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.

Use of MELD scores in alcoholic hepatitis

The Series paper by Tejasav Sehrawat and colleagues[1] on the treatment of alcoholic hepatitis was highly informative. However, treatment of this condition hinges on being able to reliably predict the patient outcome. The Model for End-stage Liver Disease (MELD) score has been advocated for both predicting outcome and directing treatment with guidelines proposing a threshold of 20 or higher for therapeutic intervention. The original MELD score includes three variables: serum bilirubin, serum creatinine, and the International Normalised Ratio (INR). However, inter-laboratory variability in the INR and creatinine measurement might contribute to an overall mean variation in calculated MELD of 4·8 points (range 2·0–11·0).[2] The methods by which creatinine is measured might also be affected by hyperbilirubinaemia. Bilirubin can substantially affect the result of a colorimetric assay at values more than 170 µmol/L (9·9 mg/dL) and of an enzymatic assay at values more than 340 µmol/L (19·9 mg/dL).[3] This effect was supported by the results of a study of the MELD-sodium score[4] in which there was poor agreement in the creatinine measurement at higher concentrations of bilirubin. Muscle mass, influenced by age, sex, and nutritional status, also affects creatinine concentrations: poor muscle mass might lead to the underestimation of renal dysfunction on the basis of creatinine measurement. Patients with alcoholic hepatitis are almost invariably malnourished[1] and these patients consequently might have unrepresentative MELD values.

Generally, the pre-2016 United Network for Organ Sharing modification of MELD has been applied to alcoholic hepatitis. However, although this MELD calculation might be prognostic, it has not been shown to be predictive of the therapeutic response to corticosteroid therapy.[5] Several alternative versions of MELD, incorporating serum sodium, sarcopenic indices, gene signatures, and lactate, have been developed. Inclusion of an alternative measure of renal function that corrects for factors which might influence creatinine concentrations, the Glomerular filtration Rate Assessment In Liver disease (GRAIL), has been used to create the GRAIL-MELD-Na score.[6] Whether any of these variations in MELD can be routinely made use of in alcoholic hepatitis is still uncertain and perhaps these multiple versions of MELD reflect the weakness of the original score when applied to different clinical scenarios.

A further development is the combination of the MELD with the Lille score.[7] The Lille score includes a dynamic component (the evolution of bilirubin concentrations over 7 days) but also incorporates age, the INR, and a measure of renal function based on serum creatinine. Thus, some of the components of the Lille score are at a similar risk of inaccurate measurement as the MELD score. Although the combination of scores might have been shown to improve overall accuracy, this double-counting of laboratory measurements risks compounding and exaggerating inaccuracy in some patients.

Therefore, pre-existing concerns about the accuracy of MELD should be even more pronounced in patients with alcoholic hepatitis. By definition, these patients have marked hyperbilirubinaemia and so are at the greatest risk of inaccuracy of serum creatinine measurement. The most susceptible patients are sarcopenic, and the depletion of muscle bulk in these patients will lead to an underestimation of renal dysfunction on the basis of creatinine measurement. MELD might therefore be least accurate in patients who are the most jaundiced and malnourished. Over-reliance on creatinine-based prognostic scores risks the inappropriate categorisation of a patient with severe alcoholic hepatitis.

I declare no competing interests.

Ewan Forrest
ewan.forrest@ggc.scot.nhs.uk

Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow G4 0SF, UK

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Probiotics and COVID-19

We appreciate the interest in probiotics to assist with the management of COVID-19 in Joyce Mak and colleagues' recent Correspondence[1] in *The Lancet Gastroenterology & Hepatology*, but we would like to propose a more balanced and optimistic view on this topic. Further to our recent review,[2] we feel that physicians now appreciate that although COVID-19 is mainly a respiratory disease, the gut can act as a reservoir for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] Citing meta-analyses of randomised trials that investigate the effect of probiotics on preventing respiratory tract infections, Mak and colleagues conclude that probiotics have a

"modest efficacy".[1] The odds ratio in the cited Cochrane meta-analysis is 0·53 (95% CI 0·37–0·76).[4] We believe that the efficacy of a treatment that leads to twice as great a reduction in the number of cases is far from modest. The potential for probiotics to reduce the risk and severity of viral respiratory tract infections is supported by clinical and experimental studies on influenza, rhinovirus, and respiratory syncytial virus.[2] Although none of these effects have been tested with SARS-CoV-2, some probiotic stains do have antiviral activity against other coronaviruses.[2] Given the importance of strain-to-strain differences, the selection of probiotics for testing needs to made on the basis of documented attributes.

