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These conflicting findings are further reinforcement that greater case numbers are urgently required to accurately inform our understanding of individual risk.

Collating and analysing rapidly emerging data will be vital for identifying modifiable risk factors for severe COVID-19 among liver transplant recipients. For example, different immunosuppression regimens might confer differential risk and changes to these medications might mitigate the risk of COVID-19 complications.

Although early data suggest that the effects of COVID-19 on the liver might be modest and reflect infection severity among patients without pre-existing liver disease, the effects of COVID-19 on those with liver transplants or established liver disease remain unclear.² We call on all those caring for patients with previous liver transplantation and other forms of chronic liver disease to use registries to pool details of COVID-19 cases and so permit the rapid large-scale collaborative analyses that are required to inform clinical care.

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- 1 Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol* 2020; published online April 9. [https://doi.org/10.1016/S2468-1253\(20\)30116-3](https://doi.org/10.1016/S2468-1253(20)30116-3).
- 2 Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; 5: 428–30.

Probiotics and COVID-19: one size does not fit all

As of April 20, 2020, coronavirus disease 2019 (COVID-19) has affected more than 2 million people globally. In February, 2020, China's National Health Commission and National Administration of Traditional Chinese Medicine suggested the use of probiotics in patients with severe COVID-19.¹ We reviewed the evidence for the role of probiotics in COVID-19-related illnesses (appendix).

In China, 58–71% of patients with COVID-19 were given antibiotics, and diarrhoea occurred in 2–36% of patients.^{2–4} When antibiotics are used, reinforcement of colonic flora using probiotics has been proposed to reduce susceptibility to subsequent infections. Although a 2012 meta-analysis⁵ showed that probiotics have modest efficacy in reducing antibiotic-associated diarrhoea, the largest randomised, placebo-controlled trial (involving 2941 participants) showed that a 21-day treatment of combined *Lactobacilli* and *Bifidobacteria* did not reduce antibiotic-associated diarrhoea.⁶ Even if probiotics are useful, they are unlikely to have a direct effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; most patients with COVID-19 present with respiratory symptoms. However, gut-lung crosstalk has been proposed in the pathogenesis of certain respiratory conditions. Two meta-analyses reported modest efficacy of probiotics in reducing the incidence and duration of respiratory tract infections of viral origin.^{7,8} During the COVID-19 pandemic, 2–47% of infected patients required invasive mechanical ventilation.^{3,4} Two randomised controlled trials showed that critically ill patients on mechanical ventilation who were given probiotics (*Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*) developed substantially less ventilator-associated

pneumonia compared with placebo.^{9,10} However, the efficacy of probiotics in reduction of intensive care unit mortality and inpatient mortality is uncertain.

Scarce data are available on the effect of COVID-19 on intestinal microbiota. A small case series from China revealed that some patients with COVID-19 showed microbial dysbiosis with decreased *Lactobacillus* and *Bifidobacterium*.¹¹ However, animal studies (as yet, not peer-reviewed) showed that *Lactobacillus acidophilus* and *Bacillus clausii* did not reduce coronavirus receptor expression in the murine small intestine compared with control and post-*Salmonella* infection models.¹² Not all probiotics are likely to be the same. *Lactobacilli* and *Bifidobacteria* are only two types of non-pathogenic bacteria and we must consider whether they can really tip the balance of a diverse gut ecosystem in combating COVID-19. To date, the rationale for using probiotics in COVID-19 is derived from indirect evidence. Blind use of conventional probiotics for COVID-19 is not recommended until we have further understanding of the pathogenesis of SARS-CoV-2 and its effect on gut microbiota. It is likely that a novel and more targeted approach to modulation of gut microbiota as one of the therapeutic approaches of COVID-19 and its comorbidities will be necessary.

