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The Intestinal Microbiota and Susceptibility to Infection in Immunocompromised Patients

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Abstract

Purpose of Review—Many infections of immunocompromised patients originate from the gastrointestinal tract. The pathogenesis of these infections often begins with alteration of the intestinal microbiota. Understanding the microbiota and how it can either cause or prevent infection is vital for the development of more effective prevention and treatment of these infections. This article reviews and discusses recent work providing insight into the intestinal microbiota of these at-risk immunocompromised patients.

Recent findings—Studies continue to support the premise that commensal bacteria, largely anaerobic, serve to maintain microbial stability and colonization resistance by preventing overgrowth or domination with more pathogenic bacteria, through interactions within the microbial community and with the host. In patients with immune suppression due to high-dose chemotherapy or hematopoietic stem cell transplantation, disruption of the microbiota through antibiotics as well as impairment of host immunity gives rise to perturbations favoring intestinal domination by pathogenic species, leading to increased bacterial translocation and susceptibility to systemic infection.

Summary—An understanding of the intestinal microbiota and the impact of antibiotics will help to guide our treatment of these gut-originating infections.

Keywords

microbiota; microbiome; gastrointestinal tract; neutropenia; immunosuppression

Introduction

The intestinal tract is home to a great many pathogens encountered in patients with immune suppression, particularly those receiving high-dose chemotherapy or undergoing hematopoietic stem cell transplantation. Infections caused by intestinal bacteria are among the most difficult and challenging to treat, with great potential to become life-threatening.

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Depending on the risk and potential severity, antibiotics can be administered prophylactically in order to prevent these infections. Combined with appropriate empirical treatment, this can be a well-justified approach that saves lives. [1–5].

Antibiotic resistance among bacterial pathogens, however, has become problematic and diminishes the effectiveness of antibiotic-mediated prophylaxis [6–8]. In this setting, the benefit of antibiotic prophylaxis must be balanced against the detrimental effect of antibiotics on the patient's microbiota and microbiome. A greater understanding of the microbiota may help us to understand these infections better. In this article, we will review clinical and experimental studies that are beginning to define the role of the host microbiota in resistance and susceptibility to infections caused by rogue antibiotic-resistant bacteria and how antibiotic administration can inadvertently increase susceptibility to a range of infections.

Intestinal Microbiota and Host Mucosal Barrier

A diverse community of microorganisms comprise and define the intestinal microbiota. The host intestinal tract harbors a local immune system specifically designed to manage and control the microbiota, and prevent dissemination into host tissues; this includes gut-associated lymphoid tissues, such as Peyer's patches, dendritic cells, and specific T- and B-cell subsets [9]. In addition, intestinal epithelial cells produce antimicrobial peptides such as defensins which serve to maintain and stabilize bacterial populations within the intestine. Goblet cells produce a mucus layer which also resist bacterial penetration [9,10]. In patients who develop systemic bacterial infection following treatment with cytotoxic chemotherapy, mucosal barrier injury occurs, in which one or several parts of this protective system are damaged [11].

The Role of Healthy Gut Commensals

Many prior studies have shown evidence that the intestinal microbiota is largely comprised of anaerobic commensal bacteria that are essentially non-pathogenic and contribute to maintaining stability and preventing overgrowth or infection with pathogenic bacteria. Studies with animal models demonstrated that antibiotic administration prior to pathogen exposure can markedly increase host susceptibility to infection [12]. Antibiotic-induced susceptibility to *Salmonella* or *Shigella* infections was found to be associated with a loss of obligate anaerobic bacteria belonging, as defined in the pre-molecular genotyping era, to the *Bacteroides* genus [13,14].

Subsequent studies in humans demonstrated that the normal flora prevents intestinal colonization by exogenous bacteria, leading to the concept of “colonization resistance” [15,16]. Analysis of the human fecal flora by quantitative culture demonstrated that many antibiotics, particularly those with an anaerobic spectrum, resulted in marked expansion of *Enterococcus* and Enterobacteriaceae in the intestinal tract [17–19].

