications. It is considered good practise to retrial an inhaled medication that has not been used for one year or more. **Appendix IIIe** provides a framework for restarting inhaled medications under these circumstances.

8.4 Inhaler devices

There has been a large increase in the number of different types of inhaler devices available for bronchodilators, inhaled steroids and combinations of these medications. Different devices have different delivery characteristics and may require different inhalation techniques and inspiratory

flow rates to ensure effective use.[499] It is therefore important to understand the availability of particular medications through particular devices. Where delivery may be compromised, consider whether a valved holding chamber or an alternative device or medication would maximise the delivered dose. Environmental impact and cost-effectiveness are other key things for consideration when selecting an appropriate device-medication combination.

An assessment must be made of the person's ability to use a device before prescribing a medication – for example, prescribing terbutaline sulphate rather than salbutamol because a turbohaler would be preferable for an individual.[499] There have been developments in dry powder inhaler delivery with the NICE approval of dry powder colistimethate sodium, tobramycin and mannitol.[485,498] It has been recognised that completing a DRA and education, particularly around technique, are key when commencing these medications to assess suitability and limit side effects such as cough.

The NHS Business Services Authority state that medication delivered via an inhaler must be prescribed by brand rather than generically.[500] It is also helpful to think about the number of different medications and devices that a person with CF requires, and consider medication choices that limit these where possible.

8.5 Nebuliser devices

There are increasing types of nebuliser systems available. The most common types are conventional nebulisation systems, ultrasonic nebuliser systems, adaptive aerosol delivery nebuliser systems (AAD) and VMT nebuliser systems. There is little evidence to recommend one type of nebuliser device over another from randomised trials demonstrating improved clinical efficacy or patient preference. There is, however, an indication that new nebuliser technologies such as AAD and VMT are quicker and quieter than conventional systems. These devices may also provide better deposition[501] and more consistent dosing.[502] Further high-quality trials are needed to confirm these suggestions.[503]

Many new medications are licenced for administration with a specific nebuliser system, for example Cayston® with the PARI eFlow® or eTrack® and Altera® handset. It is important to note that different nebuliser systems have different delivery characteristics and therefore the delivered dose may vary depending on the device used. See **Appendix IIIh** for further information on recommended drug device combinations. Where a choice is made to deliver an inhaled medication through a device which is not named on the SPC, there must be consideration over whether there is sufficient data to ensure a safe and effective dose is delivered. There should be an awareness that delivering medications through an alternative device is an off-label use and should be discussed with the prescriber.

Where devices are changed, for example the Ineb® AAD devices are being discontinued, then a repeat DRA may be needed for an alternative device. Physiotherapists should consider if the delivery characteristics and delivered dose are likely to change with the alternative device and repeat the DRA as indicated. Education will need to be given about changes to the device and any associated changes with the priming dose of the medication. For example, moving from colistimethate sodium via an Ineb® AAD device to an eFlow® or eTrack® VMT device requires a change in priming dose from 1 million units in 1ml of liquid to 2 million units in 2mL in order to deliver an equivalent dose. It is also important to provide education on changes to aerosol output and the required adjustments to inhalation technique, particularly maintaining an effective mouth seal, as well as reassurance regarding the delivered medication dose when changing delivery devices.

It is helpful to consider the number of different medications and devices that the person with CF requires and consider medication choices that limit these. There are some possibilities around mixing medications to reduce treatment burden, but thought must be given around the legalities and appropriateness of doing so. **Appendix IIIh** provides a summary of medication compatibility.

8.6 Timing of medications

It is suggested that nebulised antibiotics are taken after physiotherapy and after bronchodilators to ensure best deposition and protection from bronchoconstriction.[460,461]

Questions remain around the optimal timing of dornase alfa. Studies have suggested that inhalation either before or after airway clearance is equally effective.[504,505] Others suggest that inhalation 30 minutes before airway clearance may improve small airway patency more than inhalation post-airway clearance.[506] Recognising the variation in the outcomes of these studies and the advances in CF management and lung health since they were conducted, advice around timing of dornase alfa with airway clearance should consider symptom burden (secretion load, tenacity and ease of clearance) alongside treatment burden when advising on optimal timing. There is also variation on the advised gap between administration of

dornase alfa and inhaled antibiotics varies across the UK and is largely based on the strongly held beliefs of physiotherapists and tradition.[507] The gap advised may impact the complexity of an individual's treatment programme, their treatment burden and adherence;[507] individualised treatment plans are recommended.

Hypertonic sodium chloride and mannitol dry powder for inhalation should be taken immediately prior to or during airway clearance as they are thought to have an immediate mode of action. This may be directed by individual preference.

8.7 Combining inhaled medication with ACTs

It is possible to combine some nebuliser devices delivering hypertonic sodium chloride with an airway clearance device, such as an eFlow® nebuliser with some PEP devices. Combining techniques is attractive as a strategy to decrease treatment burden and may also be driven by a wish to optimise deposition, but there is no evidence to firmly demonstrate these outcomes. People with CF may like combining airway clearance with nebulisation and find it less time-consuming,[303] but there is a suggestion that combining airway clearance devices with nebulisation may decrease lung deposition.[508] The addition of an airway clearance device to a nebuliser is not identified in the SPC of any nebulised medication and so this action creates an off-label use of the medication. Clinicians must consider whether there is sufficient data to ensure a safe and effective dose is delivered and discuss this with the prescriber.

8.8 Cleaning and maintenance of equipment

Advice about cleaning of inhalers can be found within the medication SPC or patient information leaflet.

Advice about cleaning of nebuliser devices can be found in the manufacturer's information such as handbooks. Appropriate cleaning and maintenance of nebuliser equipment is essential to avoid bacterial contamination of the equipment, to decrease the risk of acquiring pathogens and to ensure efficiency of the delivery of inhaled medication.[509–511]

Maintaining cleaning regimens can be particularly challenging in the hospital environment and thought should be given as to how appropriate regimens can be supported.[509,511] See **section 16** on infection prevention and control for more information.

8.9 Recommendations

- Inhaled medication (inhalers and nebulisers) must be prescribed by brand and not generically where possible *(QoE – moderate)*.
- A DRA should be performed to assess suitability and/or effectiveness of the inhaled medication for the individual *(QoE – moderate)*.
- Where bronchoconstriction is present on a DRA, a further DRA with pre-medication of a bronchodilator is advisable *(QoE – moderate)*.
- An assessment of the ability of the person to use an inhaler or nebuliser device should be made before commencing treatment *(QoE – low)*.
- Regular reassessment of the response to bronchodilators should be carried out where appropriate *(QoE – moderate)*.
- Consideration should be given to using intelligent nebuliser technologies such as AAD and VMT *(QoE – moderate)*.
- Relaxed tidal volume breathing through the mouth and not the nose is recommended for people using nebulised antibiotics through a conventional nebuliser system *(QoE – very low)*.
- Expiratory filters should be used when nebulising antibiotics to avoid environmental contamination, reduce exposure of others to the medication and to avoid damage to property *(QoE – very low)*.

8.10 Good practice points

- Physiotherapists should take into account the current lack of data for inhaled therapy in those prescribed CFTR modulators and consider the context of new research as it is published prior to applying it to wider groups of people with CF.
- Physiotherapists should remain up to date with national and regional commissioning policies related to inhaled therapy.
- Physiotherapists should remain aware of inhaler and nebuliser developments to ensure the most appropriate device for each medication is utilised.
- Physiotherapists must ensure that the medication and device issued to the

person are compatible and will deliver a comparable dose to the medication and device combination stated within the SPC.

- Appropriate education on the use, cleaning and maintenance of inhalation devices and treatment strategy should be given to the person with CF or their family or carers, and ongoing support provided.
- Off-label use of medication should be agreed with the prescriber.
- A mouthpiece offers advantages in lung deposition for some individuals, though a mask may be more suitable for those who cannot maintain a proper seal or require supplemental oxygen.
- The device and appropriate parts must be replaced appropriately and in accordance with the manufacturer's guidance.
- There should be ongoing monitoring for subjective and/or objective bronchial hyper-reactivity to inhaled medications once long-term treatment is established.
- A risk assessment should be considered acknowledging the potential for risks for pregnant staff and the potential for increased risk of respiratory irritation or allergic reactions for staff with hyper-reactive airways with exposure to aerosolised medicines during a DRA. Any identified potential risk should be further explored according to local risk assessment policies to determine appropriate actions.

8.11 Research recommendations

- Clinical consensus is needed on the recommended time between administering dornase alfa and inhaled antibiotics.
- The effects of reduced use of non-CFTR modulator treatments on the longer-term efficacy of CFTR modulators is uncertain and more research into this is needed.[512]

9. Oxygen therapy

Oxygen therapy is commonly prescribed for the treatment of hypoxaemia for people with CF. Chronic and recurrent airway infection and inflammation leading to progressive lung damage results in chronic hypoxaemia and can lead to cor pulmonale.[513] Episodic hypoxaemia can occur during sleep, exercise, air travel, at altitude, and during infective exacerbations of CF.[514]

Individuals with respiratory disease are most at risk of compromised gas exchange during sleep and exercise. The development of nocturnal hypoxaemia and hypercapnia are poor prognostic signs in CF.[515] Chronic hypoxaemia may up-regulate airway inflammation, contribute to persistence of *P. aeruginosa* infection and inhibit CFTR function.[514] There is no universally accepted method of measuring hypoxaemia in CF, leading to a lack of uniformity among published studies.[513]

There are currently no CF-specific guidelines to inform best practice regarding supplementary oxygen therapy in CF.

9.1 Supplemental oxygen

Oxygen therapy is associated with some adverse effects, such as suppression of respiratory drive and decreased mobility due to tethering to a device.[513] There are also psychological implications, including issues with self-image and increased burden of care.[514] Adherence to oxygen therapy may be poor if no benefit is felt and often improves when oxygen therapy provides symptomatic relief.[515]

The practical use of oxygen in CF is complex.[516,517] Supplemental oxygen has a role in emergency care, respiratory exacerbation, chronic long-term use, sleep and exercise. It can also be used with NIV, during air travel and at altitude. Oxygen requirements may differ during each of these situations and should therefore be assessed independently to ensure adequate oxygen prescription for each scenario. Physiotherapists may be involved in the assessment, set-up and monitoring of oxygen therapy in CF.

Further investigation into the role of supplementary oxygen in CF is required to determine the benefits of long-term oxygen therapy, administered continuously and during sleep and exercise, to inform when and how best to use oxygen therapy in the management of CF.[513,518] Optimal 'target oxygen saturations' in people with CF have not been investigated.[519]

The introduction of CFTR modulator therapy has resulted in rapid clinical improvement in some individuals with advanced disease. The number of patients requiring oxygen therapy has reduced and suggests a major impact on the life expectancy of people with CF. Longer term data is required, but this trend is likely to continue as further research allows earlier access to modulator therapies.

9.1.1 Emergency oxygen

People with CF may become critically ill and require emergency oxygen therapy, or may require supplemental oxygen during a hospital admission for an acute exacerbation. In adults with CF, the time spent with oxygen saturations lower than 90% is greater during an infective exacerbation than in the stable state.[514] Those with advanced CF may suffer from exacerbations similar to those in advanced chronic obstructive pulmonary disease (COPD), with associated hypoxaemia and hypercapnia.[519] There is limited CF-specific guidance on the use of emergency oxygen; much of the information available is extrapolated from COPD guidelines and other respiratory research.

9.1.2 Target oxygen saturations and delivery methods

It is recommended that emergency oxygen therapy is prescribed to achieve a normal or near-normal target oxygen saturation range of 94–98% for most acutely ill patients with no risk of hypercapnia.[519] Oxygen can be delivered by nasal cannula at 2–6L/min or face mask at 5–10L/min in this group.[519]

People with CF with advanced lung disease may demonstrate hypoxaemia and hypercapnia. Those at risk of hypercapnic respiratory failure should be prescribed emergency oxygen with a target oxygen saturation range of 88–92%,[519,520] delivered via 28% venturi mask at 4L/min, 24% venturi mask at 2–3L/m, or nasal cannula at 1–2L/min. If arterial blood gases then show a normal $PaCO_2$, the target oxygen saturation range can be adjusted to 94–98%.[519]

People with CF may demonstrate high respiratory rates when critically ill or during an infective exacerbation. Those with a respiratory rate greater than 30 breaths per minute may benefit from oxygen supplied via venturi mask with the flow rate increased by 50% above the recommended level, to ensure gas flow rate exceeds inspiratory flow rate.[519]

There is little evidence to support the use of humidification, but it may be beneficial in those who require high flow oxygen for more than 24 hours, those who experience upper airway

discomfort and dryness and those who have thick secretions that are difficult to expectorate. This can also be achieved with the use of nebulised normal saline.[519] Nasal high flow (NHF) systems can also be used to deliver humidified oxygen.[521]

9.1.3 Emergency oxygen and hypercapnia

Adequate oxygenation should be maintained and excessive hypercapnia and acidosis avoided.[519,521,522] In severe CF where there is evidence of acute respiratory failure, a trial of either NHF or NIV should be considered.[523]

Although not specific to CF, NHF has been found to reduce breathlessness, improve respiratory failure, reduce the need for NIV and reduce intubation rates significantly more than conventional oxygen therapy.[524–526] Individuals established on NHF should be closely monitored to ensure detection of treatment failure which includes a high respiratory rate, low SpO_2 and thoracoabdominal asynchrony.[525,527,528] The development of clinical guidelines to include flow settings, indications and contraindications is urgently needed.[524] Large, high-quality studies are required comparing NHF, conventional oxygen therapy and NIV.[525]

9.1.4 Arterial blood gases

Arterial blood gases are required when hypoxaemia is unexpected, oxygen saturations are deteriorating despite optimal management, there is increased breathlessness in previously stable hypoxaemia, or there are risk factors for hypercapnic respiratory failure.[519] For most people who require blood gas sampling, either arterial blood gases or arterialised earlobe blood gases may be used to obtain an accurate measure of pH and pCO_2. However, the arterial oxygen tension (PaO_2) is less accurate in earlobe blood gas samples, potentially underestimating the oxygen tension by 0.5–1kPa, so oximetry should be monitored carefully if earlobe blood gas specimens are used.[519]

9.1.5 Weaning supplemental oxygen

Oxygen should be weaned in stable individuals with oxygen saturations in the target range and discontinued when SpO_2 is within the target range on room air, on two consecutive observations.[519] Observations in stable individuals should be performed every four hours. SpO_2 should be monitored for at least five mins after any changes or after stopping oxygen.[519]

9.1.6 Recommendations

- CF Centres should have a local pathway or standard operating procedure for supplemental oxygen provision to enable timely assessment and facilitate a systematic and proactive approach to assessment and treatment planning, ensuring involvement of people with CF *(QoE – high)*.
- All people with CF requiring emergency oxygen should be admitted to a Specialist CF Centre. If this is not possible for geographical reasons, cases should be discussed and managed according to a protocol agreed by the Specialist CF Centre *(QoE – high)*.
- A target oxygen saturation range should be prescribed for all people with CF at time of admission *(QoE – high)*.
- Target oxygen saturations should be 94–98% unless there is risk of hypercapnic respiratory failure, in which case the target should be 88–92% *(QoE – high)*.
- NIV or NHF should be considered in people with acute respiratory failure with severe disease *(QoE – high)*.
- People with CF who have had hypercapnic respiratory failure should be given an oxygen alert card with recommendations for target oxygen saturation range and oxygen prescription based on previous blood gas measurements *(QoE – high)*.

9.1.7 Good practice points

- Oxygen supplied via venturi at a flow rate of 50% greater than the recommended flow rate may be beneficial in those with respiratory rates of greater than 30 breaths per minute.
- People with CF prescribed oxygen should be given an oxygen information sheet where possible.
- Consider nasal high flow in hypoxemic individuals with close monitoring for signs of treatment failure.

9.2 Long-term oxygen therapy

The progression of CF respiratory disease often results in chronic hypoxaemia and a myriad of complications associated with this. Long-term oxygen therapy (LTOT) is often prescribed to treat hypoxaemia and prevent these complications. Screening for hypoxaemia should be carried out regularly, especially in patients with severe CF.[523]

Published studies regarding oxygen in CF primarily concern the effects of nocturnal and ambulatory oxygen.[513,521,529–533] There are no studies available that analyse the effects of LTOT in CF and recommendations for use are generally extrapolated from COPD research and guidelines.

Formal LTOT assessment should be completed after a period of ideally 8 weeks of stability. If LTOT is ordered during an acute exacerbation, it should be limited to those with oxygen saturations less than 92% who are breathless, with symptoms that increase when oxygen is stopped.[534] Suitability for LTOT is assessed by performing two arterial blood gases, usually three weeks apart.[534] When oxygen titration is complete, arterial blood gases should be reassessed to determine whether adequate oxygenation has been reached without precipitating hypercapnia.[534] Arterialised capillary blood gases and transcutaneous carbon dioxide ($TcCO_2$) can be used in place of arterial gases for monitoring.

In adults with CF, LTOT should be prescribed for those with a resting PaO_2 of 7.3kPa or below. LTOT should also be prescribed for people with CF with a resting PaO_2 of 8kPa or lower in the presence of peripheral oedema, polycythaemia, or evidence of pulmonary hypertension.[534] There is little evidence to guide when LTOT is indicated in children with CF, but it is generally thought that LTOT should be considered if they are hypoxaemic to improve school attendance and for those who obtain symptomatic relief.[514,515] LTOT can also relieve dyspnoea when NIV is not tolerated in children with CF.[515]

9.2.1 LTOT and hypercapnia

As with emergency oxygen, supplemental oxygen may cause hypercapnia, and close monitoring of $PaCO_2$ after commencing LTOT is essential in those at risk of developing hypercapnic respiratory failure.[513] A retrospective study found that a baseline $PaCO_2$ greater than 6.5kPa at LTOT assessment strongly correlated with the development of progressive hypercapnia requiring NIV within 12 months of commencing LTOT.[521]

9.2.2 End-of-life care

At end of life, oxygen should be used for those with oxygen saturations less than 90% or for those who report significant relief of breathlessness with oxygen.[519] Palliative oxygen therapy may be considered if breathlessness is unresponsive to all other treatments.[534]

9.2.3 Delivery methods

The needs of the individual should be considered when selecting the delivery device and interface. Regular follow-up by a healthcare professional experienced in oxygen therapy is required, either in hospital or at home.

9.2.4 Recommendations

- LTOT should be prescribed in adults with CF with resting PaO_2 of 7.3kPa or below *(QoE – moderate)*.
- LTOT should be prescribed in adults with CF with resting PaO_2 of 8kPa or below in the presence of peripheral oedema, polycythaemia, or pulmonary hypertension *(QoE – moderate)*.
- LTOT should be used for a minimum of 15 hours per day, but 24 hrs per day may give additional benefits *(QoE – moderate)*.

9.3 Nocturnal oxygen therapy

Sleep-related hypoxaemia is defined as nocturnal oxygen saturations less than 93.8%.[535–537] Time spent with oxygen saturations below 93.8% can be 5–30% of total sleep time before nocturnal hypoxaemia is considered of consequence.[289,514,537] Some literature defines nocturnal hypoxaemia as oxygen saturations of less than 90% for more than 10% of the night.[521]

Development of nocturnal hypoxaemia and hypercapnia are known to be poor prognostic indicators in CF.[534] However, there are no CF-specific guidelines to suggest the optimum time for initiation of nocturnal supplementary oxygen in people with CF.[521,534] Consequently, individuals may be treated sub-optimally and should be regularly reviewed to ensure the most appropriate therapy.[538]

Although not yet studied in people with CF, chronic and intermittent hypoxaemia has been linked to low-grade systemic inflammation in other disorders and could worsen the already present airway inflammation and tissue destruction characteristic of CF lung disease.[289]

Before daytime resting hypoxaemia develops, people with CF with worsening disease, particularly those with FEV_1 less than 65% predicted[518,529,534,539–541] or with resting baseline oxygen saturations of 93–94%[539] can develop nocturnal or sleep time oxygen desaturation. This is due to a combination of worsening V/Q mismatch in a supine posture, physiologic changes in the mechanics of respiration and de-recruitment of ventilatory muscles, especially during the rapid

eye movement (REM) portion of sleep.[534,535,539,540] It has been demonstrated that there can be evidence of sleep-related desaturation, in the absence of daytime or sleep-related hypoxaemia, which may be clinically significant.[521,529,535,539,542] However, where exertional desaturation occurs it is prudent to assess for nocturnal desaturation.[513]

Nocturnal desaturation has been associated with greater difficulty in performing treatment, increased exertional dyspnoea and impairment in neurocognitive performance, development of pulmonary hypertension and the inability to perform normal physical function.[514,537,539]

Overnight oximetry is widely available and should be utilised to assess for nocturnal desaturation. Monitoring evening PaO_2 and morning $PaCO_2$ have been shown to be better predictors of nocturnal desaturation than spirometry. Additionally, evening PaO_2 in those with moderate-to-severe disease (PaO_2 42–84mmHg) contributed significantly to the prediction of a rise in $TcCO_2$ from non-REM to REM sleep.[529]

There is little evidence identifying significant benefit from the provision of supplemental nocturnal oxygen in advanced lung disease. There were no significant improvements in sleep arousal, sleep quality, total sleep time or indeed survival statistics.[518,521,530,534,543] Additionally, no change was identified in mood or social maintenance.[513] Nocturnal oxygen did, however, improve non-REM and REM sleep, nocturnal oxygenation and participation in activities of daily living such as school and work attendance.[96,513,522,529,534,536]

9.3.1 Nocturnal oxygen therapy and hypercapnia

Studies have shown that $PaCO_2$ can increase in some people with CF when nocturnal oxygen is administered, particularly in those with an FEV_1 less than 29% predicted.[513,534,539] It is therefore recommended that when nocturnal supplemental oxygen is prescribed, $TcCO_2$ or arterialised capillary CO_2 (in the absence of more invasive arterial blood gas analysis) should be measured, to monitor for potential CO_2 retention and guide appropriate management, including the consideration of NIV.[515,518,523,534]

9.3.2 Assessment for other sleep disorders

Poor sleep quality can result in detrimental psychological, physiological and neurocognitive effects on both children and adults. With the emergence of CFTR modulator therapy and improved patient prognosis, risk factors for sleep-disordered breathing and obstructive sleep apnoea such as obesity, diabetes and cardiovascular diseases are on the increase.[544] Screening questionnaires such as the Epworth Sleepiness Scale and performing polysomnography can be useful in diagnosis.[544,545]

9.3.3 Recommendations

- In people with CF with FEV_1 less than 65% predicted or a daytime oxygen saturation less than 94%, overnight oximetry monitoring is advised to ensure nocturnal desaturation is not missed *(QoE – moderate)*.
- Regular monitoring of $TcCO_2$ (or $PaCO_2$) is required in guiding the application of supplementary oxygen and the initiation of NIV *(QoE – moderate)*.
- Spirometry results and measurements of awake resting oxygenation should not be used to predict nocturnal desaturation *(QoE – low)*.
- Nocturnal oximetry should be considered in people with moderate-to-severe lung disease even with preserved awake resting oxygen saturations *(QoE – moderate)*.
- Nocturnal oxygen should be prescribed with caution and further analysis of $PaCO_2$ should be undertaken to ensure no adverse effects occur, such as nocturnal hypercapnia *(QoE – moderate)*.

9.3.4 Good practice points

- In people with CF reporting headache, assess for nocturnal oxygen desaturation and hypercapnia.
- Polysomnography is useful for measuring sleep architecture. The Epworth Sleepiness Scale and polysomnography can help in diagnosing sleep disorders.
- Simple overnight oximetry is widely available and provides clinically useful data in cases where nocturnal desaturation is suspected.

9.4 Ambulatory oxygen

Ambulatory oxygen therapy (AOT) describes the use of supplemental oxygen during exercise or activity, for example during airway clearance in CF.[534] There are some studies considering the use of AOT in exercise but rarely during activities of daily living.

People with advanced CF lung disease are likely to have reduced exercise tolerance;[546] AOT minimises desaturation during exercise and can reduce episodes of desaturation during airway clearance and activities of daily living.[532] AOT has been shown to offer improvements in both intensity and endurance during exercise, and thus can maximise the benefit of exercise programmes.[513,531,534] Despite the improvement in oxygenation and exercise duration with oxygen supplementation, peak work capacity and oxygen uptake did not improve in exercise studies.[531–533] The use of supplemental oxygen has been shown to result in raised CO_2 levels,[513,525] and it is unclear what advice to give patients for whom AOT is impractical or decline to use it.[547]

9.4.1 Assessment

Desaturation on exertion may be identified during annual exercise tests and this is likely to develop before the need for LTOT.[532,534] Assessment should be considered if patients are experiencing breathlessness that is impacting on activity or exercise levels. The degree of desaturation and options for AOT should be reviewed in partnership with the person with CF. A formal AOT assessment can then be carried out, including consideration of the individual's views.

Assessment for AOT is based on measurement of SpO_2 using a finger or earlobe probe, to measure desaturation on exercise, defined as a drop in SpO_2 of 4% or greater up to 90%,[514] and to assess response to AOT. Assessment should also consider the most appropriate device and setting to correct exercise desaturation to the individual's target oxygen saturation.

9.4.2 Delivery methods

Where the respiratory rate is high, oxygen through a venturi mask at a flow rate sufficient to exceed the individual's peak tidal and exertional inspiratory flow can offer advantages over oxygen therapy delivered by nasal cannulae. People with CF with high respiratory rates should be supplied with AOT equipment which is able to deliver the required high flow rates. It is worth considering that equipment delivering higher flow rates is likely to be heavier, supplying reduced hours of use, and that portability and duration of use declines considerably above 6L/m.[517,534]

Assessment should consider daily activity and treatment programmes which may include exertion related to a person's work and sport activities.[517] If the person with CF already has an LTOT prescription, it is likely that they will require a different flow rate for activity and exercise.[517]

An exploratory study suggests that using nasal high flow therapy (NHFT) during exercise in people with CF with advanced lung disease appears to be beneficial in increasing walking distance, reducing their respiratory rate and CO_2 retention, and achieving a better control of dyspnoea and comfort when compared with conventional oxygen.[548]

AOT requirements should be reviewed regularly, especially if AOT commenced during an exacerbation or when unwell. An initial review should take place after 4–6 weeks to consider if this therapy is still indicated. Home visits may be useful to identify problems with equipment or set-up and to further assess activities undertaken during daily activity. Further reviews should be carried out every six months when stable, or sooner if there are clinical changes. Supplemental oxygen should improve participation in and maximise the benefits of exercise.[531,533]

9.4.3 Recommendations

- AOT should be assessed by monitoring desaturation on exertion either using a formal exercise test or during specific activities *(QoE – low)*.
- Desaturation requiring consideration for AOT or LTOT is defined as a drop in SpO_2 of 4% or greater up to 90% *(QoE – low)*.

9.4.4 Good practice points

- People with CF should be routinely monitored for exertional desaturation, annually as a minimum and more frequently as necessary.
- A venturi device for delivery of ambulatory oxygen may be considered where the respiratory rate is high.
- Consideration should be given to the type of supplemental oxygen for exercise delivery equipment suitable for the individual and the types of activities they will undertake.

9.5 Oxygen for air travel

Air travel is common for people with CF. Due to lack of evidence, there is no known threshold of resting sea level oxygen saturations or FEV_1 that will reliably predict hypoxaemia or complications during air travel in CF. Guidance is mostly based on research in COPD and may not be directly transferable to CF.[549]

The **BTS Clinical Statement on air travel for passengers with respiratory disease** gives detailed advice and recommendations.[549]

CF teams should consider the person's previous flight experience, flight duration, destination, medications, equipment and, if relevant, the time since the last exacerbation when giving advice.[549,550] Desaturation during flight or at altitude is considered unlikely if FEV_1 is greater than 40% and resting saturations are greater than 92–94%.[516]

9.5.1 Contraindications to air travel

The following are generally considered to be contraindications to commercial air travel:

- Untreated respiratory failure
- Untreated pneumothorax
- Active infection representing a risk to others, such as TB, SARS, MERS, COVID-19, bronchogenic cysts.
- Type 2 respiratory failure if the FiO_2 required at altitude increases the risk of the patient retaining CO_2.[549]

9.5.2 Flight assessment or hypoxic challenge test (HCT)

The hypoxic challenge test (HCT) is a method of assessing whether people need in-flight supplemental oxygen. The HCT involves a 15% normobaric oxygen challenge, which simulates the partial pressure of oxygen at altitude.

HCT is recommended in adults with lung disease with:

- resting oxygen saturations of 95% or less, and in whom there are concerns about hypercapnia
- desaturation to less than 84% on 6MWT or shuttle walk test and in whom there are concerns about hypercapnia persistent symptoms and/or frequent exacerbations despite optimal treatment regardless of resting sea level SpO_2
- existing or previous hypercapnia and those at risk of hypercapnia, including those taking medication which can cause respiratory depression
- a history of type 2 respiratory failure already on LTOT at sea level.

Adapted from the **BTS Clinical Statement on Air Travel**.[549]

An HCT is not required in those who are stable and have had no hospital admissions, exacerbations, or significant changes to treatment since a previous HCT.

For pregnant people with CF, the Royal College of Obstetricians and Gynaecologists guidance should also be consulted.[549]

If HCT results demonstrate PaO_2 less than 6.6kPa or oxygen saturations less than 85%, in-flight oxygen is recommended.[549] Whilst the HCT can be a more accurate predictor of people who are likely to desaturate during air travel, it is not available at all hospitals and does not replicate a two week holiday where the individual may return in poorer health than when they left.

9.5.2.1 HCT in paediatrics

HCT should be considered in:

- infants less than one year old with a history of neonatal chronic respiratory problems
- children who are old enough for spirometry and whose FEV_1 is less than 50% predicted
- children who are too young to reliably perform spirometry who have been assessed as having severe lung disease
- children who have had long-term oxygen commenced or used within the last six months.

If oxygen saturations fall below 90% during HCT, in-flight oxygen is advised. Infants and children who are oxygen-dependent at sea level will need their oxygen flow rate doubled at flight altitude.[549]

9.5.2.2 If HCT is unavailable

If HCT is not readily available and there are no concerns about hypercapnia, people with CF already on LTOT should be advised that they will need a flow rate 2L/min greater than their baseline flow rate.[549]

9.5.3 Other pre-flight screening

SpO_2, SaO_2 and PaO_2 during CPET correlate with those measured during HCT, and since an exercise test is carried out at annual review, this can contribute to pre-flight screening for patients considering air travel.[551]

9.5.4 Practicalities of assessment and in-flight supplemental oxygen

People with CF who meet the requirements for HCT assessment should be advised to plan ahead and seek advice before booking air travel and be provided with advice and support to book extra

services required with the airline such as in-flight oxygen and airport assistance.

Many airlines no longer provide routine medical oxygen, and oxygen delivery devices provided via NHS contracts are not insured for use off UK soil. Portable oxygen concentrators are now easily available for private lease or purchase and may now enable higher flows to be delivered if the person with CF can use pulsed oxygen and is able to trigger this throughout the flight.

If oxygen is required at ground level, it will not be provided by the airlines within the airport.

9.5.5 Advice for people with CF requiring in-flight oxygen

- If a portable oxygen concentrator is going to be used in-flight patient must gain approval from the airline.[549]
- Consider booking an aisle seat near the toilets to minimise further in-flight activity and consequent energy and oxygen expenditure.[549,550]
- To avoid further desaturation:
  - avoid sleep while in the air
  - avoid alcohol immediately prior to or during the flight to stay well hydrated
  - have a small carbohydrate meal.
- All medications should be kept in hand luggage to avoid issues with delayed or lost hold baggage.[549]

Airlines will generally require passengers to complete a medical information form (MEDIF) to supply in-flight oxygen but may also require this for the individual to take onboard portable cylinders or concentrators. The MEDIF usually includes an individual's personal details and a signature for a permission statement for the release to the airline of clinical information pertinent to the flight. Some carriers request a doctor's letter.

All arrangements and costs associated with in-flight oxygen will vary between airlines. If individuals travel with the same airline regularly, they should consider requesting a Frequent Travellers Medical Card (FREMEC). Once registered, details will be stored, and any assistance required can be easily accessed. This may not be shared between airlines.

9.5.6 Recommendations

- If the results of a HCT show desaturations to less than 90% then in-flight oxygen is recommended and should be titrated to achieve saturations of 90% *(QoE – low)*.
- If the individual is already on LTOT and there is no evidence of hypercapnia, then recommend increasing normal flow rate at sea level by 2L/m *(QoE – low)*.

9.5.7 Good practice points

- When travelling abroad people with CF should be advised to plan ahead and seek advice before booking, from their airline as well as their CF team.
- People with CF at higher risk of hypoxaemia should be offered advice regarding sleep, alcohol, hydration and diet.
- People with CF should be assessed by their CF Centre and advised whether they meet the criteria for a HCT.
- People with CF who cannot tolerate withdrawal of oxygen for short periods of time should not travel by air.
- The use of a portable oxygen concentrator may be prohibited under 10,000ft by some airlines. Therefore, it cannot be used during take-off and landing.
- Passengers must take out adequate travel insurance to cover outward and return journeys and the stay at their destination.

9.5.8 Research recommendations

- The value of HCT in assessing people with CF before air travel.[549,550]
- Determining reliable cut-off values for CPET which could then contribute to preflight screening.[551]

9.6 Oxygen equipment

There are few published studies considering this topic and technological advances mean that the results are outdated quickly. **Equipment used in the provision of oxygen can be divided into three categories:**

1. **Source –** concentrators, cylinders and liquid.
2. **Delivery –** cannula, masks, conservers and tracheal devices.
3. **Supplementary –** humidifiers and carrying bags/trolleys.

9.6.1 Source

All sources of oxygen can be portable or static and decisions on the most appropriate type of device will be based on lifestyle, level of activity, flow rate required and individual preference. Equipment will be delivered directly to the individual by the oxygen contractor supplying the local area.

Different contractors may source different types of equipment for their contract. This can result in slight variances in the specific equipment available in different parts of the UK, but all will have availability of a range of flow rates and portable equipment.

Some of the more portable equipment is likely to offer pulsed oxygen to minimise the size and weight of the device. Higher flows of continuous oxygen are likely to be provided by liquid oxygen. Static HomeFill concentrators are now available in some areas which enable an individual to fill small, portable cylinders that can then be used outdoors.

Oxygen concentrators are available in more than one size and flow rate, including portable oxygen concentrators (POC). These options will vary depending on supplier and location in the UK.

9.7.2 Delivery

Controlled, fixed-flow oxygen can be provided by a venturi mask, but this can result in failure of a static concentrator as the back pressure caused by the venturi valve has been known to cause static oxygen concentrators to alarm, It has also been suggested that venturi masks when used with a static oxygen concentrator can deliver lower than expected FiO_2 , so venturi masks may be a better option only when used with cylinders.[552]

Nasal cannulae are more discreet and have less impact on communication, eating and drinking. Psychological factors should also be considered such as the impact on self-image and burden of care.[516]

Oxygen-conserving devices or demand valves can be integral or separately attached to the oxygen source, delivering pulsed oxygen on inspiration. Whilst some studies have agreed that these devices can reduce oxygen usage by around 50%, it has also been shown that demand flow oxygen is not as beneficial as continuous flow oxygen during exercise or activity. In addition, some individuals, especially those who mouth breathe, may have difficulty triggering the devices; an ambulatory assessment should be carried out before it is recommended.[553] There is no evidence for the use of pulsed oxygen overnight. When considering pulsed oxygen, all individuals should be assessed using the delivery device they will be using at home.[554]

People with CF have described experiencing embarrassment around the restrictions brought to their lives when working or carrying out leisure activities while using oxygen and reported the need to plan activities carefully. They prefer using smaller devices such as POC and would like improved devices that are smaller and quieter.[555,556]

9.7.3 Supplementary

Backpacks and trolleys can be provided by the oxygen provider and are likely to improve compliance with ambulatory oxygen therapy, although many people with CF may prefer to source their own bag or carrier.[516]

Humidification devices are available for static sources of oxygen supply by bubbling oxygen through the sterile water. Despite the view that humidification will be helpful in the presence of excessive thick secretions, there is no evidence to support this other than when oxygen is supplied via a tracheostomy.[534]

9.7.4 Good practice points

- The oxygen equipment provided should be carefully considered and meet the individual requirements of their prescription and suit their lifestyle and preferences.
- Pulsed oxygen should be considered in order to reduce the oxygen usage and extend time available on the device provided. The individual will require an assessment using any device they plan to use at home.
- Equipment to carry oxygen devices should be provided and is likely to improve compliance.
- If people with CF wish to purchase their own oxygen equipment, advice should be provided that any devices purchased should be compliant with all UK and European safety standards and provide adequate oxygen to fulfil their needs.

10. Non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP)

10.1 Non-invasive ventilation (NIV)

NIV is a type of ventilatory support where a small NIV machine provides bi-level positive pressure through a mask into the airway to provide mechanical augmentation of minute ventilation. It is a flexible form of ventilation, which can be used continuously, at night or intermittently for specific treatments in the day as indicated by clinical status.

The benefits of the addition of NIV to survival are unclear. A 2019 publication reviewing UK registry data noted NIV usage improved spirometry values but did not benefit survival[557] whereas a 12-month RCT looking at NIV versus oxygen found use of NIV lead to greater survival in a small group of people with CF.[558]

Studies in CF suggest that the use of NIV may impact lung function. Lung function improvements alongside improvements in nocturnal oxygenation were noted in a small observational study of preventative use of NIV following sleep study assessment of children and young adults.[559] Reports from multiple long-term retrospective studies show a stabilisation in lung function with NIV use,[560–563] and attenuation of hypercapnia.[563]

The impact on pulmonary exacerbations is unclear; Spolenti et al found no change in frequency of exacerbations,[562] while two studies reported decreases in IV requirements[561] or pulmonary exacerbations[564] following use of NIV.[557–559]

Stabilisation of BMI is also a benefit of NIV[560] although caution should be taken when starting patients with significant gastric symptoms and there may be benefit of timing treatments around mealtimes to reduce the risk of aspiration.[565]

In clinical practice, NIV has become an accepted tool as a bridge to transplantation in CF,[566–568] and increasingly its role has developed beyond this specific indication. BTS/Intensive Care Society guidelines identify NIV as the treatment of choice for people with CF where ventilatory support is required[569] and there is observational data reporting the use of NIV to support ventilation in patients not listed for transplantation.[570,571] A retrospective report of 20 years of NIV clinical practice in 47 people with CF demonstrated that half of those treated with long-term NIV were not on the transplant list. The data suggested that in this severe CF population, NIV initiation and long-term use may have contributed to a slowing or reversal of lung function decline.[570]

NIV can also be used beyond management of respiratory failure to augment airway clearance and exercise for people with CF,[96,572] and to help with increased work of breathing.[573]

NIV can be used to support people with a history of haemoptysis or pneumothorax,[573,574] but caution and close monitoring during set up should be used to minimise the risk of the use of positive pressure for these individuals and those with advanced lung disease (see Haemoptysis **section 12.4** and Pneumothorax **section 12.5** for details on precautions with positive pressure).[565]

Depending on local policy and expertise, physiotherapists may be involved in the assessment, set-up of equipment and monitoring of NIV. If appropriate expertise is available, NIV can be provided on the CF ward and in the community.[569]

10.2 NIV for respiratory failure

10.2.1 Hypercapnic respiratory failure (type 2 respiratory failure)

Worsening hypercapnic respiratory failure, also called type 2 respiratory failure, has been strongly linked with reduced survival.[518,521,537] The prevention of the physiological, psychological and metabolic effects of sustained hypercapnia and acidosis by the early application of bi-level ventilatory support via NIV may be beneficial.[522]

NIV has become established as part of clinical practice to bridge to transplantation in adults with CF with severe, life-threatening respiratory failure.[566,567,575] Reports also describe its use beyond this in those with established chronic hypercapnic respiratory failure.

A matched case control study involving 12 adults with CF with chronic hypercapnic respiratory failure demonstrated a survival benefit and a decrease in the number of exacerbations for those established on NIV, compared to those who continued with LTOT.[576]

Reduction of pulmonary exacerbations in patients not transplant-listed was also seen in another small study of 11 people with CF established on nocturnal NIV. This study compared data one year before and after nocturnal NIV providing some support for early initiation of NIV.[571]

Whilst certain inferences on the effects of long-term NIV in chronic hypercapnic respiratory failure are impossible without control group comparisons, the continued emergence of observational data means that randomised placebo-controlled trials of long-term NIV in this group would have substantial ethical challenges. There are no studies exploring the use of short-term NIV during acute hypercapnic respiratory exacerbations.

A small qualitative study using semi-structured interviews with nine adults with CF using long-term NIV, five of whom were on the active transplant list, highlighted NIV provided positive relief from symptoms and improved QoL, suggesting this is an acceptable and valued treatment option.[577]

A small pilot study of normoxaemic patients demonstrated that early use of nocturnal NIV improved the index of global ventilation and halved the number of exacerbations per year, however spirometry remained unchanged.[578,579]

10.2.2 NIV for hypoxic respiratory failure (type 1 respiratory failure)

Three RCTs involving 27 adults with CF assessed the use of NIV for nocturnal hypoventilation.[522,543,580] These showed in single night studies that both NIV and oxygen therapy can correct nocturnal desaturation. Compared to oxygen therapy, NIV attenuates increases in hypercapnia during sleep.[522,580] When used over six weeks, NIV improved chest symptoms, exertional dyspnoea and peak exercise capacity compared with placebo.[543] There are variable reports on personal tolerance and preference for oxygen therapy or NIV.

10.2.3 NIV for end-of-life care

Guidance on the management of NIV in palliative care is limited. A 10-year review of 49 adults with CF found that 65% established on NIV died on the NIV, with only 16% having their settings changed.[563] Changes to NIV settings at the end of life should be led by patient symptoms and comfort.[563]

10.2.4 NIV for airway clearance

NIV to support ACT has become recognised as a treatment option for people with CF[581] and is considered in individuals with more severe lung disease,[582] during infective exacerbations[583] or in individuals having difficulty with expectoration.[96,581–583] NIV for ACT may also be considered for individuals who have a good response to IPPB[581] or those who desaturate with other ACTs.[572] Its action may decrease respiratory muscle fatigue, augment cough by creating greater tidal volumes and prevent airway closure.[564]

The use of NIV for ACT can be a good starting point to introduce NIV to individuals who may benefit from nocturnal support in the future. Creating a good understanding of and relationship with NIV has been reported as important in NIV usage success.[584] For those established on NIV for ventilation, settings may need to be altered to augment airway clearance, in partnership with the person with CF, for example to allow larger volumes or slower rates.[585] Masks can be used for ACT, or mouthpieces may be preferred for ease of expectoration.[585]

The short-term effects of using of NIV for ACT over one or two days have been investigated in two studies with adults with CF during infective exacerbations,[586,587] and in one adult[83] and one paediatric study[588] with stable people with CF. Slightly longer-term studies have been completed over a hospital admission[583] and a three-month period.[107] Results have included decreased fatigue[583,586–588] and lower respiratory rates during airway clearance,[586–588] while improvements in oxygenation,[83,586] respiratory muscle strength,[586] LCI[107] and FEV_1[583] have also been highlighted. None of the RCTs have shown a difference in sputum expectorated when using NIV-assisted ACT versus usual ACT,[589] although published work based on semi-structured interviews with individuals established on NIV for ACT have reported improved ease of sputum clearance[584,590] alongside lower levels of fatigue[584] and lower levels of breathlessness during ACT.[83,107,583,584,586–590]

More research is needed into the longer-term effects of the addition of NIV to ACT. One group reported non-significant trends towards fewer hospital admissions and increased home IV antibiotic use in a cohort of 14 people with CF who had used NIV for ACT over a one-year period.[573] A second study which retrospectively reviewed people with CF using NIV showed a significant reduction in hospital admissions in the year after NIV was introduced.[564] Data from 11 people with CF using NIV for ACT highlighted that while all reported NIV was beneficial, actual recorded usage time was lower than self-reported usage – indicating NIV for ACT may not be used for all ACT sessions even in those who find it beneficial.[591] The current literature shows a divide in preference for NIV-assisted ACT[583,586,590] and usual ACT,[83] while this may be due to differences in the study cohorts, it is essential to consider personal preference for all ACT interventions.

All the current publications have methodological limitations, such as small sample sizes, possible effects of concurrent treatments and non-standardised ACTs used with NIV or as the control. This, and the short-term nature of these studies, makes it difficult to draw robust conclusions to the effect NIV has when added to ACT or which patients may benefit most. No studies have compared the effect of NIV-assisted ACT to oxygen-supported clearance in those who desaturate. More robust research is needed into the use of NIV as an adjunct to ACT to fully identify short and long-term benefits and possibly guide individual preference.[96]

10.2.5 NIV for exercise

Clinically, NIV has been reported to be used during exercise to decrease dyspnoea, improve oxygenation and ultimately improve exercise tolerance in people with CF with advanced respiratory disease.[522,569] One RCT involving 13 children with CF compared the effect of no NIV and use of NIV on 6MWT on a treadmill.[291] The results show some improvement in distance completed, improved FEV_1 and FVC and less reduction in post-test peripheral oxygen saturation when NIV was used.

A preliminary cross-over study involving nine adults with CF demonstrated significant improvement in peripheral oxygen saturations and some improvement in blood gases during submaximal cycle tests when NIV was combined with oxygen in comparison to oxygen alone. There was no difference in endurance shown in this study and patient satisfaction was higher when just oxygen was used.[292] Rodriguez Hortal et al conducted a study looking at the effects on incremental treadmill test results comparing use of NIV compared to oxygen alone in eight adults with CF.[592] There were no significant differences in lung function, oxygen saturation or rate or rating of perceived dyspnoea between the two groups.

There is insufficient evidence available[589] and a need for further research into the benefits of NIV for people with CF with reduced exercise tolerance.

10.2.6 NIV provision

Two reviews of NIV in CF highlight important considerations around NIV use:[565,593]

- Skilled introduction, careful physiological monitoring and education of NIV users and nursing staff.
- Ongoing careful re-evaluation as someone's clinical condition changes, during initial admission and all subsequent admissions.
- Skilled personnel who are familiar with the different properties of the ventilators and interfaces available to them.
- The provision of two ventilators and battery support to those using NIV for more than 16 hours out of 24.
- The use of humidification.
- The availability of different ventilator and interface options.
- Detailed documentation of settings and any changes to settings or ventilators.

People with CF should have access to comprehensive ventilatory support provided by skilled personnel, with access to various ventilator and interface systems keeping abreast of technology as developments occur. It is likely this may be provided a CF Physiotherapist[594] but this will vary locally.

Remote monitoring of NIV has been shown to be feasible in a small group of CF patients using NIV at home for more than three months[595] and can help to guide manipulation of settings to optimise efficacy of ventilation in the individual. Introduction of CF-specific local NIV pathways may help to promote elective rather than emergency set-up,[596] which may improve individual experience.

There is no large-scale published evidence addressing infection control issues specifically in relation to NIV.[597] A small study swabbed seven NIV machines which had been used by people with CF with chronic *P. aeruginosa* or *B. cepacia* infection and found no microbial contamination of the machines.[598] Until large-scale studies confirm lack of contamination, it should be considered that equipment used in delivering NIV may be exposed to potentially infectious material during routine use through contact with the skin, mucous membranes and respiratory secretions.[597] Where possible, single-use equipment is encouraged and appropriate decontamination of all other component parts taken between users, in line with manufacturers' instructions.

10.2.7 NIV and the CFTR modulator era

A review of UK Registry data in 2019 indicated that the use of NIV was increasing in the UK CF population.[557] However, with the roll-out of CFTR modulators for the majority of people with CF in the UK, the trend for NIV use may change.[599] The effects of CFTR modulators have led to greater clinical stability for many people with CF, and with this the frequency of need for NIV interventions is unknown in this new population.

While there is limited information available at present about the effects of modulator therapy and

NIV use, comparison of UK Registry data from 2019 to 2024 indicates a trend for fewer people using NIV.[2,600] Additionally, a 2021 review by Wadsworth and Bright-Thomas found that of 14 people with CF on NIV that started Kaftrio, 22% were able to come off NIV completely with a further 36% able to reduce their NIV requirements or oxygen use.[601]

With the limited data indicating potentially fewer people using NIV in the future, CF teams need to make provisions to ensure continued competence and proficiency in managing NIV interventions for those who require it.

10.3 Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) is a type of breathing support where a small CPAP machine provides a positive pressure of air through a mask into the airway. CPAP prevents sleep disordered breathing difficulties such as obstructive sleep apnoea (OSA) where the individual experiences complete or partial collapse of the upper airway with an associated decrease in oxygen levels or wakening. CPAP helps to keep the airway open and increases the level of oxygen in the lungs. CPAP can be used during airway clearance to help splint open collapsible airways.

Untreated sleep disordered breathing, including OSA, can lead to poorer pulmonary, cardiovascular and metabolic outcomes for people with CF.[544] Additionally, Vendrusculo and colleagues reported that children with sleep-disordered breathing had lower exercise capacities and daily physical activity levels.[602]

Symptoms of OSA are increasingly being reported in people with CF, including snoring, difficulty breathing or mouth breathing during sleep, and daytime sleepiness.[603] Risk factors for OSA differ between adults and children, with upper airway conditions including inflamed sinuses and enlarged tonsils predominately the cause for children with CF.[603]

Obesity is a main risk factor for adults with CF, which historically has led to a low incidence of OSA in this population.[604] However, with the introduction of CFTR modulators, where weight gain is now easier for many individuals with CF, the incidence of OSA is likely to increase. Data is emerging indicating that OSA and nocturnal hypoxemia are increasingly common in adults with CF,[545] but that individuals may have no risk factors[605] and thus screening and investigation through sleep studies should be considered.[544,605]

10.4 Recommendations

- NIV should be considered for all people with CF demonstrating nocturnal hypoventilation with a rise in pCO_2 despite optimal treatment *(QoE – moderate)*.
- NIV should be considered for those in ventilatory failure for improved oxygenation, improved clinical stability or control of symptoms related to hypercapnia *(QoE – moderate)*.
- NIV should be considered if fatigue is limiting airway clearance *(QoE – low)*.
- NIV should be considered as an adjunct where desaturation is present during airway clearance *(QoE – low)*.
- NIV should be considered where there is difficulty clearing secretions with other techniques *(QoE – low)*.
- NIV-supported exercise could be considered in those with chronic hypercapnic respiratory failure established on long-term NIV to help increase exercise tolerance *(QoE – very low)*.
- Screening for sleep-related breathing disorders should be considered for all individuals with CF, especially those displaying known risk factors *(QoE – low)*.
- CPAP should be considered for those with obstructive sleep apnoea *(QoE – moderate)*.

10.5 Good practice points

- To minimise risk associated with use of positive pressure, especially in those with advanced lung disease, appropriate radiological investigations and medical review should be done before starting NIV to ensure the presence of an undrained pneumothorax or other contraindications to NIV use are excluded.
- Appropriate monitoring and review should be carried out during the use of NIV and CPAP to ensure optimal therapy is applied. Review may be within clinic, home visits or inpatient stays. Frequency of review will be determined by the needs of the individual.
- A selection of ventilators, interfaces, mouthpieces, nasal pillows, nasal masks, full face masks and total face masks should be available and used appropriately according to individual assessment.
- Hospital policies to reduce the likelihood of cross-infection during NIV or CPAP

treatment must be developed in conjunction with local infection control teams.

- NIV may be used to facilitate airway clearance and for ventilatory support in both adults and children.
- If nocturnal ventilation is indicated, prior use of NIV for ACT may help reduce patient anxiety and ease the process of initiation due to patient familiarity with the device.
- NIV may be considered for use during exercise where dyspnoea or oxygenation limits activity despite optimal regimen and oxygen therapy. Use of NIV during exercise should be monitored carefully as little is known about the outcomes of this intervention.
- NIV should be used with caution in people with CF with significant gastric symptoms such as extensive gastric distension, ileus, nausea and vomiting and gastro-oesophageal reflux. Careful planning to avoid meals may improve tolerability.
- With potentially fewer people with CF requiring NIV post-CFTR modulators, it is vital that clinicians maintain their competency in managing this intervention and link with or refer to local specialists to ensure optimal services.

10.6 Research recommendations

- Optimal use of NIV for exercise support.
- Contamination of NIV machines on a larger scale.
- Work on OSA
- NIV use in post-modulator populations.

11. Musculoskeletal (MSK) issues

MSK problems specific to CF occur in addition to those of the general age-matched population.[606] The combination of abnormal respiratory mechanics, CF-related bone disease (CFBD) and muscle weakness lead to a high incidence of MSK pain, fractures and postural changes.[242,265,304,606–610] These secondary complications can hinder an individual's ability to carry out activities of daily living, treatment and exercise and contribute to the overall morbidity and mortality of the CF population.[607,609,611,612] It is essential that these secondary complications are investigated and optimally managed to help maintain quality of life for people with CF.[613]

As people with CF age and as life expectancy is further increased for those eligible and able to take CFTR modulators, MSK conditions common in the older-aged general population such as osteoarthritis, fragility fracture and 'frozen shoulder' will present more frequently.[614]

Physiotherapists will need to be able to accurately screen, assess and manage these and other MSK conditions.

11.1 Posture and thoracic kyphosis

The muscles of the trunk have a dual role for respiration and posture[304,615,616] and will prioritise the needs of respiration.[607,617] In CF, this altered neuromuscular control may compromise spinal stability leaving the spine vulnerable to injury and lead to postural adaption[607,618] and MSK problems.[36,607,617–619]

Increased thoracic kyphosis is a common postural change in people with CF and occurs as a result of:[242,304,607,611,620]

- altered respiratory mechanics:
  - altered neuromuscular control
  - increased work of breathing
  - hyperinflation
  - an excessive, prolonged cough
- muscle weakness
- thoracic fracture secondary to low bone mineral density (BMD).

In addition, sitting in slouched postures, an inability to lie in thoracic extension, and pain, may further contribute to a muscle imbalance.[607,611,620,621] Postural changes and tightening of the pectoralis muscles have been noted in children from the age of seven[620,622] and MSK problems begin to present during the prepubescent years and are present by puberty.[607,621]

The association between worsening severity of CF lung disease and increasing thoracic kyphosis has been found in many studies but is not universally agreed.[611,620,623–627] One study which showed the prevalence of thoracic kyphosis to be significantly less amongst children with CF than previously reported, concluded this was likely to be associated with the overall improvements in pulmonary status of children.[626] In the era of CFTR modulators and the improved pulmonary status of both children and adults, further understanding of posture and thoracic kyphosis is needed.

The importance of maintaining 'good' posture through physical exercise and stretching is highlighted in a study that shows children and adolescents with CF present with a series of postural changes compared with healthy children.[628] Other studies have suggested this is also important to prevent pain and to address the poor body image and reduced self-confidence that people with CF report.[606,611]

Lack of clarity in the literature about measuring thoracic kyphosis, whether taken in habitual or corrected postures and the method of assessment used, make studies difficult to compare.[629] The current gold standard for measuring thoracic kyphosis is a standing lateral radiograph, which provides a Cobb angle. This method does have limitations of high cost and radiation exposure, and often fails to represent the full contour of the thoracic spine.[629] Thoracic kyphosis can also be measured with the Flexicurve, which is inexpensive, easy to use, and in the general population has high levels of reliability and validity.[606,629]

11.2 Cystic fibrosis related bone disease (CFBD) and fracture

Optimising bone health is essential for the CF population and the most effective strategies are early recognition, prevention, and treatment.[630]

The reasons for CFBD are multifactorial:[608,631–636]

- CFTR dysfunction
- Vitamin D, K and calcium deficiency
- Malnutrition

- Delayed puberty
- Hypogonadism
- Decreased physical activity
- Respiratory infection
- Systemic inflammation
- Exogenous glucocorticoids and CFD.

In children with CF, deficits in trabecular and cortical bone have been observed[637] and studies report the prevalence of osteoporosis to be 23.5% and osteopenia to be 38% in young adults with CF.[630] As life expectancy for people with CF increases, the incidence of low BMD and fracture (and the associated pain and disability) may increase.[638] CFTR modulator therapy may improve bone density by directly targeting dysfunctional CFTR and by influencing other risk factors for CFBD and research is ongoing in this area.[637]

Puberty is important for the development of bone density and is a time when there is both peak bone growth velocity and bone density accrual.[639] Therefore, during childhood and the pubertal growth spurt, regular weight-bearing exercises will enhance the building of a stronger skeleton through a higher peak bone mass and a larger bone size.[288] This type of exercise should continue throughout an individual's life.

Optimising bone health needs to be managed by the MDT, using existing CF guidelines, and physiotherapists should aim to input into this process.[288,637] Severity of pulmonary disease is related to BMD in people with CF; screening guidelines for bone health in children with CF should target individuals with the poorest clinical status, particularly in regard to lung function, BMI and total fat percentage.[640] Dual-energy X-ray absorptiometry (DEXA) scans are used to assess BMD and to guide intervention, which may include specialised drug treatments.[641]

Fracture rates are higher in the CF population,[642,643] with an increased incidence of 20% for nonvertebral and 27% for vertebral fractures.[636] Vertebral fractures are most common at the thoracic level[642] and when present may contribute to the development of an increased thoracic kyphosis. In the CF population, there is evidence of fracture under-reporting,[608,621] and vertebral fractures may be asymptomatic.[644] Fracture prediction tools have been proposed for use in clinical practice, such as FRAX score.[645]

Rib and vertebral fractures can result in significant pain and individuals should receive adequate analgesia and physiotherapy advice as a priority, to enable chest expansion and optimise airway clearance. Additionally, IV antibiotics and increased mucolytic therapies may be required.[643] People with CF may have slower rates of fracture healing[614] and physiotherapists may need to make appropriate adjustments to rehabilitation programmes.

There are no CF-specific guidelines to manage osteoporosis in postmenopausal women and men over 50. A recent UK consensus statement recommends that people with osteoporosis should undertake impact and resistance exercises to improve strength, balance and posture and individuals at risk of falls should undertake a balance exercise programme.[646]

11.3 Pain

Pain is a frequent problem in both children and adults with CF. It is associated with reduced QoL, depression, anxiety, higher rates of pulmonary exacerbation and an increased risk for lung transplant.[647–649] Pain negatively impacts on the ability to participate in disease-related daily care[5,44] and, together with physical functioning, is the strongest predictor of survival in CF.[609] Altered clinical outcome as a result of moderate-to-severe pain appears to be independent of age, sex or lung function.[647]

Pain is under-reported by people with CF and is under-recognised and sub-optimally managed by clinicians.[609,630,650] Studies show that the incidence of MSK pain ranges from 12% to 65% and activities of daily living are impacted in 50% of those with MSK pain.[608,651] Back pain is reported by up to 79% of the adult population and has been shown to significantly affect posture.[610]

Pain assessment should be a routine part of clinical care and accurate assessment of the cause of pain should guide optimal, evidence-based management. A recent systematic review suggested that further research is needed to explore the measurement properties of instruments assessing pain in CF.[649]

Persistent (chronic) pain, including chronic back pain has been reported in the CF population.[625] A review of persistent pain is beyond the scope of these guidelines, but MDT involvement or a referral to a specialist pain team should be considered best practice to manage the multidimensional aspects of persistent pain.[652]

11.4 Inflammatory joint disease and scoliosis

Episodes of joint pain (arthralgia) are well recognised in people with CF, usually starting after 10 years of age. Whilst much of this is mechanical in nature, it is reported that an inflammatory arthritis is present in 5–10% of people with CF.[2,412,653] CF-associated arthritis (CFA) and hypertrophic pulmonary osteoarthropathy (HPOA) are reported, but clinical manifestations are not consistently described in the literature. There is no formal definition of CFA or any evidence base for treatment. The most clinically useful diagnostic summary for CFA remains that from Pertuiset et al in 1992.[654] They suggest that CFA should be diagnosed if there is an inflammatory arthritis without articular infection, without evidence of periosteal change on X-ray and after exclusion of another cause of inflammatory arthritis.[612]

Joint pain in CF requires a thorough diagnostic work-up, as poor management of joint symptoms affects QoL, an individual's ability to carry out activities of daily living and ability to exercise.[612] Inflammatory arthritis presents with joint pain and swelling, and early morning stiffness lasting more than 30 minutes; the combination of these symptoms requires assessment by a rheumatologist to exclude other conditions such as rheumatoid arthritis, and to consider treatment options.[608,652] All inflammatory joint conditions, including CFA, require multidisciplinary input from the CF team and the rheumatology team to ensure optimal care.[612]

Scoliosis is not common in young children with CF, but the incidence is higher in adolescents with CF than in the general population[655,656] and is associated with a negative effect on lung function.[622,657–659] Contributary factors are proposed to be altered ventilation from airway obstruction, hyperinflation and air trapping.[255,613]

11.5 Skeletal muscle function

Skeletal muscle atrophy, weakness and fatigue are common in people with CF.[232] As the life expectancy of people with CF increases, the age-related loss of skeletal muscle (sarcopenia) also increases which may further exacerbate the risk of adverse events such as falls and fractures.[660] Interventions that improve skeletal muscle function or offset losses in muscle mass are therefore of considerable importance in people with CF and this is an area of ongoing research.

11.6 Screening and prevention of MSK dysfunction

Postural changes have been noted in children from the age of seven;[607,661] MSK problems by puberty.[607] It has been suggested that children as young as pre-school should receive regular screening for spinal or other postural abnormalities to minimise or potentially prevent secondary MSK impairments.[607]

MSK screening tools that aim to pro-actively identify problems have been developed and used in adult cohorts for early intervention. A thoracic spine movement screen, questions about pain and posture, and a validated pain questionnaire allow clinicians to select the appropriate and optimal care pathway.[662–664] More recently, paediatric specific screening tools have been developed and have begun to be used.[665,666]

Posture assessment cannot be considered in isolation from movement and muscle activation[667] and should be individualised.

11.7 Treatment

Physiotherapy must emphasize the importance of physical exercise and postural care, as well as addressing the unique complications which occur as people with CF live longer.[613] There is an increasing body of evidence demonstrating the role of physiotherapy MSK techniques for the prevention and management of non-inflammatory pain and postural changes, in both adults and children with CF.[177,606,607,621,668,669]

MSK treatments include joint mobilisations, techniques to address muscle dysfunction and tightness, postural awareness, education and strengthening exercises. A review of the literature concluded that larger studies are required to assess the effectiveness of manual therapy techniques.[670]

Studies in children with CF have found that the incidence of postural problems are directly related to the amount of regular exercise taken; 90% of children with postural issues reported doing little or no exercise. The studies conclude that to minimise postural issues, exercise should be incorporated into lifestyle from an early age.[620,668]

Improvements in posture and thoracic kyphosis are achievable for people with CF. However, a stretching programme of the muscles most commonly affected in CF may not be sufficient to address the multifactorial nature of altered posture.[611] In the general population there is also

no consensus on the most effective treatment methods, but education, manual techniques and exercise are recommended.[667]

11.8 Recommendations

- Regular weight-bearing activities should be encouraged to optimise BMD *(QoE – moderate)*.
- CF Physiotherapists should assess MSK symptoms and should refer to MSK specialists at the CF Centre and if this is not available, a referral to local MSK specialist should be made, to provide optimal and individually tailored management *(QoE – moderate)*.
- When required, referrals should be made to a rheumatology or pain specialist to provide optimal care *(QoE – high)*.
- Fracture history should be recorded, and optimal physiotherapy care provided *(QoE – high)*.

11.9 Good practice points

- All individuals with CF should have an annual MSK screen from age seven or earlier if necessary, to proactively identify postural problems and to ask about pain, including MSK pain.
- MSK screening tools may be useful to guide assessment. The Manchester Adult MSK screening tool (**Appendix IV**) provides a validated outcome measure for pain assessment and includes a matrix to signpost appropriate care pathways for those people with CF who have problems with pain or posture.[659,661,662] Paediatric tools have been developed but are not yet validated.[666,671]
- Exercise should be encouraged to help improve posture, develop postural awareness and prevent the progression of postural problems.
- Individual posture and ergonomic advice should be given to all individuals and should encompass advice for home, school, the workplace and other daily activities. Habit formation that will maintain optimal muscle balance and posture should be encouraged.
- People with CF should be made aware that they can seek advice about posture, pain and MSK issues. When MSK problems or acute injuries occur, prompt assessment and treatment to enable a timely return to daily activities, sport and exercise should be given, or onward referrals made.

11.10 Research recommendations

- Bone health and fracture history in people with CF, and whether this correlates with DEXA or age.
- Records of MSK problems and posture concerns reported by adults, children and young people with CF in the last year, including the site or type of problem.
- Number of referrals made for MSK pain and services available to people with CF, such as being seen by the CF team or referred to a GP or other MSK team.
- Pain management strategies used by people with CF.
- Prevalence of CFA in the CF population.

12. Management of specific issues

12.1 Pelvic health

Pelvic health issues are prevalent within people with CF. Wider access for many to CFTR modulators has improved health, fertility and life expectancy for people with CF therefore more may develop CFD, experience pregnancies, go through menopause and reach old age; all additional risk factors for pelvic health issues, leading to an increased prevalence.

Appropriate care and support should be offered to all people with CF, and physiotherapists should assess for urinary incontinence (UI) and faecal incontinence (FI) to identify prevalence and educate on treatment options. Many individuals may experience embarrassment around symptoms which could prevent them from seeking support.[672–675]

12.1.1 Bladder dysfunction and urinary incontinence

People with CF are affected by incontinence more than the general population; prevalence ranges from 5% to 15% for men and 30% to 76% for women.[676] One study reported increased incidence of UI in males with CF aged 18–50 when compared with age-matched controls. This was associated with higher levels of anxiety and depression.[677] The impact of UI on QoL can be significant[678] and is reported to increase both with age and severity of symptoms.[679]

Underreporting is common and assessment should include evaluation of urinary frequency and urinary urgency alongside UI.[672,673,680] Vigilant and sensitive surveillance for UI is recommended to ensure that individuals can access support and treatment as required.[672–674,678,681]

There are different types of urinary incontinence to consider:

- **Stress urinary incontinence (SUI) –** involuntary loss of urine on effort or physical exertion such as coughing or sporting activities.
- **Urge urinary incontinence (UUI) –** involuntary loss of urine associated with urgency.
- **Mixed urinary incontinence (MUI) –** both SUI and UUI.
- **Post-micturition dribble (PMD) –** involuntary loss of urine immediately after finishing passing urine, usually on rising from the toilet or leaving the bathroom.[682]

The risk factors associated with UI in CF are multi-factorial and may include:

- poor nutritional status in younger people[683]
- imbalance of the muscles of respiration, posture and continence
- increased intra-abdominal pressure associated with persistent cough and constipation.[684]

Cough is the most commonly reported cause of SUI and symptoms are associated with forced expiratory manoeuvres. The amount of leakage reported varies greatly and can be a few drops to emptying the full bladder.[674,681] People with CF affected by SUI may be reluctant to perform airway clearance treatment and lung function procedures effectively due to the increased risk of urinary incontinence.

The occurrence of SUI seems to increase at times when cough is worse, such as during a pulmonary exacerbation; the occurrence and severity of UI increases as disease progresses.[673,674] Analysis of scores from a MSK screening tool that uses validated questionnaires to assess pain and UI also demonstrated an association between the presence of low back pain and symptoms of UI in females with CF.[685]

Three studies have addressed the assessment and treatment of the pelvic floor muscles.[685–688] An improvement in pelvic muscle endurance was reported following a three-month programme of pelvic floor exercises in a small, self-selected group of women with CF.[686] A three-month intervention of pelvic floor muscle training, electrical stimulation, biofeedback and bladder training resulted in reports of significantly fewer episodes of leakage, sustained at three months following the treatment period, and an improvement in electromyography and ultrasound imaging measures.[688] An abstract report describes improvement in symptoms of both back pain and SUI reported by women with CF who were taught pelvic floor muscle exercises.[685]

12.1.1.1 First-line treatments

- Pelvic floor muscle training, including 'The Knack' and counterbracing against increases in intra-abdominal pressure, with consideration given to ACT, spirometry, exercise and lifting. Care should be taken when teaching pelvic floor exercises as evidence suggests 40% of women with incontinence incorrectly perform a pelvic floor contraction with verbal education alone.[689]
- Fluid advice – limitation of caffeine, carbonated drinks and alcohol.

- Three-day bladder diary.
- Consider the **Squeezy App** and guidance from Bladder & Bowel UK and Pelvic Obstetric and Gynaecological Physiotherapy (POGP).

12.1.1.2 Recommendations

- Annual screening for urinary incontinence for men and women. Physiotherapists should ask about UI symptoms as part of their routine assessment; this should start in paediatric care *(QoE – high)*.
- Both preventative and active strategies for the management of UI should be implemented *(QoE – low)*.
- Where UI is identified, further assessment with the International Consultation on Incontinence Questionnaire short form (ICIQ-UI SF; **Appendix Va**) and appropriate referrals to local continence services, pelvic health physiotherapy or urogynaecology services is recommended *(QoE – low)*.
- Individuals with UI should be given advice on positioning and posture when performing airway clearance, spirometry or exercise *(QoE – low)*.
- Techniques such as AD may impose less stress on the pelvic floor and the use of 'The Knack' during airway clearance may reduce episodes of incontinence. Maintaining a normal lumbar lordosis rather than lumbar flexion should help to maximise pelvic floor function *(QoE – low)*.
- Undiagnosed or poorly controlled CFD may also contribute to UI through polydipsia and/or polyuria and therefore liaising with the MDT about screening for CFD is suggested *(QoE – very low)*.

12.1.1.3 Research recommendations

- Evaluate the effect of CF modulators on urinary continence for children and adults with CF.

12.1.2 Bowel dysfunction and faecal incontinence

An increased prevalence of bowel dysfunction and faecal incontinence (FI) is reported in adults with CF compared to the general population[681,690,691] with a variety of questionnaires used to survey symptoms and the impact on QoL. Two studies report bowel dysfunction and FI in children and adults with CF.[675,692] FI is associated with coughing, sneezing, laughing and activities which cause increased pressure on the pelvic floor, as described in SUI. A recent study[691] also describes an association with vaginal delivery. However, due to the extensive gastrointestinal comorbidity in CF, the precise mechanism of bowel dysfunction and FI is unknown and is likely multifactorial.

12.1.2.1 Recommendations

- Every individual with CF should be screened for FI and symptoms of bowel dysfunction as part of routine assessment of pelvic health *(QoE – low)*.
- Communication with the MDT, especially Specialist CF dietitians, is essential to consider the impact of pancreatic enzyme replacement therapy (PERT), constipation and colonic microbiota on bowel function *(QoE – low)*.
- When someone reports symptoms of bowel dysfunction and FI, further assessment with appropriate questionnaires, such as St Marks (**Appendix Vb**) or Wexner (**Appendix Vc**), and referral to continence and or colorectal services should be considered *(QoE – low)*.

12.1.2.2 Research recommendations

- Evaluate the effect CFTR modulators on FI for children and adults with CF.

12.1.3 Impact of CFTR modulators on UI and FI

A recent abstract reported a reduction in UI symptoms and ICIQ score at six and 12 months following the introduction of CFTR modulators. Further studies are required to investigate the effect of CFTR modulators on UI for people with CF.[693]

Limitation of pre-CFTR modulator data relating to UI and FI is acknowledged. Whilst reduction in pulmonary exacerbations, cough and the prescription of antibiotics which cause disruptive changes in the gut microbiota may result in less pelvic incontinence, factors such as rapid increase in BMI, pregnancy rates and an ageing population will necessitate ongoing screening for and treatment of urinary and faecal incontinence.[691]

12.1.4 Pelvic organ prolapse in females

The incidence of pelvic organ prolapse (POP) in females in with CF is largely unknown. Risk factors for POP include a chronic cough, chronic constipation, increased BMI, pregnancy and advancing age.[694,695] With access to CFTR modulator therapy and longer life expectancies, there will be a likely increased incidence due to the increased risk factors in the aging population.

The symptoms of prolapse in females can include vaginal heaviness or dragging, presence of a bulge within or outside of the vagina and difficulties emptying the bladder or bowel. POP in females

that are within the vagina can be improved with conservative treatments. Those that are outside the vagina will require a surgical review.[695]

The ICIQ-VS (**Appendix Vd**) can be a useful tool to help with further screening of POP.[680]

12.1.4.1 Recommendations

- Pelvic floor muscle training to include **The Knack** and counterbracing against increases in intra-abdominal pressure, with consideration given to ACT, spirometry, exercise and lifting *(QoE – low)*.
- Constipation management with fluid and fibre advice and laxatives as appropriate and referral to Specialist CF dietetic services *(QoE – low)*.
- Toileting positions to minimise straining of the pelvic floor muscles *(QoE – low)*.
- Consider referral to Pelvic Health Physiotherapy, Urogynaecology or Colorectal teams for further input and assessment such as vaginal pessary management or surgical opinion *(QoE – low)*.

12.1.4.2 Research recommendations

- Evaluate the prevalence of pelvic organ prolapse for children and adults with CF.

12.1.5 Menopause

There are similarities between CF exacerbations and menopausal symptoms, such as night sweats, joint pain, headaches and fatigue. **NICE guidance NG23**[696] recommends discussion of management options for women over the age of 40 who present with menopausal symptoms, but there is limited information regarding the age at which women with CF experience menopausal symptoms. One study with a small sample size reports earlier age at menopause compared to the general population, with half reporting worsening of CF symptoms at menopause.[697]

With widely available CFTR modulators and advances in CF care, the likelihood of women with CF experiencing menopausal symptoms will increase. Studies are required around the treatment of women with CF, in particular the use of HRT where microvascular complications, CFD, CF-related altered hepatic metabolism and interaction of CFTR modulators may need to be considered.[698,699]

Further investigation of the impact of menopausal reduction in bone mineral density is required in this population already at increased risk of osteoporosis.[700]

12.1.5.1 Recommendations

- People with CF experiencing menopausal symptoms should be encouraged to track symptoms to aid further support *(QoE – low)*.
- People with CF may experience menopausal symptoms at a younger age than the general population and require earlier discussions regarding management *(QoE – low)*.
- Menopausal reduction in bone mineral density should be considered, in view of the existing CF-related increased risk of osteoporosis *(QoE – low)*.

12.1.5.2 Research recommendations

- Study of bone mineral density in pre-, peri- and post-menopausal women with CF compared with the non-CF population.

12.1.6 Sexual and reproductive health (SRH)

People with CF have identified that they may prefer to seek guidance from their CF team on SRH issues including contraception, fertility, STIs, cervical screening and sexual dysfunction.[699,701] Due to the impact on health and longevity with increased access to CFTR modulators, it is likely that people with CF will increasingly encounter SRH concerns. Educational training to CF teams will ensure healthcare provision continues to reflect emerging CF care demands. Further studies are required in this area of care.

12.1.6.1 Recommendations

- Facilitate timely and accessible SRH discussions with appropriate MDT members with onwards referral where necessary *(QoE – low)*.

12.1.6.2 Research recommendations

- Study of changing sexual and reproductive health concerns and healthcare needs in response to an ageing CF population.

12.1.7 Good practice points

- A sensitive and open approach with early recognition of pelvic health symptoms and concerns for everyone with CF.
- People with CF should be taught effective pelvic floor bracing or The Knack during activities that increase intra-abdominal pressure such as airway clearance, spirometry and exercise.

- The Manchester Adult MSK screening tool should be utilised (Appendix IV), including the ICIQ-UI SF (also separately available in Appendix Va) which provides a validated outcome measure to assess symptoms of UI.
- Physiotherapists should have an awareness of MDT pelvic health referral options and signpost to information.
- Consider the use of an annual screen for menopause symptoms for women with CF age 40 years and above, such as Menopause Matters.
- Physiotherapists may consider undertaking specialist pelvic health training to support emerging CF healthcare needs.

12.2 Pregnancy and parenthood

Parenthood is a normal life milestone that many people with CF wish to experience. A survey from five CF Centres in the USA found that 80% of its responding adolescents and young adults with CF intended to have children.[702] CF teams, as part of routine CF Centre care, are now more frequently required to support women with CF through one, if not multiple, pregnancies. Pregnancy and parenthood bring unique challenges for people with CF, requiring Specialist physiotherapy advice and intervention throughout all stages including pre-conception, during pregnancy, immediately post-birth and during later stages of parenthood.

12.2.1 Pregnancy and CFTR modulators

Since the introduction of CFTR modulators, the rate of pregnancy for CF women has increased.[2,703] CFTR modulators have been well-tolerated in pregnancy[704] but little evidence on their safety in pregnancy exists.[705] While research on the safety of CFTR modulators in pregnancy is ongoing,[706] a current task force statement of experts from Europe, Australia and New Zealand concluded that all CFTR modulators are "probably safe" during pregnancy due to no toxicity in animals at normal doses.[707] There have been case reports of pregnancies on modulator therapy with few complications and good overall tolerance and outcomes for mothers and babies.[662,708–710] Due to the limited safety data, women with CF and their partners should have a risk/benefit discussion with their CF teams and allowed to make informed decisions regarding risk to mother and child from continuation or cessation of CFTR modulators during pregnancy and breastfeeding.[703,704,711]

There is a risk of health deterioration for women with CF who stop modulator therapy, which may reverse when restarting therapy.[709] Women with CF who stop CFTR modulators should be closely monitored for possible deterioration, with regular physiotherapy reviews for airway clearance and inhalation therapy.

