Published in final edited form as:
Curr Opin Microbiol. 2015 February ; 0: 121–125. doi:10.1016/j.mib.2014.11.010.

The rest of the story: the microbiome and gastrointestinal infections

Jhansi L. Leslie[a] and **Vincent B. Young**[a,b,#]

[a]Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI

[b]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI

Abstract

Bacterial infectious diseases are studied primarily as a host-pathogen dyad. However it is increasingly apparent that the gut microbial community is an important participant in these interactions. The gut microbiota influences bacterial infections in a number of ways, including via bacterial metabolism, stimulation of host immunity and direct bacterial antagonism. This review focuses on recent findings highlighting the interplay between the gastrointestinal microbiota, its host and bacterial pathogens; and emphasizes how these interactions ultimately impact our understanding of infectious diseases.

Introduction

Classically, infectious diseases are viewed as a two-way interaction between a host and an invading pathogen. However, recent studies increasingly demonstrate that this perception is an over simplification. Appreciation that most organisms are colonized with distinct polymicrobial communities, collectively termed the microbiota, has lead to a reexamination of the concept of microbes in the context of health and disease [1]. Experiments in germ-free organisms, which lack a microbiota, show that the acquisition of symbiotic microbes is critical for normal development of the host [2,3]. In addition to host development, there is increasing appreciation that the microbiota plays a role in determining susceptibility and outcome of infections (Table 1).

This review focuses on studies exploring interactions between the microbiota and either a host or a pathogen and endeavors to highlight how integration of the microbiota in to the

[#]Author for correspondence: Vincent B. Young, 1520B MSRB I SPC 5666, 1150 W. Medical Center Dr., Ann Arbor, MI 48109-5666, Office: 1-734-764-2237, Fax: 1-734-764-4168, youngvi@umich.edu.

Address of Institution:
University of Michigan Medical School, 1500 E Medical Center Dr., Ann Arbor, MI 48109 USA

investigation of host-pathogen interactions can ultimately lead to a more complete understanding of infectious diseases.

Host-Microbiota interactions: more than the sum of the parts

While it is becoming evident that few, if any, sites within the human body are truly sterile, the gastrointestinal tract is the most densely colonized site in the human body [4,5]. The adult gastrointestinal tract is primarily colonized by anaerobic bacteria that broadly belong to two phyla; Firmicutes and Bacteroidetes [6]. The presence and composition of the gut microbiota are important determinates of host physiology and health, while ‘dysbiosis’ or an altered gut microbial community is associated with states of disease [7,8]. Understanding the interplay between the gut microbiota and the host is an important topic of investigation.

Metabolic interactions

The symbioses between a host and associated communities are integral to the physiology of both. At the core of these interactions is metabolism as the gut bacterial community is important to the metabolic potential of the host. While therapeutic doses of antibiotics are known to alter the microbiome, low doses of antibiotics given early in life lead to lasting effects in composition of the gut microbial community [9]. These changes are associated with long-term alterations in host metabolism, which may predispose the host to diet dependent obesity [10].

Host-microbiota metabolism is tightly linked; disruption of the microbiota shifts the gastrointestinal metabolic profile towards one that supports the growth of bacterial pathogens. In the context of *C. difficile* infection, a study correlating colonization resistance to community structure demonstrates that communities that are drastically different in terms of membership can provide resistance to colonization by *C. difficile* [11••]. Rather than the community structure, the commonality between these resistant communities was their metabolic profile. Specifically, the susceptible community had a significant increase in key metabolites utilized by *C. difficile* such as carbon sources and primary bile acids like taurocholate.

Bile acid metabolism is a process that depends on both the host and the microbiota. The host synthesizes and secretes primary bile acids. Bile not actively recovered in the distal ileum is conjugated by the colonic microbiota into secondary bile acids which are then absorbed by the host in the colon (the role microbiota and bile acid metabolism is reviewed here [12]). However, antibiotic mediated alterations of the microbiota disrupts host-microbiota bile acid metabolism leading to increased levels of primary bile acids in the large bowel, setting up an advantageous environment for germination of *C. difficile* spores [13]. The importance of bile acids in the pathogenesis of *C. difficile* is underscored by findings that suggest that *Clostridium scindens*, a bacterium that can convert primary to secondary bile acids, partially restores colonization resistance to C. *difficile* [14,15].

Regulation of immune response

Many aspects of host immune function are regulated by signals produced by the microbiome, such as metabolites. Butyrate, one short chain fatty acid produced by members of the microbiota, facilitates the development of localized immunity in the form of populations of peripheral anti-inflammatory T regulatory cells [16,17]. The immunomodulatory aspect of T_{regs} has been shown to play a role in persistent bacterial infections [18]. Since phylogenetically diverse members of the microbial community are able to elicit the differentiation of peripheral T_{regs}, this suggests that there is likely functional redundancy in composition of the gut microbial communities, such that different community structures provide the same function [19,20].

