

The Intestinal Microbiome in Infectious Diseases: The Clinical Relevance of a Rapidly Emerging Field

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The field of infectious disease is undergoing a paradigm shift as the intestinal microbiome is becoming understood. The aim of this review is to inform infectious disease physicians of the potential relevance of the intestinal microbiome to their practice. We searched Medline using both index and text words relating to infectious diseases, microbiome, and probiotics. Relevant articles published up through 2017 were reviewed within Rayyan. The review illustrates pathophysiologic concepts linking the microbiome and infectious diseases; specifically, the intestinal microbiome's relevance to early immune development, the microbiome and enteric infections, the microbiome's relevance in compromised hosts, and antimicrobial resistance. Within each subject, there are specific examples of diseases and at-risk patient populations where a role for the microbiome has been strongly established. This provides an overview of the significance of the intestinal microbiome to microbiology, pediatric and adult infectious diseases with an underpinning of concepts useful for the practicing clinician.

Keywords. immunology; infectious diseases; intestinal microbiome; microbiology.

The fields of clinical microbiology and infectious diseases are undergoing a paradigm shift as the intricate interactions between the intestinal microbiome, the immune system, and human pathogens are slowly being untwined. The human microbiome is the collective genome of trillions of bacteria, archaea, fungi, viruses, and eukaryotes, which can be conceptualized as a complex ecosystem existing within and on the human host (see list of definitions in [Table 1](#)) [1]. The largest and most heterogeneous of these microbial communities is found in the gastrointestinal tract. Infectious disease physicians and microbiologists, long trained in recognizing and treating individual human pathogens, are increasingly recognizing a need to incorporate the findings arising from the nascent microbiome field into their daily clinical practice.

Much of the current understanding of the intestinal microbiome is made possible by the application of culture-independent, high-throughput deoxyribonucleic acids sequencing techniques to describe the community structures and functions of the microorganisms (microbiota) residing in the human intestinal tract. These techniques are described in detail in several excellent reviews [2, 3] and briefly in [Table 2](#).

As the genetic composition and functionality of the bacterial intestinal microbiome is charted in greater detail, essential roles have emerged for the intestinal microbiome in human physiology. Conceptualized as “the last undiscovered human organ” [4], the intestinal microbiome influences the development and differentiation of the immune system (described in more detail below), it is critical in energy metabolism and catabolism, and it modulates bile and lipid metabolism, endocrine regulation, neurologic signaling, and drug metabolism, among other roles. Imbalance in the microbiota composition or function, or dysbiosis, also associate with numerous diseases ranging from inflammatory bowel disease and atopy to diabetes, obesity, and arthritis [5, 6]. Due to the infancy of intestinal microbiome research, animal studies and associative data predominate the field. Although numerous studies correlate microbiome composition and function with disease states, studies are widely heterogeneous, and few clearly demonstrate a clear pathophysiologic mechanism and causality.

This review attempts to offer the clinical microbiologist and infectious disease physician 2 things: (1) an overview of concepts that can provide a pathophysiologic frame of reference for the interaction between the microbiome and infectious diseases and (2) specific examples of infectious diseases and at-risk patient populations where a role for the microbiome has been strongly established. This is supplemented by a tabular ([Table 4](#)) and pictorial overview ([Figure 1](#)) of all those infectious diseases in which a clinical correlation between a disease and the microbiome exist.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched Medline using both index and text words for infectious diseases, microbiome, and probiotics. The full search query and database details can be found in [Table 3](#). Relevant articles

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Table 1. List of Definitions

