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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Gut Microbiota as Biosensors in Patients With Cirrhosis

Most of the cirrhosis-related burden results from complications such as hepatic encephalopathy (HE), ascites, and infections.[1] HE, which has distinct overt and covert stages, represents a particularly challenging alteration of the gut–liver–brain axis.[2] Indeed, most current treatments for HE are focused on the microbiome, but there remains room for improvement.[3,4] Cirrhosis-associated gut microbial alterations are likely a consequence of factors related to advancing liver disease, reduction in bile flow, impaired mucosal and systemic immune response, and concomitant medications such as lactulose, rifaximin, absorbable antibiotics, and proton pump inhibitors.[5,6] These conspire to create a milieu that can encourage potentially pathogenic taxa at the expense of those associated with benefit at all gastrointestinal tract locations.[5] Although in human beings it is difficult to determine whether the microbiota are the chicken or the egg with regard to cirrhosis, these microbial patterns can be potentially useful as prognosticators.

Use of biosensors to detect internal processes has been used in several ecosystems. These can be as simple as enumeration of specific organisms or complicated based on changes in metabolic processes. An important concept in the development of biosensors is the balance between keystone organisms and indicator organisms. Keystone organisms are those that play a disproportionately large role in the prevalence and population levels of other species within their ecosystem or community.[7] On the other hand, indicator species are used to monitor environmental changes, assess the efficacy of management, and provide warning signals for impending ecologic shifts.[8]

These concepts can be extrapolated into the human gut microbiota to translate the immense complex clinically applicable formulae. The cirrhosis dysbiosis ratio was created to evaluate the contribution of potentially beneficial or keystone taxa (*Lachnospiraceae*, *Ruminococcaceae*) compared with those that may be indicator taxa (*Enterobacteriaceae*).[9] Indeed, cirrhotic patients with a lower cirrhosis dysbiosis ratio were more likely to have worse disease, and this indicator was sensitive to change with progression, liver transplant, and probiotic therapy, and was stable in patients whose clinical course remained stable.[5,9] A similar ratio also was created for salivary microbial changes in cirrhosis.[10] Both stool and salivary microbiota changes could predict the development of 90-day hospitalizations.[10,11]

However, the cirrhosis complication in which microbiota may have the greatest contribution remains HE.[3] It is tempting to assume that the contribution of microbiota toward HE development stems from urease expression and resultant ammonia generation.[5,12] However, several microbial taxa associated with overt HE (OHE) are not urease positive but could be associated with local, hepatic, brain, and systemic inflammation.[13] The specific microbiota associated with ammonia-related astrocytic changes vs inflammation-associated white matter changes are distinct but have a higher relative abundance in HE patients.[14] Distinct salivary and gut microbial profiles have been used to detect covert HE in outpatients with cirrhosis.[15]

However, most of these studies have been performed in stable outpatients, whereas the OHE stage usually is treated as an inpatient. OHE is treated with microbiome-modifying therapies such as lactulose and rifaximin, along with antibiotics needed for intercurrent or precipitating infections, which makes the interpretation of microbial contribution challenging.[3] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Sung et al[16] studied this very challenging population admitted with HE with appropriate inpatient and outpatient controls and longitudinal follow-up evaluation. The investigators showed, as expected, that microbial diversity was affected in the acute period, but the incomplete recovery and subsequent relative increase of *Veillonella parvula* is intriguing. This microbe has been associated with cirrhosis progression, and usually is an oral microbe that is affected by proton pump inhibitor therapy.[17,18] The investigators were able to follow up patients longitudinally and found the key taxa belonging to a wide variety of phyla and their ratios could predict HE recurrence and mortality. There also was widespread gene function change in patients with OHE compared with the remaining groups, although function was not directly queried. Another intriguing finding was the higher concentration of *Lactobacillus* in patients who died. This has been shown in prior studies of cirrhosis, even in patients without lactulose.[15,19] Although several members of *Lactobacillus* are beneficial probiotic species, the role of this taxon needs further analysis in the setting of HE.[19] The study builds on prior reports in which the stool microbial patterns also could predict 30-day outcomes in cirrhotic inpatients across single and multicenter platforms.[20,21] Interestingly, despite assumed differences pertaining to diet, disease etiology, genetic background, and socioeconomic status, the microbial profile for inpatients in Taiwan was similar to that found in prior Western studies.[21] This indicates that the toll that cirrhosis, multiple hospitalizations, and frequent antibiotic use exact on microbial health may be high universally.

This study contributes to growing evidence that microbiota not only affect the disease process in cirrhosis and HE at a given time point, but also could be used to prognosticate this underserved population. Larger multicenter studies are needed to ensure widespread generalizability of microbe-based diagnostics and predictive modeling.

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