CRITICAL CARE

COMMENTARY

During critical illness the gut does not pass the acid test

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See related research by Osuka *et al.*, http://ccforum.com/content/16/4/R119

Abstract

The composition and function of intestinal microflora are emerging as integral to both health and disease. During critical illness the normal microbiota are rapidly replaced by pathogenic species as a result of both the physiologic stress itself and the use of antibiotics. In this report, the authors use fecal pH as a surrogate marker to determine the predictive value of the functional output of the intestinal microflora during critical illness. Fecal pH appears to be highly predictive of outcome from critical illness, and may reflect the output of key organic acids such as the short-chain fatty acids, lactic acid, and other important products of the gut microflora.

In the previous issue of *Critical Care*, Osuka and colleagues from the Osaka University Hospital and School of Medicine examine fecal pH as a proxy for composition and functional alterations in the gut flora that predict outcome in critically ill patients [1]. This work builds on and extends their previous work examining the role of alterations in the intestinal microflora on the systemic immune response syndrome (SIRS) and mortality during critical illness [2].

In the present study the authors demonstrate that when the pH level is increased or decreased by one, the incidence of bacteremia and mortality is increased. As an explanation for this finding, the authors measured various levels of organic acids including lactic acid, succinic acid, acetic acid, and formic acid. Propionic acid and butyric acid, cytoprotective short-chain fatty acids produced by intestinal bacteria, were also examined. The data seem to show that the various levels of these acids in feces play a major role in determining fecal pH. Although

somewhat noisy, the fecal bacterial counts seemed to suggest that microbial composition was a determinant of organic fecal acid levels and hence pH. As might be expected, *Bacteroidaceae* were decreased in patient groups and there was a proliferation of *Pseudomonas* and a decrease in *Enterobacteriaceae*. The use of multiple antibiotics among these patient populations probably explains these findings, as *Pseudomonas* spp. tend to be more resistant to antibiotics than other Gram-negative bacteria.

The authors imply that perturbations in the intestinal microflora from the use of antibiotics, as well as due to the catabolic stress itself, have a major impact on fecal pH that may then be used as a global marker to predict outcome [1]. This finding is important and is the first of its kind to suggest that it may be possible to identify biomarkers within the complex ecology of the gut that predict outcome. The gut represents the most diverse and fragile microenvironment and ecosystem in the human body and can become dramatically altered by critical illness and its invariable treatment with powerful antibiotics and vasoactive agents [3-5]. Precisely how this perturbed ecosystem shifts the various microbes or microbial population into evolutionary trajectories that cause SIRS and mortality remains a mystery. This outstanding group of investigators has been working diligently to characterize these changes, and in this report provides the practicing clinician with a possible tool to use as a guide that will signal when the patient's evolving microbiome may be entering the danger zone.

Whether changes in pH are a cause of or a consequence of the resulting SIRS and mortality in this study cannot be inferred from the data presented. Although the authors imply that bacteremia was more frequent in the patients with extreme pH values and that mortality, on average, was higher among these groups, we cannot infer causality between the two events. Although the data were not presented, many patients probably died without bacteremia and conversely many patients with bacteremia probably survived. While the authors speculate that pH might shift bacteria to translocate as a mechanism of provoking SIRS and mortality, the pathophysiology of

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gut-derived sepsis is emerging to be much more complex than previously hypothesized [3-5]. In this context we must be careful not to be excessively speculative on the mechanisms just yet.

The gut during critical illness is a black box. There are regional and spatio-temporal constraints that have prevented in-depth high-resolution tracking of the microbe, their genes, and their gene products through the course of critical illness. Even in the current era of metagenomic, metatranscriptomic, and proteomic analysis of fecal samples, as the authors point out, pH is regionally specified and is influenced by many rapidly and constantly changing variables. Microbes spatially nested within clinically unreachable sites may have profound influences on the systemic immune system that remain unknown. The promise of meta-omics is that we will be able to reach these sites and gain a more comprehensive readout of how the disappearing microbiome and the emerging pathobiome affect the inflammatory response and the ultimate outcome of the patient.

The study by Osuka and colleagues is limited because of the use of culture-based interrogation of the microflora and because the pH was not specified by region. Yet what is very clear is that there is a gold mine in front of us. The authors have shown us a glimpse of what we can learn by mining and tracking key physiologic variables in feces, which while limited in their ability to provide molecular details, are clear biological beacons pointing us toward recovery or deterioration. Osuka and colleagues have taught us a lesson; we must pay attention to the effect of our therapies on the most fragile and perhaps most important biological determinant for survival – the composition and function of the growing microbial community in the gut. We anxiously look forward to continued work by this group.

Abbreviations
SIRS, systemic immune response syndrome.

Competing interests
The author declares that he has no competing interests.

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