Term	List of Definitions
Microbiome	The collection of all genomes of microorganisms from a defined environment, such as the human intestine.
Microbiota	The collection of all microorganisms in a defined environment, such as the human intestine. Virome: The collection of all viruses in a defined environment, such as the human intestine.
Mycobiome	The collection of all fungi in a defined environment, such as the human intestine.
Resistome:	The collection of all antimicrobial resistance genomes derived from microorganisms from a defined environment, such as the human intestine.
Ecosystem	The complex of a community of organisms and its environment functioning as an ecological unit.
Ecology	The totality or pattern of relations between organisms and their environment.
Commensal microbiome	Often referred to as an ensemble of microorganisms that reside in close proximity and in mutualistic relation with the host. However, the more correct term describing the resident microbiota in the intestines may be "Amphibiont" organisms that may have a pathogenic (detrimental), commensal (neutral), or symbiotic relationship (beneficial) with the host. We therefore use the term, "resident microbiota" in this review to describe the aggregate (pathogenic, commensal, symbiotic) endogenous microbiota in the intestine.
Pathobionts	Potentially pathogenic microorganisms residing in the microbiota.
Dysbiosis	A perturbation that departs from an otherwise balanced ecology to prolong, exacerbate, or induce a detrimental health effect.
Prebiotics	Nutritional substrates that promote the growth of microbes that confer a health benefit on the host.
Probiotics	A live microorganism that, when administered in adequate amounts, confer a health benefit on the host.
Synbiotics	Formulations consisting of a combination of pre- and probiotics.
Fecal Microbiota Transplantation (FMT)	The introduction of a liquid filtrate of stools from a healthy donor into the gastrointestinal tract of an ill patient.
Selective Decontamination of the Digestive Tract (SDD)	Use of daily antibiotics with the aim of preventing hospital-acquired infections while preserving the anaerobic microbiota.

published up through 2017 were reviewed within Rayyan. Articles published in English, French, German, and Dutch were included. Articles were screened by abstract and only included if there was a correlation between the risk, prevention, or treatment of an infectious disease and either the composition of the microbiome or manipulation of the microbiome. Manipulation included pre-, pro-, and synbiotics, fecal microbiota transplantation (FMT), or antimicrobial therapies. Only human studies were included. [Table 4](#) provides a summary of the search findings, with an overview of all infectious diseases in which treatment targeting the microbiome has been tested.

THE MICROBIOME AND EARLY IMMUNE DEVELOPMENT

The microbiome plays a vital role in preventing infectious diseases as early as birth. Millions of years of evolution have shaped the interactions between bacterial communities and

the human body, and there are elegant mutualistic relationships between the human host and microbiota. An infant may first be exposed to bacteria as early as in utero and upon delivery undergoes rapid intestinal colonization. The patterns of colonization are in part nonrandom and can be shaped by mode of delivery, breastfeeding, geography, genetics, antibiotics, and age [7]. Specific bacterial colonization is required for normal neonatal immune development [8], as is most clearly evidenced in germ-free mice who have highly aberrant gut-associated lymphoid tissue development in germ-free mice [9] and immunoglobulin A-producing B-cell maturation [10]. The commensal microbiome is implicated in shaping T-cell subsets, specifically effector T cell [11] and colonic T-regulatory cell generation [12, 13]. Finally, the microbiota and intestinal epithelium continually interact, leading to innate and adaptive immune signaling that likely maintain intestinal immune homeostasis throughout life.

Table 2. Techniques Used to Study the Structure and Function of the Intestinal Microbiome

Name	Purpose	Method
Biomarker Sequencing	Studies of the sequence variation of 1 ubiquitous gene (eg, 16S ribosomal ribonucleic acid [RNA] for bacteria) to describe microbial composition within an environmental study	Next-generation sequencing
Metagenomics	Studies of the function of all genetic material within an environmental study	Next-generation sequencing
Metatranscriptomics	Studies of gene expression at the RNA level	Next-generation sequencing
Metaproteomics	Studies of gene expression at the protein level	Liquid or gas chromatography, mass spectrometry
Metabolomics	Studies of metabolite formation by the microbiota	Liquid or gas chromatography, mass spectrometry