12.2.2 Preconception

Historically women with CF were thought to be less fertile than the general population,[712,713] with fertility problems linked to health status, delayed menarche and increased cervical mucus consistency.[703,712] This idea, alongside gaps in knowledge around fertility for women with CF has been shown to influence use of contraception,[714] leading to unplanned pregnancy being common.[703,715] With the use of CFTR modulators, potentially negating some of the issues which influenced fertility such as increased cervical mucus, there has been a rise in unplanned pregnancies.[703,713,716] Data indicates that outcomes for women with CF who planned their pregnancy are better for both mothers and their babies.[717]

It is important that discussions with women with CF around fertility and family planning begin in adolescence and continue into adulthood,[704,713,714,716,718] providing knowledge about potential fertility to allow informed choices about contraception. Women with CF have expressed wanting transparent conversations with their CF clinicians about their reproductive goals and options, revolving around shared and informed decision-making, as well as the desire for individualised pre-conception plans.[719,720] Women may discuss sexual activity and pregnancy intentions with physiotherapists, and open communication and liaison with the wider CF MDT is essential as family planning is complex.[714]

Pregnancy is generally well-tolerated in women with CF with no long-term reduction in lung function seen.[721] However, many women with CF do experience difficulties in maintaining stability of their health during pregnancy and pre-pregnancy risk factors for this include CFD, inadequate nutrition, *B. cepacia* or MRSA colonisation and poor or declining lung function over the last year.[703,722,723]

A good health status at baseline with FEV_1 greater than 60% predicted is associated with a lower risk of developing complications during pregnancy, delivery, and post-partum.[724–729] Additionally, a BMI of at least 22kg/m^2 is recommended prior to conception for better health outcomes.[730] However, there is emerging evidence that baseline disease severity, although potentially impactful on infant outcomes, does not affect disease progression during or after pregnancy, therefore it should be considered that women with severe CF can manage pregnancy.[731]

Baseline maternal demographics such as lower lung function, Pseudomonas colonisation and pancreatic insufficiency have been linked to infant complications such as low birth weight and premature birth.[722,731,732] However, data is emerging showing that pregnancy can be tolerated in women with CF with FEV_1 less than 50% with no link between FEV_1 and gestation age.[733]

Due to the potential complications, pregnancies should be carefully planned wherever possible, with genetic counselling, optimisation of health pre-conception and close monitoring during and after pregnancy to detect any decline in health status.[726] Physiotherapists should work with women with CF who are planning pregnancy to optimise airway clearance, inhalation therapy and exercise regimes.

12.2.3 Antenatal period

Normal changes that occur during pregnancy may adversely affect the pregnant woman with CF, with registry data indicating that women with CF experience more complications during pregnancy than women without CF.[729,734] For optimal outcomes during pregnancy, interdisciplinary working between obstetrics, maternal health and CF teams is recommended[735] with more frequent reviews.[736]

One small study reported a non-significant trend that women who did not recover their lung function after pregnancy had a significant lung function decline at three months of pregnancy.[737] To prevent early decline, close monitoring, interventions and optimisation therapies should be used to manage pregnancy side-effects. Treatment for decline in lung function or nutrition should be proactive during and after pregnancy to ensure the best outcome for both mother and baby.[725]

There are no prospective studies evaluating physiotherapy interventions during pregnancy. However, pregnancy has a significant impact on respiratory status and physiotherapy requirements are likely to change throughout the antenatal period.[712,724,738] Physiological and mechanical changes encountered during pregnancy affect the breathing pattern, and some women may benefit from help to differentiate between the dyspnoea that occurs during respiratory exacerbations that require treatment and normal physiological breathlessness of pregnancy, the management of which should be taught early.[725] Nasal obstruction may occur during pregnancy due to the increased amount of blood flowing through the body causing mouth breathing and/or snoring. Effective sinus management should be taught using saline spray or nasal lavage.[725]

Side effects of pregnancy such as morning sickness and nausea can be detrimental to physiotherapy routines, and discussions with pregnant women with CF around ability to complete ACTs are key to enable adjustments, such as consideration of gentle breathing techniques like AD.

Positioning for ACTs will require modifications potentially from an early stage in the pregnancy when nausea can impact on airway clearance and sitting, standing and head-up positions should be considered. The supine position should be avoided during the second and third trimesters because of the pressure of the foetus on the inferior vena cava which can decrease venous return and cardiac output.

As pregnancy progresses a reduction in functional residual capacity causes early airway closure into closing volumes and may lead to a risk of hypoxia and impaired secretion clearance due to atelectasis.[725] Additionally, the displacement of the diaphragm upwards may create a V/Q mismatch, further affecting ventilation and reducing residual volume.[739] Proactive monitoring and escalation of treatment strategies with a low threshold for positive pressure (such as NIV and intermittent positive pressure breathing) may help to minimise these risks.

A retrospective review of pregnancies from one Centre in 2008 suggested that women with an FEV_1 less than 60% were more likely to need frequent changes in ACTs and may require the addition of positive pressure during hospital admission to enhance ACT effectiveness and reduce work of breathing.[738] However, a comparative review of this data to 2021–2023 data indicates that in the current era more women are managing pregnancy without admissions or additional positive inspiratory pressure.[740] Nevertheless, close monitoring by a Specialist CF maternal clinic with physiotherapeutic input should remain, as adaptions to ACTs were still required irrespective of CFTR modulator status.[740] A specialist physiotherapist is well-placed to check quality and adherence of ACTs and inhaled therapies throughout pregnancy to prevent pulmonary exacerbations[739] and plan the support required post-delivery.

Additional nebulised medications are commonly used during pregnancy when the use of systemic preparations is limited by concerns about possible teratogenicity. Proactive use of mucoactive agents such as dornase alfa, hypertonic sodium chloride and inhaled dry powder mannitol will help to optimise airway clearance when it is limited by physiological changes.

During pregnancy, biomechanical changes such as softening of ligaments, low muscle tone, increasing weight and enlarging breasts and

abdomen may affect posture and activity.[725] Patients may experience neck and back pain because of lumbar lordosis. Pregnant women with CF should be encouraged to continue exercising with emphasis on mobility for thoracic spine and shoulders alongside strengthening of muscles around the pelvic girdle.[725] As pregnancy advances, the abdominal muscles become progressively stretched and can become separated down the midline. If a patient experiences pain or muscular herniation a stabilising binder should be considered for airway clearance.[725]

Pregnant women with CF should be advised to modify their exercise programmes to avoid contact sports and reduce overheating and dehydration that can occur with activity. Walking, swimming, and prenatal yoga are recommended forms of exercise that can be utilised to maintain fitness levels during pregnancy. Oxygen saturation should be monitored during exercise; if SaO_2 falls below 90% supplemental oxygen should be given.[725] Additionally, pregnant women with CF should also be advised to complete daily pelvic floor exercises with instruction on the Knack technique, to prevent UI.

Pregnancy after lung transplant usually requires little Specialist CF physiotherapy input, but the physiotherapist will have a role in monitoring for signs of possible infection or rejection episodes and maintaining posture, mobility, pelvic floor and physical strength. Women with CF may still have upper airway and nasal obstruction, and sinus infections may occur.[719,725]

12.2.4 Post-partum

12.2.4.1 Neonatal period

In the first few days after delivery consideration needs to be given to the new mother's ability to maintain her own health alongside caring for her child. Factors which will influence this ability will include the type of delivery the woman experiences (caesarean section [C-section] or vaginal), health status and support mechanisms. Completing ACTs and nebulised medication is essential to stabilise and improve pulmonary function once the baby has arrived, and to prevent decline in lung function in the post-partum period. A retrospective review of pregnancies over 10 years at one UK CF Centre reported some women experienced moderate falls in lung function immediately after delivery, which persisted at 12 months post-partum,[721] so close monitoring and MDT support in the early post-partum period is essential.

C-section deliveries are common for women with CF, with one registry study finding no association between clinical variables such as lung function and the type of delivery.[732] French CF registry data indicates that women with low lung function and who were not on CFTR modulators pre-conception have higher rates of C-sections.[741]

If the delivery is via C-section, or if there are significant tears post vaginal delivery, pain post-partum may affect mobility and coughing which may impact effectiveness of ACT, and so adequate analgesia should be offered.[739] Early mobilisation in the immediate post-partum period is important and can help facilitate ACT.[713]

To help new mothers fit in ACT and nebulised therapies, regimes should be adapted if needed to optimise effect while being time efficient. Adjuncts such as PEP or OPEP should be considered to help to recruit any lung areas which have been restricted during the later stages of pregnancy, or to offer a simple and effective ACT. Nebulised therapies should be reviewed with focus on time-efficient and quiet equipment, with consideration of reducing compressor noise where possible to allow nebulisation during a baby's nap time.[725]

12.2.4.2 Motherhood after the first few weeks

There is conflicting evidence about the effect of parenthood on mothers with CF. One study looking at parenthood reported decreases in BMI and FEV_1 in the year following birth;[742] however another review looking at the long-term effects on mothers up to 11 years after pregnancy reported that pregnancy and motherhood did not appear to accelerate disease progression.[728] Both studies did report an increase in pulmonary exacerbations,[728,742] with the longer-term study also noting more illness-related visits and a decrease in some domains of QoL.[728]

While the effect of CFTR modulator medications in parenthood is largely unknown, the recent work of Kazmerski et al reported that CFTR modulator use prevented decline in lung function in the first year of parenthood but did not prevent decreases in BMI or occurrence of pulmonary exacerbations.[742]

Mothers with CF have described their child as being a motivating factor to stay well and that while initially it can feel difficult, disruptions to treatments ease as motherhood progresses.[743] Physiotherapists need to provide ongoing support and guidance to mothers to optimise regimes for ACT, inhalation therapies and exercise which fit in with the changing demands of motherhood.

12.2.4.3 Fatherhood

Approximately 95% of men with CF are infertile due to a congenital bilateral absence of vas deferens (CBAVD) with abnormalities of semen volume, pH and constituents.[739] Although there has been improvement in fertility with CFTR modulators in

women with CF, men with CF are highly unlikely to experience improved fertility status due to CBAVD. There are currently no case reports of rescue of fertility in men with CF treated with ivacaftor since its approval in 2012.[718]

With the development of assisted reproductive technology (ART), more men with CF are becoming fathers.[744] It is recommended that adult men with CF are referred to a urologist with expertise in sexual medicine and infertility.[745] Other than ART, alternative paths to parenthood include adoption and fostering.[718]

Whilst fathers do not experience pregnancy, they are subject to many of the demands and challenges of parenthood planning and managing young children.[744] Pre-optimisation of health status during parenthood planning should be considered to minimise physical health deterioration of new fathers after birth. New fathers' adherence to treatments may reduce while caring for a newborn, and strategies to help fit therapies into childcare routines should be explored.[718]

One small study showed no significant change in disease trajectory for men with CF who became fathers; however, half of fathers with a FEV_1 less than 40% at the time of the birth of their child had died or received a lung transplant before their child was two years old.[744] Data from the UK Registry ranging from 2015 to 2019 highlighted that fatherhood negatively impacted on FEV_1 and BMI, with an increase in pulmonary exacerbations.[742] CFTR modulator use was seemingly protective of changes in lung function, but not BMI or occurrences of exacerbations.[742]However, this registry study pre-dates the widespread use of CFTR modulator therapy. Further studies are required to understand the full impact of fatherhood on clinical outcome in this CFTR modulator-treated cohort.

12.2.5 Recommendations

- ACTs should continue throughout pregnancy and be regularly reviewed and modified as pregnancy progresses with consideration to side-effects and the degree of breathlessness and discomfort *(QoE – very low)*.
- Pregnant women should be familiar with using a fast, efficient nebuliser system. This is good preparation for the post-partum period where time can be limited when caring for the newborn child *(QoE – very low)*.
- All pregnant women with CF should be given postural awareness advice, strengthening and stability exercises for the lumbosacral and pelvic floor regions. Onward referrals to MSK and women's health services for further input should be completed as appropriate *(QoE – very low)*.
- Proactive assessment for ambulatory oxygen desaturation is recommended and supplementary oxygen can be utilised to maintain SpO_2 above 90% in foetal oxygenation *(QoE – very low)*.
- Analgesia should be optimised post-delivery to minimise impact on mobility, ACT and coughing *(QoE – very low)*.
- Patients who stop CFTR modulator therapy pre- or during pregnancy and/or breastfeeding should be reviewed and closely monitored regarding airway clearance and inhalation therapy requirements *(QoE – low)*.

12.2.6 Good practice points

- Individualised preconception and parenthood health information should be offered to all people with CF as appropriate.
- Optimisation of health status should be considered for all people with CF entering parenthood.
- Pregnant women with CF should be taught early to differentiate between the dyspnoea that occurs during respiratory exacerbations that require treatment and normal physiological breathlessness of pregnancy.
- ACTs should be reviewed regularly throughout pregnancy and modified as necessary, including consideration of positioning and introduction of positive pressure support.
- Close monitoring through a specialist maternal health clinic or collaboration with obstetric colleagues is recommended.
- Proactive use of mucoactive agents such as dornase alfa, hypertonic sodium chloride and inhaled dry powder mannitol (Bronchitol®) will help to optimise airway clearance when it is limited by physiological changes with consideration of time-efficient nebuliser systems.
- If mechanical pain, diastasis-rectus or muscular herniation occurs during pregnancy, a stabilising binder can be useful.
- If nasal obstruction is an issue during pregnancy, effective sinus managements techniques should be taught.

- Gastro-oesophageal reflux during pregnancy should be identified and treated if present.
- The importance of pelvic floor exercises during and after pregnancy should be stressed, and the Knack taught, to be used preceding any forced expiratory manoeuvres.
- Early mobilisation and chest physiotherapy post-partum is recommended, with analgesia as required in the immediate post-partum period.
- Advice should be provided for managing treatments post-partum including family assistance, combining treatments such as hypertonic sodium chloride and PEP, using nap times for airway clearance and planning who can clean equipment.

12.2.7 Research recommendation

- Changes to physiotherapy interventions with pregnancy and parenthood to support best practice.

12.3 Liver disease

It is estimated that between 20 and 40% of all people with cystic fibrosis have CF-associated liver disease (CFLD). CFLD is an early complication of CF that occurs mostly in the first decade of life, particularly in those with a history of meconium ileus or pancreatic insufficiency and severe mutations.[746] Although clinically heterogenous, approximately 5 to 10% of all people with CF develop multilobular cirrhosis in the first decade of life.[747] CFLD that is identified later than this, tends towards a stable, non-progressive course in later life.[748]

The independent risk factors associated with cirrhosis in CFLD are:

- being male
- *P. aeruginosa* airway infection
- CFD.[747]

CFLD is associated with a polymorphism in the alpha-1-antitrypsin gene.[749] The annual prevalence of CFLD has increased from 203.4 to 228.3 per 1000 patients from 2008 to 2013 in a UK prospective study.[747] If cirrhosis and/or portal hypertension is present, this is classified as severe CFLD.[748] The presence of CFLD is associated with a higher mortality compared to those without liver disease.[747] Cirrhosis is associated with a higher all-cause mortality and shorter overall survival compared with non-cirrhotic CFLD. However, most deaths in a UK CF Registry study were in adults (97.5%) and secondary to non-hepatic complications (96%). **It is suggested that liver cirrhosis is a systemic syndrome a – contributory factors include:**

- increased susceptibility to infection
- sarcopenia
- renal dysfunction
- cardiomyopathy.

All of the above make an individual more susceptible to cardiorespiratory failure during infectious exacerbations.[747]

There remains no data examining the efficacy of airway clearance in people with CFLD. However, it must be recognised that massive splenomegaly and the resulting abdominal distension, impaired nutritional intake due to gastric compression and impaired diaphragmatic function can cause dyspnoea.[652]

CFLD is associated with multiple endocrinopathies, some directly related to liver dysfunction and some as a consequence of liver dysfunction.[750] These factors affect treatment pathways and considerations for the physiotherapist when assessing people with CF. Those individuals with severe CFLD will have some known endocrine comorbidities and special attention should be paid when considering treatment options. **The following are the most important comorbidities to consider when planning treatment:**

- Vitamin D deficiency, as this is further exacerbated in those with underlying CFLD due to biliary stasis.
- BMI and nutritional status, which may be impaired over and above typical CF nutritional status impairment; since nutritional status is associated with linear growth, maintenance of BMI, pulmonary function and survival in CF, optimisation of nutrition and lean mass is a crucial component of CF care.
- Bone disease and osteoporosis – individuals with CFLD have a 1.8-fold higher frequency of CF bone disease compared to matched controls with CF. This is likely a combination of the above factors in addition to vitamin K deficiency, hypogonadism and IGF-1 deficiency.
- Impaired glucose metabolism and CFD are more common in individuals with CFLD with cirrhosis. CFLD is an independent risk factor in the development of CFD. The combination of CFLD and CFD is also independently associated

with poor clinical outcomes including decline in pulmonary function, increased risk of hospitalisation, impaired nutritional status and increased risk of mortality.[750]

A recent publication looking at physical activity and liver disease in adolescents with CF tells us that CFLD negatively affects fat-free mass.[751] Physiotherapists should pay particular attention to exercise prescription in this complex population. There should be a focus on strength work with functional weight-bearing exercises to reduce the impact of osteoporosis and improve lean mass, paying close attention to blood glucose levels during exercise prescription. Working closely with dietitians to optimise nutritional status and glycaemic control is important.

12.3.1 Recommendations

- Individuals with CFLD should have frequent review by CF physiotherapists to ensure adequate airway clearance with quick escalation to use of positive pressure via PEP or NIV as adjuncts to airway clearance to aid good basal ventilation and secretion clearance in the presence of hepatomegaly *(QoE – moderate)*.
- Vigilance with monitoring haemoptysis and clotting factors with every treatment to prevent undue risk from bleeding (either intrapulmonary or variceal). Although platelet volume is often impaired chronically in CFLD, more important is large daily change in platelets or haemoglobin *(QoE – high)*.
- In the presence of such high nutritional demands it is imperative that safe exercise and strength training takes place within the context of adequate nutrition and diabetic control, with close interdisciplinary review between Dietetics, CFD Specialist Nurses and Physiotherapists *(QoE –moderate)*.

12.3.2 Good practice points

- Abdominal distension due to hepatosplenomegaly or ascites may restrict diaphragm excursion and cause basal atelectasis. In these circumstances, supine positioning should be avoided; ACTs may be more comfortable and effective in an upright or side lying (head raised) position.
- Use of PEP in the prevention of atelectasis should be considered.
- Contact sports should be avoided in those with hepatosplenomegaly.
- Physiotherapists should work closely with dietitians to optimise nutritional status and glycaemic control where required to allow the individual to remain as active as possible.
- Effective exercise programmes are essential to prevent sarcopenia and reduce or delay the onset of osteoporosis.
- In the presence of abnormal clotting, manual techniques should be avoided. Potential for haemoptysis is increased also; physiotherapists should be vigilant and refer to haemoptysis guidelines should this occur.
- Deficiency in regulatory mechanisms result in derangement in the extracellular fluid volume, and may lead to ascites, oedema or pleural effusion. Careful attention to positioning for airway clearance and during exercise is important.
- In the presence of active variceal bleeding, physiotherapy may need to be discontinued or carried out with extreme caution.
- Intensification of airway clearance (including treatment during anaesthesia) may be required if repeated anaesthetics are required for monitoring and management of oesophageal varices.
- Anaemia should be considered as a cause of breathlessness when carrying out respiratory assessment and anaemia may affect ability to exercise.
- In those with hepato-pulmonary syndrome, monitoring of oxygen saturations during exercise and any physiotherapy interventions is important, with frequent assessment of nocturnal oxygenation and oxygen requirements during exercise.

12.3.3 Research recommendations

- Research should be carried out around liver disease-associated sarcopenia and its implications for exercise intolerance and frailty.

12.4 Haemoptysis

Haemoptysis is the expectoration of blood from the lower airways, which can range from a minor streaking of blood in the sputum to massive bleeding that can have life-threatening consequences due to airway obstruction, hypoxaemia and haemodynamic instability.

Although haemoptysis is thought to be a common complication of CF, there is huge variation in the literature on incidence. It is thought to occur in approximately 9% of the CF population,[752] but there is some reporting of mild haemoptysis to be as high as 60%.[753,754] Adults are nearly four times more likely to experience haemoptysis than children,[755] with the first episode usually occurring between 18 and 30 years of age.[753,754] Massive haemoptysis (MH) occurs in approximately 1 to 4.1% of all people with CF and is rarely seen in children younger than 10 years.[753,754]

There is little evidence to fully assess the impact of CFTR modulators on incidence of haemoptysis in the CF population; one observational study analysing data from US and UK registries comparing those taking ivacaftor to matched controls showed a downward trend in incidence of pulmonary complications including haemoptysis.[756] This study did not assess the impact of Kaftrio, but UK CF Registry data does suggest that there may have been a potential reduction in annual incidence of haemoptysis.

Incidence of any haemoptysis in those under the age of sixteen years is very low and reported in absolute numbers, with 16 young people reported in 2019[600] reducing to less than five in 2024.[2] A similar change was seen in adults, where a higher percentage of those 16 years or older experienced haemoptysis in 2019 (6.6%)[600] compared to 2024 (2.4%).[2] Similar trends are also seen in annual overall incidence of MH (0.6% versus 0.1% respectively) with no reported cases in those under the age of 16.[2,600] US data also suggests that there may have been a decrease in incidence of MH in recent years, however no reduction in frequency of haemoptysis overall.[757]

Bleeding usually arises from a bronchial artery, but many reports have also suggested aberrant origin of haemorrhages from non-bronchial collateral vessels or from anastomosis between bronchial and non-bronchial circulation.[758] Knowledge of the precise pathogenesis of haemoptysis is limited but has been attributed to the persistent inflammation of the airways and vascular growth, which results in hypertrophied bronchial arteries.[759] Chronic and acute inflammation weakens the vessel walls and often leads to episodic or persistent bleeding into the bronchial lumen. Whilst the most common cause is infective exacerbation, a small case series has reported catamenial haemoptysis where the expectoration of blood coincides with menses which improved following initiation of CFTR modulators.[760]

Risk factors shown to be associated with haemoptysis in CF are older age, more advanced lung disease and the presence of *P. aeruginosa*,[755] with MH more likely to be associated with the presence of *S. aureus* in sputum cultures.[759] Identifying predictors for MH is challenging as it is not exclusive to advanced disease and older age.[761] A retrospective study has identified that the presence of bronchial arteries with a diameter of 3.5mm or above and hypertrophied systemic non-bronchial arteries on CT angiography significantly correlates with MH, when compared to those with end-stage disease and no haemoptysis (p=0.002).[762] This may therefore serve as a possible risk predictor for MH.

12.4.1 Diagnosing and treating haemoptysis

Diagnostic investigation of haemoptysis includes:

- history taking
- clinical chemistry
- chest radiography
- contrast-enhanced CT with pulmonary angiography (CTPA) (in the case of moderate to large volume haemoptysis) – this is used to identify hypertrophied vessels, localising the source of bleeding to help plan subsequent treatment intervention such as bronchial arterial embolisation (BAE).

Rigid bronchoscopy can be performed as a diagnostic measure in identification of the bleeding vessel. However, there are some limitations to this and unless the vessel is bleeding at the time of bronchoscopy it is often difficult to localise. CTPA has been shown to have higher sensitivity and specificity when compared to bronchoscopy for diagnosing bronchial arterial abnormalities.[763]

Differentiation of severity of haemoptysis is necessary as treatment differs. This is based on volume of blood expectorated. Estimation of this can be challenging and is often under- or overestimated.[764] Much of the literature considers the definitions of haemoptysis as follows.[764,765]

- **Scant haemoptysis:** less than 5ml
- **Mild haemoptysis:** 5ml to less than 50ml in 24 hours
- **Moderate haemoptysis:** 50ml to less than 250ml in 24 hours
- **Massive haemoptysis:** more than 250ml in 24 hours or more than 100mls for 2 days or more

Mild or moderate haemoptysis is commonplace and often associated with pulmonary exacerbation. Generally, this is self-limiting and is managed conservatively, usually responding to a course of antibiotic therapy. Other medical treatments which may be considered alongside antibiotics are vitamin K, blood replacement and tranexamic

acid.[754,766,767] In the event of a MH the aim of initial management is maintenance of gas exchange by maintaining the airway, administering oxygen and positioning with the bleeding side down, if known. Nebulised adrenalin may be administered where active haemoptysis does not settle spontaneously. Once stabilised, BAE is an accepted and effective method of controlling the bleeding.[758]

Whilst there are no randomised control studies investigating BAE as a treatment option for MH, recently published small retrospective single-centre cohort studies ranging from five to 20 years' duration evaluated the safety, effectiveness and outcomes following BAE.[762,768–770] In addition, a four-year prospective observational study reported outcomes following BAE in individuals with both MH and sub-massive haemoptysis.[771] Whilst the reported outcomes differ slightly between studies, most highlight recurrence rates following initial intervention ranging from 30 to 60%,[768–771] with repeat BAE being required in 37 to 58.8% of cases,[762,771] and a median recurrence-free period of 3.9 years.[769] The median number of interventions was two per individual, ranging from one to seven.[762,768]

Bandaralage et al (2021) failed to identify any variables or risk factors associated with the need for repeat BAE but identified that each recurrent episode of haemoptysis requiring BAE was significantly associated with increased risk of mortality, ranging from 9 to 14.8% at 12 months.[762,768,771] Similarly, Flight et al (2017) were unable to identify any statistically significant factors associated with mortality.[771] Floridi et al (2022) have recently evaluated the role of BAE in the management of sub- massive haemoptysis in a five-year retrospective cohort study with 13 people with CF. The study was limited by small participant numbers but reported slightly lower recurrence rates, with 69.2% haemoptysis-free at six months, and also identified that early intervention is associated with a reduction in recurrence severity. They concluded that in the case of sub-massive haemoptysis BAE had potential to improve QoL and should be considered for bridging for transplantation.[772]

Serious adverse events following BAE are rare but can include cerebral vascular accident, paraplegia and transverse myelitis. Reporting of less serious complications is more common but incidence varies in the literature, ranging from 5.2 to 60.8%,[761,771] likely due to differences in recording of adverse events. The most common of these is post-procedural chest pain.[761,762,768–772] Pain is commonly not severe, although one study reporting 20-year experience of BAE in an Australian tertiary centre reported some cases of chronic pain syndrome requiring months of narcotic analgesic drugs.[768]

There are no published studies regarding the physiotherapeutic management of haemoptysis. North American guideline based on a Delphi consensus provide some guidance.[767] Whilst there was no representation from physiotherapy on the expert panel, these guidelines do include recommendations regarding physiotherapeutic strategies for managing haemoptysis.

12.4.2 Management

12.4.2.1 Scant or mild haemoptysis

For scant, mild haemoptysis, there is no evidence to indicate that alteration in treatment strategies is necessary, and there is good consensus to suggest that stopping airway clearance and all inhaled therapies is inappropriate.[767] It has been suggested that enhanced airway clearance to aid the removal of purulent secretions contributing to the pulmonary exacerbation may be beneficial.[766]

12.4.2.2 Moderate haemoptysis

In the management of moderate haemoptysis, modification of physiotherapy is prudent. In theory, positive pressure treatments may aggravate friable vessels; it is worth considering discontinuing these in favour of more controlled breathing techniques such as ACBT or AD. Percussive devices and oscillatory devices should also be used with caution. Whilst there are concerns that ACTs may dislodge a clot and exacerbate bleeding, this is unlikely and if bleeding is related to the underlying infection and inflammation, clearance of airway secretions is an important component of care.[767] For those with mild to moderate haemoptysis, the benefits of continuing all inhaled therapies should be balanced alongside the risks with each individual; therapy should be withheld only if it seems to exaggerate or provoke bleeding.[767]

12.4.2.3 Massive haemoptysis (MH)

In the event of MH, strongly consider temporarily stopping all airway clearance with continual assessment and review.[767] There is also strong consensus regarding the recommendation to withhold NIV in the event of MH in many circumstances.[767] The use of hypertonic sodium chloride and dornase alfa has been suggested to present a risk, although this remains unproven. Hypertonic sodium chloride might be considered more of a risk due to potential to irritate the airways, induce cough and therefore possibly provoke bleeding; there is strong recommendation to consider stopping this in the event of MH.[767]

There is no guidance regarding modification of inhaled mannitol (Bronchitol®) in the event of haemoptysis as the consensus guidelines pre-date its licence. However, as it has a similar mode

of action as hypertonic sodium chloride and has the potential to provoke uncontrolled coughing it should follow the same recommendations. There is also suggestion from the limited evidence that the benefit of continuing all other inhaled therapies outweighs the risks and therefore should only be withheld if they seem to exaggerate or provoke bleeding.[767] Whilst Flume et al (2009) found a decreased incidence of haemoptysis in patients who were using dornase alfa long-term in clinical practice stopping this during and for 48 hours after an acute episode if massive is considered best practice.

12.4.3 Exercise and haemoptysis

There is a lack of published studies regarding exercise following haemoptysis. Exercise and habitual physical activity guidelines[254] based on consensus opinion of physiotherapy experts worldwide, recommend ceasing exercise following moderate or massive haemoptysis, resuming a gradual exercise programme after 24 to 48 hours of no new bleed.

12.4.3.1 Exercise and recurrent haemoptysis

Some individuals may experience recurrent haemoptysis despite BAE. There are no published studies but emerging evidence through individual case reporting suggests that physical activities or triggers which increase heart rate such as salbutamol, caffeine-based drinks or anxiety can provoke episodes of haemoptysis. The proposed mechanism is not clear, but it is suggested that the increase in pulmonary artery blood flow and blood pressures, as a result of the increase in heart rate, causes break through bleeding in small blood vessels around areas of infection. Inhaled medications have also been shown to provoke recurrent bleeding in some individuals. Where there is clear association, the risks versus the benefits of withdrawing the inhaled therapy might be considered. More studies are required to gain clearer understanding of factors that may be associated with recurrent haemoptysis and how to manage this in the long-term.

12.4.4 Perspective of people with CF

In 2020 Roman et al reported results of a small survey exploring the perspectives of people with CF around haemoptysis.[773] Open questions revealed 77% of 32 respondents who had experienced haemoptysis found the first experience 'scary', 'frightening' 'worrying' or 'jarring'. Half of respondents described negative impact on their QoL associated with worsening anxiety and stress, fear of bleeding in public or other life impacts. Fear of recurrent haemoptysis had prompted some to reduce activity, travel less and modify work schedules. It is important for health care professionals to recognise the distress caused by haemoptysis and to support management of anxiety. Displaying sensitivity to individual experience and offering proactive advice about how to manage future events may be helpful. Respondents were keen for research to better understand triggers of haemoptysis which may help to alleviate anxiety.[773]

12.4.5 Recommendations

- For mild haemoptysis there should be no immediate change to airway clearance, exercise, NIV or inhalation therapies *(QoE – low)*.
- For moderate haemoptysis vigorous exercise should be ceased for 24 to 48 hours *(QoE – low)*.
- For massive haemoptysis airway clearance, vigorous exercise and NIV should be temporarily ceased *(QoE – low)*.
- Consider stopping hypertonic sodium chloride *(QoE – low)*.
- Continue other inhaled therapies unless they appear to aggravate or provoke bleeding; temporarily cease and reassess once bleeding settles *(QoE – low)*.

12.4.6 Good practice points

- Physiotherapists should be aware of anxiety related to haemoptysis and offer proactive advice around management of future episodes.
- Physiotherapists should be aware of the potential for recurrent haemoptysis, including after BAE.

12.4.6.1 Mild haemoptysis

- Continue airway clearance, inhaled therapies and exercise, but with close monitoring of symptoms combined with medical management to treat underlying infection.

12.4.6.2 Moderate haemoptysis

- Physiotherapy interventions should be modified following clinical assessment. This should include careful consideration of the benefits and risks of altering treatment regimes, recognising that maintaining effective airway clearance is an important component of ongoing treatment of underlying infection. Treatment modifications should include the following:
  - Avoiding the use of positive pressure techniques (internal, external or oscillatory) for 24 to 48 hours after a bleed. Consider

ACTs such as ACBT or AD which utilise controlled coughing.
- Minimising vigorous or excessive coughing.
- Continuing all inhaled therapies but consider stopping on an individual basis if identified as potential trigger to uncontrolled coughing or further bleeding.
- Ceasing physical exercise for 24 to 48 hours after a bleed.
- Maintaining physical activity with careful monitoring of physiological status.
- Temporarily ceasing NIV or, where considered too great a risk, consider temporarily reducing inspiratory pressures until bleeding settles.

12.4.6.3 Massive haemoptysis

- Acute management should prioritise assessment and maintenance of airway and physiological status, using **NICE guidance** on recognising and responding to deterioration or risk of deterioration.[774]
- Optimise oxygenation and humidification.
- Careful positioning with high side lying, bleeding side down. Cease all physiotherapy treatments, inhaled mucolytics and exercise.
- Following embolisation, in liaison with interventional radiologist, resume normal airway clearance and a graduated exercise programme.
- Ensure adequate analgesia if chest pain limits effective airway clearance.
- Psychological support and reassurance in resuming normal activity and treatments may be required.

12.4.6.4 Recurrent haemoptysis

- Where individuals experience ongoing haemoptysis despite BAE, identification and modification of potential triggers (including inhaled therapies) may be required while taking into consideration individual needs.
- Where exercise has been identified as a trigger:
  - avoid increasing HR more than 20 to 30 bpm above resting heart rate
  - keep heart rate below 120–130 bpm maximum
  - where resting heart rate is above 100 bpm, limit physical activity, avoiding an increase or spike in heart rate during active bleeding episodes and the acute recovery period following this.
- Avoid or reduce caffeinated drinks.
- If tachycardia associated with salbutamol is identified as a trigger, consider reducing the dose or an alternative bronchodilator.

12.4.7 Research recommendations

- Clinical consensus is needed on how and when to alter maintenance inhaled therapies during acute episodes of haemoptysis.
- Clinical consensus is needed on how and when to alter airway clearance and physical exercise during acute episodes of haemoptysis.
- Explore and gain understanding on potential triggers and how to manage these for people with CF who experience ongoing recurrent haemoptysis.

12.5 Pneumothorax

Spontaneous pneumothorax is defined as the presence of air in the pleural cavity and is frequently considered a poor prognostic indicator in CF, with an average survival rate of 24 to 30 months in adults following the initial episode.[766,775–778] A small paediatric study suggested survival rate to be slightly better at 48 months.[779] Pneumothorax has been identified to be one of the factors associated with increased risk of mortality ($p<0.0001$) in children with CF admitted to PICU, although overall survival outcomes are improved.[780]

UK CF Registry data from 2024 reported overall annual incidence of pneumothorax (requiring chest drain) to be 0.0% (n=5), with no reported incidence in people with CF below 16 years of age.[2] This is similar to the evidence in the literature which reports annual incidence of spontaneous pneumothorax to be approximately 0.64% (1 in 167 people with CF),[766,775,781,782] with a median age of incidence of 23 years.[781]

There is little evidence to fully assess the impact of widespread use of CFTR modulators on incidence of pneumothorax in the CF population but an observational study analysing data from US and UK registries comparing those on ivacaftor to matched controls showed a non-significant reduction in incidence of pulmonary complication which included pneumothorax (requiring a chest drain).[756] Most recent UK CF Registry data also appears to indicate decreased incidence of pneumothorax (requiring a chest drain) reporting overall incidence as 0.3% in 2019 versus 0.1% in 2023 and 0.0% in 2024, with no instances in those below 16 years of age.[2,783] US data also indicates a possible decrease in incidence of pneumothorax in recent years.[412]

A published review suggests anatomical risk factors such as cysts, subpleural blebs and bullae, all commonly identified in the lungs of people with CF, are associated with pneumothoraces.[782] These areas are prone to distention due to gas trapping from small airway obstruction. There is supporting evidence associating severe airflow obstruction with pneumothorax, with 75% of individuals experiencing a pneumothorax having an FEV_1 less than 40% predicted and many observed to have high residual volumes.[784] Specific pathogens and nebulised therapies have been linked to an increase in risk of pneumothorax, though it is more likely that their presence reflects the severity of airways disease and airflow limitation.[785]

Clinical presentation of pneumothorax in CF may occasionally be asymptomatic, but more often presents with sudden onset of chest pain and breathlessness. It has the potential to result in respiratory failure, particularly in individuals with severe disease manifestation. Diagnostic investigation can be challenging with chest X-rays having the potential to be misleading, particularly in advanced CF. There should be low justification for a chest CT scan as this accurately assesses pneumothorax size and supports clinical decision-making for ongoing medical management.

The primary goal for medical management strategies is to re-expand the lung. Small asymptomatic pneumothoraces may be managed conservatively and resolve spontaneously, however, as 20 to 75% experience recurrence, more aggressive management is justified in this population.[775,786–789] Management strategies include high flow oxygen therapy and chest drain placement; the latter may be combined with preventative interventions such as pleurodesis.

Surgical pleurodesis or pleural abrasion using video assisted thoracoscopic surgery (VATS) appears to be the most effective and preferred management option,[766,775,777] although a Cochrane review identified no RCTs assessing efficacy of either chemical or surgical pleurodesis in people with CF.[790] Pleural procedures, including pleurodesis do not have a significant adverse effect on the outcome of later lung transplantation[778] and are no longer considered an absolute contraindication.[791] Recently endobronchial valve therapy has been reported as a potential novel management strategy for persistent air leak in people with CF deemed too high risk for surgery, or where there is concern chemical pleurodesis may unnecessarily increase risk of complications at lung transplantation.[791,792]

To promote resolution of pneumothorax it is suggested that supplemental oxygen at high flow rates generates a partial pressure gradient between the pleural cavity and end capillary blood by decreasing the partial pressure contribution of nitrogen, theoretically increasing the reabsorption of gas from the pleural cavity. Increased rates of reabsorption whilst on oxygen were demonstrated in a small prospective study of 10 people with CF, including children.[779] It is recognised that individuals remain at risk of respiratory deterioration, despite medical management with insertion of intercostal drain. Lord et al identify several contributing factors which include pleural pain, immobility and underlying lung volume loss.[782] They stress the need for prompt, early management which should include IV antibiotics and adequate analgesia to allow effective airway clearance and early mobilisation under the supervision of experienced CF physiotherapists.

There are no published studies advocating the physiotherapy adaptations required with a pneumothorax, although there are two consensus guidelines available that provide some recommendations regarding physiotherapy interventions. These have been based on results of a worldwide informal survey regarding exercise management[791] and expert opinion by a Delphi consensus regarding airway clearance techniques, NIV, inhaled therapies and general activities.[767] It should be noted that the latter did not have physiotherapy representatives on the expert panel.

Flume et al highlight that it is generally considered appropriate to continue airway clearance as reducing airway obstruction by clearing mucus may aid resolution and/or prevent any worsening of the pneumothorax[767]. There is little guidance recommending the most appropriate ACT, but techniques that are based on controlled breathing such as ACBT or AD may be more favourable.[793]

Flume et al[767] strongly recommend withholding positive pressure techniques due to the risk of increasing intrapleural pressure and potential to cause progression of the pneumothorax. Whilst it did not reach good consensus, there is suggestion that when a chest drain is in situ, it may not be necessary in all circumstances to withhold positive pressure. There is no guidance on when to resume positive pressure techniques following resolution of pneumothorax; it is suggested to adhere to local guidelines with individual risk benefit assessments. The point at which spirometry is resumed may provide some guidance, but again this remains contentious in the absence of supporting evidence. Confirmation of radiological resolution is key to reducing risk with such procedures, and it is advised that individuals wait two to three weeks after successful pleurodesis before resuming activities that increase intrapleural pressure.[776,794] Where pneumothoraces have been managed conservatively it may be necessary to extend this period up to three months to reduce the risk of recurrence.[782]

Individuals with respiratory failure who develop pneumothorax should be admitted and monitored closely.[782] There is strong recommendation to withhold NIV in most circumstances,[767] although there are individual case reports where a chest drain has been sited and NIV support remains a necessity.[795] Recommendations state that this should be undertaken in an appropriate high-level care setting.[767]

There is no published evidence on the use of inhaled therapies with pneumothorax. There is, however, strong recommendations to maintain all aerosol therapies,[767] which should be reviewed and optimised by the CF team to ensure ease of airway clearance.[782,793]

There is little evidence on exercise management during pneumothorax but there is some guidance for the acute recovery period from two weeks after resolution. Flume et al highlight good consensus on avoiding activities that may increase intrathoracic pressure such as weightlifting.[767] Swisher et al are more specific and recommend avoiding lifting weights that are greater than 5lb and activities that produce the Valsalva manoeuvre.[254] Gradual upper body exercise should be resumed following removal of chest drain over two to four weeks.[254]

Consensus was not sufficient to make a definitive recommendation on when to resume exercise at higher intensities,[767] although there is guidance for the general population, where it is advised that sports that involve extreme exertion and physical contact should be deferred until full resolution and that activities involving scuba diving should be discouraged permanently.[776] It is suggested that people with CF reduce exercise intensity initially with low-grade activity being encouraged,[793] to ensure airway clearance prior to carrying out physical exercise in order to minimise vigorous coughing during exertion,[254] gradually returning to normal physical exercise activities.

12.5.1 Recommendations

- Airway clearance should be continued, with avoidance of techniques that increase positive pressure in favour of more controlled techniques such as ACBT and AD *(QoE – low)*.
- Inhaled therapies should be reviewed, and those that optimise airway clearance should be continued *(QoE – low)*.
- NIV should be withheld, or in circumstances where ventilatory requirements are such that it cannot be withheld, close monitoring in high-level care settings should take place *(QoE – low)*.
- Upper limb weightlifting over 5lb should be avoided for two weeks post resolution and airway clearance is advisable prior to exercise to minimise the risk of coughing during exertion *(QoE – low)*.
- Inhaled therapies should be continued, particularly mucolytics to optimise airway clearance *(QoE – low)*.

12.5.2 Good practice points

- Individuals should be taught how to avoid paroxysms of coughing.
- Ensure appropriate and adequate hydration and maintain use of inhaled therapies to ensure ease of airway clearance.
- Ensure appropriate analgesia to enable the individual to participate in airway clearance, maintain thoracic expansion and commence early mobilisation.
- Encourage cardiovascular exercise at lower intensity, gradually increasing post-resolution with the aim of resuming normal activities.
- Avoid upper limb resistance exercises until at least two weeks after resolution.
- Gradual re-introduction of therapy techniques using positive pressure when manoeuvres such as respiratory function testing is resumed.
- Scuba diving should be avoided permanently and there should be caution around high-altitude activities following a pneumothorax.

12.5.3 Research recommendations

- Clinical consensus is needed on how and when to alter maintenance inhaled therapies with acute pneumothorax.
- Clinical consensus is needed on how and when to alter airway clearance and physical exercise with acute pneumothorax.
- Clinical consensus is needed on how and when to alter NIV with acute pneumothorax.

12.6 Critical care

Admission to the critical care or intensive care unit is associated with a poor prognosis in CF. Factors associated with a poor outcome include prior colonisation with *B. cepacia* complex, rapid decline in FEV_1 and severe exacerbation.[796] Positive outcomes are associated with potentially reversible conditions, such as the acute management of haemoptysis or pneumothorax[797] and post-operative management. Confirmed diagnosis of COVID-19 in those post-transplant and with a lower FEV_1 poses an increased risk of requiring mechanical support.[798]

Endotracheal intubation (mechanical ventilation) is associated with a poor prognosis in people with CF.[799,800] However, the outcome of treatment with NIV is good[800,801] and many centres may manage NIV in high-dependency or ward areas. Extracorporeal membrane oxygenation (ECMO) is used on critical care as a salvage strategy in people with CF with respiratory failure and is being increasingly used as a bridge to lung transplantation.[802,803] The use of ECMO has emerged as a promising intervention that can avoid invasive ventilation and allows individuals to eat, move around and undertake airway clearance while awaiting lung transplantation.[804–807] Ambulation whilst on ECMO has been shown to be an independent predictor of successful bridge to transplant.[808]

There are no published studies on physiotherapy for people with CF who are intubated and ventilated. The NICE guideline 'Rehabilitation after critical illness in adults', should be adhered to as appropriate.[809] These national guidelines should also be applied to those receiving ECMO.[810] Rehabilitation on ECMO requires a careful, multidisciplinary approach, and should be led by staff who have completed a competency for moving individuals on ECMO.[810]

12.6.1 Recommendations

- Ensure regular airway clearance is continued and optimise humidification *(QoE – low)*.
- Ensure good positioning for optimal ventilation and drainage of secretions *(QoE – low)*.
- During a critical care stay and as early as clinically possible, perform a short clinical assessment to determine the individual's risk of developing physical and non-physical morbidity *(QoE – moderate)*.[809]
- For those at risk of physical and non-physical morbidity, perform a comprehensive clinical assessment to identify their current rehabilitation needs. This should include assessments by healthcare professionals experienced in critical care and rehabilitation *(QoE – moderate)*.[809]
- For those at risk, agree short-term and medium-term rehabilitation goals, based on the comprehensive clinical assessment. The individual's family and/or carer should also be involved *(QoE – moderate)*.[809]
- The comprehensive clinical assessment and the rehabilitation goals should be collated and documented in the individual's clinical records *(QoE – moderate)*.[809]
- For those at risk, start rehabilitation as early as clinically possible, based on the comprehensive clinical assessment and the rehabilitation goals. Rehabilitation should include:
  - measures to prevent avoidable physical and nonphysical morbidity, including a review of previous and current medication *(QoE – moderate)*
  - an individualised, structured rehabilitation programme with frequent follow-up reviews. The details of the structured rehabilitation programme and the reviews should be collated and documented in the individual's clinical records *(QoE – moderate)*.[809]
- For individuals on ECMO, ambulation and rehabilitation should be aided by physiotherapists trained in managing people on ECMO *(QoE – low)*.

12.6.2 Good practice points

- To ensure optimal management there needs to be excellent communication and liaison between both the critical care and CF physiotherapy teams and the wider MDT.
- The use of timetables to protect airway clearance and rehabilitation time may be beneficial.

12.6.3 Research recommendations

- A case series approach (single or multicentre) would be useful to explore the effectiveness of airway clearance and rehabilitation interventions in people with CF admitted to critical care. The heterogeneity and the low number of people with CF admitted to critical care may explain why there have been no current published studies of physiotherapy and/or rehabilitation interventions.

12.7 Physiotherapy before bilateral lung transplant (prehab)

Physiotherapy before lung transplant can be a complex balance of airway clearance, inhalation therapy and exercise training. Interventions may be influenced by skeletal muscle weakness, poor bone health, low BMI, pain and fatigue. The goal of physiotherapy in people with CF prior to bilateral lung transplant is clinical and physical optimisation alongside maintaining QoL.[811]

The wider availability of CFTR modulators and the benefits on clinical trajectory and longer life expectancy are emerging.[812] There is potential that the introduction of CFTR modulators could delay the referral for lung transplantation in those able to take them and for exercise to play an even larger role in optimising the future lung health trajectory.[812]

Frailty is common in people with CF undergoing lung transplant assessment; in a recent study a higher frailty index at listing was significantly associated with worsening waitlist status, post-transplant mortality and graft failure despite waitlist times.[813] A study of paediatric lung transplant registrants including young people with CF found those with the worst functional status as defined by the Lansky Play Performance Scale had a higher association with death or removal from the waiting list.[814] As the CF population ages and is projected to live longer with wider availability of CF modulators, pulmonary and extrapulmonary complications increase the medical complexity and decision-making for lung transplantation.[813] There is potential for the average age of people with CF undergoing lung transplantation to increase, therefore alongside the end-stage lung disease frailty, there is potential for a greater age-related frailty component. However, it is important to note this potential delayed need for lung transplant may not be the case for all people with CF, particularly those not able to take CF modulators.

The physiotherapy assessment of people with CF for lung transplantation includes exercise testing. The ECFS exercise working group recommend the 6MWT in severe CF disease and work up for lung transplant, and the 1-min STS test in lung transplant candidates.[168] In a recent retrospective study of CF Centres across the world before the widespread availability of CF modulators, W_{peak} was identified to be the measure most strongly associated with two-year risk of death or lung transplant, making it a useful marker for referral and listing: probability of death or lung transplant was 45.2% for those with a W_{peak} less than 49.2% predicted.[169] Further research into the impact of HEMT on lung transplantation and frailty in people with CF before lung transplantation is needed.

The evidence for pre-transplant rehabilitation specific to people with CF is limited. The evidence for pre-transplant rehabilitation is generally limited to non-randomised and observational studies.[815–817] Evidence from a systematic review including exercise training before lung transplantation demonstrated exercise training can maintain or improve functional exercise capacity in chronic lung diseases including CF.[815] A single-centre cohort study of people with CF participating in three centre-based supervised exercise sessions a week before lung transplant maintained their 6MWT distance and improved their bicep/quadricep training volume.[817]

Individually tailored exercise programmes to maintain and improve functional capacity, including strength and flexibility should be offered to all awaiting lung transplantation. Due to ventilatory limitations with severe CF disease, interval and strength training are often better tolerated than continuous aerobic exercise.

There is emerging evidence for the use of virtual pulmonary rehabilitation[818] and this option provides access for people with CF on the lung transplant waiting list to pulmonary rehab classes without the risk of cross infection. A pilot study of telerehabilitation for individuals with CF awaiting lung transplantation reported home-based pulmonary rehabilitation had significantly better adherence than hospital-based pulmonary rehab.[819]

Although evidence is limited, supplemental oxygen and NIV may facilitate exercise training in those with severely affected respiratory function.[811,817,820] The use of short and long-term goal setting is encouraged by clinical experts, however there is currently no evidence in CF.

The NHS clinical commissioning position has recently recommended the use of veno-veno ECMO (VV-ECMO) including for people with CF as a bridge to lung transplant to be available as a treatment option.[821] Recent case reports including people with CF who underwent VV-ECMO bridge to transplant concluded physiotherapy management of airway clearance and active rehabilitation on ECMO is safe and feasible and an integral part of the management of this cohort.[805,822]

12.7.1 Recommendations

- Every person with CF being considered for lung transplant should have individually tailored exercise programmes that include interval training, strength training and flexibility and these should be reviewed regularly by a physiotherapist or exercise practitioner *(QoE – low)*.

- Exercise training before lung transplantation in chronic lung diseases can maintain or improve functional exercise capacity *(QoE – low)*.
- On CPET testing, a W_{peak} of less than 49.2% predicted may indicate an increased risk of lung transplant or death within two years *(QoE – low)*.

12.7.2 Good practice points

- Every person with CF on the lung transplant waiting list should be educated on the benefits of prehabilitation.
- Individuals should be offered different modes of exercise delivery where possible including hospital, community or virtual.
- Evaluation of exercise capacity and frailty ahead of lung transplantation is important, including monitoring frailty while on the lung transplant waiting list.
- Ambulatory oxygen therapy may be used during exercise, following a formal assessment by a physiotherapist, where improvement in exercise performance or symptoms is demonstrated.
- NIV can be used to support exercise; settings should be adjusted from baseline settings to achieve symptomatic comfort.
- Short and long-term goals should be completed with each individual to facilitate and motivate rehabilitation.
- Physiotherapy including active rehabilitation and airway clearance is integral for people with CF who undergo ECMO as a bridge to lung transplant.

12.7.3 Research recommendations

- Evaluate the impact of CFTR modulators on timing of listing for lung transplantation.
- Evaluate the outcome measures used to assess frailty and exercise capacity in people with CF listed for lung transplantation, including further research into the use of W_{peak} as a marker for lung transplant referral and listing in the CFTR modulator era.
- Define the rehabilitation needs of people with CF awaiting transplant.
- Define the efficacy of exercise interventions in people with CF awaiting transplant, with regards to the type (endurance, strengthening or combined), intensity, duration and mode of delivery (hospital, community, virtual).

12.8 Physiotherapy following bilateral lung transplant

Lung transplantation is a treatment undertaken to improve the QoL and survival in carefully selected people with CF with advanced lung disease.[169,196,823] Following lung transplantation, there is a marked improvement in pulmonary function. However, individuals still experience physical impairments, such as limited exercise capacity around 40–60% of predicted normal values, early-onset of metabolic acidosis and skeletal muscle weakness, all of which persist for years after transplant surgery.[815] In the early post-transplant phase, this is likely due to deconditioning from end-stage disease at the point of transplant, and the extended intensive care and hospital stay following surgery, which can vary from three to six weeks or more if complications ensue.[815]

Additionally, side effects of immunosuppressant medications which are taken long-term following lung transplantation include adverse effects on bone and skeletal muscle cellular structure.[824,825] Lung transplant recipients with CF remain at risk of skeletal fragility despite prompt initiation of post-transplant anti-osteoporosis therapy.[825] Lung transplant patients also face psychological stressors throughout the course of the transplant journey, which can significantly impact QoL, physical functioning and adherence to recovery regimes.[826]

Physiotherapy input following lung transplantation can be extremely diverse and includes the management of the individual in the intensive care unit, on the ward and as an outpatient. Physiotherapy includes treatments to improve functional capacity, muscle strength, joint range of movement and postural alignment.[811] Other MSK issues may also need to be addressed, along with appropriate short-term and long-term goal setting. **Physiotherapy input may also involve:**

- respiratory weaning from tracheostomy
- NIV and oxygen support
- liaison with gyms and pulmonary rehabilitation centres
- organisation of nebuliser units
- preparation for employment or other major life goals.[811]

The majority of post-lung transplant studies investigate the effects of exercise and activity of daily living in a mixed population, including those

with COPD, emphysema, interstitial lung disease, pulmonary hypertension, alpha-1 antitrypsin deficiency, and alveolitis fibrotisans.[826–842] These studies include participants with both single and bilateral lung transplant. A recent review of lung transplantation rehabilitation[843] and a systematic review (2020) of exercise training for lung transplant candidates identified a total of 11 post-transplant studies:[815] four RCTs,[832,840–842] one quasi-experimental,[836] three pilot research studies,[833,838,839] two observational studies[827,829] and a retrospective analysis.[837] Results from these studies indicate that exercise training appears to be beneficial both before and after lung transplantation; however, the evidence for direct causation is limited.

One RCT compared the effects of pulmonary rehabilitation with standard care and showed a significant change in chest wall expansion and health-related QoL measured using the COPD Assessment Test, but no significant changes in the 6MWT, modified Medical Research Council dyspnoea scale, or hand grip strength.[841] The rehabilitation program consisted of chest-wall stretching, controlled breathing techniques and personalised exercise of 20–30 minutes cycling and treadmill two to three times per day for four weeks.

Another RCT of lung transplant recipients who participated in a 20-week supervised HIIT programme three times a week, showed improvements in one-repetition max arm press and leg press, and mental aspect of the 36-Item Short Form Survey (SF-36), compared to a control group.[842]

A further study compared exercising on a whole-body vibration platform (WBVT) to the same exercises on the floor.[840] Improvement in 6MWD was significantly higher in the WBVT group compared with the control group (83.5m [95% CI 65.4 to 101.7] versus 55.2m [95% CI 37.5 to 72.8]; p=0.029). Also, peak work rate increased significantly more in the WBVT group than in the control group (16.8W [95% CI 13.5 to 20.5] versus 12.6 W [95% CI 9.0 to 16.1]; p=0.042). No adverse events related to the intervention occurred during the study.

A final RCT found that three months of supervised training, initiated immediately after hospital discharge, improved functional recovery (daily walking time, movement intensity during walking and daily steps, measured by SenseWear Pro Armband and DynaPort activity monitors) and cardiovascular morbidity of patients up to one year after lung transplantation.[832]

A study investigating exercise performance in people with CF before and after bilateral lung transplant showed exercise capacity improved post-transplant but remained below the age-matched healthy controls.[831] An increase was shown between peak exercise arterial-venous oxygen difference pre- and post-transplantation but was not of statistical significance. The investigators concluded that an impaired oxygen extraction was the predominant mechanism limiting exercise capacity after transplantation and that this abnormality could not be solely explained by deconditioning or anaemia.

Lung transplant recipients with CF have a prevalence rate of post-transplant fractures of 21% but their occurrence is neither associated with pre-transplant BMD, post-transplant BMD changes nor mortality.[825] BMD declines most significantly in the first few months post-transplant, and then progressively increases over up to five years, without marked improvement in pre-transplant values.[825] In a review of handgrip strength testing in lung transplant candidates and recipients, figures improved from 21.1kg before rehabilitation to 35.7kg after rehabilitation.[844] Authors therefore concluded that handgrip strength is a quick and easy assessment tool that should be used with lung transplant recipients.

A study looking at experiences and perceptions of receiving and prescribing rehabilitation in adults with CF undergoing lung transplantation reported six key findings:[812]

1. Structured exercise benefits both physical and mental health.
2. CF-specific physiological impairments were a large barrier.
3. Supportive in-person or virtual relationships facilitated participation.
4. CF-specific evidence and resources are needed.
5. Telerehabilitation experiences during the COVID-19 pandemic resulted in preferences for a hybrid model.
6. Virtual platforms and clinical workflows require further optimisation.

12.8.1 Recommendations

- All people with CF should receive a structured exercise programme following discharge from hospital after lung transplant *(QoE – very low)*.
- People with CF should be offered both in-person and option of telerehabilitation post-lung transplant *(QoE – very low)*.
- Handgrip strength should be tested after lung transplant *(QoE – very low)*.

12.8.2 Good practice points

- NIV may be needed post-extubation, particularly in those who have used it as a bridge to transplant.
- Liaison with the pain management team may be necessary to ensure effective airway clearance and participation in an exercise regimen.
- Due to vagal nerve denervation and impaired cough reflex post-transplant, appropriate ACTs should be used.
- The use of any positive or negative pressure adjuncts will be discussed with the surgeons before use due to the effect on the bronchial anastomosis.
- An individually tailored exercise programme including cardiovascular and resistance and flexibility work to improve functional capacity should be introduced in line with the individual's goals. Resistance exercise is important to help combat the effects of the long-term steroids required with the immunosuppression regimen.
- High-dose steroid therapy following a rejection episode can increase the risk of tendonitis, tendon rupture and osteoporotic changes. Care must be taken when advising on exercise programmes.
- Liaison with the dietitian will be important to ensure that the exercise programme prescribed does not exceed calorific intake.

12.8.3 Research recommendations

- Define the acute and long-term rehabilitation needs of people with CF post-transplant.
- Evaluate the presence of long-term secondary effects of transplant on peripheral muscle function and dysfunction in people with CF.
- Define the efficacy of exercise interventions in people with CF post-transplant, with regards to the type (endurance, strengthen or combined) intensity, duration and mode of delivery (hospital, community, virtual).
- Explore perceived benefits and barriers to exercise in people with CF post-transplant.

12.9 Palliative and end-of-life care

12.9.1 What is palliative care?

WHO defines palliative care for both adults and children as follows: "Palliative care is an approach that improves the quality of life of patients and their families facing problems associated with a life-threatening illness. This is provided through the prevention and relief of suffering through early identification, accurate assessment and treatment of pain and other problems, physical, psychosocial, and spiritual".[845]

Palliative care:

- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process
- intends neither to hasten nor to postpone death
- integrates the psychological and spiritual aspects of care
- offers a support system to help individuals live as actively as possible until death
- offers a support system to help the family cope during the individual's illness and in their own bereavement.

12.9.2 Symptom burden and palliative care needs in CF

Caring for people with CF can be complex, with many individuals experiencing several distressing physical and psychological symptoms. A recent US study found that 78% of those surveyed (median FEV_1 57%, range 16–110%) were experiencing at least one unmet physical or psychological care need,[846] with physical symptoms adversely affecting daily living (such as lack of energy) and psychological needs (such as fears about my CF getting worse) being the most prevalent.[846] Results indicate that unmet care needs may be more strongly correlated with perceived symptom burden than with objective clinical factors such as FEV_1. This crucial distinction highlights that even patients with relatively preserved lung function can experience significant psychological symptoms and functional limitations due to their CF, which may go unaddressed if care is solely focused on spirometry results.

The most common physical symptoms often stated in surveys are fatigue and pain and the most common psychological symptoms are anxiety and fear about their condition.[846,847] With this in mind, the introduction of palliative care should not be

delayed until the time when death is imminent; discussions with people with CF and their loved ones should start early[848] and run parallel to usual care to ensure they get the benefits of both therapeutic approaches.[849] Some data shows that certain individuals may be more likely to report higher palliative care needs than others. These include females, those with higher symptom burden and those not on CFTR modulators.[846,850] Females consistently report a higher prevalence of unmet care needs, though it remains unclear whether this discrepancy stems from genuinely poorer clinical outcomes in females or is influenced by underreporting among men due to societal expectations regarding health and care-seeking behaviours. Clinical teams must be aware of this disparity when screening patients, fostering an environment where all individuals, regardless of gender, feel confident to openly discuss any unmet care needs.

The CFF recommends that structured screening of symptoms should start early with specific symptom management conversations initiated at annual review from age 12, or with disease milestones such as referral for lung transplant, hypercapnia and daytime oxygen requirement at rest.[851] Others suggest palliative care services are introduced if FEV_1 falls below 50%.[852] It may be helpful in these situations to use a screening tool such as the Integrative Palliative Care Outcome Scale (IPOS)[851,853] or Supportive Care Needs Survey Short Form 34 (SCNS-34) to help facilitate discussions.[846] Palliative care discussions and screening should be flexible to the individual's needs and requests, including the option of home-based or hybrid reviews.[854]

Early, integrated palliative care input is essential in the management of these complex, often untreated symptoms.[849,854–856] Once introduced, palliative care teams should remain involved throughout the individual's lifespan,[857] to provide ongoing care to both the individual as well as supporting family and carers. Feedback from people with CF and carers suggests that CF teams could improve their delivery of palliative care, especially the more advanced skills such as end-of-life discussions and advance care planning.[858] Increased collaboration between CF and palliative care teams may improve specialist knowledge sharing and address learning needs.[859] Having a dedicated palliative care clinician integrated within the CF team may improve collaboration and responsiveness to symptoms.[860,861]

12.9.3 Advance care planning and discussions about symptoms and treatment choices

Advance care planning (ACP) conversations, focusing on goals of care, prognosis and treatment decisions, are recommended for all individuals with advanced lung disease.[862] These discussions should begin early, ideally in an outpatient setting and with a familiar member of the CF team, which may be an experienced physiotherapist.[863–865] Studies demonstrate that people with CF have expressed a need for an openness to participate in ACP discussions with their CF team[865] and they are generally comfortable talking about this subject.[854,863,866] ACP may empower individuals to actively participate in their care planning[867] and provide clinical teams with essential insights into the individual's needs and wishes. However, the rate of completion of such documents remains low in adults with CF due to barriers from the clinical team such as lack of training and confidence[858,859] and fear of causing distress,[868] and is often not completed until the terminal hospitalisation.[869]

Most people with CF die in hospital[870] and this is likely due to the intensity of treatments and the complexity of predicting the terminal stage. It is essential to provide early opportunities for people with CF to make an ACP, discussing topics such as their preferred place of care and death.[867,870] Having these discussions early may give CF teams and people with CF time to build relationships with community teams to facilitate the individual's wishes if dying at home or in a hospice is their preference.

In paediatric care, evidence has shown caregivers are included more than children in ACP discussions. Introducing ACP discussions early can increase congruence between the young person and caregiver and may allow caregivers to be more prepared and feel more in control of uncertain situations.[871] Structured ACP documentation is available and recommended to empower healthcare professionals to initiate these discussions.[872]

12.9.4 End-of-life care in CF

The CFF define that people with CF have advanced lung disease if:[523]

- they have FEV_1 less than 40% predicted when stable, or
- have been referred for lung transplantation evaluation, or
- one or more of the following characteristics
  - previous ICU admission for respiratory failure
  - hypercapnia

- daytime supplemental oxygen requirement at rest
- pulmonary hypertension
- severe functional impairment from respiratory disease
- 6MWT distance less than 400m.

People with CF can often live for several years with advanced lung disease and recover from multiple acute deteriorations during the slow decline in their health, making the timing of death difficult to predict.[849,873] During this potentially long, chronic 'terminal phase' of CF, prognosis is uncertain due to individuals experiencing additional disease complications and increased symptom burden, associated with an intensive daily therapy regime.[849,866,874–876] However, it has been shown that rapid lung function decline in the first year of advanced lung disease has been associated with worse outcomes.[877]

Early discussions about an individual's care and wishes are therefore essential to prepare and plan for unexpected or sudden deteriorations that may occur. Within CF, active treatment and palliative care are often provided in parallel, as both therapeutic models help identify and treat symptoms in end-stage disease.[849,873,878]

Although most people with CF die from respiratory failure, technological advances such as NIV and ECMO, have provided alternative treatment choices for those with end-stage disease. Lung transplantation is a potential option for people with advanced disease, although it must be acknowledged that not all individuals are eligible or choose this option. In addition, organ availability remains an issue in the UK, with 40% of individuals dying on the waiting list.[849,878–881] Awaiting lung transplant can further complicate end-of-life care as the person with CF, their family and the MDT must balance the hope of transplantation alongside the reality of death whilst waiting for organs.[849,875]

12.9.5 Physiotherapist's role in end-of-life CF care

Physiotherapists have a key role in end-stage disease management. Physiotherapists focus on maximising functional ability and comfort to enhance QoL and this continues to apply during end-stage disease management and end-of-life care.[882,883] In conjunction with multidisciplinary and medication strategies, physiotherapy techniques can help alleviate many of the symptoms experienced at end-of-life, such as breathlessness, anxiety, fear, secretions and pain.

Interventions may need to be adapted to consider the individual's condition and needs[882] and to ensure comfort. Considerations or airway clearance adaptations may include positioning, length and frequency of sessions, use of adjuncts and review of NIV settings and interfaces if appropriate.[563] While it is important to appreciate the benefits these techniques provide, it is also important to acknowledge the potential burden they impose.

Few studies have directly addressed the input of physiotherapy during end-of-life care. In a retrospective analysis[882] common treatments included ACTs with ACBT, IPPB, NIV, exercise, anxiety management and relaxation techniques, with a reduction in the use of adjuncts such as PEP and OPEP. It is important to note that many individuals continued with ACTs to within 24 hours of death.[882]

12.9.6 Following the death of a person with CF

CF teams may find it beneficial to reflect on the deaths of people with CF under their care,[855] taking the opportunity to review the quality of care provided against guidelines, learn from experiences and highlight any training needs. Caring for people with CF at the end of life can impact the wellbeing of the CF team, and staff must be empowered with the skills and support to optimise their self-care. Such training and support may be provided by their embedded CF Psychologist or via their Trust wellbeing services.

12.9.7 Recommendations

- Physiotherapy treatment should focus on optimising QoL and symptom control in those with advanced disease *(QoE – low)*.
- Physiotherapy ACTs need to be tailored to the individual needs of the person with CF *(QoE – low)*.
- Consider NIV as a physiotherapy adjunct to increase ease of sputum clearance and reduce oxygen desaturations and breathlessness *(QoE – low)*.[586,590]
- People with CF should be offered physiotherapy input and support in the last stages of life *(QoE – low)*.
- Consider referral or seek advice from palliative care services with regards to people with CF with high symptom burden such as pain or breathlessness which limit the efficacy of physiotherapy treatments *(QoE – low)*.
- People with CF should be screened annually for symptom burden from the age of 12. Tools such as IPOS screen for symptom burden and may help initiate advance care planning *(QoE – low)*.

- Introduce palliative care services in the moderate stages of disease (FEV_1 below 50%) and continue input throughout the individual's lifespan *(QoE – low)*.

12.9.8 Good practice points

- Good communication between the CF team, the palliative care team, the person with CF and their family is paramount during all aspects of the terminal stages. The CF team must consider the person with CF and their family's level of understanding, concern, and fear of the unknown when discussing any treatment changes and be prepared to answer questions.
- Early discussions around treatment choices and the preferred place of death should take place between the person with CF and the MDT and be documented clearly. If appropriate physiotherapists can lead on these conversations.
- If an individual's preferred place of death is home or hospice, physiotherapy input needs to be provided and/or supported in this setting, and if necessary, training should be provided by the physiotherapy team to hospice staff, community palliative care team or the individual's family around NIV and physiotherapy treatment.
- Frequent short treatment sessions may be required to maximise symptomatic relief but minimise burden during end-of-life care.
- Consider positive pressure such as NIV to reduce work of breathing and provide symptomatic relief during ACTs, exercise or to support breathlessness management pre- and post-activities of daily living such as washing or dressing.
- People with CF using NIV may choose to remove their NIV in the terminal stages. Physiotherapists should be prepared to discuss with individuals and families what may happen when they remove their NIV and liaise with the wider MDT to optimise symptom control medications if this is the individual's wish.
- Individuals who are 24-hour NIV-dependent will have two machines to alternate (day and night) and should have more than one face interface to alternate to reduce the risk of pressure areas.
- The use of nasal masks or mouthpiece interfaces for short periods may enable individuals at the end of their life to speak to relatives and drink and eat more easily.
- To optimise individual independence, if they are NIV-dependant, consider setting up their NIV on a trolley to enable them to mobilise more easily.
- Physiotherapists need to consider how to support their colleagues and manage their own emotions when caring for people with CF at end-of-life. The opportunity to reflect as a team or individually should be available for all staff and teams should promote positive coping strategies.
- Education and support should be provided to physiotherapists undertaking advance care planning discussions to help empower staff, promote discussions and reduce emotional fatigue.
- Consider use of structured ACP documentation to guide advance care planning discussions.
- Consider formal integration of palliative care clinicians into the CF team.

12.9.9 Research recommendations

- Explore the role of the physiotherapist in supporting people with CF who choose to die at home or in a hospice.
- Explore physiotherapists experiences and challenges of providing physiotherapy interventions towards the end of a person with CF's life.
- What access is there to palliative care teams across UK CF Centres?

13. Cystic fibrosis screen positive, inconclusive diagnosis (CFSPID) and CFTR-related disorders (CFTR-RD)

13.1 CFSPID

NBS can result in the recognition of infants with a positive NBS result that do not meet diagnostic criteria for CF and have an unclear outcome (see precise definition below). These infants are given the designation, cystic fibrosis screen positive, inconclusive diagnosis, or CFSPID. In 2019 the ECFS published **updated guidance for the management of CFSPID**, including a harmonised definition with the CF Foundation in the US.[884]

CFSPID definition[19,884,885]

A positive NBS for CF

AND EITHER

A sweat chloride value of less than 30mmol/L and two CFTR variants (at least one of which has unknown phenotypic consequence)

OR

An intermediate sweat chloride value (30–59mmol/L) and one or no CF-causing variants.

An infant with a CFSPID designation is, by definition, well and does not have CF. They are however at risk of developing a CFTR-related disorder (CFTR-RD) or CF later in life.

Rates of conversion from CFSPID to a CF diagnosis range from 6% to 48%, depending on the NBS protocol used.[886,887] Infants with an intermediate sweat chloride (30–59mmol/L) are more likely to convert. Programmes that use more extensive DNA analysis are more likely to identify infants with CFSPID and those infants are less likely to convert to a CF diagnosis.[888] Infants with CFSPID who do not convert are at risk of developing a CFTR-RD, but the extent of this risk is not currently quantified.

The ECFS guidance provides a suggested timescale for follow-up.[888] The guidance proposes clinical evaluation and minimal investigations for children who are well. Considering data from the prospective French study (DPAM), there is no evidence to support routine respiratory culture for infants and children with CFSPID who are well.[889] For symptomatic children, it is less clear. It is reasonable to undertake respiratory culture if a child has a persistent cough and initiate treatment appropriately based upon the results.

The ECFS guidance suggests that these infants are reviewed by a Paediatrician with a special interest in CF.[888] It is not explicit whether this should be in a CF clinic or general respiratory clinic. There are pros and cons to both options. If a child with CFSPID is referred to a physiotherapist, it is important they work closely with the physician to provide consistent and appropriate messaging to the family. Routine airway clearance is not indicated unless there is conversion to a CF or CFTR-RD diagnosis. A survey of CF Centres in the UK and Ireland showed a wide variation in how these individuals are managed, however.[890]

Children with a CFSPID designation are well and most will remain well. Some may convert to a CF diagnosis and should move on to standard CF care pathways. Some may develop persistent symptoms as is common in childhood, and the management of this cohort is challenging, requires clear communication, good team-working and consistent messaging from healthcare professionals.

Many of the references used are based on expert consensus. These publications are a based on the best available evidence from cohort studies and case series reviews. This is the soundest methodological process currently available for studying this population.

13.1.1 Recommendations

- When a person with CFSPID is referred to physiotherapy, the physiotherapist should undertake a full respiratory assessment, including history (cough, infections) and auscultation *(QoE – low)*.
- There is no evidence to support routine ACTs for people with CFSPID *(QoE – low)*.
- Activity should be encouraged in line with that of the general population *(QoE – low)*.
- Respiratory cultures should be obtained only in cases of persistent symptoms (including samples for respiratory viruses) *(QoE – low)*.

13.1.2 Good practice points

- For children with a CFSPID designation who are well, the European guidance suggests a more thorough evaluation just prior to school entry. If imaging and spirometry are reassuring at this point, then discharge to primary care may be discussed with the family, possibly with an appointment with the child when they are older to explain the implications of this finding. If discharge happens then the family and the primary care physician require clear information.

13.1.3 Research recommendation

- Ongoing evaluation will be required to understand the longitudinal outcomes in this cohort, highlighting those who may be at risk of developing lung disease and may therefore benefit from early physiotherapy input.

13.2 CFTR-related disorders (CFTR-RD)

CF is often categorised by a wide variability of clinical expression in terms of disease severity and rate of progression.[891] With over 2,000 known CFTR variants, CFTR protein dysfunction should be viewed as existing on a continuum and for some variants, the reduction in activity may not be sufficient to lead to a multiorgan or 'classic' CF phenotypic presentation.[892]

The term CFTR-RD has been developed from previous descriptions of atypical or nonclassical CF and is defined as "a clinical condition with evidence of CFTR protein dysfunction that does not fulfil the diagnostic criteria for CF".[891]

Clinical presentations include CBAVD, acute recurrent or chronic pancreatitis and disseminated bronchiectasis.[891] Some will have no detectable lung disease.

To date, there is no documented evidence outlining the need for physiotherapy intervention for individuals diagnosed with CFTR-RD. At present, few adult services have dedicated CFTR-RD diagnostic clinics and there is no precedent set on standardised physiotherapy involvement. However, it may be pragmatic to consider that for those presenting with a bronchiectasis phenotype, physiotherapy input could be clinically indicated to support optimal lung health.[893] **Additionally, the recent publication from the ECFS diagnostic network working group states:[894]**

- "A chest radiograph and pulmonary function tests should be performed in all individuals. If either of these are abnormal, a thoracic CT to evaluate for bronchiectasis and/or bronchial wall thickening is recommended."
- "Whenever possible, a respiratory specimen (spontaneous or induced sputum, or cough/throat swab if not expectorating) should be collected for microbiological analysis."

For many CF physiotherapy clinicians, these are tasks which are a routine part of their clinical practice, and physiotherapists may be well placed to provide this clinical support.

The implementation of alternative methods of lung monitoring such as LCI may be advantageous in monitoring those with normal spirometry, who could be at risk of developing lung disease.[51]

13.2.1 Recommendations

- More research is required to determine the need for standardised physiotherapy input within this cohort *(QoE – low)*.
- An individualised approach should be adopted *(QoE – low)*.
- For those presenting with evidence of bronchiectasis, physiotherapy review should be undertaken *(QoE – low)*.

13.2.2 Good practice point

- Pulmonary function tests and sputum analysis are important objective measures to assess for potential lung-related issues and may fit into a physiotherapy scope of practice.

13.2.3 Research recommendation

- Ongoing evaluation will be required to understand the longitudinal outcomes in this cohort, highlighting those who may be at risk of developing lung disease and may therefore benefit from early physiotherapy input.

14. Complementary therapies

'Complementary therapy' and 'alternative medicine' are terms often used to describe treatments outside the usual medical treatment remit. The evidence base for the use of complementary therapy in CF in the UK is limited and based on a questionnaire sent to all adult and paediatric CF Centres in the UK in 2016, and repeated in 2024. Of the 26 Centres who responded to the survey in 2024, 31% stated CTs are integrated into their care of people with CF and are applied by either the physiotherapist (75%), an external 'complementary therapist', or another member of the MDT. Some of the most common therapies described under this umbrella include acupuncture and massage therapy. Salt cave and salt lamps (halotherapy) are not currently used as a treatment by the CF MDT; however, they have been reported in the 2016 and 2024 questionnaire responses to be of interest to people with CF.

Although there may be evidence for some complementary therapies in the non-CF population, such as acupuncture in the management of chronic pain,[895] research relating specifically for the use of complementary therapies in people with CF is lacking and there is insufficient evidence to support or refute their use. Many physiotherapists have an interest in complementary therapies and some techniques such as therapeutic massage and relaxation form core training at an undergraduate level with further courses such as acupuncture and acupressure available and targeted at experienced physiotherapists.

