Commentary

Probiotics in the intensive care unit: why controversies and confusion abound

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Abstract

Probiotics are living microorganisms that, when administered in adequate amounts, confer health benefits on the host. Because probiotics are not marketed as pharmaceuticals, they are commercially available without rigorous scientific documentation of their efficacy for many health-related claims. Results from existing clinical trials are both confusing and controversial. The evidence base is relatively limited, includes studies with varied designs, assesses multiple probiotic preparations across discrepant disease states, and provides conflicting results. Recent advances in the delineation of probiotics' mechanisms of action offer the opportunity to construct a more logical framework within which future trials are designed.

In this era of increasing antimicrobial resistance and limited activity in the antibiotic pipeline, novel nonantibiotic strategies for prevention of nosocomial infections are of particularly intense interest. The current issue of *Critical Care* brings us the findings of Forestier and colleagues [1], who demonstrated that oral administration of a probiotic *Lactobacillus* preparation delayed respiratory tract colonization with *Pseudomonas aeruginosa*. This delay in colonization resulted in a reduced rate of ventilator-associated pneumonia caused by *P. aeruginosa* in the probiotic-treated patients.

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) currently endorse guidelines defining probiotics as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [2]. Because probiotics are commercially marketed as dietary supplements or complementary and alternative medicine products, they are not subjected to the same rigorous review by the US Food and Drug Administration as conventional pharmaceutical products or devices. As a result, the scientific documentation of many probiotic-related health claims is lacking. At present, peer-reviewed data from randomized, double-blind, placebo-controlled clinical trials support the efficacy of probiotics for treating and preventing acute diarrhea and antibiotic-induced diarrhea and for preventing cow milk-induced food allergies. Less rigorous data suggest efficacy in traveler's diarrhea, relapsing *Clostridium difficile*-induced colitis, and urinary tract infections. Other areas of investigation include dental carries, respiratory infections, irritable bowel syndrome, inflammatory bowel disease, and asthma [3].

Although proponents of probiotics will herald the results of the study by Forestier and colleagues [1] as the latest in a long series of studies confirming that probiotics are beneficial across an array of illnesses, critics will note that there are multiple studies showing a lack of efficacy with these agents. More troubling, one recent multi-center, randomized, placebo-controlled study showed increased mortality in pancreatitis patients given a novel probiotic preparation [4]. The mortality difference in this study was driven primarily by between group differences in bowel ischemia—not infectious complications of the probiotic—and lacks a mechanism that is clearly attributable to the administration of the probiotic. The controversy surrounding probiotics will likely grow as ongoing trials using probiotics in ventilator-associated pneumonia are nearing completion and the results will soon be publicly reported.

Much of the current confusion surrounding the efficacy of probiotics results from differences in study designs, discrepant study populations, and inconsistencies specific to the probiotic, including the strain used (dose administered,

FAO = Food and Agriculture Organization of the United Nations; GI = gastrointestinal; TLR = Toll-like receptor; WHO = World Health Organization.

product formulation, and route of administration). These disparate results also stem from the fact that we currently have the cart in front of the horse: we have pursued multiple avenues of clinical investigations with probiotics despite our lack of insight regarding these agents' mechanisms of action. In line with the FAO/WHO definition, probiotics were originally thought to provide benefit by repopulating the gut with 'friendly flora' that essentially over-grew potentially pathogenic organisms. This theory fell out of favor when it was demonstrated that the beneficial effects of probiotics were seen without measurable changes in host flora and often persisted beyond the window of colonization. Subsequent theories of probiotics' mechanism of action focused on enhancement of barrier function and local antibacterial effects [5-7]. Although both of these mechanisms clearly exist, neither accounts for the observation that ingestion of nonviable probiotics or injection of probiotic derivatives offers similar benefit to ingestion of living organisms [8].

The theory that best explains probiotics' mechanism of action is immunomodulation resulting from crosstalk between the gastrointestinal (GI) probiotic elements, the GI mucosa, and underlying mucosal lymphoid elements [9]. This theory is extrapolated from the observation that commensal bacteria within the gut lumen interact with Toll-like receptor-2 (TLR-2) and TLR-4 on the appendages extended from dendritic cells within the lamina propria [10]. This interaction stimulates dendritic cell maturation and the production of cytokines that drive naïve T-helper cells (Th0) to mature into balanced Th1, Th2, and Th3/Tr1 helper subsets [11]. Such interactions between commensals and dendritic cells also activate plasma cells, resulting in IgA-producing cells [12,13]. Commensal organisms additionally interact with TLR-9, thereby producing an anti-inflammatory cytokine milieu rich in interleukin-10 [14]. In aggregate, these cellular mechanisms provide intestinal host defense mechanisms and regulate both local and systemic inflammation. Using probiotics to ensure adequate bacterial colonization has been demonstrated to maintain this balanced immune response [15].

It is currently unknown whether there are optimal probiotic species, doses, and/or formulations. Another area of particular clinical interest is whether combination therapy is superior to single-agent therapy. The recent findings of the Dutch Acute Pancreatitis Study Group mandate that we also evaluate the ideal route(s) of probiotic administration [4]. Eventually, it may be possible to pair individual probiotic organisms with specific disease states or desired goals. However, it is also increasingly evident that a comprehensive understanding of probiotics' mechanisms of action will be the key element in resolving these multiple controversies. We should not lose sight of this goal as increased knowledge regarding our ability to modulate the systemic immune system also promises novel therapeutic targets and therapeutic agents. Such understanding will also help us to avoid further trials demonstrating increased mortality in probiotic-treated patients.

Competing interests

The authors declare that they have no competing interests.

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