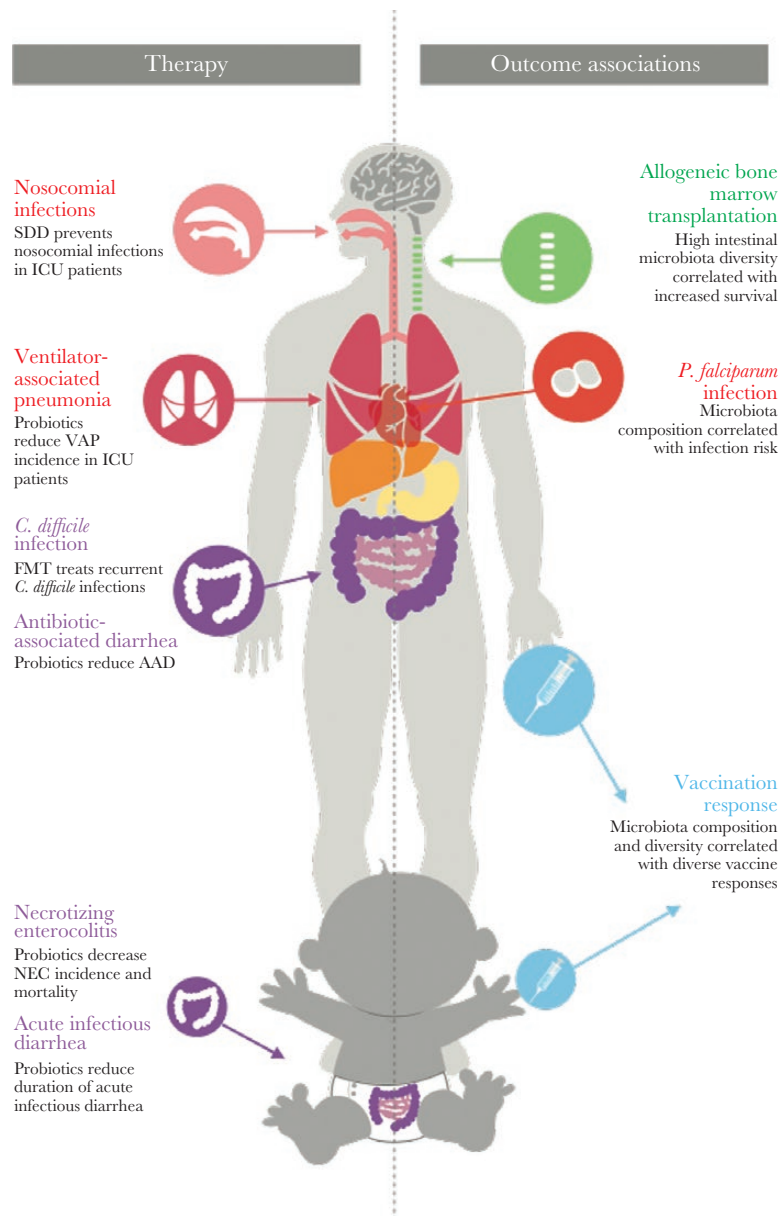


Figure 1. A schematic overview of the infectious diseases in which there is a proven therapeutic role for microbiome manipulation through either probiotics or fecal microbiota transplantation (left panel) and an overview of the subjects for which there is a strong correlation between microbiome composition and risk of infectious disease (right panel). AAD, antibiotic-associated diarrhea; ICU, intensive care unit; NEC, necrotizing enterocolitis; *P. falciparum*, *Plasmodium falciparum*; SDD, selective digestive tract decontamination; VAP, ventilator-associated pneumonia.

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) illustrates how aberrant microbiome colonization in neonates can predispose to clinically relevant infectious disease. Although the pathophysiology of NEC is incompletely understood, a prevailing hypothesis is that NEC follows aberrant gut microbiome colonization, and factors such as premature birth and peri- or neonatal antibiotic administration may predispose for acquisition of NEC via perturbed microbial colonization patterns [14, 15]. Necrotizing enterocolitis disease risk primarily correlates with Proteobacteria (the phylum containing many aerobic Gram-negative pathogens) and anaerobic

depletion [14, 16]. A body of literature also supports the use of probiotics (see Table 1 and Table 4) to prevent and or treat NEC, although the literature remains conflicting. Meta-analyses show significantly decreased relative risks for severe NEC and mortality only in preterm infants >1000 grams receiving enteral probiotic supplementation [17]. When used as medication, probiotics are not regulated by the US Food and Drug Administrations, and there are broad concerns about their content, infectious potential, and contamination, and inadequate data about the best form and duration of supplementation. These issues have limited the implementation of probiotic use in neonatal units in routine