It is beyond the scope of these guidelines to produce a full systematic review of all complementary therapies.

14.1 Acupuncture and acupressure

Acupuncture involves the insertion of needles into the skin and acupressure uses the application of physical pressure. Points are selected on the body following Western medicine principles to provide neuromuscular stimulation or traditional Chinese medicine (TCM) principles of balancing flow of energy (Qi) along meridians in the body.[896] There is a growing use of acupuncture in respiratory conditions and anecdotal evidence that individuals are requesting acupuncture as a treatment modality.[897–899]

In 2010, Carrolan et al mapped the use of acupuncture treatment in adults with CF in 20 Specialist adult CF Centres in the UK.[900] Four Centres were providing acupuncture treatment by physiotherapists, most commonly treating back pain, breathlessness, headaches, joint pain, anxiety, sinus pain and pleuritic chest pain. There are studies in people with CF which have demonstrated improvements in parameters such as QoL, exercise capacity, and decreased anxiety and dyspnoea scores using acupuncture techniques.[898,899,901–903]

It has been reported that "acupuncture is not widely available in UK Adult CF Centres mainly due to lack of trained professionals available to provide a service". Some Centres have funded non-NHS acupuncturists to provide a service to patients, but this is not a consistent offering nationally as funding varies from Centre to Centre. Carrolan's study demonstrates that 71% of the surveyed physiotherapist respondents felt that acupuncture treatment should be carried out by a physiotherapist with acupuncture training, rather than a fully qualified (but non-health professional trained) acupuncturist.[900]

Acupuncture is considered relatively safe, but as it is an invasive procedure it carries undeniable risk with pneumothorax being a rare but dangerous potential complication. The incidence of serious events like pneumothorax could differ depending on the style of acupuncture and the training of therapists. However, there are a growing number of case studies from different countries highlighting the risks.[895–908] Whilst these are only single institution case studies, they all raise the importance of individuals having access to an accredited and registered acupuncturist and clinicians having a high index of suspicion for pneumothorax if a patient complains of chest pain following acupuncture.

14.1.1 Good practice points

- There is no lower age limit for when acupuncture or acupressure can be performed, though children may have a more acute response to acupuncture and it is therefore advisable to trial acupressure first.
- In the absence of physiotherapists trained in practicing Western-style acupuncture, individuals may be referred to a fully qualified TCM or Five Element acupuncturist to benefit fully from this holistic treatment approach. Visit the **British Acupuncture Council website** for guidance.

14.2 Massage

Massage has benefits such as improving circulation, decreasing some forms of oedema and reducing MSK pain and tension.[898] Massage therapy has also been shown to help relieve stress and pain, as well as promote wellbeing and relaxation.[909] Zink et al in 2019 conducted a pilot study in 24 people with CF aged 8 to 21 over a 10-to-12-week period. Their purpose was to evaluate massage therapy on QoL. They concluded that massage therapy was found to significantly reduce muscle tightness, marginally reduce pain and aid relaxation and thoracic excursion in participants with CF. There was no statistically significant improvement in QoL scores.[910] Short-term benefits of massage and MSK physiotherapy on pain reduction in adults with CF have also been documented,[911] but longer-term, large-scale studies are needed.

Common symptoms of chronic illness such as anxiety and depression may be alleviated by massage.[898] A small RCT in children with CF noted subjective improvements in both anxiety levels and mood of parents and children using parent-administered massage therapy.[912] Abstracts highlighting the importance of massage therapy to adults with CF during inpatient admissions have also been documented.[909,913] A 2023 review of manual therapies in CF care, of which massage was included, concluded that there was limited research in this area, and difficulties with comparison of literature due to variations in methodology and interventions. Positive trends related to subjective measures regarding pain and ease of breathing were noted, but further research is required.[914] Massage and relaxation techniques are commonly used in end-of-life care, but benefits versus burden should be carefully considered.[915]

Contraindications must be noted, and massage should not be performed over pitting oedema, areas of impaired tissue integrity and fractures. Caution should be exercised in individuals with prolonged bleeding times.[898]

Aromatherapy massage, using plant-derived, aromatic essential oils combined with massage to promote physical and psychological wellbeing in CF has limited documentation and is currently only cited in pilot studies in abstract form. Subjectively all six adult participants with CF reported improvement in anxiety and possible ease in airway clearance.[916] There is ongoing interest in the area of essential oils on bacterial and biofilms of *P. aeruginosa* isolates from people with CF, but no firm conclusions have been drawn.[917,918]

14.2.1 Good practice points

- Consider the use of massage therapy for the relief of MSK pain.
- Consider the use of massage therapy to help decrease anxiety in people with CF and their carers.
- Contraindications to massage therapy must be noted.

14.3 Halotherapy (salt caves, salt lamps)

For centuries, especially in Eastern Europe, people have visited natural salt caves for the healing and therapeutic properties of the air. Halotherapy can be delivered in artificially constructed 'salt caves' that stimulate the conditions of a natural cave by dispensing dry aerosol micro particles of salt. Other modes of halotherapy delivery are via salt inhalers or 'salt pipes'. Suggested mechanisms of action are mucolytic, antibacterial, anti- inflammatory, immunomodulating and hyposensitizing.[919]

Evidence to support halotherapy use is limited and primarily involving people with COPD or asthma. One study carried out a randomised double-blind study into the use of a salt room with halogenerator (treatment group) or a salt room without halogenerator (control group) in children aged between five and 13 years with mild asthma.[920] Both the control and treatment group had twice weekly 45-minute sessions for seven weeks. The treatment group received salt aerosols produced by a halogenerator. A halogenerator brings a flow of clean, dry air that is saturated with highly dispersed negatively charged particles of sodium chloride into the chamber. The study had small numbers (29 in the treatment group and 26 controls) but found a statistically significant improvement in bronchial hyper-responsiveness and in most parameters of QoL questionnaire in the treatment group. They found no improvement in spirometry or fractional exhaled nitric oxide levels following treatment.[920]

Another study explored the efficacy of salt cave halotherapy in 139 individuals with chronic respiratory conditions, including only five people with CF.[921] Improvements in flow-volume loop parameters and decreased bronchial resistance measured by plethysmography were reported after 10 to 20 daily one-hour sessions. Two smaller studies have also shown benefit. Six people with CF had five 45-minute salt cave halotherapy sessions on consecutive days and showed improvement in lung function and sputum production.[922] The second study with 13 people with CF showed

no significant change in lung function, but improvements in Borg dyspnoea index scores, SNOT-20 scores and subjective health perception levels with no adverse effects.[923]

In 2018, a paper highlighted a list of contraindications for halotherapy, which include hyperthyroidism, active tuberculosis, high-grade hypertension, cardiovascular and respiratory failure, acute-stage blood disorders, contagious diseases, fever, open wounds and malignant diseases.[919] Giangioppo et al refer to the risk of cross infection in relation to halotherapy: "sitting in a salt room for extended periods with other respiratory patients can also promote the spread of infection".[924]

There is minimal evidence available evaluating the efficacy of salt spray inhaler or salt pipe use in CF. Rabbani et al explored the use of salt spray inhalers in 20 people with non-CF bronchiectasis, using the inhaler for 25 minutes per day for two months.[925] After a two-month treatment course no significant improvements were identified in lung function tests, 6MWT results or QoL questionnaires. However, there were no significant adverse effects.

There is also no evidence available to suggest salt lamps might have a physiologically beneficial impact on the respiratory health of people with CF. There have, however, been no reports of adverse side effects as a result of its use in any studies. The benefits to emotional health and wellbeing provided by salt lamps have been extensively documented (although not specifically in CF), if not scientifically supported.[922,926]

In summary, the evidence supporting the use of halotherapy is weak due to poor quality of study design, methodology and data collection. Furthermore, with halotherapy having more popularity in Eastern Europe, many of the papers were not available in English and are beyond the scope of this document. Exploratory studies have demonstrated that halotherapy may have some benefit for people with CF, though many of the studies have looked at COPD or asthma populations.

14.3.1 Good practice points

- Where people demonstrate an interest in halotherapy, physiotherapists should offer inhaled hypertonic sodium chloride as a safe and known alternative where appropriate.
- There is no information regarding infection control precautions and management when using halotherapy and physiotherapists should advise people with CF accordingly.

14.4 Other complementary therapies

14.4.1 Art therapy

Art therapy may be defined as a form of psychotherapy involving the encouragement of free self-expression through painting, drawing or modeling used as a remedial or diagnostic activity, though definitions may vary. Research on the use of art therapy in CF is lacking so no recommendations are available. However, an abstract from 2023 using art therapy online, in small groups for children with CF aged 5 to 11 found it a useful platform to share concerns and experience peer support.[927]

14.4.2 Singing

Many families feel singing is a good form of treatment for children with CF. A Cochrane review, updated in 2019, reported there is insufficient evidence to recommend singing as an effective adjunct treatment in individuals with CF, however, they should be encouraged to participate but not replace current modalities.[928] In Scotland, the 2015 Breath Cycle project evaluated the benefits of classical singing techniques and breathing control on respiratory health in adults with CF. Only 14 individuals completed the pilot study, reducing the authors' ability to find statistically significant differences. Improvements were suggested in tidal breathing during exercise, FEV_1 and LCI.[929] A literature review in 2018[930] on singing lessons for respiratory health reviewed 17 studies in a variety of pathologies, including three in CF and all with small numbers. It concluded generally that singing may be used as an adjunctive treatment for respiratory disease. However, as mentioned above, this should not replace current airway clearance modalities in CF.

14.5 Research recommendations

- Longer term studies using larger sample sizes and RCT study design are necessary to help confirm recommendations of complementary therapies including acupuncture, massage and halotherapy specifically within CF.
- It is important to gain information and insight into the use and interest of complementary therapies from people with CF and their carers to help guide which areas of complementary therapy research should be prioritised.

15. Adherence

Adherence is defined as:[931]

"The extent to which the patient's behaviour matches agreed recommendations from the prescriber."

This term is described as preferable to compliance, defined as:[931]

"The extent to which the patient's behaviour matches the prescriber's recommendations."

Concordance is a wider concept that does not focus solely on participating in treatment but is based on the idea that consultations are a negotiation between equals. It recognises the rights of people to decide whether or not to take prescribed medicines.[932] Adherence is considered the preferred term for medication or treatment-taking behaviours.[931,933]

People with CF need multiple medications to control symptoms and slow disease progression.[16] Studies prior to the widespread availability of CFTR modulators suggest the median number of daily medications prescribed is seven.[934] These treatments take a mean time of 108 minutes a day[934] posing significant challenges in terms of scheduling around education, work and families.[935] People with CF need to complete many daily non-medication-based treatments, including airway clearance, activity and structured exercise, taking dietary supplements and monitoring dietary intake.[16] In view of this sustained treatment burden, poor adherence has been identified as the greatest cause of treatment failure and monitoring adherence to prescribed therapy is identified as a priority.[936]

Following the large-scale availability of CFTR modulators in the UK, there has been some uncertainty about the need for some standard therapies. Clinical trials of CFTR modulators were as add-on therapy[937,938] but studies have identified that less treatments are being prescribed and adhered to in the era of CFTR modulators.[939,940] There is no clear data at present about the long-term outcomes of the discontinuation of standard therapies. There is data that adherence to CFTR modulators may be sub-optimal.[941,942] It should also be acknowledged that at least 10% of people with CF are unable to take CFTR modulators and rely on standard therapies. Adherence remains important for the CF community.[943]

Many influences and barriers to adherence are reported in the literature:

1. Lack of knowledge.[944]
2. Communication.[945]
3. Self-efficacy (the belief that the individual can perform the behaviour.[39]
4. Perceived illness severity.[946]
5. Coping styles.[947]
6. Depression.[948]
7. Family factors.[949]
8. Support.[950]
9. Parental supervision.[951]
10. Characteristics of the treatment regimen.[949]
11. Problems with fitting treatment into lifestyle.
12. A perception that treatment does not help or may be harmful itself.
13. Physical consequences or side-effects of the treatment.[952]

Adherence is recognised as variable depending on the treatment,[945] for example optimal adherence to pancreatic enzymes does not predict optimal adherence to nebulised medications. It may also vary for a single treatment in an individual at different times.[953] Adherence levels in people with CF have been found to decline into adolescence and young adulthood,[954] which may reflect the transition from family administration of treatment to independence. Adherence may be influenced by changes in the prescribed regimen or by intervention to enhance one aspect of the regimen where a drop in other aspects may be seen.[955] Ongoing comprehensive assessment of adherence patterns is needed.[943]

15.1 Measuring adherence

Methods of measuring adherence vary in objectivity and validity. The most common method of assessment is self-report. When compared to more objective measures, self-report strategies over-estimate adherence.[942,956,957] The reasons for this are multifactorial and may include inaccurate recall, optimism and a reluctance to admit behaviour that is not in keeping with the agreed treatment plan.[945] This social desirability bias may be particularly important for people with CF where

decisions on life-saving procedures such as lung transplants are potentially influenced by adherence reports and data.

Daily diary methods are more accurate[945] but are time- and resource-consuming and so not appropriate for long-term clinical use. Prescription refill methods such as medicines possession ratio and proportion of days covered are more objective but still over-estimate adherence as there is no guarantee all dispensed medication is taken.[936,942] Other direct measurements such as blood levels are used, but these are limited in accuracy and in practicality for long-term use[958] as well as being unsuitable for the measurement of many physiotherapy treatments such as airway clearance.

Electronic data capture is the most objective adherence measure and its use in adherence trials is increasing. Pill bottles, nebulisers, inhalers and some methods of airway clearance can be electronically monitored to log the exact date and time of use. This data can be used by people with CF and their families and shared with clinical teams to understand and optimise adherence.[959] Early devices had high rates of malfunction, but they are now more reliable.[936] For some applications of this technology such as pill bottles, there can be issues such as with specially packed medications which have challenges when decanted.[936,942] Electronic data capture is a way to optimise preventative care and improve activation.[943]

15.2 Adherence to airway clearance

Most studies assessing adherence to airway clearance have used questionnaires or telephone diaries to assess adherence. They assess adherence to airway clearance overall rather than providing individual data for different techniques. Reported adherence rates to airway clearance range from 33.3 $\pm$ 43.15% to 91.2%.[960] A pilot study using electronic data capture suggested adherence rates to OPEP were 45% compared to self-reported adherence of 100%.[955]

Project Fizzyo worked together with engineers and designers to develop electronically chipped airway clearance devices and wearable activity trackers.[86,87] It looked at associations between quality and quantity of ACTs and FEV_1 in children and young people with CF. The study identified that ACTs are beneficial when performed as recommended, but most people use techniques that do not improve lung function. They concluded that there is an opportunity to optimise therapy and reduce the burden for people with CF by supporting effective ACTs.[86,87]

An Australian study in adults with CF looked at developing a PEPtrac device to accurately measure and provide preliminary clinical data of adherence and technique characteristics such as expiratory duration and pressure properties, in supervised vs unsupervised ACTs.[961] Numbers were low but concluded that this device could accurately measure adherence and technique data when using PEP/OPEP devices unsupervised by adults with CF.

With the introduction of CFTR modulators, the CF community have placed more emphasis on reducing treatment burden to aid adherence.[26,962] It is essential that there is access to accurate methods of measuring the clinical benefit of ACTs to understand whether ACTs be safely stopped and under what individual circumstances.

15.3 Adherence to exercise and activity

Despite exercise and activity being widely advocated as beneficial, there is very little adherence data. Adherence levels to exercise have been assessed as higher than adherence to airway clearance.[277] Overall, people with CF report a preference for exercise as compared to other treatments.[949,963,964] Exercise is regarded as socially acceptable[965] and an area over which people feel they have control.[966] Lack of energy, lack of good health, lack of self-discipline, and lack of time were noted as the most frequent barriers to exercise.[967]

The desire to replace airway clearance techniques with exercise was evidenced in the original James Lind Alliance research questions for CF.[968]

It remains unclear whether digital health technologies[969] and interventions[970] improve adherence to exercise. Both Cochrane systematic reviews on this topic add low-certainty evidence of little or no improvement.[970,971]

15.4 Adherence to inhaled medication

Monitoring adherence to inhaled medication has become easier and more accurate using adaptive aerosol delivery technology, which provides detailed monitoring including date, time, completeness of dose and time taken to nebulise, and with chipped vibrating mesh devices. This electronic data capture suggests that adherence to nebulised medications can be low or variable.[972–974] Monitoring allows greatly improved accuracy in identifying adherence levels and is acceptable to

people with CF.[956,959,973] When measured objectively using electronic data capture, long-term adherence rates to nebulised treatments are 36% in adults[956] and 67% in children.[973]

A significant study utilising electronic data capture is **CFHealthHub**.[959] This programme involved the development of a behaviour change intervention which was tested in a large RCT. The intervention was data-logging nebulisers, a digital platform and behavioural change sessions with trained clinical interventionists which was compared to usual care with data-logging nebulisers. While significant differences were not seen in pulmonary exacerbations and lung function, adherence was significantly improved along with a lower perceived CF treatment burden.[959]

15.5 Why is adherence important?

Adherence research has been highlighted as a high priority by policy makers and the WHO.[933] Poor adherence has implications for people with CF, their family, the CF team, leading to unnecessary exacerbations and resulting in additional antibiotics and hospitalisations. This is expensive, undermines QoL, can lead to antibiotic-related adverse events and may reduce life expectancy.[958,975] People with CF who collect less prescription medication are more likely to be admitted to hospital for a pulmonary exacerbation and incur higher healthcare costs.[976] Studies have demonstrated the importance of adherence to inhaled treatments on health outcomes, with people collecting four or more courses per year of nebulised tobramycin being 60% less likely to be admitted to hospital than those collecting one,[977] and greater adherence to dornase alfa being associated with shorter inpatient stays.[978]

15.6 Strategies to impact on adherence

A Cochrane systematic review identified evidence for psychological interventions to improve adherence.[979] Positive effects were seen predominantly with behavioural and educational interventions but with an impact on dietary intake and nutritional status rather than on other aspects of treatment, so are less applicable to physiotherapy-related treatments.[979]

Self-management strategies such as educational approaches have also been assessed.[980] The trials included used self-report outcomes to assess adherence and gave conflicting and unclear results. One study assessed a wide-ranging programme aimed at self-management of CF demonstrated no differences in adherence to physiotherapy-related treatments such as airway clearance, exercise and inhalation therapy,[981] whereas an airway clearance and inhalation therapy specific programme demonstrated improved adherence outcomes but with wide confidence intervals.[982]

There are some small-scale pilot studies looking at strategies to impact on adherence. These have included 'token economy',[983] which found variable improvements in adherence to exercise which may have been related to the type of reward. Motivational interviewing is also an area of interest to researchers, but little evidence of significant impact on adherence has yet been demonstrated.

The use of interventions to support habit formation is showing promise with high adherers reporting stronger habit compared with low adherers. Habit may be a promising target for self-management interventions[984]. There are ongoing studies that will enhance future understanding of strategies to impact on adherence.

A Cochrane review assessing interventions for enhancing medication adherence found that outcomes are inconsistent from study to study.[971] It identified that interventions are mostly complex and not very effective, so that the full benefits of treatment cannot be realised. It highlighted that research in this area needs advances, including improved design of feasible long-term interventions, objective adherence measures, and sufficient study power to detect improvements clinical outcomes.[971]

15.7 Recommendations

- Consideration should be given to using devices which utilise electronic data capture to record adherence to tailor treatments and adherence interventions to the individual, optimise preventative care, make best use of financial resources and improve activation *(QoE – moderate)*.
- Where adherence levels are measured, this should be to different treatments and over time *(QoE – moderate)*.
- To support adherence clinicians should aim to use the quickest and simplest technique, combination of techniques or device possible *(QoE – low)*.
- Habit formation, self-management and educational strategies should be considered when addressing adherence patterns *(QoE – moderate)*.

- Monitoring and interventions to support adherence to CFTR modulators, including the impact of adherence to conventional treatments, should be provided *(QoE – moderate)*.

15.8 Good practice points

- Physiotherapists should work with the MDT to develop a consistent and co-ordinated approach to supporting adherence.
- Physiotherapists should be aware that adolescence may bring lower participation and adherence with treatments at home and remote monitoring activities.
- Physiotherapists should spend time during consultations aiming to understand the person's adherence patterns.
- Treatments should be rationalised or combined where possible and appropriate, so the person with CF has the simplest and quickest treatment regimen possible.
- People with CF and their families should be supported to monitor and optimise adherence to treatment.

15.9 Research recommendations

- There is a need for studies assessing long-term adherence to airway clearance, exercise and physical activity using objective data capture methods.
- There is a need to assess the variation in adherence to different ACTs.
- There is a need for studies assessing long-term adherence to airway clearance, inhaled therapies and exercise in the CFTR modulator era.
- There is a need for high quality studies to assess the impact of strategies aiming to enhance adherence to airway clearance, exercise and physical activity, and inhaled therapies.

16. Infection prevention and control (IPC)

There are several infection control guidance documents from NICE, CFF and CF Trust, providing specific guidance around segregation, cross infection, and surveillance. There is, however, a lack of physiotherapy-specific guidance.

This chapter will highlight the current and recommended infection prevention and control (IPC) practices identified both nationally and internationally. Whilst this information and associated advice is based on the current evidence it should also be taken in combination with local IPC policies.

It should be noted that it is beyond the scope of this guidance to discuss settings beyond the hospital environment or comment on other infection control risks.

This document is designed to complement the overarching guidance.

16.1 IPC in CF Centres

16.1.1 Segregation

Infection in the airways of people with CF drives inflammation-associated bronchiectatic changes and respiratory decline. Primary prevention of these infections through effective IPC is an important management strategy.[985] Much of the literature mentions segregation of people with CF with specific pathogens, based on respiratory tract culture results, including *B. cepacia* complex (including epidemic strains of *B. cenocepacia* ET12), transmissible strains of *P. aeruginosa* (for example, Liverpool Epidemic strain [LES] and Australian Epidemic strain [AES-1]),[986,987] MRSA, non-*P. aeruginosa*, and more recently NTM (more specifically *M. abscessus*). There is clear evidence that increased incidence of bacterial infection occurs when cohort segregation is not implemented.[988,989]

Cohort segregation appears to interrupt the spread of infection, reducing the morbidity and mortality associated with chronic infection.[990,991] However, cohort isolation alone will not provide enough protection against dominant strains of specific pathogens.[992–994]

It is recognised that people with epidemic strains of *P. aeruginosa* require more hospitalisations, have an associated increased resistance to antibiotics and have a faster rate of clinical decline.[991] It is therefore logical to assume that all people with CF pose a significant risk to each other and that segregation will only work if minimal contact and optimal IPC strategies are employed.[995]

Epidemiological studies have identified that nosocomial transmission of CF-specific pathogens during synchronous hospital clinic attendances is a more likely route of transmission than social contact outside the hospital environment,[14,991] suggesting that indirect transmission is a likely factor in acquisition.

Rowbotham et al[985] reports the findings of an extension of an RCT[996] where the first acquisition of *P. aeruginosa* following segregation was 289 weeks as compared to 52 weeks in the non-segregated arm. This strongly suggests that cohort segregation is indeed a worthy endeavour.

16.1.2 Aerosols

Many of the pathogens that affect people with CF can be found in the natural environment. Most initial acquisitions of these infections are thought to be from the environment but the significance of the relationship between these environmental pathogens and those found in people with CF remains unclear.[997–1001]

In the hospital setting, there is evidence to suggest that person-to-person cross-infection can occur[165,1000,1002–1008] **This could happen through:**[999,1000,1003–1005]

- direct and indirect (fomite) contact transmission
- infectious respiratory droplet transmission (above 5µm)
- airborne transmission (droplet nuclei less than 5µm).

People with CF expectorate respiratory secretions in the form of droplets and droplet nuclei during cough manoeuvres. These have been shown to have high yields of viable pathogens within them.[165,993,1006–1012] *P. aeruginosa* and *B. cepacia* complex can survive for long periods in water; *P. aeruginosa* can persist suspended in sputum on dried surfaces for up to eight days.[999,1013–1015] Clifton et al suggested that mucoid strains of *P. aeruginosa* have a longer half-life and therefore have an increased survival advantage, surviving in droplet nuclei for up to 45 minutes.[1009] *M. abscessus* has also been shown to be viable for 24 hours after cough aerosolization.[1001]

Transmission of CF pathogens is considered to be via the airborne route and is responsible for the cross-infective spread of epidemic strains of *P. aeruginosa* and *B. cepacia* during identified

outbreaks, recognising that cross-infection continued to occur despite segregation, rigorous contact-based precautions and decontamination of environments.[1015]

Respiratory activities such as breathing, talking, sneezing and coughing influence the volume of airborne particles potentially carrying pathogens.[1008] Higher velocity activities such as sneezing and coughing further enhance transmission of any respiratory infections. Wood and Zuckerman identified higher risk of infectious aerosol particle production during periods of exacerbation when coughing was more prevalent and when respiratory function or airway clearance occurred.[1011,1016] *P. aeruginosa* droplets were identifiable at one to two metres following conversation[1010] highlighting the potential risk for cross-infection within waiting rooms and the associated difficulty in maintaining a safe distance between people with CF.

Wainwright et al reported that therapies including physiotherapy and inhalation of nebulised mucoactive agents which induce coughing are likely to result in similar cough-induced aerosols seen with voluntary cough and greater than those detected in tidal breathing.[1007] This suggests that enhanced IPC practices should be employed during periods of nebulisation and airway clearance.

During cough manoeuvres droplets greater than 5µm have been shown to travel up to three metres from the source but are unable to stay airborne for long. Droplet nuclei less than 5µm are of respirable range, can travel further (up to five to ten m) and stay airborne for longer (up to three hours).[165,998,1007,1011,1014,1015,1017] Airborne contamination has been detected in CF clinics, wards, corridors, and pulmonary function testing rooms.[1014,1015,1017–1021] The highest rates of airborne contamination were shown to occur after airway clearance and pulmonary function tests and persist in confined spaces.[1014,1019,1020] Air contamination after spirometry only reduced to extremely low levels 30 minutes after the individual left the room.[1004,1005,1016]

Increasing the air exchange and room ventilation rate in clinical areas allows greater removal of pathogens from the air and in theory reduces the risk of airborne pathogen transmission.[1009] Modifying the flow of people with CF through clinics by avoiding use of waiting in communal areas and enhancing IPC procedures within the clinic setting has reduced the rates of transmission.[1004,1005,1022–1024]

There is growing concern that these studies have shown the potential for airborne transmission although definitive evidence of this remains limited.[1001,1002,1009,1016,1017,1025] It has been suggested that the use of enhanced air exchange and ventilation or negative pressure rooms will reduce the risk of airborne transmission, but this needs further research.[1005,1009,1011,1025–1027] When sputum samples are required, it may be worth obtaining them before clinic attendance to minimise cough aerosols in the environment.[1011]

Surgical masks are effective at reducing airborne *P. aeruginosa* load by around 90% when worn by people with CF during cough manoeuvres, and it has been surmised that by reducing droplet and droplet nuclei spread, this reduces the risk of surface contamination and airborne transmission[1011,1028] although this remains controversial.[1003–1005,1016] Masks may be poorly tolerated in young children and those with respiratory distress; in these circumstances both Wood and Zuckerman proposed that good cough etiquette, enhanced air exchanges in the clinical environment, longer wash out periods between patients or negative pressure rooms should be considered.[1011,1016] People with CF should wear face masks in high risk and communal areas such as through hospital corridors, in the X-ray department or when visiting pharmacy, but face masks may not be required in individual hospital rooms during examination or admission.[985,1011,1029] Chen identified a reduced incidence of *B. cepacia* when people with CF wore masks and gloves outside of individual rooms.[1030]

16.1.3 Transmission

Both direct and indirect person-to-person infection transmission should be considered when identifying the source of new infection. Direct cross-infective transmission via droplets is less likely as a result of individual and cohort segregation.[1029] Clinical strains of *P. aeruginosa*, *B. cepacia* and *M. abscessus* have been recovered from hospital water supplies and surrounding surfaces such as drains and showers. It is unclear whether the original route of contamination was environmental or from a person with CF.[1000,1003,1014,1031–1033] CF pathogens have been detected in CF clinic settings, on surfaces of instruments and furniture.[1019] *M. abscessus* has been shown to be potentially spread by surface contamination of an inpatient room.[1001]

Whole genome sequencing has enabled species identification of pathogens, specifically *M. abscessus* isolates. Yan analysed the *M. abscessus* isolates of 14 people with CF and found clusters of genomically similar isolates.[1029] When epidemiological analysis was performed there were multiple cross-over periods of outpatient clinic attendance, suggesting that it was at these clinic attendances when cross-infection occurred.[1029,1034]

Rowbotham identified *P. aeruginosa* and Bcc on the hands of healthcare workers and could be transmitted for up to 180 minutes.[985] Skin and fingernails of healthcare workers and the use of false nails encouraged bacterial contamination, therefore diligent hand hygiene and wearing of gloves when engaged in clinical care is recommended.[1021]

Zuckerman found bacterial contamination on the hands of people with CF was common, and the bacteria identified at the beginning of the clinic visit was not the same as that identified at the end.[1019] **Possible routes for contamination, either via aerosols, droplets or fomites were:**[164,993,1015,1019,1029,1034,1035]

- contaminated equipment including respiratory devices
- high touch surfaces
- hand shaking
- door handles
- table surfaces
- soap dispensers
- chairs
- handwash basins
- bed linen.

Epidemic strains were found to be more prevalent, possibly surviving longer due to the longer half-life.[1009]

Alcohol gel was sufficient at removal of surface bacteria and recommended more regularly during clinic visits.[167,1019]

Chlorine-based products and vaporised hydrogen peroxide have been used been used as part of final cleaning regimen of rooms that have been occupied by people with CF with *M. abscessus*.[1029] Chlorine-based products have also been used for surface cleaning in rooms of those with *P. aeruginosa*.[1014] Bleach has been used in drains where *P. aeruginosa* has been isolated.[1014] UV light was shown to be effective at killing *P. aeruginosa*, *B. cepacia*, *Stenotrophomonas maltophilia* and NTM (*M. abscessus*).[1000,1036,1037] Others recommend using EPA-registered hospital disinfectant or detergent.[1003]

Although Grade quality of the evidence was considered low or very low on much of the evidence, RCTs into IPC issues are not considered ethical.[985] There is, however, a wealth of evidence to support the benefit of segregation.

With the increased use of digital technology, face-to-face clinic contact with the MDT and people with CF could be less frequent. With a reduction in frequency of clinics, the likelihood of cross-infection could be reduced.[985] Although each hospital has its own challenges and physical resource limitations, a unified approach to infection control practices is needed across hospitals caring for people with CF.[1029]

16.1.4 Recommendations

- Develop a robust local IPC strategy which recognises the requirement for individual and respiratory microbiology cohort segregation *(QoE – moderate)*.
- Use respiratory microbiological data to segregate people with *P. aeruginosa*, *B. cepacia* or *M. abscessus* infections, for example by using separate outpatient clinics. This should also extend to physiotherapy sessions and use of treatment rooms and gym spaces *(QoE – moderate)*.
- The local IPC policy should include recommendations for cleaning and decontaminating rooms and equipment used between people with CF and the use of agents with activity against CF pathogens including *M. abscessus (QoE – high)*.
- During inpatient care, ensure all physiotherapy manoeuvres and exercise are conducted in individual rooms. If a physiotherapy gym is to be used it should be by no more than one person with CF at a time with appropriate surface cleaning and decontamination. The time between people with CF using the gym should be optimised according to air exchanges and room ventilation *(QoE – moderate)*.
- Ensure appropriate cleaning and decontamination of all multiuse physiotherapy and exercise equipment between people with CF *(QoE – moderate)*.
- Stethoscopes or pulse oximeters should be for individual use where possible and appropriately decontaminated after use and between people with CF *(QoE – low)*.
- Covered sputum pots should be used for respiratory secretion containment and appropriately disposed *(QoE – moderate)*.
- Water-repellent gowns and gloves should be used when performing airway clearance or direct clinical care to prevent the possibility of fomite cross-transmission both for inpatients and outpatients. This is in line with contact and transmission-based precautions *(QoE – moderate)*.
- People with CF should be encouraged to practise hand washing or use alcohol-based hand gel frequently, especially in the outpatient

environment before use of a spirometer or other handheld apparatus *(QoE – moderate)*.

- Consider requiring that people with CF use surgical masks in communal areas of the hospital to reduce the risk of environmental contamination and airborne transmission of potential pathogens *(QoE – low)*.
- When carrying out spirometry in standard airflow rooms, consider allowing a washout period between people with CF *(QoE – low)*.
- Consider specification of room ventilation (number of air changes per hour) when planning new CF facilities to reduce the risk of airborne transmission of CF pathogens *(QoE – moderate)*.

16.1.5 Good practice points

- Consider allowing time after spirometry to allow droplets to settle before cleaning and disinfecting the room, unless the room has enhanced ventilation.
- The fingernails of healthcare workers should be kept trimmed and artificial nails are not advised.
- Audit and enhance staff adherence to cleaning and hand hygiene.
- When cross-infection in the outpatient setting is a concern, consider minimising cough inducing and aerosol generating procedures in outpatient rooms by collecting sputum and cough swab specimens at home prior to appointment. Consideration must be given to the individual's ability to provide a quality sample in the home environment.
- Appropriate cough etiquette should be encouraged: cough or sneeze into a tissue or your elbow not your hands; discard any tissues into an appropriate bin; wash hands after using a tissue.
- Optimise infection control practices and processes in physiotherapy and pulmonary function laboratories.
- During inpatient stays, people with CF should be accommodated in single rooms with en-suite basin, toilet and shower.
- In outpatient clinics, people with CF should avoid using communal waiting areas – instead they should be given an individual clinic room on arrival to clinic. Increase usage of telehealth consultations where possible will reduce cross-infection risk.

16.2 Nebulisers and airway clearance devices

There is an ever-increasing variety of medical devices available for nebulised therapy and airway clearance, and subsequently, a variety of devices may be used over time by a single patient.

16.2.1 Nebuliser devices

Nebuliser contamination by various clinically significant pathogens, including *B. cepacia*, *S. maltophilia* and *P. aeruginosa* have been well-documented.[1036–1041] In addition, yeast and moulds have also been cultured in high prevalence from nebulisers, even after washing and drying.[1042] There is little evidence to support correlation between the organisms cultured from nebulisers and an individual's own respiratory samples.[1036–1039] Nonetheless, these findings highlight the need for rigorous nebuliser device cleaning and disinfection, as a contaminated nebuliser device could potentially result in re-infection of the airways, or represent a source of new infection.

16.2.2 Airway clearance devices

There are few studies investigating the contamination of airway clearance devices, but a recent study found that 28 out of 30 devices tested were contaminated with bacteria – these were mainly environmental bacteria, but five samples were positive for pathogenic bacteria.[1043] Cleaning, defined as soaking in hot soapy water, rinsing and air-drying resulted in complete eradication in half of the samples, partial eradication in 30% and failure to eradicate in the remainder.

16.2.3 Current guidelines

The CF Foundation IPC guideline gives recommendations for nebuliser maintenance both in hospital and at home.[1035] The use of disposable nebuliser devices in hospital is advocated. After each use, any residual medication should be rinsed out with sterile water and the components replaced after 24 hours. **At home they recommend cleaning with dish detergent followed by disinfection with one of multiple methods:**

1. Boiling in water.
2. Dishwasher.
3. Steaming.
4. 70% alcohol soak.
5. 3% hydrogen peroxide soak.

Both cold methods of disinfection require rinsing with sterile water. The final step is complete air-drying. These steps should be carried out after each use.

A comprehensive review on nebuliser device hygiene in CF exists[1044] and offers recommendations on cleaning and disinfection practises for nebuliser devices in hospital and at home (Appendices VI, VII).

Nebulisers should be washed with detergent after each use and disinfected immediately using thermal disinfection. **Following disinfection parts can be:**

- stored in the disinfector unit until used the next time (within 24 hours) – this recommendation supports the findings of two studies investigating steam disinfection of nebuliser and airway clearance devices in a baby bottle disinfector.[1045,1046] Steam was found to be a safe, effective, simple method of disinfection for nebulisers inoculated with common pathogens including *S. aureus*, *P. aeruginosa*, *B. multivorans* and *M. abscessus*. Furthermore, Hohenwarter found that active drying of components was found to be a source of recontamination and that components could be safely left undisturbed in the disinfector until required.[1045]
- left to air dry – this method is not definitive as the review cites two recent papers showing how NTM and *S. aureus* (MSSA and MRSA) can survive on plastic surfaces for 24 hours during the air drying process.

These guidelines can be used in conjunction with manufacturers' instructions to drive local policy and inform advice given to people with CF.

To date there are no such guidelines for airway clearance devices, although each manufacturer provides information with the devices. However, good practise would suggest that the procedures for the nebuliser devices should apply for hygiene of airway clearance devices.

Similarly, there is little from the literature to guide the frequency of changing bacterial filters and patient tubing from devices such as the IPPB device. The American Association for Respiratory care (AARC) **clinical practice guideline for the IPPB** recommends that IPPB circuits should be changed between individuals, when visibly soiled, or according to institutional infection control policy.[397]

A simple, clear, consistent approach to the maintenance of these devices is a significant step in overcoming the barriers to this part of an individual's daily routine.

16.2.4 Good practice points

- Nebuliser components and airway clearance devices should be washed with detergent after each use.
- Washing nebuliser and airway clearance device components is essential to remove residual medication or debris.
- Steam disinfection represents an effective, safe and simple method of disinfection of nebuliser and airway clearance devices.
- Sterile water should be used for the final rinse if disinfection of nebuliser and airway clearance devices is not possible.
- Air drying after cleaning and disinfection of nebuliser and airway clearance devices is effective in most cases.

16.2.5 Research recommendation

- Literature review to formulate universal guidelines for the cleaning and hygiene of airway devices and adjuncts.

16.3 Education and adherence to IPC recommendations

16.3.1 Healthcare professionals

While most CF Centres educate people with CF and families appropriately regarding cleaning and disinfection methods for nebuliser and airway clearance devices, there is variability around how often the guidelines are reviewed and practiced. Specifically, the recommended time interval of nebuliser cleaning and disinfection appears to be highly variable among CF Centres.[1047]

Despite increased evidence and recognition that the implementation of strict IPC procedures decreases the spread of pathogenic bacteria in CF there is continued evidence that healthcare professionals, people with CF and their families are inadequately fulfilling recommendations put in place to improve IPC practice.[985,1021,1048–1050]

Local audits and then targeted healthcare professional education and skills programmes have been shown to improve adherence to IPC on a local level.[985,1051] Educational IPC posters visible in clinical areas are thought to improve accountability of people with CF and healthcare professionals.[1049] Education on the requirement of personal protective equipment (PPE) such as gowns and gloves enhanced adherence to infection control measures.

Despite declining inpatient admission rates for since the introduction of CFTR modulators, education for inpatient healthcare professionals remains important as people with CF are still being hospitalised.

Universal approaches to IPC developed for CF closely mirror the approaches used to prevent COVID-19 including universal mask use, social distancing , and frequent hand hygiene.[1051] The COVID-19 pandemic has likely changed perceptions about IPC, not only among healthcare professionals, people with CF and their families, but among the general public as the rationale for mitigation strategies for COVID-19 were widely promoted.

Targeted education for inpatient ward healthcare professionals not generally considered part of the CF care team, is recommended to obtain consistent practices. Similarly, findings suggest that universal and repeated discussions between care teams and people with CF and their families regarding IPC practices and their rationale could improve future implementation by reducing knowledge and attitude barriers.[1051]

There is a large variation in CF Centres' IPC practices, possibly because of suboptimal knowledge of the best evidence, lack of or conflicting evidence, inadequate resources, or a combination of these. IPC practice guidelines for Centres to follow are necessary for better and standardised care of people with CF.

Barriers to healthcare professional implementation and adherence to IPC recommendations have been identified as:[1021,1048]

- Reduced access to available recommendations.
- Reduced knowledge of the content of the recommendations.
- Reduced time available or support to adhere to recommendations.
- Low confidence in ability to change behaviours of people with CF.
- Lack of confidence in a healthcare professional's own ability to adequately fulfil the recommendations.

16.3.2 Good practice points

- Improved awareness and access to IPC guidelines for healthcare professionals.
- Enhanced IPC education, skills workshops and training for healthcare professionals.
- Sharing successful IPC guidance and interventions between CF Centres.
- IPC educational posters in clinical areas.
- Local audits of IPC adherence to inform strategies to reduce local barriers to staff adherence to recommendations.
- More work is needed to link adherence to IPC guideline adherence with improved patient outcomes.

16.4 People with CF and their families

Poor adherence behaviours are well-documented in people with chronic disease and specifically people with chronic respiratory disease.[1052] The treatment burden associated with airway clearance and nebuliser therapy has also been well-documented, and it has been shown that adherence to these therapies has been variable.[956]

The care of respiratory equipment may be considered a mundane and insignificant practise to people with CF. The incidence of nebuliser contamination improved after a single education session, which included written and oral instructions.[1041] Families of younger children with CF had better adherence to IPC practices, such as cleaning and disinfecting of nebuliser equipment, than adolescents and adults with CF. This may be due to better integration of newer recommendations into the care of younger children with CF, where families may have heightened concerns regarding the impact of these practices on their child's health, and that older people with CF with advancing disease may need increased support to adhere to recommendations.[1053]

People with CF, their families and caregivers may not implement and adhere to IPC recommendations due to:[1053]

- inadequate awareness of IPC recommendations
- reduced understanding of risks and therefore the benefits of adhering to IPC recommendations
- time constraints
- impact of deteriorating health on ability to perform recommended IPC practices, such as cleaning and disinfecting physiotherapy and nebuliser equipment.

16.4.1 Recommendations

- Physiotherapists working in CF should have full awareness and understanding of the local and national IPC recommendations *(QoE – moderate)*.

- Physiotherapists working in CF must have an awareness and understanding of the manufacturers' recommendations for cleaning and disinfecting specific physiotherapy and nebuliser equipment *(QoE – low)*.
- Physiotherapists working in CF have a pivotal role in educating and supporting people with CF and their families and caregivers in specific IPC recommendations:
  - Performing hand hygiene.
  - Containing and disposing of sputum.
  - Cleaning and disinfection of physiotherapy and nebuliser equipment.
  - Cough etiquette.
  - Avoiding contact with other people with CF. *(QoE – moderate)*.

16.4.2 Good practice points

- Education is an essential tool to improve acceptance of and adherence to hygiene protocols and to drive positive outcomes.
- Enhanced regular IPC education and skill training.
- Specific education and training on nebuliser and physiotherapy equipment cleaning and disinfection.
- Increased frequency of discussions around IPC recommendations.
- Offer increased support to those with deteriorating health to perform recommended IPC practices such as cleaning and disinfecting nebuliser equipment.
- Consider peer-to-peer education using digital health opportunities and social media as a vehicle for communication.

17. Physiotherapist prescribing

Non–medical prescribing refers to the prescribing and management of medicines by specially trained nurses, optometrists, pharmacists, physiotherapists, podiatrists, radiographers, dietitians and paramedics working within their clinical competence and specialism as either independent and/or supplementary prescribers.[1054]

Physiotherapists in the UK gained independent prescribing rights in 2013 and obtained limited controlled drug prescribing rights in 2015:[1055,1056]

"The physiotherapist independent prescriber may prescribe any licensed medicine from the British National Formulary (BNF), within national and local guidelines for any condition within the practitioner's area of expertise and competence within the overarching framework of human movement, performance and function. They may also mix medicines prior to administration and may prescribe from a restricted list of controlled drugs as set out in Regulations."

The **NHSE long-term workforce plan** encourages increasing the number of independent prescribers and allied health professions (AHPs) acting as senior decision makers, in appropriate settings, as part of increasing the scope and reach of AHP roles to help manage demand productively.[1057]

Physiotherapist prescribers are required to undertake CPD specific to prescribing within their specialist area in addition to the CPD relating to non-prescribing areas of practice.[1058] All ACPCF members who are undertaking their training to be an independent prescriber or who are annotated by the HCPC as prescribers are able to join the ACPCF Independent Prescribers (ACPCF IP) group. The ACPCF IP group have study days twice a year to support prescribing CPD specific to CF and to provide a network for sharing both knowledge and experience. The group has seen recent rapid growth in the numbers from 11 members in 2015, to 27 members in 2019, to 47 members in 2023, highlighting that physiotherapist prescribing has a key role and is being adopted with increasing frequency by principle and advanced practice physiotherapists working in CF.

In 2023 the ACPCF IP group conducted an online practice survey of all its members; 27 out of the total 47 members completed the survey. All respondents were annotated as supplementary and independent prescribers working across both paediatric (52%) and adult (44%) services in CF. Fifty-four percent of respondents felt their ability to independently prescribe frequently negated the need for medical involvement for prescribing.

The trend in medicines prescribed was for inhaled medications including inhaled mucolytics (93%), bronchodilators (89%) and antibiotics (89%); there were also a high proportion of respondents prescribing oral antibiotics (65%). One respondent was prescribing IV medications, and 16% prescribing modulators, demonstrating the continuing advances and progression in practice of physiotherapy prescribers in CF. Many of the respondents reported that they attend ACPCF IP meetings to augment their prescribing CPD, demonstrating how important these UK meetings are.

As it stands, physiotherapists practicing in the Republic of Ireland are not able to become non-medical prescribers, as dictated by their CORU state registration. In January 2023 the Irish Society of Chartered Physiotherapists (ISCP) released **a press statement** calling upon the Department of Health to change legislation to allow physiotherapists to become non-medical prescribers, to enhance delivery of care. At time of publication, no such changes have been made.[1058]

17.1 Regulation of physiotherapist prescribing practice

Physiotherapist prescribers must only prescribe once they have successfully completed an HCPC-approved prescribing programme and had their entry on the HCPC register annotated to show their prescribing status.

The HCPC 'Standards for Prescribing' outline the standards of prescribing proficiency required for physiotherapists annotated as prescribers on the HCPC register. These are in addition to the general standards of proficiency for physiotherapists that apply to all registrants.[1059]

The Royal Pharmaceutical Society **A Competency Framework for Prescribers** and the CSP **Practice Guidance for Physiotherapist Supplementary and Independent Prescribers** provide details of prescribing competencies and practice guidance that must be maintained to ensure safe and effective prescribing, including information on the assessment, consultation and prescribing governance.[1054,1055]

Physiotherapist prescribers must meet the requirements of HCPC, CSP and their employer to ensure they are prescribing safely, in line with best practice, local and national guidance.[1059,1060]

Physiotherapist prescribers must also ensure that they have adequate indemnity for their prescribing practice and should ensure that their practice has been endorsed by their employer, which may require an addition to their job description.

17.2 Recommendations

- All CF MDTs should review whether the addition of a physiotherapist prescriber may enhance the service they offer *(QoE – low)*.
- Advanced Physiotherapists within a CF service ought to consider NMP training as part of their annual CPD and/or job planning review to support people with CF under their care and CF services *(QoE – moderate)*.
- Physiotherapist prescribers working in CF must undertake CPD specific to both CF and prescribing. This can be achieved through attendance on ACPCF IP group events. Additional CPD activities may include CF conferences, peer supervision, local medicine reviews and journal clubs *(QoE – moderate)*.
- Physiotherapist prescribers working in CF should be part of any local clinical governance teams/ programmes monitoring quality improvement in CF care *(QoE – low)*.

17.3 Good practice points

- Physiotherapist prescribers working in CF should be endorsed by the CF Centre MDT and improve experiences of people with CF without compromising safety or access to quality care.
- Physiotherapist prescribers working in CF must remain up to date with CF medication guidance relevant to their prescribing practice, which may include local guidelines, CF Trust guidance, commissioning guidance and NICE appraisals.
- Physiotherapist prescribers working in CF should help people with CF make informed decisions about their treatment and support use of appropriately prescribed medicines to best effect.[1061,1062]
- Physiotherapist prescribers working in CF should have access to a local non-medical or independent prescribing forum to support long-term CPD and development needs.

17.4 Research recommendations

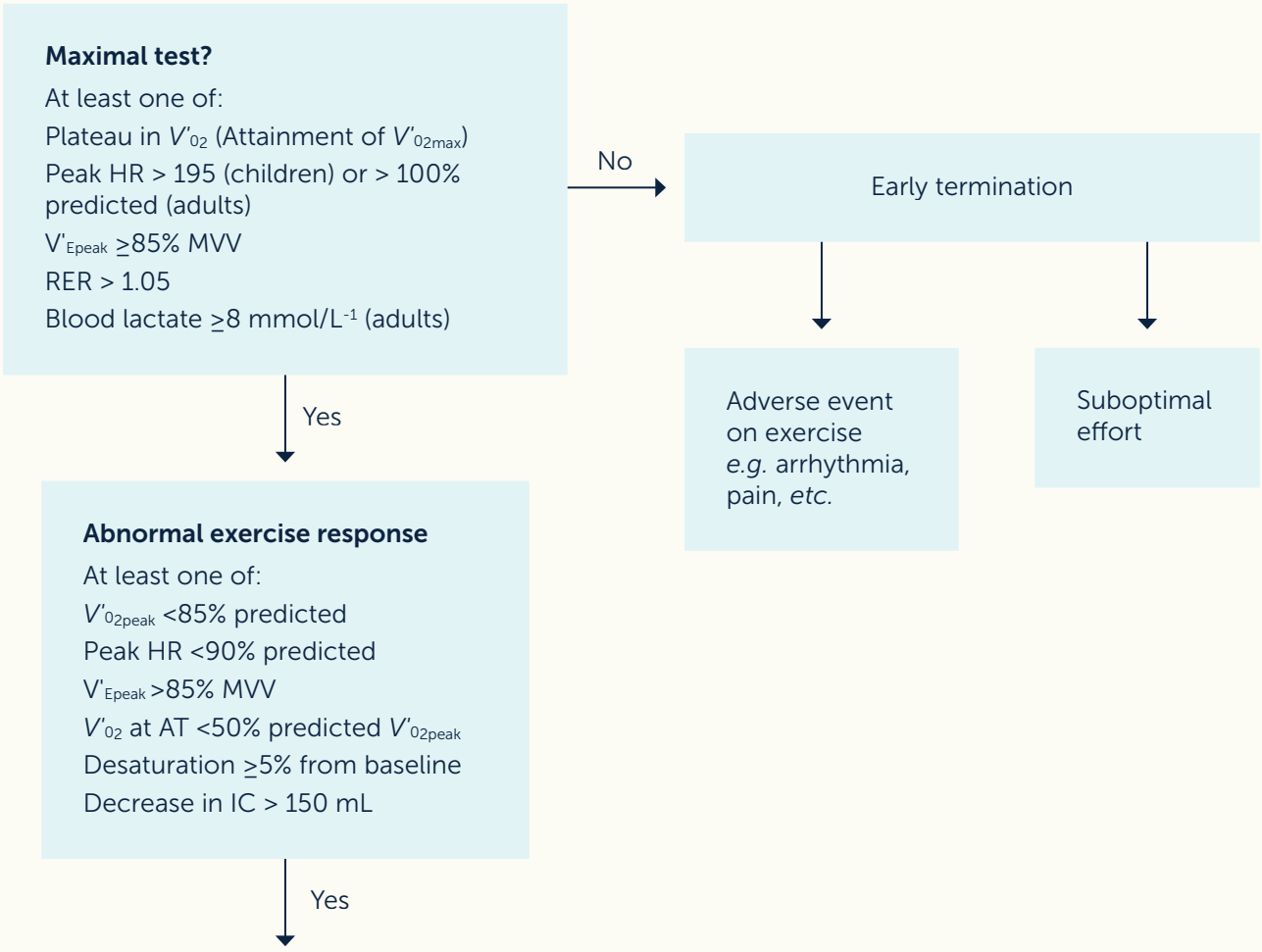
- Continued evaluation of the evolution of ACPCF IP prescribing practice.
- Evaluation of views of MDTs and people with CF on CF physiotherapy independent prescribing practice.
- Evaluation of the impact of ACPCF IP biannual meetings on the CPD of CF independent prescribing physiotherapists.
- Assessment of how an independent prescribing qualification can impact job role and career progression in physiotherapy.
- Assessment of barriers to obtaining independent prescribing qualifications for physiotherapists working in CF.

18. Appendices

Appendix I: Exercise

Appendix Ia

Schematic overview of how to determine whether a maximal effort has been given and the cause(s) of any exercise limitation.



	Respiratory limitation	Cardiovascular limitation	Peripheral muscle limitation	Peripheral deconditioning
V'_{O2peak}	Reduced	Reduced	Reduced	Reduced
V'_{O2} at AT	Normal	Normal/ reduced	Likely reduced	Reduced
Peak HR	Reduced	Likely normal	Reduced	Normal
V'_E/MVV	>85%	<85%	<85%	<85%
S_{pO2}	Normal/ reduced	Normal	Normal	Normal

Figure reproduced with permission from: Radtke T, et al. ERS Statement on standardisation of cardiopulmonary exercise testing in chronic lung disease. Eur Respir Rev 2019; 18:28(154).

Appendix Ib

CPET Case Study Patient

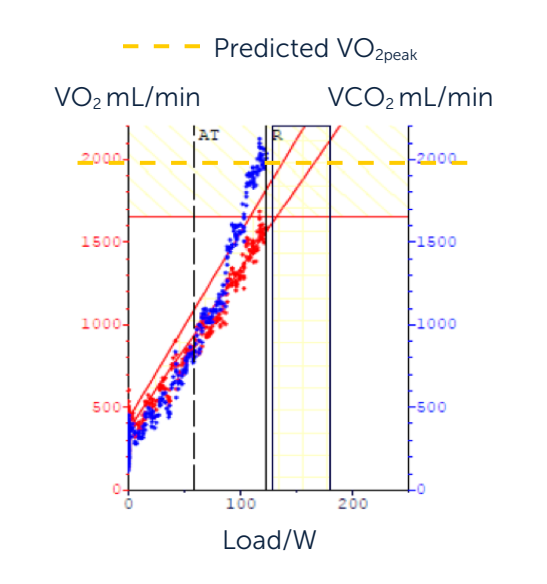
Patient A (FEV_1 95% predicted), male (p.Phe508del/p.Ala457Pro, c.1369G>C) and aged 13 years attended for CPET at annual review. He attained a VO_{2peak} of 38.7 mL/kg/min (84% predicted), and a peak heart rate (HR_{peak}) of 184 beats/min. He had significant breathing reserve at peak exercise (V_{Epeak} 77L/min versus calculated MVV 108 L/min), meaning that he was not ventilatory limited during exercise. His anaerobic threshold (AT) occurred at 40% predicted VO_{2peak}.

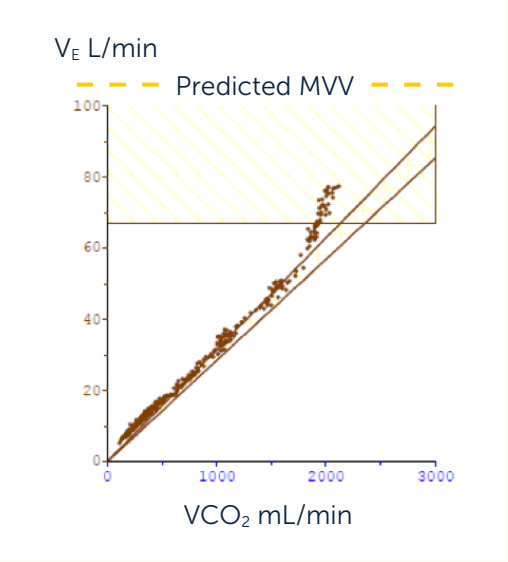
Taken collectively, the above CPET data suggested suboptimal exercise capacity, with deconditioning suggested by early onset of the AT. Selected data from panels 3, 4, and 5 of his 9-panel plot are displayed in **Appendix IIc**.

His physiotherapy team constructed an individualised exercise programme. Improvements in both exercise capacity and physical conditioning were evident upon retesting five months later (see **Appendix Id**). His VO_{2peak} had increased to 43.2 mL/kg/min (96% predicted), and AT had improved to 48% predicted VO_{2peak}. An identical HR_{peak} and similar breathing reserve were recorded.

Case example illustrating an exercise-limited and deconditioned person with CF

(Selected data [Panels 3,4,5 shown] from CPET are displayed)





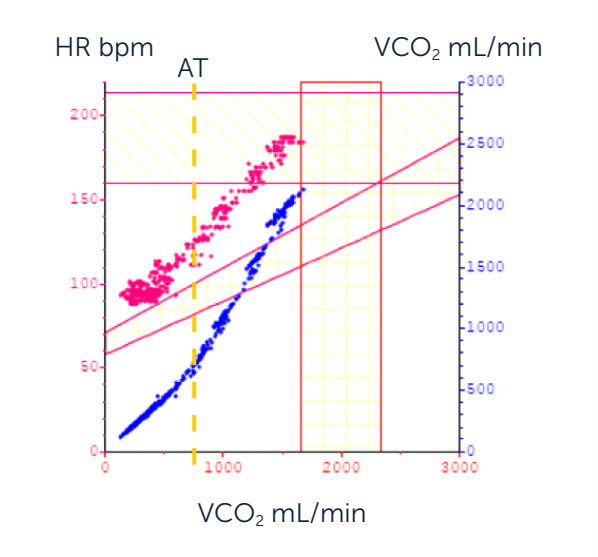
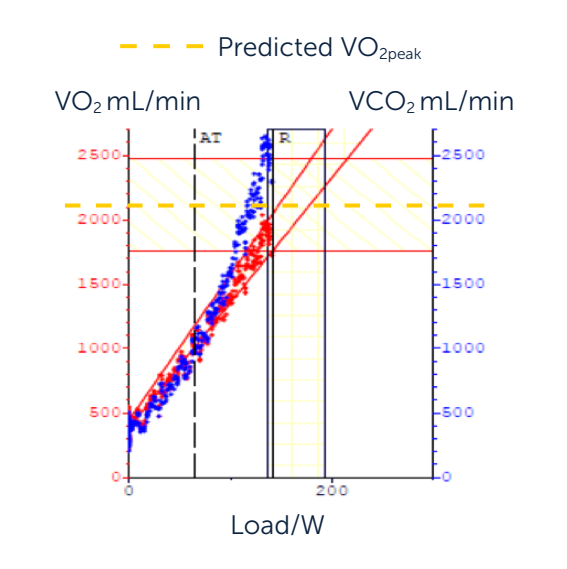
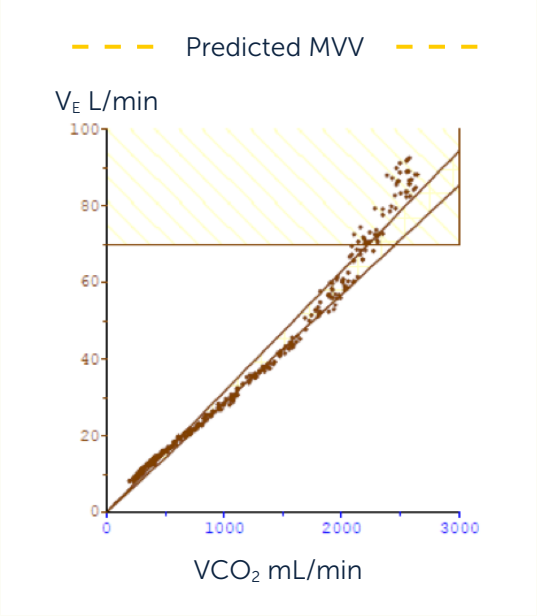


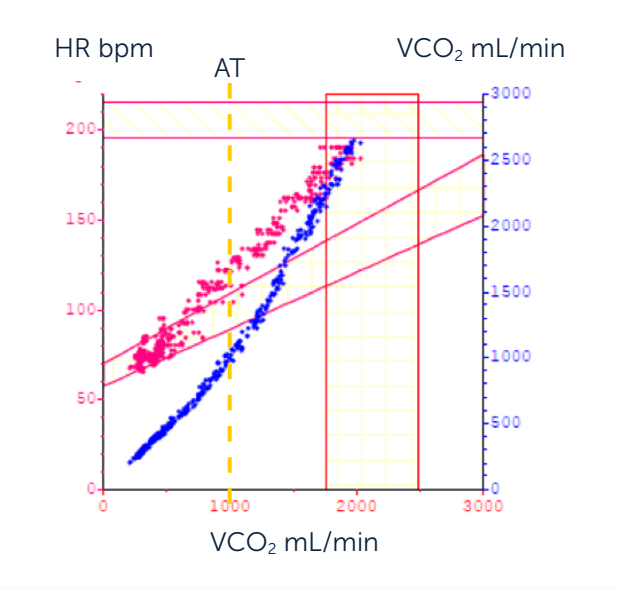
Figure reproduced with permission from: Urquhart and Saynor, Paediatr Respir Rev 2018; 27:28-32.

Improvements in exercise capacity and AT in same patient following individualised exercise programme

(Selected data [Panels 3,4,5 shown] from CPET are displayed)







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Appendix Ic

Standard operating procedure for maximal cardiopulmonary exercise testing (CPET)

Following a short rest period, an unloaded phase should be undertaken. This phase is important for assessing baseline pulmonary gas exchange and ventilation associated with vertical leg movements. This phase also allows the individual further familiarisation with exercise on the treadmill cycle ergometer and to warm up adequately. Since most cycle ergometers cannot provide a true minimum load of 0 W, a workload of 10 W should be used. A three minute duration is recommended, however in individuals with severe lung disease and/or severe deconditioning this phase may be shorter (but not less than two minutes) in order to perform the incremental exercise phase before the participant fatigues. If a treadmill is used, the lowest speed may be chosen for baseline measurements, such as 1.0-1.6 km/hour.[1]

After resting and unloaded phases, an incremental exercise phase to exhaustion should begin. Whilst the 2015 European statement on exercise testing in CF[2] recommends the Godfrey 'step' incremental protocol[3] (workload increases each minute on the minute), others have recommended the use of ramp incremental testing protocols.[4-6] Although it has not yet been directly investigated in people with CF, ramp and uniform minute-by-minute incremental protocols are both acceptable and provide similar outcomes, when total duration of the incremental phase is the same in healthy individuals. Importantly, whichever incremental protocol is used should be adapted to the individual's characteristics in order to allow adequate evaluation and follow-up. To assist with this and achieving a target incremental test duration of 8-12 minutes, a CF-specific equation to predict peak workload is now available[7] (Equation 1). Based on standard measures of anthropometry and FEV_1, this equation can be used to help calculate individualised workload increments for a cycle ergometry testing protocol:

W_{peak} (W) = –142.865 + 2.998 × Age (years) – 19.206 × Sex (0 = male;1 = female) + 1.328 × Height (cm) + 23.362 × FEV_1 (L)

Equation 1.

The most recent statement from the European Respiratory Society[1] also provides additional, alternative formulae and a CF example.

As outlined in the European Respiratory Society consensus document,[1] monitoring patients at the end of the incremental exercise phase (ie upon exhaustion) is important. They should be encouraged to continue unloaded pedalling or 2-3 minutes at a reduced speed of ~30 rpm when cycling (or very slow walking when on the treadmill). A prolonged recovery period may be necessary for some patients and observation during this time may identify any changes improvement in exercise recovery time after pulmonary rehabilitation and exercise programmes. During this period, cardiovascular monitoring (ECG, blood pressure, SpO_2 etc) should be performed. Since delayed post-exercise heart rate recovery is frequently observed in lung disease patients and associated with dynamic hyperinflation[8] and poor prognosis, HR recordings may offer additional useful information. Furthermore, assessment of perceived exertion, dyspnoea and leg fatigue should be performed using standardised scales suggested by Borg and others. In line with European Respiratory Society recommendations,[1] gas exchange measurements can be terminated, and the mask/mouthpiece removed in order to make the participant more comfortable (unless these measurements are required for specific evaluations during the recovery phase. In addition, inspiratory capacity manoeuvres may be performed during this phase of testing to assess the rate of recovery of dynamic hyperinflation, but this is mainly done for research purposes.[1]

Where maximal CPET has been used, it is important to confirm whether a maximal effort has been achieved in order to interpret the data accurately. The algorithm prided by the ERS Taskforce[1] is presented in Figure 1 to assist with this decision-making process. Additionally, when time allows and the participant is able, supramaximal verification has been shown to improve the reproducibility and accuracy[6,9] of maximal CPET outcome measures and confirm whether an individual has worked maximally. Such verification testing has been shown to be safe and well tolerated in both children/adolescents with mild to moderate CF as well as adults and/or those with more severe CF pulmonary disease.[8]

If full CPET testing is unavailable it is recommended that the same ramp cycle and treadmill protocols be performed with all other measures available and using predictive metabolic equations to estimate oxygen consumption in lieu of direct gas analysis.[10] This should be undertaken with caution as predictive equations can only provide an estimate of 'true' exercise capacity.

References

1 ATS/ACCP. Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211–277.

2 Hebestreit H et al. (2015). Statement on Exercise Testing in Cystic Fibrosis. Respiration; 90:332-351.

3 Godfrey S. (1970). Exercise tests in assessing children with lung or heart disease. Thorax, 25: 258.

4 Radtke T, et al. ERS Statement on standardisation of cardiopulmonary exercise testing in chronic lung disease. Eur Respir Rev. 2019 Dec 18;28(154).

5 Causer AJ, et al. (2018). Cardiopulmonary exercise testing with supramaximal verification produces a safe and valid assessment of VO_{2max} in people with cystic fibrosis: a retrospective analysis. J Appl Physiol, 125(4):1277-1283.

6 Saynor ZL, Barker AR, Oades PJ, Williams CA. (2013). Reproducibility of maximal cardiopulmonary exercise testing for young patients with cystic fibrosis. J Cyst Fibros, 12(6): 644-50.

7 Hulzebos JH, Werkman MS, van Brussel M, Takken T. (2012). Towards an individualized protocol for workload increments in cardiopulmonary exercise testing in children and adolescents with cystic fibrosis. J Cyst Fibros, 11(6): 550-4.

8 Guenette JA, Chin RC, Cory JM, et al. (2013). Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm Med, 2013: 956081.

9 Saynor ZL, Barker AR, Oades PJ, Williams CA. (2013). A protocol to determine a valid VO_{2max} in young cystic fibrosis patients. J Sci Med Sport. 16(6): 539-44.

10 Werkman MS, Hulzebos EH, Helders PJ, Arets BG, Takken T. (2014). Estimating peak oxygen uptake in adolescents with cystic fibrosis. Arch Dis Child. 99(1): 21-5.

Appendix Id

Cardiopulmonary exercise test summary report	
Hospital name: **Patient's surname:** **Patient's name:** **DOB:** **Consultant:** **Indication(s) for conducting the test:**	**Department:** **Test date:** **Type of ergometer and metabolic cart:** **Reason for referral:** **Clinical diagnosis:**
Technical	
Protocol	Describe exercise protocol employed, work increment as a function of time and total incremental exercise duration.
Technical comments	Review criteria outlined in **Appendix Ia** to establish whether the test has led to the limit of tolerance. Report the source of equation used to express physiological variables as a fraction of predicted normal values.
Reason for termination of test	Report the reason(s) indicated by the patient for terminating the test (breathlessness, leg discomfort or both). Indicate whether the patient complied well with the incremental effort or claimed discomfort with the exercise or breathing apparatus as a contributing factor to exercise limitation.
Exercise response	
Aerobic capacity/anaerobic threshold*	A VO_{2peak} of .... mL/min/kg (...% predicted normal) was achieved along with a peak workload of .... Watts (...% predicted normal) *or peak speed of ... km/hour.* Anaerobic threshold (AT) occurred at .... mL/min/kg (...% predicted VO_{2max}). Corresponding values were .... METs at AT and.... METs at the limit of tolerance. Indicate whether VO_2/work rate slope (.... mL/min/Watt) was within the normal range.
Cardiovascular response	Peak HR was .... beats/min (% predicted normal). Indicate any abnormalities detected by the ECG recordings and report systolic and diastolic BP at the limit of tolerance. Conclude if cardiovascular response was normal.
Ventilatory response	Peak V_E was .... L/min (...% MVV)**. Report the change from baseline in inspiratory capacity (delta IC = ... mL). Report shortness of breath score ..... Conclude whether exercise limitation was of ventilatory origin.
Gas exchange	Report ventilatory equivalents for VO_2 and VCO_2 at AT and at peak exercise. Report resting and peak SpO_2. Report the V_E/VCO_2 slope values. Conclude whether gas exchange response to exercise was normal.

Metabolic	RER values were .... at rest, ... at AT and .... at the limit of tolerance.
Summary	
Conclusion:	Comment on patient's effort and exercise capacity taking into consideration peak values for work rate, *speed*, VO_2 and AT. Comment on potential ventilatory, cardiovascular or peripheral muscle limitation or simply poor effort. Compare the results with previous tests on the same patient and indicate when the test should be repeated.

*Anaerobic threshold (AT) determined from breath-by-breath gas exchange measurements or blood lactate measurements.

** Report, if MVV was measured directly (sprint method) or estimated (provide equation).

Anaerobic threshold (AT); blood pressure (BP); heart rate (HR); inspiratory capacity (IC); metabolic equivalent (MET); maximum voluntary ventilation (MVV); respiratory exchange ratio (RER); peak oxygen saturation (SpO_2); carbon dioxide production (VCO_2); minute ventilation (V_E); oxygen uptake (VO_2).

Text in *italics* refers to treadmill exercise outcomes.

Please note that this summary report is augmented by data tables and graphs of exercise data summarised in table 4 of the main manuscript [Radtke T, et al. ERS Statement on standardisation of cardiopulmonary exercise testing in chronic lung disease. Eur Respir Rev. 2019 Dec 18;28(154)].

Appendix Ie
The Borg perceived exertion scale

15-point scale

- **6** – 20% effort
- **7** – 30% effort – Very, very light – rest
- **8** – 40% effort
- **9** – 50% effort – Very light – gentle walking
- **10** – 55% effort
- **11** – 60% effort – Fairly light
- **12** – 65% effort
- **13** – 70% effort – Somewhat hard – steady pace
- **14** – 75% effort
- **15** – 80% effort – Hard
- **16** – 85% effort
- **17** – 90% effort – Very hard
- **18** – 95% effort
- **19** – 100% effort – Very, very hard
- **20** – Exhaustion

Borg G. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14(5):377-81.

Borg G, et al. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. Med Sci Sports Exerc 1983; 15(6):523-528.

Borg GAV. Borg's Rating of Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics, 1998.

Appendix II: Sinus disease

Appendix IIa

SN5 Questionnaire

Date: _____

Chronic Rhinosinusitis Screening Questionnaire

Thank you for taking the time to fill out this questionnaire. Your responses will help us improve our understanding of how diseases of the nose and sinuses affect children with cystic fibrosis, so that we can better identify and treat these problems.

Age: _____ **Gender:** M F

Over the past 12 weeks, has your child complained of any of the following on a daily basis?		
Nasal congestion or obstruction?	Yes	No
Facial pain, pressure, or fullness?	Yes	No
Smelly drainge from the front of the nose, or back into the throat?	Yes	No
Decreased sense of smell?	Yes	No

Adapted from Hassanzad, M. et al. (2019) 'Evaluation of Quality of Life in Terms of Sinonasal Symptoms in Children with Cystic Fibrosis'. Biomolecular concepts: 10(1); 91–98 (doi: 10.1515/bmc-2019-0011).

SN-5 (Si11onasal-S)

Instruction: Please help us understand the impact of sinus and/or nasal problems on your child's quality of life by checking one box for each question below. Thank you.

In the past 4 weeks, how often have these been a problem for your child?	None of the time	Hardly any time at all	A small part of the time	Some of the time	A good part of the time	Most of the time	All of the time
Sinus infection Nasal discharge, bad breath, daytime cough, post-nasal drip, headache, facial pain or head banging.							
Nasal obstruction Stuffy or blocked nose, nasal congestion, reduced sense of smell, trouble breathing with mouth closed.							
Allergy symptoms Sneezing, itchy nose/eyes, need to rub nose/eyes, or watery eyes							
Emotional distress Irritable, frustrated, sad, restless, or trouble sleeping because of nose or sinus illness							
Activity limitations Missed school/daycare, lost time with family/friends, unable to do projects because of nose or sinus illness							

Appendix IIb

Sino-nasal outcome test (SNOT-22)

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Sino-nasal outcome test (SNOT-22)

I.D: _____ Date: _____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale:	No problem	Very mild problem	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be		5 most important items
1. Need to blow nose	0	1	2	3	4	5		○
2. Nasal blockage	0	1	2	3	4	5		○
3. Sneezing	0	1	2	3	4	5		○
4. Runny nose	0	1	2	3	4	5		○
5. Cough	0	1	2	3	4	5		○
6. Post-nasal discharge	0	1	2	3	4	5		○
7. Thick nasal discharge	0	1	2	3	4	5		○
8. Ear fullness	0	1	2	3	4	5		○
9. Dizziness	0	1	2	3	4	5		○
10. Ear pain	0	1	2	3	4	5		○
11. Facial pain/pressure	0	1	2	3	4	5		○
12. Decreased sense of smell/taste	0	1	2	3	4	5		○
13. Difficulty falling asleep	0	1	2	3	4	5		○
14. Wake up at night	0	1	2	3	4	5		○
15. Lack of a good night's sleep	0	1	2	3	4	5		○
16. Wake up tired	0	1	2	3	4	5		○
17. Fatigue	0	1	2	3	4	5		○
18. Reduced productivity	0	1	2	3	4	5		○
19. Reduced concentration	0	1	2	3	4	5		○
20. Frustrated/restless/irritable	0	1	2	3	4	5		○
21. Sad	0	1	2	3	4	5		○
22. Embarrassed	0	1	2	3	4	5		○

2. Please mark the most important items affecting your health (maximum of 5 items)

Appendix IIc

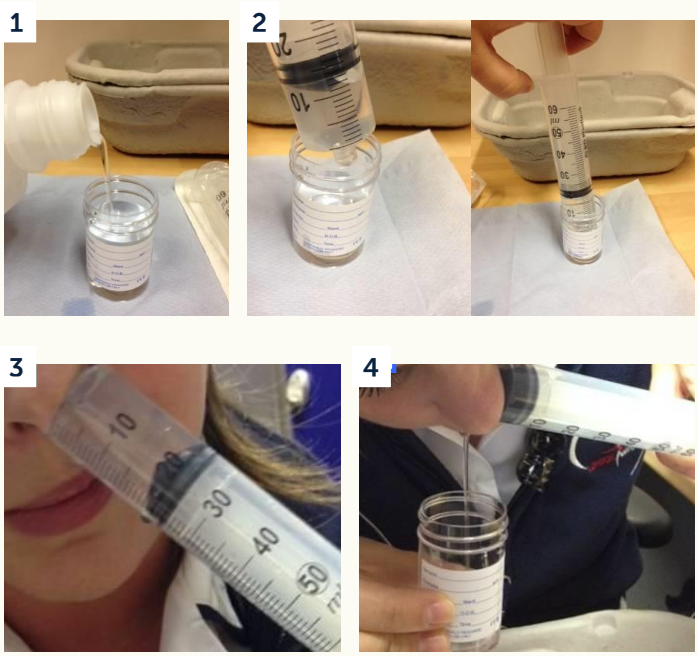
How to take a nasal rinse sample

Equipment required:

- 0.9% Saline (~50ml)
- 60ml Luer-lok syringe (short nozzle end)
- 1 wide aperture sample pot
- Disposable bowl
- Tissues

****IF TAKING A COUGH SWAB OR SPUTUM SAMPLE – PLEASE TAKE THIS BEFORE SINUS SAMPLE SO NOT CONTAMINATED****

1. On a flat surface, pour 40-50ml of 0.9% saline into the sample pot
2. Syringe out the 0.9% saline into the 60ml syringe – turn upwards and void any air from the top of the syringe
3. Leaning over the bowl in sink/ on lap, place the syringe tightly against the nostril to ensure a good seal (warn the patient they may still be able to feel the nozzle of the syringe in their nose)
4. Place the sample pot under the other nostril (this may require a second pair of hands) to collect ~5-10mls of solution. When you have enough, encourage pt to gently blow out any residual fluid into the pot
5. Send off sample as "sinus antral lavage" for MC&S
6. Allow patient to blow their nose and then dispose of bowl and fluid cleared into a yellow bin.



Appendix IId

Pari sinus

In principle the PARI SINUS® can be used with all medications approved for inhalation.

Practical experience in the use of PARI SINUS® with numerous different solutions and medications has already been gathered. In relation to the treatment objectives outlined below, the information on named solutions and medications is based on pilot or case studies, or is of an empirical nature.

