Cystic Fibrosis why we're here

Research in focus

Gut symptoms of cystic fibrosis

Fighting for a Life Unlimited

Foreword

Many people with cystic fibrosis (CF) will experience CF-related complications of the gastrointestinal (GI) tract. Currently, little is known about how the physiological and biochemical changes within the intestines lead to symptoms such as pain, visible bloating and flatulence, which can all affect the quality of life for people with cystic fibrosis. Relief of these symptoms was identified as the second highest health priority by people with CF in 2017[1]. As people with CF are leading longer and healthier lives, due to the availability of improved treatment and care, it is similarly increasingly important to address these symptoms to help ensure that all people with CF can live a long and full life.

The Cystic Fibrosis Trust is funding two research projects with the aim of achieving this. In the lab, we're funding a Strategic Research Centre (SRC) to explore whether a type of medicine used for other conditions may be beneficial for the treatment of severe blockages in the intestines which can occur in people with cystic fibrosis, known as Distal Intestinal Obstructive Syndrome (DIOS). In the clinic, we're funding research to investigate new methods of studing intestinal symptoms in people with cystic fibrosis. The results of the two research studies, if successful, could lead to clinical trials of new medicines that would treat these painful and embarrassing symptoms of cystic fibrosis.

Dr Lucy Allen
Director of Research

What is CF?

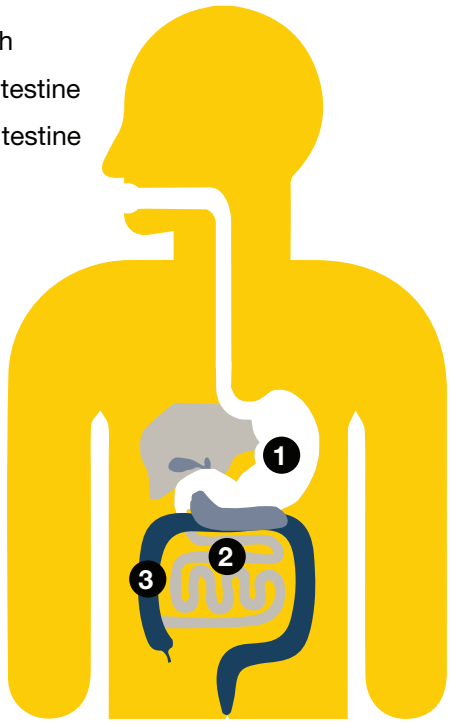
Cystic fibrosis is a rare, inherited condition that affects over 10,600 people in the UK. It is caused by a defective gene called 'CFTR', which controls the movement of chloride and water in and out of cells. The defect causes the internal organs – especially the lungs and digestive system – to become clogged with thick, sticky mucus. This results in chronic infections and inflammation in the lungs and in the digestive system, blockages, bloating and difficulty breaking down food. Some adults with CF may also develop CF-related diabetes (CFRD) and forms of arthritis, osteoporosis and liver problems that are related to having cystic fibrosis.

About the digestive system

The digestive system begins with swallowing food, which then moves down the oesophagus into the stomach where the food is broken down. It is then passed into the intestines, where the food is digested to allow fluid and nutrients to be absorbed into the body. Any undigested material is then excreted as faeces.

The intestines are one continuous, very long tube. The first part of the intestines is known as the 'small intestine' and the second part is known as the 'large intestine', which is shorter and much wider than the small intestine. Digested food continuously moves through the intestines, where muscles in the intestinal wall push it along. The surface of the intestines is lined with cells, which support digestion and produce mucus and water to help keep food in the intestines moving and well hydrated. The lining of the intestines has many hairpin-like folds to increase its surface area and thus the amount of nutrients that can be absorbed.

1. Stomach
2. Small intestine
3. Large intestine



How is digestion within the gut affected in CF?

The CF protein CFTR is present in the cells that line the small intestine and in the first part of the large intestine. Its role is to aid the enzymic-digestion of food and keep the intestines well hydrated. It does this by releasing chloride (adding water) and an alkaline chemical called bicarbonate. The bicarbonate both neutralises stomach acid to allow digestive enzymes to work effectively and maintains the properties of the mucus. When CFTR is faulty in CF, the transport of chloride and bicarbonate either stops or doesn't work well enough. This means that the both the food and mucus in the intestines become dehydrated and too acidic, less food is absorbed into the body, and the intestines may become blocked.

