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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Gut Microbiome Composition Is Associated with COVID-19 Disease Severity

Yeoh KY, Zuo T, Lui GCY, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 2021;70:698–706.

A growing body of evidence suggests that severity of illness from COVID-19 is largely determined by the patient's aberrant immune response to the virus. A critical unanswered question is: what patient factors determine this immune response? The gut microbiota closely cooperate with the host immune system and are altered in many immunologic diseases. The SARS-CoV-2 virus (which causes COVID-19) infects and actively replicates in enterocytes in the intestine (Science 2020 Jul 3;369(6499):50–54, Sci Immunol 2020 May 13;5(47):eabc3582, Nat Med 2020 Jul;26:1077–1083), thereby causing symptomatic gastrointestinal disease in a subset of patients (Gastroenterol 2020;159:320–334), which suggests the possibility that SARS-CoV-2 interacts (directly or indirectly) with commensal bacteria in the intestine. Therefore, identifying a possible relationship between gut microbiota and COVID-19 may reveal microbial species involved in disease pathogenesis and/or microbial biomarkers for disease severity.

Yeoh et al addressed this knowledge gap by performing a cohort study to investigate how the gut microbiome of COVID-19 patients correlates with disease severity and related inflammatory markers. Research subjects were recruited from 2 hospitals in Hong Kong, with SARS-CoV-2 infection confirmed by quantitative reverse-transcription polymerase chain reaction. Non–COVID-19 control subjects were recruited before the pandemic from a gut microbiome survey study or from colonoscopy trials. Disease severity was classified as mild (no radiographic evidence of pneumonia), moderate (pneumonia with fever and respiratory tract symptoms), severe (respiratory rate >30 breaths per minute or hypoxemia with oxygen saturations <93% on room air), or critical (respiratory failure requiring mechanical ventilation or organ failure requiring intensive care). Overall, blood and stool samples of 100 patients with COVID-19 (average age 36.4 years) and 78 patients without COVID-19 (average age 45.5 years) were studied. Only 87 of the 100 patients with COVID-19 were included in the final analysis (13 patients provided stool samples after recovery). Within the COVID-19 cohort, mild, moderate, severe, and critical disease was observed in 47%, 45%, 5%, and 3% of patients, respectively, 34% received antibiotics, and 46% received antivirals before stool collection.

The study authors found that in comparing the microbiota composition of hospitalized COVID-19 patients with non–COVID-19 subjects, members of the phylum *Bacteroidetes* were more abundant in COVID-19 patients (mean 23.9% vs 12.8%) while *Actinobacteria* were more abundant in non–COVID-19 individuals (26.1% vs 19.0%; $P < .05$). Without controlling for use of antibiotics, the gut microbiota of COVID-19 patients were primarily enriched with taxa such as *Ruminococcus gnavus*, *Ruminococcus torques*, and *Bacteroides dorei*, and depleted of *Bacteroides adolescentis*, *Eubacterium rectale*, and *Faecalibacterium prausnitzii* relative to non–COVID-19 patients ($P < .05$). Among hospitalized COVID-19 patients, inflammatory markers such as CXCL10, interleukin (IL) 10, tumor necrosis factor (TNF) α, aspartate transaminase, γ-glutamyltransferase, C-reactive protein, lactate dehydrogenase, N-terminal pro–B-type natriuretic peptide, and erythrocyte sedimentation rate were significantly associated with changes in microbiota composition: Six species depleted in the COVID-19 cohort negatively correlated with CXCL10, 5 species negatively correlated with IL-10, and 2 species negatively correlated with TNF-α and CCL2. From 42 stool samples collected from 27 patients up to 30 days after the patients tested negative for COVID-19, the authors found that gut microbiota of recovered patients were enriched with *Bifidobacterium dentium* and *Lactobacillus ruminis*, regardless of whether they had received antibiotics, and depleted in *Eubacterium*

rectale, *Ruminococcus bromii, Faecalibacterium prausnitzii*, and *Bifidobacterium longum*.

Based on these results, the authors concluded that gut microbiota composition is associated with the magnitude of immune response to COVID-19, and therefore with clinical disease severity. The authors also found that gut microbiome dysbiosis persisted after clearance of SARS-CoV-2 and thus could be a factor in developing persistent symptoms or multisystem inflammation syndromes that are seen in some patients following clearing the virus.

Comment. The gut microbiota play important roles in regulating the development and function of the innate and adaptive immune systems. Commensal microorganisms control immune gut homeostasis by regulating the balance of pro-inflammatory responses such as those of T_H17 T cells vs anti-inflammatory regulatory T cells (Proc Natl Acad Sci 2010;107:12204–12209). Disease severity in COVID-19 is a consequence not only of viral infection, but also of aberrant host immune responses, including a vast release of cytokines by the immune system that leads to uncontrolled inflammation and multi-organ failure (Nat Rev Immunol 2020;20:363–374). Yeoh et al sought to characterize the relationship between the gut microbiota and host immunity in patients with COVID-19 by sequencing gut bacterial species and measuring circulating inflammatory markers from COVID-19 patients and matched control subjects. The authors demonstrated that the gut microbiota composition was altered in COVID-19 and that these changes in gut flora were significantly associated with disease severity. These findings suggest the possibility that depletion as well as enrichment of specific immunomodulatory gut microorganisms contribute to a more severe COVID-19 clinical course.

