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COVID UNANSWERED QUESTIONS

What do we know about covid-19's effects on the gut?

Not just a respiratory infection, covid can cause symptoms throughout the body. Gastrointestinal symptoms are common in both acute and long covid, with gut issues often persisting long after initial infection. **Katharine Lang** investigates

Katharine Lang *freelance journalist*

What gastrointestinal symptoms can covid-19 cause?

Lack of appetite, nausea, vomiting, diarrhoea, and abdominal pain. These may not be the symptoms people expect with covid, but around 50% of people experience them after SARS-CoV-2 infection, and in some people they're the only symptoms.[1] Gastrointestinal (GI) symptoms may be the first sign of infection or may develop later and persist as part of long covid.

Sheena Cruickshank, immunologist at the University of Manchester, tells *The BMJ* why doctors didn't initially recognise GI symptoms as part of covid-19. "The frequency of gastric symptoms—anorexia, pain, diarrhoea, vomiting, rectal bleeding—has varied considerably from 12-61% in publications," she says, explaining that this variance may be due to GI symptoms not being reported as linked to covid. "However, it's clear that this has the potential to be a major symptom."

When SARS-CoV-2, the virus that causes covid, enters the lungs it gains entry to epithelial cells by binding to angiotensin converting enzyme 2 (ACE2) receptors. These receptors are found on epithelial cells in many parts of the body and are numerous on those of the small and large intestines.[2]

Cruickshank says, "One of the reasons for the gut symptoms may be that the ACE2 receptors that the virus uses to enter and hijack cells are found on our gut epithelial cells. We know that viral RNA has been isolated from stool samples, although this may not be infectious." This evidence was gathered early in the pandemic from studies in China,[3 4] which found SARS-CoV-2 RNA in stool samples from patients in hospital. More recent research[5] has confirmed that faecal shedding of viral RNA happens in around half of covid patients and that this is associated with GI symptoms.

Stephen Griffin, virologist at the University of Leeds, explains why we shouldn't be surprised that so many people experience GI symptoms. He says, "The receptor for SARS-CoV-2, ACE2, is widely expressed within the blood vessels and lining of the gut, and we know that the virus can be detected, recovered from, and sequenced both in stool samples and in wastewater from the environment—which is an excellent, real time way to monitor infections and genetic variability."

How might the virus cause GI symptoms?

Once the virus is in the gut it interacts with ACE2, increasing the production of inflammatory cytokines and damaging the mucous membrane barrier.[6] In severe cases this inflammation can result in ulceration of the oesophagus, stomach, and duodenum,[7] but more commonly it causes nausea, vomiting, abdominal discomfort, and diarrhoea.

"The other aspect of disease caused by the virus relates to damage done to the blood vessels and lining of the bowel," says Griffin. "The virus is known to cause microclots in a multitude of tissues, and the bowel is no exception. In addition, the integrity of the bowel lining can be disrupted, allowing commensal bacteria to enter the blood and cause infections."

What gut symptoms are seen in long covid?

"Such bowel symptoms are often prominent in patients with long covid as well," Griffin tells *The BMJ*, "and can include motility problems [dyspepsia/reflux/ulcers], long term continuation of acute symptoms, and so called 'functional disorders' that are actually caused by virus induced inflammation of the liver, pancreas, and biliary tract, which themselves can cause systemic problems."

He adds that "a post-covid incidence of irritable bowel syndrome and possibly inflammatory bowel disease has been noted by some studies."

How does covid affect the microbiome?

Notable changes occur to the commensal flora in the bowels of covid patients, Griffin tells *The BMJ*, "and such 'dysbiosis' can affect myriad aspects of bowel health and even our immunity. This can include responses to vaccines." Significant alterations in the gut microbiome include decreased numbers of *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii*, and *Eubacterium rectale*—gut bacteria known to influence immune responses.[8]

This change in gut bacteria was also associated with an increase in inflammatory cytokines and blood markers of tissue damage, which was greater in more severe covid. The study also found that the changes in gut bacteria persisted after people had recovered from covid, which may help to explain the gut symptoms of long covid.

Daniel Altmann, immunologist at Imperial College London, tells *The BMJ*, "So much of immunological disease can be mapped back to immune subset

programming by differential abundance of bacterial species in a state of eubiosis [balanced microbiota] versus dysbiosis [alterations to the normal gut bacteria balance]. Often, this is at the level of differential production of immune-active short-chain fatty acids and other metabolites by bacterial species."

He notes that butyrate, one of these metabolites, has been found to suppress inflammation[9] and that gut bacterial species that produce butyrate metabolites, such as *F prausnitzii*, are less abundant in people with covid and long covid.[8]

Can a healthy microbiome reduce covid severity?

Cruickshank explains that a diverse gut microbiome could help prevent severe covid. "Our gut microbiota provide important anti-pathogen functions directly," she says—"for example, by competing for niches and nutrition with pathogens and by making antimicrobial factors. More indirectly, the microbiota are vital for a good gut barrier, which in itself can prevent infections, and our gut microbiota are important for the development and function of immune cells."

She tells *The BMJ* that people whose gut microbiome is likely to be less diverse—those with malnutrition or obesity—have a higher risk of severe covid. "Obesity and malnutrition can also directly alter the function of immune cells, making them less able to deal with new threats, and can reduce gut barrier integrity," says Cruickshank. "This is due to a condition called metabolic inflammation or meta-inflammation, a state of chronic low level inflammation.

"Generally speaking, a more diverse microbiome is more likely to be more functional and therefore better for us. Addressing underlying risk factors like meta-inflammation is also very important, so again diet has a huge role to play."

And studies suggest that encouraging a diverse microbiome can help relieve symptoms. One study gave probiotic capsules to people experiencing GI and non-GI symptoms of covid for an average of 108 days. It found that those given the probiotic (but not the control group) showed a significant improvement in cough, fatigue, and overall wellbeing, as well as in GI symptoms.[10]

Another study gave a novel formula of gut microbiota (SIM01) to patients admitted to hospital with covid, finding that these patients produced more antibodies against SARS-CoV-2 and had significantly reduced proinflammatory markers in their blood plasma when compared with control participants.[11] Not only did the formula restore the patients' commensal bacteria and suppress opportunistic pathogens in the gut but it also reduced the viral load in the nose and throat.

This approach has also shown benefits in long covid. Researchers in Hong Kong gave a six month course of SIM01 or placebo to people with long covid symptoms that had lasted more than four weeks. Significantly higher proportions of those receiving the synbiotic preparation (SIM01) reported improvement not only in gut symptoms but also in fatigue, memory and concentration, and general health.[12]

A healthy diet high in fruit and vegetables may also help protect against covid. One large study[13] found that a diet high in fruit, vegetables, and other healthy plant based foods was associated with a lower risk and lower severity of covid, even when considering other socioeconomic risk factors. A diverse diet, high in plants, encourages the development of a diverse microbiome,[14] so this study increases the evidence for the microbiome's role in defending against diseases including covid.

So, clinicians need to be aware that GI symptoms may be a person's only sign of covid infection and that lingering gut symptoms could be a part of long covid, rather than having any other cause. But the good news is that a diverse microbiome could help to minimise the likelihood of severe or lasting GI symptoms from covid.

As has often been advised, having a wide variety of plants in your diet not only helps your gut microflora to thrive but can also boost your immune system to help prevent infections.

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