More recent studies utilizing culture-independent methods have continued to provide evidence of beneficial interactions between commensal bacteria and the host. Anaerobes with identified beneficial functions include *Lactobacillus rhamnosus*, *Bacteroides*

thetaiotamicron, *Bacteroides fragilis*, *Bifidobacterium infantis*, *Faecalibacterium prausnitzii*, *Clostridium* XIVa group bacteria, and *Barnesiella* spp [9–11,20]. These bacteria have been noted to regulate protective host functions such as increasing tight junction strength, decreasing intestinal permeability, enhancement of epithelial repair, increasing mucus production from goblet cells, and secretion of antimicrobial peptides from epithelial cells.

Gram-Negative Bloodstream Infections

Although Enterobacteriaceae such as *Escherichia coli* are often considered major colonizers of the lower intestinal tract, under normal circumstances they in fact constitute only a very small fraction of the normal intestinal microbiota [21]. Impairment of colonization resistance following antibiotic treatment results in marked expansion of Enterobacteriaceae, an outcome that undoubtedly contributes to patient-to-patient transmission of antibiotic resistant strains within hospitals. A recent study at the National Institutes of Health was able to track and document the transmission of a carbapenem-resistant *Klebsiella pneumonia*e strain to 17 other patients through detection of single-nucleotide polymorphisms using whole-genome sequencing [22]. This study provided essential insights into the transmission of this organism to other patients within the hospital.

Systemic infection with enteric Gram-negative aerobic bacteria is of particular concern in patients with severe neutropenia. Multicenter clinical studies have demonstrated that prophylactic administration of fluoroquinolones can significantly reduce the incidence of Gram-negative bacteremia [3,23], and subsequent meta-analysis was able to demonstrate a significant mortality benefit [2,24].

A recent study characterizing the intestinal microbiota of 94 patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) patients demonstrated that fluoroquinolone administration markedly reduced the incidence of intestinal domination by Gram-negative bacteria, where intestinal domination was defined as colonization of at least 30% of the intestinal microbiota [25]. Furthermore, intestinal domination by aerobic Gram-negative bacteria was significantly associated with subsequent development of Gram-negative bacteremia, confirming that these infections indeed originate from the gut, and that the intestinal microbiota is disrupted and becomes displaced by an overgrowth of Gram-negative bacteria prior to bloodstream infection.

How and why pathogenic Gram-negative bacteria achieve states of intestinal domination remains an active area of investigation. Inflammation induced by intestinal infection can induce Gram-negative expansion in the gut, although the mechanism for this was undefined [26,27]. Neutrophil recruitment into the gut lumen has been associated with expansion of luminal Enterobacteriaceae [28], while a more recent study demonstrated that nitrate produced by the host gut during inflammatory responses provides a growth advantage for Enterobacteriaceae by enhancing their ability to respire anaerobically [29], thus providing a mechanism for their relative expansion in the intestine. Oral administration of vancomycin to mice can also result in a marked increase in the density of Gram-negative bacteria, presumably resulting from the depletion of obligate anaerobes from the gut [30,31]. In some

cases, antibiotic induced expansion of *Escherichia coli* can predispose host to the development of colitis [32]. Administration of a diverse microbiota to chronically infected mice can lead to clearance of *Salmonella typhimurium* from the gut lumen, suggesting that some components of the normal flora either displace *S. typhimurium* or create an inhospitable environment [33]. Recent studies using the murine *Salmonella typhimurium* model of intestinal infection demonstrated that bacteria belonging to the Porphyromonadaceae family are associated with resistance to intestinal infection, suggesting that this subset of obligately anaerobic bacteria belonging to the Bacteroidetes phylum provides colonization resistance against at least some pathogenic Gram-negative bacteria [34].

Viridans-group Streptococcal Bloodstream Infections

Bloodstream infection with viridans streptococci is a potentially life-threatening complication seen in patients with neutropenia due to chemotherapy. From a clinical and epidemiologic standpoint, these infections are marked by some notable characteristics.

The incidence of this infection varies considerably across different institutions [35], and has been observed in close association with conditions favoring oral mucositis, such as pre-engraftment phase of HSCT and high-dose cytosine arabinoside [36]. This suggests that the upper gut mucosa is the portal of entry for this infection, and practices favoring upper gut mucosal damage can predispose to viridans streptococcal bloodstream infections [37].

Patients with this infection can develop a toxic-shock-like syndrome, leading to high mortality [36]. Centers encountering this infection have adopted prophylaxis strategies to prevent these infections, such as administration of penicillin or vancomycin [5,38]. Administration of intravenous vancomycin during the peri-transplant period in allo-HSCT is currently a routine practice in some centers [5].