The authors found that gut commensal species depleted in the COVID-19 cohort were linked to an increased concentration of the inflammatory marker CXCL10. The depleted species included *Bifidobacterium adolescentis*, *Eubacterium rectale*, and *Faecalibacterium prausnitzii*, which are known to play immunomodulatory roles in the human gastrointestinal system. Specifically, the levels of *Faecalibacterium prausnitzii* in the gut microbiota negatively correlate with risk of relapse in inflammatory bowel disease, which suggests that the species might down-regulate autoinflammatory responses such as those seen in COVID-19 infections (Clin J Gastroenterol 2018;11:1–10). In a small study of gut microbiota alterations in 15 COVID-19 patients hospitalized in Hong Kong, Zuo et al also found an inverse correlation between the abundance of *Faecalibacterium prausnitzii* and COVID-19 disease severity (Gastroenterol 2020;159:944–955). Together, these findings from 2 separate cohorts indicate that specific depleted gut commensal microbes may play significant roles in preventing the aggressive host immune responses that characterize severe COVID-19.

Yeoh et al also found an enrichment of *Ruminococcus gnavus*, *Ruminococcus torques*, *Bacteroides dorei*, and *Bacteroides vulgatus* in COVID-19 patients, species whose roles in immune dysfunction is well established in the literature. The Ruminococcus family, primarily mucolytic bacteria, has been found to be enriched in the gut microbiome of inflammatory bowel disease patients (Clin J Gastroenterol 2018;11:1–10), underscoring a possible role for these bacteria in promoting autoimmune responses such as those seen in COVID-19. Gou et al similarly found that *Ruminococcus gnavus* was more prevalent in COVID-19 patients and positively correlated with inflammatory markers (https://www.medrxiv.org/content/10.1101/2020.04.22.20076091v1). Zuo et al found that baseline abundance of *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus* negatively correlated with COVID-19 severity. They also demonstrated that the Bacteroides phylum correlated inversely with SARS-CoV-2 load in fecal samples. Together, these studies suggest that enrichment of the Bacteroides family in COVID-19 patients may help clear the virus, as these microbiota have been shown to down-regulate colonic angiotensin-converting enzyme 2 expression, thereby reducing the ability of SARs-CoV-2 to replicate in enterocytes. However, this theory has not yet been directly investigated (Gastroenterol 2020;159:944–955). Finally, one open question raised by the paper is whether these enriched species in COVID-19 patients play an active role in disease pathogenesis or simply flourish opportunistically due to a depletion of other gut microorganisms. An alternative explanation for their results is that the changes in gut microbiota are a result of the immune response or other changes associated with the disease.

One of the main limitations of this study is that antibiotic use, which is known to disrupt composition of gut flora, was not completely adjusted for. In addition, the use of empiric antibiotics in hospitalized COVID-19 patients may make it difficult to extrapolate the results of this study to other COVID-19 populations. Another limitation of the study is that the prevalence of comorbid conditions such as hyperlipidemia, diabetes, heart disease, and HIV, which are known to affect gut microbiota, was not equal between the COVID-19 and non−COVID-19 cohorts. In addition, COVID-19 subjects were younger (average age 36.4 years) compared with the non–COVID-19 control subjects (average age 45.5 years), and gut microbiota are known to evolve with age (J Am Geriatr Soc 2015;63:776–781). Therefore, larger studies controlling for comorbidities and age are needed to further elucidate the relationship between COVID-19 and gut microbiota composition. Further research is required to determine mechanisms of how specific gut microbes may affect the immune response to SARS-CoV-2 infection. Additional studies are also required to assess changes in the gut microbiome across ranges of COVID-19 disease severity (particularly severe disease) in different patient populations and with longer follow-up.

The findings from this paper are consistent with the growing consensus that COVID-19 is an immunologic disease, not just an infectious disease. An important implication

of this research is that specific gut microbes could be analyzed to risk stratify COVID-19 patients. Furthermore, if additional studies support the contention that the gut microbiota play an important role in the pathogenesis of COVID-19, then modification of gut species (or their metabolites) may serve as a novel approach to mitigating severe disease. Indeed, multiple clinical trials are currently exploring the impact of probiotics on COVID-19 (Br J Nutr 2020; https://doi.org/10.1017/S000711452000361X).