Table 3. Review Search Criteria

Review Search Criteria		
No.	Searches	Results
1	exp Enterocolitis, Necrotizing/ or exp Sepsis/ or exp Pneumonia, Ventilator-Associated/ or exp Pseudomonas aeruginosa/ or exp Critical Illness/ or exp Diarrhea/ or exp Clostridium difficile/ or exp Vaccination/ or exp Gastroenteritis/ or exp Stem Cell Transplantation/ or ("necrotizing enterocolitis" or NEC or sepsis or septic or "systemic infection" or "ventilator-associated pneumonia" or VAP or aeruginosa or (critical* adj ill*) or diarrhea or difficile or clostridium or vaccin* or Gastroenteritis or "stem cell").ti,ab,kf.	927 799
2	"Gastrointestinal Microbiome"/ or dysbiosis/ or ("gut flora" or "fecal bacteria" or "commensal bacteria" or "fecal bacterial flora" or "enteric bacterial flora" or microbiome or "commensal microbes" or "gut microflora" or "intestinal microbial communities" or "intestinal bacteria" or dysbiosis or resistomes or metagenom*).ab. /freq=2	7082
3	exp probiotics/ or exp prebiotics/ or exp synbiotics/ or exp Bifidobacterium/ or exp "Fecal Microbiota Transplantation"/ or (probiotic* or microbial supplement* or prebiotic* or synbiotic* or bifidobacterium or BBG-01 or clostridium scindens or bifidobacteria or bifidobacterium or "fecal microbiota transplantation" or FMT or fecal suspension or "fecal transplantation" or "fecal transfer" or "fecal infusion" or bacteriotherapy or "fecal donation" or selective decontamination).ab. /freq=2	18 450
4	(2 or 3) and 1	5447
5	exp animals/ not humans/	4 240 420
6	4 not 5	4463
Search 01-02-2017 in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.		

clinical practice and underscores the difficulty of modulating the intestinal microbiome safely in fragile populations [18].

THE MICROBIOME AND ENTERIC INFECTIONS

Enteric Viral Infections

The intestinal microbiome must increasingly be considered in host-pathogen interactions. Viral enteric infections illustrate the trilateral relationship binding infectious disease pathogens, intestinal microbiota, and host immunity. Numerous pediatric enteric viruses including polio, norovirus, and rotavirus have likely evolved to exploit the "bacterial" microbiota for immune evasion, entry, and replication in the gut. Polio virus (1) has diminished replication and cell entry in mice intestines whose bacteria have been depleted by antibiotics and (2) also uses bacterial surface polysaccharides (such as lipopolysaccharides) to enhance infectivity [19]. In antibiotic-depleted mice, rotavirus similarly has diminished replication and infectivity [20].

The bacterial microbiota can also calibrate innate immune responses to viruses. When flagellin derived from *Escherichia coli* is given to mice with rotavirus infections, the infection is cleared through Toll-like receptor-5 activation of innate immune defenses [21]. In addition, when the microbiota is disrupted with antibiotics during a murine norovirus infection, the innate immune system is capable of clearing the norovirus infection via interferon-λ signaling [22]. Although these findings are in mice, there is considerable potential relevance for the practicing clinician. The long-held belief that antibiotics have no effect on viral infections is challenged by these animal models demonstrating how antibiotic-induced alteration of the microbiota impacts both viral replication and host viral immunity.

Enteric Bacterial Infections

A key concept underpinning the importance of the intestinal microbiota to infectious diseases is termed colonization resistance. The microorganisms residing in the intestine can have