What are the intestinal symptoms of CF?

Intestinal symptoms of CF range from flatulence and bloating, to painful and severe blockage of the intestines. The most severe intestinal complication of CF is 'Distal Intestinal Obstructive Syndrome' or DIOS – a blockage in the part where the small intestine joins the large intestine. It is complication that is unique to CF, and more than 1 in 20 people with CF experience DIOS. It is three times more common in adults than in children.[2]

In 2017 a list of the CF community's top 10 health priorities was published, and relief of GI symptoms was rated as the second highest.[1] A follow-up survey to further explore and better understand these symptoms was published in 2020. Of the 145 people with CF who responded, over 40% reported symptoms of wind, stomach cramps and bloating (visible to other people) on most days, and cited symptoms of stomach cramps, pain and bloating as most affecting their quality of life. Two thirds of people with CF who responded commented that their symptoms had caused them to miss school or work.[3]

"During my A levels, I'd struggle to do a full week at school, without something happening, like having to go to hospital or I wouldn't feel well enough. It wasn't just the pain, I was so tired all of the time and being so bloated made it so much harder to do everything."

Grace, 19, talking about her DIOS symptoms

Grace

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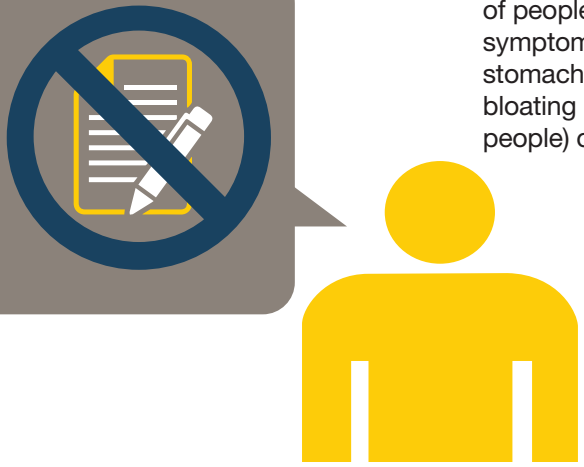
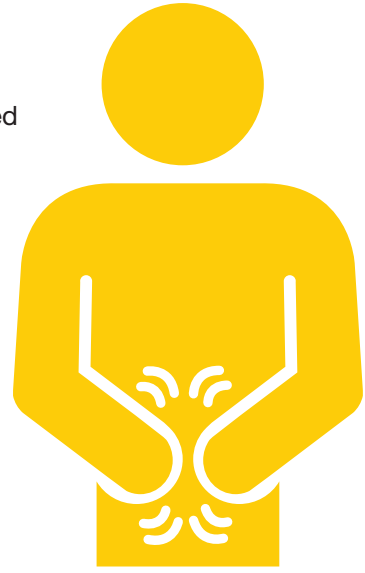


40%+

of people with CF reported symptoms of wind, stomach cramps and bloating (visible to other people) on most days.



What the Trust is doing?

The Trust is funding research to better understand how the biochemical and physiological changes within the gut of those with CF lead to these symptoms. This will hopefully lead to the development of more effective, less invasive, and better tolerated treatments for conditions such as DIOS, and ultimately a better quality of life for people with cystic fibrosis.

Monitoring intestinal symptoms

Questionnaires are currently used to gain important information on the frequency, severity and day-to-day impact of the intestinal symptoms related to cystic fibrosis. However, they do not provide insights into the cellular mechanisms of intestinal pain and blockages. Currently used methods to investigate the physiology of these symptoms include endoscopy and radiation-based therapies. Endoscopies are uncomfortable and invasive, adding to the already high burden of care in people with cystic fibrosis. As radiation-based therapies such as CT scans and X-rays are used in a number of other aspects of CF care, further exposure should be minimised to reduce life-time radiation exposure. We must find more informative and less invasive methods, both to understand the gut symptoms of CF and assess the effectiveness of new medicines in clinical trials.