Medication	Usual indication	Prescrip-tion	Delivery system	Reconsti-tuting	Notes
Saline 0.9%	Treatment and prevention of chronic rhinosinovitis.	2.5ml as needed, up to 4 times daily	PARI SINUS® nebuliser	N/A	Osmotic Instructions for use (empirical)
Mucoclear 3% (hypertonic saline solution)	Treatment and prevention of chronic rhinosinovitis.	4ml, 2-4 times daily	PARI SINUS® nebuliser	N/A	Instructions for use (empirical)
Nebusal 7% (hypertonic saline solution)	Treatment and prevention of chronic rhinosinovitis.	4ml, 2-4 times daily	PARI SINUS® nebuliser	N/A	Instructions for use (ongoing study)
Pulmozyme (dornase alfa)	Treatment and prevention of chronic rhinosinovitis. Positively affect both symptoms and QoL in comparison to isotonic saline.	2.5mg in 2.5ml, once daily	PARI SINUS® nebuliser	N/A	Mucolytic Publication (pilot study)
Budesonide	Treatment and prevention of signs and symptoms of seasonal and perennial allergic rhinitis. Treatment of signs and symptoms of nasal polyps.	1mg/2ml, once daily	PARI SINUS® nebuliser	N/A	Anti-inflammatory Publication (case study)
Gernebcin (tobramycin)	*P. aeruginosa* infection. Further research is needed to establish the potential benefits of these therapies.	80mg/2ml, once daily	PARI SINUS® nebuliser with PARI LC® Sprint sinus handset with filter attachment.		Antibiotic Publication (pilot study)

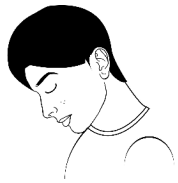
Colistimethate sodium (Colomycin)	*P. aeruginosa* infection. Further research is needed to establish the potential benefits of these therapies.	**Paediatric over eight years:** 2mu twice daily. **Adult:** 2mu twice daily. Ideally 12 hours between doses	PARI SINUS® nebuliser with PARI LC® Sprint sinus handset with filter attachment.	**1mu:** 1mu Colomycin reconstituted with 4ml water for injection or sodium chloride 0.9%. **2mu:** 2mu Colomycin reconstituted with 4ml water for injection or sodium chloride 0.9%.	Syringes needed (5ml) In case of bronchoconstriction, or where already using nebulised salbutamol, Colomycin may be reconstituted with two vials of salbutamol 2.5mg. Must be used immediately, do not store in fridge for later use. If reconstituting with water for injection or sodium chloride 0.9%, acceptable to reconstitute two doses of Colomycin and store second dose in fridge to be used within 24 hours or discard.

Appendix IIe

How to use a nasal spray

Before use

- Shake the bottle before use, and remove cap
- You will need to prime the nasal spray if it is new, or if you have not used it for 2 weeks or more (see manufacturer instructions for how to do this).

Step 1		Clear the nose by gently blowing or by performing nasal douching.	This prepares the nasal area by removing mucus that otherwise prevent the medicated spray it from reaching the nasal lining
Step 2		Bring your head forward, placing your chin on your chest	This position closes off the back of the throat and allows the spray to reach the correct area inside the nose
Step 3		Hold the spray in the opposite hand to the nostril in which you are about to apply the spray. For example, use the left hand to apply the spray in the right nostril and the right hand for the left nostril.	This ensures you aim the spray at the correct angle, pointing it away from the septum which has only a thin layer of membrane and can be easily damaged.
Step 4		Place the end of the spray bottle just inside the nostril aiming away from the septum pointing to the ear or eye.	This will ensure the spray is aimed toward the fleshy turbinate's inside the nose which are often the main area of inflammation in the nose.
Step 5		Activate the spray. You may breathe in gently and steadily through your nose. Do not sniff hard.	Not sniffing hard reduces the risk of the medication being swallowed or 'tasted'.
Step 6		Breathe out through your mouth. Put the bottle into the opposite hand and repeat steps 4,5 and 6 in the other nostril.	

- If you need to administer two sprays into each nostril, repeat steps 3 to 6 again.
- Once you have finished, wipe the nozzle so that it is clean, and put the cap back on
- It may take a few weeks before you notice any improvement in your symptoms. Please always use your nasal spray as prescribed by your doctor or pharmacist.

Adapted from: BSACI. Standard Operating Procedure - Topical Nasal Corticosteroid Spray. 2023.
www.bsaci.org/wp-content/uploads/2023/11/Nasal-corticosteroid-SOP-BSACI.pdf

Appendix IIf
The MYGIND position

Introduction

This position is used to administer topical steroid solution to the forehead sinus area (frontal sinuses), which is difficult to reach with nasal rinses alone. This can be especially useful after a surgery that affects the opening of the frontal sinus.

How to do

- Hang your head off the side of the bed, then apply the drops to the nasal cavity (up your nostrils), allowing gravity to drain the drops to the desired area.
- Keep your head hanging upside down for about five minutes before returning to an upright position.
- Repeat these steps one to two times per day, or follow any instructions you've been given.

Appendix III: Medications

Appendix IIIa

Drug response assessment (DRA) standard operating procedure (SOP)

1. Scope

This SOP has been developed for use by qualified HCPC-registered physiotherapists working within a CF Centre who have been assessed as competent to perform DRAs (including medicine administration component) and review use of inhaled and nebulised medicine.

2. Aims and objectives

- To standardise the procedure for the performance of DRAs and follow-up of new inhaled/nebulised medicine and the information provided to people with CF and those that care for them, to minimise the risk of adverse events.
- To give the responsibility of performing the entire DRA procedure, including medicine administration component, to one competent individual. This will avoid parts of the procedure being missed accidentally and minimise the risks to patient safety.
- To streamline the process of performing DRAs, to improve clinical efficiency.

3. Standards

3.1 Procedure for DRA under physiotherapist supervision

3.1.1 Location of DRA

- DRAs should be routinely performed in hospital in a single occupant room with easy access to medical assistance and oxygen therapy in case of an adverse event.
- It is recommended that an in-hospital DRA is performed for any inhaled or nebulised drug that the individual is naïve to, or if they have not taken the drug for more than 12 months, or there has been a significant change in their health since they last took a dose
- All 'virtual' or home DRAs are considered 'at risk' and a thorough multidisciplinary risk assessment should be undertaken prior to deciding on this course of action (risk assessment should consider: lung function, DRA history; failed/passed DRAs in the past, if/ when they have failed why did they fail, are they considered 'atopic'?). This process and the team members involved should be documented in the notes.

3.1.2 Restart of inhaled medicine without a DRA

- **Framework for restarting inhaled medication (FRIM)** should be used to risk assess the safety of a restart of inhaled medication without a formal DRA process in the following circumstances:
  - More than 12 months since last test dose of trial drug.
  - No adverse events associated with using the drug previously.
  - No significant change in clinical condition since last taken.

3.1.3 Preparation for DRA

- Ensure that medicine is therapeutically indicated as detailed in current Summary of Product Characteristics (SPC), available on the **electronic Medicines Compendium (eMC) website**. In the case of nebulised 7% and 3% hypertonic saline, which are classed as medical devices, please refer to current Instructions for Use (IFU).
- If a medicine is to be used outside of stated therapeutic indications or if dose recommended is not the standard adult dose, a CF consultant, or competent physiotherapist independent prescriber (IP) must have approved use and documented this in the medical notes. Note that amikacin, amphotericin, ceftazadime, meropenem, tauroldine solution and vancomycin are used 'off-label' when nebulised, so there is no

nebulisation-specific information in the SPC for these medicines. It is recommended local Patient Information Leaflets (PILs) are produced for these 'off label' inhaled medications.

- Ensure that there are no known contraindications to medicine use as detailed in SPC, IFU or local PILs and that the individual is not known to have an allergy to it. If any contraindications or allergies to the medicine are identified, this must be discussed with a CF consultant prior to DRA and an appropriate plan must be made to minimise any risks if the DRA is considered to be the best course of action. This should be documented by the CF consultant in the medical notes.
- Ensure that the following have been considered with the individual in relation to their circumstances, in conjunction with a CF consultant, specialist respiratory registrar or competent physiotherapist IP and a decision has been made to proceed with DRA:
  - special warnings and precautions of use
  - interaction with other medicinal products and other forms of interaction
  - fertility, pregnancy and lactation
  - effects on ability to drive and use machines as detailed in SPC IFU or local PILs.
- The DRA medicine should be prescribed by a physician or competent physiotherapist IP as a STAT dose. For details of advised medicine prescriptions see **Appendix IIIh** 'Nebulised Medication Overview'.
- Drug and food allergies should be recorded as locally advised by the prescriber but should be checked with the individual by the physiotherapist (and added to if required) prior to administration of DRA medicine.

3.1.4 Pre-DRA

- On arrival to the clinical area the individual with CF should be shown immediately to their single occupant room. Ideally a window will be kept open, and the door will be closed throughout the DRA process.
- Local and national Infection Prevention and Control (IPC) guidelines should be adhered to throughout the DRA process.
- Inform the individual of therapeutic indication of medicine as detailed in current PIL, available on eMC website, IFU or local PILs available for 'off label' use nebulisers.
- Inform the individual of the most commonly reported potential adverse effects of medicine as detailed in PIL, IFU or local patient information leaflets. Depending on the medicine being assessed, there may be a number of additional less commonly reported side effects. Inform the individual that this is the case.
- Gain informed verbal consent to undergo DRA. If the individual is unable to give informed verbal consent due to lack of mental capacity, it may still be appropriate for them to undergo DRA, if it is considered to be in their best interests. In this situation, the individual's carer is required to take on the responsibility of undergoing training for administration of the medicine in the community.
- Obtain all equipment, paperwork (including prescription, which must be present at point of medicine administration) and medicine/constituents that will be required during DRA.

3.1.5 Pre-DRA objective assessment

- Peripheral oxygen saturations (SpO_2) should be measured.
- Spirometry should be performed. The American Thoracic Society/European Respiratory Society criteria for acceptable repeatability of spirometry readings[1063] should be adhered to during the DRA and all subsequent medicine follow-ups.
- If the individual is unable to perform spirometry, auscultation pre- and post-DRA can be used to detect wheeze or bronchospasm alongside SpO_2.
- Auscultate to identify any retained secretions or wheeze.

- For DRAs of Bronchitol®, the Bronchitol® Initiation Dose Assessment (BIDA)[484] should be followed and the form completed. This determines when spirometry and SpO_2 should be measured in relation to the inhalation of increasing doses of Bronchitol®.

3.1.6 Pre-DRA bronchodilator

- The individual should administer their usual short-acting inhaled or nebulised bronchodilator, to reduce risk of bronchospasm. If not prescribed a short-acting bronchodilator, liaise with a CF consultant, specialist respiratory registrar or competent physiotherapist IP regarding whether prescription of such medicine may be appropriate.
- Wait appropriate length of time for bronchodilator medicine to take effect if applicable: 20 minutes following $beta_2$ agonist bronchodilator such as salbutamol; 45 minutes following antimuscarinic bronchodilator such as ipratropium bromide.

3.1.7 Administration of DRA medicine by physiotherapist

- It is recommended that the prescriber should not also administer the medication. If a physiotherapist IP has prescribed the medicine, it is not recommended they administer it. In this instance, a different CF physiotherapist, an NMC registered CF CNS or ward nurse (Band 5 or above) would be responsible for the medicines administration component and the demonstration and assessment of medicine preparation (if applicable).
- Occasionally, local policy will permit the prescriber to administer the medicine. If permitted there needs to be:
  - a clear rational, for example to ensure that the pathway for patient care does not build in unnecessary extra steps or processes
  - a thorough risk assessment and a process in place to limit errors, for example the prescription should be checked prior to administration by a person who usually administers medicines such as a nurse, pharmacist or physiotherapist.
- Remain with the individual throughout the entire DRA procedure to optimise patient safety.
- Make a positive identification of the individual by confirming demographic details and PID, to ensure that medicine is administered to the correct person.
- Check the prescription as follows:
  - full name
  - date of birth
  - allergies
  - ward
  - consultant
  - drug approved name
  - correct dose
  - route
  - prescriber's signature
  - date of prescription
  - special instructions.
- Advise the individual to decontaminate their hands before medicine/constituents are handled and prepared.
- Check the medicine prior to administration as follows
  - dose being administered
  - expiry dates of medicine/constituents.

- During administration of DRA medicine, follow SPC, IFU or local PILs as appropriate with regards to:
  - preparation of DRA medicine, such as mixing of nebuliser solution
  - correct operation of inhaler/nebuliser device in accordance with manufacturer's instructions
  - recommended procedure for inhalation of medicine.
- If preparation of medicine requires mixing of powder with a solvent (Colomycin®, Promixin®, Cayston®, amikacin or meropenem) the physiotherapist should demonstrate the procedure. The individual or carer can then be observed performing this by the physiotherapist to assess their ability to do this accurately and safely if required.
- The physiotherapist should also assess the person's ability to inhale the medicine using the correct procedure.
- The physiotherapist should sign the prescription to indicate the time at which the medicine is administered.
- If an adverse effect occurs during the DRA, inhalation should be ceased and a physician informed, if appropriate (dependent on severity). If a severe adverse effect occurs, medical assistance should be summoned immediately and appropriate treatment provided.

3.1.8 Following DRA

- Ask the individual to describe any adverse effects experienced and rate the severity using a numerical recognition scale (NRS) from 0—10, where '10' is the worst adverse effect imaginable. The severity of any adverse effects may determine whether or not a trial period of medicine is undertaken. If a severe adverse effect occurs or if an adverse effect not stated in the SPC occurs, it should be reported to the MRHA **Yellow Card Scheme** in a timely manner

DRAs of Bronchitol®

- As discussed previously, the BIDA[484] should be followed and the form completed. This determines when spirometry (performed by a competent practitioner) and SpO_2 should be measured in relation to the inhalation of increasing doses of Bronchitol®.

3DRAs of other medicines

- Spirometry should be performed by a competent practitioner five minutes after end of inhalation to assess for medicine-induced bronchospasm.
- SpO_2 should be measured and auscultation completed.
- Assess for the presence of any constriction:

$$\% \text{ constriction} = \left(\frac{\text{pre-DRA } FEV_1 - \text{post-DRAV } FEV_1}{\text{Pre-DRA } FEV_1} \times 100 \right)$$

3.1.9 Passed DRA – medicine suitable for use

- 10% constriction or less.
- 11-15% constriction and the individual is asymptomatic.

3.1.10 Failed DRA

- 11-15% constriction and the individual is symptomatic
- 15% constriction or more
- Ensure these findings are due to bronchospasm rather than loosened and retained sputum. If this is thought to be the case encourage airway clearance and consider repeat spirometry.
- Allow a further 10 minutes observed recovery time and repeat spirometry. If more than 15% constriction continues give a post-DRA bronchodilator to reverse bronchospasm, allow a further 10 minutes observed recovery time and repeat spirometry.
- Once constriction has recovered to 10% or less and the individual is not symptomatic, monitoring can be stopped and they are safe to leave.
- If constriction remains above 10% persistently, seek urgent medical review and continue to monitor the individual closely.

3.1.11 If DRA failed

- Consider repeat DRA at a later date when the individual is well if it is identified that they were unwell and this is the possible cause of failed DRA).
- Consider a DRA for an alternative medicine.
- If you are unsure how to proceed escalate to a CF consultant or discuss with the CF specialist team.

3.1.12 Information provided for patients continuing with trial period of medicine

The physiotherapist should provide information detailed in SPC, IFU or local PILs on the following:

1. Preparation of medicine, such as mixing of nebuliser solution.
2. Correct operation of inhaler or nebuliser device in accordance with manufacturer's instructions.
3. Recommended procedure for inhalation of medicine.
4. Daily dose schedule and recommended interval between doses. If there is no documented recommended interval between doses, for twice daily medicine, the locally agreed recommendation is ideally 10 to 12 hours (minimum of 8 hours) between doses.
5. Optimum timing of medicine in relation to other prescribed inhaled or nebulised medicine and airway clearance. In general, this would be as follows:
    a. **short-acting inhaled/nebulised bronchodilator**
    b. **inhaled or nebulised mucolytic or osmotic agent** prior to ACT. In the case of dornase alfa however, current evidence[1064] indicates that its benefit is not affected by timing with regards to time of day used or ACT. Therefore, in the absence of strong evidence to suggest that one timing regimen is superior to another, the timing of dornase alfa inhalation can be largely based on practical or individual preference. However, if nebulised prior to ACT we recommend at least a 30-minute interval between the end of inhalation and the commencement of ACT based on evidence that dornase alfa makes CF sputum pourable within this time frame[1065,1066].
    c. **inhaled or nebulised antibiotic** following ACT. These should also be taken within active period of preceding short-acting bronchodilator, for example no longer

than four hours following salbutamol or ipratropium bromide. Consideration should be given to potential interaction between inhaled antibiotics and dornase alfa as this may lead to dornase alfa inactivity.

d. **inhaled/nebulised steroid** following ACT.

6. Before use, all medicine and its constituents, should be checked to ensure that the correct dose is being administered and the expiry date has not been exceeded.
7. If a dose of medicine is missed or forgotten, what action to take, if any.
8. If too much medicine is taken or if it is swallowed accidentally, the individual should seek advice from their medical team as soon as possible during normal working hours, or GP or local A&E department out of hours.
9. If any adverse effects occur during trial period, the individual should stop medicine use and medical advice should be sought as above. If they stop the medicine for any other reason, medical advice should also be sought, as this may lead to worsening chest symptoms.
10. If, during the trial period, a new situation regarding precautions of taking the medicine arises, for example if they become pregnant or they have been commenced on a new medicine that should not be taken in conjunction with trial medicine, they should inform their CF team. In this situation, a CF consultant, specialist respiratory registrar or competent physiotherapist NMP should assess risks and benefits of the individual continuing with the trial medicine.
11. Manufacturer's instructions for the care, cleaning and sterilisation of the inhaler or nebuliser device and related consumables should be followed where applicable.
12. If required for nebulisation (see local guidance), filter pads used within PARI Filter/ Valve Sets should be discarded and replaced following each dose.
13. Appropriate storage of medicine and constituents.
14. Safe disposal of empty packaging and administration equipment such as capsule cards, glass ampoules, inhaler devices, components of nebuliser chambers in the community (see Table 1 below for locally agreed guidance at the West Midlands Adult CF Centre). Advice should include time after which administration devices should be discarded, for example TOBI® Podhaler® devices should be discarded after 7 days.

Table 1

Component/constituent for disposal	Safe disposal in community
Residual unwanted medicine e.g. residual volume in eFlow®rapid handset	Sharps box
Residual unwanted diluents e.g. water for injections/0.9% sodium chloride solution in open ampoule	Pour down sink
Empty plastic ampoules	Domestic waste
Empty glass ampoules	Sharps box
Used syringes	Domestic waste
Inhaler devices (Bronchitol®, Colobreathe®, TOBI Podhaler®)	Domestic waste
Empty capsules and capsule cards (inhaled medicines)	Domestic waste

Any unused medicine or its constituents (opened or unopened) that are unwanted e.g. due to intolerance/exceeding expiry date	Return to community or hospital pharmacy
eFlow®rapid and PARI TurboBOY®: plastic components of nebuliser chambers, PARI TurboBOY® connection tubing	Household re-cycling
eFlow®rapid aerosol heads	Return to hospital for clinical waste disposal
eFlow®rapid and PARI TurboBOY®: live parts of nebuliser devices e.g. air compressor/control unit, power adaptors, grey eFlow®rapid nebuliser connection cord	Return to PARI Medical Ltd or to hospital for electrical waste disposal
I-neb®: mouthpiece, discs, medicine chamber and lid, drug guide and washing basket	Domestic waste
I-neb®: I-neb body (control unit), power cord and battery charger	Patient to return to Philips Respironics

15. Any medicine specific instructions/precautions stated in SPC, IFU or local PILs not already covered above such as:

a. If medicine should only be inhaled using the administration device(s) and related consumables recommended by the medicine manufacturers and if stipulated, no other medicine should be inhaled via a device/consumable designed for a specific medicine.

b. If the medicine should not be mixed with any other medicinal product in a nebuliser chamber.

c. Whether the appearance of the medicine may vary despite being stored as recommended.

d. The appropriate discarding of any opened but unused medicine or constituent, for example:

- Only 1ml of 2.5ml dornase alfa ampoule is required for one dose within the I-neb® device and the remaining 1.5ml should be discarded. Opened ampoules of any medicine should never be stored for re-use.
- There will always be a residual volume of medicine in a regular eFlow®rapid handset at the end of inhalation which should be discarded.

e. In the event of haemoptysis, cease dornase alfa and seek appropriate medical assistance and advice. Re-start 48 hours following last episode, unless otherwise instructed.

f. As far as is feasible, nebulised antibiotics should be inhaled in a well-ventilated room, away from other people. This may not be possible however if a person's carer is supervising them, for instance.

g. If a mixed, refrigerated, second dose of meropenem has changed significantly in colour from when it was first mixed, it should not be used. Second doses must be used within 12 hours of original mixing.

3.1.13 Completion of DRA

- Ensure the individual has returned to pre-DRA level of wellness if they experienced any adverse effects during DRA, before they leave hospital if an outpatient, or before being left unsupervised if an inpatient.
- If the individual agrees to trial a medicine following a passed DRA, arrangements should be made to supply sufficient medicine for duration of trial period. For most medicines there is one month trial period (six weeks for Bronchitol®). However, antibiotics being used for attempted pathogen eradication may be prescribed for up to three months.

3.1.14 Post-DRA room cleaning

- Following the DRA appropriate cleaning of the room should take place according to local IPC guidance.

3.1.15 Documentation of DRA details

- The following information should be recorded on the '**CF physiotherapy inhaler/ nebuliser follow-up record**' which should be inserted into the individual's medical records:
  - all objective measurements such as spirometry results, SpO_2, auscultation.
  - the ability of the individual or their carer to prepare nebuliser solutions which require mixing (if applicable)
  - the individual's ability to use the inhaler or nebuliser device correctly
  - the individual's ability to follow recommended procedure for inhalation
  - subjective data such as adverse effects
  - education provided relating to new medicine.
- Completed BIDA forms used for DRAs of Bronchitol® should be filed with completed 'CF Physiotherapy drug response assessment (DRA) proforma'.
- Document in individual's main clinical record that DRA of medicine has been performed (and for details of this, refer to 'CF Physiotherapy drug response assessment (DRA) proforma') and the outcome.
- File any paper recording sheets in the individual's medical records as per local policy.

3.2 Medicine follow-up

3.2.1 Initial follow-up

The use of all new inhaled or nebulised medicine should be reviewed following a trial period of one month, with the exception of Bronchitol® which requires a 6 week follow-up. This review will be completed by qualified HCPC registered physiotherapists working within the CF centre who are competent to perform DRAs of medicine.

- Ask the individual to describe any adverse effects experienced and rate the severity using a numerical recognition scale from 0—-10, where '10' is the worst adverse effect imaginable. The severity of any adverse effects may determine whether or not medicine is continued on a long-term basis.
- Spirometry should be performed by a competent practitioner and SpO_2 measured.
- Discuss with the individual and CF consultant, specialist respiratory registrar or competent physiotherapist NMP, as appropriate, potential continuation of medicine based on the above.
- Record all objective data such as spirometry results, SpO_2 and subjective data on the '**CF Physiotherapy inhaler/nebuliser follow-up record**'.
- Assess individual's understanding of the new medicine and whether they continue to use and store it appropriately. Record any education and advice provided at initial follow-up on the '**CF Physiotherapy inhaler/nebuliser follow-up record**'.

- Insert 'CF Physiotherapy inhaler/nebuliser follow-up record' into their medical records, alongside the 'CF Physiotherapy drug response assessment (DRA) proforma'.

3.2.2 If continuing with medicine after intial follow-up

- Advise if the medicine is to be taken continuously on a daily basis or on an alternating month basis. If it is to be taken on an alternating month basis, ensure the individual is aware of what medicine, if any, should be taken in the new medicine 'off' month (this should be agreed with a CF consultant, specialist respiratory registrar or competent physiotherapist NMP).
- Contact pharmacist regarding completion of initial follow-up, as appropriate. They will provide information on obtaining future supplies of medicine, if required.

3.2.3 Six-month follow-up

The use of all new inhaled or nebulised medicine should be reviewed following a period of six months. This review will be completed by qualified HCPC registered physiotherapists working within the CF Centre.

This should be performed as described in section 3.2.1 initial follow-up with six month data and information.

3.2.4 If continuing with medicine long-term following six-month follow-up

- Contact pharmacist regarding completion of six month pharmacy medicine follow-up.

4. Responsibilities and roles

It is the responsibility of each physiotherapist who has been assessed as competent to perform DRAs and reviews of inhaled or nebulised medicine to ensure that they are familiar with:

- the contents of this SOP and adhere to it when performing DRAs
- the most up-to-date SPC, IFU and local PILs relating to specific medicines.

It is also the responsibility of each CF CNS and ward nurse to be familiar with the above, should they need to perform the administration and training component of the DRA, to avoid a physio NMP prescribing the medicine and then administering it.

4.1 Training Requirements

Qualified HCPC-registered physiotherapists who are undergoing competency training for performing DRAs of inhaled and nebulised medicine should:

- have worked within the CF Centre, consistently for a minimum of one year
- be Band 6 or above
- familiarise themselves with the contents of this SOP
- familiarise themselves with the contents of most up-to-date SPC, IFU and local PILs relating to specific medicines
- undergo appropriate Electronic Prescribing training as required locally (for administration rights)
- have completed the appropriate local medicines management training modules (please refer to local policy)
- receive education from CF specialist pharmacist
- undergo assessment of understanding of all medicines that will be administered by DRA competent physiotherapist or specialist nurse.

In order to establish competence, the physiotherapist will undergo assessment by a competent assessor in which they must:

- demonstrate the ability to prepare all medicines which require mixing used at the centre such as nebulised Colomycin®, Cayston®, meropenem and amikacin
- complete a final competency assessment against required standards, in which they are observed performing an entire DRA of two inhaled and two nebulised medicines.

Related appendices

- Nebulised Medication Overview
- Example of Medicine Administration Competency SOP
- Example of Competency Assessment Document
- CF Physiotherapy inhaler/nebuliser follow-up record

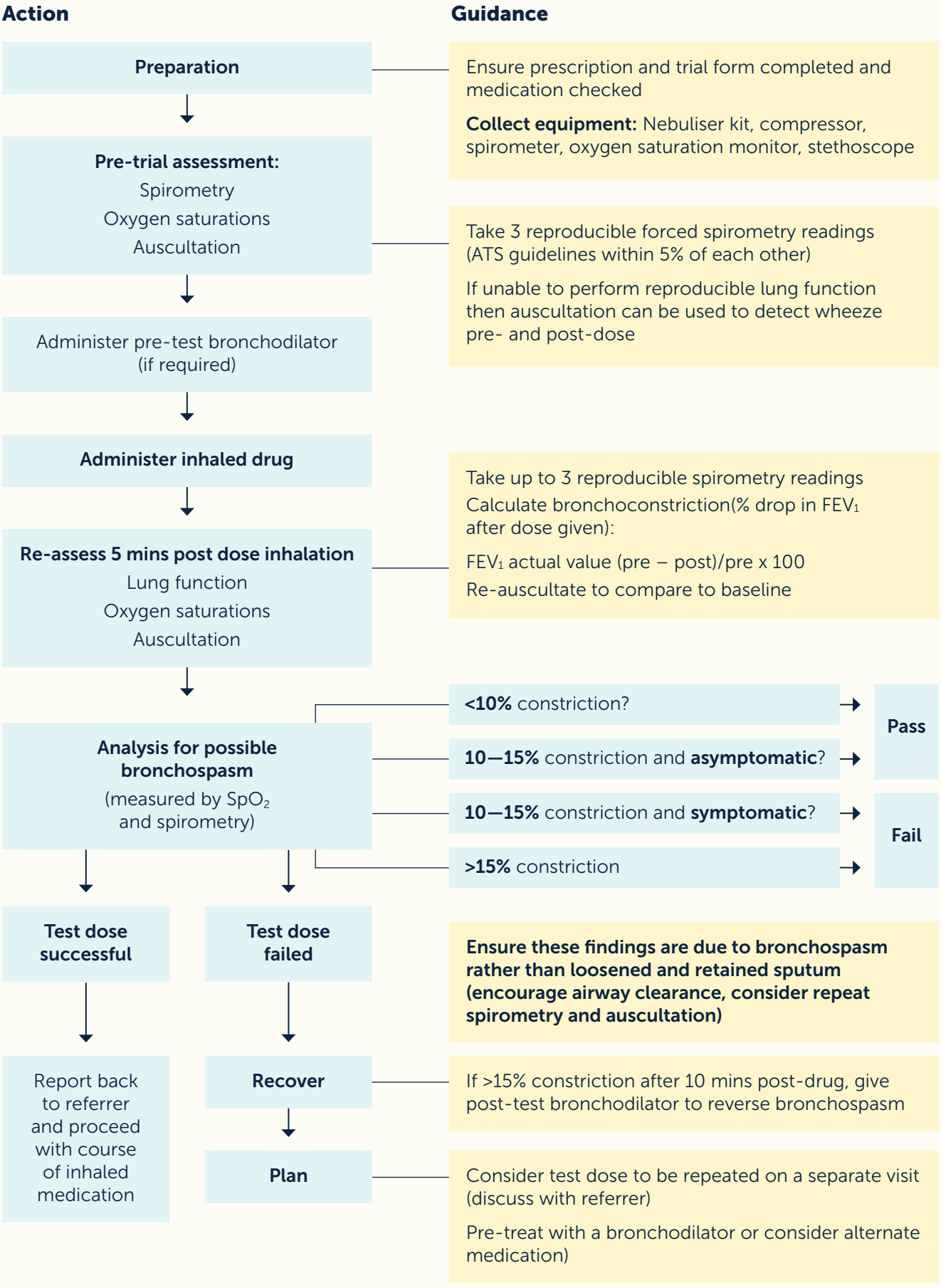
With thanks to S. Cameron*,

Edited for ACPCF NMP Group by C. Brown* 20th December 2023 and with thanks to the ACPCF independent prescribing group

*West Midlands Regional Adult Cystic Fibrosis (CF) Centre, University Hospitals Birmingham (UHB) NHS Foundation Trust.

Appendix IIIb
DRA flowchart

Adapted from RBH NHS Trust with kind permission



Appendix IIIc

CF physiotherapy inhaler/nebuliser follow-up record

File in main medical notes, according to date of first drug review

Patient name & PID / label:	Inhaler/nebuliser (state constituents if applicable)	
	Date of DRA	
	Date of initial follow-up	
	Date of 6-month follow-up	

Observations

Assessment	FEV_1	FEV_1% predicted	SpO_2
Pre-DRA	L	%	%
Initial follow-up	L	%	%
6-month follow-up	L	%	%

Tolerance of medicine

Follow-up	Adverse reaction(s) reported & severity (NRS scale 1—10, where 10 most severe)	Continuing with medicine?
Initial		
6-month		

For individuals continuing with medicine

(✓if individual/carer has correct understanding OR insert your initials if re-advised)

In accordance with PIL/IFU and *CF physiotherapy DRA SOP* assess individual's/carer's understanding of the following:	Initial review	6-month review
Medicine preparation (include time by which prepared drug must be used)		
Operation of administration device		
Procedure for inhalation		
Daily dose schedule (including recommended time between doses)		
Order/timing in relation to other inhaled/nebulised medicine & ACT (including time by which medicine should be taken following short-acting bronchodilator)		
Checking expiry date of medicine/constituents for each dose		
Action if missed dose		
Action if too much medicine taken/swallowed accidentally		

If adverse effects occur, should cease use & seek appropriate medical assistance/advice		
If new precautions of use arises in future, cease use & seek medical advice		
If medicine should only be taken using specific device/consumables		
If no other medicine should be taken using device/consumables for new medicine		
Manufacturer's instructions for care of (including cleaning and sterilisation, if appropriate) administration device and consumables		
If required for nebulisation, filter pads are discarded & replaced for each dose		
Appropriate storage of medicine/constituents		
Safe disposal of unused drug & constituents/administration equipment		
On any other drug specific instructions/precautions in PIL, IFU or local PIL if not covered above		

Follow-up

(physio to initial box)

In accordance with CF Physiotherapy DRA SOP:	Initial review	6-month review
Contact pharmacist re: obtaining further medicine supplies, if required		
Advise individual regarding date of medicine review. **Date agreed:**		

If antibiotic, advise on ongoing regimen and note any changes (✓)

Continuous use short-term for attempted eradication. **Duration:**		Continuous use long-term.		Alternating months. **Alternating antibiotic(s):**	

Follow up	Additional comments
Initial	
6-month	

Follow up	Physiotherapist name (print)	Signature	Date	ID number	Designation
Initial					
6-month					

With thanks to S. Cameron, Edited for ACPCF IP Group by C. Brown Jan 2020/4.

West Midlands Regional Adult Cystic Fibrosis (CF) Centre, University Hospitals Birmingham (UHB) NHS Foundation Trust.

Appendix IIId

Example of a Medicine Administration Competency SOP

1. Summary	For qualified physiotherapists registered with the HCPC working within a CF Centre to demonstrate competence in the completion of DRAs and the administration of inhaled and nebulised medicine (including medicines administration component) through skill, knowledge and application. Competency achievement is required before the physiotherapist can perform DRAs alone.
2. Scope	Administration of DRAs of inhaled/nebulised medicine.
3. Applicable to	Qualified HCPC-registered physiotherapists, Bands 6 and above who will be administering DRAs of inhaled and nebulised medicine within the CF Centre.
4. Related policy and legislation	All relevant local policies, procedures and guidelines (under the following headings) should be accessible on the Trust intranet site. The most up-to-date version must always be used. • Estates & Facilities • Health and Safety • Information Communications Technology • Infection Control • Information Governance • Medical Devices • Medicines Management • Nursing • Safety & Governance **HCPC** **Standards of conduct, performance and ethics.** **Standards of proficiency for physiotherapists.** **Chartered Society of Physiotherapy** Code of Members' Professional Values and Behaviour. The physiotherapist should always refer to the most up-to-date policy available.
5. Eligible to assess	Qualified assessor who is competent to administer medicine.
6. Standard to be achieved	The physiotherapist must be able to perform the skill safely and effectively without support and demonstrate appropriate background knowledge of both the procedure (detailed in the 'CF physiotherapy DRA SOP') and the medicine to be administered. The physiotherapist should, at all times, adhere to relevant local policies, procedures and guidelines and also regulatory body standards and codes of conduct (see section 4. above).
7. Training required	Supervised practice in clinical setting with a competent practitioner.

8. Training and resources available	**Local training as appropriate, for example:** • Trust Preceptorship module • Medicine Step up module • Electronic Prescribing module **Awareness of appropriate national resources such as:** • **BNF online: BNF (British National Formulary) | NICE** • **Electronic medicines compendium: Home - electronic medicines compendium (emc)** • **Medicines and healthcare products regulatory agency: Yellow Card | Making medicines and medical devices safer**
9. Author	This document has been developed and modified from the HEFT Amended MM34 Medicine Administration Competency (2014) by CF Physiotherapist Sarah Cameron and edited by Catherine Brown for the ACPCF NMP group Jan 2020.

With thanks to S. Cameron,

Edited for ACPCF iP Group by C. Brown Jan 2020 and reviewed 2024.

West Midlands Regional Adult Cystic Fibrosis (CF) Centre, University Hospitals Birmingham (UHB) NHS Foundation Trust.

Appendix IIIe

Framework for Restarting Inhaled Medications in Cystic Fibrosis (FRIM-CF)

The Clinical Commissioning Policy: **Inhaled Therapy for Adults and Children with Cystic Fibrosis Reference: NHS England A01/P/b 4.1** states that all patients should be prescribed a supervised test dose in the hospital environment before commencing therapy. This test dose or drug response assessment (DRA) monitors for bronchospasm and any adverse reactions to the inhaled therapy **Appendix III (england.nhs.uk)**. This also applies to the devolved nations of the UK.

Until recently, it was common practice to re-trial most inhaled medications in hospital if it had been more than 12 months since the patient last took it. However, during Covid-19, the model of patient care changed, and patients came to hospital less. A risk assessment was developed to identify patients who may safely **restart** an inhaled medication without a new DRA, this has since been adapted into the FRIM below.

This does not apply to someone starting a specific inhaled antibiotic or mucoactive medication for the first time

This FRIM risk assessment must be completed by the CF specialist team (CF specialist physiotherapist, consultant, CNS and pharmacist) to decide the appropriateness of **restarting** the inhaled medication without a DRA. Those who participate in this discussion and the decision made should be clearly documented in the patient's medical record.

Risk assessment:

Has the patient had the inhaled medication previously? **YES / NO**

NB the patient must have safely taken the same brand of inhaled medication previously and passed a previous DRA – if the previous hospital DRA is for TOBI but the patient has been prescribed Bramitob, for instance, they would still require a face-to-face DRA.

If NO, then DO NOT proceed with the FRIM risk assessment.

If YES, then please complete the table below before proceeding.

If you answer **NO** to questions 1—7 below you may proceed to restart the medication without a new DRA.

If you answer **YES** to any questions, then please clearly document the discussion and final decision as to whether restarting without a DRA is appropriate.

Patient's name:	**Hospital number:**	
Drug:		
1. Is the patient's FEV_1< 55% predicted (skip to Q2 if patient is unable to perform repeatable lung function)	**YES** (May not be appropriate to restart without a new DRA, please discuss further with MDT) Document here:	**NO**

2. Has there been a significant change in the patient's condition since they last had the inhaled medication? E.g. has the patient's lung function dropped >10% since they last took the inhaled medication, have they developed recent ABPA and/or more reactive airways?	**YES** (Discussion with the MDT) Document here:	**NO**
3. Has the patient had any adverse reactions associated with the inhaled drug previously?	**YES** Document here:	**NO**
4. Has the patient failed DRAs in the past?	**YES** Document here:	**NO**
5. Is the patient considered atopic or are they thought to have CF asthma?	**YES** (This is not a contraindication in itself but should prompt more in-depth discussion with the MDT) Document here:	**NO**
6. Do you have concerns that the patient/carer may not be able to respond appropriately if there is an adverse event at home?	**YES**	**NO**
7. Is there another reason the patient **should have** a repeat DRA? E.g they are now old enough to complete repeatable lung function, MDT opinion that DRA is required	**YES** Document here:	**NO**
Is restarting the inhaled medication without a new DRA appropriate?	**YES / NO** **Reasons:**	
Signed:	**MDT members involved in discussion:**	
Designation:	**Date:**	

If a restarting the inhaled medication without a new DRA is deemed appropriate, please check the following before proceeding (refer to the Hospital Trust's DRA SOP for further detail):

1. Up to date drug allergies.
2. Current clinical status (is the patient well enough to proceed without a new DRA?).
3. The patient/carer has access to a bronchodilator if required.
4. The patient/carer is aware of possible adverse reactions to the inhaled drug, including appropriate safety netting advice, for example what circumstances to use the bronchodilator and who to contact if an adverse event occurs at home.
5. The patient/carer is aware of how to take the inhaled medication – including dosage, how to reconstitute (if appropriate), how to store, timing around airway clearance, how to use the nebuliser device and who to contact for more supplies.
6. Has a follow up phone call or clinic appointment booked?

Once you have completed the above FRIM please place a copy in your patient's medical records and complete this very short survey. The ACPCF IP group wish to collect your experience of using the FRIM and will share the overall results.

Thank you

forms.office.com/Pages/ResponsePage.aspx?id=l5-6Hk8LF0u3f7LUSHrTxLsJ33sTnJlFgM584N88UzxUNUlSUTlOUlRCNEFaNjNBTDlPVDdJWUYxQi4u

Nicola Collins, ACPCF IP Group

Appendix IIIf

Example of Competency Assessment Document

ASSESSMENT OF COMPETENCE IN PERFORMING DRAs AND ADMINISTRATION OF INHALED/NEBULISED MEDICINE

This document has been developed to record the assessment of competence of qualified HCPC registered physiotherapists working within a CF Centre performing DRAs of inhaled and nebulised medicine. The HEFT *Medicine Administration Competency* (2014) has formed the basis of this document.

Physiotherapists undergoing competency assessment must first have completed the training requirements stated in the **'SOP for the performance of Drug Response Assessments (DRAs) and follow-up review of inhaled and nebulised medicines'**

1. Supervised practice

Supervised practice of inhaled/nebulised medicine (state name below)	Date	Assessor name	Assessor signature
Inhaled drug 1:			
Inhaled drug 2:			
Nebulised drug 1:			
Nebulised drug 2:			

2. Assessment of competence in nebuliser solution preparation

Assessment of competence in mixing nebuliser solutions	Date	Pass/fail	Assessor name	Assessor signature	Trust ID no.
Nebulised colistimethate sodium: • **Colomycin®** • **Promixin®**					
Cayston®					
Amikacin					
Meropenem					

3. Final competence assessment

To establish competence, the physiotherapist must demonstrate that the following components of the DRA (as detailed fully in 'SOP for the performance of Drug Response Assessments (DRAs) and follow-up review of inhaled and nebulised medicines' and in accordance with the Trust's Medicines Policy) are considered/ completed to a satisfactory standard	Assessment of competence (pass/fail against each component)	
	1st attempt	2nd attempt
Preparation - prior to DRA **1.** Medicine is therapeutically indicated **2.** Contraindications/allergies & precautions to use considered and decision made to proceed with DRA **3.** Inform patient of therapeutic indication **4.** Inform patient of potential side effects **5.** Gain patient's (or carer's, if applicable) informed verbal consent to undergo DRA **6.** Spirometry and SpO_2 measured (if DRA of Bronchitol® BIDA should be followed) **7.** Obtain all medicine/constituents, equipment & paperwork including prescription (EP or paper chart) to minimise risk of interruption **8.** Ensure patient administers own bronchodilator, as appropriate **9.** Ensure in area where easy access to medical assistance, oxygen supply		
Patient identification & administration **1.** Remain with patient throughout DRA **2.** Make a positive identification of patient **3.** Check the prescription (should be present at point of administration). Check drug & food allergies on prescription & add to if required, in discussion with patient/carer **4.** Use personal protective equipment as appropriate & standard infection control precautions throughout the procedure (advise patient to do the same as appropriate) **5.** Check medicine/constituents are correct prior to administration & expiry dates not exceeded **6.** Follow SPC, IFU or local patient information leaflet with regards to: **a.** preparation of DRA **b.** correct operation of inhaler/nebuliser device **c.** recommended procedure for inhalation of medicine **7.** If medicine preparation requires mixing of powder/solvent, demonstrate procedure for the patient/carer. Patient/carer can then be observed performing this to assess ability. **8.** Assess patient's ability to inhale medicine using correct procedure **9.** Sign prescription to indicate time medicine administered **10.** If adverse effect occurs, inhalation should be ceased & a physician informed if appropriate or medical assistance summoned immediately		

Following DRA **1.** Ask patient to describe any adverse effect(s). Severe adverse effects should be reported to the MRHA *Yellow Card Scheme* and Pharmacy **2.** Spirometry should be completed 5 minutes following end of inhalation and SpO_2 measured (if DRA of Bronchitol® BIDA should be followed) **3.** Calculate % constriction to determine (along with consideration of any adverse effects) whether appropriate to pursue trial period of medicine **4.** Deal appropriately and safety with and >10% constriction, escalating if required		
Information provided for patients/carers continuing with trial period of medicine As detailed in PIL, IFU and local patient information leaflets and DRA SOP: **1.** Preparation of medicine **2.** Correct operation of inhaler/nebuliser device in accordance with manufacturer's instructions **3.** Recommended procedure for inhalation of medicine **4.** Daily dose schedule & recommended interval between doses **5.** Optimum timing of medicine in relation to other prescribed inhaled/ nebulised medicine & ACT **6.** Action to take if a dose of medicine is missed/forgotten **7.** Action to take if too much medicine taken or swallowed accidentally **8.** Action to take if experiences adverse effects **9.** Action to take if stops using medicine **10.** Action to take if new situation re: precautions of taking medicine arises **11.** *Manufacturer's instructions for the care of (including cleaning and sterilisation, if appropriate) the inhaler/nebuliser device and related consumables* **12.** If required for nebulisation, filter pads used within PARI Filter/Valve Sets should be discarded & replaced following each dose **13.** Appropriate storage of medicine/constituents **14.** Safe disposal of empty packaging and administration equipment **15.** Any medicine specific instructions/precautions not already covered		
Completion of DRA **1.** Patient returned to pre-DRA level of wellness, if experienced adverse effects during DRA, before leaving hospital (out-patient) or before being left unsupervised (in-patient) **2.** If patient to continue with trial period of medicine make arrangements for supply		

Documentation of DRA details **1.** Complete the *'CF Physiotherapy drug response assessment (DRA) proforma'* (if Bronchitol® DRA, BIDA should also be completed) and insert in main clinical record **2.** Document in main clinical record that DRA of medicine has been performed (and for details of this, refer to *'CF Physiotherapy drug response assessment (DRA) proforma'*) and the outcome e.g. for 1 month follow-up of medicine, patient not to continue with medicine **3.** File and paper records in patient's medical records		

Assessment of competence in performing full DRA procedure	Date	Pass/fail	Assessor name	Assessor signature	Trust ID no.
Inhaler or nebuliser name (1st attempt):					
Inhaler or nebuliser name (2nd attempt if failed 1st):					

Competence statement

This is to state that .....has passed the medicine administration competency for performing DRAs of inhaled and nebulised drugs used within the West Midlands Regional Adult CF Centre on .....(date)

With thanks to S. Cameron,

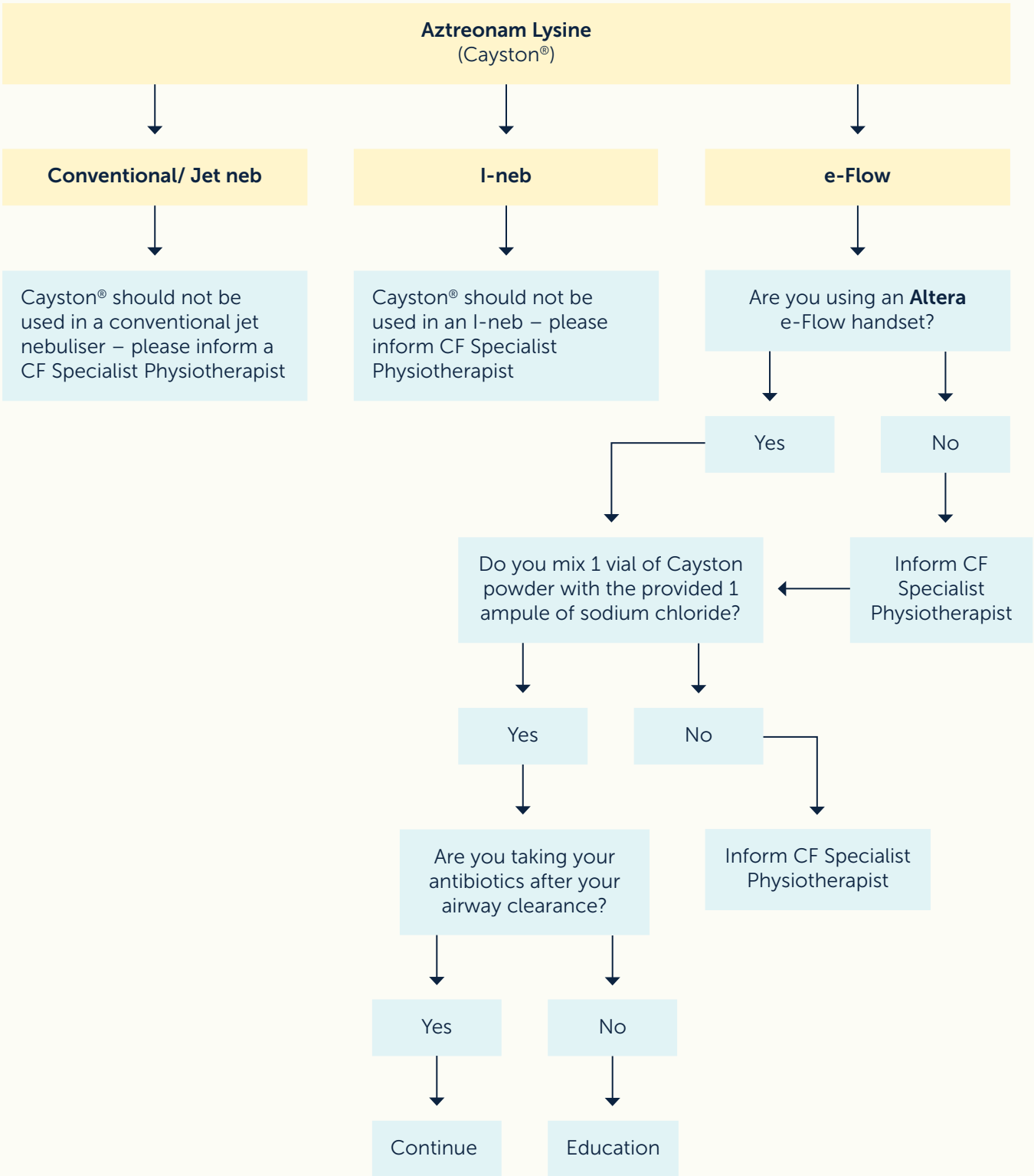
Edited for ACPCF IP Group by C. Brown Jan 2020 and reviewed 2024

West Midlands Regional Adult Cystic Fibrosis (CF) Centre, University Hospitals Birmingham (UHB) NHS Foundation Trust.

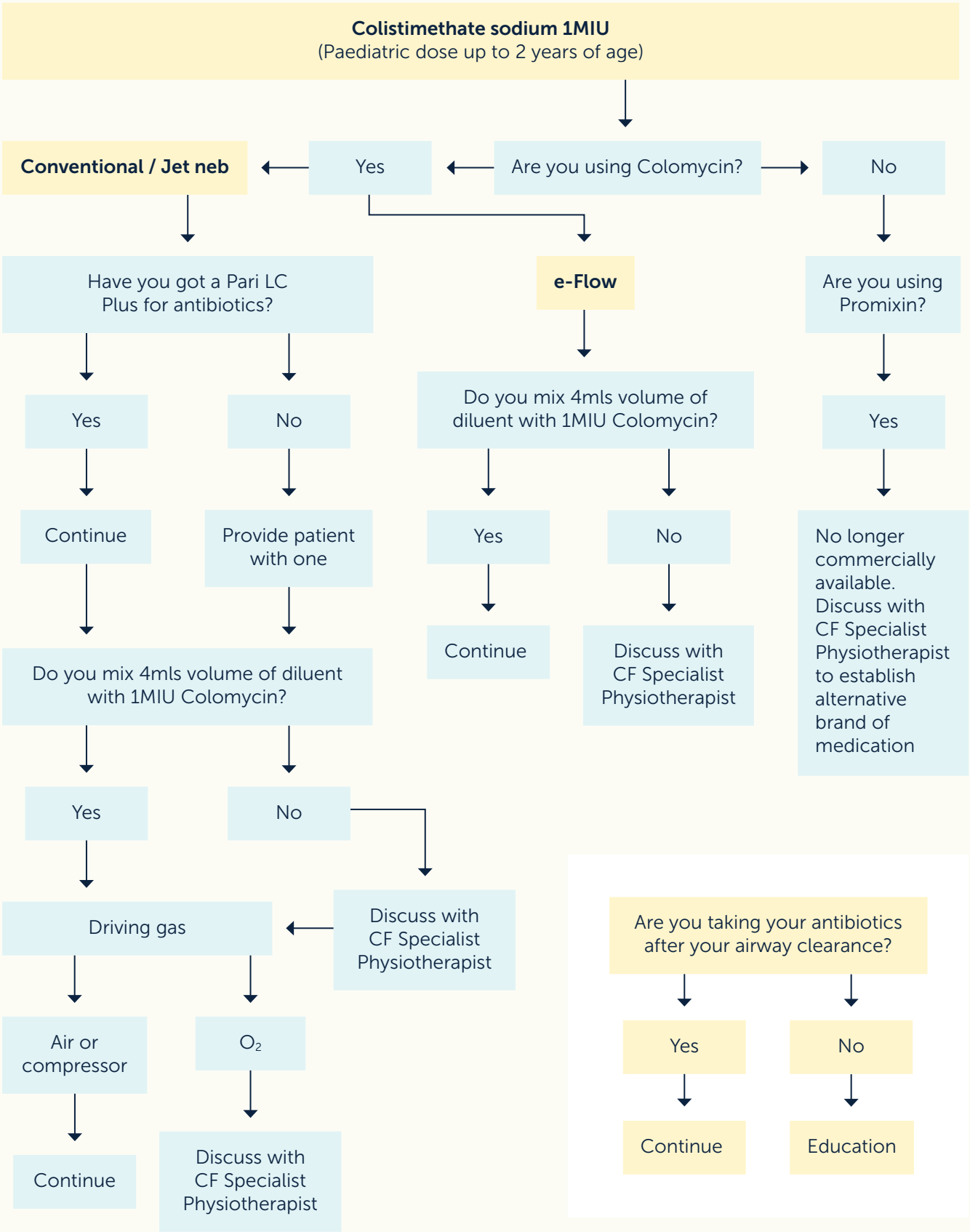
Appendix IIIg

Examples of flowcharts for nebulised medications in people with Cystic Fibrosis

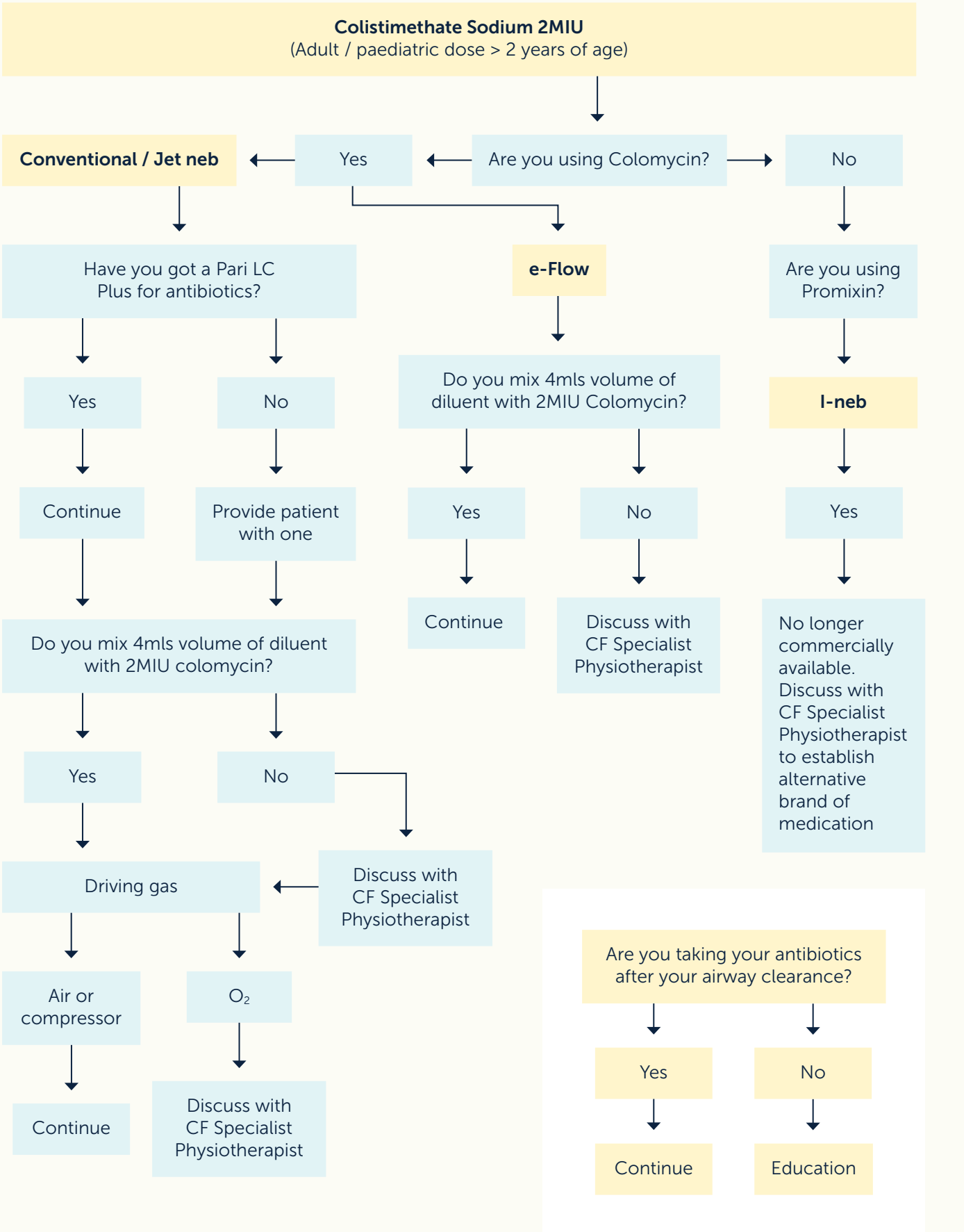
Appendix IIIg1



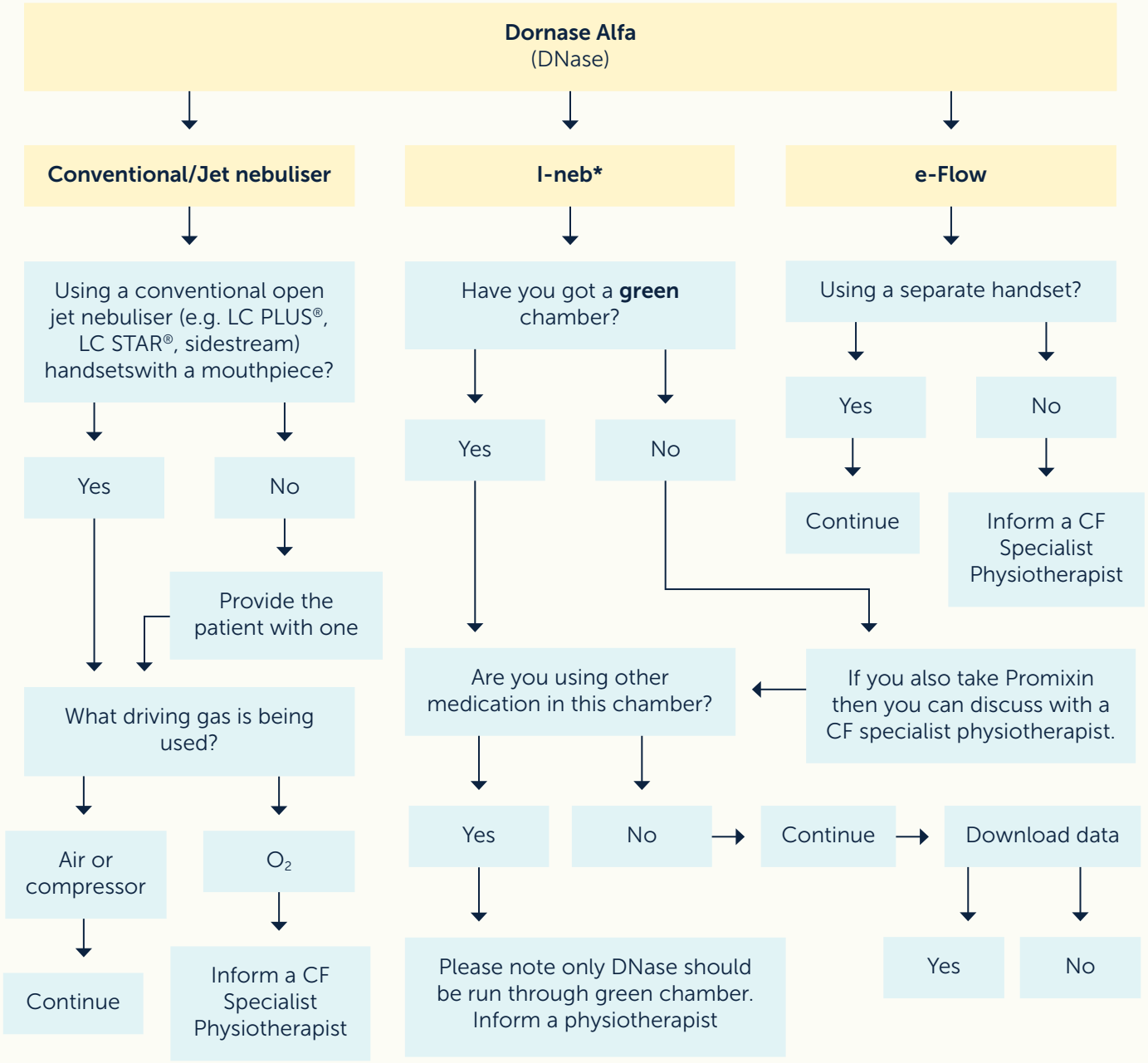
Appendix IIIg2

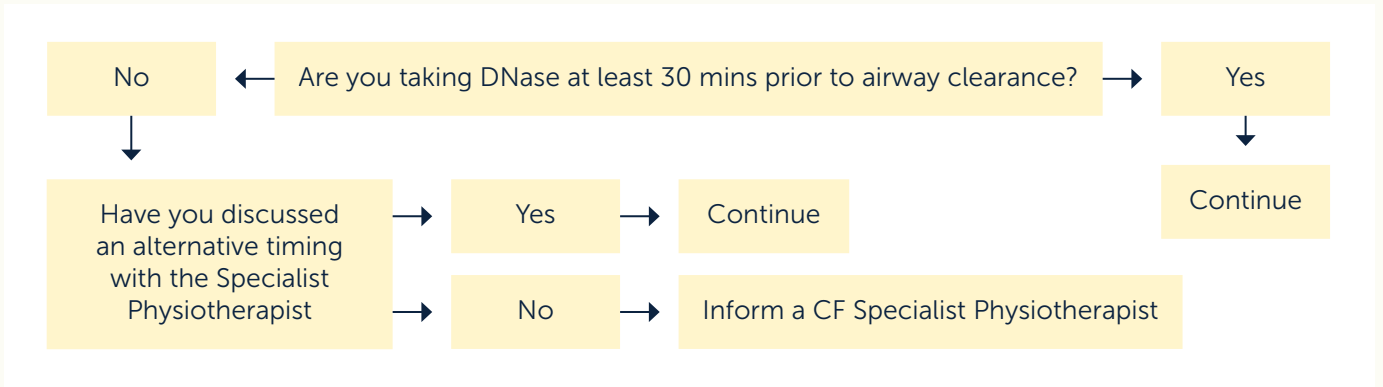


Appendix IIIg3



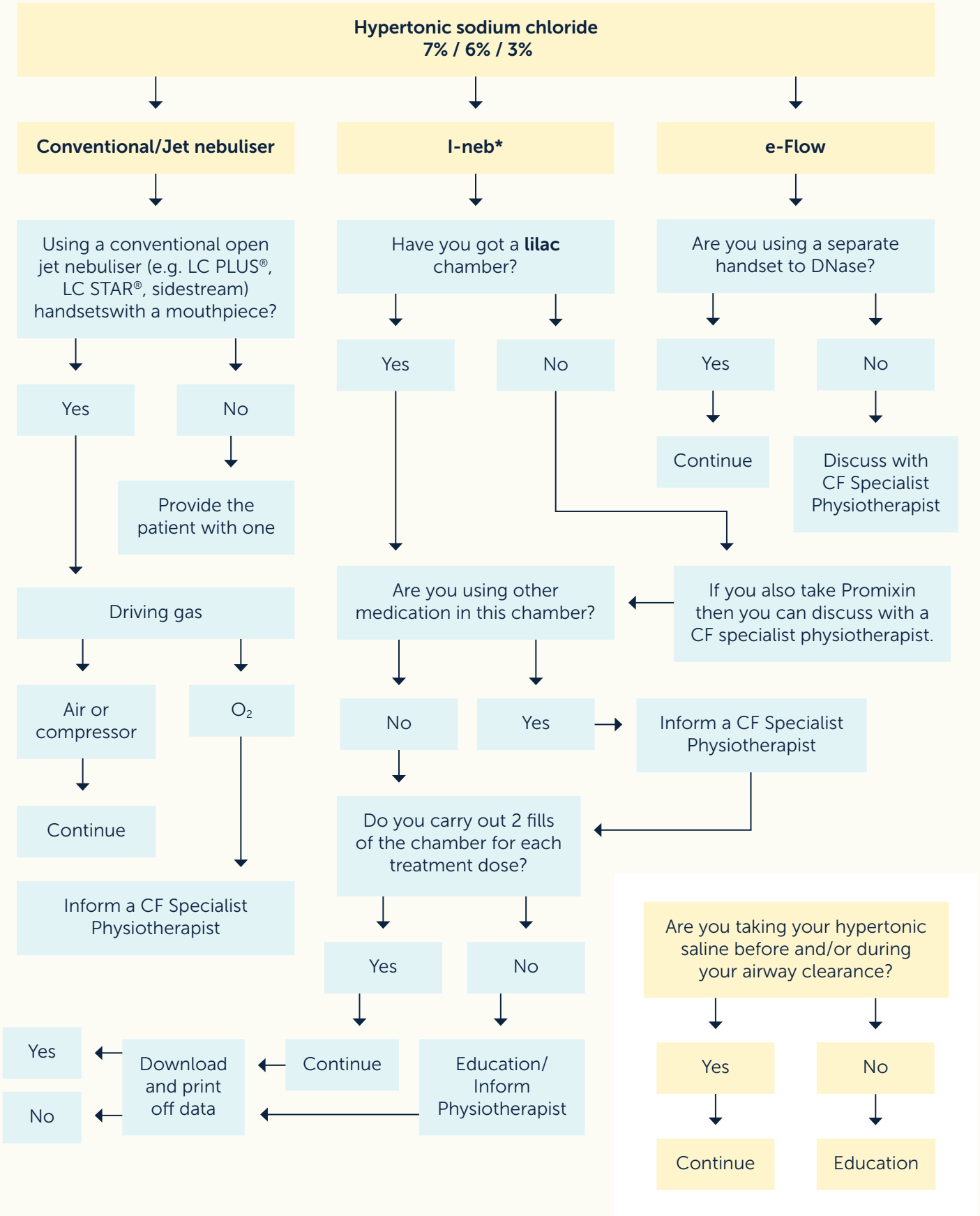
Appendix IIIg4





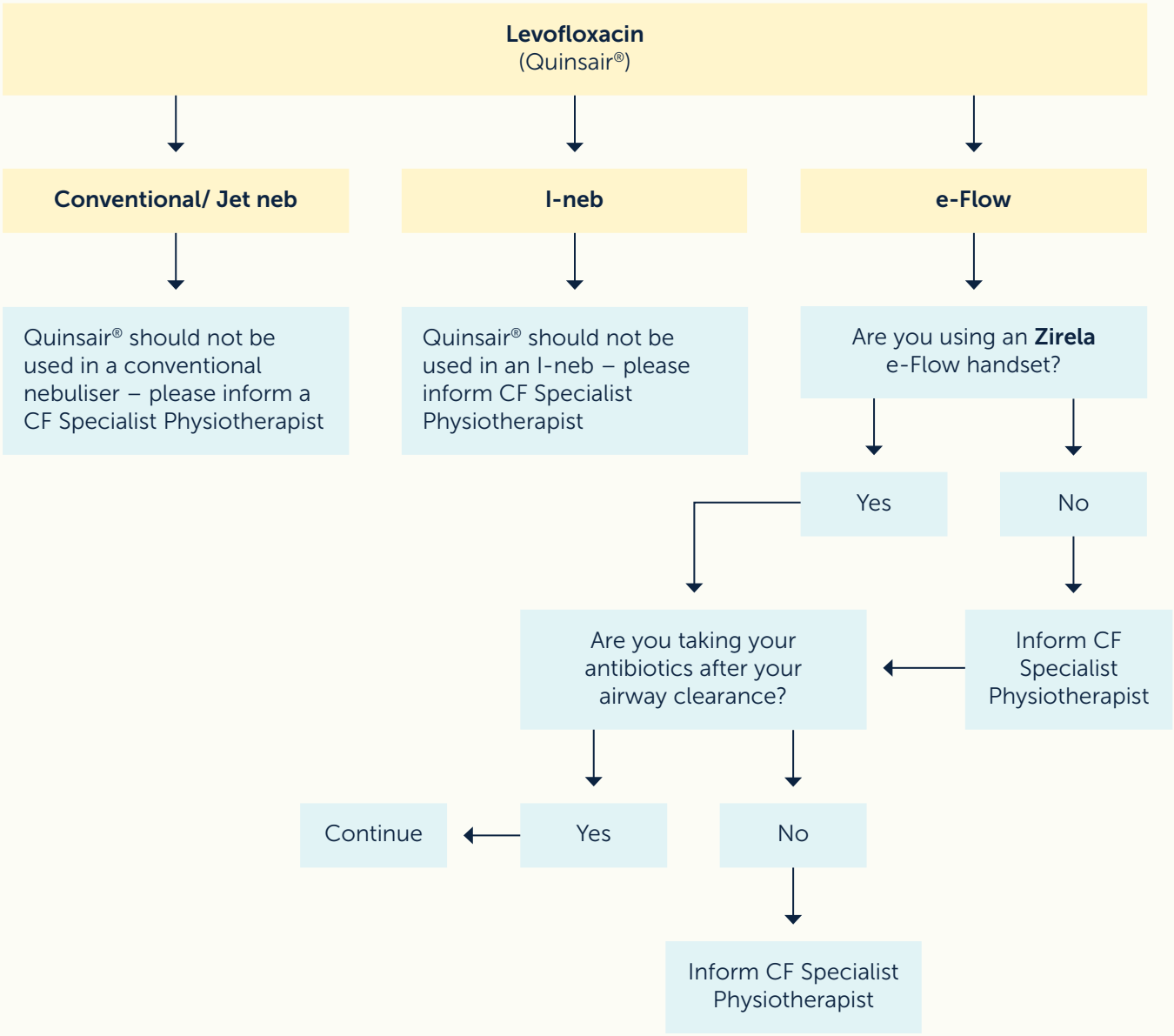
*Although the I-neb is no longer commercially available, its use may still be relevant where consumables are available.

Appendix IIIg5

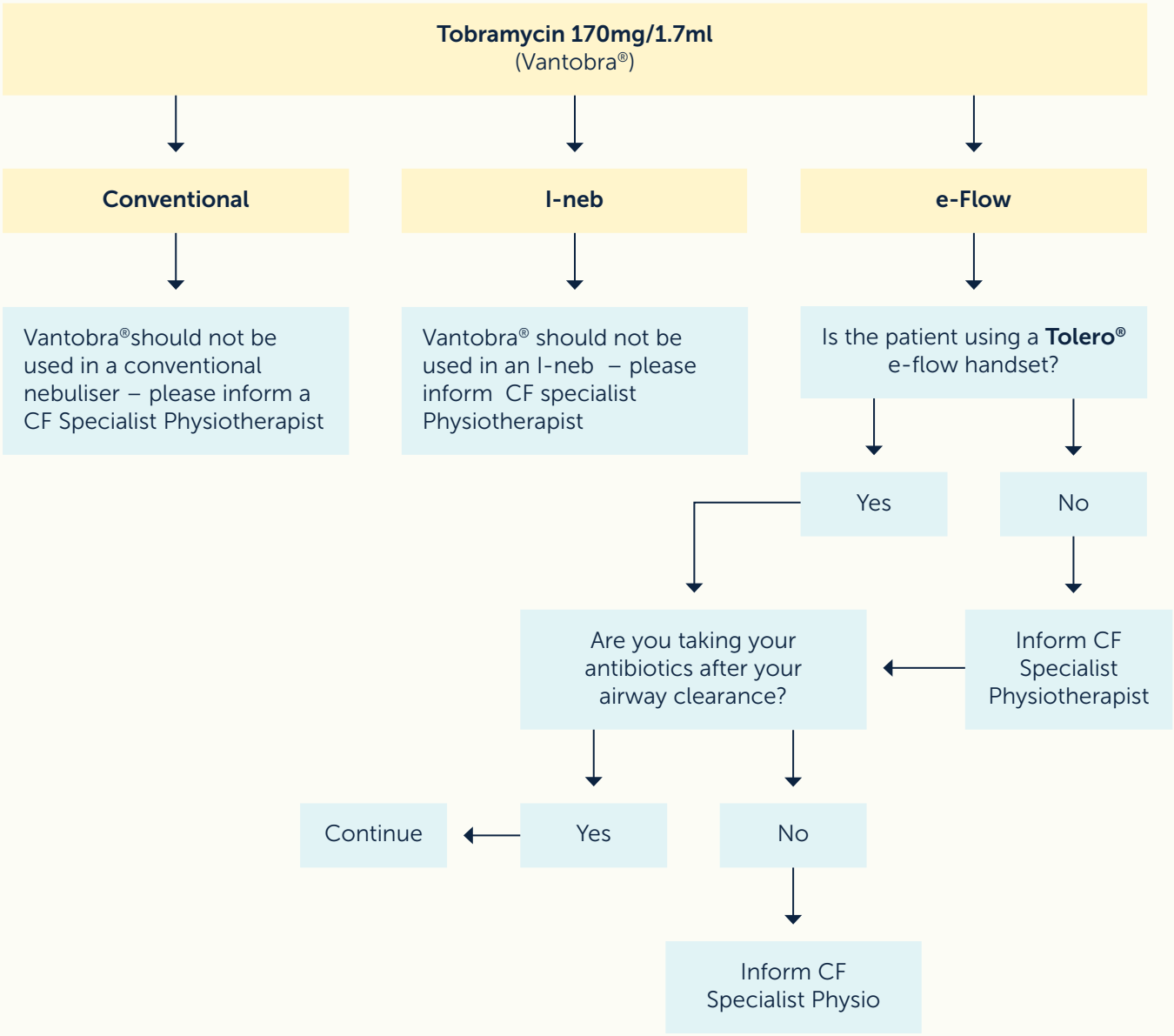


*Although the I-neb is no longer commercially available its use may still be relevant where consumables are still available.

