
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.

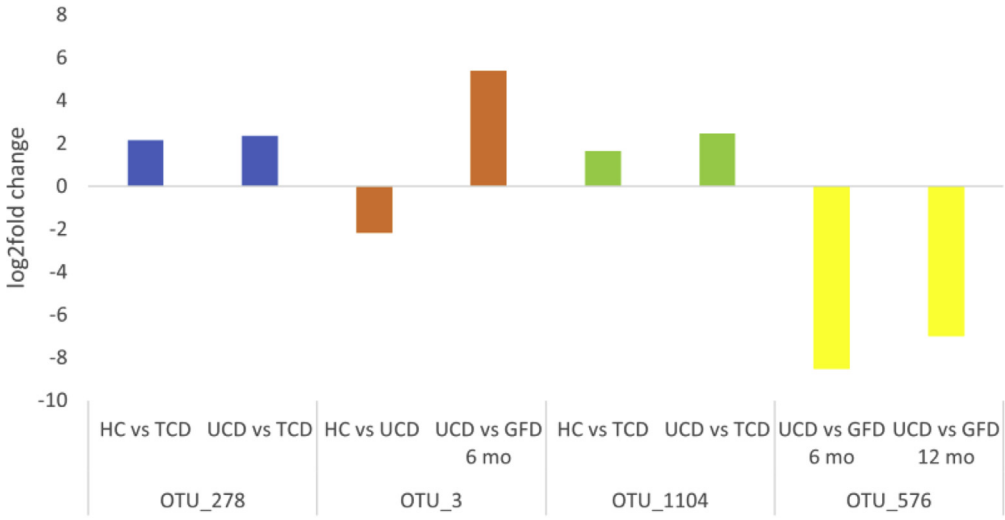


**Figure 1.** Statistically significant differences (log2-fold change) in relative abundance of operational taxonomic units belonging to the genus *Akkermansia* in distinct 2-group comparisons (adjusted $P < .05$). A negative log2-fold change represents a lower abundance in the second group of the comparison.

effect of a gluten-free diet.[1] Di Biase et al[2] are correct in their assessment that several of their fecal microbiota findings are in accordance with ours, whereas others are not. We believe that some of these discrepancies are to be anticipated and may be the result of the distinct microbial function of community members when studied at the low levels of phylogenetic hierarchy.

With reference to *Akkermansia*, our 16S rRNA sequencing showed that certain operational taxonomic units belonging to the genus were lower at disease diagnosis than for healthy control subjects (Figure 1). These findings are consistent with their study, as well as the study by Bodkhe et al,[3] who demonstrated a respective decrease in the relative abundance of amplicon sequence variants belonging to the same genus. Some operational taxonomic units were at higher levels in patients on treatment with gluten-free diet, whereas others were further reduced after a gluten-free diet (Figure 1). Such discrepant observations highlight the need for high-resolution delineation of the gut microbiome composition at both species and strain levels, which remains challenging with current approaches to amplicon sequencing. Importantly, attributing identity down to the genus or even species level should not necessarily confer a phenotype or function. The most notable example is with *Escherichia coli*, in which at least 8 phenotypically distinct pathovars are currently recognized,[4] including the strain *E coli* Nissle, which has long been recognized as a probiotic. The advent of high-throughput sequencing, further developments in sequencing output and reductions in relative cost, and advances in bioinformatic tools and computational power now allow us to portray the microbial community at species and strain levels and interrogate its role in health and disease.

Our study points to specific bacterial groups in which we should concentrate our next efforts to understand the role of the gut microbiota in the underlying pathogenesis of celiac disease. Among the various mechanisms we propose in which the gut microbiota may be implicated in celiac disease pathogenesis, Dr Tobi and colleagues[5] suggest another: the Paneth cells and their secreted products defensins.

*KONSTANTINA ZAFEIROPOULOU*
Human Nutrition, School of Medicine, Dentistry and Nursing
College of Medical, Veterinary and Life Sciences
University of Glasgow
Glasgow, Scotland

*RICHARD HANSEN*
Department of Paediatric Gastroenterology
Royal Hospital for Children
Glasgow, Scotland

*KONSTANTINOS GERASIMIDIS*
Human Nutrition, School of Medicine, Dentistry and Nursing
College of Medical, Veterinary and Life Sciences
University of Glasgow
Glasgow, Scotland

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**Conflicts of interest**
RH has received speaker's fees, conference support or consultancy fees from Nutricia and 4D Pharma. KG reports personal fees from Nutricia, research grants and personal fees from Nestle, personal fees from Dr Falk and Baxter, Abbott, Servier.

