Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Intestinal microbiota transplantation: do not forget the metabolites

In *The Lancet Gastroenterology & Hepatology,* Siu Lam and colleagues[1] highlight research demonstrating that sterile-filtered intestinal microbiota transplant (IMT; referred to as faecal microbiota transplant by Lam and colleagues) has comparable efficacy with conventional IMT in treating recurrent *Clostridioides difficile* infection, suggesting that soluble factors or those less than 0·2 μm in size within an IMT contribute to its efficacy. The authors provide a welcome review of the gut virome (and mycobiome) as potential mediators; however, the contribution of another group of soluble factors—gut metabolites arising from microbiome–host interactions—also merits highlighting.

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For example, IMT for recurrent *C difficile* infection restores microbially derived bile-metabolising enzymes, including bile salt hydrolases, which causes restoration of the perturbed bile acid milieu of the gut towards premorbid composition.[2] These changes directly impact the life cycle of *C difficile*; specifically, degradation of taurocholic acid by bile salt hydrolases removes a potent endogenous bile acid trigger for *C difficile* germination, while restoration of secondary bile acids (including lithocholic acid) prevents *C difficile* growth and toxin activity.[2] Furthermore, these bile acid changes might provide wider effects on host physiology; IMT for recurrent *C difficile* infection is associated with upregulated farnesoid X receptor activity, which has implications for gut barrier function of the host and metabolic and immune function.[3]

Other microbial metabolite systems have also been investigated. IMT restores short-chain fatty acids including valerate, which directly impairs the growth of *C difficile* without any apparent deleterious effect on commensal gut bacteria.[4] *C difficile* uses the gut amino acid proline as an energy source; but, it is outcompeted for proline by restored bacteria after successful IMT.[4] Marked changes are seen in the glycan profile of the host after IMT, which potentially represents changes in the gut microbiome-mediated glycan degradation.[4]

This axis is relevant beyond recurrent *C difficile* infection. The pertinence of gut microbial metabolites to a range of conditions—metabolic, inflammatory, and otherwise—is increasingly recognised; and the potential of IMT as a treatment strategy is being explored. Recent data demonstrate that gut microbe-mediated conversion of lithocholic acid to other bile acid metabolites is reduced in patients with inflammatory bowel disease (IBD; a disease state in which IMT is of particular interest), and that it is inversely associated with T-helper-17-related gene expression,[5] suggesting a key mechanism by which IMT could potentially benefit IBD.

Bacteriophages and fungi present clear challenges for exploitation as novel microbiome therapeutics, both from a regulatory and technical perspective. Conversely, there are multiple routes by which gut microbial metabolites can be administered, including probiotics, purified enzymes, or directly as metabolites themselves. As such, gut microbial metabolites should not be forgotten by IMT researchers.

BHM has received consultancy fees from Finch Therapeutics Group and Ferring Pharmaceuticals, and speaker fees from Yakult. JRM has received consultancy fees from EnteroBiotix and Cultech, and speaker fees from Falk Forum. JRM is the chair of the data safety monitoring board for a clinical trial of a probiotic to treat oncological disease. BHM, JAKM, and JRM are coapplicants on a related patent application (EP3775157A1).

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Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens

Recently, there have been reports of children with a severe acute form of hepatitis in the UK, Europe, the USA, Israel, and Japan.[1] Most patients present with gastrointestinal symptoms and then progress to jaundice and, in some cases, acute liver failure. So far, no common environmental exposures have been found, and an infectious agent remains the most plausible cause. Hepatitis viruses A, B, C, D, and E have not been found in these

patients, but 72% of children with severe acute hepatitis in the UK who were tested for an adenovirus had an adenovirus detected, and out of 18 subtyped cases in the UK, all were identified as adenovirus 41F.[1,2] This is not an uncommon subtype, and it predominantly affects young children and immunocompromised patients. However, to our knowledge, adenovirus 41F has not previously been reported to cause severe acute hepatitis.

SARS-CoV-2 has been identified in 18% of reported cases in the UK and 11 (11%) of 97 cases in England with available data tested SARS-CoV-2 positive on admission; a further three cases had tested positive within the 8 weeks prior to admission.[2] Ongoing serological testing is likely to yield greater numbers of children with severe acute hepatitis and previous or current SARS-CoV-2 infection. Eleven of 12 of the Israeli patients were reported to have had COVID-19 in recent months,[3] and most reported cases of hepatitis were in patients too young to be eligible for COVID-19 vaccinations. SARS-CoV-2 infection can result in viral reservoir formation.[4] SARS-CoV-2 viral persistence in the gastrointestinal tract can lead to repeated release of viral proteins across the intestinal epithelium, giving rise to immune activation.[5] Such repeated immune activation might be mediated by a superantigen motif within the SARS-CoV-2 spike protein that bears resemblance to Staphylococcal enterotoxin B,[6] triggering broad and non-specific T-cell activation. This superantigen-mediated immune-cell activation has been proposed as a causal mechanism of multisystem inflammatory syndrome in children.[4,7]

Acute hepatitis has been reported in children with multisystem inflammatory syndrome, but co-infection of other viruses was not investigated.[8] We hypothesise that the recently reported cases of severe acute hepatitis in children could be a consequence of adenovirus infection with intestinal trophism in children previously infected by SARS-CoV-2 and carrying viral reservoirs (appendix). In mice, adenovirus infection sensitises to subsequent Staphylococcal-enterotoxin-B-mediated toxic shock, leading to liver failure and death.[9] This outcome was explained by adenovirus-induced type-1 immune skewing, which, upon subsequent Staphylococcal enterotoxin B administration, led to excessive IFN-γ production and IFN-γ-mediated apoptosis of hepatocytes.[9] Translated to the current situation, we suggest that children with acute hepatitis be investigated for SARS-CoV-2 persistence in stool, T-cell receptor skewing, and IFN-γ upregulation, because this could provide evidence of a SARS-CoV-2 superantigen mechanism in an adenovirus-41F-sensitised host. If evidence of superantigen-mediated immune activation is found, immunomodulatory therapies should be considered in children with severe acute hepatitis.

We declare no competing interests.

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See **Online** for appendix

Effect of the COVID-19 pandemic on procedure volumes in gastroenterology in the Netherlands

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The COVID-19 pandemic has challenged health-care systems across the globe. Reallocation of resources and personnel to COVID-19 wards severely affected all aspects of care, including closure of outpatient clinics and cancellation or postponement of procedures.[1,2] We aimed to quantify the effect of the COVID-19 pandemic on nationwide procedure volumes in gastroenterology in the Netherlands during the early and later stages of the pandemic.

We used claims data extracted from the Dutch national health insurers information system (Vektis) to identify all gastroenterological health-care activities performed from Jan 1, 2019, to March 28, 2021, as part of a diagnosis treatment combination plan with a hepatogastroenterologist as the treating physician. The activities were analysed overall and across procedure types and diagnosis groups of interest (appendix pp 2–5). We compared absolute and relative

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