



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

has been shown to inhibit apoptosis, regulate signalling pathways to produce cytokines, maintain intestinal epithelial homeostasis, and allow recovery of gut mucosal health, thereby attenuating inflammation.^{8,9} We believe that studies of bacteriotherapy in SARS-CoV-2 are needed to evaluate the potential effects on intestinal mucosal inflammation and microbiome homeostasis.

Finally, products available for bacteriotherapy are not the same and have different potential effects. Thus, the conclusions of each study must be considered separately, and the results of meta-analyses that collate data obtained from studies done with different products can be misleading.

We declare no competing interests.

*Giancarlo Ceccarelli,
Carolina Scagnolari, Francesco Pugliese,
Claudio M Mastroianni,
Gabriella d’Ettore
giancarlo.ceccarelli@uniroma1.it

Department of Public Health and Infectious Diseases (GC, CMM, Gd’E), Department of Anaesthesia and Intensive Care Medicine (FP), and Laboratory of Virology, Department of Molecular Medicine (CS, FP), Sapienza University of Rome, Rome 00161, Italy; Azienda Ospedaliero, University Policlinico Umberto I of Rome, Rome, Italy (GC, FP, CMM, Gd’E); and Pasteur Institute Italy, Cenci Bolognietti Foundation, Rome, Italy (CS, FP)

- Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020; **5**: 644–45.
- Effenberger M, Grabherr F, Mayr L, et al. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; published online Apr 20. DOI:10.1136/gutjnl-2020-321388.
- Zhang H, Kang Z, Gong H, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut* 2020; **69**: 1010–18.
- Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487**: 477–81.
- Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020; **76**: 14–20.
- Perlot T, Penninger JM. ACE2—from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes Infect* 2013; **15**: 866–73.
- Tan Z, Dong W, Ding Y, Ding X, Zhang Q, Jiang L. Changes in cecal microbiota community of suckling piglets infected with porcine epidemic diarrhoea virus. *PLoS One* 2019; **14**: e0219868.

- Ceccarelli G, Statzu M, Santinelli L, et al. Challenges in the management of HIV infection: update on the role of probiotic supplementation as a possible complementary therapeutic strategy for cART treated people living with HIV/AIDS. *Expert Opin Biol Ther* 2019; **19**: 949–65.
- Liu Q, Yu Z, Tian F, et al. Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier. *Microb Cell Fact* 2020; **19**: 23.

Authors’ reply

We thank Eric Giannoni and colleagues and Giancarlo Ceccarelli and colleagues for their comments on our Correspondence.¹ New data have since highlighted that patients with COVID-19 have an altered gut microbiome with depletion of beneficial commensals (*Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia* and *Lachnospiraceae* taxa) and enrichment of opportunistic pathogens (*Clostridium hathewayi*, *Actinomyces viscosus*, *Bacteroides nordii*) during hospitalisation.² Importantly, gut microbiome configuration was associated with COVID-19 disease severity, and altered gut microbiota persisted even after clearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), suggesting that the virus might inflict prolonged harm to human microbiome homeostasis.³ Other risk factors for severe COVID-19, including old age, obesity, and diabetes mellitus,³ have been shown to be associated with gut dysbiosis, which might contribute to the poor prognosis of COVID-19.⁴

During this crucial moment, with more than 6 million confirmed cases of COVID-19 globally, we understand that the situation is desperate, and it is not uncommon to try all alternative measures. In the absence of a vaccine or effective therapy for COVID-19, we agree that probiotics represent a complementary approach for the prevention and restoration of SARS-CoV-2-induced mucosal damage or inflammation through the modulation of gut microbiota. Probiotics exert their beneficial effects through several different mechanisms, and substantial differences appear

to exist between different probiotic bacterial species and strains. Organisms therefore need to be selected in a rational manner to treat different diseases.⁵ Currently, questions remain concerning which patients should receive probiotics, what is the best way to deliver probiotics, how to ensure optimal delivery, and whether there is variation in efficacy among different populations. As the world waits in semi-lockdown mode, continued scientific progress for COVID-19 prevention or treatment is highly important, and probiotics represent one option. We call for robust and well planned studies that can facilitate the identification of probiotic strains, including both well documented probiotics and novel COVID-19-specific probiotics, that might result in reduced susceptibility to COVID-19 or less severe disease.

JWYM reports grants from Janssen, the Hong Kong College of Physicians, and the Hong Kong Society of Gastroenterology, outside the submitted work. FKL reports grants from Olympus Hong Kong and China, Pfizer, AstraZeneca, Takeda Pharmaceuticals, Takeda (China) Holdings, and Given Imaging, and personal fees from the American Gastroenterological Association, Medical Association of Guangdong Province, Olympus Hong Kong and China, Pfizer, AstraZeneca, Takeda Pharmaceuticals, EA Pharma, Takeda (China) Holdings, Associação dos Médicos Hospitalares da Função Pública de Macau, Pfizer Upjohn Korea, Fujifilm, Ministry of Health Singapore, and Japanese Gastroenterological Endoscopy Society. FKL is also an advisor and commentator for evidence-based medicine for the Ministry of Health of the People’s Republic of China, Pfizer, AstraZeneca, Ministry of Health Singapore, American College of Physicians Journal Club, and *Nature Reviews Gastroenterology & Hepatology*, outside the submitted work. SCN reports grants from Ferring and personal fees from Takeda, AbbVie, Janssen, and Tillotts, outside the submitted work.

Joyce W Y Mak, Francis K L Chan,
*Siew C Ng
siewchiengng@cuhk.edu.hk

Center for Gut Microbiota Research, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (JWYM, FKL, SCN)

- Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020; **5**: 644–45.
- Zuo T, Zhang F, Lui GCY, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology* 2020; available online May 20. DOI:10.1053/j.gastro.2020.05.048.