One cancer center reported a significant reduction in the incidence of viridans streptococcal bloodstream infections in patients treated with vancomycin following allo-HSCT [5]. Interestingly, study of the microbiota in recipients from the same institution revealed that approximately 40% of patients developed intestinal domination with viridans streptococci irrespective of preventative vancomycin [25].

It is likely, although not proven, that the previous high rate of viridans streptococcal bacteremia resulted from intestinal domination by these strains. Despite this high rate of intestinal domination, none of the patients developed bacteremia. This suggests that vancomycin does not prevent intestinal domination by streptococci, but rather exerts its beneficial effects by preventing the progression of intestinal domination to clinical bloodstream infection. This contrasts with fluoroquinolone prophylaxis, where protective effects were evident in the microbiota. The implication is that systemic vancomycin protects the bloodstream but not the gut; in fact this is consistent with the fact that penetration of intravenous vancomycin into gut is essentially zero [39].

Vancomycin-Resistant Enterococcus (VRE) Bloodstream Infections

VRE bloodstream infections have increasingly become a major cause of bloodstream infection in patients with high-risk neutropenia [40–44]. In allo-HSCT recipients, VRE has become the most common pre-engraftment bloodstream infection at many transplant centers [43]. Studies using deep 16S rRNA gene sequencing of intestinal bacteria has demonstrated that VRE has a remarkable ability to densely populate the small and large bowel in antibiotic-treated mice [30]. In these settings, VRE dominates the gut such that it occupies over 98% of the intestinal microbiota, therefore leaving less than 2% relative abundance for all other bacterial inhabitants.

It seems clear from numerous studies that antibiotic administration is the primary driver of VRE colonization [45–47]. Intestinal domination by VRE has notable consequences in allo-HSCT recipients during pre-engraftment. Longitudinal study of the intestinal microbiota in allo-HSCT has shown that VRE domination precedes VRE bloodstream infection, and prior administration with metronidazole was strongly associated with VRE domination, suggesting that disruption of anaerobic microbiota is effective in promoting VRE intestinal domination [25].

The observation that intestinal anaerobes protect against VRE is not a new one; older studies have shown that administration of antibiotics with potent anti-anaerobic activity act to interfere with colonization resistance, and allows for VRE to predominate [45–47], and has been implicated in increasing the transmission of VRE from carriers to vulnerable patients. Interestingly, an early clinical study of VRE-colonized patients with acute leukemia noted an associated between *C. difficile* disease and VRE bloodstream infection, but the authors recognized the possibility that metronidazole, given as treatment for *C. difficile*, was actually responsible for the predisposition to VRE colonization and infection [48].

Perhaps not surprisingly, a prevailing prior assumption was that vancomycin is naturally the primary risk factor for VRE colonization. However, examination of the microbiota in allo-HSCT recipients has shown that systemic vancomycin does not appear to promote VRE domination [25]. This would be consistent with the negligible gut penetration of intravenous vancomycin, as discussed above [39].

Although reduction in the frequency of obligate anaerobes in the gut is associated with intestinal VRE expansion, it remains unclear which particular commensal members would be most important for resisting domination by VRE. Studies using murine models have started to identify the microbiota components most likely to maintain colonization resistance and offer protection against domination by VRE. Using transplantation of complete and fractionated fecal flora, followed by deep 16S rRNA gene sequencing, colonization with bacteria belonging to genus Barnesiella, a group of obligate anaerobic commensals, was strongly associated with protection against VRE [49].

Clostridium difficile infections (CDI) in the compromised host

Infection with *Clostridium difficile* is highly associated with preceding antibiotic therapy, leading to the widely accepted notion that the intestinal microbiota provides protection

against this pathogen [50]. *C. difficile* is acquired by the ingestion of spores which germinate and give rise to vegetative bacteria that replicate in the gut lumen and produce toxins A and B, which become internalized by colonic epithelial cells where they glucosylate Rho GTPases and lead to a loss of epithelial integrity [50]. Thus, CDI involves at least three steps (germination, replication and toxin expression) and the normal intestinal microbiota may provide protection by interfering with one or multiple of these steps. At this time, however, it remains unclear how the microbiota protects against CDI, although one study indicates that induction of IL-1β plays a role in defense against *C. difficile* [51]. Several studies suggest that specific members of the microbiota provide protection and that the overall complexity of the intestinal microbiota may be protective. Deep 16S rRNA gene sequence analysis of the microbiota of patients with recurrent *C. difficile* infection had relatively reduced microbial diversity in their feces [52]. More extensive analysis demonstrated that protection from CDI can be mediated by bacteria belonging to the Lachnospiraceae, a family of Gram-positive obligate anaerobes [53].