In research part-funded by a Trust Venture and Innovation Award (VIA), Professor Alan Smyth, Dr Christabella Ng and colleagues at the University of Nottingham have recently shown that it is feasible to use Magnetic Resonance Imaging (MRI) to understand more about what causes the intestinal symptoms of cystic fibrosis. MRI is not an invasive procedure like endoscopy and involves no radiation. During their research studies, they followed the movement of food through the intestinal tract over time and found it takes longer to pass through the body in people with CF in comparison to people with no intestinal symptoms.[4]

"This research helps us understand the mechanisms behind gut symptoms in CF and will help choose suitable drugs and dietary interventions for clinical trials. MRI may also provide new outcome measures for clinical trials of treatments for gastrointestinal symptoms in cystic fibrosis."

Professor Alan Smyth, University of Nottingham

Understanding the cause of DIOS

Current treatments for DIOS include taking regular, unpleasant tasting laxatives to remove the blockages, and sometimes requires surgery. In order to develop more effective treatments for DIOS, it is important to understand what causes it on a cellular level.

The cause of DIOS is unknown and there are many factors that may contribute to its development. These range from variations in function of the cell types that line the intestine wall, to the different activity of proteins on the surface of these cells. Researchers also believe CF causes an imbalance of the types of natural bugs within the intestines, which may contribute to the development of DIOS.

The Trust is funding an SRC to investigate the cellular contributions to DIOS in more detail,[5] led by Professor Soraya Shirazi-Beechey. She is working alongside colleagues at the University of Bristol in the UK, Rotterdam in the Netherlands and Hannover in Germany. A focus of their SRC is whether some types of medicine already used for other conditions could be an effective treatment for DIOS, a process known as drug re-purposing. They hope that they can improve the fluidity and movement of digested food within the gut and allow the natural bugs within the guts to go back to normal.

The potential of NHE3 blockers to treat DIOS

Two proteins in intestinal cells are thought to contribute to the dehydration within the gut in people with CF: the CFTR protein, and a protein called NHE3. SRC Co-Investigator Professor Ursula Seidler and colleagues at the University of Hannover have recently published some results investigating the potential of 'NHE3 blocker' medicines to treat the symptoms of DIOS in a mouse model of cystic fibrosis.[6]

Within the CF intestines, the CFTR protein is either under-active or inactive. At the same time, the NHE3 protein, which removes sodium and water from the intestines, is overactive. The overall effect is that the inside of the intestines becomes very dehydrated and acidic, clogging the gut with mucus and making the material within the gut dehydrated and much harder to move.

In a mouse model of CF, Professor Seidler found that three NHE3 blocker medicines were able to decrease water reabsorption from the intestines and increase alkalinity in the intestine.

Professor Soraya Shirazi-Beechey

"Professor Seidler's research has shown that it is possible to enhance the intestinal fluidity using already-licenced drugs. In combination with confirmatory studies by colleagues within our SRC programme, the results provide a strong basis for planning of future clinical trials to test the effect of these drugs in treating DIOS in individuals with cystic fibrosis. It means we could make real progress in the fight to restore digestive comfort to everyone with cystic fibrosis."

Professor Soraya Shirazi-Beechey, University of Liverpool, SRC Principal Investigator

Digestive problems are a debilitating issue for people with CF and we're urgently looking for ways to treat and manage these symptoms. We hope to see results from the work we're funding soon that will set the direction for future treatments.

"Having a less invasive way of dealing with DIOS would be really life-changing"

Grace, 19, who has cystic fibrosis

Thank you

The Cystic Fibrosis Trust is very grateful to the Castella family for their support for the research discussed within this report, along with many other trusts, organisations and individuals that contribute to our ground-breaking research.

References

1. Rowbotham N et al 2018 Thorax 73, 383-390, & cysticfibrosis.org.uk/news/your-research-priorities-revealed

2. 5.7% of all people with CF experience DIOS according to data from UK CF Registry Annual Data Report 2019, published in August 2020. cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources

3. Smith S et al 2020 BMJ Open Resp Res 7: e0000614

4. Ng C et al 2020 J of Cystic Fibrosis, DOI.org/10.1016/j.jcf.2020.06.004

5. cysticfibrosis.org.uk/the-work-we-do/research/cf-research-topics/understanding-and-treating-symptoms/src-11-shirazi-beechey

7. Tan et al 2021 Br J Pharmacol, 178 1018-1036

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