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- National Health Committee of the People's Republic of China, National Administration of Traditional Chinese Medicine. Diagnostic and therapeutic guidance for 2019 novel coronavirus disease (version 5). <http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fca1e3e13a/files/ab6bec7f93e64e7f998d802991203cd6.pdf> (accessed April 15, 2020).
- Wong SH, Lui RNS, Sung JY. COVID-19 and the digestive system. *J Gastroenterol Hepatol* 2020; published online March 25. DOI:10.1111/jgh.15047.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; published online Feb 28. DOI:10.1056/NEJMoa2002032.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–13.
- Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* 2012; 307: 1959–69.
- Allen SJ, Wareham K, Wang D, et al. *Lactobacilli* and *Bifidobacteria* in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2013; 382: 1249–57.
- King S, Glanville J, Sanders ME, Fitzgerald A, Varley D. Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. *Br J Nutr* 2014; 112: 41–54.
- Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev* 2015; CD006895.
- Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. *Am J Respir Crit Care Med* 2010; 182: 1058–64.
- Zeng J, Wang CT, Zhang FS, et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. *Intensive Care Med* 2016; 42: 1018–28.
- Xu K, Cai H, Shen Y, et al. Management of coronavirus disease-19 (COVID-19): the Zhejiang experience. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020; 49: (in Chinese).
- Feng Z, Wang Y, Qi W. The small intestine, an underestimated site of SARS-CoV-2 infection: from red queen effect to probiotics. *Preprints* 2020; published online March 10. DOI:10.20944/preprints202003.0161.v1 (preprint).

Resumption of daily services in a gastroenterology department in Guangzhou, China, in the wake of COVID-19

We read with interest the Rapid Review by Iacucci and colleagues,¹ which examined how the coronavirus disease 2019 (COVID-19) pandemic was affecting the use of endoscopy services for inflammatory bowel disease, management of emergency cases, and prioritisation of access to endoscopy in the post-pandemic period.

The peak of the initial COVID-19 outbreak appears to have passed in China, with decreasing numbers of new domestic cases observed since late February.² As a result of this decrease in new cases, our gastroenterology department at the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, resumed daily service on March 2, 2020. Before admission, patients must make appointments online and undergo strict triage based on exposure history, COVID-19 symptoms, and the medical services they need.

Before they can receive further medical services in our department, patients who have fever or respiratory symptoms, with or without a history of exposure to COVID-19, must have real-time PCR (rtPCR) testing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after having throat swabs collected, routine blood tests, and chest CT at our hospital's fever clinic. Patients who have a clear exposure history, overseas travel history, or signs of inflammation on chest CT images, and individuals in need of hospitalisation, surgery, chemotherapy, haemodialysis, or other invasive procedures should have throat swabs taken for SARS-CoV-2 rtPCR testing, along with routine blood tests and chest

CT if necessary. All other patients are not being tested for SARS-CoV-2 by rtPCR and are proceeding directly to different medical services on the basis of their medical need. For example, emergency patients are admitted or referred to the emergency room and patients who seek outpatient services are referred to non-emergency clinics for all types of digestive diseases or to expert clinics for inflammatory bowel disease, neuroendocrine tumours, etc.

Gastroenterologists and hepatologists are responsible for this triage in outpatient services. To prevent patients from gathering (to ensure adequate social distancing), clinic time is allocated in 30-min blocks, with patients making appointments by smartphone app first. Only one patient is allowed to enter the consulting room at any time and is seen by one physician in each consulting room. Precautions against the airborne spread of COVID-19, such as urging patients to wear face masks and to keep 1 m apart when waiting in line, are strictly observed. For emergency patients without SARS-CoV-2 rtPCR test results, we observe meticulous protection protocols to ensure lifesaving operations are done and to prevent potential nosocomial infection. For example, medical workers operate in an isolated ward with protective gear including N95 masks, face shields or goggles, disposable hat and shoe covers, gowns, and double-layer rubber gloves. We resumed non-emergency clinics for all types of digestive disease, seeing 50 patients per day in February, increasing to 100–150 per day in March, and reaching full capacity (300 cases per day) from April 20, 2020. The expert clinics resumed at half capacity (an average of 60 cases per day) on March 2, 2020, and have returned to normal operation (120 cases per day) since April 20, 2020.

For patients who need to be admitted to hospital, only patients and their next of kin who have negative SARS-CoV-2 rtPCR results from throat swabs are allowed to



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For the Chinese translation see
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