Using a murine models of *C. difficile* infection, components of innate immunity have been shown to be important for defense against *C. difficile* infection, including TLR signaling and TLR-signalled neutrophil recruitment to the intestine [54–56]. This suggests that approaches to increase innate immune defense following antibiotic treatment may have therapeutic potential. Immune responses to *C. difficile* infection have also demonstrated that Nod1 (nucleotide-binding oligomerization domain 1) enhances neutrophil recruitment to the colon [57].

Fecal microbiota transplantation (FMT) has been gaining notoriety as an effective way to cure patients with recurrent CDI, often succeeding in instances where other treatments have failed [58]. There are now published manuscripts which review its effectiveness and discuss the logistics of performing FMT [59–61]. Most recently, a randomized controlled clinical trial of FMT versus conventional antibiotic treatment with vancomycin demonstrated a 81% rate of resolution with duodenal infusion of donor feces compared to only 23% and 31% for vancomycin treatment with or without bowel lavage, respectively [62].

Although very effective, concerns about the transmission of potential pathogens continue to limit enthusiasm for fecal transplantation. Efforts to identify specific bacteria or bacterial consortia that can protect against recurrent CDI have had some success. Tvede and Rask-Madsen [63] demonstrated that a combination of ten bacterial species administered rectally could cure patients with recurrent CDI. More recently, a study in mice demonstrated that fecal transplantation from normal mice into chronically *C. difficile* infected mice eliminated infection [64]. Fractionation of the fecal microbiota and reconstitution of mice with six different bacterial isolates also reduced *C. difficile* infection. Deep 16S rRNA gene sequence analysis of reconstituted mice demonstrated that introduction of the six-species cocktail resulted in marked expansion of other bacterial species and the redevelopment of a highly diverse microbiota. This study suggested that adoptively transferred bacteria do not directly inhibit *C. difficile* but may facilitate the redevelopment of a diverse flora.

Conclusion

The intestinal microbiota is closely involved in many of the infectious complications seen in immunocompromised patients. Enterobacteriaceae, viridans streptococci, VRE, and *C. difficile* appear capable of existing within a normal microbiota as relatively unassuming inhabitants, but have the potential to rise as opportunistic pathogenic organisms by exploiting an impaired host immune system combined with an unstable microbiota. A fuller appreciation of the complex interactions of the microbiota and the events preceding the development of infection would greatly help to increase our understanding of these infections.

The role played by antibiotics in each infection varies. In Gram-negatives, prophylactic fluoroquinolones can prevent Gram-negative infections in neutropenic patients by resisting Gram-negative colonization. On the other hand, systemic vancomycin is effective at preventing viridans streptococcal infections by protecting against bloodstream infection without impacting colonization. Finally, disruption of anaerobic bacteria is most clearly associated with intestinal domination by VRE, so minimizing the use of antibiotics with anti-anaerobic activity may be the best preventive strategy.

Prevention and treatment of bacterial infections has been extensively investigated and has led to tailored antibiotic regimens for specific clinical scenarios. More recent studies are revealing how antibiotic treatment of one infection predisposes to another infection by altering the composition of the host's microbiota. Our increasing understanding of the commensal microbiota and its relationship with the host should eventually enable us to reduce colonization and invasion by antibiotic-resistant pathogens. Continued investigation of the dynamics of the intestinal microbiota in the clinical setting will inform clinical practice and, we believe, result in novel treatment strategies, including re-introduction of healthy bacterial flora or administration of probiotic combinations for specific infections.

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Key Points

- The intestinal microbiota is critically important in many infections affecting immunocompromised patients.
- Recent studies continue to support the hypothesis that commensal bacteria, largely anaerobic, are part of a normal microbiota, and that disruption of these commensals results in susceptibility to infection.
- Further understanding of the role of the intestinal microbiota in infections of immunocompromised patients will inform development of future treatment strategies and principles.