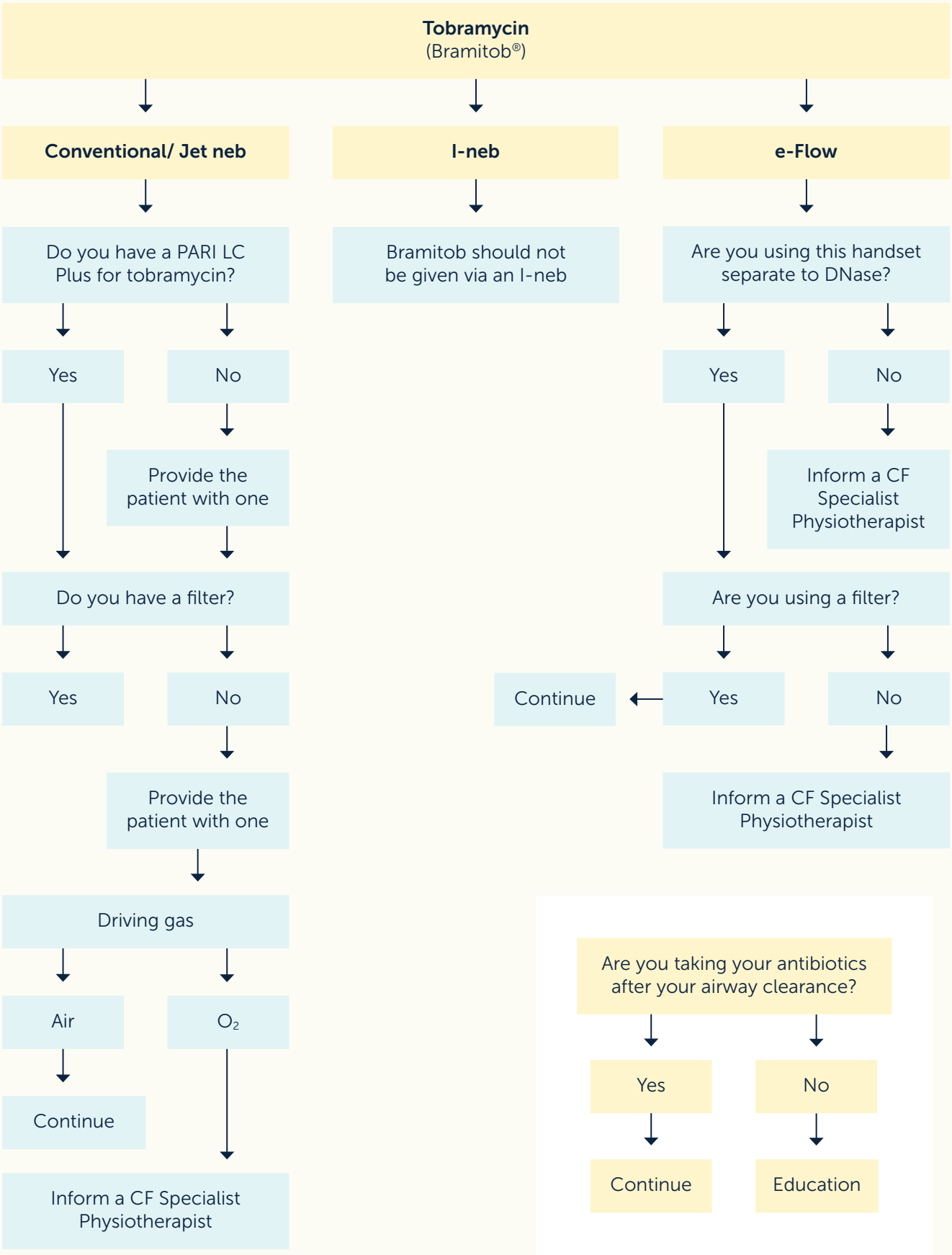
Appendix IIIg6



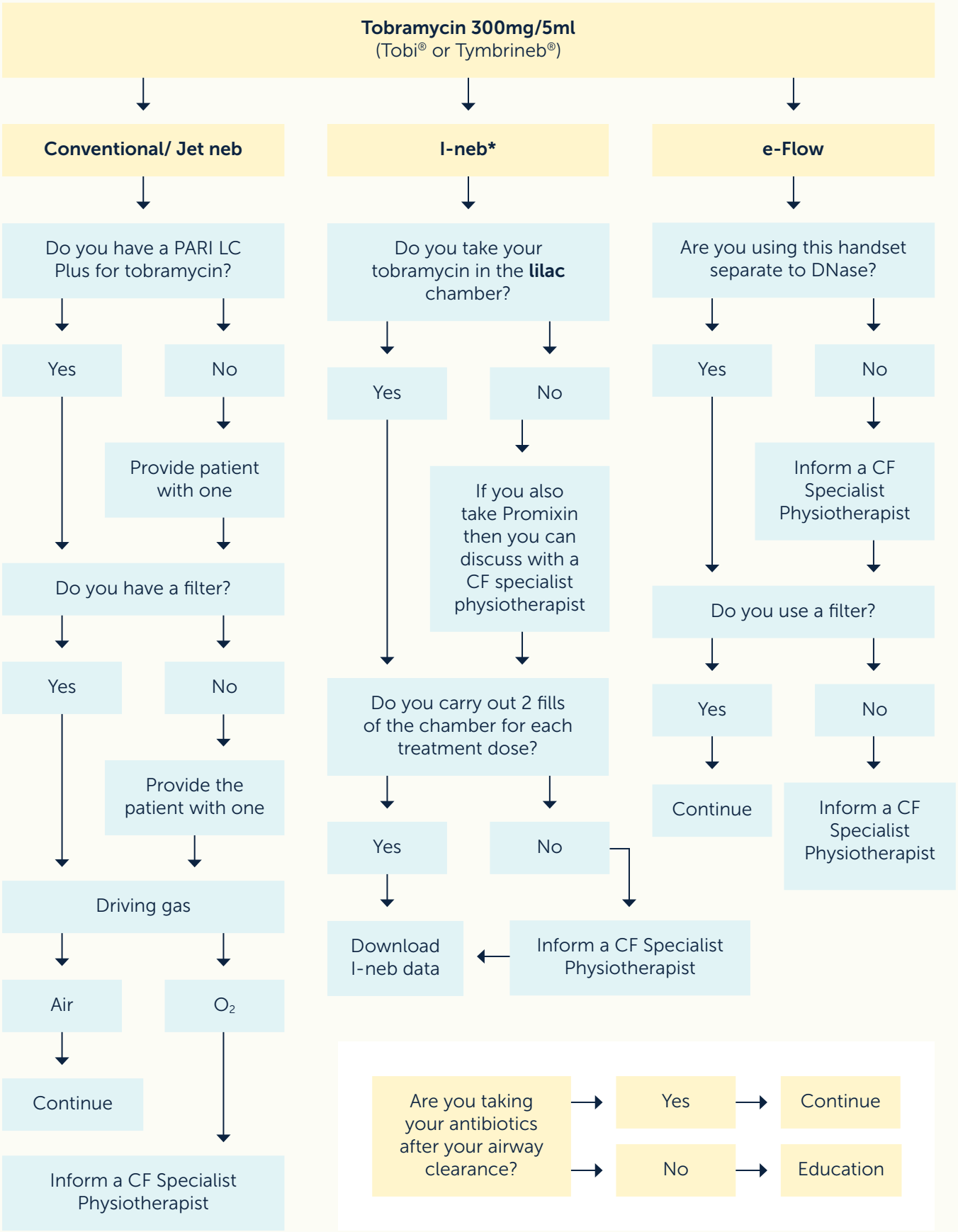
Appendix IIIg7



Appendix IIIg8



Appendix IIIg9



*Although the I neb is no longer commercially available its use may still be relevant where consumables are still available.

Appendix IIIh

Nebulised/inhaled medications for people with CF overview

This is a quick reference guide to the nebulised and inhaled medications used in CF. It is intended to only be used by clinicians who have received appropriate training and who are familiar with the SPC of each licensed medicine and the indications, prescription and delivery details of the commonly used 'off-label' medicines used for inhalation in CF.

Note that all people commencing a new nebulised/inhaled medication listed in the table below, or when the medication has not been used for the last 12 months, should have a supervised drug response assessment (DRA) as per documented DRA procedure. An observed dose may be considered where a nebulised/inhaled drug has been prescribed and taken in the past but exceeds 12 months. Rationale for this should be considered within a framework for re-starting inhaled medications (FRIM) as per documented FRIM procedure (see **appendix IIIe**). Please refer to your clinical commissioning policy and NICE guidance regarding the criteria for use of the licensed medications.

For any medications not included in this overview please refer to the British National Formulary (BNF) for prescribing information. Useful administration advice for inhalers not included in this overview advice can be found at **rightbreathe.com**

Useful definitions

'Licensed' medications

"A marketing authorisation or product licence defines a medicine's terms of use: its summary of product characteristics (SPC) outlines, among other things; the indication(s), recommended dose(s), contraindications, and special warnings and precautions for use on which the licence is based, and it is in line with such use that the benefits of the medicine have been judged to outweigh the potential risks. Furthermore, a licensed medicine: has been assessed for efficacy, safety, and quality; has been manufactured to appropriate quality standards; and when placed on the market is accompanied by appropriate product information and labelling."[1]

'Off-label' use of medications

There are clinical situations when the use of medicines outside the terms of the licence ('off-label') may be judged by the prescriber to be in the best interest of the patient based on available evidence. This has become common practice in inhaled medications in CF where licensed options are limited. In the table below we use the term **'off-label'** where use is outside of the medicine's licence.[1]

Medication	Usual indication	Prescription	Delivery system	Reconstituting	Notes
Amikacin Use as a nebuliser is '**off-label**'. N.B Arikayce® liposomal 590mg nebuliser solution is available but is not licensed for use in CF. It is licensed for use in adults with non-CF related refractory NTM disease caused by *Mycobacterium avium* complex (MAC).	*Mycobacterium abscessus*	**Paediatric:** **<12 years:** 250mg twice daily. **>12 years:** 500mg twice daily. **Adult:** 500mg twice daily. In paediatrics and adults ideally 12 hours between doses.	Conventional compressor & PARI LC Plus or Sprint with filter attachment. Some centres advise that patients can use eFlow®rapid with a **regular eFlow®rapid handset** with filter attachment to reduce treatment time, though there is no robust data to support this.	**250mg:** 1ml Amikacin for injection (250mg/ml) with 3ml sodium chloride 0.9%. **500mg:** 2ml Amikacin for injection (250mg/ml) with 2ml sodium chloride 0.9%.	Glass ampoules, preferably issue syringes and needles.

Amphotericin (Ambisome) Use as a nebuliser is '**off-label**'.	*Aspergillus*	**Paediatric:** **<10 years:** 5mg twice daily. **>10 years:** 10mg twice daily. **Adult:** 25mg twice daily Ideally 12 hours between doses.	Conventional compressor & PARI LC® Plus or Sprint with filter attachment.	**5mg:** 50mg vial Amphotericin with 10ml water for injection. Use 1ml of this solution and dilute further with 2ml of water for injection (minimum volume of 3ml for nebulisation). **10mg:** 50mg vial Amphotericin with 10ml water for injection. Use 2ml of solution and dilute with a further 1ml of water for injection (minimum volume of 3ml for nebulisation). **25mg:** 50mg vial Amphotericin with 12ml sterile water. 6ml to be nebulised. Remaining mixed solution can be kept in fridge for second daily dose (discarded if not used within 24 hours).	Liposomal amphotericin (Ambisome) should be prescribed NOT the non-lipid amphotericin (Fungizone). Rubber bung on vial not removable therefore will need syringes (10ml) and needles.
Aztreonam (Cayston®)	*Pseudomonas aeruginosa* Is also used '**off-label**' for *Burkholderia cepacia* >6 years Consider '**off-label**' use in <6 years if clinically indicated	75mg three times daily. Minimum 4 hours between doses.	eFlow®rapid using **Altera®** handset with filter attachment (Altera® handset included in monthly Cayston® pack).	1 vial aztreonam powder (75mg) with 1 ampoule sodium chloride 0.17% (included in Cayston® pack).	**Keep in fridge but can be kept out of a fridge but below 25°C for 28 days.** Usual starting regimen is 28 days on/28 days off. Alternating with another inhaled antibiotic or continuous treatment may be indicated if deterioration in month off treatment.

Ceftazidime Use as a nebuliser is '**off-label**'.	*Burkholderia cepacia*	1g twice daily. Ideally 12 hours between doses.	Conventional compressor & PARI LC® Plus or Sprint with filter attachment.	Reconstitute 1g with 3ml water for injection.	Tastes awful which can impact tolerance.
Colistimethate sodium (Colomycin)	*Pseudomonas aeruginosa*	**Paediatric:** **< 2 years:** 1 MIU twice daily **>2 years:** 2MIU twice daily. **Adult:** 2MIU twice daily. Ideally 12 hours between doses.	eFlow®rapid with a **regular eFlow®rapid handset** OR a conventional compressor & PARI LC® Plus or Sprint with filter attachment.	**1MIU:** 1MIU Colomycin reconstituted with 4ml water for injection or sodium chloride 0.9%. **2MIU:** 2MIU Colomycin reconstituted with 4ml water for injection or sodium chloride 0.9%.	Syringes needed (5ml) In case of bronchoconstriction, or where already using nebulised salbutamol, Colomycin may be reconstituted with 2 vials of salbutamol 2.5mg **Must be used immediately, do not store in fridge for later use.** If reconstituting with water for injection or sodium chloride 0.9%, acceptable to reconstitute 2 doses of Colomycin and store second dose in fridge **to be used within 24 hours** or discard.
Colistimethate sodium (Colobreathe®)	*Pseudomonas aeruginosa* >6 years	1.66MIU (one capsule) twice daily. Ideally 12 hours between doses.	Turbospin® powder inhaler (inhaler in pack).	No reconstitution required. One capsule to be inhaled twice daily.	Cough may be an issue and can be related to technique.

Dornase alfa (DNase/ Pulmozyme®)	Mucolytic >6 years Consider '**off-label**' use in <6 years if clinically indicated.	**Paediatric (off label):** **<2 years:** discuss with CF **> 2years:** 2.5mg once daily pharmacist. **Adult:** 2.5mg once daily. The SPC states 'some patients over the age of 21 years may benefit from twice daily dosage'. Consider twice daily in patients with severe disease or during exacerbations.	Conventional compressor & open-vent jet nebuliser such as PARI LC® Plus or Sprint or Sidestream **OR** eFlow®rapid with a **regular eFlow®rapid handset**. '**Off-label**' use with the I-neb is supported by data.	No reconstitution required. **eFlow®rapid or conventional compressor:** 2.5mg in 2.5ml (1 vial). **I-neb:** 1 fill of green chamber (discard remainder).	**Keep in fridge.** **Do not complete airway clearance for 30 mins post nebulisation.** Consider potential interaction with nebulised antibiotics when recommending a treatment regimen.
Hypertonic sodium chloride 7% (Nebusal®, Resp-ease®) Note 6% & 3% (Mucoclear®) also available **This is classed as a medical device rather than a medicine, please refer to current instructions for use (IFU)**	Osmotic agent. Recommended if DNase not tolerated OR as an additional therapy if clinical deterioration or difficulty clearing chest despite DNase.	**Paediatric:** **<2 years:** discuss with CF pharmacist **>2 years:** 4 ml once-twice daily of 3-7% as tolerated. Younger patients should be initiated on 3% **Adult:** 7% in 4 ml (1 vial) twice daily. Can increase to four times daily if needed.	Conventional compressor & open vent jet nebuliser such as PARI LC® Plus or Sprint or sidestream, **OR** I-neb OR eFlow®rapid with a **regular eFlow®rapid handset**.	No reconstitution required. **I-neb:** 2 fills of lilac chamber (discard remainder). **eFlow®rapid or conventional compressor:** 4ml (1 vial).	Often used as required rather than regular twice a day. Can be used with conventional compressor & PARI LC® Plus or Sprint alongside PARI PEPTM S, Aerobika® or Acapella®. This may impede deposition but may improve adherence and clearance.

Levofloxacin (Quinsair®)	*Pseudomonas aeruginosa* >18 years Consider '**off-label**' use in <18 years if clinically indicated.	240mg twice daily. Ideally 12 hours, minimum 8 hours between doses.	eFlow®rapid using **Zirela® handset** with filter attachment (Zirela® handset included in monthly Quinsair® pack).	No reconstitution required. 2.4ml (240mg) vial via the eFlow®rapid using **Zirela® handset** with filter attachment.	Keep in the foil package to protect the neb from light. Usual starting regimen is 28 days on/28 days off. Alternating with another inhaled antibiotic as required. Bitter taste of levofloxacin can impact tolerance. Anecdotally sucking dark chocolate/strong tasting sweets after dose can improve tolerance. Note unusually high systemic absorption compared with other nebulised antibiotics (approx. 50%). Caution should be exercised with concurrent use of other fluroquinolones such as Ciprofloxacin. Clinicians should be aware of the risk of systemic side effects of levofloxacin and ensure people prescribed levofloxacin have been counselled on the possible side effects and the need to discontinue treatment if they experience these (MHRA alert **www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-reminder-of-the-risk-of-disabling-and-potentially-long-lasting-or-irreversible-side-effects**)

Mannitol (Bronchitol®)	Recommended if DNase not tolerated OR if clinical deterioration despite DNase. >18 years Consider '**off-label**' use in <18 years if clinically indicated.	400mg twice daily. The doses should be taken morning and night with the evening dose taken 2-3 hours before bedtime.	Osmohaler inhaler device in pack.	No reconstitution required. Ten capsules to be inhaled twice daily. Note multiple inhalations may be needed to inhale each capsule contents via the inhaler.	Cough is expected, if coughing too much consider if technique could be improved. Note that anecdotally some people who feel tight chested with a full dosing regimen have found a reduced dose ('**off-label**') beneficial for airway clearance, e.g. some completing 10 capsules once daily, some reducing the number of capsules per dose.
Meropenem Use as a nebuliser is '**off-label**'.	*Pseudomonas aeruginosa* and *Burkholderia cepacia* if unable to tolerate or continuing to deteriorate on licensed alternatives. *Mycobacterium abscessus*. Used where sensitivities indicate OR as an alternating neb with Amikacin if continuing to deteriorate.	**Paediatric:** **6-12 years:** 125mg twice daily. **>12 years:** 250mg twice daily. **Adult:** 250mg twice daily. Ideally 12 hours between doses.	Conventional compressor & PARI LC® Plus or Sprint with filter attachment. Some centres advise that patients can use eFlow®rapid with a **regular eFlow®rapid handset** with filter attachment to reduce treatment time, though there is no robust data to support this.	**125mg:** 500mg Meropenem to be reconstituted with 8ml water for injection. 2.5ml of this solution is then mixed with 0.5mls water for injection. This 3mls is then nebulised. **250mg:** 500mg Meropenem to be reconstituted with 8ml water for injection. 4ml (250mg) to be nebulised.	Rubber bung on vial not removable therefore will need syringes (10ml) and needles. Remaining mixed solution can be kept in fridge for second daily dose (discarded if not used within 12 hours or if discolouration observed).
Tauroldine solution 2% Use as a nebuliser is '**off-label**'.	*Burkholderia cepacia* Post-transplant	4ml of 2% solution twice daily. Ideally 12 hours between doses.	Conventional compressor & PARI LC® Plus or Sprint with filter attachment.	Pre-made, draw up as needed. Keep in fridge once used for first time. Discard as per pharmacy instructions.	Rubber bung on vial not removable therefore will need syringes (5ml) and needles.

Tobramycin (Bramitob)	*Pseudomonas aeruginosa* **'off label'** use for *Burkholderia cepacia* >6 years Consider **'off-label'** use in <6 years if clinically indicated.	300mg (4mls) twice daily. Ideally 12 hours, minimum 6 hours between doses.	Licenced through conventional compressor & PARI LC® Plus or Sprint with filter attachment. Some centres advise that patients can use **'off-label'** with Ineb or eFlow®rapid with a **regular eFlow®rapid handset** with filter attachment to reduce treatment time. There is robust data to support delivery of Bramitob with the eFlow®rapid but not with the I-neb.	**Conventional compressor or eFlow®rapid:** 300mg in 4ml (1 vial). **I-neb:** 2 fills of lilac chamber.	**Keep in fridge** (allow to come to room temperature before nebulising, this can reduce viscosity and therefore treatment time). Only licensed in children over 6 but is used >6 months. Usual starting regimen is 28 days on/28 days off (unless eradication 3 months continuously), however alternating with another inhaled antibiotic may be indicated if deterioration in month off treatment.
Tobramycin (TOBI® or Tymbrineb)	*Pseudomonas aeruginosa* **'off label'** use for *Burkholderia cepacia* >6 years Consider **'off-label'** use in <6 years if clinically indicated.	TOBI® or Tymbrineb are chemically identical. 300mg (5mls) twice daily. Ideally 12 hours, minimum 6 hours between doses.	Licenced through conventional compressor & PARI LC® Plus or Sprint with filter attachment. **'Off-label'** use with an I-neb or eFlow®rapid with a **regular eFlow®rapid handset** with filter attachment is supported by robust data.	**Conventional compressor or eFlow®rapid:** 300mg in 5ml (1 vial). **I-neb:** 2 fills of lilac chamber.	**Keep in fridge** (allow to come to room temperature before nebulising). Only licensed in children over 6 but is used off licence in >6 months. Usual starting regimen is 28 days on/28 days off (unless eradication 3 months continuously), however alternating with another inhaled antibiotic may be indicated if deterioration in month off treatment.
Tobramycin (TOBI Podhaler® inhalation powder)	*Pseudomonas aeruginosa* **'off label'** use for *Burkholderia cepacia* >6 years	4x28mg capsules (112mg) twice daily. Ideally 12 hours, minimum 6 hours between doses.	Podhaler inhaler device in pack.	Four capsules (4x28mg, 112mg total) to be inhaled twice daily.	Cough may be an issue and can be related to technique.

Tobramycin (Vantobra®)	*Pseudomonas aeruginosa* **'off label'** use for *Burkholderia cepacia* >6 years Consider **'off-label'** use in <6 years if clinically indicated.	170mg twice daily. Ideally 12 hours, minimum 6 hours between doses.	eFlow®rapid using **Tolero® handset** with filter attachment (Tolero® handset included in monthly Vantobra® pack).	No reconstitution required. 1.7ml (170mg) vial via the eFlow®rapid using **Tolero® handset** with filter attachment.	**Keep in fridge** (allow to come to room temperature before nebulising). Usual starting regimen is 28 days on/28 days off (unless eradication 3 months continuously), however alternating with another inhaled antibiotic may be indicated if deterioration in month off treatment.
Vancomycin Use as a nebuliser is **'off-label'**.	*MRSA*	**Paediatric:** 5mg/kg twice daily. **Adult:** 250mg twice daily. Ideally 12 hours between doses. Usually a five day duration of treatment for eradication. **Always state 500mg vials to be issued from pharmacy not 1g vials.**	Conventional compressor & PARI LC® Plus or Sprint with filter attachment.	**Use 500mg vial.** Reconstitute 500mg Vancomycin with 8ml water for injection. **Paediatric dose (5mg/kg):** Draw up required dose and make up to a total of 4ml with water for injection. **250mg:** 4ml of reconstituted solution to be nebulised and remaining 4ml to be kept in fridge for second daily dose, discard if not used within 24 hours.	Rubber bung on vial not removable therefore will need syringes (10ml) and needles.

Although the I neb is no longer commercially available its use may still be relevant where consumables are still available.

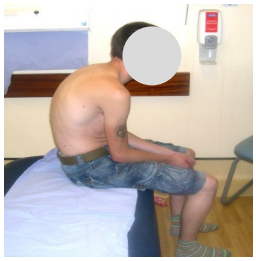
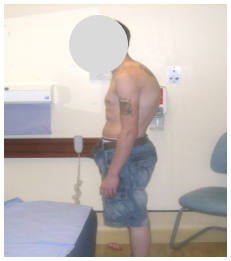
References

1 Medicines and Healthcare products Regulatory Agency (2014) Off-label or unlicensed use of medicines: prescribers' responsibilities. Available at: www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities [Accessed 24/07/2025]

Appendix IV

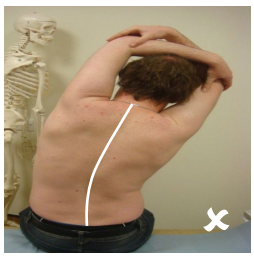
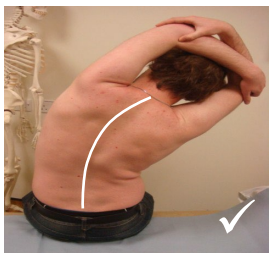
Manchester Musculoskeletal Screening Tool

1. Do you have any episodes of pain? **Y / N**
   (If yes, complete MPQ)
2. Do you have any episodes of leaking urine, or an urgent or frequent need to pass water? **Y / N**
   (If yes, complete ICIQ)
3. Do you have any concerns about your posture? **Y / N**
4. What is the cause of pain? Musculoskeletal **Y / N**
   Other: (e.g. surgery, gout, unknown)
   .....
5. Is there a fixed thoracic kyphosis?

In sitting:

6. Is patient able to lift both arms straight above head level with ears?
7. With arms across chest is patient able to rotate upper body to 45°?
8. With arms above head is patient able to lean to 30°?

Date:

Name:

DOB:

Height:

Gender: M/ F

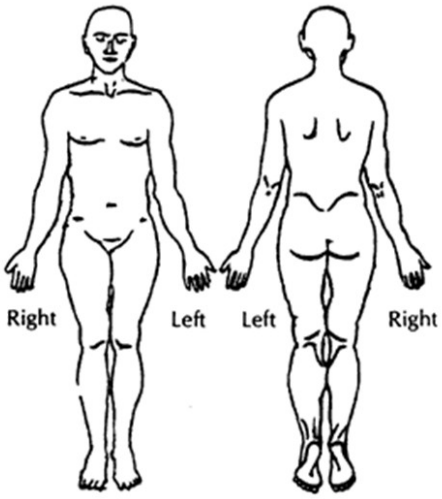
Microbiological group:

FEV_1 today:

Diabetes: Y / N

Experiencing exacerbation: Y / N

Mark site of pain on body chart



Score (admin use only)

Q	Y	N
1		
2		
3		
4		
5		
6		
7		
8		
MPQ	Max 50	
VAS	Max 100	
ICIQ	Max 21	
Outcome	A-G	

Outcome

Refer to Screening Pathway Matrix for outcome:

A. If all ticks are in shaded boxes then no action required (see 'Recommendation' on page 4)
B. Posture and exercise leaflet
C. Pelvic floor leaflet
D. Musculoskeletal physiotherapy assessment
E. Refer to continence specialist
F. Patient declined intervention, screen in 1 year
G. Refer for specialist assessment

Therapist name/signature:

Manchester Musculoskeletal Screening Tool: MPQ

Short Form McGill Pain Questionnaire

A. Please describe your pain during the last 7 days (✓one box on each line.)

	None	Mild	Moderate	Severe
1. Throbbing	0 ☐	1 ☐	2 ☐	3 ☐
2. Shooting	0 ☐	1 ☐	2 ☐	3 ☐
3. Stabbing	0 ☐	1 ☐	2 ☐	3 ☐
4. Sharp	0 ☐	1 ☐	2 ☐	3 ☐
5. Cramping	0 ☐	1 ☐	2 ☐	3 ☐
6. Gnawing	0 ☐	1 ☐	2 ☐	3 ☐
7. Hot/burning	0 ☐	1 ☐	2 ☐	3 ☐
8. Aching	0 ☐	1 ☐	2 ☐	3 ☐
9. Like a weight	0 ☐	1 ☐	2 ☐	3 ☐
10. Tender	0 ☐	1 ☐	2 ☐	3 ☐
11. Splitting	0 ☐	1 ☐	2 ☐	3 ☐
12. Tiring/exhausting	0 ☐	1 ☐	2 ☐	3 ☐
13. Sickening	0 ☐	1 ☐	2 ☐	3 ☐
14. Fearful	0 ☐	1 ☐	2 ☐	3 ☐
15. Punishing/cruel	0 ☐	1 ☐	2 ☐	3 ☐

B. Rate your pain during the past 7 days

The following line represents pain of increasing intensity from "no pain" to "worst possible pain".
Place a vertical line (|) across the line in the position that best describes your pain during the **past 7 days**.

No pain ——————————————— **Worst possible pain**

C. Present pain intensity

0 ☐ No pain
1 ☐ Mild
2 ☐ Discomforting
3 ☐ Distressing
4 ☐ Horrible
5 ☐ Excruciating

Investigator's use only:

*** Visual Analogue Scale (VAS) score:** ☐☐☐ mm

*** MPQ Score:**

S = *sum of 1-11* Max:33 **A** = *sum of 12-15* Max:12 **E** = *C* Max:5

Total MPQ score = *S+A+E* Max:50

MANCHESTER ADULT CYSTIC FIBROSIS CENTRE

Manchester Musculoskeletal Screening Tool: ICIQ

ICIQ-UI Short Form CONFIDENTIAL

Initial number

d	d	m	m	y	y

Today's date

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

d	d	m	m	y	y

2. Are you (tick one)**:**

Female ☐ Male ☐

3. How often do you leak urine?
(Tick one box)

never ☐ 0
about once a week or less often ☐ 1
two or three times a week ☐ 2
about once a day ☐ 3
several times a day ☐ 4
all the time ☐ 5

4. We would like to know how much urine you think leaks.
How much urine do you usually leak (whether you wear protection or not)?
(Tick one box)

none ☐ 0
a small amount ☐ 2
a moderate amount ☐ 4
a large amount ☐ 6

5. Overall, how much does leaking urine interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

not at all — a great deal

ICIQ score: sum scores 3+4+5 ☐☐

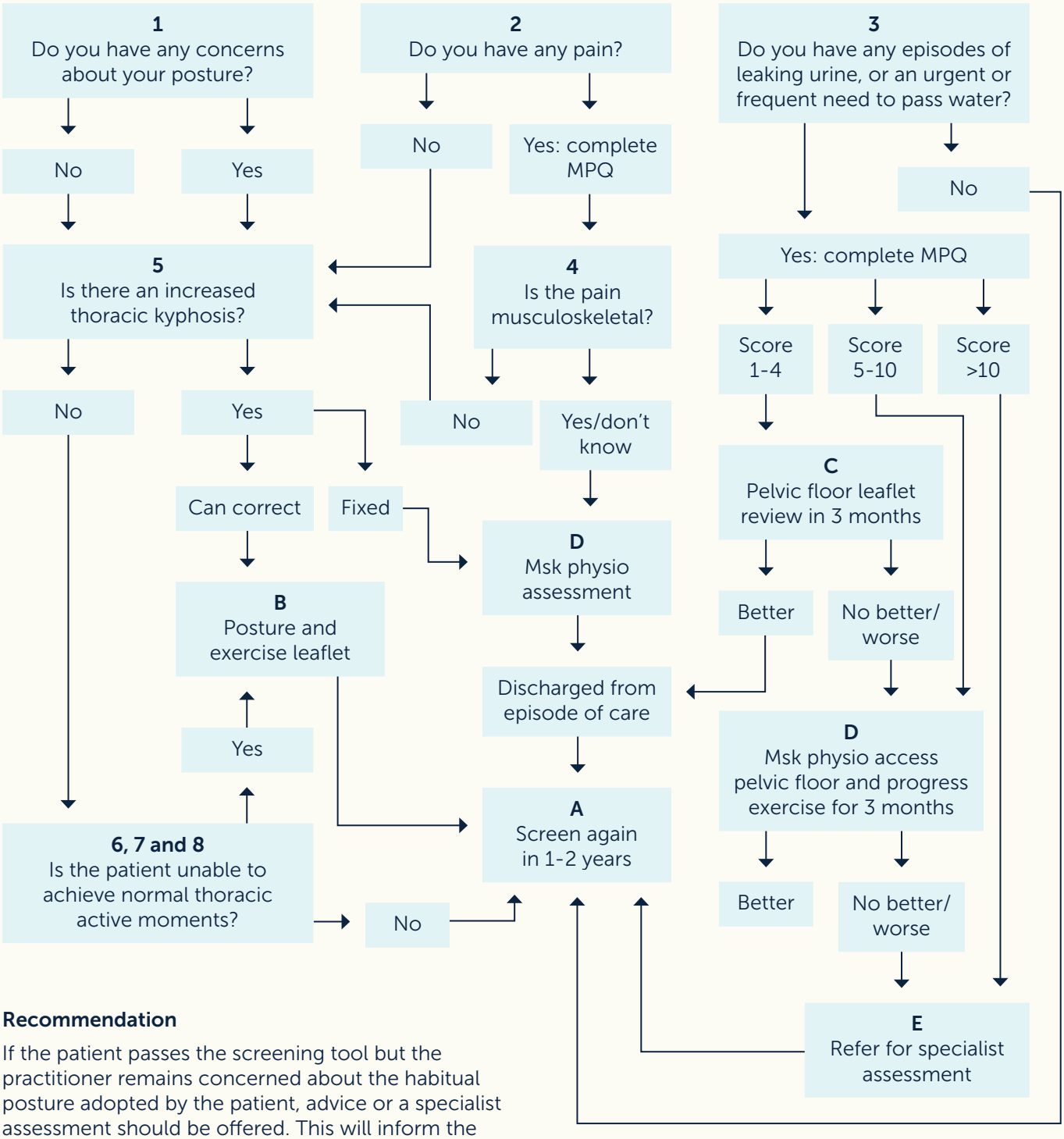
6. When does urine leak?
(Please tick all that apply to you)

never – urine does not leak ☐
leaks before you can get to the toilet ☐
leaks when you cough or sneeze ☐
leaks when you are asleep ☐
leaks when you are physically active/exercising ☐
leaks when you have finished urinating and are dressed ☐
leaks for no obvious reason ☐
leaks all the time ☐

MACFC
MANCHESTER ADULT CYSTIC FIBROSIS CENTRE

Thank you very much for answering these questions.

Screening Pathway Matrix



Recommendation

If the patient passes the screening tool but the practitioner remains concerned about the habitual posture adopted by the patient, advice or a specialist assessment should be offered. This will inform the patient about optimal postures which may prevent problems in the future.

Disclaimer

This material has been developed by the Manchester University NHS Foundation Trust (MFT) and is to be used as a guide only in conjunction with local practices and guidelines. Use of this material is not a substitute for the exercise of appropriate professional skill and judgement. Manchester University NHS Foundation Trust shall not be liable to any person for any loss or damage which may arise from the use of this material.

Appendix V: Pelvic health

Appendix Va

ICIQ-UI

Today's date d d m m y y

ICIQ-UI Short Form CONFIDENTIAL Initial number

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

d d m m y y

2. Are you (tick one)**:**

Female ☐ Male ☐

3. How often do you leak urine?

(Tick one box)

never ☐ 0
about once a week or less often ☐ 1
two or three times a week ☐ 2
about once a day ☐ 3
several times a day ☐ 4
all the time ☐ 5

4. We would like to know how much urine you think leaks.

How much urine do you usually leak (whether you wear protection or not)?

(Tick one box)

none ☐ 0
a small amount ☐ 2
a moderate amount ☐ 4
a large amount ☐ 6

5. Overall, how much does leaking urine interfere with your everyday life?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

not at all a great deal

ICIQ score: sum scores 3+4+5 ☐☐

6. When does urine leak?

(Please tick all that apply to you)

never – urine does not leak ☐
leaks before you can get to the toilet ☐
leaks when you cough or sneeze ☐
leaks when you are asleep ☐
leaks when you are physically active/exercising ☐
leaks when you have finished urinating and are dressed ☐
leaks for no obvious reason ☐
leaks all the time ☐

Thank you very much for answering these questions.

Appendix Vb
St Marks Questionnaire

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4
				No	**Yes**
Need to wear a pad or plug				0	2
Taking constipating medicines				0	2
Lack of ability to defer defecation for 15 minutes				0	4

Never, no episodes in the past four weeks; rarely, 1 episode in the past four weeks; sometimes, >1 episode in the past four weeks but <1 a week; weekly, 1 or more episodes a week but <1 a day; daily, 1 or more episodes a day.

Add one score from each row: minimum score = 0 = perfect continence; maximum score = 24 = totally incontinent.

Appendix Vc
Wexner questionnaire

	Frequency				
Type of incontinence	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad					
Lifestyle alteration	0	1	2	3	4

Never, 0; rarely, <1/month; sometimes, <1/week,≥1/month; usually, <1/day, ≥1/week; always, ≥1/day.

0, perfect; 20, complete incontinence.

Appendix Vd

ICIQ-VS

ICIQ-VS 10/05 CONFIDENTIAL Initial number | | | | | | | | | |

Vaginal symptoms questionnaire

Many people experience vaginal symptoms some of the time. We are trying to find out how many people experience vaginal symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**.

Please write in today's date: d d m m y y

Please write in your date of birth: d d m m y y

Vaginal symptoms

1a. Are you aware of dragging pain in your lower abdomen?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

1b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

2a. Are you aware of soreness in your vagina?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

3a. Do you feel that you have reduced sensation or feeling in or around your vagina?

not at all ☐ 0
a little ☐ 1
somewhat ☐ 2
a lot ☐ 3

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

Prolapse is a common condition affecting the normal support of the pelvic organs, which results in descent or 'dropping down' of the vaginal walls and/or the pelvic organs themselves. This can include the bladder, the bowel and the womb. Symptoms are usually worse on standing up and straining (e.g. lifting, coughing or exercising) and usually better when lying down and relaxing.

Prolapse may cause a variety of problems. We are trying to find out how many people experience prolapse, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**.

4a. Do you feel that your vagina is too loose or lax?

not at all ☐ 0
a little ☐ 1
somewhat ☐ 2
a lot ☐ 3

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

5a. Are you aware of a lump or bulge coming down in your vagina?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

6a. Do you feel a lump or bulge come out of your vagina, so that you can feel it on the outside or see it on the outside?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

7a. Do you feel that your vagina is too dry?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

8a. Do you have to insert a finger into your vagina to help empty your bowels?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

9a. Do you feel that your vagina is too tight?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

Sexual matters

We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**.

10. Do you have a sex life at present?

yes ☐ 1
no, because of my vaginal symptoms ☐ 0
no, because of other reasons ☐ 2

If NO, please go to question 14

11a. Do worries about your vagina interfere with your sex life?

not at all ☐ 0
a little ☐ 1
somewhat ☐ 2
a lot ☐ 3

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

12a. Do you feel that your relationship with your partner is affected by vaginal symptoms?

not at all ☐ 0
a little ☐ 1
somewhat ☐ 2
a lot ☐ 3

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

13. How much do you feel that your sex life has been spoilt by vaginal symptoms?
Please ring a number between 0 (not at all) and 10 (a great deal)

0	1	2	3	4	5	6	7	8	9	10
not at all										a great deal

Quality of life

We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**.

14. Overall, how much do vaginal symptoms interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)

0	1	2	3	4	5	6	7	8	9	10
not at all										a great deal

Thank you very much for answering these questions.

ICIQ-VS 10/05

Vaginal symptoms questionnaire scoring

(This section is for administrative use only)

Patient number ☐☐ ☐☐ ☐☐ ☐☐☐

Vaginal symptoms score

Vaginal symptom score = 2x(dragging pain) + 2x(soreness in vagina) + (reduced sensation) + 2x(vagina too loose) + 2x(lump felt inside) + 2x(lump seen outside) + 2x(vagina too dry) + (faecal evacuation)

Symptom*	Score	Weighted score
Q1. 'dragging pain'		x 2 =
Q2. 'soreness in vagina'		x 2 =
Q3. 'reduced sensation'		x 1 =
Q4. 'vagina too loose'		x 2 =
Q5. 'lump felt inside'		x 2 =
Q6. 'lump seen outside'		x 2 =
Q7. 'vagina too dry'		x 2 =
Q8. 'faecal evacuation'		x 1 =
	Total vaginal symptoms score	

*(Note: Q9, 'vagina too tight', is primarily for detecting a potential post-treatment complication and is therefore not included in the scoring)

Sexual matters score

Sexual matters score = (sex-life spoilt) + 8x(worries about vagina interfere with sex-life) + 8x(relationship affected)

Sexual matter	Score	Weighted score
Q11. 'worries about vagina interfere with sex-life'		x 8 =
Q12. 'relationship affected'		x 8 =
Q13. 'sex life spoilt'		x 1 =
	Total sexual matters score	

Quality of life score

Quality of life	Score
Q14. 'quality of life affected'	

Appendix VI: Summary of evidence-based best practice guidelines relating to nebuliser hygiene in CF

- New nebuliser parts should be washed and disinfected before first use **(Recommendation 2)**.
- During a hospital admission and at home, wash the nebuliser parts after each use **(Recommendation 3)**.
- Nebulisers should be washed and re-disinfected immediately prior to use after greater than 24 hours of inactivity **(Recommendation 4)**.

At home recommendations	Inpatient recommendations
Wash hands thoroughly with soap and water and use hand disinfector gel before starting the cleaning process **(Recommendation 1)**	Wash hands thoroughly with soap and water and use hand disinfector gel before starting the cleaning process. Gloves should be worn by healthcare professionals with hand hygiene performed after removal of gloves **(Recommendation 1)**
Disconnect nebuliser from the compressor unit and dissemble into their constituent components **(Recommendation 11)**	Disconnect nebuliser from the compressor unit and dissemble into their constituent components **(Recommendation 11)**
Washing Wash nebuliser components in a solution of warm tap water **(Recommendation 12)** and dishwashing liquid in accordance with the detergent manufacturer's guidance **(Recommendation 14)**. **Location** Do not wash nebuliser parts directly in kitchen or bathroom sinks **(Recommendation 8)** or the dishwasher **(Recommendation 9)**. This should be done in a dedicated plastic, glass or metal bowl in the patients' kitchen **(Recommendation 10)**. **Rinsing** Sterile water must be used during a final rinse, when immediate disinfection is not possible **(Recommendation 13)**. **Disposal of waste water** Disposal of waste water should be via the toilet, ensuring the toilet lid is closed prior to flushing **(Recommendation 17)**.	**Washing** Wash nebuliser components in a solution of warm tap water **(Recommendation 12)** and dishwashing liquid in accordance with the detergent manufacturer's guidance **(Recommendation 14)**. **Location** This should be done in a disposable bowl, metal bowl or basin **(not directly in a sink-Recommendation 5)** in the patients' room. **(Recommendation 6)** **Rinsing** Sterile water must be used during a final rinse, when immediate disinfection is not possible **(Recommendation 13)**. **Disposal of waste water** Metal bowl and waste water should be sent to the ward sluice **(Recommendation 15)**. Waste water should be disposed of here and the metal bowl should be sterilised by autoclaving **(Recommendation 16)**.
Disinfection Washed and rinsed nebulisers should be disinfected after each use **(Recommendation 7)** using an electric baby bottle steam disinfector, **(Recommendation 18)**.	**Disinfection** Washed and rinsed nebulisers should be disinfected immediately after each use **(Recommendation 7)** using an electric baby bottle steam disinfector **(Recommendation 18)**. **OR** Reusable nebulisers may be autoclaved, where the nebuliser manufacturer states that the device can be safely autoclaved **(Recommendation 19)**.

Storage Leave the disinfected nebuliser parts undisturbed in the disinfector until the next use (within 24 hours). Should the parts be disturbed (i.e. lid lifted off for any reason) then the disinfection process should be repeated and the parts left undisturbed until the next use (within 24 hours) **(Recommendation 20)**.	**Storage** Leave the disinfected nebuliser parts undisturbed in the disinfector until the next use (within 24 hours). Should the parts be disturbed (i.e. lid lifted off for any reason) then the disinfection process should be repeated and the parts left undisturbed until the next use (within 24 hours) **(Recommendation 20)**.
After disinfection Wash hands thoroughly with soap and water and use hand disinfector gel after the cleaning and disinfection process prior to reassembling the nebuliser device **(Recommendation 1)**.	**After disinfection** Wash hands thoroughly with soap and water and use hand disinfector gel after the cleaning and disinfection process prior to reassembling the nebuliser device **(Recommendation 1)**.

Appendix VII: Nebuliser manufacturers cleaning instructions

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
Philips Respironics	Sidestream Plus Reusable high efficiency nebulizer Instructions for Use Ref 1092001 Published 2013 Koninklijke Philips Electronics N.V. [online] Available at: **youtu.be/qFPF-wbRr-OM** [Accessed 15/08/19]	Side-Stream Plus	Breath enhanced jet	Wash all items in hot soapy water.	Rinse in clean water.	After each use.	Boil in water with 2-3 drops of dish washing liquid for 10 minutes.	Rinse in clean water for 2 minutes.	Air dry	1/week	May be washed once a week contained in a basket on top rack of dishwasher. To reduce risk of infection, clean and disinfect by boiling in hot water between treatments.	Every 12 months
Philips Respironics	SideStream reusable kit Phillips Respironics Published 2018 Koninklijke Philips N.V.	Side-Stream reusable kit	jet	Wash all items (except tubing) in hot, soapy water.	Rinse all parts in clean water for 2 minutes.	After each use.	Boil (except mask and tubing) in water with 2-3 drops of dish washing liquid for 10 minutes.	Rinse all parts in clean water for 2 minutes.	Air dry	1/week	Wipe mask with dry clean cloth and air dry.	After 12 months use

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
Philips Respironics	SideStream disposable kit Ref 448,448A Philips respironics Published 2013 Koninklijke Philips Electronics N.V.	Side-Stream disposable kit	jet	Wash in warm, soapy water.	Rinse in clean, cold water.	After each use.	N/A	N/A	N/A	N/A	Do not immerse tubing in water. Wipe mask with clean dry cloth an air dry.	After 30 days use
Philips Respironics	I-Neb AAD system User guide Philips Respironics Published 2015 Koninklijke Philips N.V.	I-neb	AAD + PMT	Place mouthpiece, medication chamber, medication lid and drug guide in (supplied) washing basket. Submerge the basket in warm soapy water (3 drops of liquid detergent) and move basket back and forth.	Rinse parts (still in basket) in soft, distilled or filtered water. If the water is hard, rinse with water that has been boiled and allowed to cool.	After each use.	Submerge the parts in the washing basket, in a pan of soft, distilled or filtered water with 3 drops of liquid detergent. Bring to the boil and boil for 10 minutes.	Rinse with soft, distilled or filtered water.	Shake off excess water and allow to air dry.	Once per week	Use an antiseptic wipe to wipe away any moisture around the horn and sensor port cover. Not suitable for dishwasher or microwave. Do not use bleach or any other cleaning agents.	After 6 months

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
Philips Respironics	Cleaning your Aerogen Go Philips Respironics 1118514 Rev 00	Aerogen Aeroneb Go	VMT	Wash the nebulizer unit (medication cup &cap, nebulizer body, base and mouthpiece) in solution of warm water and dish washing soap. Do not soak.	Rinse under running, hot, tap water.	Rinse after each use, wash daily.	Rinse under running, hot, tap water. Bring a pan of distilled water to the boil and leave parts immersed in boiling water for maximum 20 minutes.	N/A	Shake off excess water and allow parts to fully air dry.	Optional weekly		1 year warranty

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
PARI	PARI LC Family Instructions for Use (Cleaning and disinfection at home) Published 2016 PARI Pharma GmbH. [online] Available at: **www.pari.com/uk/products/pari-lc-plus-nebuliser/pari-lc-plus-nebuliser/** [Accessed 15/08/19]	Pari LC Pari LC Plus Pari LC Plus Junior Pari Baby Pari LC Star	Breath enhanced jet	Place all disassembled components in warm tap water with a little dishwashing liquid for at least 5 minutes.	Rinse all parts thoroughly in running water.	After each use.	**A.** Place all parts in boiling water for 5 minutes. Using a clean pot and fresh water with reduced calcium content. **B.** Standard thermal disinector for baby bottles with a run time of at least 6 minutes. **C.** Specialist chemical cleaning in a hospital setting only, as per manufacturer's instructions.	For chemical disinfection rinse all parts thoroughly in running water.	Place on a dry, clean and absorbent surface and let them dry completely. When dry, wrap in a clean, lint-free cloth.	After cleaning	Remove all parts from pot or disinfector a s soon as disinfection has finished. Dry the parts.	After 1 year

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
PARI	PARI LC SPRINT Family Instructions for Use Published 2015 PARI Pharma GmbH. [online] Available at: **www.pari.com/int/service/hygienic-processing-at-home/** [Accessed 15/08/19]	PARI LC SPRINT PARI LC SPRINT Sinus PARI LC SPRINT Baby PARI LC SPRINT Junior PARI LC SPRINT Star	Breath enhanced jet	Place all disassembled components in warm tap water with a little dish washing for 5 minutes.	Rinse all parts thoroughly in running water.	After each use.	**A.** Boil in water for 5 minutes - use a clean pot and fresh water with reduced calcium content. **B.** Standard disinfector for baby bottles - run time of at least 6 minutes. **C.** Specialist chemical cleaning in a hospital setting only, as per manufacturer's instructions.	N/A if method A, B or C used. For method D, rinse after disinfection in running water.	Place on a dry, clean and absorbent surface and let dry completely.	After cleaning	Wrap in clean, lint-free cloth and keep in dry, dust-free environment. NOTICE The LC interrupter is not designed to withstand exposure to microwaves, and must therefore not be disinfected in a microwave oven.	After 1 year

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
PARI	Instructions for use eFlow® rapid nebuliser system Published 2018 PARI Pharma GmbH. [online] Available at: **www.pari.com/int/service/hygienic-processing-at-home/** [Accessed 15/08/19]	eFlow® Rapid Tolero® Zirela® Altera®	VMT	Place in warm tap water with a little dish washing for 5 minutes.	Rinse under running tap water.	Immediately after each use.	**A.** Thermal disinfector with operating time of 6 minutes. **B.** boil in distilled water for at least 5 minutes.	Not specified.	Place on dry, clean surface and allow to dry completely.	At least once/ day	Store in a clean, dust-free place eg nebuliser bag Microwave disinfector not suitable.	Nebuliser handset 1 year Aerosol head 3-6 months

Manufacturer	Web link/ reference	Name of device	Type	Recommendations							Other	Replace
				Wash	Rinse after washing	Frequency of washing	Disinfect	Rinse after disinfection	Dry	Frequency of disinfecting		
Omron Healthcare Inc.	Omron Instruction Manual Microair® vibrating mesh technology Model NE-U22V Published OMRON Healthcare Inc. 2007. [online] Available at: **omronhealthcare.com/products/microair-nebulizer-neu22v/** [Acccessed 15/08/19]	Microair® Model NE-U22V	VMT	Nebulise a small amount of distilled water for 1-2 minutes.	Rinse with distilled water.	After each use.	Make disinfecting solution of **A.** 1 part white vinegar, 3 parts distilled water or **B.** Mild detergent soap (dishwashing soap in distilled water) Nebulise a small amount of the solution for 1-2 minutes. Soak parts in the disinfecting solution for 10-15 minutes.	Rinse with distilled water.	**A.** gently wipe with a soft clean cloth. **B.** allow to air dry in a clean environment.	Daily - after the last treatment of the day	Store in storage case or in clean environment. Do not use household bleach. Do not rinse in strong running water. Not suitable for microwave oven.	

19. References

1 Chartered Society of Physiotherapy. Code of Members' Professional Values and Behaviour. 2019. Available at: csp.org.uk/system/files/publication_files/000529_Code%20of%20Members%20Professional%20Values%20and%20Behaviours%202019.pdf

2 Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2024 Annual Data Report. 2025. Available at: cysticfibrosis.org.uk/sites/default/files/2025-10/CFT_2024_Annual_Data_Report_v7.pdf

3 NHS Staff Council Job Evaluation Group. National Profiles for Physiotherapy. 2023. Available at: nhsemployers.org/system/files/2023-11/Physiotherapy.pdf

4 Chartered Society of Physiotherapy. Quality Assurance Standards for Physiotherapy Service Delivery. 2012. Available at: csp.org.uk/system/files/csp_quality_assurance_standards.pdf

5 Chartered Society of Physiotherapy. Dealing with Change at Work; A CSP Steward's Toolkit. 2025. Available at: csp.org.uk/system/files/documents/2025-04/Change%20Toolkit%20Complete%20Feb%202020.pdf

6 Chartered Society of Physiotherapy. Scope of practice for support workers. 2019. Available at: csp.org.uk/networks/associates-support-workers/scope-practice-support-workers

7 Chartered Society of Physiotherapy. Optimising Capability in the Physiotherapy Support Worker Workforce. 2020. Available at: csp.org.uk/system/files/publication_files/001701_Optimising%20Capability_MOB1st_Final-stitched_V5.pdf

8 Health and Care Professions Council. Standards of Conduct, Performance and Ethics. 2024. Available at: hcpc-uk.org/standards/standards-of-conduct-performance-and-ethics/

9 NHS Health Education England. Allied Heath Professions' Support Worker Competency, Education and Career Development Framework. 2021. Available at: hee.nhs.uk/sites/default/files/documents/AHP_Framework%20Final_0.pdf

10 Cystic Fibrosis Trust. Pseudomonas Aeruginosa Infection in People with Cystic Fibrosis. Suggestions for Prevention and Infection Control. 2004. Available at: cysticfibrosis.org.uk/sites/default/files/2020-12/Pseudomonas%20aeruginosa.pdf

11 Cystic Fibrosis Trust. Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis. 2022. Available at: cysticfibrosis.org.uk/sites/default/files/2023-01/CF%20Lab%20Standards%20FINAL.pdf

12 Cystic Fibrosis Trust. The Burkholderia Cepacia Complex. Suggestions for Prevention and Infection Control. 2004. Available at: cysticfibrosis.org.uk/sites/default/files/2020-12/Burkholderia%20cepacia.pdf

13 Cystic Fibrosis Trust. Methicillin-Resistant Staphylococcus Aureus (MRSA). 2008. Available at: cysticfibrosis.org.uk/sites/default/files/2020-12/MRSA.pdf

14 Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax. 2016;71(Suppl 1):i1-i22. doi:**10.1136/thoraxjnl-2015-207360**

15 NICE. Transition from Children's to Adults' Services for Young People Using Health or Social Care Services [NG43]. 2016. Available at: **nice.org.uk/guidance/ng43/resources/transition-from-childrens-to-adults-services-for-young-people-using-health-or-social-care-services-pdf-1837451149765**

16 UK CF Trust. Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK (Third Edition). 2024. Available at: **cysticfibrosis.org.uk/sites/default/files/2024-08/Standards%20for%20the%20clinical%20care%20of%20children%20and%20adults%20with%20cystic%20fibrosis%20in%20the%20UK%202024.pdf**

17 Cystic Fibrosis Trust. Mycobacterium abscessus; Recommendations for infection prevention and control. Published online 2017. Available at: **cysticfibrosis.org.uk/sites/default/files/2020-12/NTM%20guidelines%20Mar%202018.pdf**

18 NICE. Cystic Fibrosis: Quality Standard [QS168]. 2018. Available at: **nice.org.uk/guidance/qs168/resources/cystic-fibrosis-pdf-75545607159493**

19 Munck A, Mayell SJ, Winters V, et al. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. Journal of Cystic Fibrosis. 2015;14(6):706-713. doi:**10.1016/j.jcf.2015.01.001**

20 Rosenfeld M, Gibson RL, McNamara S, et al. Early pulmonary infection, inflammation, and clinical outcomes in infants with cystic fibrosis*. Pediatr Pulmonol. 2001;32(5):356-366. doi:**10.1002/ppul.1144**

21 Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A. Cystic Fibrosis Diagnosed After 2 Months of Age Leads to Worse Outcomes and Requires More Therapy. Pediatrics. 2007;119(1):19-28. doi:**10.1542/peds.2006-1498**

22 Tiddens HAWM. Detecting early structural lung damage in cystic fibrosis. Pediatr Pulmonol. 2002;34(3):228-231. doi:**10.1002/ppul.10134**

23 Robinson P. Paediatric origins of adult lung disease bullet 7: Cystic fibrosis. Thorax. 2001;56(3):237-241. doi:**10.1136/thorax.56.3.237**

24 Gibson RL, Burns JL, Ramsey BW. Pathophysiology and Management of Pulmonary Infections in Cystic Fibrosis. Am J Respir Crit Care Med. 2003;168(8):918-951. doi:**10.1164/rccm.200304-505SO**

25 Prasad SA, Main E, Dodd ME. Finding consensus on the physiotherapy management of asymptomatic infants with cystic fibrosis. Pediatr Pulmonol. 2008;43(3):236-244. doi:**10.1002/ppul.20741**

26 Davies G, Rowbotham NJ, Smith S, et al. Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials. Journal of Cystic Fibrosis. 2020;19(3):499-502. doi:**10.1016/j.jcf.2019.10.025**

27 Khan TZ, Wagener JS, Bost T, Martinez J, Accurso FJ, Riches DWH. Early Pulmonary Inflammation in Infants with Cystic Fibrosis. Am J Respir Crit Care Med. 1995;151(4):1075-1082. doi:**10.1164/ajrccm/151.4.1075**

28 Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. BMJ. 1995;310(6994):1571-1572. doi:**10.1136/bmj.310.6994.1571**

29 Ranganathan S, Dezateux C, Bush A, et al. Airway function in infants newly diagnosed with cystic fibrosis. The Lancet. 2001;358(9297):1964-1965. doi:**10.1016/S0140-6736(01)06970-7**

30 Ranganathan SC, Stocks J, Dezateux C, et al. The Evolution of Airway Function in Early Childhood Following Clinical Diagnosis of Cystic Fibrosis. Am J Respir Crit Care Med. 2004;169(8):928-933. doi:**10.1164/rccm.200309-1344OC**

31 Aurora P, Kozlowska W, Stocks J. Gas mixing efficiency from birth to adulthood measured by multiple-breath washout. Respir Physiol Neurobiol. 2005;148(1-2):125-139. doi:**10.1016/j.resp.2005.05.027**

32 Kozlowska WJ, Bush A, Wade A, et al. Lung Function from Infancy to the Preschool Years after Clinical Diagnosis of Cystic Fibrosis. Am J Respir Crit Care Med. 2008;178(1):42-49. doi:**10.1164/rccm.200710-1599OC**

33 Martínez TM, Llapur CJ, Williams TH, et al. High-Resolution Computed Tomography Imaging of Airway Disease in Infants with Cystic Fibrosis. Am J Respir Crit Care Med. 2005;172(9):1133-1138. doi:**10.1164/rccm.200412-1665OC**

34 Sly PD, Brennan S, Gangell C, et al. Lung Disease at Diagnosis in Infants with Cystic Fibrosis Detected by Newborn Screening. Am J Respir Crit Care Med. 2009;180(2):146-152. doi:**10.1164/rccm.200901-0069OC**

35 Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA. Early Lung Disease in Infants and Preschool Children with Cystic Fibrosis. What Have We Learned and What Should We Do about It? Am J Respir Crit Care Med. 2017;195(12):1567-1575. doi:**10.1164/rccm.201606-1107CI**

36 Lannefors L, Button BM, McIlwaine M. Physiotherapy in infants and young children with cystic fibrosis: current practice and future developments. J R Soc Med. 2004;97 Suppl 44(Suppl 44):8-25.

37 Jedlicka-Köhler I, Götz M, Eichler I. Parents' recollection of the initial communication of the diagnosis of cystic fibrosis. Pediatrics. 1996;97(2):204-209.

38 Finney JW, Hook RJ, Friman PC, Rapoff MA, Christophersen ER. The Overestimation of Adherence to Pediatric Medical Regimens. Children's Health Care. 1993;22(4):297-304. doi:**10.1207/s15326888chc2204_5**

39 Czajkowski DR, Koocher GP. MEDICAL COMPLIANCE AND COPING WITH CYSTIC FIBROSIS. Journal of Child Psychology and Psychiatry. 1987;28(2):311-319. doi:**10.1111/j.1469-7610.1987.tb00213.x**

40 Gudas LJ, Koocher GP, Wypij D. Perceptions of medical compliance in children and adolescents with cystic fibrosis. J Dev Behav Pediatr. 1991;12(4):236-242.

41 Myers L. Adherence to Treatment in Medical Conditions. (Myers LB, Midence K, eds.). CRC Press; 2020. doi:**10.1201/9781003072348**

42 Sermet-Gaudelus I, Mayell SJ, Southern KW. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. Journal of Cystic Fibrosis. 2010;9(5):323-329. doi:**10.1016/j.jcf.2010.04.008**

43 Cohen RWF, Folescu TW, Boechat MCB, Fonseca VM, Marques EA, Leão RS. High-resolution computed tomography findings in young infants with cystic fibrosis detected by newborn screening. Clinics. 2019;74:e1399. doi:**10.6061/clinics/2019/e1399**

44 Mott LS, Park J, Murray CP, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax. 2012;67(6):509-516. doi:**10.1136/thoraxjnl-2011-200912**

45 Esther CR, Muhlebach MS, Ehre C, et al. Mucus accumulation in the lungs precedes structural changes and infection in children with cystic fibrosis. Sci Transl Med. 2019;11(486). doi:**10.1126/scitranslmed.aav3488**

46 DeBoer EM, Kimbell JS, Pickett K, et al. Lung inflammation and simulated airway resistance in infants with cystic fibrosis. Respir Physiol Neurobiol. 2021;293:103722. doi:**10.1016/j.resp.2021.103722**

47 Deschamp AR, Hatch JE, Slaven JE, et al. Early respiratory viral infections in infants with cystic fibrosis. Journal of Cystic Fibrosis. 2019;18(6):844-850. doi:**10.1016/j.jcf.2019.02.004**

48 Davies G, Thia LP, Stocks J, et al. Minimal change in structural, functional and inflammatory markers of lung disease in newborn screened infants with cystic fibrosis at one year. Journal of Cystic Fibrosis. 2020;19(6):896-901. doi:**10.1016/j.jcf.2020.01.006**

49 Aurora P, Duncan JA, Lum S, et al. Early Pseudomonas aeruginosa predicts poorer pulmonary function in preschool children with cystic fibrosis. Journal of Cystic Fibrosis. 2022;21(6):988-995. doi:**10.1016/j.jcf.2022.04.013**

50 Carzino R, Frayman KB, King L, Vidmar S, Ranganathan S. Regional differences in infection and structural lung disease in infants and young children with cystic fibrosis. Journal of Cystic Fibrosis. 2020;19(6):917-922. doi:**10.1016/j.jcf.2019.10.018**

51 Horsley A. Lung clearance index in the assessment of airways disease. Respir Med. 2009;103(6):793-799. doi:**10.1016/j.rmed.2009.01.025**

52 Koucký V, Komárek A, Pohunek P. Repeatability of lung clearance index in infants with cystic fibrosis and recurrent wheeze. Pediatr Pulmonol. 2022;57(7):1608-1617. doi:**10.1002/ppul.25921**

53 Davies G. Does newborn screening improve early lung function in cystic fibrosis? Paediatr Respir Rev. 2022;42:17-22. doi:**10.1016/j.prrv.2020.08.005**

54 Kieninger E, Yammine S, Korten I, et al. Elevated lung clearance index in infants with cystic fibrosis shortly after birth. European Respiratory Journal. 2017;50(5):1700580. doi:**10.1183/13993003.00580-2017**

55 Hoo AF, Thia LP, Nguyen TTD, et al. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. Thorax. 2012;67(10):874-881. doi:**10.1136/thoraxjnl-2012-201747**

56 Davies G, Stocks J, Thia LP, et al. Pulmonary function deficits in newborn screened infants with cystic fibrosis managed with standard UK care are mild and transient. European Respiratory Journal. 2017;50(5):1700326. doi:**10.1183/13993003.00326-2017**

57 Korten I, Oestreich MA, Frey U, et al. Respiratory symptoms do not reflect functional impairment in early CF lung disease. Journal of Cystic Fibrosis. 2021;20(6):957-964. doi:**10.1016/j.jcf.2021.04.006**

58 Sandvik RM, Schmidt MN, Voldby CM, et al. Nationwide lung function monitoring from infancy in newborn-screened children with cystic fibrosis. ERJ Open Res. 2023;9(5):00317-02023. doi:**10.1183/23120541.00317-2023**

59 Prasad SA, Main E. Routine airway clearance in asymptomatic infants and babies with cystic fibrosis in the UK: obligatory or obsolete? Physical Therapy Reviews. 2006;11(1):11-20. doi:**10.1179/108331906X98886**

60 Andrews K, Smith M, Cox NS. Physiotherapy: At what cost? Parents experience of performing chest physiotherapy for infants with cystic fibrosis. Journal of Child Health Care. 2021;25(4):616-627. doi:**10.1177/1367493520976481**

61 Button BM, Heine RG, Catto-Smith AG, Phelan PD, Olinsky A. Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis. Arch Dis Child. 1997;76(2):148-150. doi:**10.1136/adc.76.2.148**

62 Heine RG, Button BM, Olinsky A, Phelan PD, Catto-Smith AG. Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. Arch Dis Child. 1998;78(1):44-48. doi:**10.1136/adc.78.1.44**

63 Freitas DA, Chaves GS, Santino TA, et al. Standard (head-down tilt) versus modified (without head-down tilt) postural drainage in infants and young children with cystic fibrosis. Cochrane Database of Systematic Reviews. 2018;2021(4). doi:**10.1002/14651858.CD010297.pub3**

64 Maayan Ch, Bar-Yishay E, Yaacobi T, et al. Immediate Effect of Various Treatments on Lung Function in Infants with Cystic Fibrosis. 1989;55(3):144-151. doi:**10.1159/000195725**

65 Main E, Rand S. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. Cochrane Database of Systematic Reviews. 2023;2023(5). doi:**10.1002/14651858.CD002011.pub3**

66 Costantini D, Brivio A, Brusa D, Delfino R, Fredella C, Russo M. PEP-mask versus postural drainage in CF infants a long-term comparative trial [abstract]. Paediatric Pulmonology. 2001;Suppl 22(308).

67 Kiernan N, Johnstone B, Anderson P, Stewart R. Positive expiratory pressure (PEP) therapy. What pressures do we achieve in young children with cystic fibrosis? A single-centre study. BMJ Paediatr Open. 2020;4(1):e000792. doi:**10.1136/bmjpo-2020-000792**

68 Sharp KM, Wilkinson JD. A proactive approach pays off in screened infants with CF. Journal of Cystic Fibrosis. 2008;7:S77. doi:**10.1016/S1569-1993(08)60296-9**

69 Dixon E. P458 Let's Talk About PEP- Baby: Outcomes of a UK survey, investigating infant positive expiratory pressure (iPEP) practice. Journal of Cystic Fibrosis. 2024;23:S208. doi:**10.1016/S1569-1993(24)00752-5**

70 Corten L, Morrow BM. Autogenic Drainage in Children With Cystic Fibrosis. Pediatric Physical Therapy. 2017;29(2):106-117. doi:**10.1097/PEP.0000000000000355**

71 Lievens L, Vandenplas Y, Vanlaethem S, Van Ginderdeuren F. The effects of assisted autogenic drainage, combined or not with bouncing on gastroesophageal reflux in infants. Acta Paediatr. 2022;111(4):866-872. doi:**10.1111/apa.16224**

72 Byrne NM, Rutter S. 238 Paediatric physiotherapy review following the introduction of newborn screening in cystic fibrosis. Journal of Cystic Fibrosis. 2011;10:S60. doi:**10.1016/S1569-1993(11)60253-1**

73 Ferguson KV, Old K. 210 What airway clearance is being carried out by the cystic fibrosis (CF) population in the UK? Results from a UK national survey conducted by the Cystic Fibrosis Trust. Journal of Cystic Fibrosis. 2013;12:S102. doi:**10.1016/S1569-1993(13)60351-3**

74 Edwards E, Harnett N, Bolton M. P384 Physiotherapy management of infants with cystic fibrosis in the UK and Ireland. Journal of Cystic Fibrosis. 2019;18(S166).

75 Main E. Airway clearance research in CF: the 'perfect storm' of strong preference and effortful participation in long-term, non-blinded studies. Thorax. 2013;68(8):701-702. doi:**10.1136/thoraxjnl-2012-203054**

76 McIlwaine M, Wong LT, Chilvers M, Davidson GF. Long-term comparative trial of two different physiotherapy techniques; postural drainage with percussion and autogenic drainage, in the treatment of cystic fibrosis. Pediatr Pulmonol. 2010;45(11):1064-1069. doi:**10.1002/ppul.21247**

77 Sontag MK, Quittner AL, Modi AC, et al. Lessons learned from a randomized trial of airway secretion clearance techniques in cystic fibrosis. Pediatr Pulmonol. 2010;45(3):291-300. doi:**10.1002/ppul.21179**

78 Chapman N, Watson K, Hatton T, et al. Methods Used to Evaluate the Immediate Effects of Airway Clearance Techniques in Adults with Cystic Fibrosis: A Systematic Review and Meta-Analysis. J Clin Med. 2021;10(22):5280. doi:10.**3390/jcm10225280**

79 Lauwers E, Ides K, Van Hoorenbeeck K, Verhulst S. Outcome measures for airway clearance techniques in children with chronic obstructive lung diseases: a systematic review. Respir Res. 2020;21(1):217. doi:**10.1186/s12931-020-01484-z**

80 Pryor JA, Tannenbaum E, Scott SF, et al. Beyond postural drainage and percussion: Airway clearance in people with cystic fibrosis. Journal of Cystic Fibrosis. 2010;9(3):187-192. doi:**10.1016/j.jcf.2010.01.004**

81 Bradley JM, Moran FM, Stuart Elborn J. Evidence for physical therapies (airway clearance and physical training) in cystic fibrosis: An overview of five Cochrane systematic reviews. Respir Med. 2006;100(2):191-201. doi:**10.1016/j.rmed.2005.11.028**

82 van der Schans C, Postma D, Koeter G, Rubin B. Physiotherapy and bronchial mucus transport. European Respiratory Journal. 1999;13(6):1477-1486. doi:**10.1183/09031936.99.13614879**

83 Stanford G, Parrott H, Bilton D, Agent P, Banya W, Simmonds N. Randomised cross-over trial evaluating the short-term effects of non-invasive ventilation as an adjunct to airway clearance techniques in adults with cystic fibrosis. BMJ Open Respir Res. 2019;6(1):e000399. doi:**10.1136/bmjresp-2018-000399**

84 Stanford G, Bilton D, Charman S, et al. 157 A randomized controlled trial to determine the most sensitive outcome measure of airway clearance in cystic fibrosis. Journal of Cystic Fibrosis. 2022;21:S92-S93. doi:**10.1016/S1569-1993(22)00848-7**

85 Morrison L, Thornton CS. Quality over quantity: the next ACT in airway clearance in cystic fibrosis. European Respiratory Journal. 2023;62(3):2301354. doi:**10.1183/13993003.01354-2023**

86 Filipow N, Stanojevic S, Raywood E, et al. Real-world effectiveness of airway clearance techniques in children with cystic fibrosis. European Respiratory Journal. 2023;62(3):2300522. doi:**10.1183/13993003.00522-2023**

87 Raywood E, Shannon H, Filipow N, et al. Quantity and quality of airway clearance in children and young people with cystic fibrosis. Journal of Cystic Fibrosis. 2023;22(2):344-351. doi:**10.1016/j.jcf.2022.09.008**

88 McIlwaine M, Button B, Nevitt SJ. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database of Systematic Reviews. 2019;2019(11). doi:**10.1002/14651858.CD003147.pub5**

89 Morrison L, Milroy S. Oscillating devices for airway clearance in people with cystic fibrosis. Cochrane Database of Systematic Reviews. Published online April 30, 2020. doi:**10.1002/14651858.CD006842.pub5**

90 Wilson LM, Morrison L, Robinson KA. Airway clearance techniques for cystic fibrosis: an overview of Cochrane systematic reviews. Cochrane Database of Systematic Reviews. 2019;2019(1). doi:**10.1002/14651858.CD011231.pub2**

91 Main E, Prasad A, van der Schans CP. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. Cochrane Database of Systematic Reviews. 2005;2013(2). doi:**10.1002/14651858.CD002011.pub2**

92 Warnock L, Gates A. Airway clearance techniques compared to no airway clearance techniques for cystic fibrosis. Cochrane Database of Systematic Reviews. 2023;2023(4). doi:**10.1002/14651858.CD001401.pub4**

93 Mckoy NA, Wilson LM, Saldanha IJ, Odelola OA, Robinson KA. Active cycle of breathing technique for cystic fibrosis. Cochrane Database of Systematic Reviews. 2016;2016(7). doi:**10.1002/14651858.CD007862.pub4**

94 Burnham P, Stanford G, Stewart R. Autogenic drainage for airway clearance in cystic fibrosis. Cochrane Database of Systematic Reviews. 2021;2021(12). doi:**10.1002/14651858.CD009595.pub3**

95 Cabillic M, Gouilly P, Reychler G. Techniques manuelles de drainage bronchique des adultes et adolescents : quel niveau de preuve ? Rev Mal Respir. 2018;35(5):495-520. doi:**10.1016/j.rmr.2015.12.004**

96 Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. Cochrane Database of Systematic Reviews. 2017;2017(2). doi:**10.1002/14651858.CD002769.pub5**

97 Heinz KD, Walsh A, Southern KW, Johnstone Z, Regan KH. Exercise versus airway clearance techniques for people with cystic fibrosis. Cochrane Database of Systematic Reviews. 2022;2022(6). doi:**10.1002/14651858.CD013285.pub2**

98 Stanford G, Davies JC, Charman SC, et al. WS14.01 Outcome measures for airway clearance – better the devil you know? Perspectives from adults with cystic fibrosis (CF). Journal of Cystic Fibrosis. 2022;21:S26-S27. doi:**10.1016/S1569-1993(22)00231-4**

99 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. European Respiratory Journal. 2005;26(2):319-338. doi:**10.1183/09031936.05.00034805**

100 Davies JC. Monitoring Respiratory Disease Severity in Cystic Fibrosis. Respir Care. 2009;54(5):606-617. doi:**10.4187/aarc0493**

101 Pittman JE, Davis SD. Decline in Forced Expiratory Volume in 1 Second in Cystic Fibrosis—Watch the Pendulum Swing. J Pediatr. 2016;169:7-9. doi:**10.1016/j.jpeds.2015.10.033**

102 Rodriguez Hortal MC, Hjelte L. Time Point to Perform Lung Function Tests Evaluating the Effects of an Airway Clearance Therapy Session in Cystic Fibrosis. Respir Care. 2014;59(10):1537-1541. doi:**10.4187/respcare.02823**

103 Sylvester KP, Clayton N, Cliff I, et al. ARTP statement on pulmonary function testing 2020. BMJ Open Respir Res. 2020;7(1):e000575. doi:**10.1136/bmjresp-2020-000575**

104 Pfleger A, Steinbacher M, Schwantzer G, Weinhandl E, Wagner M, Eber E. Short-term effects of physiotherapy on ventilation inhomogeneity in cystic fibrosis patients with a wide range of lung disease severity. Journal of Cystic Fibrosis. 2015;14(5):627-631. doi:**10.1016/j.jcf.2014.12.017**

105 Grosse-Onnebrink J, Mellies U, Olivier M, Werner C, Stehling F. Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients. Pediatr Pulmonol. 2017;52(5):625-631. doi:**10.1002/ppul.23670**

106 O'Neill K, Moran F, Tunney MM, et al. Timing of hypertonic saline and airway clearance techniques in adults with cystic fibrosis during pulmonary exacerbation: pilot data from a randomised crossover study. BMJ Open Respir Res. 2017;4(1):e000168. doi:**10.1136/bmjresp-2016-000168**

107 Rodriguez Hortal MC, Nygren-Bonnier M, Hjelte L. Non-invasive Ventilation as Airway Clearance Technique in Cystic Fibrosis. Physiotherapy Research International. 2017;22(3):e1667. doi:**10.1002/pri.1667**

108 Voldby C, Green K, Rosthøj S, et al. The effect of time-of-day and chest physiotherapy on multiple breath washout measures in children with clinically stable cystic fibrosis. PLoS One. 2018;13(1):e0190894. doi:**10.1371/journal.pone.0190894**

109 Buonpensiero P, Gregorio F De, Pasqua A Di, et al. WS15.6 Short term effects of Positive Expiratory Pressure mask breathing on distribution of lung ventilation in cystic fibrosis patients: a preliminary report with electrical impedance tomography. Journal of Cystic Fibrosis. 2016;15:S25-S26. doi:**10.1016/S1569-1993(16)30150-3**

110 Forster E, Swingwood E, Nicholas B, Bateman K. 302 Comparison of airway clearance techniques (ACT) in the cystic fibrosis (CF) population: a single case study report. Journal of Cystic Fibrosis. 2014;13:S125. doi:**10.1016/S1569-1993(14)60437-9**

111 Wettstein M, Radlinger L, Riedel T. Effect of Different Breathing Aids on Ventilation Distribution in Adults with Cystic Fibrosis. PLoS One. 2014;9(9):e106591. doi:**10.1371/journal.pone.0106591**

112 Dwyer TJ, Daviskas E, Zainuldin R, et al. Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: a randomised crossover trial. European Respiratory Journal. 2019;53(4):1801793. doi:**10.1183/13993003.01793-2018**

113 Mentore K, Froh DK, de Lange EE, Brookeman JR, Paget-Brown AO, Altes TA. Hyperpolarized HHe 3 MRI of the Lung in Cystic Fibrosis. Acad Radiol. 2005;12(11):1423-1429. doi:**10.1016/j.acra.2005.07.008**

114 Trimble A, Zeman K, Wu J, Ceppe A, Bennett W, Donaldson S. Effect of airway clearance therapies on mucociliary clearance in adults with cystic fibrosis: A randomized controlled trial. PLoS One. 2022;17(5):e0268622. doi:**10.1371/journal.pone.0268622**

115 Smith L, Marshall H, Norquay G, et al. P211 129Xe ventilation MRI and LCI to assess acute maximal exercise as a method of airway clearance. Journal of Cystic Fibrosis. 2019;18:S116-S117. doi:**10.1016/S1569-1993(19)30504-1**

116 Vendrusculo FM, Johnstone Z, Dhouieb E, Donadio MVF, Cunningham S, Urquhart DS. Airway clearance physiotherapy improves ventilatory dynamics during exercise in patients with cystic fibrosis: a pilot study. Arch Dis Child. 2019;104(1):37-42. doi:**10.1136/archdischild-2017-314365**

117 Buchs C, Coutier L, Vrielynck S, Jubin V, Mainguy C, Reix P. An impulse oscillometry system is less efficient than spirometry in tracking lung function improvements after intravenous antibiotic therapy in pediatric patients with cystic fibrosis. Pediatr Pulmonol. 2015;50(11):1073-1081. doi:**10.1002/ppul.23301**

118 Hatziagorou E, Avramidou V, Kirvassilis F, Tsanakas J. Use of lung clearance index to assess the response to intravenous treatment in cystic fibrosis. Hippokratia. 2015;19(1):47-52.