pathogenic, commensal (lack of benefit or harm), or symbiotic relationships with the host. Enteric bacteria causing infections can be exogenous pathogens or pathobionts—potentially pathogenic microorganisms already part of the resident microbiota (Table 1). Along with providing protection against exogenous pathogens, an important function of the resident microbiota is to protect the host from enteric pathobiont overgrowth and eventual invasion [23]. This symbiotic conceptualization of the microbiota protecting the host against enteric infections and the host protecting the colonizing microbiota is termed colonization resistance [24]. The resistance provided by the microbiota against enteric pathogens can be divided into direct and indirect mechanisms. On the one hand, resident microbiota can inhibit or even kill pathogens directly via metabolic byproducts (bacteriocins, acids, peptides) [25], or it can outcompete pathogens for space, metabolites, and nutrients [26]. On the other hand, the microbiota can indirectly inhibit intestinal pathogens by calibrating host immune responses to them [13, 23]. Microbiota also can indirectly stimulate production of mucin, the protective mucin layer over the epithelium. Perturbation of this resident microbiota is therefore a common starting point for subsequent risk of true infection by pathobionts normally kept in check by these mechanisms. Antibiotic therapy is the most common cause of microbiome perturbation—rapidly and markedly decreasing bacterial microbiota diversity and abundance [27].

Clostridium difficile

The most well known example of this phenomenon is *Clostridium difficile* infection after antibiotic use. *Clostridium difficile* thrives after antibiotic use. Antibiotics deplete sensitive microbiota resulting in decreased microbiota signaling and diminished local and systemic immune responses to *C difficile*. Antibiotic use also increases the availability of primary bile acids, which the bacteria thrive upon, improving their colonization and triggering germination [28]. Diminished microbiota

Table 4. Overview of the Infectious Diseases or Patient Groups With Risk of Infectious Disease in Which the Microbiome Has Been Targeted for Prevention or Treatment and Tested in Human Clinical Trials

Patient Category	Disease	Target and Known Effects	Key Refs.
Critically ill, adult	VAP	SDD for the prevention of respiratory tract infections. Probiotics for the prevention of VAP. Moderate evidence supports the indication.	[1, 2]
	Mortality	SDD and probiotics for the prevention of mortality. Strong evidence for SDD. No conclusions possible based on limited evidence for probiotics.	[2–5]
Critically ill, neonatal	Necrotizing enterocolitis	Probiotics for the prevention of NEC. Strong evidence supporting derived from meta-analyses supporting probiotics for prevention of NEC severity and mortality. However, recent RCT, not included in the meta-analysis, showed no benefit of probiotic in NEC.	[6, 7, 39]
	Candidemia	Probiotics tested for prevention of candidemia, <i>Candida</i> colonization, and candiduria. No conclusions possible based on limited evidence	[8]
	Late-onset sepsis	Probiotics for the prevention of late-onset sepsis in preterm infants. Moderate evidence supporting probiotics for the prevention of late-onset mortality.	[7, 9]
Surgical	Trauma	Probiotics for the prevention of “infectious complications” and mortality. SDD for prevention of “infectious complications and mortality.” Heterogeneous studies, with some support for use, no conclusions possible based on limited evidence.	[10, 11]
	Post-GI surgery	Probiotics for the prevention of infectious complications and mortality. Heterogenous studies, with some support for use. No conclusions possible based on limited evidence.	[12, 13]
Oncology and hematology	HSCT and chemotherapy complications	Microbiome composition and diversity can act as a predictor for the risk of blood stream and other infections. FMT (study ongoing) and probiotics to decrease infectious complications and GvHD—no conclusions possible based on limited evidence to date.	[14–16]
	Mucositis	Probiotics for the prevention and treatment of chemotherapy and radiation-induced mucositis and diarrhea. Few studies, significant heterogeneity, no conclusions possible based on limited evidence.	[17, 18]
HIV	Disease progression	Probiotics and synbiotics for improvement of immune function. Small, heterogeneous studies, no conclusions possible based on limited evidence.	[19]
	Diarrhea	Probiotics to decrease diarrhea in HIV patients. Small, heterogeneous studies, no conclusions possible based on limited evidence.	[20]
Upper respiratory	Upper respiratory tract infection	Probiotics for prevention of URTI in children. Small, heterogeneous studies, some support of use, no conclusions possible based on limited evidence.	[21, 22]
Gastrointestinal	<i>Clostridium difficile</i> and antibiotic-associated diarrhea	FMT effective as treatment for refractory <i>C difficile</i> . Bacteriotherapy for prevention. Probiotics for prevention. Moderate quality evidence suggests probiotics are safe and effective.	[23–25]
	Acute infectious gastroenteritis	Probiotics for the prevention and treatment of infectious gastroenteritis. Evidence supports probiotics use in the treatment of persistent diarrhea in pediatric patients and shortening and reducing stool frequency in adults and infants.	[26, 27]
	Traveler’s diarrhea	Probiotics for the prevention of traveler’s diarrhea. Limited and inconclusive evidence that probiotics prevent traveler’s diarrhea.	[28, 29]
	Amebiasis	Probiotics for the treatment of amebiasis in children. No conclusions possible based on limited evidence.	[30]
	<i>Helicobacter pylori</i>	Probiotics for the adjunctive treatment of <i>H pylori</i> . No evidence probiotics improve eradication.	[31]
	Spontaneous bacterial peritonitis	Probiotics for the prevention of SBP in patients with ascites. No evidence that probiotics prevent SBP.	[32]
Urogenital	Urinary tract infection	Probiotics for the prevention of (recurrent) UTI. No significant benefit, no conclusions possible based on limited evidence.	[33]
Antimicrobial resistance	Multiresistant infections or colonization	FMT for treatment of multidrug-resistant colonization and AMR genes. FMT can reduce antibiotic-resistant organisms and genes, but evidence to date of clinical consequences only in case series and reports.	[34–36]
Vaccines	Polio vaccine, rotavirus vaccine	Antibiotics (azithromycine) to improve oral polio vaccine efficacy showed no effect. There is a significant association between microbiome composition and rotavirus vaccine.	[37, 38]