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# Famotidine and Coronavirus Disease 2019

Dear Editors:

Yeramaneni et al[1] reported results from a retrospective study testing associations between the use of famotidine and outcomes among patients with coronavirus disease

2019 (COVID-19). Like our recent retrospective study on the same topic,[2] they classified the use of famotidine based on exposure within 24 hours after hospital admission and followed patients with COVID-19 for death for up to 30 days. Interestingly, although our study found a nearly 2-fold protective association between the use of famotidine and death or intubation (adjusted hazard ratio, 0.42; 95% confidence interval [CI], 0.21–0.85), Yeramaneni et al found no association between famotidine and death (adjusted odds ratio, 1.59; 95% CI, 0.94–2.71). Why might the 2 studies, so similar in design, have such different results?

First, it is possible that differences related to institutional patterns of use of famotidine underlie the discrepancy in study findings. For example, if famotidine was often used for stress ulcer prophylaxis in critically patients at Yeramaneni et al's institution, then patients who received famotidine may have been sicker at baseline than those who did not. Sixteen percent of patients used famotidine in Yeramaneni et al's study compared with 5% in ours, implying a fundamental difference related to institutional patterns of use. Before matching, patients who used famotidine at Yeramaneni et al's institution were sicker in almost every way (higher oxygen requirements, more comorbidities, etc), whereas this was not true in our cohort. After matching, differences within Yeramaneni et al's cohort are likely to persist in the unmatched categories. Given the significant baseline differences between those who used famotidine and those who did not, these residual confounders would likely bias results toward showing harm associated with famotidine.

Second, home use of famotidine may help to explain the differences between studies. An assumption of our study was that use of famotidine in the hospital represented a continuation of home use of famotidine. Intriguingly, home use of famotidine in Yeramaneni et al's study seemed to have the opposite relationship with death compared with use in the hospital (adjusted odds ratio, 0.49 [95% CI, 0.16–1.52] for home use of famotidine vs 1.59 [95% CI, 0.94–2.71] for use of famotidine in the hospital). This hint of an interaction between home and hospital use of famotidine is puzzling and suggests that hospital use of famotidine does not represent a continuation of home use in Yeramaneni et al's study. An analysis of home use of famotidine in Yeramaneni et al's prematched cohort, excluding those who used famotidine in the hospital, would be interesting. One possibility is that early, but not late, use of famotidine may be beneficial in COVID-19.[3]

Examining the totality of evidence, what do we have? Our study and other retrospective studies of famotidine suggest there may be an association between the use of famotidine and improved outcomes among hospitalized patients with COVID-19[4,5]; this was also suggested by a case series of famotidine with quantitative symptom tracking in nonhospitalized patients.[3] The data from Yeramaneni et al and other retrospective studies[6,7] show no association. We agree with Yeramaneni et al that famotidine should only be used as COVID-19 therapy in the context of a clinical trial. Such trials are ongoing, and the results of these trials will be the crucial next step in answering the question of whether there is a role for famotidine in the treatment of COVID-19.[8,9]

*DANIEL E. FREEDBERG*
*TIMOTHY C. WANG*
*JULIAN A. ABRAMS*
Division of Digestive and Liver Diseases
Columbia University Irving Medical Center
New York, New York

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**Conflicts of interest**
The authors disclose no conflicts.

**Most current article**

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# Famotidine and Mortality in Coronavirus Disease 2019

Dear Editors:

We read with great interest the study by Yeramaneni et al[1] in which the authors have retrospectively analyzed the effect of famotidine on 30-day mortality in hospitalized patients with Coronavirus Disease 2019 (COVID-19). In a matched cohort of 410 patients who received famotidine and 746 who did not, 30-day mortality was higher with famotidine (15.1% vs 9.8%, $P = .007$). A few points merit consideration. First, the authors adjusted the 2 groups for World Health Organization severity within 48 hours of admission. World Health Organization severity level 5 includes patients on mechanical ventilation or extracorporeal membrane oxygenation. Of all patients, 6.3% and 0.5% in the famotidine and nonfamotidine groups, respectively, were classified as World Health Organization severity level 5, leading to a mismatch. Even the postmatch famotidine group had a higher proportion of patients with concomitant steroids, antiviral, and tocilizumab use because of severe disease. The mortality in the famotidine group among patients on mechanical ventilation was extremely high: 63 patients required mechanical ventilation and 62 (99%) patients died. In such patients, any drug is unlikely to be of much benefit. Second, the use of steroids and tocilizumab in the cohort was associated with higher mortality. In contrast, prior studies suggest reduced mortality in patients receiving steroids and tocilizumab.[2,3]