119 Wallaert E, Perez T, Prevotat A, Reychler G, Wallaert B, Le Rouzic O. The immediate effects of a single autogenic drainage session on ventilatory mechanics in adult subjects with cystic fibrosis. PLoS One. 2018;13(3):e0195154. doi:**10.1371/journal.pone.0195154**

120 Walicka-Serzysko K, Postek M, Jeneralska N, Cichocka A, Milczewska J, Sands D. The effects of the addition of a new airway clearance device to chest physiotherapy in children with cystic fibrosis pulmonary exacerbations. J Mother Child. 2020;24(3):16-24. doi:**10.34763/jmotherandchild.20202403.2013.d-20-00008**

121 Reamer C, O'Malley C, Nufer J, Savant A. Improved outcomes in cystic fibrosis using modified Re-Education of Airway Clearance Technique (REACT) programme. BMJ Open Qual. 2020;9(3):e000890. doi:**10.1136/bmjoq-2019-000890**

122 Smith LJ, Marshall H, Bray J, et al. The effect of acute maximal exercise on the regional distribution of ventilation using ventilation MRI in CF. Journal of Cystic Fibrosis. 2021;20(4):625-631. doi:**10.1016/j.jcf.2020.08.009**

123 Stahl M, Wielpütz MO, Graeber SY, et al. Comparison of Lung Clearance Index and Magnetic Resonance Imaging for Assessment of Lung Disease in Children with Cystic Fibrosis. Am J Respir Crit Care Med. 2017;195(3):349-359. doi:**10.1164/rccm.201604-0893OC**

124 Kent L, Reix P, Innes JA, et al. Lung clearance index: Evidence for use in clinical trials in cystic fibrosis. Journal of Cystic Fibrosis. 2014;13(2):123-138. doi:**10.1016/j.jcf.2013.09.005**

125 McLeod C, Wood J, Tong A, et al. The measurement properties of tests and tools used in cystic fibrosis studies: a systematic review. European Respiratory Review. 2021;30(160):200354. doi:**10.1183/16000617.0354-2020**

126 Stanford GE, Jones M, Charman SC, et al. Clinimetric analysis of outcome measures for airway clearance in people with cystic fibrosis: a systematic review. Ther Adv Respir Dis. 2022;16. doi:**10.1177/17534666221122572**

127 McIlwaine MP, Alarie N, Davidson GF, et al. Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis. Thorax. 2013;68(8):746-751. doi:**10.1136/thoraxjnl-2012-202915**

128 Miller AC, Harris LM, Cavanaugh JE, et al. The Rapid Reduction of Infection-Related Visits and Antibiotic Use Among People With Cystic Fibrosis After Starting Elexacaftor-Tezacaftor-Ivacaftor. Clinical Infectious Diseases. 2022;75(7):1115-1122. **doi:10.1093/cid/ciac117**

129 Egan ME. Cystic fibrosis transmembrane conductance receptor modulator therapy in cystic fibrosis, an update. Curr Opin Pediatr. 2020;32(3):384-388. doi:**10.1097/MOP.0000000000000892**

130 Gursli S, Quittner A, Jahnsen RB, Skrede B, Stuge B, Bakkeheim E. Airway clearance physiotherapy and health-related quality of life in cystic fibrosis. PLoS One. 2022;17(10):e0276310. doi:**10.1371/journal.pone.0276310**

131 Mussaffi H, Fireman EM, Mei-Zahav M, Prais D, Blau H. Induced Sputum in the Very Young. Chest. 2008;133(1):176-182. doi:**10.1378/chest.07-2259**

132 Jochmann A, Artusio L, Robson K, et al. Infection and inflammation in induced sputum from preschool children with chronic airways diseases. Pediatr Pulmonol. 2016;51(8):778-786. doi:**10.1002/ppul.23366**

133 Sagel SD, Kapsner R, Osberg I, Sontag MK, Accurso FJ. Airway Inflammation in Children with Cystic Fibrosis and Healthy Children Assessed by Sputum Induction. Am J Respir Crit Care Med. 2001;164(8):1425-1431. doi:**10.1164/ajrccm.164.8.2104075**

134 Blau H, Linnane B, Carzino R, et al. Induced sputum compared to bronchoalveolar lavage in young, non-expectorating cystic fibrosis children. Journal of Cystic Fibrosis. 2014;13(1):106-110. doi:**10.1016/j.jcf.2013.05.013**

135 Suri R, Marshall LJ, Wallis C, Metcalfe C, Shute JK, Bush A. Safety and use of sputum induction in children with cystic fibrosis. Pediatr Pulmonol. 2003;35(4):309-313. doi:**10.1002/ppul.10226**

136 Gershman NH, Liu H, Wong HH, Liu JT, Fahy J V. Fractional analysis of sequential induced sputum samples during sputum induction: Evidence that different lung compartments are sampled at different time points☆☆☆. Journal of Allergy and Clinical Immunology. 1999;104(2):322-328. doi:**10.1016/S0091-6749(99)70374-X**

137 Nocker RET, Out TA, Weller FR, de Riemer MJ, Jansen HM, van der Zee JS. Induced sputum and bronchoalveolar lavage as tools for evaluating the effects of inhaled corticosteroids in patients with asthma. Journal of Laboratory and Clinical Medicine. 2000;136(1):39-49. doi:**10.1067/mlc.2000.107305**

138 Ronchetti K, Tame JD, Paisey C, et al. The CF-Sputum Induction Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. Lancet Respir Med. 2018;6(6):461-471. doi:**10.1016/S2213-2600(18)30171-1**

139 Aitken ML, Greene KE, Tonelli MR, et al. Analysis of Sequential Aliquots of Hypertonic Saline Solution-Induced Sputum From Clinically Stable Patients With Cystic Fibrosisa. Chest. 2003;123(3):792-799. doi:**10.1378/chest.123.3.792**

140 Ahmed B, Bush A, Davies JC. How to use: bacterial cultures in diagnosing lower respiratory tract infections in cystic fibrosis. Arch Dis Child Educ Pract Ed. 2014;99(5):181-187. doi:**10.1136/archdischild-2012-303408**

141 Henig NR. Sputum induction as a research tool for sampling the airways of subjects with cystic fibrosis. Thorax. 2001;56(4):306-311. doi:**10.1136/thorax.56.4.306**

142 Alexis NE, Hu SC, Zeman K, Alter T, Bennett WD. Induced Sputum Derives from the Central Airways. Am J Respir Crit Care Med. 2001;164(10):1964-1970. doi:**10.1164/ajrccm.164.10.2104051**

143 Al-Saleh S, Dell SD, Grasemann H, et al. Sputum Induction in Routine Clinical Care of Children with Cystic Fibrosis. J Pediatr. 2010;157(6):1006-1011.e1. doi:**10.1016/j.jpeds.2010.06.001**

144 Eyns H, De Wachter E, Malfroot A, Vaes P. Acute Pain Perception During Different Sampling Methods for Respiratory Culture in Cystic Fibrosis Patients. J Pain Symptom Manage. 2018;55(3):872-880. doi:**10.1016/j.jpainsymman.2017.11.004**

145 Ordoñez CL, Kartashov AI, Wohl MEB. Variability of markers of inflammation and infection in induced sputum in children with cystic fibrosis. J Pediatr. 2004;145(5):689-692. doi:**10.1016/j.jpeds.2004.06.054**

146 Ahmed MI, Kulkarni H, Shajpal S, et al. Early detection of non-tuberculous mycobacteria in children with cystic fibrosis using induced sputum at annual review. Pediatr Pulmonol. 2019;54(3):257-263. doi:**10.1002/ppul.24220**

147 Zampoli M, Pillay K, Carrara H, Zar HJ, Morrow B. Microbiological yield from induced sputum compared to oropharyngeal swab in young children with cystic fibrosis. Journal of Cystic Fibrosis. 2016;15(5):605-610. doi:**10.1016/j.jcf.2016.01.001**

148 ECFS Clinical Trials Network, ECFS Physiotherapy Working Group. SOP 2.4/001/01 Sputum Induction for Expectorating Young Children.

149 ECFS Clinical Trials Network, ECFS Physiotherapy Working Group. SOP 2.4/001/03 Sputum Induction for Expectorating Older Children and Adults.

150 ECFS Clinical Trials Network, ECFS Physiotherapy Working Group. SOP 2.4/001/02 for Sputum Induction for Non-Expectorating Young Children.

151 ECFS Clinical Trials Network, ECFS Physiotherapy Working Group. SOP 2.4/001/04 Sputum Induction for Non-Expectorating Older Children and Adults.

152 Schultz A, Balaguruswamy S, Dentice R, Dobler CC, Geake J, Gibson P, et al. Thoracic Society of Australia and New Zealand position statement: The safe clinical use of sputum induction for bio-sampling of the lower airways in children and adults. Respirology. 2024;29(5):372–378. doi.org/10.1111/resp.14707

153 Weiszhar Z, Horvath I. Induced sputum analysis: step by step. Breathe. 2013;9(4):300-306. doi:**10.1183/20734735.042912**

154 Stafler P, Zaks-Hoffer G, Scheuerman O, et al. Diagnostic value of sputum cultures in children under 2 years of age with chronic suppurative lung diseases. Pediatr Pulmonol. 2020;55(12):3421-3428. doi:**10.1002/ppul.25103**

155 Davidson WJ, Dennis J, The S, Litoski B, Pieron C, Leigh R. Identification and validation of nebulized aerosol devices for sputum induction. Can Respir J. 2014;21(2):101-106. doi:**10.1155/2014/925305**

156 Robinson M, Hemming AL, Regnis JA, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. Thorax. 1997;52(10):900-903. doi:**10.1136/thx.52.10.900**

157 Rodwell LT, Anderson SD. Airway responsiveness to hyperosmolar saline challenge in cystic fibrosis: A pilot study. Pediatr Pulmonol. 1996;21(5):282-289. doi:**10.1002/(SICI)1099-0496(199605)21:5<282::AID-PPUL3>3.0.CO;2-P**

158 Kelly MG, Brown V, Martin SL, Ennis M, Elborn JS. Comparison of Sputum Induction Using High-Output and Low-Output Ultrasonic Nebulizers in Normal Subjects and Patients With COPD. Chest. 2002;122(3):955-959. doi:**10.1378/chest.122.3.955**

159 Zemanick ET, Wagner BD, Robertson CE, et al. Assessment of Airway Microbiota and Inflammation in Cystic Fibrosis Using Multiple Sampling Methods. Ann Am Thorac Soc. 2015;12(2):221-229. doi:**10.1513/AnnalsATS.201407-310OC**

160 Ho SA, Ball R, Morrison LJ, Brownlee KG, Conway SP. Clinical value of obtaining sputum and cough swab samples following inhaled hypertonic saline in children with cystic fibrosis. Pediatr Pulmonol. 2004;38(1):82-87. doi:**10.1002/ppul.20035**

161 De Boeck K, Alifier M, Vandeputte S. Sputum induction in young cystic fibrosis patients. European Respiratory Journal. 2000;16(1):91-94. doi:**10.1034/j.1399-3003.2000.16a16.x**

162 Reinhardt N, Chen CIU, Loppow D, et al. Cellular profiles of induced sputum in children with stable cystic fibrosis: comparison with BAL. European Respiratory Journal. 2003;22(3):497-502. doi:**10.1183/09031936.03.00043603**

163 Araújo L, Moreira A, Palmares C, Beltrão M, Fonseca J, Delgado L. Induced sputum in children: success determinants, safety, and cell profiles. J Investig Allergol Clin Immunol. 2011;21(3):216-221.

164 Simonds A, Hanak A, Chatwin M, et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technol Assess (Rockv). 2010;14(46). doi:**10.3310/hta14460-02**

165 Knibbs LD, Johnson GR, Kidd TJ, et al. Viability of Pseudomonas aeruginosa in cough aerosols generated by persons with cystic fibrosis. Thorax. 2014;69(8):740-745. doi:**10.1136/thoraxjnl-2014-205213**

166 Bryant JM, Harris SR, Parkhill J, et al. Whole-genome sequencing to establish relapse or re-infection with Mycobacterium tuberculosis: a retrospective observational study. Lancet Respir Med. 2013;1(10):786-792. doi:**10.1016/S2213-2600(13)70231-5**

167 Kapnadak SG, Hisert KB, Pottinger PS, Limaye AP, Aitken ML. Infection control strategies that successfully controlled an outbreak of Mycobacterium abscessus at a cystic fibrosis center. Am J Infect Control. 2016;44(2):154-159. doi:**10.1016/j.ajic.2015.08.023**

168 Saynor ZL, Gruet M, McNarry MA, et al. Guidance and standard operating procedures for functional exercise testing in cystic fibrosis. European Respiratory Review. 2023;32(169):230029. doi:**10.1183/16000617.0029-2023**

169 Radtke T, Urquhart DS, Braun J, et al. Cardiopulmonary Exercise Testing Provides Prognostic Information in Advanced Cystic Fibrosis Lung Disease. Ann Am Thorac Soc. 2024;21(3):411-420. doi:**10.1513/AnnalsATS.202304-317OC**

170 Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. European Respiratory Review. 2019;28(154):180101. doi:**10.1183/16000617.0101-2018**

171 Urquhart DS, Saynor ZL. Exercise testing in cystic fibrosis: Who and why? Paediatr Respir Rev. 2018;27:28-32. doi:**10.1016/j.prrv.2018.01.004**

172 Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. Journal of Cystic Fibrosis. 2024;23(1):12-28. doi:**10.1016/j.jcf.2023.12.002**

173 Button BM, Wilson C, Dentice R, et al. Physiotherapy for cystic fibrosis in Australia and New Zealand: A clinical practice guideline. Respirology. 2016;21(4):656-667. doi:**10.1111/resp.12764**

174 Hebestreit H, Arets HGM, Aurora P, et al. Statement on Exercise Testing in Cystic Fibrosis. 2015;90(4):332-351. doi:**10.1159/000439057**

175 Radtke T, Faro A, Wong J, Boehler A, Benden C. Exercise testing in pediatric lung transplant candidates with cystic fibrosis. Pediatr Transplant. 2011;15(3):294-299. doi:**10.1111/j.1399-3046.2010.01471.x**

176 Hebestreit H, Hulzebos EHJ, Schneiderman JE, et al. Cardiopulmonary Exercise Testing Provides Additional Prognostic Information in Cystic Fibrosis. Am J Respir Crit Care Med. 2019;199(8):987-995. doi:**10.1164/rccm.201806-1110OC**

177 Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The Prognostic Value of Exercise Testing in Patients with Cystic Fibrosis. New England Journal of Medicine. 1992;327(25):1785-1788. doi:**10.1056/NEJM199212173272504**

178 Pianosi P. Peak oxygen uptake and mortality in children with cystic fibrosis. Thorax. 2005;60(1):50-54. doi:**10.1136/thx.2003.008102**

179 Saynor ZL, Barker AR, Oades PJ, Williams CA. The Effect of Ivacaftor in Adolescents With Cystic Fibrosis (G551D Mutation). Pediatric Physical Therapy. 2014;26(4):454-461. doi:**10.1097/PEP.0000000000000086**

180 van der Haak N, King SJ, Crowder T, Kench A, Painter C, Saxby N. Highlights from the nutrition guidelines for cystic fibrosis in Australia and New Zealand. Journal of Cystic Fibrosis. 2020;19(1):16-25. doi:**10.1016/j.jcf.2019.05.007**

181 UK CF Trust. Cystic Fibrosis Diabetes factsheet. Preprint posted online 2023.

182 UK CF Trust. Management of Cystic Fibrosis Diabetes (Second Edition). 2022. Available at: **cysticfibrosis.org.uk/sites/default/files/2023-04/CF%20Trust%20Diabetes%20Consensus.pdf**

183 Quon BS, Wilkie SS, Ramsook AH, et al. Qualitative dimensions of exertional dyspnea in adults with cystic fibrosis. J Appl Physiol. 2016;121(2):449-456. doi:**10.1152/japplphysiol.00391.2016**

184 Pritchard A, Burns P, Correia J, et al. ARTP statement on cardiopulmonary exercise testing 2021. BMJ Open Respir Res. 2021;8(1):e001121. doi:**10.1136/bmjresp-2021-001121**

185 Saynor ZL, Barker AR, Oades PJ, Williams CA. A protocol to determine valid in young cystic fibrosis patients. J Sci Med Sport. 2013;16(6):539-544. doi:**10.1016/j.jsams.2013.01.010**

186 Saynor ZL, Barker AR, Oades PJ, Williams CA. Reproducibility of maximal cardiopulmonary exercise testing for young cystic fibrosis patients. Journal of Cystic Fibrosis. 2013;12(6):644-650. doi:**10.1016/j.jcf.2013.04.012**

187 Causer AJ, Shute JK, Cummings MH, et al. Cardiopulmonary exercise testing with supramaximal verification produces a safe and valid assessment of $\dot{V}$ <scp>o</scp> 2max in people with cystic fibrosis: a retrospective analysis. J Appl Physiol. 2018;125(4):1277-1283. doi:**10.1152/japplphysiol.00454.2018**

188 Poole DC, Jones AM. Measurement of the maximum oxygen uptake $\dot{V}O_{2max}$: $\dot{V}O_{2peak}$ is no longer acceptable. J Appl Physiol. 2017;122(4):997-1002. doi:**10.1152/japplphysiol.01063.2016**

189 Hulzebos EHJ, Bomhof-Roordink H, van de Weert-van Leeuwen PB, et al. Prediction of Mortality in Adolescents with Cystic Fibrosis. Med Sci Sports Exerc. 2014;46(11):2047-2052. doi:**10.1249/MSS.0000000000000344**

190 Takken T, Mylius CF, Paap D, et al. Reference values for cardiopulmonary exercise testing in healthy subjects – an updated systematic review. Expert Rev Cardiovasc Ther. 2019;17(6):413-426. doi:**10.1080/14779072.2019.1627874**

191 Mylius CF, Krijnen WP, van der Schans CP, Takken T. Peak oxygen uptake reference values for cycle ergometry for the healthy Dutch population: data from the LowLands Fitness Registry. ERJ Open Res. 2019;5(2):00056-02018. doi:**10.1183/23120541.00056-2018**

192 Blanchard J, Blais S, Chetaille P, et al. New Reference Values for Cardiopulmonary Exercise Testing in Children. Med Sci Sports Exerc. 2018;50(6):1125-1133. doi:**10.1249/MSS.0000000000001559**

193 Hulzebos E, Dadema T, Takken T. Measurement of physical activity in patients with cystic fibrosis: a systematic review. Expert Rev Respir Med. 2013;7(6):647-653. doi:**10.1586/17476348.2013.839248**

194 Urquhart D, Blacklock S, Fynn D. The belief that maximal exercise effort is expended on shuttle testing may be unfounded in children with cystic fibrosis. Pediatr Pulmonol. 2014;49(S38):373.

195 Gulmans VA, van Veldhoven NH, de Meer K, Helders PJ. The six-minute walking test in children with cystic fibrosis: reliability and validity. Pediatr Pulmonol. 1996;22(2):85-89. doi:**10.1002/(SICI)1099-0496(199608)22:2<85::AID-PPUL1>3.0.CO;2-I**

196 Ramos KJ, Smith PJ, McKone EF, et al. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. Journal of Cystic Fibrosis. 2019;18(3):321-333. doi:**10.1016/j.jcf.2019.03.002**

197 Martin C, Chapron J, Hubert D, et al. Prognostic value of six minute walk test in cystic fibrosis adults. Respir Med. 2013;107(12):1881-1887. doi:**10.1016/j.rmed.2013.10.001**

198 Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. European Respiratory Journal. 2014;44(6):1428-1446. doi:**10.1183/09031936.00150314**

199 Andrade Lima C, Dornelas de Andrade A, Campos SL, Brandão DC, Mourato IP, Britto MCA de. Six-minute walk test as a determinant of the functional capacity of children and adolescents with cystic fibrosis: A systematic review. Respir Med. 2018;137:83-88. doi:**10.1016/j.rmed.2018.02.016**

200 Selvadurai HC, Cooper PJ, Meyers N, et al. Validation of shuttle tests in children with cystic fibrosis. Pediatr Pulmonol. 2003;35(2):133-138. doi:**10.1002/ppul.10197**

201 Urquhart DS, Hebestreit H, Saynor Z, Radtke T. 'Gold-standard' field test is a non-sequitur. Pulmonology. 2023;29(2):173-173. doi:**10.1016/j.pulmoe.2022.07.016**

202 Vendrusculo FM, Heinzmann-Filho JP, Campos NE, Gheller MF, de Almeida IS, Donadio MVF. Prediction of peak oxygen uptake using the modified shuttle test in children and adolescents with cystic fibrosis. Pediatr Pulmonol. 2019;54(4):386-392. doi:**10.1002/ppul.24237**

203 Elkins MR, Dentice RL, Bye PT. Validation of the MST-25: an extension of the modified shuttle test (MST). Journal of Cystic Fibrosis. 2009;8:S70. doi:**10.1016/S1569-1993(09)60276-9**

204 Corda J, E. Holland A, Berry C Du, Westrupp N, Cox NS. Validation of the 25 level modified shuttle test in children with cystic fibrosis. Pediatr Pulmonol. 2023;58(8):2240-2248. doi:**10.1002/ppul.26452**

205 del Corral T, Gómez Sánchez Á, López-de-Uralde-Villanueva I. Test-retest reliability, minimal detectable change and minimal clinically important differences in modified shuttle walk test in children and adolescents with cystic fibrosis. Journal of Cystic Fibrosis. 2020;19(3):442-448. doi:**10.1016/j.jcf.2019.10.007**

206 Vardhan V, Palekar T, Dhuke P, Baxi G. Normative values of incremental shuttle walk test in children and adolescents: an observational study. Int J Pharma Bio Sci. 2017;8(4). doi:**10.22376/ijpbs.2017.8.4.b478-483**

207 Pinho T, Jácome C, Pinto J, Marques A. Reference equation for the incremental shuttle walk test in Portuguese children and adolescents. Pulmonology. 2019;25(4):208-214. doi:**10.1016/j.pulmoe.2019.02.009**

208 Lanza F de C, Zagatto E do P, Silva JC, et al. Reference Equation for the Incremental Shuttle Walk Test in Children and Adolescents. J Pediatr. 2015;167(5):1057-1061. doi:**10.1016/j.jpeds.2015.07.068**

209 Probst VS, Hernandes NA, Teixeira DC, et al. Reference values for the incremental shuttle walking test. Respir Med. 2012;106(2):243-248. doi:**10.1016/j.rmed.2011.07.023**

210 Doeleman WR, Takken T, Bronsveld I, Hulzebos EHJ. Relationship between lung function and Modified Shuttle Test performance in adult patients with cystic fibrosis: a cross-sectional, retrospective study. Physiotherapy. 2016;102(2):184-188. doi:**10.1016/j.physio.2015.10.015**

211 Filipow N, Bladen M, Raywood E, et al. Using reference equations to standardise incremental shuttle walk test performance in children and young people with chronic conditions and facilitate the evaluation of exercise capacity and disease severity. BMJ Open. 2024;14(3):e075733. doi:**10.1136/bmjopen-2023-075733**

212 Gruet M, Saynor Z. Assessment of Peripheral Muscle Function in Cystic Fibrosis: Why and How? Respir Care. 2019;64(2):238-240. doi:**10.4187/respcare.06692**

213 Combret Y, Boujibar F, Gennari C, et al. Measurement properties of the one-minute sit-to-stand test in children and adolescents with cystic fibrosis: A multicenter randomized cross-over trial. PLoS One. 2021;16(2):e0246781. doi:**10.1371/journal.pone.0246781**

214 Vaidya T, Chambellan A, de Bisschop C. Sit-to-stand tests for COPD: A literature review. Respir Med. 2017;128:70-77. doi:**10.1016/j.rmed.2017.05.003**

215 Radtke T, Puhan MA, Hebestreit H, Kriemler S. The 1-min sit-to-stand test—A simple functional capacity test in cystic fibrosis? Journal of Cystic Fibrosis. 2016;15(2):223-226. doi:**10.1016/j.jcf.2015.08.006**

216 Kohlbrenner D, Benden C, Radtke T. The 1-Minute Sit-to-Stand Test in Lung Transplant Candidates: An Alternative to the 6-Minute Walk Test. Respir Care. 2020;65(4):437-443. doi:**10.4187/respcare.07124**

217 Gruet M, Peyré-Tartaruga LA, Mely L, Vallier JM. The 1-Minute Sit-to-Stand Test in Adults With Cystic Fibrosis: Correlations With Cardiopulmonary Exercise Test, 6-Minute Walk Test, and Quadriceps Strength. Respir Care. 2016;61(12):1620-1628. doi:**10.4187/respcare.04821**

218 Haile SR, Fühner T, Granacher U, Stocker J, Radtke T, Kriemler S. Reference values and validation of the 1-minute sit-to-stand test in healthy 5–16-year-old youth: a cross-sectional study. BMJ Open. 2021;11(5):e049143. doi:**10.1136/bmjopen-2021-049143**

219 Houchen-Wolloff L, Daynes E, Watt A, Chaplin E, Gardiner N, Singh S. Which functional outcome measures can we use as a surrogate for exercise capacity during remote cardiopulmonary rehabilitation assessments? A rapid narrative review. ERJ Open Res. 2020;6(4):00526-02020. doi:**10.1183/23120541.00526-2020**

220 Radtke T, Hebestreit H, Puhan MA, Kriemler S. The 1-min sit-to-stand test in cystic fibrosis — Insights into cardiorespiratory responses. Journal of Cystic Fibrosis. 2017;16(6):744-751. doi:**10.1016/j.jcf.2017.01.012**

221 Vendrusculo FM, Bueno GS, Gheller MF, et al. Peripheral muscle strength is associated with aerobic fitness and use of antibiotics in patients with cystic fibrosis. Int J Clin Pract. 2021;75(5). doi:**10.1111/ijcp.14050**

222 Ritchie H, Nahikian-Nelms M, Roberts K, Gemma S, Shaikhkhalil A. The prevalence of aberrations in body composition in pediatric cystic fibrosis patients and relationships with pulmonary function, bone mineral density, and hospitalizations. Journal of Cystic Fibrosis. 2021;20(5):837-842. doi:**10.1016/j.jcf.2021.04.004**

223 Martínez-García M del M, Rodríguez-Juan JJ, Ruiz-Cárdenas JD. Influence of sex gap on muscle strength and functional mobility in patients with cystic fibrosis. Applied Physiology, Nutrition, and Metabolism. 2020;45(4):387-392. doi:**10.1139/apnm-2019-0484**

224 Gibson HT, McDonald CM, Derrick JW, Eggett DL, Bellini SG. Evaluating Changes in Handgrip Strength in Children With Cystic Fibrosis: A Pilot Study. Nutrition in Clinical Practice. 2018;33(2):261-267. doi:**10.1002/ncp.10067**

225 Contreras-Bolívar V, Olveira C, Ruiz-García I, et al. Handgrip Strength: Associations with Clinical Variables, Body Composition, and Bone Mineral Density in Adults with Cystic Fibrosis. Nutrients. 2021;13(11):4107. doi:**10.3390/nu13114107**

226 Boat T, Hente E, Hardie W, et al. Body composition and functional correlates of CF youth experiencing pulmonary exacerbation and recovery. Pediatr Pulmonol. 2023;58(2):457-464. doi:**10.1002/ppul.26207**

227 Kocaaga E, Inal-Ince D, Dogru D, et al. Exercise performance in children and adolescents with cystic fibrosis with and without abnormal glucose tolerance: a single center cross-sectional study. Physiother Theory Pract. 2024;40(2):230-240. doi:**10.1080/09593985.2022.2116300**

228 Sánchez-Torralvo FJ, Porras N, Ruiz-García I, et al. Usefulness of Muscle Ultrasonography in the Nutritional Assessment of Adult Patients with Cystic Fibrosis. Nutrients. 2022;14(16):3377. doi:**10.3390/nu14163377**

229 Donadio MVF, Cobo-Vicente F, San Juan AF, et al. Is exercise and electrostimulation effective in improving muscle strength and cardiorespiratory fitness in children with cystic fibrosis and mild-to-moderate pulmonary impairment?: Randomized controlled trial. Respir Med. 2022;196:106798. doi:**10.1016/j.rmed.2022.106798**

230 Bellini SG, Chapman P, Szendre K, et al. Changes in handgrip strength in children with cystic fibrosis compared to children without cystic fibrosis. Clin Nutr ESPEN. 2021;42:206-211. doi:**10.1016/j.clnesp.2021.01.038**

231 Wilschanski M, Munck A, Carrion E, et al. ESPEN-ESPGHAN-ECFS guideline on nutrition care for cystic fibrosis. Clinical Nutrition. 2024;43(2):413-445. doi:**10.1016/j.clnu.2023.12.017**

232 Troosters T, Langer D, Vrijsen B, et al. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. European Respiratory Journal. 2009;33(1):99-106. doi:**10.1183/09031936.00091607**

233 Machado Rodrigues F, Demeyer H, Hornikx M, et al. Validity and reliability of strain gauge measurement of volitional quadriceps force in patients with COPD. Chron Respir Dis. 2017;14(3):289-297. doi:**10.1177/1479972316687210**

234 Gruet M, Vallier JM, Mely L, Brisswalter J. Long term reliability of EMG measurements in adults with cystic fibrosis. Journal of Electromyography and Kinesiology. 2010;20(2):305-312. doi:**10.1016/j.jelekin.2009.05.001**

235 Gruet M, Decorte N, Mely L, et al. Skeletal muscle contractility and fatigability in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2016;15(1):e1-e8. doi:**10.1016/j.jcf.2015.05.004**

236 Dassios T. Determinants of respiratory pump function in patients with cystic fibrosis. Paediatr Respir Rev. 2015;16(1):75-79. doi:**10.1016/j.prrv.2014.01.001**

237 Dekerlegand R, Hadjiliadis D, Swisher A, Parrott J, Heuer A, Myslinski M. Clinical predictors of inspiratory muscle strength in adults with stable cystic fibrosis: a pilot study. Cardiopulm Phys Ther J. 2017;28(4):136-146.

238 Heinzmann-Filho JP, Marostica PJC, Donadio MVF. Ventilatory muscle strength in cystic fibrosis patients: a literature review. Monaldi Archives for Chest Disease. 2015;77(3-4). doi:**10.4081/monaldi.2012.147**

239 Aris RM, Renner JB, Winders AD, et al. Increased Rate of Fractures and Severe Kyphosis: Sequelae of Living into Adulthood with Cystic Fibrosis. Ann Intern Med. 1998;128(3):186-193. doi:**10.7326/0003-4819-128-3-199802010-00004**

240 Denton JR, Tietjen R, Gaerlan PF. Thoracic kyphosis in cystic fibrosis. Clin Orthop Relat Res. 1981;(155):71-74.

241 Hart N, Polkey MI, Clément A, et al. Changes in Pulmonary Mechanics with Increasing Disease Severity in Children and Young Adults with Cystic Fibrosis. Am J Respir Crit Care Med. 2002;166(1):61-66. doi:**10.1164/rccm.2112059**

242 Gruet M, Troosters T, Verges S. Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical implications and response to therapeutic interventions. Journal of Cystic Fibrosis. 2017;16(5):538-552. doi:**10.1016/j.jcf.2017.02.007**

243 Higgins LW, Robertson RJ, Kelsey SF, et al. Exercise intensity self-regulation using the OMNI scale in children with cystic fibrosis. Pediatr Pulmonol. 2013;48(5):497-505. doi:**10.1002/ppul.22639**

244 Pianosi PT, Huebner M, Zhang Z, McGrath PJ. Dalhousie Dyspnea and Perceived Exertion Scales: Psychophysical properties in children and adolescents. Respir Physiol Neurobiol. 2014;199:34-40. doi:**10.1016/j.resp.2014.04.003**

245 McGrath PJ, Pianosi PT, Unruh AM, Buckley CP. Dalhousie dyspnea scales: construct and content validity of pictorial scales for measuring dyspnea. BMC Pediatr. 2005;5(1):33. doi:**10.1186/1471-2431-5-33**

246 Urquhart DS, Vendrusculo FM. Clinical interpretation of cardiopulmonary exercise testing in cystic fibrosis and implications for exercise counselling. Paediatr Respir Rev. 2017;24:72-78. doi:**10.1016/j.prrv.2015.09.009**

247 Wilson LM, Ellis MJ, Lane RL, et al. Development of the A-STEP: A new incremental maximal exercise capacity step test in cystic fibrosis. Pediatr Pulmonol. 2021;56(12):3777-3784. doi:**10.1002/ppul.25667**

248 Shelley J, Fairclough SJ, Knowles ZR, et al. A formative study exploring perceptions of physical activity and physical activity monitoring among children and young people with cystic fibrosis and health care professionals. BMC Pediatr. 2018;18(1):335. doi:**10.1186/s12887-018-1301-x**

249 Shelley J, Boddy LM, Knowles ZR, Stewart CE, Dawson EA. Physical activity and associations with clinical outcome measures in adults with cystic fibrosis; a systematic review. Journal of Cystic Fibrosis. 2019;18(5):590-601. doi:**10.1016/j.jcf.2019.03.003**

250 Williams CA, Barker AR, Denford S, et al. The Exeter Activity Unlimited statement on physical activity and exercise for cystic fibrosis: methodology and results of an international, multidisciplinary, evidence-driven expert consensus. Chron Respir Dis. 2022;19. doi:**10.1177/14799731221121670**

251 Bradley J, O'Neill B, Kent L, et al. Physical activity assessment in cystic fibrosis: A position statement. Journal of Cystic Fibrosis. 2015;14(6):e25-e32. doi:**10.1016/j.jcf.2015.05.011**

252 Gruet M, Saynor ZL, Urquhart DS, Radtke T. Rethinking physical exercise training in the modern era of cystic fibrosis: A step towards optimising short-term efficacy and long-term engagement. Journal of Cystic Fibrosis. 2022;21(2):e83-e98. doi:**10.1016/j.jcf.2021.08.004**

253 Radtke T, Smith S, Nevitt SJ, Hebestreit H, Kriemler S. Physical activity and exercise training in cystic fibrosis. Cochrane Database of Systematic Reviews. 2022;2022(8). doi:**10.1002/14651858.CD002768.pub5**

254 Swisher AK, Hebestreit H, Mejia-Downs A, et al. Exercise and Habitual Physical Activity for People With Cystic Fibrosis. Cardiopulm Phys Ther J. 2015;26(4):85-98. doi:**10.1097/CPT.0000000000000016**

255 Kenis-Coskun O, Karadag-Saygi E, Bahar-Ozdemir Y, Gokdemir Y, Karadag B, Kayhan O. The involvement of musculoskeletal system and its influence on postural stability in children and young adults with cystic fibrosis. Ital J Pediatr. 2017;43(1):106. doi:**10.1186/s13052-017-0426-0**

256 Ozipek M, Arikan H, Calik-Kutukcu E, et al. Deviations of body functions and structure, activity limitations, and participation restrictions of the International Classification of Functioning, Disability, and Health model in children with cystic fibrosis and non–cystic fibrosis bronchiectasis. Pediatr Pulmonol. 2020;55(5):1207-1216. doi:**10.1002/ppul.24708**

257 Godfrey S, Mearns M. Pulmonary Function and Response to Exercise in Cystic Fibrosis. Arch Dis Child. 1971;46(246):144-151. doi:**10.1136/adc.46.246.144**

258 Stein R, Selvadurai H, Coates A, Wilkes DL, Schneiderman-Walker J, Corey M. Determination of maximal voluntary ventilation in children with cystic fibrosis. Pediatr Pulmonol. 2003;35(6):467-471. doi:**10.1002/ppul.10298**

259 Moser C, Tirakitsoontorn P, Nussbaum E, Newcomb R, Cooper DM. Muscle Size and Cardiorespiratory Response to Exercise in Cystic Fibrosis. Am J Respir Crit Care Med. 2000;162(5):1823-1827. doi:**10.1164/ajrccm.162.5.2003057**

260 de Meer K, Gulmans VAM, van der Laag J. Peripheral Muscle Weakness and Exercise Capacity in Children with Cystic Fibrosis. Am J Respir Crit Care Med. 1999;159(3):748-754. doi:**10.1164/ajrccm.159.3.9802112**

261 Selvadurai HC, Allen J, Sachinwalla T, Macauley J, Blimkie CJ, Van Asperen PP. Muscle Function and Resting Energy Expenditure in Female Athletes with Cystic Fibrosis. Am J Respir Crit Care Med. 2003;168(12):1476-1480. doi:**10.1164/rccm.200303-363OC**

262 Arikan H, Yatar İ, Calik-Kutukcu E, et al. A comparison of respiratory and peripheral muscle strength, functional exercise capacity, activities of daily living and physical fitness in patients with cystic fibrosis and healthy subjects. Res Dev Disabil. 2015;45-46:147-156. doi:**10.1016/j.ridd.2015.07.020**

263 Erickson ML, Seigler N, McKie KT, McCully KK, Harris RA. Skeletal muscle oxidative capacity in patients with cystic fibrosis. Exp Physiol. 2015;100(5):545-552. doi:**10.1113/EP085037**

264 Lamhonwah A, Bear CE, Huan LJ, Chiaw PK, Ackerley CA, Tein I. Cystic fibrosis transmembrane conductance regulator in human muscle: Dysfunction causes abnormal metabolic recovery in exercise. Ann Neurol. 2010;67(6):802-808. doi:**10.1002/ana.21982**

265 Wells GD, Wilkes DL, Schneiderman JE, et al. Skeletal Muscle Metabolism in Cystic Fibrosis and Primary Ciliary Dyskinesia. Pediatr Res. 2011;69(1):40-45. doi:**10.1203/PDR.0b013e3181fff35f**

266 Divangahi M, Balghi H, Danialou G, et al. Lack of CFTR in Skeletal Muscle Predisposes to Muscle Wasting and Diaphragm Muscle Pump Failure in Cystic Fibrosis Mice. PLoS Genet. 2009;5(7):e1000586. doi:**10.1371/journal.pgen.1000586**

267 Tousson A, Van Tine BA, Naren AP, Shaw GM, Schwiebert LM. Characterization of CFTR expression and chloride channel activity in human endothelia. American Journal of Physiology-Cell Physiology. 1998;275(6):C1555-C1564. doi:**10.1152/ajpcell.1998.275.6.C1555**

268 Poore S, Berry B, Eidson D, McKie KT, Harris RA. Evidence of Vascular Endothelial Dysfunction in Young Patients With Cystic Fibrosis. Chest. 2013;143(4):939-945. doi:**10.1378/chest.12-1934**

269 Rodriguez-Miguelez P, Thomas J, Seigler N, et al. Evidence of microvascular dysfunction in patients with cystic fibrosis. Am J Physiol Heart Circ Physiol. 2016;310(11):H1479-85. doi:**10.1152/ajpheart.00136.2016**

270 Giacchi V, Rotolo N, Amato B, et al. Heart Involvement in Children and Adults with Cystic Fibrosis: Correlation with Pulmonary Indexes and Inflammation Markers. Heart Lung Circ. 2015;24(10):1002-1010. doi:**10.1016/j.hlc.2015.03.006**

271 Sellers ZM, De Arcangelis V, Xiang Y, Best PM. Cardiomyocytes with disrupted CFTR function require CaMKII and Ca^{2+} -activated Cl – channel activity to maintain contraction rate. J Physiol. 2010;588(13):2417-2429. doi:**10.1113/jphysiol.2010.188334**

272 Hebestreit H, Kieser S, Rüdiger S, et al. Physical activity is independently related to aerobic capacity in cystic fibrosis. European Respiratory Journal. 2006;28(4):734-739. doi:**10.1183/09031936.06.00128605**

273 Moorcroft AJ, Dodd ME, Webb AK. Exercise testing and prognosis in adult cystic fibrosis. Thorax. 1997;52(3):291-293. doi:**10.1136/thx.52.3.291**

274 Beaudoin N, Bouvet GF, Coriati A, Rabasa-Lhoret R, Berthiaume Y. Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis. Med Sci Sports Exerc. 2017;49(2):231-237. doi:**10.1249/MSS.0000000000001104**

275 Buntain HM, Greer RM, Schluter PJ, et al. Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. Thorax. 2004;59(2):149-155. doi:**10.1136/thorax.2003.006726**

276 Hind K, Truscott JG, Conway SP. Exercise during childhood and adolescence: A prophylaxis against cystic fibrosis-related low bone mineral density? Journal of Cystic Fibrosis. 2008;7(4):270-276. doi:**10.1016/j.jcf.2008.02.001**

277 Schneiderman-Walker J, Pollock SL, Corey M, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. J Pediatr. 2000;136(3):304-310. doi:**10.1067/mpd.2000.103408**

278 Kriemler S, Kieser S, Junge S, et al. Effect of supervised training on FEV1 in cystic fibrosis: A randomised controlled trial. Journal of Cystic Fibrosis. 2013;12(6):714-720. doi:**10.1016/j.jcf.2013.03.003**

279 Hebestreit H, Kieser S, Junge S, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. European Respiratory Journal. 2010;35(3):578-583. doi:**10.1183/09031936.00062409**

280 Klijn PHC, Oudshoorn A, van der Ent CK, van der Net J, Kimpen JL, Helders PJM. Effects of Anaerobic Training in Children With Cystic Fibrosis. Chest. 2004;125(4):1299-1305. doi:**10.1378/chest.125.4.1299**

281 Urquhart D, Sell Z, Dhouieb E, et al. Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis. Pediatr Pulmonol. 2012;47(12):1235-1241. doi:**10.1002/ppul.22587**

282 Dwyer TJ, Zainuldin R, Daviskas E, Bye PTP, Alison JA. Effects of treadmill exercise versus Flutter® on respiratory flow and sputum properties in adults with cystic fibrosis: a randomised, controlled, cross-over trial. BMC Pulm Med. 2017;17(1):14. doi:**10.1186/s12890-016-0360-8**

283 Shoemaker MJ, Hurt H, Arndt L. The evidence regarding exercise training in the management of cystic fibrosis: a systematic review. Cardiopulm Phys Ther J. 2008;19(3):75-83.

284 Rand S, Prasad SA. Exercise as part of a cystic fibrosis therapeutic routine. Expert Rev Respir Med. 2012;6(3):341-352. doi:**10.1586/ers.12.19**

285 Ruf K, Winkler B, Hebestreit A, Gruber W, Hebestreit H. Risks associated with exercise testing and sports participation in cystic fibrosis. Journal of Cystic Fibrosis. 2010;9(5):339-345. doi:**10.1016/j.jcf.2010.05.006**

286 Webb AK, Dodd ME. Exercise and sport in cystic fibrosis: benefits and risks. Br J Sports Med. 1999;33(2):77-78.

287 Speechly-Dick ME, Rimmer SJ, Hodson ME. Exacerbations of cystic fibrosis after holidays at high altitude — a cautionary tale. Respir Med. 1992;86(1):55-56. doi:**10.1016/S0954-6111(06)80150-2**

288 Putman MS, Anabtawi A, Le T, Tangpricha V, Sermet-Gaudelus I. Cystic fibrosis bone disease treatment: Current knowledge and future directions. Journal of Cystic Fibrosis. 2019;18:S56-S65. doi:**10.1016/j.jcf.2019.08.017**

289 Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic Fibrosis Adult Care. Chest. 2004;125(1):1S-39S. doi:**10.1378/chest.125.1_suppl.1S**

290 Burtin C, Hebestreit H. Rehabilitation in Patients with Chronic Respiratory Disease Other than Chronic Obstructive Pulmonary Disease: Exercise and Physical Activity Interventions in Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis. 2015;89(3):181-189. doi:**10.1159/000375170**

291 Lima CA, de Andrade A de FD, Campos SL, et al. Effects of noninvasive ventilation on treadmill 6-min walk distance and regional chest wall volumes in cystic fibrosis: Randomized controlled trial. Respir Med. 2014;108(10):1460-1468. doi:**10.1016/j.rmed.2014.04.006**

292 Bellini R, Cazzarolli C. Non-invasive ventilation during exercise in severe cystic fibrosis subjects: a preliminary study. In: Cystic Fibrosis. European Respiratory Society; 2018:PA1318. doi:**10.1183/13993003.congress-2018.PA1318**

293 Lloyd RS, Faigenbaum AD, Stone MH, et al. Position statement on youth resistance training: the 2014 International Consensus. Br J Sports Med. 2014;48(7):498-505. doi:**10.1136/bjsports-2013-092952**

294 Ruddy J, Emerson J, Mcnamara S, et al. Yoga as a Therapy for Adolescents and Young Adults with Cystic Fibrosis: A Pilot Study. Glob Adv Health Med. 2015;4(6):32-36. doi:**10.7453/gahmj.2015.061**

295 Russell S. Yoga Improves Posture and Physical Performance in Adult Persons with Cystic Fibrosis. 2014.

296 McNamara C, Johnson M, Read L, et al. Yoga Therapy in Children with Cystic Fibrosis Decreases Immediate Anxiety and Joint Pain. Evidence-Based Complementary and Alternative Medicine. 2016;2016(1). doi:**10.1155/2016/9429504**

297 Denford S, Mackintosh KA, McNarry MA, Barker AR, Williams CA. Promotion of physical activity for adolescents with cystic fibrosis: a qualitative study of UK multi disciplinary cystic fibrosis teams. Physiotherapy. 2020;106:111-118. doi:**10.1016/j.physio.2019.01.012**

298 Lorenc AB, Wang Y, Madge SL, Hu X, Mian AM, Robinson N. Meditative Movement for Respiratory Function: A Systematic Review. Respir Care. 2014;59(3):427-440. doi:10.4187/respcare.02570

299 Carr SB, Ronan P, Lorenc A, Mian A, Madge SL, Robinson N. Children and Adults Tai Chi Study (CF-CATS2): a randomised controlled feasibility study comparing internet-delivered with face-to-face Tai Chi lessons in cystic fibrosis. ERJ Open Res. 2018;4(4):00042-02018. doi:**10.1183/23120541.00042-2018**

300 Goetz DM, Frederick CK, Perez G, Borowitz D. Airway clearance after highly effective CFTR modulators: Normalizing life and reducing treatment burden. Pediatr Pulmonol. 2023;58(8):2375-2380. doi:**10.1002/ppul.26502**

301 Kienenberger ZE, Farber TO, Teresi ME, et al. Patient and Caregiver Perceptions of Airway Clearance Methods Used for Cystic Fibrosis. Can Respir J. 2023;2023:1-9. doi:**10.1155/2023/1422319**

302 Willis LD. Comparison of Airway Clearance Therapies for Cystic Fibrosis: A Cochrane Review Summary With Commentary. Respir Care. 2022;67(7):889-892. doi:**10.4187/respcare.10050**

303 Bolton M. 268 Evaluation of the Aerobika® OPEP therapy combined with the hypertonic saline through the breath actuated AeroEclipse® nebuliser as a physiotherapy treatment for adolescents with cystic fibrosis. Journal of Cystic Fibrosis. 2017;16:S130. doi:**10.1016/S1569-1993(17)30608-2**

304 McIlwaine MP, Lee Son NM, Richmond ML. Physiotherapy and cystic fibrosis: what is the evidence base? Curr Opin Pulm Med. 2014;20(6):613-617. doi:**10.1097/MCP.0000000000000110**

305 International Physiotherapy Group for Cystic Fibrosis. Physiotherapy for People with Cystic Fibrosis: From Infant to Adult (Seventh Edition). 2019. Available at: ecfs.eu/sites/default/files/general-content-files/working-groups/IPG%20CF_Blue%20Booklet_7th%20edition%202019.pdf

306 Webber BA. The Brompton Hospital Guide to Chest Physiotherapy. 5th ed. Blackwell Scientific; 1988.

307 Webber B. The Active Cycle of Breathing Exercises. 1990.

308 Daniels T. Physiotherapeutic management strategies for the treatment of cystic fibrosis in adults. J Multidiscip Healthc. 2010;3:201-212. doi:**10.2147/JMDH.S8878**

309 Webber B. Is Postural Drainage Necessary? Proceedings of the 10th International Cystic Fibrosis Congress, Sydney, Australia. Excerpta Medica, Asia Pacific Congress Series. 1988;74(29).

310 Partridge C, Pryor J, Webber B. Characteristics of the Forced Expiration Technique. Physiotherapy. 1989;75(3):193-194. doi:**10.1016/S0031-9406(10)62805-2**

311 van der Schans CP. Forced expiratory manoeuvres to increase transport of bronchial mucus: a mechanistic approach. Monaldi Arch Chest Dis. 1997;52(4):367-370.

312 McIlwaine M. Chest physical therapy, breathing techniques and exercise in children with CF. Paediatr Respir Rev. 2007;8(1):8-16. doi:**10.1016/j.prrv.2007.02.013**

313 Osman LP, Roughton M, Hodson ME, Pryor JA. Short-term comparative study of high frequency chest wall oscillation and European airway clearance techniques in patients with cystic fibrosis. Thorax. 2010;65(3):196-200. doi:**10.1136/thx.2008.111492**

314 Pryor JA, Webber BA, Hodson ME, Batten JC. Evaluation of the forced expiration technique as an adjunct to postural drainage in treatment of cystic fibrosis. Br Med J. 1979;2(6187):417-418. doi:**10.1136/bmj.2.6187.417**

315 Pryor JA, Webber BA, Hodson ME, Warner JO. The Flutter VRP1 as an adjunct to chest physiotherapy in cystic fibrosis. Respir Med. 1994;88(9):677-681. doi:**10.1016/S0954-6111(05)80066-6**

316 Pike S. 125. Comparison of flutter VRP1 and forced expirations (FE) with active cycle of breathing techniques (ACBT) in subjects with cystic fibrosis (CF). Neth J Med. 1999;54:S55-S56. doi:**10.1016/S0300-2977(99)90177-8**

317 Hofmeyr JL, Webber BA, Hodson ME. Evaluation of positive expiratory pressure as an adjunct to chest physiotherapy in the treatment of cystic fibrosis. Thorax. 1986;41(12):951-954. doi:**10.1136/thx.41.12.951**

318 Pisi G, Chetta A. Airway clearance therapy in cystic fibrosis patients. Acta Biomed. 2009;80(2):102-106.

319 Webber BA, Hofmeyr JL, Morgan MDL, Hodson ME. Effects of postural drainage, incorporating the forced expiration technique, on pulmonary function in cystic fibrosis. Br J Dis Chest. 1986;80:353-359. doi:**10.1016/0007-0971(86)90088-4**

320 Schöni MH. Autogenic drainage: a modern approach to physiotherapy in cystic fibrosis. J R Soc Med. 1989;82 Suppl 16(Suppl 16):32-37.

321 Agostini P, Knowles N. Autogenic drainage: the technique, physiological basis and evidence. Physiotherapy. 2007;93(2):157-163. doi:**10.1016/j.physio.2006.07.005**

322 Swisher A, von Berg K. Commentary on "Autogenic Drainage in Children with Cystic Fibrosis." Pediatr Phys Ther. 2017;29(2):117.

323 Cystic Fibrosis Trust. Airway Clearance for Babies and Young Children with Cystic Fibrosis. 2021. Available at: cysticfibrosis.org.uk/sites/default/files/2021-03/INF18-J%20-%20Airway_clearance_for_babies_young_children_v3_web.pdf

324 Van Ginderdeuren F, Vandenplas Y, Deneyer M, Vanlaethem S, Buyl R, Kerckhofs E. Influence of bouncing and assisted autogenic drainage on acid gastro-oesophageal reflux in infants. Pediatr Pulmonol. 2017;52(8):1057-1062. doi:**10.1002/ppul.23677**

325 McCormack P, Burnham P, Southern KW. A systematic Cochrane Review of autogenic drainage (AD) for airway clearance in cystic fibrosis. Paediatr Respir Rev. 2019;29:23-24. doi:**10.1016/j.prrv.2018.06.002**

326 McCormack P, Burnham P, Southern KW. Autogenic drainage for airway clearance in cystic fibrosis. Cochrane Database of Systematic Reviews. 2017;2017(10). doi:**10.1002/14651858.CD009595.pub2**

327 Pfleger A, Theissl B, Oberwaldner B, Zach MaximilianS. Self-administered chest physiotherapy in cystic fibrosis: A comparative study of high-pressure pep and autogenic drainage. Lung. 1992;170(6). doi:**10.1007/BF00177578**

328 App EM, Kieselmann R, Reinhardt D, et al. Sputum Rheology Changes in Cystic Fibrosis Lung Disease Following Two Different Types of Physiotherapy. Chest. 1998;114(1):171-177. doi:**10.1378/chest.114.1.171**

329 Żak M, Gauchez H, Boberski M, Stangret A, Kempinska-Podhorodecka A. Effectiveness of Autogenic Drainage in Improving Pulmonary Function in Patients with Cystic Fibrosis. Int J Environ Res Public Health. 2023;20(5):3822. doi:**10.3390/ijerph20053822**

330 McIlwaine M, Bradley J, Elborn JS, Moran F. Personalising airway clearance in chronic lung disease. European Respiratory Review. 2017;26(143):160086. doi:**10.1183/16000617.0086-2016**

331 West K, Wallen M, Follett J. Acapella vs. PEP mask therapy: A randomised trial in children with cystic fibrosis during respiratory exacerbation. Physiother Theory Pract. 2010;26(3):143-149. doi:**10.3109/09593980903015268**

332 Prasad S, Hussey J, Campling J. Paediatric Respiratory Care; a Guide for Physiotherapists and Health Professionals. Springer Science + Business Media; 1995.

333 Christensen EF, Jensen RH, Schønemann NK, Petersen KD. Flow-dependent properties of positive expiratory pressure devices. Monaldi Arch Chest Dis. 1995;50(2):150-153.

334 Darbee JC, Ohtake PJ, Grant BJB, Cerny FJ. Physiologic evidence for the efficacy of positive expiratory pressure as an airway clearance technique in patients with cystic fibrosis. Phys Ther. 2004;84(6):524-537.

335 Braggion C, Cappelletti LM, Cornacchia M, Zanolla L, Mastella G. Short-term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: A cross-over randomized study. Pediatr Pulmonol. 1995;19(1):16-22. doi:**10.1002/ppul.1950190104**

336 van Winden C, Visser A, Hop W, Sterk P, Beckers S, de Jongste J. Effects of flutter and PEP mask physiotherapy on symptoms and lung function in children with cystic fibrosis. European Respiratory Journal. 1998;12(1):143-147. doi:**10.1183/09031936.98.12010143**

337 McIlwaine PM, Wong LT, Peacock D, Davidson AGF. Long-term comparative trial of positive expiratory pressure versus oscillating positive expiratory pressure (flutter) physiotherapy in the treatment of cystic fibrosis. J Pediatr. 2001;138(6):845-850. doi:**10.1067/mpd.2001.114017**

338 McIlwaine PM, Wong LT, Peacock D, Davidson AGF. Long-term comparative trial of conventional postural drainage and percussion versus positive expiratory pressure physiotherapy in the treatment of cystic fibrosis. J Pediatr. 1997;131(4):570-574. doi:**10.1016/S0022-3476(97)70064-7**

339 Orlik T, Wyka-Wojeńska A. The role of positive expiratory pressure (PEP) in physiotherapy of patients with cystic fibrosis. Comparison with oscillating positive expiratory pressure (OPEP). Advances in Rehabilitation. 2018;32(1):39-45. doi:**10.5114/areh.2018.76989**

340 Elkins M, Jones A, van der Schans CP. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. In: Elkins M, ed. Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2006. doi:**10.1002/14651858.CD003147.pub3**

341 Pryor J, Prasad N. Physiotherapy for Respiratory and Cardiac Problems: Adults and Paediatrics (Physiotherapy Essentials). 3rd edition. Churchill Livingston; 2002.

342 Zach MS, Oberwaldner B. Effect of positive expiratory pressure breathing in patients with cystic fibrosis. Thorax. 1992;47(1):66-67. doi:**10.1136/thx.47.1.66-b**

343 Oberwaldner B, Evans JC, Zach MS. Forced expirations against a variable resistance: A new chest physiotherapy method in cystic fibrosis. Pediatr Pulmonol. 1986;2(6):358-367. doi:**10.1002/ppul.1950020608**

344 Mestriner RG, Fernandes RO, Steffen LC, Donadio MVF. Optimum design parameters for a therapist-constructed positive-expiratory-pressure therapy bottle device. Respir Care. 2009;54(4):504-508.

345 Santos MD, Milross MA, Eisenhuth JP, Alison JA. Pressures and Oscillation Frequencies Generated by Bubble-Positive Expiratory Pressure Devices. Respir Care. 2017;62(4):444-450. doi:**10.4187/respcare.05164**

346 Rogers D, Doull IJM. Physiological principles of airway clearance techniques used in the physiotherapy management of cystic fibrosis. Current Paediatrics. 2005;15(3):233-238. doi:**10.1016/j.cupe.2005.02.007**

347 Konstan MW, Stern RC, Doershuk CF. Efficacy of the Flutter device for airway mucus clearance in patients with cystic fibrosis. J Pediatr. 1994;124(5):689-693. doi:**10.1016/S0022-3476(05)81356-3**

348 Pryor J. Physiotherapy for airway clearance in adults. European Respiratory Journal. 1999;14(6):1418-1424. doi:**10.1183/09031936.99.14614189**

349 Volsko TA, DiFiore J, Chatburn RL. Performance comparison of two oscillating positive expiratory pressure devices: Acapella versus Flutter. Respir Care. 2003;48(2):124-130.

350 Smiths Medical. Acapella® Vibratory PEP Therapy System: Maximizing Therapy Effectiveness, Empowering Patient Compliance. 2016. Available at: **vitalitymedical.com/pub/pdf/product-brochure-pep.pdf**

351 Morrison L, Milroy S. Oscillating devices for airway clearance in people with cystic fibrosis. Cochrane Database of Systematic Reviews. Published online May 4, 2017. doi:**10.1002/14651858.CD006842.pub4**

352 Wilson A. Oscillating devices for airway clearance in people with cystic fibrosis: A Cochrane review summary. Int J Nurs Stud. 2018;88:165-166. doi:**10.1016/j.ijnurstu.2018.02.007**

353 Van Fleet H, Dunn DK, McNinch NL, Volsko TA. Evaluation of Functional Characteristics of 4 Oscillatory Positive Pressure Devices in a Simulated Cystic Fibrosis Model. Respir Care. 2017;62(4):451-458. doi:**10.4187/respcare.04570**

354 Coppolo DP, Schloss J, Suggett JA, Mitchell JP. Non-Pharmaceutical Techniques for Obstructive Airway Clearance Focusing on the Role of Oscillating Positive Expiratory Pressure (OPEP): A Narrative Review. Pulm Ther. 2022;8(1):1-41. doi:**10.1007/s41030-021-00178-1**

355 Warwick WJ, Hansen LG. The long-term effect of high-frequency chest compression therapy on pulmonary complications of cystic fibrosis. Pediatr Pulmonol. 1991;11(3):265-271. doi:**10.1002/ppul.1950110314**

356 McIlwaine M, Button B, Dwan K. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database of Systematic Reviews. Published online June 17, 2015. doi:**10.1002/14651858.CD003147.pub4**

357 Scherer TA, Barandun J, Martinez E, Wanner A, Rubin EM. Effect of High-Frequency Oral Airway and Chest Wall Oscillation and Conventional Chest Physical Therapy on Expectoration in Patients With Stable Cystic Fibrosis. Chest. 1998;113(4):1019-1027. doi:**10.1378/chest.113.4.1019**

358 Fainardi V, Longo F, Faverzani S, Tripodi MC, Chetta A, Pisi G. Short-term effects of high-frequency chest compression and positive expiratory pressure in patients with cystic fibrosis. J Clin Med Res. 2011;3(6):279-284. doi:**10.4021/jocmr697w**

359 Arens R, Gozal D, Omlin KJ, et al. Comparison of high frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. Am J Respir Crit Care Med. 1994;150(4):1154-1157. doi:**10.1164/ajrccm.150.4.7921452**

360 Phillips GE, Pike SE, Jaffé A, Bush A. Comparison of active cycle of breathing and high-frequency oscillation jacket in children with cystic fibrosis. Pediatr Pulmonol. 2004;37(1):71-75. doi:**10.1002/ppul.10358**

361 Varekojis SM, Douce FH, Flucke RL, et al. A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. Respir Care. 2003;48(1):24-28.

362 Warwick WJ, Wielinski CL, Hansen LG. Comparison of expectorated sputum after manual chest physical therapy and high-frequency chest compression. Biomed Instrum Technol. 2004;38(6):470-475. doi:**10.2345/0899-8205(2004)38[470:COESAM]2.0.CO;2**

363 Darbee JC, Kanga JF, Ohtake PJ. Physiologic evidence for high-frequency chest wall oscillation and positive expiratory pressure breathing in hospitalized subjects with cystic fibrosis. Phys Ther. 2005;85(12):1278-1289.

364 Oermann CM, Sockrider MM, Giles D, Sontag MK, Accurso FJ, Castile RG. Comparison of high-frequency chest wall oscillation and oscillating positive expiratory pressure in the home management of cystic fibrosis: A pilot study*. Pediatr Pulmonol. 2001;32(5):372-377. doi:**10.1002/ppul.1146**

365 Tecklin JS, Scanlin T, Clayton RG. High Frequency Chest Wall Oscillation vs. Traditional Postural Drainage with Percussion and Vibration in Cystic Fibrosis – a Large, Long-term, Controlled Study. Journal of the Israeli Physical Therapy Society. 2009;11(3):26.

366 Banks A, Davies G, Agent P, Osman L, Bilton D, Hodson M. The use of high frequency chest wall oscillation during an acute infective pulmonary exacerbation of cystic fibrosis. European Respiratory Journal. 2012;40(Suppl 56):P3374. Available at: **publications.ersnet.org//content/40/Suppl_56/P3374.abstract**

367 Stites SW, Perry G V., Peddicord T, Cox G, McMillan C, Becker B. Effect of High-Frequency Chest Wall Oscillation on the Central and Peripheral Distribution of Aerosolized Diethylene Triamine Penta-acetic Acid as Compared to Standard Chest Physiotherapy in Cystic Fibrosis. Chest. 2006;129(3):712-717. doi:**10.1378/chest.129.3.712**

368 Oermann CM, Swank PR, Sockrider MM. Validation of an Instrument Measuring Patient Satisfaction With Chest Physiotherapy Techniques in Cystic Fibrosis. Chest. 2000;118(1):92-97. doi:**10.1378/chest.118.1.92**

369 Morrison L, Innes S. Oscillating devices for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev. 2017;5(5):CD006842. doi:**10.1002/14651858.CD006842.pub4**

370 West ME, Spielberg DR, Roach DJ, et al. Short-term structural and functional changes after airway clearance therapy in cystic fibrosis. Journal of Cystic Fibrosis. 2023;22(5):926-932. doi:**10.1016/j.jcf.2023.01.017**

371 Leemans G, Belmans D, Van Holsbeke C, et al. The effectiveness of a mobile high-frequency chest wall oscillation (HFCWO) device for airway clearance. Pediatr Pulmonol. 2020;55(8):1984-1992. doi:**10.1002/ppul.24784**

372 Mikesell CL, Kempainen RR, Laguna TA, et al. Objective Measurement of Adherence to Out-Patient Airway Clearance Therapy by High-Frequency Chest Wall Compression in Cystic Fibrosis. Respir Care. 2017;62(7):920-927. doi:**10.4187/respcare.05349**

373 Modi A, et al. Adherence to airway clearance therapies in patients with cystic fibrosis [abstract]. J Cyst Fibrosis. 2006;5:S97.

374 Newhouse PA, White F, Marks JH, Homnick DN. The Intrapulmonary Percussive Ventilator and Flutter Device Compared to Standard Chest Physiotherapy in Patients wit Cystic Fibrosis. Clin Pediatr (Phila). 1998;37(7):427-432. doi:**10.1177/000992289803700705**

375 Natale JE, Pfeifle J, Homnick DN. Comparison of Intrapulmonary Percussive Ventilation and Chest Physiotherapy. Chest. 1994;105(6):1789-1793. doi:**10.1378/chest.105.6.1789**

376 Homnick DN, White F, de Castro C. Comparison of effects of an intrapulmonary percussive ventilator to standard aerosol and chest physiotherapy in treatment of cystic fibrosis. Pediatr Pulmonol. 1995;20(1):50-55. doi:**10.1002/ppul.1950200110**

377 McInturff S, Shaw L, Hodgkin J, Rumble L, Bird F. Intrapulmonary percussive ventilation (IPV) in the treatment of COPD. Respir Care. 1985;30(10):885.

378 Marks JH, Hare KL, Saunders RA, Homnick DN. Pulmonary Function and Sputum Production in Patients With Cystic Fibrosis. Chest. 2004;125(4):1507-1511. doi:**10.1378/chest.125.4.1507**

379 Innocenti D, Castellani C, Masi E, Galici V, Macconi L, Taccetti G. Can percussive intrapulmonary ventilation improve the efficacy of physiotherapy in children with cystic fibrosis? Monaldi Archives for Chest Disease. Published online March 13, 2023. doi:**10.4081/monaldi.2023.2480**

380 Reychler G, Keyeux A, Cremers C, Veriter C, Rodenstein DO, Liistro G. Comparison of Lung Deposition in Two Types of Nebulization. Chest. 2004;125(2):502-508. doi:**10.1378/chest.125.2.502**

381 Reychler G, Wallemacq P, Rodenstein DO, Cumps J, Leal T, Liistro G. Comparison of Lung Deposition of Amikacin by Intrapulmonary Percussive Ventilation and Jet Nebulization by Urinary Monitoring. Journal of Aerosol Medicine. 2006;19(2):199-207. doi:**10.1089/jam.2006.19.199**

382 Nelson H. Postural drainage of the lungs. BMJ. 1934;2(3840):251-255. doi:**10.1136/bmj.2.3840.251**

383 Lorin MI, Denning CR. Evaluation of postural drainage by measurement of sputum volume and consistency. Am J Phys Med. 1971;50(5):215-219.

384 Cecins NM, Jenkins SC, Pengelley J, Ryan G. The active cycle of breathing techniques—to tip or not to tip? Respir Med. 1999;93(9):660-665. doi:**10.1016/S0954-6111(99)90107-5**

385 Murray JF. The Ketchup-Bottle Method. New England Journal of Medicine. 1979;300(20):1155-1157. doi:**10.1056/NEJM197905173002008**

386 Hardy K. A Review of Airway Clearance: New Techniques, Indications, and Recommendations. Respir Care. 1994;39(5):440-452.

387 Sutton PP, Lopez-Vidriero MT, Pavia D, Newman SP, Clarke SW. Effect of chest physiotherapy on the removal of mucus in patients with cystic fibrosis. Am Rev Respir Dis. 1983;127(3):390-391. doi:**10.1164/arrd.1983.127.3.390**

388 McCarren B, Alison JA, Herbert RD. Vibration and its effect on the respiratory system. Australian Journal of Physiotherapy. 2006;52(1):39-43. doi:**10.1016/S0004-9514(06)70060-5**

389 King M, Phillips DM, Gross D, Vartian V, Chang HK, Zidulka A. Enhanced Tracheal Mucus Clearance with High Frequency Chest Wall Compression. American Review of Respiratory Disease. 1983;128(3):511-515. doi:**10.1164/arrd.1983.128.3.511**

390 Reisman JJ, Rivington-Law B, Corey M, et al. Role of conventional physiotherapy in cystic fibrosis. J Pediatr. 1988;113(4):632-636. doi:**10.1016/S0022-3476(88)80370-6**

391 Thomas J, Cook DJ, Brooks D. Chest Physical Therapy Management of Patients with Cystic Fibrosis: A Meta-analysis. Am J Respir Crit Care Med. 1995;151(3_pt_1):846-850. doi:**10.1164/ajrccm/151.3_Pt_1.846**

392 Button B, Heine R, Catto-Smith A, Phelan P. Postural drainage in cystic fibrosis: Is there a link with gastro-oesophageal reflux? J Paediatr Child Health. 1998;34(4):330-334. doi:**10.1046/j.1440-1754.1998.00236.x**

393 Button BM, Heine RG, Catto-Smith AG, et al. Chest physiotherapy in infants with cystic fibrosis: To tip or not? A five-year study. Pediatr Pulmonol. 2003;35(3):208-213. doi:**10.1002/ppul.10227**

394 Button BM, Roberts S, Kotsimbos TC, et al. Gastroesophageal Reflux (Symptomatic and Silent): A Potentially Significant Problem in Patients With Cystic Fibrosis Before and After Lung Transplantation. The Journal of Heart and Lung Transplantation. 2005;24(10):1522-1529. doi:**10.1016/j.healun.2004.11.312**

395 Webber B, Pryor J. Physiotherapy skills: techniques and adjuncts. In: Physiotherapy for Respiratory and Cardiac Problems. Churchill Livingstone; 1993:113-172.

396 Bott J, Keilty SE, Noone L. Intermittent Positive Pressure Breathing A Dying Art? Physiotherapy. 1992;78(9):656-660. doi:**10.1016/S0031-9406(10)61571-4**

397 Sorenson HM, Shelledy DC, AARC. AARC clinical practice guideline. Intermittent positive pressure breathing--2003 revision & update. Respir Care. 2003;48(5):540-546.

398 Gates A, Faulkner J, Midwinter A, Flight WG. WS21.5 "Real world" use of intermittent positive pressure breathing in the acute management of adults with cystic fibrosis. Journal of Cystic Fibrosis. 2016;15:S34. doi:**10.1016/S1569-1993(16)30180-1**

399 Brown R, Giannoulatos K, Wadsworth LE. P214 A comparison of airway clearance devices in adult cystic fibrosis patients: NIPPY Clearway2 versus Intermittent Positive Pressure Breathing (IPPB). Journal of Cystic Fibrosis. 2022;21:S126. doi:**10.1016/S1569-1993(22)00543-4**

400 Sands D, Walicka-Serzysko K, Milczewska J, et al. Efficacy of the Simeox® Airway Clearance Technology in the Homecare Treatment of Children with Clinically Stable Cystic Fibrosis: A Randomized Controlled Trial. Children. 2023;10(2):204. doi:**10.3390/children10020204**

401 Physio Assist. Simeox User Manual. 2019. Available at: **physioassist.com/wp-content/uploads/2025/05/PhysioAssist-SIMEOX-User-manual-EN.pdf**

402 Hamidfar R, Murris-Espin M, Mahot M, et al. Feasibility of home initiation of an airway clearance device (SIMEOX) by telecare in people with non-cystic fibrosis bronchiectasis: a pilot study. BMJ Open Respir Res. 2023;10(1):e001722. doi:**10.1136/bmjresp-2023-001722**

403 Giovannetti P, Morin L, Reynaud-Gaubert M. Safety and Efficacy of an Innovative Airway Clearance Device Versus Manual Chest Physiotherapy Techniques For Airway Secretion Clearance: a Feasibility Study. European Journal of Respiratory Medicine. 2020;2(1). doi:**10.31488/ejrm.107**

404 Walicka-Serzysko K, Postek M, Milczewska J, et al. Late Breaking Abstract - Effects of a new airway clearance technology in children with cystic fibrosis - A homecare randomized controlled trial. In: Paediatric Cystic Fibrosis (CF). European Respiratory Society; 2021:PA3379. doi:**10.1183/13993003.congress-2021.PA3379**

405 Schmidt H, Toth M, Kappler-Schorn C, Siebeneich U, Bode SFN, Fabricius D. Short-term effects of a novel bronchial drainage device: A pilot cohort study in subjects with cystic fibrosis. Health Sci Rep. 2022;5(5). doi:**10.1002/hsr2.812**

406 Krajewska J, Zub K, Słowikowski A, Zatoński T. Chronic rhinosinusitis in cystic fibrosis: a review of therapeutic options. European Archives of Oto-Rhino-Laryngology. 2022;279(1):1-24. doi:**10.1007/s00405-021-06875-6**

407 Suy P, Coudert A, Vrielynck S, Truy E, Hermann R, Ayari-Khalfallah S. Evolution of sinonasal clinical features in children with cystic fibrosis. Int J Pediatr Otorhinolaryngol. 2019;124:47-53. doi:**10.1016/j.ijporl.2019.05.030**

408 Mulinda C, Yang N, Gudis DA. Pediatric Unified Airway. Otolaryngol Clin North Am. 2023;56(1):137-146. doi:**10.1016/j.otc.2022.09.010**

409 Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology journal. 2020;0(0):1-464. doi:**10.4193/Rhin20.600**

410 Kang SH, Meotti CD, Bombardelli K, Piltcher OB, de Tarso Roth Dalcin P. Sinonasal characteristics and quality of life by SNOT-22 in adult patients with cystic fibrosis. European Archives of Oto-Rhino-Laryngology. 2017;274(4):1873-1882. doi:**10.1007/s00405-016-4426-2**

411 Johnson BJ, Choby GW, O'Brien EK. Chronic rhinosinusitis in patients with cystic fibrosis—Current management and new treatments. Laryngoscope Investig Otolaryngol. 2020;5(3):368-374. doi:**10.1002/lio2.401**

412 Cystic Fibrosis Foundation. Patient Registry Annual Data Report. Published online 2023. Available at: **cff.org/medical-professionals/patient-registry**

413 Uyttebroek S, Dupont L, Jorissen M, Van Gerven L. Upper Airway Disease in Adults with Cystic Fibrosis in the Era of <scp>CFTR</scp> Modulators. Laryngoscope. 2023;133(11):2898-2909. doi:**10.1002/lary.30642**

414 Rafeey M, Jabbari Moghaddam Y, Rezaeeyan S. Sinonasal Manifestations in Children with Cystic Fibrosis. Iran J Pediatr. 2019;In Press(In Press). doi:**10.5812/ijp.66015**

415 Ferril GR, Nick JA, Getz AE, et al. Comparison of radiographic and clinical characteristics of low-risk and high-risk cystic fibrosis genotypes. Int Forum Allergy Rhinol. 2014;4(11):915-920. doi:**10.1002/alr.21412**

416 Halderman AA, Lee S, London NR, et al. Impact of high- versus low-risk genotype on sinonasal radiographic disease in cystic fibrosis. Laryngoscope. 2019;129(4):788-793. doi:**10.1002/lary.27595**

417 Degrugillier F, Simon S, Aissat A, et al. Unsolved severe chronic rhinosinusitis elucidated by extensive CFTR genotyping. Clin Case Rep. 2019;7(11):2128-2134. doi:**10.1002/ccr3.2443**

418 Mamat Nasir MSN, Aziz ME, Tuan Sharif SE, Ibrahim R, Abdullah B. Clinical symptoms of chronic rhinosinusitis with nasal polyps (eosinophilic and non-eosinophilic) are related to sinus computed tomography but not to endoscopic findings. Acta Otorrinolaringologica (English Edition). 2022;73(4):203-209. doi:**10.1016/j.otoeng.2021.03.004**

419 Beswick DM, Schlosser RJ. Chronic rhinosinusitis in people with Cystic Fibrosis: Expanding evidence and future directions. Journal of Cystic Fibrosis. 2022;21(5):737-738. doi:**10.1016/j.jcf.2022.07.016**

420 Wang C, Johnson R, Horani S, Brown C, Mitchell R, Shah G. Chronic rhinosinusitis and endoscopic sinus surgery in children admitted for pulmonary exacerbations of cystic fibrosis. Int J Pediatr Otorhinolaryngol. 2021;140:110548. doi:**10.1016/j.ijporl.2020.110548**

421 Weinstock MS, Shaffer AD, Stapleton AL. Predictors of sinonasal disease onset, progression, and severity in pediatric cystic fibrosis patients. Am J Otolaryngol. 2021;42(5):103016. doi:**10.1016/j.amjoto.2021.103016**

422 Eischen E, Gliksman MF, Segarra D, et al. Correlation between CT imaging and symptom scores in cystic fibrosis associated chronic sinusitis. Am J Otolaryngol. 2023;44(4):103858. doi:**10.1016/j.amjoto.2023.103858**

423 Ni JS, Kompelli AR, Nguyen SA, Schlosser RJ, Clemmens C, Soler ZM. The Sinus and Nasal Quality of Life Survey (SN-5) in the Management of Pediatric Chronic Rhinosinusitis: A systematic review and meta-analysis. Int J Pediatr Otorhinolaryngol. 2018;111:162-169. doi:**10.1016/j.ijporl.2018.06.010**

424 Habib ARR, Buxton JA, Singer J, Wilcox PG, Javer AR, Quon BS. Association between Chronic Rhinosinusitis and Health-Related Quality of Life in Adults with Cystic Fibrosis. Ann Am Thorac Soc. Published online May 26, 2015:150526140002000. doi:**10.1513/AnnalsATS.201504-191OC**

425 Savastano V, Bertin S, Vittori T, Tripodi C, Magliulo G. Evaluation of chronic rhinosinusitis management using the SNOT-22 in adult cystic fibrosis patients. Eur Rev Med Pharmacol Sci. 2014;18(14):1985-1989.