Abbreviations: AMR, antimicrobial resistance; FMT, fecal microbiota transplant; GI, gastrointestinal; GvHD, graft-versus-host disease; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; NEC, necrotizing enterocolitis; SBP, spontaneous bacterial peritonitis; RCT, randomized control trial; SDD, selective digestive tract decontamination; URTI, upper respiratory tract infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

NOTE: Please see Supplementary Material for list of references.

reduces *C difficile*’s need to compete for nutrients such as host carbohydrates, giving it a competitive advantage over non-pathogenic bacteria [28].

The clear relation between *C difficile* infection and antibiotic use makes it a prime target for microbiota-based therapy. It is, at the moment, the only infection (and disease) with a

proven treatment indication with FMT. Fecal microbiota transplantation describes the introduction of a liquid filtrate of stools from a healthy donor into the gastrointestinal tract of an ill patient. A randomized, open-label trial demonstrated that FMT is significantly more effective for the treatment of recurrent *C difficile* infection than oral antibiotic therapy with vancomycin [29]. Fecal microbiota transplantation not only reconstitutes the bacterial diversity and richness of the microbiota but also transfers biologic products such as bile acids, proteins, and bacteriophages, which may contribute to its high success rate in *C difficile* infections [30]. *Clostridium difficile* infection is also one of the first infectious diseases where rationally designed microbial supplementation may become a feasible therapeutic alternative to FMT. Several studies demonstrate that specific bacteria or consortia can prevent *C difficile* infection [31, 32].

THE MICROBIOME AND COMPROMISED HOSTS

Specific sets of patients may have higher risks of microbiome perturbation leading to infectious disease. Those groups with the highest evidence for an etiologic role for the microbiome are critically ill and oncologic patients.

CRITICALLY ILL PATIENTS

Critically ill patients have a dramatically altered microbiome, and specific microbiome patterns have been associated with detrimental clinical outcomes [33]. Although antibiotics are key in treating infections and sepsis in critically ill patients, they may deplete protective microbiota [34]. In addition, critically ill patients' microbiota sustain injury via hypoxic injury, disrupted epithelial permeability, altered gut motility, intraluminal pH values, and treatment with vasopressors, opioids, and parenteral or enteral nutrition [35]. These factors can facilitate rapid expansion of hospital-acquired pathogens or pathobionts, including vancomycin-resistant enterococcal infections [36] as well as Gram-negative *Enterobacteriaceae* invasion and infection [37].