Mak and colleagues mention that the rationale for using probiotics in COVID-19 is based on indirect evidence.[1] This assertion is true for all interventions in the context of this novel disease. Ideally, preventive and therapeutic interventions should be tested in randomised controlled trials before implementation in clinical practice. In a pandemic affecting millions of people, disregarding practices that are not supported by solid evidence against this specific pathogen is not realistic. Clinicians have adopted a more pragmatic approach, and issued recommendations based on evidence from other viral infections, sepsis, and general intensive care management.[5] Currently, there is no evidence from randomised controlled trials that any medication can prevent or improve the outcomes of COVID-19, and there are hundreds of ongoing trials of antivirals, immune-modulating agents, convalescent plasma, and steroids. On the basis of limited evidence showing that Bacillus Calmette-Guérin (BCG) vaccination provides heterologous protection against respiratory tract infections, randomised trials have been launched to assess whether BCG vaccination can reduce the incidence and severity of COVID-19.[6] We propose that well documented probiotic strains deserve the same level of interest, and call for trials with probiotics to reduce the risk and help treat COVID-19.

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Eric Giannoni, David Baud, Varvara Dimopoulou Agri, Glenn R Gibson, Gregor Reid
eric.giannoni@chuv.ch

Clinic of Neonatology (EG, VDA) and Materno-Fetal and Obstetrics Research Unit (DB), Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Lausanne CH-1011, Switzerland; Food and Nutritional Sciences, St Joseph's Hospital, University of Reading, UK (GRG); Department of Microbiology and Immunology, University of Western Ontario, London, ON, Canada (GR); and Canadian R&D Centre for Human Microbiome and Probiotics, Lawson Health Research Institute, London, ON, Canada (GR)

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We read with interest Joyce Mak and colleagues' Correspondence[1] in *The Lancet Gastroenterology & Hepatology* on the role of probiotics in illnesses related to COVID-19. Although we largely agree with the authors' conclusions, we believe that use of probiotics in the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has wider implications.

SARS-CoV-2 has been postulated to affect gut inflammation both directly and indirectly, infecting intestinal epithelial cells through the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2, and inducing pro-inflammatory chemokine and cytokine release.[2,3] Recent studies suggest that SARS-CoV-2 instigates an acute intestinal inflammatory response, highlighted in laboratory tests by elevated levels of faecal calprotectin and serum interleukin-6, and clinically evidenced by diarrhoea.[2]

Although gastrointestinal disorders are frequent in COVID-19, nothing is known regarding the ability of SARS-CoV-2 to affect the host microbial flora. However, previous studies have shown that ACE2 expressed in the intestinal epithelium regulates the ecology of the gut microbiome through intestinal amino acid homoeostasis[4] and that ACE2 receptors are markedly downregulated by the entry of SARS-CoV-2 into cells through membrane fusion.[5] The intestinal downregulation of ACE2 can consequently lead to an altered microbiota that confers susceptibility to inflammation of the gut.[4–6] Moreover, other coronaviruses, such as the porcine epidemic diarrhoea virus, are able to directly cause microbial dysbiosis, with decreases in the proportion of beneficial bacteria and increases in harmful bacteria.[7]

Given this evidence, bacteriotherapy could represent a complementary resource for the prevention and restoration of SARS-CoV-2 intestinal mucosa damage through the modulation of gut microbiota and decreasing related inflammation. In other infections, such as HIV, in which intestinal inflammation and related microbiota impairment can affect gut epithelial barrier function, bacteriotherapy (through microbiota surface compounds and metabolites)