426 Habib AR, Quon BS, Buxton JA, et al. The Sino-Nasal Outcome Test–22 as a tool to identify chronic rhinosinusitis in adults with cystic fibrosis. Int Forum Allergy Rhinol. 2015;5(12):1111-1117. doi:**10.1002/alr.21607**

427 Virgin FW. Clinical chronic rhinosinusitis outcomes in pediatric patients with cystic fibrosis. Laryngoscope Investig Otolaryngol. 2017;2(5):276-280. doi:**10.1002/lio2.78**

428 Passarelli Mantovani R, Sandri A, Boaretti M, et al. Longitudinal monitoring of sinonasal and oral bacterial reservoirs to prevent chronic lung infection in people with cystic fibrosis. ERJ Open Res. 2020;6(3):00115-02020. doi:**10.1183/23120541.00115-2020**

429 Sobin L, Kawai K, Irace AL, et al. Microbiology of the Upper and Lower Airways in Pediatric Cystic Fibrosis Patients. Otolaryngology–Head and Neck Surgery. 2017;157(2):302-308. doi:**10.1177/0194599817702332**

430 Mainz JG, Naehrlich L, Schien M, et al. Concordant genotype of upper and lower airways P aeruginosa and S aureus isolates in cystic fibrosis. Thorax. 2009;64(6):535-540. doi:**10.1136/thx.2008.104711**

431 Wilson P, Lambert C, Carr SB, Pao C. Paranasal sinus pathogens in children with cystic fibrosis: Do they relate to lower respiratory tract pathogens and is eradication successful? Journal of Cystic Fibrosis. 2014;13(4):449-454. doi:**10.1016/j.jcf.2014.03.003**

432 Erdmann N, Schilling T, Hentschel J, et al. Divergent dynamics of inflammatory mediators and multiplex PCRs during airway infection in cystic fibrosis patients and healthy controls: Serial upper airway sampling by nasal lavage. Front Immunol. 2022;13. doi:**10.3389/fimmu.2022.947359**

433 Lucas SK, Feddema E, Boyer HC, Hunter RC. Diversity of cystic fibrosis chronic rhinosinusitis microbiota correlates with different pathogen dominance. Journal of Cystic Fibrosis. 2021;20(4):678-681. doi:**10.1016/j.jcf.2021.03.022**

434 Gitomer SA, Poore TS, Anand GS, Cañadas KT. Differing rates of fungi in sinonasal cultures from pediatric sinusitis patients. Int J Pediatr Otorhinolaryngol. 2022;156:111125. doi:**10.1016/j.ijporl.2022.111125**

435 Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (Update): Adult Sinusitis. Otolaryngology–Head and Neck Surgery. 2015;152(S2). doi:**10.1177/0194599815572097**

436 Okafor S, Kelly KM, Halderman AA. Management of Sinusitis in the Cystic Fibrosis Patient. Immunol Allergy Clin North Am. 2020;40(2):371-383. doi:**10.1016/j.iac.2019.12.008**

437 Chitsuthipakorn W, Kanjanawasee D, Hoang MP, Seresirikachorn K, Snidvongs K. Optimal Device and Regimen of Nasal Saline Treatment for Sinonasal Diseases: Systematic Review. OTO Open. 2022;6(2). doi:**10.1177/2473974X221105277**

438 Shah GB, De Keyzer L, Russell JA, Halderman A. Treatment of chronic rhinosinusitis with dornase alfa in patients with cystic fibrosis: a systematic review. Int Forum Allergy Rhinol. 2018;8(6):729-736. doi:**10.1002/alr.22082**

439 Mainz JG, Schien C, Schiller I, et al. Sinonasal inhalation of dornase alfa administered by vibrating aerosol to cystic fibrosis patients: A double-blind placebo-controlled cross-over trial. Journal of Cystic Fibrosis. 2014;13(4):461-470. doi:**10.1016/j.jcf.2014.02.005**

440 Mainz JG, Schumacher U, Schädlich K, et al. Sino nasal inhalation of isotonic versus hypertonic saline (6.0%) in CF patients with chronic rhinosinusitis — Results of a multicenter, prospective, randomized, double-blind, controlled trial. Journal of Cystic Fibrosis. 2016;15(6):e57-e66. doi:**10.1016/j.jcf.2016.05.003**

441 Mainz JG, Schaedlich K, Schien C, et al. Sinonasal inhalation of tobramycin vibrating aerosol in cystic fibrosis patients with upper airway Pseudomonas aeruginosa colonization: results of a randomized, double-blind, placebo-controlled pilot study. Drug Des Devel Ther. Published online February 2014:209. doi:**10.2147/DDDT.S54064**

442 Aanaes K, von Buchwald C, Hjuler T, Skov M, Alanin M, Johansen HK. The Effect of Sinus Surgery with Intensive follow-up on Pathogenic Sinus Bacteria in Patients with Cystic Fibrosis. Am J Rhinol Allergy. 2013;27(1):e1-e4. doi:**10.2500/ajra.2013.27.3829**

443 Liang J, Higgins T, Ishman SL, Boss EF, Benke JR, Lin SY. Medical management of chronic rhinosinusitis in cystic fibrosis: A systematic review. Laryngoscope. 2014;124(6):1308-1313. doi:**10.1002/lary.24503**

444 Merrill TB, Tyes J, Woodard TD. Is Elexacaftor/Tezacaftor/Ivacaftor Effective in Treating Sinonasal Disease in Patients with Cystic Fibrosis? Laryngoscope. 2024;134(2):501-503. doi:**10.1002/lary.30937**

445 Sergeev V, Chou FY, Lam GY, Hamilton CM, Wilcox PG, Quon BS. The Extrapulmonary Effects of Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Cystic Fibrosis. Ann Am Thorac Soc. 2020;17(2):147-154. doi:**10.1513/AnnalsATS.201909-671CME**

446 Stone RG, Short C, Davies JC, McNally P. Chronic rhinosinusitis in the era of CFTR modulator therapy. Journal of Cystic Fibrosis. 2024;23(2):208-213. doi:**10.1016/j.jcf.2023.08.009**

447 Stapleton AL, Kimple AJ, Goralski JL, et al. Elexacaftor-Tezacaftor- Ivacaftor improves sinonasal outcomes in cystic fibrosis. Journal of Cystic Fibrosis. 2022;21(5):792-799. doi:**10.1016/j.jcf.2022.03.002**

448 Beswick DM, Han EJ, Mace JC, et al. Factors that predict pursuing sinus surgery in the era of highly effective modulator therapy. Int Forum Allergy Rhinol. 2024;14(4):807-818. doi:**10.1002/alr.23270**

449 Beswick DM, Khatiwada A, Miller JE, et al. Impact of highly effective modulator therapy on chronic rhinosinusitis and health status: 2-year follow-up. Journal of Cystic Fibrosis. 2024;23(2):214-218. doi:**10.1016/j.jcf.2023.09.013**

450 Beswick DM, Humphries SM, Miller JE, et al. Objective and patient-based measures of chronic rhinosinusitis in people with cystic fibrosis treated with highly effective modulator therapy. Int Forum Allergy Rhinol. 2022;12(11):1435-1438. doi:**10.1002/alr.23016**

451 Sheikh S, Ho ML, Eisner M, et al. Elexacaftor-Tezacaftor-Ivacaftor Therapy for Chronic Sinus Disease in Cystic Fibrosis. JAMA Otolaryngology–Head & Neck Surgery. 2023;149(12):1075. doi:**10.1001/jamaoto.2023.2701**

452 Tagliati C, Pantano S, Lanni G, et al. Sinus Disease Grading on Computed Tomography Before and After Modulating Therapy in Adult Patients with Cystic Fibrosis. J Belg Soc Radiol. 2022;106(1). doi:**10.5334/jbsr.2812**

453 Wucherpfennig L, Triphan SMF, Wege S, et al. Magnetic resonance imaging detects improvements of pulmonary and paranasal sinus abnormalities in response to elexacaftor/tezacaftor/ivacaftor therapy in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2022;21(6):1053-1060. doi:**10.1016/j.jcf.2022.03.011**

454 Wucherpfennig L, Wuennemann F, Eichinger M, et al. Long-term effects of lumacaftor/ivacaftor on paranasal sinus abnormalities in children with cystic fibrosis detected with magnetic resonance imaging. Front Pharmacol. 2023;14. doi:**10.3389/fphar.2023.1161891**

455 Shakir S, Echevarria C, Doe S, Brodlie M, Ward C, Bourke SJ. Elexacaftor-Tezacaftor-Ivacaftor improve Gastro-Oesophageal reflux and Sinonasal symptoms in advanced cystic fibrosis. Journal of Cystic Fibrosis. 2022;21(5):807-810. doi:**10.1016/j.jcf.2022.06.003**

456 Castellanos CX, Osterbauer B, Hasday S, Keens TG, Koempel J, Ference EH. Improvement in sinonasal quality-of-life indicators for pediatric patients with cystic fibrosis treated with elexacaftor-tezacaftor-ivacaftor. Int Forum Allergy Rhinol. 2023;13(1):72-75. doi:**10.1002/alr.23036**

457 Tipirneni KE., Woodworth BA. Medical and Surgical Advancements in the Management of Cystic Fibrosis Chronic Rhinosinusitis. Curr Otorhinolaryngol Rep. 2017;5(1):24-34. doi:**10.1007/s40136-017-0139-3**

458 Rau JL. The inhalation of drugs: advantages and problems. Respir Care. 2005;50(3):367-382.

459 Frost F, Fothergill J, Winstanley C, Nazareth D, Walshaw M. S20 Inhaled aztreonam lysine recovers lung function and improves quality of life in acute pulmonary exacerbations of cystic fibrosis. In: Biomarkers and Treatments in Cystic Fibrosis. BMJ Publishing Group Ltd and British Thoracic Society; 2019:A13.2-A14. doi:**10.1136/thorax-2019-BTSabstracts2019.26**

460 Heijerman H, Westerman E, Conway S, Touw D. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus. Journal of Cystic Fibrosis. 2009;8(5):295-315. doi:**10.1016/j.jcf.2009.04.005**

461 Bott J, Blumenthal S, Buxton M, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Thorax. 2009;64(Suppl 1):i1-i52. doi:**10.1136/thx.2008.110726**

462 Johnstone Z, Brown C, Gates A, Day H. P479 Independent prescribing in cystic fibrosis, a survey of UK physiotherapy practice. Journal of Cystic Fibrosis. 2024;23:S213. doi:**10.1016/S1569-1993(24)00772-0**

463 NICE. Cystic Fibrosis: Diagnosis and Management [NG78]. 2017. Available at: **nice.org.uk/guidance/ng78/resources/cystic-fibrosis-diagnosis-and-management-pdf-1837640946373**

464 NICE. Colistimethate Sodium and Tobramycin Dry Powders for Inhalation for Treating Pseudomonas Lung Infection in Cystic Fibrosis: Technology Appraisal Guidance [TA276]. 2013. Available at: **nice.org.uk/guidance/ta276/resources/colistimethate-sodium-and-tobramycin-dry-powders-for-inhalation-for-treating-pseudomonas-lung-infection-in-cystic-fibrosis-pdf-82600615817413**

465 NICE. Mannitol Dry Powder for Inhalation for Treating Cystic Fibrosis: Technology Appraisal Guidance [TA266]. 2012. Available at: **nice.org.uk/guidance/ta266/resources/mannitol-dry-powder-for-inhalation-for-treating-cystic-fibrosis-pdf-82600555351237**

466 NHS England Clinical Reference Group for Cystic Fibrosis. Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. 2014. Available at: **england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf**

467 NHS England Specialised Services Clinical Reference Group for Specialised Respiratory. Clinical Commissioning Policy: Levofloxacin Nebuliser Solution for Chronic Pseudomonas Lung Infection in Cystic Fibrosis (Adults). 2018. Available at: **england.nhs.uk/wp-content/uploads/2018/08/Levofloxacin-nebuliser-solution-for-chronic-Pseudomonas-lung-infection-in-cystic-fibrosis-adults.pdf**

468 NHS England Specialised Services Clinical Reference Group for Cystic Fibrosis. Clinical Commissioning Policy: Continuous aztreonam lysine for cystic fibrosis (all ages). Published online 2016. Available at: **england.nhs.uk/wp-content/uploads/2018/07/Continuous-aztreonam-lysine-for-cystic-fibrosis-all-ages.pdf**

469 Smith S, Rowbotham NJ, Edwards CT. Short-acting inhaled bronchodilators for cystic fibrosis. Cochrane Database of Systematic Reviews. 2022;2022(6). doi:**10.1002/14651858.CD013666.pub2**

470 Smith S, Edwards CT. Long-acting inhaled bronchodilators for cystic fibrosis. Cochrane Database of Systematic Reviews. 2017;2021(5). doi:**10.1002/14651858.CD012102.pub2**

471 Balfour-Lynn IM, Welch K, Smith S. Inhaled corticosteroids for cystic fibrosis. Cochrane Database of Systematic Reviews. 2019;2021(4). doi:**10.1002/14651858.CD001915.pub6**

472 Scottish Medicines Consortium. Medicines advice. Available at: **scottishmedicines.org.uk/medicines-advice/**

473 CF STORM. Available at: **cfstorm.org.uk/**

474 Mayer-Hamblett N, Ratjen F, Russell R, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. Lancet Respir Med. 2023;11(4):329-340. doi:**10.1016/S2213-2600(22)00434-9**

475 Ren C, Psoter K, Sabadosa K, et al. P113 Home reported outcomes (HERO-2) in people with cystic fibrosis taking elexacaftor/tezacaftor/ivacaftor: self-reported changes in use of chronic daily therapies at enrollment. Journal of Cystic Fibrosis. 2023;22:S98. doi:**10.1016/S1569-1993(23)00488-5**

476 ClinicalTrials.gov. Inhaled Therapy Adherence and Outcomes to Kaftrio in Cystic Fibrosis. Available at: **clinicaltrials.gov/study/NCT05519020**

477 Sloan CM, Sherrard LJ, Einarsson GG, et al. Inhaled antimicrobial prescribing for Pseudomonas aeruginosa infections in Europe. Journal of Cystic Fibrosis. 2024;23(3):499-505. doi:**10.1016/j.jcf.2023.11.012**

478 Haworth CS, Banks J, Capstick T, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017;72(Suppl 2):ii1-ii64. doi:**10.1136/thoraxjnl-2017-210927**

479 ClinicalTrials.gov. Finding the Optimal Regimen for Mycobacterium Abscessus Treatment (FORMaT). Available at: **clinicaltrials.gov/study/NCT04310930**

480 Frost F, Young GR, Wright L, et al. The clinical and microbiological utility of inhaled aztreonam lysine for the treatment of acute pulmonary exacerbations of cystic fibrosis: An open-label randomised crossover study (AZTEC-CF). Journal of Cystic Fibrosis. 2021;20(6):994-1002. doi:**10.1016/j.jcf.2020.12.012**

481 Holzer FJ, Olinsky A, Phelan PD. Variability of airways hyper-reactivity and allergy in cystic fibrosis. Arch Dis Child. 1981;56(6):455-459. doi:**10.1136/adc.56.6.455**

482 British Thoracic Society. Current best practice for nebuliser treatment. The Nebulizer Project Group of the British Thoracic Society Standards of Care Committee. Thorax. 1997;52 Suppl 2:S1-3.

483 Dodd ME, Abbott J, Maddison J, Moorcroft AJ, Webb AK. Effect of tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis. Thorax. 1997;52(7):656-658. doi:**10.1136/thx.52.7.656**

484 Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C. Short report: Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child. 2001;84(5):432-433. doi:**10.1136/adc.84.5.432**

485 Electronic Medicines Compendium. SmPC: Bronchitol 40 mg inhalation powder, hard capsules. 2022. Available at: **medicines.org.uk/emc/product/4085/smpc**

486 Electronic Medicines Compendium. SmPC: Promixin 1 million International Units (IU) Powder for Nebuliser Solution. 2023. Available at: **medicines.org.uk/emc/product/4/smpc**

487 Electronic Medicines Compendium. SmPC: Colomycin 1 million International Units (IU) Powder for solution for injection, infusion or inhalation. 2023. Available at: **medicines.org.uk/emc/product/1094/smpc**

488 Electronic Medicines Compendium. SmPC: Colomycin 2 million International Units (IU) Powder for solution for injection, infusion or inhalation. 2023. Available at: **medicines.org.uk/emc/product/9664/smpc**

489 Electronic Medicines Compendium. SmPC: Bramitob 300 mg/4ml Nebuliser Solution. 2022. Available at: **medicines.org.uk/emc/product/6451/smpc**

490 Electronic Medicines Compendium. SmPC: Cayston 75 mg powder and solvent for nebuliser solution. 2023. Available at: **medicines.org.uk/emc/product/4456/smpc**

491 Electronic Medicines Compendium. SmPC: Tobi 300 mg/5 ml Nebuliser Solution. 2019. Available at: **medicines.org.uk/emc/product/262/smpc**

492 Electronic Medicines Compendium. SmPC: Tobi Podhaler 28 mg inhalation powder, hard capsules. 2025. Available at: **medicines.org.uk/emc/product/4757/smpc**

493 Electronic Medicines Compendium. SmPC: Vantobra 170mg nebuliser solution. 2023. Available at: **medicines.org.uk/emc/product/7362/smpc**

494 Electronic Medicines Compendium. SmPC: Tobramycin (Tymbrineb) 300mg/5ml Nebuliser Solution PL 00289-1437. 2023. Available at: **medicines.org.uk/emc/product/8830/smpc**

495 Electronic Medicines Compendium. SmPC: Pulmozyme 2500 U/ 2.5ml, nebuliser solution. 2017. Available at: **medicines.org.uk/emc/product/1112/smpc**

496 Electronic Medicines Compendium. SmPC: Quinsair 240 mg nebuliser solution. 2024. Available at: **medicines.org.uk/emc/product/7202/smpc**

497 Elkins MR, Robinson M, Rose BR, et al. A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis. New England Journal of Medicine. 2006;354(3):229-240. doi:**10.1056/NEJMoa043900**

498 Electronic Medicines Compendium. SmPC: Colobreathe 1,662,500 IU Inhalation Powder, Hard Capsules. 2024. Available at: **medicines.org.uk/emc/product/15872/smpc**

499 Capstick TG, Clifton IJ. Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. Expert Rev Respir Med. 2012;6(1):91-103. doi:**10.1586/ers.11.89**

500 NHS Business Services Authority. Brand Name Prescribing Update. 2017. Available at: **surreyccg.res-systems.net/PAD/Content/Documents/2/Enc%20B%20-%20UKMi_QA_Brand-name_prescribing_Update_Nov2017.pdf**

501 Mullinger B, Sommerer K, Herpich C, Meyer G. Inhalation therapy can be improved in CF patients by controlling the breathing pattern during inspiration. J Cyst Fibros. 2004;3:S65.

502 Potter R, Hatley R. Precise dose delivery of colistimethate sodium using prototype I-neb AAD system. J Cyst Fibrosis. 2005;4(Suppl. 1):S30.

503 Stanford G, Morrison L, Brown C. Nebuliser systems for drug delivery in cystic fibrosis. Cochrane Database of Systematic Reviews. 2023;2023(11). doi:**10.1002/14651858.CD007639.pub3**

504 Fitzgerald DA, Hilton J, Jepson B, Smith L. A Crossover, Randomized, Controlled Trial of Dornase Alfa Before Versus After Physiotherapy in Cystic Fibrosis. Pediatrics. 2005;116(4):e549-e554. doi:**10.1542/peds.2005-0308**

505 Wilson CJ, Robbins LJ, Murphy JM, Chang AB. Is a longer time interval between recombinant human deoxyribonuclease (dornase alfa) and chest physiotherapy better?: A multi-center, randomized crossover trial. Pediatr Pulmonol. 2007;42(12):1110-1116. doi:**10.1002/ppul.20704**

506 van der Giessen LJ, de Jongste JC, Gosselink R, Hop WC, Tiddens HA. RhDNase before airway clearance therapy improves airway patency in children with CF. Pediatr Pulmonol. 2007;42(7):624-630. doi:**10.1002/ppul.20636**

507 Brown C, Archer M, Carson L, et al. P352 "Mind the Gap"; variation in advice given to cystic fibrosis patients regarding the gap between inhalation of Dornase Alfa and inhaled antibiotics across the UK. Journal of Cystic Fibrosis. 2019;18:S157. doi:**10.1016/S1569-1993(19)30644-7**

508 Laube BL, Geller DE, Lin TC, Dalby RN, Diener-West M, Zeitlin PL. Positive expiratory pressure changes aerosol distribution in patients with cystic fibrosis. Respir Care. 2005;50(11):1438-1444.

509 Lannefors L, Heslop K, Teirlinck C. Nebuliser systems, contamination, microbial risks, cleaning and effect on function. Eur Respir Rev. 2000;10:571e5.

510 Webb A, Dodd M, Bush A. Nebulised antibiotics in cystic fibrosis and non-CF bronchiectasis in children and adults. In: Boe J, O'Driscoll R, Dennis J, eds. Practical Handbook of Nebuliser Therapy. Martin Dunitz; 2004.

511 MacFarlane M, Carson L, Crossan A, Bell J, Moore JE, Millar BC. Nebuliser cleaning and disinfection practice in the home among patients with cystic fibrosis. J Infect Prev. 2020;21(1):14-22. doi:**10.1177/1757177419855603**

512 NICE. Ivacaftor–Tezacaftor–Elexacaftor, Tezacaftor–Ivacaftor and Lumacaftor–Ivacaftor for Treating Cystic Fibrosis: Technology Appraisal Guidance [TA988]. 2024. Available at: **nice.org.uk/guidance/ta988/resources/ivacaftortezacaftorelexacaftor-tezacaftorivacaftor-and-lumacaftorivacaftor-for-treating-cystic-fibrosis-pdf-82615917119173**

513 Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. Cochrane Database of Systematic Reviews. 2013;2013(8). doi:**10.1002/14651858.CD003884.pub4**

514 Urquhart DS. Assessment of hypoxia in children with cystic fibrosis. Arch Dis Child. 2005;90(11):1138-1143. doi:**10.1136/adc.2005.071795**

515 Balfour-Lynn IM, Field DJ, Gringras P, et al. BTS guidelines for home oxygen in children. Thorax. 2009;64(Suppl 2):ii1-ii26. doi:**10.1136/thx.2009.116020**

516 Dinwiddie R, Madge S, Prasad SA, Balfour-Lynn IM. Oxygen therapy for cystic fibrosis. J R Soc Med. 1999;92(37_suppl):19-22. doi:**10.1177/014107689909237S04**

517 Dodd ME, Haworth CS, Kevin Webb A. A practical approach to oxygen therapy in cystic fibrosis. J R Soc Med. 1998;91(34_suppl):30-39. doi:**10.1177/014107689809134S06**

518 Milross MA, Piper AJ, Dobbin CJ, Bye PTP, Grunstein RR. Sleep disordered breathing in cystic fibrosis. Sleep Med Rev. 2004;8(4):295-308. doi:**10.1016/j.smrv.2004.03.004**

519 O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respir Res. 2017;4(1):e000170. doi:**10.1136/bmjresp-2016-000170**

520 Sarkar M, Madabhavi I, Kadakol N. Oxygen-induced hypercapnia: physiological mechanisms and clinical implications. Monaldi Archives for Chest Disease. Published online November 18, 2022. doi:**10.4081/monaldi.2022.2399**

521 Dobbin CJ, Milross MA, Piper AJ, Sullivan C, Grunstein RR, Bye PTP. Sequential use of oxygen and bi-level ventilation for respiratory failure in cystic fibrosis. Journal of Cystic Fibrosis. 2004;3(4):237-242. doi:**10.1016/j.jcf.2004.07.002**

522 Gozal D. Nocturnal ventilatory support in patients with cystic fibrosis: comparison with supplemental oxygen. European Respiratory Journal. 1997;10(9):1999-2003. doi:**10.1183/09031936.97.10091999**

523 Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. Journal of Cystic Fibrosis. 2020;19(3):344-354. doi:**10.1016/j.jcf.2020.02.015**

524 Macé J, Marjanovic N, Faranpour F, et al. Early high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure in the ED: A before-after study. Am J Emerg Med. 2019;37(11):2091-2096. doi:**10.1016/j.ajem.2019.03.004**

525 Kang H, Zhao Z, Tong Z. Effect of High-Flow Nasal Cannula Oxygen Therapy in Immunocompromised Subjects With Acute Respiratory Failure. Respir Care. 2020;65(3):369-376. doi:**10.4187/respcare.07205**

526 Xu C, Yang F, Wang Q, Gao W. Comparison of High Flow Nasal Therapy with Non-Invasive Ventilation and Conventional Oxygen Therapy for Acute Hypercapnic Respiratory Failure: A Meta-Analysis of Randomized Controlled Trials. Int J Chron Obstruct Pulmon Dis. 2023;Volume 18:955-973. doi:**10.2147/COPD.S410958**

527 Kim NY, Shin JS, Jeong OJ, Kim WY. Factors associated with unsuccessful high-flow nasal cannula therapy in patients presenting to the emergency department for acute hypoxemic respiratory failure. Int Emerg Nurs. 2023;66:101236. doi:**10.1016/j.ienj.2022.101236**

528 Spicuzza L, Schisano M. High-flow nasal cannula oxygen therapy as an emerging option for respiratory failure: the present and the future. Ther Adv Chronic Dis. 2020;11. doi:**10.1177/2040622320920106**

529 Milross MA, Piper AJ, Norman M, et al. Predicting Sleep-Disordered Breathing in Patients With Cystic Fibrosis. Chest. 2001;120(4):1239-1245. doi:**10.1378/chest.120.4.1239**

530 Zinman R, Corey M, Coates AL, et al. Nocturnal home oxygen in the treatment of hypoxemic cystic fibrosis patients. J Pediatr. 1989;114(3):368-377. doi:**10.1016/S0022-3476(89)80553-0**

531 McKone EF, Barry SC, FitzGerald MX, Gallagher CG. The role of supplemental oxygen during submaximal exercise in patients with cystic fibrosis. European Respiratory Journal. 2002;20(1):134-142. doi:**10.1183/09031936.02.00492001**

532 Nixon PA, Orenstein DM, Curtis SE, Ross EA. Oxygen Supplementation during Exercise in Cystic Fibrosis. American Review of Respiratory Disease. 1990;142(4):807-811. doi:**10.1164/ajrccm/142.4.807**

533 Marcus CL, Bader D, Stabile MW, Wang CI, Osher AB, Keens TG. Supplemental Oxygen and Exercise Performance in Patients with Cystic Fibrosis with Severe Pulmonary Disease. Chest. 1992;101(1):52-57. doi:**10.1378/chest.101.1.52**

534 Suntharalingam J, Wilkinson T, Annandale J, et al. British Thoracic Society quality standards for home oxygen use in adults. BMJ Open Respir Res. 2017;4(1):e000223. doi:**10.1136/bmjresp-2017-000223**

535 Coffey MJ, FitzGerald MX, McNicholas WT. Comparison of Oxygen Desaturation during Sleep and Exercise in Patients with Cystic Fibrosis. Chest. 1991;100(3):659-662. doi:**10.1378/chest.100.3.659**

536 Spier S, Rivlin J, Hughes D, Levison H. The Effect of Oxygen on Sleep, Blood Gases, and Ventilation in Cystic Fibrosis. American Review of Respiratory Disease. 1984;129(5):712-718. doi:**10.1164/arrd.1984.129.5.712**

537 Young AC, Wilson JW, Kotsimbos TC, Naughton MT. The impact of nocturnal oxygen desaturation on quality of life in cystic fibrosis. Journal of Cystic Fibrosis. 2011;10(2):100-106. doi:**10.1016/j.jcf.2010.11.001**

538 Piper A. Sleep Disordered Breathing in Children: A Comprehensive Clinical Guide to Evaluation and Treatment (Respiratory Medicine). In: 2012:365-383.

539 Katz ES. Cystic Fibrosis and Sleep. Clin Chest Med. 2014;35(3):495-504. doi:**10.1016/j.ccm.2014.06.005**

540 Versteegh FG, Bogaard JM, Raatgever JW, Stam H, Neijens HJ, Kerrebijn KF. Relationship between airway obstruction, desaturation during exercise and nocturnal hypoxaemia in cystic fibrosis patients. Eur Respir J. 1990;3(1):68-73.

541 Frangolias DD, Wilcox PG. Predictability of Oxygen Desaturation During Sleep in Patients With Cystic Fibrosis. Chest. 2001;119(2):434-441. doi:**10.1378/chest.119.2.434**

542 Gómez Punter RM, Girón Moreno RM, Vázquez Espinosa E, et al. Desaturations During 6-Minute Walk Test and Predicting Nocturnal Desaturations in Adult Subjects With Cystic Fibrosis. Respir Care. 2019;64(1):48-54. doi:**10.4187/respcare.06171**

543 Young AC, Wilson JW, Kotsimbos TC, Naughton MT. Randomised placebo controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. Thorax. 2008;63(1):72-77. doi:**10.1136/thx.2007.082602**

544 Jagpal SK, Jobanputra AM, Ahmed OH, Santiago T V., Ramagopal M. Sleep-disordered breathing in cystic fibrosis. Pediatr Pulmonol. 2021;56(S1). doi:**10.1002/ppul.25028**

545 Welsner M, Dietz-Terjung S, Stehling F, et al. Obstructive sleep apnea and nocturnal hypoxemia in adult patients with cystic fibrosis. BMC Pulm Med. 2022;22(1):446. doi:**10.1186/s12890-022-02243-0**

546 Shah AR, Keens TG, Gozal D. Effect of supplemental oxygen on supramaximal exercise performance and recovery in cystic fibrosis. J Appl Physiol. 1997;83(5):1641-1647. doi:**10.1152/jappl.1997.83.5.1641**

547 Coates AL. Oxygen Therapy, Exercise, and Cystic Fibrosis. Chest. 1992;101(1):2-4. doi:**10.1378/chest.101.1.2**

548 Spoletini G, Watson R, Lim WY, et al. Nasal high-flow therapy as an adjunct to exercise in patients with cystic fibrosis: A pilot feasibility trial. Journal of Cystic Fibrosis. 2021;20(5):e46-e52. doi:**10.1016/j.jcf.2021.03.005**

549 Coker RK, Armstrong A, Church AC, et al. BTS Clinical Statement on air travel for passengers with respiratory disease. Thorax. 2022;77(4):329-350. doi:**10.1136/thoraxjnl-2021-218110**

550 Ahmedzai S, Balfour-Lynn IM, Bewick T, et al. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. Thorax. 2011;66(Suppl 1):i1-i30. doi:**10.1136/thoraxjnl-2011-200295**

551 Edvardsen E, Akerø A, Skjønsberg OH, Skrede B. Pre-flight evaluation of adult patients with cystic fibrosis: a cross-sectional study. BMC Res Notes. 2017;10(1):84. doi:**10.1186/s13104-017-2386-2**

552 Pepperell JCT, Fraser C, McClue G. P139 The use of venturi masks with oxygen concentrators. Thorax. 2011;66(Suppl 4):A123-A124. doi:**10.1136/thoraxjnl-2011-201054c.139**

553 Bliss PL, McCoy RW, Adams AB. A Bench Study Comparison of Demand Oxygen Delivery Systems and Continuous Flow Oxygen. Respir Care. 1999;48(8).

554 McDonald CF. Ambulatory oxygen delivery—an answer: But what is the question? Respirology. 2019;24(4):294-295. doi:**10.1111/resp.13505**

555 Caneiras C, Jácome C, Moreira E, et al. A qualitative study of patient and carer experiences with home respiratory therapies: Long-term oxygen therapy and home mechanical ventilation. Pulmonology. 2022;28(4):268-275. doi:**10.1016/j.pulmoe.2021.05.010**

556 Moretta P, Molino A, Martucci M, et al. Subject Preferences and Psychological Implications of Portable Oxygen Concentrator Versus Compressed Oxygen Cylinder in Chronic Lung Disease. Respir Care. 2021;66(1):33-40. doi:**10.4187/respcare.07829**

557 Archangelidi O, Carr SB, Simmonds NJ, Bilton D, Banya W, Cullinan P. Non-invasive ventilation and clinical outcomes in cystic fibrosis: Findings from the UK CF registry. Journal of Cystic Fibrosis. 2019;18(5):665-670. doi:**10.1016/j.jcf.2018.11.006**

558 Milross MA, Piper AJ, Dwyer TJ, Wong K, Bell SC, Bye PTP. Non-invasive ventilation versus oxygen therapy in cystic fibrosis: A 12-month randomized trial. Respirology. 2019;24(12):1191-1197. doi:**10.1111/resp.13604**

559 Parisi GF, Papale M, Manti S, Mulè E, Rotolo N, Leonardi S. Observational study of sleep-related breathing disorders and preventive non-invasive ventilation in cystic fibrosis. In: Cystic Fibrosis. European Respiratory Society; 2019:PA339. doi:**10.1183/13993003.congress-2019.PA339**

560 Biglia C, Demichelis S, Di Tria R, Bena C, Sciolla M, Messore B. WS01.2 Non-invasive ventilation in adult cystic fibrosis patients with severe lung disease. Journal of Cystic Fibrosis. 2020;19:S1. doi:**10.1016/S1569-1993(20)30166-1**

561 Wadsworth L, Riley D, Bright-Thomas RJ. ePS1.01 Long-term outcomes of adult patients with cystic fibrosis requiring non-invasive ventilation. Journal of Cystic Fibrosis. 2020;19:S37. doi:**10.1016/S1569-1993(20)30281-2**

562 Spoletini G, Pollard K, Watson R, et al. Noninvasive Ventilation in Cystic Fibrosis: Clinical Indications and Outcomes in a Large UK Adult Cystic Fibrosis Center. Respir Care. 2021;66(3):466-474. doi:**10.4187/respcare.07862**

563 Wadsworth L, Belcher J, Bright-Thomas R. Non-invasive ventilation is associated with long-term improvements in lung function and gas exchange in cystic fibrosis adults with hypercapnic respiratory failure. Journal of Cystic Fibrosis. 2021;20(5):e40-e45. doi:**10.1016/j.jcf.2021.05.011**

564 Bogoni PF, Meschi A, Bellini R, et al. ePS3.01 Long-term effects of non-invasive ventilation for airway clearance in cystic fibrosis. Journal of Cystic Fibrosis. 2019;18:S44. doi:**10.1016/S1569-1993(19)30259-0**

565 Jobanputra A, Jagpal S, Marulanda P, Ramagopal M, Santiago T, Naik S. An overview of noninvasive ventilation in cystic fibrosis. Pediatr Pulmonol. 2022;57(S1). doi:**10.1002/ppul.25753**

566 Hill AT, Edenborough FP, Cayton RM, Stableforth DE. Long-term nasal intermittent positive pressure ventilation in patients with cystic fibrosis and hypercapnic respiratory failure (1991–1996). Respir Med. 1998;92(3):523-526. doi:**10.1016/S0954-6111(98)90302-X**

567 Madden BP, Kariyawasam H, Siddiqi AJ, Machin A, Pryor JA, Hodson ME. Noninvasive ventilation in cystic fibrosis patients with acute or chronic respiratory failure. European Respiratory Journal. 2002;19(2):310-313. doi:**10.1183/09031936.02.00218502**

568 Spoletini G, Pollard K, Watson R, et al. P250 Pattern of use of NIV: 10-year experience of a large UK adult cystic fibrosis centre. Journal of Cystic Fibrosis. 2019;18:S127. doi:**10.1016/S1569-1993(19)30543-0**

569 Davidson AC, Banham S, Elliott M, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1-ii35. doi:**10.1136/thoraxjnl-2015-208209**

570 Flight WG, Shaw J, Johnson S, et al. Long-term non-invasive ventilation in cystic fibrosis — Experience over two decades. Journal of Cystic Fibrosis. 2012;11(3):187-192. doi:**10.1016/j.jcf.2011.11.006**

571 Appendini L, Ronco L, Ferreyra G, Esposito I, Bignamini E. Noninvasive ventilation (NPPV) affects Pulmonary Exacerbation (PE) rate in Cystic Fibrosis children (CFc). In: Cystic Fibrosis. European Respiratory Society; 2018:PA3416. doi:**10.1183/13993003.congress-2018.PA3416**

572 Loukou I, Moustaki M, Douros K. The Current Practice of Noninvasive Ventilation in Patients With Cystic Fibrosis. Respir Care. 2021;66(8):1330-1336. doi:**10.4187/respcare.08755**

573 Spoletini G, Watson R, Pollard K, et al. ePS2.04 Indications and complications of NIV in patients with cystic fibrosis: 10-year experience in a large UK adult CF centre. Journal of Cystic Fibrosis. 2019;18:S42-S43. doi:**10.1016/S1569-1993(19)30252-8**

574 Spoletini G, Watson R, Pollard K, et al. Use of NIV in cystic fibrosis: 10-year experience of a large adult CF centre. In: Cystic Fibrosis. European Respiratory Society; 2019:PA337. doi:**10.1183/13993003.congress-2019.PA337**

575 Hodson ME, Madden BP, Steven MH, Tsang VT, Yacoub MH. Non-invasive mechanical ventilation for cystic fibrosis patients--a potential bridge to transplantation. Eur Respir J. 1991;4(5):524-527.

576 Sergey A, Gulsara B, Stanislav K, Victor S, Elena A, Alexander C. Home non-invasive ventilation (HNIV) improves survival in hypercapnic patients with cystic fibrosis. European Respiratory Journal. 2012;40(Suppl. 56):P1712.

577 Choyce J, Hewison A, Swift A, Whitehouse JL, Rashid R, Nash EF. EPS6.02 Investigating the experience of adults with cystic fibrosis using long-term domiciliary non-invasive ventilation. Journal of Cystic Fibrosis. 2018;17:S48. doi:**10.1016/S1569-1993(18)30270-4**

578 Papale M, Parisi G, Spicuzza L, et al. Nocturnal non invasive ventilation in normocapnic cystic fibrosis patients: a pilot study. Acta Biomed. 2021;92(2):e2021164. doi:**10.23750/abm.v92i2.11261**

579 Papale M. A31 Preventive use of nocturnal non invasive ventilation in Cystic Fibrosis: a pilot study (Abstracts from the 25th Italian Congress of Cystic Fibrosis and the 15th National Congress of Cystic Fibrosis Italian Society). Ital J Pediatr. 2020;46(S1):32. doi:**10.1186/s13052-020-0790-z**

580 Milross MA, Piper AJ, Norman M, et al. Low-flow oxygen and bilevel ventilatory support: effects on ventilation during sleep in cystic fibrosis. Am J Respir Crit Care Med. 2001;163(1):129-134. doi:**10.1164/ajrccm.163.1.2005130**

581 Warnock L, Gates A, Flight WG. ePS1.02 Use of non-invasive ventilation in cystic fibrosis in the UK: developments over a decade. Journal of Cystic Fibrosis. 2020;19:S37. doi:**10.1016/S1569-1993(20)30282-4**

582 Hoo ZH, Daniels T, Wildman MJ, Teare MD, Bradley JM. Airway clearance techniques used by people with cystic fibrosis in the UK. Physiotherapy. 2015;101(4):340-348. doi:**10.1016/j.physio.2015.01.008**

583 Dwyer TJ, Robbins L, Kelly P, Piper AJ, Bell SC, Bye PTP. Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial. J Physiother. 2015;61(3):142-147. doi:**10.1016/j.jphys.2015.05.019**

584 Rodriguez Hortal MC, Hedborg A, Biguet G, Nygren-Bonnier M. Experience of using non-invasive ventilation as an adjunct to airway clearance techniques in adults with cystic fibrosis-A qualitative study. Physiother Theory Pract. 2018;34(4):264-275. doi:**10.1080/09593985.2017.1400137**

585 Warnock L, Gates A, Flight WG. P328 Set-up and use of non-invasive ventilation for adults with cystic fibrosis: an exploratory survey of UK cystic fibrosis physiotherapists. Journal of Cystic Fibrosis. 2020;19:S147-S148. doi:**10.1016/S1569-1993(20)30657-3**

586 Holland AE. Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis. Thorax. 2003;58(10):880-884. doi:**10.1136/thorax.58.10.880**

587 Placidi G, Cornacchia M, Polese G, Zanolla L, Assael BM, Braggion C. Chest physiotherapy with positive airway pressure: a pilot study of short-term effects on sputum clearance in patients with cystic fibrosis and severe airway obstruction. Respir Care. 2006;51(10):1145-1153.

588 Fauroux B, Boulé M, Lofaso F, et al. Chest Physiotherapy in Cystic Fibrosis: Improved Tolerance With Nasal Pressure Support Ventilation. Pediatrics. 1999;103(3):e32-e32. doi:**10.1542/peds.103.3.e32**

589 Willis LD. The Role of Noninvasive Ventilation in Cystic Fibrosis: A Cochrane Review Summary With Commentary. Respir Care. 2020;65(5):719-721. doi:**10.4187/respcare.07782**

590 Stanford G, Parrott H, Bilton D, Agent P. Positive pressure – analysing the effect of the addition of non-invasive ventilation (NIV) to home airway clearance techniques (ACT) in adult cystic fibrosis (CF) patients. Physiother Theory Pract. 2015;31(4):270-274. doi:**10.3109/09593985.2014.994151**

591 Johnson A, Paul C, Duckers J, Bridges C. P329 To evaluate adherence to NIV for airways clearance at the All Wales Adult Cystic Fibrosis Centre (AWACFC). Journal of Cystic Fibrosis. 2020;19:S148. doi:**10.1016/S1569-1993(20)30658-5**

592 Hortal R, Hedborg A, Nygren-Bonnier M, Hjelte L. Incremental test with non-invasive ventilation (NIV) support vs oxygen supplementation in adult patients with cystic fibrosis. Paediatric Pulmonology. 2016;51:375.

593 Bright-Thomas RJ, Johnson SC. What is the role of noninvasive ventilation in cystic fibrosis? Curr Opin Pulm Med. 2014;20(6):618-622. doi:**10.1097/MCP.0000000000000105**

594 Beverley Z, Parrott H, Jones AL. WS13.4 Experiences of non-invasive ventilation in a large adult cystic fibrosis centre and nationally. Journal of Cystic Fibrosis. 2018;17:S24. doi:**10.1016/S1569-1993(18)30193-0**

595 Warnock L, Gates A, Flight WG. EPS6.6 Remote monitoring of home non-invasive ventilation during infective exacerbations of cystic fibrosis: a feasibility study. Journal of Cystic Fibrosis. 2017;16:S51. doi:**10.1016/S1569-1993(17)30327-2**

596 Moran P, Pilkington E, Bell N, Bateman K, Swingwood E. The development of oxygen and non-invasive ventilation pathways in an adult cystic fibrosis centre. Physiotherapy. 2019;105:e200-e201. doi:**10.1016/j.physio.2018.11.216**

597 British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. Thorax. 2002;57(3):192-211. doi:**10.1136/thorax.57.3.192**

598 Mutagi A, Nash EF, Cameron S, et al. Microbial contamination of non-invasive ventilation devices used by adults with cystic fibrosis. Journal of Hospital Infection. 2012;81(2):104-108. doi:**10.1016/j.jhin.2012.03.004**

599 Wilson J, Young A. Long-term non-invasive ventilation in cystic fibrosis: A bridge too far? Respirology. 2019;24(12):1131-1131. doi:**10.1111/resp.13712**

600 Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2019 Annual Data Report. 2019. Available at: **cysticfibrosis.org.uk/sites/default/files/2020-12/2019%20Registry%20Annual%20Data%20report_Sep%202020.pdf**

601 Wadsworth LE, Bright-Thomas RJ. P189 Impact of triple CFTR modulation therapy on non-invasive ventilation use in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2021;20:S96-S97. doi:**10.1016/S1569-1993(21)01214-5**

602 Vendrusculo FM, Campos NE, Batista Barbosa RR, de Freitas Coelho P, dos Reis Vidal P, Donadio MVF. ePS1.03 Sleep disorders, exercise capacity and daily physical activity levels in children and adolescents with cystic fibrosis. Journal of Cystic Fibrosis. 2020;19:S37-S38. doi:**10.1016/S1569-1993(20)30283-6**

603 Shakkottai A, Irani S, Nasr SZ, O'Brien LM, Chervin RD. Risk factors for obstructive sleep apnea in cystic fibrosis. Pediatr Pulmonol. 2022;57(4):926-934. doi:**10.1002/ppul.25811**

604 Reiter J, Gileles-Hillel A, Cohen-Cymberknoh M, et al. Sleep disorders in cystic fibrosis: A systematic review and meta-analysis. Sleep Med Rev. 2020;51:101279. doi:**10.1016/j.smrv.2020.101279**

605 Gallard S, West J, Duckers J, Buttress A, Bridges C. P382 Obstructive sleep apnoea in cystic fibrosis: an under-recognised complication of cystic fibrosis? Journal of Cystic Fibrosis. 2019;18:S165-S166. doi:**10.1016/S1569-1993(19)30674-5**

606 Sandsund CA, Roughton M, Hodson ME, Pryor JA. Musculoskeletal techniques for clinically stable adults with cystic fibrosis: a preliminary randomised controlled trial. Physiotherapy. 2011;97(3):209-217. doi:**10.1016/j.physio.2010.08.016**

607 Massery M. Musculoskeletal and neuromuscular interventions: a physical approach to cystic fibrosis. J R Soc Med. 2005;98 Suppl 45(Suppl 45):55-66.

608 Botton E, Saraux A, Laselve H, Jousse S, Le Goff P. Musculoskeletal manifestations in cystic fibrosis. Joint Bone Spine. 2003;70(5):327-335. doi:**10.1016/S1297-319X(03)00063-0**

609 Havermans T, Colpaert K, De Boeck K, Dupont L, Abbott J. Pain in CF: Review of the literature. Journal of Cystic Fibrosis. 2013;12(5):423-430. doi:**10.1016/j.jcf.2013.04.001**

610 Bridges C, Rees A, Caunter S, Duckers J. 151 Prevalence of musculoskeletal pain in the Welsh adult cystic fibrosis population. Journal of Cystic Fibrosis. 2015;14:S97. doi:**10.1016/S1569-1993(15)30328-3**

611 Tattersall R, Walshaw MJ. Posture and cystic fibrosis. J R Soc Med. 2003;96 Suppl 43(Suppl 43):18-22.

612 Clarke EA, Watson P, Freeston JE, Peckham DG, Jones AM, Horsley A. Assessing arthritis in the context of cystic fibrosis. Pediatr Pulmonol. 2019;54(6):770-777. doi:**10.1002/ppul.24290**

613 Oliveira VH, Mendonça KM, Monteiro KS, Silva IS, Santino TA, Nogueira PAM. Physical therapies for postural abnormalities in people with cystic fibrosis. Cochrane Database of Systematic Reviews. Published online March 30, 2020. doi:**10.1002/14651858.CD013018.pub2**

614 Lambrechts MJ, Smith MJ, Choma TJ. Orthopedic Manifestations of Cystic Fibrosis. Orthopedics. 2021;44(3). doi:**10.3928/01477447-20210415-03**

615 Hodges PW, Gurfinkel VS, Brumagne S, Smith TC, Cordo PC. Coexistence of stability and mobility in postural control: evidence from postural compensation for respiration. Exp Brain Res. 2002;144(3):293-302. doi:**10.1007/s00221-002-1040-x**

616 Hodges PW, Heijnen I, Gandevia SC. Postural activity of the diaphragm is reduced in humans when respiratory demand increases. J Physiol. 2001;537(3):999-1008. doi:**10.1111/j.1469-7793.2001.00999.x**

617 Smith MD, Russell A, Hodges PW. Disorders of breathing and continence have a stronger association with back pain than obesity and physical activity. Australian Journal of Physiotherapy. 2006;52(1):11-16. doi:**10.1016/S0004-9514(06)70057-5**

618 Buehler T, Steinmann M, Singer F, et al. Increased arterial stiffness in children with cystic fibrosis: Table 1–. European Respiratory Journal. 2012;39(6):1536-1537. doi:**10.1183/09031936.00212511**

619 Ross J, Gamble J, Schultz A, Lewiston N. Back pain and spinal deformity in cystic fibrosis. Am J Dis Child. 1987;141(12):1313-1316.

620 Schindel CS, Hommerding PX, Melo DAS, Baptista RR, Marostica PJC, Donadio MVF. Physical Exercise Recommendations Improve Postural Changes Found in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial. J Pediatr. 2015;166(3):710-716.e2. doi:**10.1016/j.jpeds.2014.12.001**

621 Dodd ME, Prasad SA. Physiotherapy management of cystic fibrosis. Chron Respir Dis. 2005;2(3):139-149. doi:**10.1191/1479972305cd078ra**

622 Fainardi V, Koo SD, Padley SPG, Lam SHY, Bush A. Prevalence of scoliosis in cystic fibrosis. Pediatr Pulmonol. 2013;48(6):553-555. doi:**10.1002/ppul.22624**

623 Okuro RT, Côrrea EP, Conti PBM, Ribeiro JD, Ribeiro MÂGO, Schivinski CIS. Influence of thoracic spine postural disorders on cardiorespiratory parameters in children and adolescents with cystic fibrosis. J Pediatr (Rio J). 2012;88(4):310-316. doi:**10.2223/JPED.2206**

624 Tejero García S, Giráldez Sánchez MA, Cejudo P, et al. Bone Health, Daily Physical Activity, and Exercise Tolerance in Patients With Cystic Fibrosis. Chest. 2011;140(2):475-481. doi:**10.1378/chest.10-1508**

625 Reilly C, Maguire I, Shanahan P, Shorthall D, McGowan N, Gallagher C. WS10.3 Thoracic kyphosis and complications in adult and paediatric CF patients – multi centre data collaboration. Journal of Cystic Fibrosis. 2012;11:S22. doi:**10.1016/S1569-1993(12)60071-X**

626 Barker N, Raghavan A, Buttling P, Douros K, Everard ML. Thoracic Kyphosis is Now Uncommon Amongst Children and Adolescents with Cystic Fibrosis. Front Pediatr. 2014;2. doi:**10.3389/fped.2014.00011**

627 Fries L, Cahill B, Arora A, Thomas R, Frederick C. Correlation between cobb angle measurement of thoracic kyphosis and severity of pulmonary disease in adults with cystic fibrosis. Pediatr Pulmonol. 2016;51:375-375.

628 Daneshmandi H, Rahmani-Nia F, Hosseini SH. Effect of carrying school backpacks on cardio-respiratory changes in adolescent students. Sport Sci Health. 2008;4(1-2):7-14. doi:**10.1007/s11332-008-0060-8**

629 Barrett E, McCreesh K, Lewis J. Reliability and validity of non-radiographic methods of thoracic kyphosis measurement: A systematic review. Man Ther. 2014;19(1):10-17. doi:**10.1016/j.math.2013.09.003**

630 Gore AP, Kwon SH, Stenbit AE. A Roadmap to the Brittle Bones of Cystic Fibrosis. J Osteoporos. 2011;2011:1-10. doi:**10.4061/2011/926045**

631 King SJ, Topliss DJ, Kotsimbos T, et al. Reduced bone density in cystic fibrosis: ΔF508 mutation is an independent risk factor. European Respiratory Journal. 2005;25(1):54-61. doi:**10.1183/09031936.04.00050204**

632 Haworth CS, Selby PL, Webb AK, et al. Low bone mineral density in adults with cystic fibrosis. Thorax. 1999;54(11):961-967. doi:**10.1136/thx.54.11.961**

633 Gensburger D, Boutroy S, Chapurlat R, et al. 201 Tibial cortical bone is impaired in adults with CF. Journal of Cystic Fibrosis. 2015;14:S110. doi:**10.1016/S1569-1993(15)30378-7**

634 Putman MS, Baker JF, Uluer A, et al. Trends in bone mineral density in young adults with cystic fibrosis over a 15 year period. Journal of Cystic Fibrosis. 2015;14(4):526-532. doi:**10.1016/j.jcf.2015.01.011**

635 Marquette M, Haworth CS. Bone health and disease in cystic fibrosis. Paediatr Respir Rev. 2016;20:2-5. doi:**10.1016/j.prrv.2016.06.003**

636 Anabtawi A, Le T, Putman M, Tangpricha V, Bianchi ML. Cystic fibrosis bone disease: Pathophysiology, assessment and prognostic implications. Journal of Cystic Fibrosis. 2019;18:S48-S55. doi:**10.1016/j.jcf.2019.08.018**

637 Ireland A, Riddell A, Colombo A, Ross-Russell R, Prentice A, Ward KA. Development of musculoskeletal deficits in children with cystic fibrosis in later childhood. Bone. 2023;170:116657. doi:**10.1016/j.bone.2022.116657**

638 Ullal J, Kutney K, Williams KM, Weber DR. Treatment of cystic fibrosis related bone disease. J Clin Transl Endocrinol. 2022;27:100291. doi:**10.1016/j.jcte.2021.100291**

639 Sermet-Gaudelus I, Castanet M, Retsch-Bogart G, Aris RM. Update on Cystic Fibrosis-Related Bone Disease: A Special Focus on Children. Paediatr Respir Rev. 2009;10(3):134-142. doi:**10.1016/j.prrv.2009.05.001**

640 Smith N, Lim A, Yap M, et al. Bone mineral density is related to lung function outcomes in young people with cystic fibrosis—A retrospective study. Pediatr Pulmonol. 2017;52(12):1558-1564. doi:**10.1002/ppul.23894**

641 NICE. Osteoporosis - prevention of fragility fractures. 2025. Available at: **cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/**

642 Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The Prevalence of Osteoporosis, Osteopenia, and Fractures Among Adults with Cystic Fibrosis: A Systematic Literature Review with Meta-Analysis. Calcif Tissue Int. 2010;86(1):1-7. doi:**10.1007/s00223-009-9316-9**

643 Kealaher E, Speight L, Stone M, Lau D, Ketchell RI, Duckers J. 202 Bone mineral density and fractures at the All Wales Adult CF Centre (AWACFC). Journal of Cystic Fibrosis. 2015;14:S110. doi:**10.1016/S1569-1993(15)30379-9**

644 Lynam A, Ballinger K, Daniels T, Arden N, Pearson C. WS11-1 Unexpected vertebral fractures in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2019;18:S19. doi:**10.1016/S1569-1993(19)30178-X**

645 Williams KM, Darukhanavala A, Hicks R, Kelly A. An update on methods for assessing bone quality and health in Cystic fibrosis. J Clin Transl Endocrinol. 2022;27:100281. doi:**10.1016/j.jcte.2021.100281**

646 Brooke-Wavell K, Skelton DA, Barker KL, et al. Strong, steady and straight: UK consensus statement on physical activity and exercise for osteoporosis. Br J Sports Med. 2022;56(15):837-846. doi:**10.1136/bjsports-2021-104634**

647 Allgood S, Dezube R, Rivers E, Lechtzin N. Impact of pain on clinical outcomes in adults with cystic fibrosis: nine years of follow-up. Pediatr Pulmonol. 2019;54:S394.

648 Bell SC, Mainz JG, MacGregor G, et al. Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: results from a cross-sectional study. BMC Pulm Med. 2019;19(1):146. doi:**10.1186/s12890-019-0887-6**

649 Lee AL, Rawlings S, Bennett KA, Armstrong D. Pain and its clinical associations in individuals with cystic fibrosis. Chron Respir Dis. 2016;13(2):102-117. doi:**10.1177/1479972316631135**

650 Dubin E, Lowers J, Dellon EP, et al. Prevalence of unmet pain and symptom management needs in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2023;22(2):352-355. doi:**10.1016/j.jcf.2022.08.006**

651 Clarke EA, Taylor JC, Watson P, et al. WS13.2 Musculoskeletal symptoms in adult with cystic fibrosis. Journal of Cystic Fibrosis. 2018;17:S23-S24. doi:**10.1016/S1569-1993(18)30191-7**

652 Leeds Regional Adult and Paediatric Cystic Fibrosis Units. The Leeds Method of Management: cystic fibrosis and liver disease. 2008. Available at: **cysticfibrosis.online/liver-transplant-2/**

653 Lawrence JM, Moore TL, Madson KL, Rejent AJ, Osborn TG. Arthropathies of cystic fibrosis: case reports and review of the literature. J Rheumatol Suppl. 1993;38:12-15.

654 Pertuiset E, Menkes CJ, Lenoir G, Jehanne M, Douchain F, Guillot M. Cystic fibrosis arthritis. A report of five cases. Br J Rheumatol. 1992;31(8):535-538. doi:**10.1093/rheumatology/31.8.535**

655 Kumar N, Balachandran S, Millner PA, Littlewood JM, Conway SP, Dickson RA. Scoliosis in Cystic Fibrosis. Spine (Phila Pa 1976). 2004;29(18):1990-1995. doi:**10.1097/01.brs.0000138307.07863.c5**

656 Hathorn C, Fall A, McGurk S, Tsirikos AI, Urquhart DS. Acquisition bias may have led to acceptance of the false null hypothesis that prevalence of scoliosis is the same in cystic fibrosis as the general population. Pediatr Pulmonol. 2014;49(2):201-201. doi:**10.1002/ppul.22947**

657 Castner LM, Nasr SZ, Arteta M. Progressive Scoliosis in a Child with Cystic Fibrosis. Case Rep Pediatr. 2019;2019:1-5. doi:**10.1155/2019/1471879**

658 Mamprin G, Donà M, Martignon M, et al. Spinal deformities in young patient with cystic fibrosis (cf): proposal of a screening and follow-up protocol. Pediatr Pulmonol. 2012;47(S35):223-446. doi:**10.1002/ppul.22682**

659 Hathorn C, Fall A, McGurk S, Tsirikos A, Urquhart D. G101(P) Incidence of scoliosis in adolescent cystic fibrosis patients. Arch Dis Child. 2014;99(Suppl 1):A43-A43. doi:**10.1136/archdischild-2014-306237.101**

660 Visser M, Schaap LA. Consequences of Sarcopenia. Clin Geriatr Med. 2011;27(3):387-399. doi:**10.1016/j.cger.2011.03.006**

661 Mandrusiak A, Giraud D, MacDonald J, Wilson C, Watter P. Muscle Length and Joint Range of Motion in Children with Cystic Fibrosis Compared to Children Developing Typically. Physiotherapy Canada. 2010;62(2):141-146. doi:**10.3138/physio.62.2.141**

662 Downes A, Flynn F, Robinson R, et al. WS02.05 Obstetric and neonatal outcomes in cystic fibrosis (CF) show minimal variability with and without elexacaftor/tezacaftor/ivacaftor (ETI). Journal of Cystic Fibrosis. 2023;22:S5. doi:**10.1016/S1569-1993(23)00197-2**

663 Ashbrook JE, Taylor J, Jones A. 258* The development of a musculoskeletal screening tool for adults with cystic fibrosis. Journal of Cystic Fibrosis. 2011;10:S65. doi:**10.1016/S1569-1993(11)60273-7**

664 Ashbrook J, Taylor J, Johnson S. 207 The development of a musculoskeletal screening tool for adults with cystic fibrosis: stage 2. Journal of Cystic Fibrosis. 2012;11:S109. doi:**10.1016/S1569-1993(12)60377-4**

665 Lock K, Nethercott S, Hamilton C, et al. Development of the Addenbrooke's MSK screening tool (AMST) for children and adolescents with cystic fibrosis. Heliyon. 2024;10(4):e25403. doi:**10.1016/j.heliyon.2024.e25403**

666 Edwards E. 449 Development of a musculoskeletal and continence assessment tool for children and adolescents with cystic fibrosis. Journal of Cystic Fibrosis. 2023;22:S236. doi:**10.1016/S1569-1993(23)01374-7**

667 Hodges PW, Cholewicki J, van Dieen JH, eds. Spinal Control: The Rehabilitation of Back Pain. 1st ed. Elsevier Health Sciences; 2013. doi:**10.1016/C2009-0-64122-2**

668 Payne SJ, Yonge CT, Legg JP. 259 The incidence of postural problems identified via the postural screening assessment used in a paediatric annual review and the relationship with the levels of exercise taken. Journal of Cystic Fibrosis. 2011;10:S65. doi:**10.1016/S1569-1993(11)60274-9**

669 Demryl A, Ben^Ami S, Levi M, et al. 371 Chest strength and mobility training: a new approach to airways clearance. Journal of Cystic Fibrosis. 2006;5:S82. doi:**10.1016/S1569-1993(06)80318-8**

670 Graziano L, Giordani B, Nico D, et al. A44 Manual therapy for musculoskeletal pain in cystic fibrosis: review of the literature. Ital J Pediatr. 2019;45(S1):43. doi:**10.1186/s13052-019-0631-0**

671 Lock KJ, Nethercott S, Hamilton C, et al. WS01.05 Development of a musculoskeletal screening tool for children and young people with cystic fibrosis (Addenbrooke's MST): initial findings. Journal of Cystic Fibrosis. 2023;22:S3. doi:**10.1016/S1569-1993(23)00191-1**

672 White D, Stiller K, Roney F. The prevalence and severity of symptoms of incontinence in adult cystic fibrosis patients. Physiother Theory Pract. 2000;16(1):35-42. doi:**10.1080/095939800307593**

673 Cornacchia M, Zenorini A, Perobelli S, Zanolla L, Mastella G, Braggion C. Prevalence of urinary incontinence in women with cystic fibrosis. BJU Int. 2001;88(1):44-48. doi:**10.1046/j.1464-410x.2001.02242.x**

674 Orr A. Questionnaire survey of urinary incontinence in women with cystic fibrosis. BMJ. 2001;322(7301):1521-1521. doi:**10.1136/bmj.322.7301.1521**

675 Neemuchwala F, Ahmed F, Nasr SZ. Prevalence of Pelvic Incontinence in Patients With Cystic Fibrosis. Glob Pediatr Health. 2017;4. doi:**10.1177/2333794X17743424**

676 Frayman KB, Kazmerski TM, Sawyer SM. A systematic review of the prevalence and impact of urinary incontinence in cystic fibrosis. Respirology. 2018;23(1):46-54. doi:**10.1111/resp.13125**

677 Burge AT, Holland AE, Sherburn M, et al. Prevalence and impact of urinary incontinence in men with cystic fibrosis. Physiotherapy. 2015;101(2):166-170. doi:**10.1016/j.physio.2014.11.001**

678 Reichman G, De Boe V, Braeckman J, Michielsen D. Urinary incontinence in patients with cystic fibrosis. Scand J Urol. 2016;50(2):128-131. doi:**10.3109/21681805.2015.1096826**

679 Vella M, Cartwright R, Cardozo L, Parsons M, Madge S, Burns Y. Prevalence of incontinence and incontinence-specific quality of life impairment in women with cystic fibrosis. Neurourol Urodyn. 2009;28(8):986-989. doi:**10.1002/nau.20732**

680 NICE. Urinary Incontinence and Pelvic Organ Prolapse in Women: Management [NG123]. 2019. Available at: **nice.org.uk/guidance/ng123/resources/urinary-incontinence-and-pelvic-organ-prolapse-in-women-management-pdf-66141657205189**

681 Chambers R, Lucht A, Reihill A, Hough J. Prevalence and impact of pelvic floor dysfunction in an adult cystic fibrosis population: a questionnaire survey. Int Urogynecol J. 2017;28(4):591-604. doi:**10.1007/s00192-016-3152-z**

682 Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61(1):37-49. doi:**10.1016/S0090-4295(02)02243-4**

683 Prasad SA, Balfour-Lynn IM, Carr SB, Madge SL. A comparison of the prevalence of urinary incontinence in girls with cystic fibrosis, asthma, and healthy controls. Pediatr Pulmonol. 2006;41(11):1065-1068. doi:**10.1002/ppul.20493**

684 Dodd ME, Langman H. Urinary incontinence in cystic fibrosis. J R Soc Med. 2005;98 Suppl 45(Suppl 45):28-36.

685 Ashbrook JE, McVean R, Jones A. Is there a relationship between stress urinary incontinence and back pain in the Manchester Adult Cystic Fibrosis Centre female population? Journal of Cystic Fibrosis. 2010;9:S74. doi:**10.1016/S1569-1993(10)60285-8**

686 McVean RJ, Orr A, Webb AK, et al. Treatment of urinary incontinence in cystic fibrosis. Journal of Cystic Fibrosis. 2003;2(4):171-176. doi:**10.1016/S1569-1993(03)00088-2**

687 Button B, Sherburn M, Chase J, Stillman B. Effect of three month physiotherapeutic intervention on incontinence in women with chronic cough relate to cystic fibrosis and COPD. Pediatr Pulmonol. 2005;Suppl 28a:369.

688 Button BM, Holland AE, Sherburn MS, Chase J, Wilson JW, Burge AT. Prevalence, impact and specialised treatment of urinary incontinence in women with chronic lung disease. Physiotherapy. 2019;105(1):114-119. doi:**10.1016/j.physio.2018.07.006**

689 Thompson JA, O'Sullivan PB. Levator plate movement during voluntary pelvic floor muscle contraction in subjects with incontinence and prolapse: a cross-sectional study and review. Int Urogynecol J Pelvic Floor Dysfunct. 2003;14(2):84-88. doi:**10.1007/s00192-003-1036-5**

690 Benezech A, Desmazes-Dufeu N, Baumstarck K, et al. Prevalence of Fecal Incontinence in Adults with Cystic Fibrosis. Dig Dis Sci. 2018;63(4):982-988. doi:**10.1007/s10620-017-4825-2**

691 Hubeaux K, Gueganton L, Nowak E, et al. Prevalence and severity of functional urinary and anorectal disorders and their impact on quality of life in cystic fibrosis. Journal of Cystic Fibrosis. 2024;23(3):579-586. doi:**10.1016/j.jcf.2023.10.011**

692 Blackwell K, Malone PSJ, Denny A, Connett G, Maddison J. The prevalence of stress urinary incontinence in patients with cystic fibrosis: an under-recognized problem. J Pediatr Urol. 2005;1(1):5-9. doi:**10.1016/j.jpurol.2004.07.001**

693 Faulkner J, Gates A, Flight WG, et al. WS10.03 Impact of triple CFTR modulator therapy on urinary incontinence symptoms in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2022;21:S20. doi:**10.1016/S1569-1993(22)00209-0**

694 Vergeldt TFM, Weemhoff M, IntHout J, Kluivers KB. Risk factors for pelvic organ prolapse and its recurrence: a systematic review. Int Urogynecol J. 2015;26(11):1559-1573. doi:**10.1007/s00192-015-2695-8**

695 Hagen S, Stark D, Glazener C, et al. Individualised pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicentre randomised controlled trial. The Lancet. 2014;383(9919):796-806. doi:**10.1016/S0140-6736(13)61977-7**

696 NICE. Menopause: Identification and Management [NG23]. 2024. Available at: **nice.org.uk/guidance/ng23/resources/menopause-identification-and-management-pdf-1837330217413**

697 Prochownik K, Jain R, Taylor-Cousar JL, et al. Menopause in people with cystic fibrosis. Menopause. Published online January 31, 2023. doi:**10.1097/GME.0000000000002155**

698 Hughan KS, Daley T, Rayas MS, Kelly A, Roe A. Female reproductive health in cystic fibrosis. Journal of Cystic Fibrosis. 2019;18:S95-S104. doi:**10.1016/j.jcf.2019.08.024**

699 West NE, Kazmerski TM, Taylor-Cousar JL, et al. Optimizing sexual and reproductive health across the lifespan in people with cystic fibrosis. Pediatr Pulmonol. 2022;57(S1). doi:**10.1002/ppul.25703**

700 Jain R, Kazmerski TM, Aitken ML, et al. Challenges Faced by Women with Cystic Fibrosis. Clin Chest Med. 2021;42(3):517-530. doi:**10.1016/j.ccm.2021.04.010**

701 Kazmerski TM, Stransky OM, Lavage DR, et al. Sexual and reproductive health experiences and care of adult women with cystic fibrosis. Journal of Cystic Fibrosis. 2023;22(2):223-233. doi:**10.1016/j.jcf.2022.09.013**

702 Leech MM, Stransky OM, Talabi MB, Borrero S, Roe AH, Kazmerski TM. Exploring the reproductive decision support needs and preferences of women with cystic fibrosis,. Contraception. 2021;103(1):32-37. doi:**10.1016/j.contraception.2020.10.004**

703 Taylor-Cousar JL. CFTR Modulators: Impact on Fertility, Pregnancy, and Lactation in Women with Cystic Fibrosis. J Clin Med. 2020;9(9). doi:**10.3390/jcm9092706**

704 Montemayor K, Tullis E, Jain R, Taylor-Cousar JL. Management of pregnancy in cystic fibrosis. Breathe. 2022;18(2):220005. doi:**10.1183/20734735.0005-2022**

705 Kroon MAGM, Akkerman-Nijland AM, Rottier BL, Koppelman GH, Akkerman OW, Touw DJ. Drugs during pregnancy and breast feeding in women diagnosed with Cystic Fibrosis - An update. Journal of Cystic Fibrosis. 2018;17(1):17-25. doi:**10.1016/j.jcf.2017.11.009**

706 Jain R, Magaret A, Vu PT, et al. Prospectively evaluating maternal and fetal outcomes in the era of CFTR modulators: the MAYFLOWERS observational clinical trial study design. BMJ Open Respir Res. 2022;9(1):e001289. doi:**10.1136/bmjresp-2022-001289**

707 Elijah J, Fitzgerald LJ, Phan H. Use of CFTR modulators in special populations, part 1: Pregnancy and lactation. Pediatr Pulmonol. 2023;58(12):3377-3385. doi:**10.1002/ppul.26706**

708 Taylor-Cousar JL, Jain R. Maternal and fetal outcomes following elexacaftor-tezacaftor-ivacaftor use during pregnancy and lactation. Journal of Cystic Fibrosis. 2021;20(3):402-406. doi:**10.1016/j.jcf.2021.03.006**

709 Nash EF, Middleton PG, Taylor-Cousar JL. Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators – an international survey. Journal of Cystic Fibrosis. 2020;19(4):521-526. doi:**10.1016/j.jcf.2020.02.018**

710 Govin B, Bullen L, Dyce P, Jackson V, Green D, Walshaw M. P387 Reviews and outcomes from a new pregnancy support service at a large cystic fibrosis centre. Journal of Cystic Fibrosis. 2023;22:S182. doi:**10.1016/S1569-1993(23)00757-9**

711 Jain R, Taylor-Cousar JL. Fertility, Pregnancy and Lactation Considerations for Women with CF in the CFTR Modulator Era. J Pers Med. 2021;11(5):418. doi:**10.3390/jpm11050418**

712 Thorpe-Beeston JG. Contraception and pregnancy in cystic fibrosis. J R Soc Med. 2009;102 Suppl 1(Suppl 1):3-10. doi:**10.1258/jrsm.2009.s19002**

713 Jain R, Kazmerski TM, Zuckerwise LC, et al. Pregnancy in cystic fibrosis: Review of the literature and expert recommendations. Journal of Cystic Fibrosis. 2022;21(3):387-395. doi:**10.1016/j.jcf.2021.07.019**

714 Traxler SA, Chavez V, Hadjiliadis D, Shea JA, Mollen C, Schreiber CA. Fertility considerations and attitudes about family planning among women with cystic fibrosis. Contraception. 2019;100(3):228-233. doi:**10.1016/j.contraception.2019.05.005**

715 Godfrey EM, Mody S, Schwartz MR, et al. Contraceptive use among women with cystic fibrosis: A pilot study linking reproductive health questions to the Cystic Fibrosis Foundation National Patient Registry. Contraception. 2020;101(6):420-426. doi:**10.1016/j.contraception.2020.02.006**

716 Daccò V, Alicandro G, Trespidi L, Gramegna A, Blasi FA. Unplanned pregnancies following the introduction of elexacaftor/tezacaftor/ivacaftor therapy in women with cystic fibrosis. Arch Gynecol Obstet. 2023;308(5):1657-1659. doi:**10.1007/s00404-023-07153-y**

717 Peng G, Taylor-Cousar JL, Lee M, et al. Association between unplanned pregnancies and maternal exacerbations in cystic fibrosis. Journal of Cystic Fibrosis. 2023;22(5):796-803. doi:**10.1016/j.jcf.2023.03.020**

718 Kazmerski TM, West NE, Jain R, et al. Family-building and parenting considerations for people with cystic fibrosis. Pediatr Pulmonol. 2022;57(S1). doi:**10.1002/ppul.25620**

719 Whitty JE. Cystic fibrosis in pregnancy. Clin Obstet Gynecol. 2010;53(2):369-376. doi:**10.1097/GRF.0b013e3181deb448**

720 McGlynn J, DeCelie-Germana JK, Kier C, Langfelder-Schwind E. Reproductive Counseling and Care in Cystic Fibrosis: A Multidisciplinary Approach for a New Therapeutic Era. 2023;13(7):1545. doi:**10.3390/life13071545**

721 Renton M, Priestley L, Bennett L, Mackillop L, Chapman S. Pregnancy outcomes in cystic fibrosis: a 10-year experience from a UK centre. Obstet Med. 2015;8(2):99-101. doi:**10.1177/1753495X15575628**

722 Vieira V de S, Feiten T dos S, Ferrari RS, Dalcin P de TR, Ziegler B. Predictive factors for premature birth and respiratory exacerbation in pregnancies of women with cystic fibrosis. J Pediatr (Rio J). 2022;98(1):33-38. doi:**10.1016/j.jped.2021.02.009**

723 Lau EMT, Barnes DJ, Moriarty C, et al. Pregnancy outcomes in the current era of cystic fibrosis care: a 15-year experience. Aust N Z J Obstet Gynaecol. 2011;51(3):220-224. doi:**10.1111/j.1479-828X.2010.01287.x**

724 Edenborough FP, Stableforth DE, Webb AK, Mackenzie WE, Smith DL. Outcome of pregnancy in women with cystic fibrosis. Thorax. 1995;50(2):170-174. doi:**10.1136/thx.50.2.170**

725 Edenborough FP, Borgo G, Knoop C, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. Journal of Cystic Fibrosis. 2008;7:S2-S32. doi:**10.1016/j.jcf.2007.10.001**

726 McArdle JR. Pregnancy in Cystic Fibrosis. Clin Chest Med. 2011;32(1):111-120. doi:**10.1016/j.ccm.2010.10.005**

727 Burden C, Ion R, Chung Y, Henry A, Downey DG, Trinder J. Current pregnancy outcomes in women with cystic fibrosis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2012;164(2):142-145. doi:**10.1016/j.ejogrb.2012.06.013**

728 Thorpe-Beeston J, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancies in women with cystic fibrosis—single centre experience 1998–2011. BJOG. 2013;120(3):354-361. doi:**10.1111/1471-0528.12040**

729 Patel EM, Swamy GK, Heine RP, Kuller JA, James AH, Grotegut CA. Medical and obstetric complications among pregnant women with cystic fibrosis. Am J Obstet Gynecol. 2015;212(1):98.e1-98.e9. doi:**10.1016/j.ajog.2014.07.018**

730 McDonald CM, Alvarez JA, Bailey J, et al. Academy of Nutrition and Dietetics: 2020 Cystic Fibrosis Evidence Analysis Center Evidence-Based Nutrition Practice Guideline. J Acad Nutr Diet. 2021;121(8):1591-1636.e3. doi:**10.1016/j.jand.2020.03.015**

731 Cohen-Cymberknoh M, Ben Meir E, Gartner S, et al. How abnormal is the normal? Clinical characteristics of CF patients with normal FEV_1. Pediatr Pulmonol. 2021;56(7):2007-2013. doi:**10.1002/ppul.25371**

732 Padoan RF, Quattrucci S, Amato A, Salvatore M, Salvatore D, Campagna G. Perinatal outcomes in women with cystic fibrosis: Data from the Italian Cystic Fibrosis Registry. Acta Obstet Gynecol Scand. 2021;100(8):1439-1444. doi:**10.1111/aogs.14190**

733 Esan O, Schlüter D, Phillips R, et al. Pregnancy rates and outcomes in women with cystic fibrosis in the UK: comparisons with the general population before and after the introduction of disease-modifying treatment, 2003–17. BJOG. 2022;129(5):743-751. doi:**10.1111/1471-0528.16957**

734 Jelin AC, Sharshiner R, Caughey AB. Maternal co-morbidities and neonatal outcomes associated with cystic fibrosis *. The Journal of Maternal-Fetal & Neonatal Medicine. 2017;30(1):4-7. doi:**10.3109/14767058.2016.1161747**

735 Frayman KB, Chin M, Sawyer SM, Bell SC. Sexual and reproductive health in cystic fibrosis. Curr Opin Pulm Med. 2020;26(6):685-695. doi:**10.1097/MCP.0000000000000731**

736 Montemayor K, Kazmerski TM, Riekert KA, et al. Clinician attitudes and practices on pregnancy planning and care in cystic fibrosis. Journal of Cystic Fibrosis. 2023;22(2):201-206. doi:**10.1016/j.jcf.2022.07.001**

737 Martín Hernández AS, Rodrigo-García M, Peláez A, Gómez Punter RM, Ancochea J, Girón Moreno RM. Evolution of Lung Function in Pregnant Women With Cystic Fibrosis. Arch Bronconeumol. 2023;59(10):685-687. doi:**10.1016/j.arbres.2023.07.011**

738 Parrott H, Madge S, Thorpe-Beeston G, Agent P. Airway clearance requirements during pregnancy. Pediatr Pulmonol. 2008;523.