Interventions aimed at altering the intestinal microbiome towards a protective phenotype in intensive care patients are understandably attractive. Probiotics exert unclear and heterogeneous influences in preventing adverse outcomes in critically ill patients (see Table 4). Selective decontamination of the digestive tract (SDD) (Table 4) is an alternative approach. The SDD is the use of daily antibiotics with the aim of preventing hospital-acquired infections while preserving the anaerobic microbiota [38]. Several studies demonstrate that SDD prevents nosocomial infections in critically ill patients and decreases overall mortality (see Table 4). However, broad implementation of SDD has been limited due to (perhaps unfounded) fear of selecting antibiotic-resistant bacteria and inducing long-lasting antibiotic resistance reservoirs [39, 40].

ONCOLOGY PATIENTS

Oncology patients undergoing chemotherapy or bone marrow transplantation also have specific microbiome-associated risks for infectious diseases [41]. Allogeneic hematopoietic stem cell transplantation is used as therapy in a range of hematologic malignancies and disorders. Ablation of the bone marrow through chemotherapy and radiation results in collateral gastrointestinal mucosal damage and alteration of the microbiome composition. Transplant patients also often receive antibiotic therapy. Those patients who can maintain a high microbiota diversity before stem cell engraftment have significantly lower (9% vs 53%) posttransplant mortality due to infection or graft-versus-host disease [42].

The microbiome also plays a role in the risk that neutropenic chemotherapy patients have for developing systemic blood stream infections. Antibiotics and chemotherapy-induced mucosal injury in combination with neutropenia can result in a progressive loss of colonization resistance [41, 43]. Sequential measurement of the microbiome before a blood stream infection in this population first shows loss of diversity and anaerobic microbiota, then microbiome domination by one bacterial strain, followed by a positive blood culture of the strain [44]. The most common pathobionts are vancomycin-resistant *Enterococcus*, *Enterobacteriaceae*, and *Streptococcus viridans*. Preservation of, particularly, anaerobic microbiota, through limitation of the use of antianaerobic antibiotics in this population may protect against such expansion and subsequent infection [44]. Novel prevention and treatment options for oncologic patients includes identification of those exact microbiota that can inhibit specific pathobionts, which can then be developed and tested as rationally developed probiotics.

ANTIMICROBIAL RESISTANCE AND THE INTESTINAL MICROBIOME

The intestinal microbiome is both a barrier against and a potential repository for antimicrobial resistance. As described above, loss of colonization resistance can also lead to acquisition and/or expansion of antibiotic resistant-pathogens. In contrast, correction of a depleted microbiome via FMT can reverse resistant pathobiont dominance and even decrease the total numbers of antibiotic resistance genes present in the microbiome [45, 46].

The genomic study of the total antibiotic resistance harbored in the microbiome is just emerging, and, although not all resistance genes can disseminate, there is great potential for transfer of endogenous and acquired resistance genes within and to the microbiota. The aggregate of antibiotic resistance genes in the microbiome has been termed the resistome, and new genomic techniques are uncovering exactly how resistance genes are acquired and spread [47, 48]. Nearly identical resistance genes can be found, for example, in Gram-positive and Gram-negative bacterial species from the same host [49]. Clinically relevant resistance genes are present in children even without recent selective antibiotic pressure [50].

This implies that the resistome can expand due to indiscriminate antibiotic use but is also an intrinsic component of the resident microbiota, compounding the ever-expanding threat of antibiotic resistance in the field of infectious disease.

FUTURE DIRECTIONS

Research findings into the role of the gut microbiome in the field of infectious diseases remain rudimentary. The majority of work has focused upon the bacteria in the microbiome, yet there is an enormous knowledge gap pertaining to its other organisms and their transkingdom interactions. Very little is known about the role of archaea, viruses, fungi, helminths, and protozoa in the intestinal microbiome and their relationship to common infectious diseases. As knowledge gaps in the microbiome are filled, balances will shift towards new treatment opportunities. Simple addition of a probiotic or heavy-handed therapy with fecal transplantation will be supplanted by tailored microbiome therapy, with selected commensal repletion differing per host and targeted infectious disease. Human studies and randomized clinical trials, with an emphasis on therapeutic reproducibility and patient safety, are absolutely essential to translating heterogeneous basic research into new therapeutic paradigms. The intestinal microbiome will undoubtedly feed the fields of clinical microbiology and infection for years to come.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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