- 3 Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020; **368**: m1198.
- 4 Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55–60.
- 5 Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC. Mechanisms of action of probiotics: recent advances. *Inflamm Bowel Dis* 2009; **15**: 300–10.

Emotional state should not be used to differentiate IBD from IBS

We congratulate Marietta Iacucci and colleagues on their recent Rapid Review¹ of recommendations to triage endoscopy during COVID-19. We would like to highlight several points with regard to their algorithm for a suspected new diagnosis of inflammatory bowel disease (IBD).

The authors state that “negative emotions...can cause symptoms that mimic IBD” and that emotional state must be assessed to help rule out irritable bowel syndrome (IBS). We argue that the inclusion of “negative emotions” in this context is potentially deleterious to patient care. To the public, IBS is already a highly stigmatised condition with the misconception that the illness might not be real.² Stigmatisation arises from medical providers, friends, and family members and can perpetuate feelings of shame and helplessness, leading to delayed management and its long-term consequences.³

In the authors’ diagnostic algorithm, an abnormal emotional state, along with normal blood tests and faecal calprotectin leads to “probably IBS”. Poor emotional health is common in IBS and IBD and does not serve to discriminate between the two conditions.⁴ Moreover, this might be exacerbated by the psychosocial shock precipitated by the COVID-19 pandemic. The dichotomised outcome of emotional state as normal versus abnormal is ambiguous and fails to capture the

complexities of psychological health; it is also pejorative and risks further stigmatisation of IBS.

Third, the step in the algorithm to “rule out IBS” after a negative stool test for infection does not follow the globally accepted diagnostic protocol for IBS. This fuels the commonly held misunderstanding among health-care professionals that IBS is a diagnosis of exclusion.⁴ Instead, this diagnosis can be made on clinical grounds using the Rome IV criteria, which has high specificity (97%) for IBS.⁵ Clinicians should not need to rule IBS out, but rather, should use clear evidence-based guidelines to make a diagnosis if patients meet criteria.⁶

We hope that the authors will consider a revision of their algorithm in figure 1 and the supporting text. We welcome a revision that eliminates the assessment of emotional state as part of the diagnostic algorithm or for differentiating IBS from IBD. We also recommend for the algorithm to be adapted to include the assessment of IBS using Rome IV criteria, which would lead to a positive diagnosis of IBS once criteria are met.

We declare no competing interests.

Johannah Ruddy, Tiffany Taft, Keith Siau, *Steven Bollipo
steven.bollipo@newcastle.edu.au

Rome Foundation, Raleigh, NC, USA (JR); Psychogastroenterology Research, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (TT); Liver Unit, University Hospitals Birmingham, Birmingham, UK (KS); John Hunter Hospital, Newcastle, NSW 2305, Australia (SB); and School of Medicine & Public Health, University of Newcastle, Newcastle, NSW, Australia (SB)

- 1 Iacucci M, Cannatelli R, Labarile N, et al. Endoscopy in inflammatory bowel diseases during the COVID-19 pandemic and post-pandemic period. *Lancet Gastroenterol Hepatol* 2020; **5**: 598–606.
- 2 Taft TH, Bedell A, Naftaly J, Keefer L. Stigmatization toward irritable bowel syndrome and inflammatory bowel disease in an online cohort. *Neurogastroenterol Motil* 2017; **29**: 10.1111/nmo.12921.
- 3 Ruddy J. From pretending to truly being OK: a journey from illness to health with postinfection irritable bowel syndrome: the patient’s perspective. *Gastroenterology* 2018; **155**: 1666–69.

- 4 Spiegel BMR, Farid M, Esrailian E, Talley J, Chang L. Is irritable bowel syndrome a diagnosis of exclusion? A survey of primary care providers, gastroenterologists, and IBS experts. *Am J Gastroenterol* 2010; **105**: 848–58.
- 5 Palsson OS, Whitehead WE, van Tilburg MAL, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. *Gastroenterology* 2016; published online Feb 13. DOI:10.1053/j.gastro.2016.02.014.
- 6 Talley NJ, Bollipo S. How can I diagnose IBS? In: Lacey B, ed. *Curbside consultation in IBS: 49 clinical questions*. Thorofare, NJ, USA: Slack, 2011.

Authors’ reply

We appreciate the comments made by Johannah Ruddy and colleagues in response to our Rapid Review,¹ the focus of which, in this unprecedented period, was on how to urgently adapt endoscopy in inflammatory bowel disease (IBD) during the COVID-19 pandemic and in the post-pandemic period. As endoscopy services in general have been severely disrupted, the article highlighted priority indications in IBD for endoscopy.

Our current practice has changed dramatically with the incorporation of telemedicine, recognition of risks to patients and staff from unnecessary visits to hospital and undergoing endoscopy, redeployment of staff, and severe curtailment of endoscopy capacity. We proposed practical triaging protocols that can be administered by a range of health-care providers for prioritisation.

The differential diagnosis between IBD and irritable bowel syndrome (IBS) was not the purpose of the algorithm that Ruddy and colleagues highlight. Selecting patients for urgent colonoscopy to investigate who might have a new diagnosis of moderate to severe IBD is one of the four essential indications in IBD for endoscopy during the pandemic.¹

Negative emotions such as anxiety and stress increase visceral sensitivity via the brain-gut axis, which is the crucial player in IBS symptoms.² Emotional state is an important component of triaging patients during the pandemic, with its serious effects on people’s emotional state, including stress, anxiety, and depression,^{3,4} which