739 Shteinberg M, Taylor-Cousar JL, Durieu I, Cohen-Cymberknoh M. Fertility and Pregnancy in Cystic Fibrosis. Chest. 2021;160(6):2051-2060. doi:**10.1016/j.chest.2021.07.024**

740 Leonardia K, Stanford G, McLoughlin V, Felton I. EPS8.02 Evolving physiotherapy airway clearance technique (ACT) interventions during cystic fibrosis (CF) pregnancy in the variant specific therapy (VST) era. Journal of Cystic Fibrosis. 2024;23:S57. doi:**10.1016/S1569-1993(24)00281-9**

741 Reynaud Q, Rousset Jablonski C, Poupon-Bourdy S, et al. Pregnancy outcome in women with cystic fibrosis and poor pulmonary function. Journal of Cystic Fibrosis. 2020;19(1):80-83. doi:**10.1016/j.jcf.2019.06.003**

742 Kazmerski TM, Jain R, Lee M, Taylor-Cousar JL. Parenthood impacts short-term health outcomes in people with cystic fibrosis. Journal of Cystic Fibrosis. 2022;21(4):662-668. doi:**10.1016/j.jcf.2022.02.006**

743 Cammidge SL, Duff AJA, Latchford GJ, Etherington C. When Women with Cystic Fibrosis Become Mothers: Psychosocial Impact and Adjustments. Pulm Med. 2016;2016:9458980. doi:**10.1155/2016/9458980**

744 Bianco B, Horsley A, Brennan A. Implications of fatherhood in cystic fibrosis. Paediatr Respir Rev. 2019;31:18-20. doi:**10.1016/j.prrv.2019.02.008**

745 Campbell K, Zarli M, Schuppe K, Wong R, Rahman F, Ramasamy R. Sexual and Reproductive Health Among Men With Cystic Fibrosis. Urology. 2023;179:9-15. doi:**10.1016/j.urology.2023.06.017**

746 Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome. Hepatology. 2002;36(6):1374-1382. doi:**10.1053/jhep.2002.37136**

747 Toledano MB, Mukherjee SK, Howell J, et al. The emerging burden of liver disease in cystic fibrosis patients: A UK nationwide study. PLoS One. 2019;14(4):e0212779. doi:**10.1371/journal.pone.0212779**

748 Valamparampil JJ, Gupte GL. Cystic fibrosis associated liver disease in children. World J Hepatol. 2021;13(11):1727-1742. doi:**10.4254/wjh.v13.i11.1727**

749 Bartlett JR. Genetic Modifiers of Liver Disease in Cystic Fibrosis. JAMA. 2009;302(10):1076. doi:**10.1001/jama.2009.1295**

750 Sherwood JS, Ullal J, Kutney K, Hughan KS. Cystic fibrosis related liver disease and endocrine considerations. J Clin Transl Endocrinol. 2022;27:100283. doi:**10.1016/j.jcte.2021.100283**

751 Dassios T, Mitakidou MR, Dhawan A, Papalexopoulou N, Gupta A, Greenough A. Physical activity and liver disease affect the fat-free mass in adolescents with cystic fibrosis. Eur J Pediatr. 2022;182(2):769-775. doi:**10.1007/s00431-022-04752-w**

752 Hurt K, Simmonds NJ. Cystic Fibrosis: Management of Haemoptysis. Paediatr Respir Rev. 2012;13(4):200-205. doi:**10.1016/j.prrv.2012.01.003**

753 Roebuck DJ, Barnacle AM. Haemoptysis and bronchial artery embolization in children. Paediatr Respir Rev. 2008;9(2):95-104. doi:**10.1016/j.prrv.2007.12.003**

754 Barben JU, Ditchfield M, Carlin JB, Robertson CF, Robinson PJ, Olinsky A. Major haemoptysis in children with cystic fibrosis: a 20-year retrospective study. Journal of Cystic Fibrosis. 2003;2(3):105-111. doi:**10.1016/S1569-1993(03)00066-3**

755 Thompson V, Mayer-Hamblett N, Kloster M, Bilton D, Flume PA. Risk of hemoptysis in cystic fibrosis clinical trials: A retrospective cohort study. J Cyst Fibros. 2015;14(5):632-638. doi:**10.1016/j.jcf.2015.02.003**

756 Bessonova L, Volkova N, Higgins M, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. Thorax. 2018;73(8):731-740. doi:**10.1136/thoraxjnl-2017-210394**

757 Mingora CM, Flume PA. Pulmonary Complications in Cystic Fibrosis: Past, Present, and Future. Chest. 2021;160(4):1232-1240. doi:**10.1016/j.chest.2021.06.017**

758 Furnari ML, Salerno S, Rabiolo A, Caravello V, Pardo F. Bronchial to subclavian shunt in a CF patient. A potential pitfall for embolization. Journal of Cystic Fibrosis. 2003;2(4):217-219. doi:**10.1016/S1569-1993(03)00095-X**

759 Flume PA, Yankaskas JR, Ebeling M, Hulsey T, Clark LL. Massive Hemoptysis in Cystic Fibrosis. Chest. 2005;128(2):729-738. doi:**10.1378/chest.128.2.729**

760 Bozkanat KM, West NE, Ladores S, et al. Catamenial haemoptysis in females with cystic fibrosis: a case series with review of management strategies. Respirol Case Rep. 2021;9(6). doi:**10.1002/rcr2.755**

761 Sheppard M, Selvadurai H, Robinson PD, Pandit C, Chennapragada SM, Fitzgerald DA. Approaches to the management of haemoptysis in young people with cystic fibrosis. Paediatr Respir Rev. 2023;46:17-22. doi:**10.1016/j.prrv.2022.10.002**

762 Dohna M, Renz DM, Stehling F, et al. Coil embolisation for massive haemoptysis in cystic fibrosis. BMJ Open Respir Res. 2021;8(1):e000985. doi:**10.1136/bmjresp-2021-000985**

763 Marshall TJ, Flower CDR, Jackson JE. The role of radiology in the investigation and management of patients with haemoptysis. Clin Radiol. 1996;51(6):391-400. doi:**10.1016/S0009-9260(96)80156-5**

764 Ibrahim WH. Massive haemoptysis: the definition should be revised. European Respiratory Journal. 2008;32(4):1131.2-1132. doi:**10.1183/09031936.00080108**

765 Efrati O, Harash O, Rivlin J, et al. Hemoptysis in Israeli CF patients — Prevalence, treatment, and clinical characteristics. Journal of Cystic Fibrosis. 2008;7(4):301-306. doi:**10.1016/j.jcf.2007.11.007**

766 Flume PA. Pulmonary Complications of Cystic Fibrosis. Respir Care. 2009;54(5):618-627. doi:**10.4187/aarc0443**

767 Flume PA, Mogayzel PJ, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC. Cystic Fibrosis Pulmonary Guidelines. Pulmonary Complications: Haemoptysis and Pneumothorax. Am J Respir Crit Care Med. 2010;182(3):298-306. doi:**10.1164/rccm.201002-0157OC**

768 Semasinghe Bandaralage SP, Tay G, Hay K, et al. Outcomes of artery embolisation for cystic fibrosis patients with haemoptysis: a 20-year experience at a major Australian tertiary centre. Intern Med J. 2021;51(9):1526-1529. doi:**10.1111/imj.15483**

769 Roussel A, Sage E, Roux A, Guth A, Mellot F, Gravel G. Bronchial artery embolization for hemoptysis in adult patients with cystic fibrosis: a single-center retrospective study. Acta radiol. 2023;64(4):1381-1389. doi:**10.1177/02841851221126833**

770 Silveira MAP da, Silveira PAP da, Beltrami FG, Scaffaro LA, Dalcin P de TR. Clinical outcomes of cystic fibrosis patients with hemoptysis treated with bronchial artery embolization. J Bras Pneumol. 2021;47(4):e20200557. doi:**10.36416/1806-3756/e20200557**

771 Flight WG, Barry PJ, Bright-Thomas RJ, Butterfield S, Ashleigh R, Jones AM. Outcomes Following Bronchial Artery Embolisation for Haemoptysis in Cystic Fibrosis. Cardiovasc Intervent Radiol. 2017;40(8):1164-1168. doi:**10.1007/s00270-017-1626-0**

772 Floridi C, Boscarato P, Ventura C, et al. Role of Bronchial Artery Embolization as Early Treatment Option in Stable Cystic Fibrosis Patients with Sub-Massive Hemoptysis: Personal Experience and Literature Review. J Clin Med. 2022;11(21):6432. doi:**10.3390/jcm11216432**

773 Romàn CM, Loughlin HC, Aliaj E, Fay RJ, Tran QT, Borowitz D. Hemoptysis from the perspective of people with cystic fibrosis. Clin Respir J. 2020;14(3):299-303. doi:**10.1111/crj.13132**

774 NICE. Acutely Ill Adults in Hospital: Recognising and Responding to Deterioration [CG50]. 2007. Available at: **nice.org.uk/guidance/cg50/resources/acutely-ill-adults-in-hospital-recognising-and-responding-to-deterioration-pdf-975500772037**

775 Flume PA. Pneumothorax in Cystic Fibrosis. Chest. 2003;123(1):217-221. doi:**10.1378/chest.123.1.217**

776 MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65(Suppl 2):ii18-ii31. doi:**10.1136/thx.2010.136986**

777 Cuenca AG, Beierle EA. Pulmonary surgery in cystic fibrosis. Semin Pediatr Surg. 2008;17(1):60-65. doi:**10.1053/j.sempedsurg.2007.10.009**

778 Curtis HJ, Bourke SJ, Dark JH, Corris PA. Lung Transplantation Outcome in Cystic Fibrosis Patients With Previous Pneumothorax. The Journal of Heart and Lung Transplantation. 2005;24(7):865-869. doi:**10.1016/j.healun.2004.05.024**

779 Robinson PD, Cooper P, Ranganathan SC. Evidence-based management of paediatric primary spontaneous pneumothorax. Paediatr Respir Rev. 2009;10(3):110-117. doi:**10.1016/j.prrv.2008.12.003**

780 Smith MA, McGarry ME, Ly NP, Zinter MS. Outcomes of Children With Cystic Fibrosis Admitted to PICUs*. Pediatric Critical Care Medicine. 2020;21(10):e879-e887. doi:**10.1097/PCC.0000000000002358**

781 MacDuff A, Tweedie J, McIntosh L, Innes JA. Pneumothorax in cystic fibrosis: Prevalence and outcomes in Scotland. Journal of Cystic Fibrosis. 2010;9(4):246-249. doi:**10.1016/j.jcf.2010.04.005**

782 Lord RW, Jones AM, Webb AK, Barry PJ. Pneumothorax in cystic fibrosis: beyond the guidelines. Paediatr Respir Rev. 2016;20:30-33. doi:**10.1016/j.prrv.2016.06.012**

783 Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2023 Annual Data Report. 2024. Available at: **cysticfibrosis.org.uk/sites/default/files/2024-11/CFT_2023_Annual_Data_Report_Oct2024%201.pdf**

784 McLaughlin FJ, Matthews WJ, Strieder DJ, Khaw KT, Schuster S, Shwachman H. Pneumothorax in cystic fibrosis: Management and outcome. J Pediatr. 1982;100(6):863-869. doi:**10.1016/S0022-3476(82)80502-7**

785 Flume PA, Strange C, Ye X, Ebeling M, Hulsey T, Clark LL. Pneumothorax in Cystic Fibrosis. Chest. 2005;128(2):720-728. doi:**10.1378/chest.128.2.720**

786 Hafen GM, Ukoumunne OC, Robinson PJ. Pneumothorax in cystic fibrosis: a retrospective case series. Arch Dis Child. 2006;91(11):924-925. doi:**10.1136/adc.2006.095083**

787 Dicken BJ, Ziegler MM. Surgical management of pulmonary and gastrointestinal complications in children with cystic fibrosis. Curr Opin Pediatr. 2006;18(3):321-329. doi:**10.1097/01.mop.0000193320.06322.fb**

788 Schuster SR, McLaughlin FJ, Matthews WJ, Strieder DJ, Khaw KT, Shwachman H. Management of pneumothorax in cystic fibrosis. J Pediatr Surg. 1983;18(4):492-497. doi:**10.1016/S0022-3468(83)80207-3**

789 Tschopp JM, Rami-Porta R, Noppen M, Astoul P. Management of spontaneous pneumothorax: state of the art. European Respiratory Journal. 2006;28(3):637-650. doi:**10.1183/09031936.06.00014206**

790 Amin R, Noone PG, Ratjen F. Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis. Cochrane Database of Systematic Reviews. 2012;2015(4). doi:**10.1002/14651858.CD007481.pub3**

791 Turcios NL. Cystic Fibrosis Lung Disease: An Overview. Respir Care. 2020;65(2):233-251. doi:**10.4187/respcare.06697**

792 Podder S, Benn B, Franco RA, Biller J, Kurman JS. Endobronchial valves for treatment of persistent air leak after secondary spontaneous pneumothorax in patients with cystic fibrosis. Chest. 2022;162(4):A2079-A2080. doi:**10.1016/j.chest.2022.08.1718**

793 Agent P. The physiotherapy management of the critically ill patient with cystic fibrosis including DIOS, pneumothorax, haemoptysis and acute respiratory failure. Pediatr Pulmonol. 2016;51:150-152.

794 Cooper BG. An update on contraindications for lung function testing. Thorax. 2011;66(8):714-723. doi:**10.1136/thx.2010.139881**

795 Haworth CS, Dodd ME, Atkins M, Woodcock AA, Webb AK. Pneumothorax in adults with cystic fibrosis dependent on nasal intermittent positive pressure ventilation (NIPPV): a management dilemma. Thorax. 2000;55(7):620-622. doi:**10.1136/thorax.55.7.620**

796 Ellaffi M, Vinsonneau C, Coste J, et al. One-year Outcome after Severe Pulmonary Exacerbation in Adults with Cystic Fibrosis. Am J Respir Crit Care Med. 2005;171(2):158-164. doi:**10.1164/rccm.200405-667OC**

797 Sood N, Paradowski LJ, Yankaskas JR. Outcomes of intensive care unit care in adults with cystic fibrosis. Am J Respir Crit Care Med. 2001;163(2):335-338. doi:**10.1164/ajrccm.163.2.2003076**

798 Naehrlich L, Orenti A, Dunlevy F, et al. Incidence of SARS-CoV-2 in people with cystic fibrosis in Europe between February and June 2020. Journal of Cystic Fibrosis. 2021;20(4):566-577. doi:**10.1016/j.jcf.2021.03.017**

799 Texereau J, Jamal D, Choukroun G, et al. Determinants of mortality for adults with cystic fibrosis admitted in Intensive Care Unit: a multicenter study. Respir Res. 2006;7(1):14. doi:**10.1186/1465-9921-7-14**

800 Efrati O, Bylin I, Segal E, et al. Outcome of patients with cystic fibrosis admitted to the intensive care unit: Is invasive mechanical ventilation a risk factor for death in patients waiting lung transplantation? Heart & Lung. 2010;39(2):153-159. doi:**10.1016/j.hrtlng.2009.06.014**

801 Vedam H, Moriarty C, Torzillo PJ, McWilliam D, Bye PTP. Improved outcomes of patients with cystic fibrosis admitted to the intensive care unit. Journal of Cystic Fibrosis. 2004;3(1):8-14. doi:**10.1016/j.jcf.2003.12.003**

802 Reid DW, Bell SC. ICU outcomes in cystic fibrosis following invasive ventilation. Respirology. 2013;18(4):585-586. doi:**10.1111/resp.12077**

803 Shafii AE, Mason DP, Brown CR, et al. Growing Experience with Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation. ASAIO Journal. 2012;58(5):526-529. doi:**10.1097/MAT.0b013e31826417d8**

804 Turner DA, Cheifetz IM, Rehder KJ, et al. Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: A practical approach*. Crit Care Med. 2011;39(12):2593-2598. doi:**10.1097/CCM.0b013e3182282bbe**

805 Rehder KJ, Turner DA, Hartwig MG, et al. Active Rehabilitation During Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation. Respir Care. 2013;58(8):1291-1298. doi:**10.4187/respcare.02155**

806 Jones A, Bilton D, Evans TW, Finney SJ. Predictors of outcome in patients with cystic fibrosis requiring endotracheal intubation. Respirology. 2013;18(4):630-636. doi:**10.1111/resp.12051**

807 Gibilaro JM, Keating C, Benvenuto L, et al. Survival in cystic fibrosis after acute respiratory failure supported by extracorporeal membrane oxygenation and/or invasive mechanical ventilation. Journal of Cystic Fibrosis. 2022;21(4):669-674. doi:**10.1016/j.jcf.2021.08.016**

808 Tipograf Y, Salna M, Minko E, et al. Outcomes of Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation. Ann Thorac Surg. 2019;107(5):1456-1463. doi:**10.1016/j.athoracsur.2019.01.032**

809 NICE. Rehabilitation after Critical Illness in Adults [CG83]. 2009. Available at: **nice.org.uk/guidance/cg83/resources/rehabilitation-after-critical-illness-in-adults-pdf-975687209413**

810 Eden A, Purkiss C, Cork G, et al. In-patient physiotherapy for adults on veno-venous extracorporeal membrane oxygenation – United Kingdom ECMO Physiotherapy Network: A consensus agreement for best practice. J Intensive Care Soc. 2017;18(3):212-220. doi:**10.1177/1751143717705801**

811 Hirche TO, Knoop C, Hebestreit H, et al. Practical Guidelines: Lung Transplantation in Patients with Cystic Fibrosis. Pulm Med. 2014;2014:1-22. doi:**10.1155/2014/621342**

812 Wickerson L, Grewal R, Singer LG, Chaparro C. Experiences and perceptions of receiving and prescribing rehabilitation in adults with cystic fibrosis undergoing lung transplantation. Chron Respir Dis. 2023;20. doi:**10.1177/14799731221139293**

813 Koutsokera A, Sykes J, Theou O, et al. Frailty predicts outcomes in cystic fibrosis patients listed for lung transplantation. The Journal of Heart and Lung Transplantation. 2022;41(11):1617-1627. doi:**10.1016/j.healun.2022.07.017**

814 Himebauch AS, Yehya N, Schaubel DE, et al. Poor functional status at the time of waitlist for pediatric lung transplant is associated with worse pretransplant outcomes. The Journal of Heart and Lung Transplantation. 2023;42(12):1735-1742. doi:**10.1016/j.healun.2023.07.003**

815 Hume E, Ward L, Wilkinson M, Manifield J, Clark S, Vogiatzis I. Exercise training for lung transplant candidates and recipients: a systematic review. European Respiratory Review. 2020;29(158):200053. doi:**10.1183/16000617.0053-2020**

816 Hoffman M, Chaves G, Ribeiro-Samora GA, Britto RR, Parreira VF. Effects of pulmonary rehabilitation in lung transplant candidates: a systematic review. BMJ Open. 2017;7(2):e013445. doi:**10.1136/bmjopen-2016-013445**

817 Nicholson JM, Goldstein RS, Nourouzpour S, et al. Pulmonary Rehabilitation in Cystic Fibrosis Lung Transplant Candidates. In: TP102. TP102 BEYOND COPD: GROWING THE REACH OF PULMONARY REHABILITATION. American Thoracic Society; 2021:A4128-A4128. doi:**10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A4128**

818 Holland AE, Cox NS, Houchen-Wolloff L, et al. Defining Modern Pulmonary Rehabilitation. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2021;18(5):e12-e29. doi:**10.1513/AnnalsATS.202102-146ST**

819 Layton AM, Irwin AM, Mihalik EC, et al. Telerehabilitation Using Fitness Application in Patients with Severe Cystic Fibrosis Awaiting Lung Transplant: A Pilot Study. Int J Telemed Appl. 2021;2021:1-7. doi:**10.1155/2021/6641853**

820 Meira L, Damas C, Vaz M, et al. Maintenance of exercise capacity in lung transplant candidates undergoing a pulmonary rehabilitation program. Eur Respir J. 2014;44(Suppl. 58):P631.

821 NHS England. Extracorporeal Membrane Oxygenation (ECMO) as a Bridge to Lung Transplant (All Ages). 2021. Available at: **england.nhs.uk/wp-content/uploads/2021/07/1803-ECMO-BTLT-Policy-Final-1.pdf**

822 Lowman JD, Kirk TK, Clark DE. Physical therapy management of a patient on portable extracorporeal membrane oxygenation as a bridge to lung transplantation: a case report. Cardiopulm Phys Ther J. 2012;23(1):30-35.

823 Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. The Journal of Heart and Lung Transplantation. 2021;40(11):1349-1379. doi:**10.1016/j.healun.2021.07.005**

824 Mathur S, Levy RD, Reid DW. Skeletal Muscle Strength and Endurance in Recipients of Lung Transplants. Cardiopulm Phys Ther J. 2008;19(3):84-93. doi:**10.1097/01823246-200819030-00003**

825 Durette G, Jomphe V, Bureau NJ, et al. Long-term bone mineral density changes and fractures in lung transplant recipients with cystic fibrosis. Journal of Cystic Fibrosis. 2021;20(3):525-532. doi:**10.1016/j.jcf.2020.09.012**

826 Rosenberger EM, Dew MA, DiMartini AF, DeVito Dabbs AJ, Yusen RD. Psychosocial Issues Facing Lung Transplant Candidates, Recipients and Family Caregivers. Thorac Surg Clin. 2012;22(4):517-529. doi:**10.1016/j.thorsurg.2012.08.001**

827 Maury G, Langer D, Verleden G, et al. Skeletal Muscle Force and Functional Exercise Tolerance Before and After Lung Transplantation: A Cohort Study. American Journal of Transplantation. 2008;8(6):1275-1281. doi:**10.1111/j.1600-6143.2008.02209.x**

828 Langer D, Gosselink R, Pitta F, et al. Physical Activity in Daily Life 1 Year After Lung Transplantation. The Journal of Heart and Lung Transplantation. 2009;28(6):572-578. doi:**10.1016/j.healun.2009.03.007**

829 Munro PE, Holland AE, Bailey M, Button BM, Snell GI. Pulmonary Rehabilitation Following Lung Transplantation. Transplant Proc. 2009;41(1):292-295. doi:**10.1016/j.transproceed.2008.10.043**

830 Wickerson L, Mathur S, Brooks D. Exercise training after lung transplantation: A systematic review. The Journal of Heart and Lung Transplantation. 2010;29(5):497-503. doi:**10.1016/j.healun.2009.12.008**

831 Oelberg DA, Systrom DM, Markowitz DH, et al. Exercise performance in cystic fibrosis before and after bilateral lung transplantation. J Heart Lung Transplant. 1998;17(11):1104-1112.

832 Langer D, Burtin C, Schepers L, et al. Exercise Training After Lung Transplantation Improves Participation in Daily Activity: A Randomized Controlled Trial. American Journal of Transplantation. 2012;12(6):1584-1592. doi:**10.1111/j.1600-6143.2012.04000.x**

833 Vivodtzev I, Pison C, Guerrero K, et al. Benefits of home-based endurance training in lung transplant recipients. Respir Physiol Neurobiol. 2011;177(2):189-198. doi:**10.1016/j.resp.2011.02.005**

834 Ihle F, Neurohr C, Huppmann P, et al. Effect of inpatient rehabilitation on quality of life and exercise capacity in long-term lung transplant survivors: A prospective, randomized study. The Journal of Heart and Lung Transplantation. Published online April 2011. doi:**10.1016/j.healun.2011.02.006**

835 Fuller LM, Button B, Tarrant B, et al. Longer Versus Shorter Duration of Supervised Rehabilitation After Lung Transplantation: A Randomized Trial. Arch Phys Med Rehabil. 2017;98(2):220-226.e3. doi:**10.1016/j.apmr.2016.09.113**

836 Candemir I, Ergun P, Kaymaz D, et al. The Efficacy of Outpatient Pulmonary Rehabilitation After Bilateral Lung Transplantation. J Cardiopulm Rehabil Prev. 2019;39(4):E7-E12. doi:**10.1097/HCR.0000000000000391**

837 Schneeberger T, Gloeckl R, Welte T, Kenn K. Pulmonary Rehabilitation Outcomes after Single or Double Lung Transplantation in Patients with Chronic Obstructive Pulmonary Disease or Interstitial Lung Disease. 2017;94(2):178-185. doi:**10.1159/000477351**

838 Andrianopoulos V, Gloeckl R, Boensch M, et al. Improvements in functional and cognitive status following short-term pulmonary rehabilitation in COPD lung transplant recipients: a pilot study. ERJ Open Res. 2019;5(3):00060-02019. doi:**10.1183/23120541.00060-2019**

839 Choi J, Hergenroeder AL, Burke L, et al. Delivering an In-Home Exercise Program via Telerehabilitation: A Pilot Study of Lung Transplant Go (LTGO). Int J Telerehabil. 2016;8(2):15-26. doi:**10.5195/ijt.2016.6201**

840 Gloeckl R, Heinzelmann I, Seeberg S, Damisch T, Hitzl W, Kenn K. Effects of complementary whole-body vibration training in patients after lung transplantation: A randomized, controlled trial. The Journal of Heart and Lung Transplantation. 2015;34(11):1455-1461. doi:**10.1016/j.healun.2015.07.002**

841 Kerti M, Bohacs A, Madurka I, et al. The effectiveness of pulmonary rehabilitation in connection with lung transplantation in Hungary. Ann Palliat Med. 2021;10(4):3906-3915. doi:**10.21037/apm-20-1783**

842 Ulvestad M, Durheim MT, Kongerud JS, Lund MB, Edvardsen E. Effect of high-intensity training on peak oxygen uptake and muscular strength after lung transplantation: A randomized controlled trial. The Journal of Heart and Lung Transplantation. 2020;39(9):859-867. doi:**10.1016/j.healun.2020.06.006**

843 Abidi Y, Kovats Z, Bohacs A, et al. Lung Transplant Rehabilitation—A Review. 2023;13(2):506. doi:**10.3390/life13020506**

844 Polastri M, Dell'Amore A, Reed RM, Pehlivan E. Handgrip Strength in Lung Transplant Candidates and Recipients. Exp Clin Transplant. 2023;21(7):547-555. doi:**10.6002/ect.2023.0092**

845 World Health Organization. Palliative care. 2020. Available at: **who.int/news-room/fact-sheets/detail/palliative-care**

846 Trandel ET, Pilewski JM, Dellon EP, et al. Prevalence of unmet palliative care needs in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2020;19(3):394-401. doi:**10.1016/j.jcf.2019.11.010**

847 DiFiglia S, Georgiopoulos A, Portenoy R, et al. 242 Palliative care needs in cystic fibrosis: Baseline data from the Improving Life with Cystic Fibrosis Multi-site Implementation Trial for Primary Palliative Care Intervention. Journal of Cystic Fibrosis. 2022;21:S143-S144. doi:**10.1016/S1569-1993(22)00932-8**

848 Basile M, Jojan L, Hobler MR, et al. Assessing Practices, Beliefs, and Attitudes about Palliative Care among People with Cystic Fibrosis, Their Caregivers, and Clinicians: Results of a Content Analysis. J Palliat Med. 2021;24(11):1650-1656. doi:**10.1089/jpm.2020.0725**

849 Sands D, Repetto T, Dupont LJ, Korzeniewska-Eksterowicz A, Catastini P, Madge S. End of life care for patients with cystic fibrosis. Journal of Cystic Fibrosis. 2011;10:S37-S44. doi:**10.1016/S1569-1993(11)60007-6**

850 Soltoff A, Boyles D, Kavalieratos D. Associations between Social Deprivation and Palliative Care Needs Among Individuals with Cystic Fibrosis. Palliat Med. 2023;37(1S).

851 Kavalieratos D, Georgiopoulos AM, Dhingra L, et al. Models of Palliative Care Delivery for Individuals with Cystic Fibrosis: Cystic Fibrosis Foundation Evidence-Informed Consensus Guidelines. J Palliat Med. 2021;24(1):18-30. doi:**10.1089/jpm.2020.0311**

852 Poch K, Trout C, Brayshaw S, et al. Advanced Care Planning in Cystic Fibrosis. Pediatr Pulmonol. 2019;54(2):465-466.

853 Georgiopoulos AM, DiFiglia S, Seng E, et al. EPS2.10 Initial validation of the Integrated Palliative Care Outcome Scale (IPOS) in adults with cystic fibrosis (CF): data from the Improving Life with CF multicentre pragmatic implementation trial. Journal of Cystic Fibrosis. 2023;22:S42-S43. doi:**10.1016/S1569-1993(23)00311-9**

854 Basile MJ, Dhingra L, DiFiglia S, et al. Development of a Cystic Fibrosis Primary Palliative Care Intervention: Qualitative Analysis of Patient and Family Caregiver Preferences. J Patient Exp. 2023;10. doi:**10.1177/23743735231161486**

855 Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis. 2018;17(2):153-178. doi:**10.1016/j.jcf.2018.02.006**

856 Dellon EP, Helms SW, Hailey CE, et al. Exploring knowledge and perceptions of palliative care to inform integration of palliative care education into cystic fibrosis care. Pediatr Pulmonol. 2018;53(9):1218-1224. doi:**10.1002/ppul.24073**

857 Baumann T, Das S, Jarrell JA, et al. Palliative Care in Pediatric Pulmonology. Children. 2021;8(9):802. doi:**10.3390/children8090802**

858 Trandel ET, Kavalieratos D, Basile M, et al. Palliative care skills in CF: Perspectives of adults with CF, caregivers, and CF care team members. Pediatr Pulmonol. 2020;55(8):2017-2024. doi:**10.1002/ppul.24806**

859 Harris-Skillman E, Chapman SJ, Lowney A, Miller M, Flight WG. P348 An insight into the confidence and skills needed to provide care at the end of life for people with cystic fibrosis. Journal of Cystic Fibrosis. 2020;19:S153. doi:**10.1016/S1569-1993(20)30676-7**

860 Curtis P, Haynes K, Davis C. P349 "More tools in the tool box": innovating palliative care for adult patients with cystic fibrosis in a regional UK unit. Journal of Cystic Fibrosis. 2020;19:S153-S154. doi:**10.1016/S1569-1993(20)30677-9**

861 Kavalieratos D, Lowers J, Moreines LT, et al. Embedded Specialist Palliative Care in Cystic Fibrosis: Results of a Randomized Feasibility Clinical Trial. J Palliat Med. 2023;26(4):489-496. doi:**10.1089/jpm.2022.0349**

862 Kapnadak SG, Ramos KJ, Dellon EP. Enhancing care for individuals with advanced cystic fibrosis lung disease. Pediatr Pulmonol. 2021;56(S1). doi:**10.1002/ppul.24937**

863 Linnemann RW, Friedman D, Altstein LL, et al. Advance Care Planning Experiences and Preferences among People with Cystic Fibrosis. J Palliat Med. 2019;22(2):138-144. doi:**10.1089/jpm.2018.0262**

864 Chen E, Homa K, Goggin J, et al. End-of-life practice patterns at U.S. adult cystic fibrosis care centers: A national retrospective chart review. Journal of Cystic Fibrosis. 2018;17(4):548-554. doi:**10.1016/j.jcf.2017.08.010**

865 Hobler MR, Engelberg RA, Curtis JR, et al. Exploring Opportunities for Primary Outpatient Palliative Care for Adults with Cystic Fibrosis: A Mixed-Methods Study of Patients' Needs. J Palliat Med. 2018;21(4):513-521. doi:**10.1089/jpm.2017.0259**

866 Dellon EP, Basile M, Hobler MR, et al. Palliative Care Needs of Individuals with Cystic Fibrosis: Perspectives of Multiple Stakeholders. J Palliat Med. 2020;23(7):957-963. doi:**10.1089/jpm.2019.0464**

867 Miller M, Lee R, Yates S, et al. How good is end of life care for patients dying with cystic fibrosis? BMJ Support Palliat Care. 2022;12(3):296-298. doi:**10.1136/bmjspcare-2020-002490**

868 Maqsood-Shah A, Corrado J, York A, Etherington C, Peckham D, Clifton I. P444 Improving advanced care planning discussions in a regional adult cystic fibrosis unit. Journal of Cystic Fibrosis. 2019;18:S183. doi:**10.1016/S1569-1993(19)30736-2**

869 Marmor M, Jonas A, Mirza A, et al. Opportunities to Improve Utilization of Palliative Care Among Adults With Cystic Fibrosis: A Systematic Review. J Pain Symptom Manage. 2019;58(6):1100-1112.e1. doi:**10.1016/j.jpainsymman.2019.08.017**

870 Cross SH, Ely EW, Kavalieratos D, Tulsky JA, Warraich HJ. Place of Death for Individuals With Chronic Lung Disease. Chest. 2020;158(2):670-680. doi:1**0.1016/j.chest.2020.02.062**

871 Aasen ERHV, Søvik ML, Størdal K, Lee A. Are We on the Same Page? Exploring Pediatric Patients' Involvement With Advance Care Planning. J Pain Symptom Manage. 2023;66(3):e353-e363. doi:**10.1016/j.jpainsymman.2023.04.003**

872 Cathcart F, Wood J, Madge S. Improving end-of-life care for adults with cystic fibrosis: an improvement project. BMJ Open Qual. 2020;9(3):e000861. doi:**10.1136/bmjoq-2019-000861**

873 Sawicki GS, Dill EJ, Asher D, Sellers DE, Robinson WM. Advance Care Planning in Adults with Cystic Fibrosis. J Palliat Med. 2008;11(8):1135-1141. doi:**10.1089/jpm.2008.0051**

874 Mitchell I, Nakielna E, Tullis E, Adair C. Cystic Fibrosis. End-stage care in Canada. Chest. 2000;118(1):80-84. doi:**10.1378/chest.118.1.80**

875 Philip JAM, Gold M, Sutherland S, et al. End-of-Life Care in Adults with Cystic Fibrosis. J Palliat Med. 2008;11(2):198-203. doi:**10.1089/jpm.2007.0106**

876 Lowton K. 'A bed in the middle of nowhere': Parents' meanings of place of death for adults with cystic fibrosis. Soc Sci Med. 2009;69(7):1056-1062. doi:**10.1016/j.socscimed.2009.07.007**

877 Hajizadeh N, Zhang M, Akerman M, et al. Survival models to support shared decision-making about advance care planning for people with advanced stage cystic fibrosis. BMJ Open Respir Res. 2021;8(1):e000794. doi:**10.1136/bmjresp-2020-000794**

878 Bourke S, Doe S, Gascoigne A, et al. An integrated model of provision of palliative care to patients with cystic fibrosis. Palliat Med. 2009;23(6):512-517. doi:**10.1177/0269216309106312**

879 Vizza CD, Yusen RD, Lynch JP, Fedele F, Alexander Patterson G, Trulock EP. Outcome of patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med. 2000;162(3 Pt 1):819-825. doi:**10.1164/ajrccm.162.3.9910102**

880 Dellon EP, Leigh MW, Yankaskas JR, Noah TL. Effects of lung transplantation on inpatient end of life care in cystic fibrosis. Journal of Cystic Fibrosis. 2007;6(6):396-402. doi:**10.1016/j.jcf.2007.03.005**

881 Macdonald K. Living in limbo - patients with cystic fibrosis waiting for transplant. British Journal of Nursing. 2006;15(10):566-572. doi:**10.12968/bjon.2006.15.10.21134**

882 Agent P, Tonkin V. 254* A retrospective analysis of physiotherapy input during a standard admission compared to a terminal admission in adults with CF. Journal of Cystic Fibrosis. 2007;6:S63. doi:**10.1016/S1569-1993(07)60234-3**

883 Agent P. Physiotherapy adaptations in end of life care in adults with cystic fibrosis – a retrospective analysis. Pediatr Pulmonol. 2006;41(29):A399.

884 Southern KW, Barben J, Gartner S, et al. Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clarification of the harmonised international definition. Journal of Cystic Fibrosis. 2019;18(6):778-780. doi:**10.1016/j.jcf.2019.04.010**

885 Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017;181:S4-S15.e1. doi:**10.1016/j.jpeds.2016.09.064**

886 Kharrazi M, Yang J, Bishop T, et al. Newborn Screening for Cystic Fibrosis in California. Pediatrics. 2015;136(6):1062-1072. doi:**10.1542/peds.2015-0811**

887 Groves T, Robinson P, Wiley V, Fitzgerald DA. Long-Term Outcomes of Children with Intermediate Sweat Chloride Values in Infancy. J Pediatr. 2015;166(6):1469-1474.e3. doi:**10.1016/j.jpeds.2015.01.052**

888 Barben J, Castellani C, Munck A, et al. Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). Journal of Cystic Fibrosis. 2021;20(5):810-819. doi:**10.1016/j.jcf.2020.11.006**

889 Munck A, Bourmaud A, Bellon G, Picq P, Farrell PM. Phenotype of children with inconclusive cystic fibrosis diagnosis after newborn screening. Pediatr Pulmonol. 2020;55(4):918-928. doi:**10.1002/ppul.24634**

890 Edwards E, Harnett N, Bolton M. P350 Physiotherapy management of cystic fibrosis screen-positive, inconclusive diagnosis (CFSPID) infants in the UK and Ireland. Journal of Cystic Fibrosis. 2019;18:S156. doi:**10.1016/S1569-1993(19)30642-3**

891 Bombieri C, Claustres M, De Boeck K, et al. Recommendations for the classification of diseases as CFTR-related disorders. Journal of Cystic Fibrosis. 2011;10:S86-S102. doi:**10.1016/S1569-1993(11)60014-3**

892 Barry PJ, Simmonds NJ. Diagnosing Cystic Fibrosis in Adults. Semin Respir Crit Care Med. 2023;44(02):242-251. doi:**10.1055/s-0042-1759881**

893 T Hill A, L Sullivan A, D Chalmers J, et al. British Thoracic Society Guideline for bronchiectasis in adults. Thorax. 2019;74(Suppl 1):1-69. doi:**10.1136/thoraxjnl-2018-212463**

894 Castellani C, De Boeck K, De Wachter E, Sermet-Gaudelus I, Simmonds N, Southern K. ECFS standards of care on CFTR-related disorders: Updated diagnostic criteria. Journal of Cystic Fibrosis. 2022;21(6):908-921. doi:**10.1016/j.jcf.2022.09.011**

895 NICE. Chronic Pain (Primary and Secondary) in over 16s: Assessment of All Chronic Pain and Management of Chronic Primary Pain [NG193]. 2021. Available at: **nice.org.uk/guidance/ng193/resources/chronic-pain-primary-and-secondary-in-over-16s-assessment-of-all-chronic-pain-and-management-of-chronic-primary-pain-pdf-66142080468421**

896 Hempen C, Wortman C V. Pocket Atlas of Acupuncture. Thieme; 2006.

897 Fleischman G. Possibilities of the treatment of cystic fibrosis with Acupuncture and Chinese Herbs: theory and case study. Am J Acupunct. 1996;24(2/3):135-142.

898 Kemper KJ, McLellan MC, Highfield ES. Massage Therapy and Acupuncture for Children With Chronic Pulmonary Disease. Clin Pulm Med. 2004;11(4):242-250. doi:**10.1097/01.cpm.0000133356.70235.ed**

899 Lin YC, Ly H, Golianu B. Acupuncture Pain Management for Patients with Cystic Fibrosis: A Pilot Study. Am J Chin Med (Gard City N Y). 2005;33(01):151-156. doi:**10.1142/S0192415X05002758**

900 Carrolan V, Agostini P, Nash E, Whitehouse J, Honeybourne D. Mapping physiotherapist use of acupuncture treatment of adults with cystic fibrosis. Journal of Cystic Fibrosis. 2010;9:S76. doi:**10.1016/S1569-1993(10)60295-0**

901 Feng J, Wang X, Li X, Zhao D, Xu J. Acupuncture for chronic obstructive pulmonary disease (COPD). Medicine. 2016;95(40):e4879. doi:**10.1097/MD.0000000000004879**

902 Gibson D, Bruton A, White P. Acupuncture for respiratory disorder: what's the point? Expert Rev Respir Med. 2010;4(1):29-37. doi:**10.1586/ers.09.63**

903 Coyle ME, Shergis JL, Huang ETY, et al. Acupuncture therapies for chronic obstructive pulmonary disease: a systematic review of randomized, controlled trials. Altern Ther Health Med. 2014;20(6):10-23.

904 Corado SC, Graça Santos M, Quaresma L, Baltazar JR. Pneumothorax after acupuncture. BMJ Case Rep. 2019;12(6):e228770. doi:**10.1136/bcr-2018-228770**

905 Sia CH, Leow AST, Leong BSH. Traumatic Pneumothorax Secondary to Acupuncture Needling. Cureus. Published online August 23, 2018. doi:**10.7759/cureus.3194**

906 Mohammad N. Bilateral tension pneumothorax after acupuncture. BMJ Case Rep. Published online April 19, 2018:bcr-2017-221550. doi:**10.1136/bcr-2017-221550**

907 Oskarsson P, Walker CA, Leigh-Smith S. Bilateral pneumothoraces following acupuncture. BMJ Case Rep. Published online August 3, 2017:bcr-2017-221310. doi:**10.1136/bcr-2017-221310**

908 Lee HJ, Kim YJ, Kim WY. Safety Concerns with Thoracoabdominal Acupuncture: Experience at a Tertiary-Care Emergency Department. Pain Medicine. 2017;18(12):2504-2508. doi:**10.1093/pm/pnx068**

909 Moran P, Hull V, Bell N, Bateman K. P389 Massage therapy in an adult cystic fibrosis centre. Journal of Cystic Fibrosis. 2019;18:S167. doi:**10.1016/S1569-1993(19)30681-2**

910 Zink KK, Chini B, Cowens J, Kremer L, Lin L. Improving Clinical Outcomes and Quality of Life with Massage Therapy in Youth and Young Adults with Cystic Fibrosis: a Pilot Study. Int J Ther Massage Bodywork. 2019;12(1):4-15.

911 Lee A, Holdsworth M, Holland A, Button B. The immediate effect of musculoskeletal physiotherapy techniques and massage on pain and ease of breathing in adults with cystic fibrosis. Journal of Cystic Fibrosis. 2009;8(1):79-81. doi:**10.1016/j.jcf.2008.07.002**

912 Hernandez-Reif M, Field T, Krasnegor J, Martinez E, Schwartzman M, Mavunda K. Children with cystic fibrosis benefit from massage therapy. J Pediatr Psychol. 1999;24(2):175-181. doi:**10.1093/jpepsy/24.2.175**

913 Hildage J, Riley DW, McVean RJ, Oxley H, Brennan A, Dodd ME. Complementary Therapy: Planning a service for adults with Cystic Fibrosis. Journal of Cystic Fibrosis. 2009;8:S75. doi:**10.1016/S1569-1993(09)60299-X**

914 Sposato Sinderholm N, Bjerså K. Manual therapies in cystic fibrosis care: a scoping review. Chiropr Man Therap. 2023;31(1):7. doi:**10.1186/s12998-023-00478-0**

915 Bush A, Amaral MD, Davies JC, Simmonds NJ, Taylor-Cousar JL, Ranganathan SC. Hodson and Geddes' Cystic Fibrosis. (Bush A, Amaral MD, Davies JC, Simmonds NJ, Taylor-Cousar JL, Ranganathan SC, eds.). CRC Press; 2023. doi:**10.1201/9781003262763**

916 Haynes F. 279 Benefits of aromatherapy massage for adult cystic fibrosis patients. Journal of Cystic Fibrosis. 2007;6:S69. doi:**10.1016/S1569-1993(07)60259-8**

917 Artini M, Papa R, Sapienza F, et al. Essential Oils Biofilm Modulation Activity and Machine Learning Analysis on Pseudomonas aeruginosa Isolates from Cystic Fibrosis Patients. Microorganisms. 2022;10(5):887. doi:**10.3390/microorganisms10050887**

918 Ragno R, Papa R, Patsilinakos A, et al. Essential oils against bacterial isolates from cystic fibrosis patients by means of antimicrobial and unsupervised machine learning approaches. Sci Rep. 2020;10(1):2653. doi:**10.1038/s41598-020-59553-8**

919 Vladeva EP, Ovcharova LP. Halotherapy – benefits and risks. Scripta Scientifica Salutis Publicae. 2018;4(0):22. doi:**10.14748/sssp.v4i0.5010**

920 Bar-Yoseph R, Kugelman N, Livnat G, et al. Halotherapy as asthma treatment in children: A randomized, controlled, prospective pilot study. Pediatr Pulmonol. 2017;52(5):580-587. doi:**10.1002/ppul.23621**

921 Chervinskaya A V, Zilber NA. Halotherapy for treatment of respiratory diseases. J Aerosol Med. 1995;8(3):221-232. doi:**10.1089/jam.1995.8.221**

922 Graepler-Mainka U, Icheva V, Herrmann G, et al. 210 Dry powder inhalation with NaCl for increasing secretolysis in cystic fibrosis patients – a pilot study. Journal of Cystic Fibrosis. 2011;10:S53. doi:**10.1016/S1569-1993(11)60226-9**

923 Achkar M Al. Halotherapy in Patients with Cystic Fibrosis: A Pilot Study. Int J Respir Pulm Med. 2015;2(1). doi:**10.23937/2378-3516/1410009**

924 Giangioppo S, Kalaci O, Radhakrishnan A, et al. Complementary and alternative medicine use in children with cystic fibrosis. Complement Ther Clin Pract. 2016;25:68-74. doi:**10.1016/j.ctcp.2016.08.006**

925 Rabbani B, Makki SSM, Najafizadeh K, et al. Efficacy of Halotherapy for Improvement of Pulmonary function Tests and Quality of Life of Non-Cystic Fibrosis Bronchiectatic Patients. Tanaffos. 2013;12(2):22-27.

926 Smith S, Rashleigh R, Roberts N. A review of halotherapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. Published online February 2014:239. doi:**10.2147/COPD.S57511**

927 Fagan C, Field J, Sharpe C, Sewell A. P371 Art therapy to facilitate interaction among children with cystic fibrosis. Journal of Cystic Fibrosis. 2023;22:S177. doi:**10.1016/S1569-1993(23)00741-5**

928 Irons JY, Petocz P, Kenny DT, Chang AB. Singing as an adjunct therapy for children and adults with cystic fibrosis. Cochrane Database of Systematic Reviews. 2019;2019(7). doi:**10.1002/14651858.CD008036.pub5**

929 Drury R. Evaluation of Breath Cycle Scottish Opera and Gartnavel General Hospital Cystic Fibrosis Service. 2015. Available at: **breathcycle.co.uk/uploads/2/5/2/7/25270799/dr_rachel_drury_-_research_paper.pdf**

930 Goldenberg RB. Singing Lessons for Respiratory Health: A Literature Review. Journal of Voice. 2018;32(1):85-94. doi:**10.1016/j.jvoice.2017.03.021**

931 Horne R. Concordance, Adherence and Compliance in Medicine Taking. Report for the National Co-OrdinatinCentre for NHS Service Delivery and Organisation R & D (NCCSDO). 2005.

932 Royal Pharmaceutical Society of Great Britain and Merck Sharpe and Dohme. Partnership in Medicine Taking: A Consultative Document. 1996.

933 World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. 2003. Available at: **iris.who.int/bitstream/handle/10665/42682/9241545992.pdf?sequence=1&isAllowed=y**

934 Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: Challenges to disease self-management. Journal of Cystic Fibrosis. 2009;8(2):91-96. doi:**10.1016/j.jcf.2008.09.007**

935 Dodd ME, Webb AK. Understanding non-compliance with treatment in adults with cystic fibrosis. J R Soc Med. 2000;93 Suppl 38(Suppl 38):2-8.

936 Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based Assessment of Adherence to Medical Treatments in Pediatric Psychology. J Pediatr Psychol. 2008;33(9):916-936. doi:**10.1093/jpepsy/jsm064**

937 Ramsey BW, Davies J, McElvaney NG, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. New England Journal of Medicine. 2011;365(18):1663-1672. doi:**10.1056/NEJMoa1105185**

938 Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. New England Journal of Medicine. 2019;381(19):1809-1819. doi:**10.1056/NEJMoa1908639**

939 Granger E, Davies G, Keogh RH. Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor? Journal of Cystic Fibrosis. 2022;21(2):316-322. doi:**10.1016/j.jcf.2021.08.014**

940 Manika K, Diamantea F, Tsakona A, et al. Use of cystic fibrosis inhaled medication before and after elexacaftor/tezacaftor/ivacaftor initiation. Journal of Cystic Fibrosis. 2024;23(1):29-31. doi:**10.1016/j.jcf.2023.05.001**

941 Hansen CME, Breukelman AJ, van den Bemt PMLA, Zwitserloot AM, van Dijk L, van Boven JFM. Medication adherence to CFTR modulators in patients with cystic fibrosis: a systematic review. European Respiratory Review. 2024;33(173):240060. doi:**10.1183/16000617.0060-2024**

942 Sutton S, Hayden J, Howlett M, et al. 485 Measuring adherence to chronic therapies over 2 years of treatment with elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis—the RECOVER Study. Journal of Cystic Fibrosis. 2023;22:S255. doi:**10.1016/S1569-1993(23)01410-8**

943 NHS RightCare. RightCare Cystic Fibrosis Toolkit. 2024. Available at: **gettingitrightfirsttime.co.uk/wp-content/uploads/2024/08/20240827-Cystic-fibrosis-toolkit_v0.23-FINAL.pdf**

944 Levers CE, Brown RT, Drotar D, Caplan D, Pishevar BS, Lambert RG. Knowledge of physician prescriptions and adherence to treatment among children with cystic fibrosis and their mothers. J Dev Behav Pediatr. 1999;20(5):335-343. doi:**10.1097/00004703-199910000-00008**

945 Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. Journal of Cystic Fibrosis. 2006;5(3):177-185. doi:**10.1016/j.jcf.2006.03.002**

946 Bucks RS, Hawkins K, Skinner TC, Horn S, Seddon P, Horne R. Adherence to Treatment in Adolescents with Cystic Fibrosis: The Role of Illness Perceptions and Treatment Beliefs. J Pediatr Psychol. 2009;34(8):893-902. doi:**10.1093/jpepsy/jsn135**

947 Abbott MDLGKJ. Ways of coping with cystic fibrosis: implications for treatment adherence. Disabil Rehabil. 2001;23(8):315-324. doi:**10.1080/09638280010004171**

948 Smith BA, Modi AC, Quittner AL, Wood BL. Depressive symptoms in children with cystic fibrosis and parents and its effects on adherence to airway clearance. Pediatr Pulmonol. 2010;45(8):756-763. doi:**10.1002/ppul.21238**

949 Abbott J, Dodd M, Bilton D, Webb AK. Treatment compliance in adults with cystic fibrosis. Thorax. 1994;49(2):115-120. doi:**10.1136/thx.49.2.115**

950 Conway SP, Pond MN, Hamnett T, Watson A. Compliance with treatment in adult patients with cystic fibrosis. Thorax. 1996;51(1):29-33. doi:**10.1136/thx.51.1.29**

951 Zindani GN, Streetman DD, Streetman DS, Nasr SZ. Adherence to treatment in children and adolescent patients with cystic fibrosis. Journal of Adolescent Health. 2006;38(1):13-17. doi:**10.1016/j.jadohealth.2004.09.013**

952 Myers LB, Horn SA. Adherence to Chest Physiotherapy in Adults with Cystic Fibrosis. J Health Psychol. 2006;11(6):915-926. doi:**10.1177/1359105306069093**

953 Shakkottai A, Townsend M, Kidwell K, Nasr S. Adherence To Medications In Cystic Fibrosis Patients: A Five-Year Retrospective Analysis. Am J Respir Crit Care Med. 2014;189(A55530).

954 Arias Llorente RP, Bousoño García C, Díaz Martín JJ. Treatment compliance in children and adults with Cystic Fibrosis. Journal of Cystic Fibrosis. 2008;7(5):359-367. doi:**10.1016/j.jcf.2008.01.003**

955 Hoo ZH, Daniels T, Bradley JM, Heller B, Rose C, Wildman M. WS14.6 Feasibility study to objectively measure airway clearance technique in cystic fibrosis. Journal of Cystic Fibrosis. 2014;13:S30. doi:**10.1016/S1569-1993(14)60093-X**

956 Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate Assessment of Adherence. Chest. 2011;140(2):425-432. doi:**10.1378/chest.09-3074**

957 Bender B, Wamboldt FS, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. Ann Allergy Asthma Immunol. 2000;85(5):416-421. doi:**10.1016/s1081-1206(10)62557-4**

958 Kettler LJ. Determinants of adherence in adults with cystic fibrosis. Thorax. 2002;57(5):459-464. doi:**10.1136/thorax.57.5.459**

959 Wildman MJ, O'Cathain A, Maguire C, et al. Self-management intervention to reduce pulmonary exacerbations by supporting treatment adherence in adults with cystic fibrosis: a randomised controlled trial. Thorax. 2022;77(5):461-469. doi:**10.1136/thoraxjnl-2021-217594**

960 O'Donohoe R, Fullen BM. Adherence of subjects with cystic fibrosis to their home program: a systematic review. Respir Care. 2014;59(11):1731-1746. doi:**10.4187/respcare.02990**

961 Ward N, Ward B, Stiller K, Kenyon A, Holland AE. Development of a device to measure adherence and pressure characteristics of positive expiratory pressure therapies used by adults with cystic fibrosis. Physiother Theory Pract. 2022;38(10):1469-1477. doi:**10.1080/09593985.2020.1858465**

962 Rowbotham NJ, Smith S, Elliott ZC, et al. A refresh of the top 10 research priorities in cystic fibrosis. Thorax. 2023;78(8):840-843. doi:**10.1136/thorax-2023-220100**

963 Moorcroft AJ, Dodd ME, Morris J, Webb AK. Individualised unsupervised exercise training in adults with cystic fibrosis: a 1 year randomised controlled trial. Thorax. 2004;59(12):1074-1080. doi:**10.1136/thx.2003.015313**

964 Moorcroft AJ, Dodd ME, Webb AK. Exercise limitations and training for patients with cystic fibrosis. Disabil Rehabil. 1998;20(6-7):247-253. doi:**10.3109/09638289809166735**

965 Orenstein DM, Higgins LW. Update on the role of exercise in cystic fibrosis. Curr Opin Pulm Med. 2005;11(6):519-523. doi:**10.1097/01.mcp.0000181476.92810.07**

966 Prasad SA, Cerny FJ. Factors that influence adherence to exercise and their effectiveness: Application to cystic fibrosis. Pediatr Pulmonol. 2002;34(1):66-72. doi:**10.1002/ppul.10126**

967 Burnett DM, Barry AN, Mermis JD. Physical Activity Level and Perception of Exercise in Cystic Fibrosis. Respir Care. 2020;65(4):500-506. doi:**10.4187/respcare.07193**

968 Rowbotham NJ, Smith S, Leighton PA, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. Thorax. 2018;73(4):388-390. doi:**10.1136/thoraxjnl-2017-210473**

969 Pinto ACPN, Piva SR, Rocha A, et al. Digital technology for delivering and monitoring exercise programs for people with cystic fibrosis. Cochrane Database of Systematic Reviews. 2023;2023(6). doi:**10.1002/14651858.CD014605.pub2**

970 Jones M, Moffatt F, Harvey A, Ryan JM. Interventions for improving adherence to airway clearance treatment and exercise in people with cystic fibrosis. Cochrane Database of Systematic Reviews. 2023;2023(7). doi:**10.1002/14651858.CD013610.pub2**

971 Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews. 2014;2014(11). doi:**10.1002/14651858.CD000011.pub4**

972 Abbott J, Dodd M, Webb AK. Health perceptions and treatment adherence in adults with cystic fibrosis. Thorax. 1996;51(12):1233-1238. doi:**10.1136/thx.51.12.1233**

973 McNamara PS, McCormack P, McDonald AJ, Heaf L, Southern KW. Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. Journal of Cystic Fibrosis. 2009;8(4):258-263. doi:**10.1016/j.jcf.2009.04.006**

974 Latchford G, Duff A, Quinn J, Conway S, Conner M. Adherence to nebulised antibiotics in cystic fibrosis. Patient Educ Couns. 2009;75(1):141-144. doi:**10.1016/j.pec.2008.08.027**

975 Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. Journal of Cystic Fibrosis. 2011;10(4):258-264. doi:**10.1016/j.jcf.2011.03.005**

976 Quittner AL, Zhang J, Marynchenko M, et al. Pulmonary Medication Adherence and Health-care Use in Cystic Fibrosis. Chest. 2014;146(1):142-151. doi:**10.1378/chest.13-1926**

977 Briesacher BA, Quittner AL, Saiman L, Sacco P, Fouayzi H, Quittell LM. Adherence with tobramycin inhaled solution and health care utilization. BMC Pulm Med. 2011;11(1):5. doi:**10.1186/1471-2466-11-5**

978 Nasr SZ, Chou W, Villa KF, Chang E, Broder MS. Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. J Med Econ. 2013;16(6):801-808. doi:**10.3111/13696998.2013.787427**

979 Goldbeck L, Fidika A, Herle M, Quittner AL. Psychological interventions for individuals with cystic fibrosis and their families. Cochrane Database of Systematic Reviews. 2014;2020(5). doi:**10.1002/14651858.CD003148.pub3**

980 Savage E, Beirne P V, Ni Chroinin M, Duff A, Fitzgerald T, Farrell D. Self-management education for cystic fibrosis. Cochrane Database of Systematic Reviews. 2014;2017(6). doi:**10.1002/14651858.CD007641.pub3**

981 Cottrell CK, Young GA, Creer TL, Holroyd KA, Kotses H. The Development and Evaluation of a Self-Management Program for Cystic Fibrosis. Pediatr Asthma Allergy Immunol. 1996;10(3):109-118. doi:**10.1089/pai.1996.10.109**

982 Downs JA, Roberts CM, Blackmorel AM, Le Souëf PN, Jenkins SC. Benefits of an education programme on the self-management of aerosol and airway clearance treatments for children with cystic fibrosis. Chron Respir Dis. 2006;3(1):19-27. doi:**10.1191/1479972306cd100oa**

983 Bernard RS, Cohen LL, Moffett K. A Token Economy for Exercise Adherence in Pediatric Cystic Fibrosis: A Single-Subject Analysis. J Pediatr Psychol. 2009;34(4):354-365. doi:**10.1093/jpepsy/jsn101**

984 Hoo ZH, Gardner B, Arden MA, et al. Role of habit in treatment adherence among adults with cystic fibrosis. Thorax. 2019;74(2):197-199. doi:**10.1136/thoraxjnl-2017-211453**

985 Rowbotham NJ, Palser SC, Smith SJ, Smyth AR. Infection prevention and control in cystic fibrosis: a systematic review of interventions. Expert Rev Respir Med. 2019;13(5):425-434. doi:**10.1080/17476348.2019.1595594**

986 Griffiths AL, Wurzel DF, Robinson PJ, Carzino R, Massie J. Australian epidemic strain pseudomonas (AES-1) declines further in a cohort segregated cystic fibrosis clinic. Journal of Cystic Fibrosis. 2012;11(1):49-52. doi:**10.1016/j.jcf.2011.08.005**

987 Vonberg RP, Gastmeier P. Isolation of Infectious Cystic Fibrosis Patients: Results of a Systematic Review. Infect Control Hosp Epidemiol. 2005;26(4):401-409. doi:**10.1086/502558**

988 Doe SJ, McSorley A, Isalska B, et al. Patient segregation and aggressive antibiotic eradication therapy can control methicillin-resistant Staphylococcus aureus at large cystic fibrosis centres. Journal of Cystic Fibrosis. 2010;9(2):104-109. doi:**10.1016/j.jcf.2009.11.009**

989 Blanchard AC, Tang L, Tadros M, et al. Burkholderia cenocepacia ET12 transmission in adults with cystic fibrosis. Thorax. 2020;75(1):88-90. doi:**10.1136/thoraxjnl-2019-214098**

990 Stoudemire W, Jiang X, Zhou JJ, et al. Cystic fibrosis program characteristics associated with adoption of 2013 infection prevention and control recommendations. Am J Infect Control. 2019;47(9):1090-1095. doi:**10.1016/j.ajic.2019.03.015**

991 Griffiths AL, Jamsen K, Carlin JB, et al. Effects of Segregation on an Epidemic Pseudomonas aeruginosa Strain in a Cystic Fibrosis Clinic. Am J Respir Crit Care Med. 2005;171(9):1020-1025. doi:**10.1164/rccm.200409-1194OC**

992 Döring G. Prevention of Pseudomonas aeruginosa infection in cystic fibrosis patients. International Journal of Medical Microbiology. 2010;300(8):573-577. doi:**10.1016/j.ijmm.2010.08.010**

993 Festini F, Buzzetti R, Bassi C, et al. Isolation measures for prevention of infection with respiratory pathogens in cystic fibrosis: a systematic review. Journal of Hospital Infection. 2006;64(1):1-6. doi:**10.1016/j.jhin.2006.02.021**

994 Koch C, Frederiksen B, Høiby N. Patient cohorting and infection control. Semin Respir Crit Care Med. 2003;24(6):703-716. doi:**10.1055/s-2004-815666**

995 Geddes D. Segregation is not good for patients with cystic fibrosis. J R Soc Med. 2008;101(1_suppl):36-38. doi:**10.1258/jrsm.2008.s18008**

996 Farrell PM, Shen G, Splaingard M, et al. Acquisition of Pseudomonas aeruginosa in Children With Cystic Fibrosis. Pediatrics. 1997;100(5):e2-e2. doi:**10.1542/peds.100.5.e2**

997 Caskey S, Stirling J, Moore JE, Rendall JC. Occurrence of Pseudomonas aeruginosa in waters: implications for patients with cystic fibrosis (CF). Lett Appl Microbiol. 2018;66(6):537-541. doi:**10.1111/lam.12876**

998 Schaffer K. Epidemiology of infection and current guidelines for infection prevention in cystic fibrosis patients. Journal of Hospital Infection. 2015;89(4):309-313. doi:**10.1016/j.jhin.2015.02.005**

999 Waters V, Ratjen F. Multidrug–resistant organisms in cystic fibrosis: management and infection–control issues. Expert Rev Anti Infect Ther. 2006;4(5):807-819. doi:**10.1586/14787210.4.5.807**

1000 Zuckerman JB, Seder DB. Infection Control Practice in Cystic Fibrosis Centers. Clin Chest Med. 2007;28(2):381-404. doi:**10.1016/j.ccm.2007.02.010**

1001 Bryant JM, Grogono DM, Rodriguez-Rincon D, et al. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium. Science (1979). 2016;354(6313):751-757. doi:**10.1126/science.aaf8156**

1002 O'Sullivan BP, Sassetti CM. Infection control in cystic fibrosis: share and share alike. The Lancet. 2013;381(9877):1517-1519. doi:**10.1016/S0140-6736(13)60740-0**

1003 Saiman L, Siegel J, Cystic Fibrosis Foundation Consensus Conference on Infection Control Participants. Infection control recommendations for patients with cystic fibrosis: Microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. Am J Infect Control. 2003;31(3 Suppl):S1-62.

1004 Zuckerman JB, Saiman L. Use of Masks in Patients with Cystic Fibrosis. Am J Respir Crit Care Med. 2018;198(12):1588-1589. doi:**10.1164/rccm.201807-1248LE**

1005 Wood ME, Stockwell RE, Bell SC. Reply to Zuckerman and Saiman: Use of Masks in Patients with Cystic Fibrosis. Am J Respir Crit Care Med. 2018;198(12):1589-1590. doi:**10.1164/rccm.201808-1476LE**

1006 Moore JE, Shaw A, Howard JL, Dooley JS, Elborn JS. Infection control and the significance of sputum and other respiratory secretions from adult patients with cystic fibrosis. Ann Clin Microbiol Antimicrob. 2004;3(1):8. doi:**10.1186/1476-0711-3-8**

1007 Wainwright CE, France MW, O'Rourke P, et al. Cough-generated aerosols of Pseudomonas aeruginosa and other Gram-negative bacteria from patients with cystic fibrosis. Thorax. 2009;64(11):926-931. doi:**10.1136/thx.2008.112466**

1008 Gralton J, Tovey E, McLaws ML, Rawlinson WD. The role of particle size in aerosolised pathogen transmission: A review. Journal of Infection. 2011;62(1):1-13. doi:**10.1016/j.jinf.2010.11.010**

1009 Clifton IJ, Peckham DG. Defining routes of airborne transmission of Pseudomonas aeruginosa in people with cystic fibrosis. Expert Rev Respir Med. 2010;4(4):519-529. doi:**10.1586/ers.10.42**

1010 Festini F, Taccetti G, Galici V, et al. A 1-m distance is not safe for children with cystic fibrosis at risk for cross-infection with Pseudomonas aeruginosa. Am J Infect Control. 2010;38(3):244-245. doi:**10.1016/j.ajic.2009.09.017**

1011 Wood ME, Stockwell RE, Johnson GR, et al. Face Masks and Cough Etiquette Reduce the Cough Aerosol Concentration of Pseudomonas aeruginosa in People with Cystic Fibrosis. Am J Respir Crit Care Med. 2018;197(3):348-355. doi:**10.1164/rccm.201707-1457OC**

1012 Wood ME, Stockwell RE, Johnson GR, et al. Cystic fibrosis pathogens survive for extended periods within cough-generated droplet nuclei. Thorax. 2019;74(1):87-90. doi:**10.1136/thoraxjnl-2018-211567**

1013 Castle J. Burkholderia cepacia: A review of an environmental saprophyte as a human pathogen. New Zealand Journal of Medical Laboratory Science. 1999;53(2):49-56.

1014 Ferroni A, Werkhauser-Bertrand A, Le Bourgeois M, et al. Bacterial contamination in the environment of hospitalised children with cystic fibrosis. Journal of Cystic Fibrosis. 2008;7(6):477-482. doi:**10.1016/j.jcf.2008.05.001**

1015 Panagea S, Winstanley C, Walshaw MJ, Ledson MJ, Hart CA. Environmental contamination with an epidemic strain of Pseudomonas aeruginosa in a Liverpool cystic fibrosis centre, and study of its survival on dry surfaces. Journal of Hospital Infection. 2005;59(2):102-107. doi:**10.1016/j.jhin.2004.09.018**

1016 Zuckerman JB, Clock SA, Prato BS, et al. Air Contamination with Bacteria in Cystic Fibrosis Clinics: Implications for Prevention Strategies. Am J Respir Crit Care Med. 2015;191(5):598-601. doi:**10.1164/rccm.201410-1877LE**

1017 Saiman L. Infection prevention and control in cystic fibrosis. Curr Opin Infect Dis. 2011;24(4):390-395. doi:**10.1097/QCO.0b013e32834748ff**

1018 Jones AM, Dodd ME, Govan JRW, et al. Prospective Surveillance for Pseudomonas aeruginosa Cross-Infection at a Cystic Fibrosis Center. Am J Respir Crit Care Med. 2005;171(3):257-260. doi:**10.1164/rccm.200404-513OC**

1019 Zuckerman JB, Zuaro DE, Prato BS, et al. Bacterial contamination of cystic fibrosis clinics. Journal of Cystic Fibrosis. 2009;8(3):186-192. doi:**10.1016/j.jcf.2009.01.003**

1020 Savant AP, O'Malley C, Bichl S, McColley SA. Improved patient safety through reduced airway infection rates in a paediatric cystic fibrosis programme after a quality improvement effort to enhance infection prevention and control measures. BMJ Qual Saf. 2014;23(Suppl 1):i73-i80. doi:**10.1136/bmjqs-2013-002315**

1021 France MW, Dodd ME, Govan JR, Doherty CJ, Webb AK, Jones AM. The changing epidemiology of Burkholderia species infection at an adult cystic fibrosis centre. Journal of Cystic Fibrosis. 2008;7(5):368-372. doi:**10.1016/j.jcf.2008.01.002**

1022 Luna RA, Millecker LA, Webb CR, et al. Molecular Epidemiological Surveillance of Multidrug-Resistant Pseudomonas aeruginosa Isolates in a Pediatric Population of Patients with Cystic Fibrosis and Determination of Risk Factors for Infection with the Houston-1 Strain. J Clin Microbiol. 2013;51(4):1237-1240. doi:**10.1128/JCM.02157-12**

1023 Saiman L, Siegel J. Infection Control in Cystic Fibrosis. Clin Microbiol Rev. 2004;17(1):57-71. doi:**10.1128/CMR.17.1.57-71.2004**

1024 Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol Generating Procedures and Risk of Transmission of Acute Respiratory Infections to Healthcare Workers: A Systematic Review. PLoS One. 2012;7(4):e35797. doi:**10.1371/journal.pone.0035797**

1025 Dennis JB, Jones AM, Davies EA, et al. Influenza B outbreak at an adult cystic fibrosis centre - Clinical impact and factors influencing spread. Journal of Cystic Fibrosis. 2020;19(5):808-814. doi:**10.1016/j.jcf.2020.04.011**

1026 Pendergrast C, Parsons D. Reducing Cystic Fibrosis (CF) cross-infection risk in a new paediatric respiratory laboratory (RL): Room design, air handling and patient-flow. Respirology. 2011;16:7.

1027 Coia JE, Ritchie L, Adisesh A, et al. Guidance on the use of respiratory and facial protection equipment. Journal of Hospital Infection. 2013;85(3):170-182. doi:**10.1016/j.jhin.2013.06.020**

1028 Driessche K Vanden, Hens N, Tilley P, et al. Surgical Masks Reduce Airborne Spread of Pseudomonas aeruginosa in Colonized Patients with Cystic Fibrosis. Am J Respir Crit Care Med. 2015;192(7):897-899. doi:**10.1164/rccm.201503-0481LE**

1029 Yan J, Kevat A, Martinez E, et al. Investigating transmission of Mycobacterium abscessus amongst children in an Australian cystic fibrosis centre. Journal of Cystic Fibrosis. 2020;19(2):219-224. doi:**10.1016/j.jcf.2019.02.011**

1030 Chen JS, Witzmann KA, Spilker T, Fink RJ, LiPuma JJ. Endemicity and inter-city spread of Burkholderia cepacia genomovar III in cystic fibrosis. J Pediatr. 2001;139(5):643-649. doi:**10.1067/mpd.2001.118430**

1031 Lalancette C, Charron D, Laferrière C, et al. Hospital Drains as Reservoirs of Pseudomonas aeruginosa: Multiple-Locus Variable-Number of Tandem Repeats Analysis Genotypes Recovered from Faucets, Sink Surfaces and Patients. Pathogens. 2017;6(3):36. doi:**10.3390/pathogens6030036**

1032 Stockwell R, Thomson R, Leong L, et al. Mycobacterium Abscessus point source outbreak in the local potable water supply affecting people with cystic fibrosis. Pediatr Pulmonol. 2019;54(S2):300. doi:**10.1002/ppul.22495**

1033 Lucero CA, Cohen AL, Trevino I, et al. Outbreak of Burkholderia cepacia complex among ventilated pediatric patients linked to hospital sinks. Am J Infect Control. 2011;39(9):775-778. doi:**10.1016/j.ajic.2010.12.005**

1034 Bryant JM, Grogono DM, Greaves D, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. The Lancet. 2013;381(9877):1551-1560. doi:**10.1016/S0140-6736(13)60632-7**

1035 Saiman L, Siegel JD, LiPuma JJ, et al. Infection Prevention and Control Guideline for Cystic Fibrosis: 2013 Update. Infect Control Hosp Epidemiol. 2014;35(S1):s1-s67. doi:**10.1086/676882**

1036 Blau H, Mussaffi H, Mei Zahav M, et al. Microbial contamination of nebulizers in the home treatment of cystic fibrosis. Child Care Health Dev. 2007;33(4):491-495. doi:**10.1111/j.1365-2214.2006.00669.x**

1037 Murray TS, O'Rourke TK, Feinn R, Drapeau G, Collins MS. Nebulizer cleaning and disinfection practices in families with cystic fibrosis: The relationship between attitudes, practice and microbe colonization. Journal of Cystic Fibrosis. 2019;18(6):823-828. doi:**10.1016/j.jcf.2019.05.008**

1038 O'Malley CA, VandenBranden SL, Zheng XT, Polito AM, McColley SA. A day in the life of a nebulizer: surveillance for bacterial growth in nebulizer equipment of children with cystic fibrosis in the hospital setting. Respir Care. 2007;52(3): 258-262.

1039 Denton M, Rajgopal A, Mooney L, et al. Stenotrophomonas maltophilia contamination of nebulizers used to deliver aerosolized therapy to inpatients with cystic fibrosis. Journal of Hospital Infection. 2003;55(3):180-183. doi:**10.1016/S0195-6701(03)00299-8**

1040 Vassal S, Taamma R, Marty N, et al. Microbiologic contamination study of nebulizers after aerosol therapy in patients with cystic fibrosis. Am J Infect Control. 2000;28(5):347-351. doi:**10.1067/mic.2000.110214**

1041 Zuana A Della, Garcia D de O, Juliani RCTP, Silva Filho LVRF da. Effect that an educational program for cystic fibrosis patients and caregivers has on the contamination of home nebulizers. Jornal Brasileiro de Pneumologia. 2014;40(2):119-127. doi:**10.1590/S1806-37132014000200004**

1042 Peckham D, Williams K, Wynne S, Denton M, Pollard K, Barton R. Fungal contamination of nebuliser devices used by people with cystic fibrosis. J Cyst Fibros. 2016;15(1):74-77. doi:**10.1016/j.jcf.2015.06.004**

1043 Manor E, Gur M, Geffen Y, Bentur L. Cleaning and infection control of airway clearance devices used by CF patients. Chron Respir Dis. 2017;14(4):370-376. doi:**10.1177/1479972317707652**

1044 Bell J, Alexander L, Carson J, et al. Nebuliser hygiene in cystic fibrosis: evidence-based recommendations. Breathe (Sheff). 2020;16(2):190328. doi:**10.1183/20734735.0328-2019**

1045 Hohenwarter K, Prammer W, Aichinger W, Reychler G. An evaluation of different steam disinfection protocols for cystic fibrosis nebulizers. Journal of Cystic Fibrosis. 2016;15(1):78-84. doi:**10.1016/j.jcf.2015.07.005**

1046 Towle D, Callan DA, Lamprea C, Murray TS. Baby bottle steam sterilizers for disinfecting home nebulizers inoculated with non-tuberculous mycobacteria. Journal of Hospital Infection. 2016;92(3):222-225. doi:**10.1016/j.jhin.2015.08.030**

1047 Kenkare Z, Murray T, Schramm C, Collins M. 342 Partnership in education–cystic fibrosis center patient education practices on home nebulizer care in relationship to published guidelines. Journal of Cystic Fibrosis. 2022;21:S202-S203. doi:**10.1016/S1569-1993(22)01032-3**

1048 Garber E, Desai M, Zhou J, et al. Barriers to adherence to cystic fibrosis infection control guidelines. Pediatr Pulmonol. 2008;43(9):900-907. doi:**10.1002/ppul.20876**

1049 Masterson T, Wildman BG, Newberry B, Omlor G, Bryson E, Kukay A. Compliance in cystic fibrosis: an examination of infection control guidelines. Pediatr Pulmonol. 2008;43(5):435-442. doi:**10.1002/ppul.20781**

1050 O'Malley CA. Infection Control in Cystic Fibrosis: Cohorting, Cross-Contamination, and the Respiratory Therapist. Respir Care. 2009;54(5):641-657. doi:**10.4187/aarc0446**

1051 Saiman L, Zhou JJ, Shah KS, et al. Barriers implementing infection prevention and control experienced by healthcare workers, people with CF and parents. Journal of Cystic Fibrosis. 2022;21(2):309-315. doi:**10.1016/j.jcf.2021.07.009**

1052 Masterson TL, Wildman BG, Newberry BH, Omlor GJ. Impact of age and gender on adherence to infection control guidelines and medical regimens in cystic fibrosis. Pediatr Pulmonol. 2011;46(3):295-301. doi:**10.1002/ppul.21366**

1053 Miroballi Y, Garber E, Jia H, et al. Infection control knowledge, attitudes, and practices among cystic fibrosis patients and their families. Pediatr Pulmonol. 2012;47(2):144-152. doi:**10.1002/ppul.21528**

1054 Royal Pharmaceutical Society. A Competency Framework for All Prescribers. 2021. Available at: **rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Prescribing%20Competency%20Framework/RPS%20English%20Competency%20Framework%203.pdf?ver=mctnrKo4YaJDh2nA8N5G3A%3d%3d**

1055 Chartered Society of Physiotherapy. Practice Guidance for Physiotherapist Supplementary and/or Independent Prescribers in the Safe Use of Medicines (4th Edition). 2021. Available at: **csp.org.uk/system/files/publication_files/PD026_PracticeGuidancePrescribing_4thEd_2018.pdf**

1056 Chartered Society of Physiotherapy. Interpretation of the Definition of Physiotherapist Prescribing. 2023. Available at: **csp.org.uk/system/files/publication_files/Scope%20of%20Prescribing_Nov23.pdf**

1057 NHS England. NHS Long Term Workforce Plan. 2023. Available at: **england.nhs.uk/wp-content/uploads/2023/06/nhs-long-term-workforce-plan-v1.2.pdf**

1058 The Irish Society of Chartered Physiotherapists. Increased Scope of Practice for Physiotherapists Will Reduce GP and Emergency Department Queues. 2023. Available at: **www.iscp.ie/news/increased-scope-of-practice-for-physiotherapists-will-reduce-gp-and-emergency-department-queues**

1059 Health and Care Professions Council. Standards for Prescribing. 2019. Available at: **hcpc-uk.org/globalassets/standards/standards-for-prescribing/standards-for-prescribing2.pdf**

1060 Chartered Society of Physiotherapy. Medicines Use in Physiotherapy Practice (5th Edition). 2021.

1061 NICE. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence [CG76]. Available at: **nice.org.uk/guidance/cg76/resources/medicines-adherence-involving-patients-in-decisions-about-prescribed-medicines-and-supporting-adherence-pdf-975631782085**

1062 NICE. Medicines Optimisation: The Safe and Effective Use of Medicines to Enable the Best Possible Outcomes [NG5]. Available at: **nice.org.uk/guidance/ng5/resources/medicines-optimisation-the-safe-and-effective-use-of-medicines-to-enable-the-best-possible-outcomes-pdf-51041805253**

1063 British Thoracic Society. A guide to performing quality assured spirometry. 2013. **www.brit-thoracic.org.uk/media/70454/spirometry_e-guide_2013.pdf**

1064 Dentice R, Elkins M. Timing of dornase alfa inhalation for cystic fibrosis. Cochrane Database of Systematic Reviews 2011;5:CD007923. doi: **10.1002/14651858.CD007923.pub2**

1065 Shak S, et al. Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proceedings of the National Academy of Sciences USA 1990;87(23):9188-92.

1066 Conway SP, Littlewood JM. RhDNase in cystic fibrosis. British Journal of Hospital Medicine. 1997;57:8 (371-372).

Cystic Fibrosis Trust

Cystic Fibrosis Trust is the charity uniting people to stop cystic fibrosis. Our community will improve care, speak out, support each other and fund vital research as we race towards effective treatments for all.

We won't stop until everyone can live without the limits of cystic fibrosis.

Cystic Fibrosis Trust
33 Creechurch Lane
London EC3A 5EB

020 3795 1555

cysticfibrosis.org.uk

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