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Evaluating the 2020 UK Surveillance Colonoscopy Guidelines on CRC Incidence After Polypectomy

Cross AJ, Robbins EC, Pack K, et al. Colorectal Cancer Risk following Polypectomy in a Multicentre, Retrospective, Cohort Study: An Evaluation of the 2020 UK Post-polypectomy Surveillance Guidelines. Gut 2021;1–14.

The prevention of colorectal cancer (CRC) is achieved through detection and removal of premalignant polyps (PMPs) with colonoscopy. Individuals who are at greater risk for metachronous advanced neoplasia based on their index examination findings are recommended to undergo follow-up surveillance colonoscopies. Current UK guidelines, which were updated in 2020, recommend a 3-year surveillance interval for individuals at high risk, which is defined as ≥2 PMPs where ≥1 polyp includes an adenoma or a serrated polyp (SP) ≥10 mm in size or exhibits high-grade dysplasia (HGD), ≥5 PMPs, or ≥1 nonpedunculated PMP that is ≥20 mm. PMPs are defined as adenomas or SPs (any hyperplastic polyp, sessile SP or traditional serrated adenomas) except for ≤5 mm hyperplastic polyps in the rectum (Gut 2020;69:201–223). Low-risk individuals, defined as those not meeting the high-risk criteria, are recommended to follow population-based CRC screening, which is currently the fecal immunochemical test in the UK (Gut 2020;69:1645–1658).

In the current retrospective study, Cross et al examined the CRC incidence after polypectomy in 17 UK facilities with the majority of colonoscopies performed during the years 2000–2010 with a median follow-up of 10.1 years. The aim of the analysis was to evaluate the ability of the updated UK guidelines to discriminate high- versus low-risk adults with respect to the postpolypectomy CRC incidence (Gut 2021; 1–14) as compared with the general population using standardized incidence ratios (SIRs). Because SPs had inconsistent data during the years studied, only individuals who had SPs and synchronous adenomas on baseline examination were included.

There were 21,318 patients included, with 368 CRC diagnoses during the study period. The 10-year cumulative incidence of CRC without surveillance examination was 1.9% (95% confidence interval [CI], 1.7–2.3), which was comparable with the incidence in the general population (SIR, 0.88; 95% CI, 0.77–1.01). Baseline characteristics for all groups associated with a higher incidence of CRC included age ≥55 years, ≥2 PMPs, adenomas exhibiting HGD or tubulovillous/villous (or unknown) histology, polyps located proximally, and an index examination within 2–90 days.

The authors examined the CRC risk without surveillance and observed that it was greater than in the general population in people with adenomas exhibiting HGD (SIR, 1.74; 95% CI, 1.21–2.42), as well as those with a minimum of 2 PMPs if ≥1 was considered advanced (SIR, 1.39; 95% CI, 1.09–1.75). The cumulative incidence of CRC at 10 years in the entire cohort after ≥1 surveillance examination was 1.6% (95% CI, 1.4–2.0), which was decreased compared with the incidence in the general population (SIR, 0.72; 95% CI, 0.61–0.85).

The low-risk group included 15,079 individuals, with a 3.1-year median time from index examination to initial surveillance. For the low-risk group, the 10-year cumulative CRC incidence without surveillance was 1.6% (95% CI, 1.3–1.9), which was lower compared with the general population (SIR, 0.75; 95% CI, 0.63–0.88). The CRC incidence decreased with 1 surveillance colonoscopy (hazard ratio [HR], 0.58; 95% CI, 0.41–0.83 for 1 surveillance; HR, 0.53; 95% CI, 0.33–0.83 for ≥2 surveillances).

The high-risk group included 6239 patients with a 2.1-year median time from index to first surveillance examination. In the high-risk cohort without surveillance, the 10-year cumulative CRC incidence was 3.3% (95% CI, 2.5–4.3), which was greater than the general population (SIR, 1.30; 95% CI, 1.03–1.62). CRC incidence also decreased in the high-risk group after 1 surveillance (HR, 0.71; 95% CI, 0.49–1.03 after 1 surveillance; HR, 0.44; 95% CI, 0.28–0.70 for ≥2 surveillances), with an SIR of 1.22 (95% CI, 0.91–1.60) compared with the general population. However, after first surveillance, the CRC incidence at 10 years increased to 4.0% (95% CI, 2.8–5.8), but this observation was attributed to advancing age.

The authors concluded that the updated UK guidelines reliably discriminate patients into low versus high risk groups for development of CRC post polypectomy. Therefore, they attested that 1 surveillance examination at a 3-year interval for high-risk patients and reverting back to population-based CRC screening for low-risk patients is appropriate.

Comment. This study found that the incidence of CRC without any surveillance examination was 1.3 times higher in those categorized as high risk when compared with the general population. The risk was increased particularly for those who had PMPs ≥20 mm, adenomas with HGD, and had polyps that were proximally located—all thought to be at an increased risk owing to the increased likelihood of a lack of complete polyp removal—but this risk decreased