In addition to altering local immune response, microbiome-derived signals regulate immune function at primary immune sites [21•]. In mice, the presence of a gut microbial community enhances levels of myelopoiesis. Compared to germ-free or antibiotic treated mice, mice with intact microbiota had increased myeloid cells and were protected from systemic infection with the pathogen *Listeria monocytogenes.* Notably in this model, myelopoiesis was only achieved in the context of colonization with live bacteria, administration of MAMPs or SCFAs was not sufficient to restore germ-free mice to levels comparable to mice with intact communities. This suggests that diverse bacterial signals modulate host immunity, tuning the immune system to respond to a given situation such as bacterial or viral infections [22,23].

While microbial products alter the host, changes in host physiology can also alter the microbiota. Due to the abundance of anaerobes in the intestines it has been assumed that the lumen is strictly anaerobic. Characterization of the structure of the GI tract has shown that there are distinct communities associated with the mucosa compared to the lumen [24]. These distinct community structures are arranged in concordance with the radial oxygen gradient that exists within the gut [25,26]. Microbial communities are not immutable and changes in oxygen maybe a key driver. Notably, exogenous oxygen exposure such as hyperbaric oxygen therapy can shift the composition of the fecal microbiota [26••]. Inflammation can also alter oxygen homeostasis in the gut via the release of reactive oxygen and nitrogen species. While obligate anaerobes are incapable of detoxifying reactive oxygen species, some facultative anaerobes thrive in the inflamed gut [27]. Bacteria from the family Enterobacteriaceae, such as *Escherichia coli* are able to utilize host-derived nitrate as an alternative electron receptor during anaerobic respiration thereby gaining a competitive edge to expand within the gut [28]. Interestingly, antibiotic therapy, a risk factor for infections by non-typhoid *Salmonella*, decreases colonization resistance to *E. coli* by increasing inflammation in the gut [29]. Thus the interplay between a host and its microbiota is central to a host's predisposition to infection.

Pathogen-Microbiota interactions: context matters

Another critical function of the microbiota is colonization resistance, or the capacity of the microbes that colonize our body to exclude pathogens. While some aspects of colonization resistance are mediated by bacterial modulation of immune response, bacteria-bacteria

interactions also play a role. Unraveling how these direct bacterial interactions affect the pathogenesis of an infection has been the focus of many recent studies.

Direct bacterial inhibition

Bacteria are constantly competing for space and nutrients. One way that bacteria gain a competitive advantage is via production of microbial products such as bacteriocins [30,31]. Bacteriocins are ribosomal synthesized microbial peptides that typically have a narrow range of bactericidal activity. While lactic acid bacteria production of bacteriocins has received much focus, many bacteria are believed to be capable of producing bacteriocins (for a comprehensive review please see [32]). Recently, bacteriocins have been appreciated as a means by which members of the gut microbiota might exclude bacterial pathogens. Human stool has been shown to contain many strains capable of producing bacteriocins [33,34]. Recently, Thuricin CD, a bacteriocin produced by a strain of *Bacillus thuringiensis* isolated from a human fecal sample, was demonstrated to have activity against *C. difficile* in a mouse model of infection [35].

As an added wrinkle of complexity in microbiota-pathogen interactions, production of bacteriocins may be driven by the context of the surrounding microbial community. In the setting of a four-strain consortium of fecal isolates that excluded *Clostridium perfringens* colonization, an isolate of *Ruminococcus gnavus* produced an anti-bacterial product only when specific members of the consortia were present [36]. The anti-bacterial substance was detected in *Ruminococcus gnavus* mono-associated mice or when it was present with the two Clostridia members of consortia, however addition of *Bacteroides thetaiotaomicron* to the community suppressed the expression of this molecule.

Competition for nutrients

Another facet of the interplay between the microbiota and invading pathogens is nutrient base interactions. In addition to microbiota-host metabolioic interactions mentioned earlier, the metabolism of microbiota plays a role in colonization resistance, as pathogens must compete with resident microbes for the nutrients they need to grow. An example of nutrient based bacterial antagonism was recently described in the case of *E. coli* strain Nissle 1917 mediated colonization resistance to infection by *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) [37••]. *E. coli* strain Nissle is a well studied probiotic originally isolated in 1917 from a solider who was protected from infectious gastroenteritis. During infection with *S.* Typhimurium, inflammation limits the availability of key nutrients like iron. Since *E. coli* strain Nissle has many redundant iron transporters, it was hypothesized that it would be a suitable competitor for *S.* Typhimurium, during infection. A single dose of *E. coli* strain Nissle after infection with *S.* Typhimurium, lead to persistent colonization by *E. coli* strain Nissle and decreased levels of *S.* Typhimurium, colonization. Furthermore, reduced *S.* Typhimurium colonization was dependent on the presence of *E. coli* Nissle iron transport and independent of its immunemodulatory effect.

While some gut microbiota -pathogen relations can be detrimental to the pathogen, pathogens can also scavenge nutrients from the gut microbiota. *S.* Typhimurium, can utilize molecular hydrogen derived from the microbiota as an alternative electron source in order to

colonize an intact gut microbial community [38]. In addition, recent work has highlighted bacterial cross-feeding during colonization by enteric pathogens [39]. Using a gnotobiotic mouse colonized with *B. thetaiotaomicron* as a model of an antibiotic treated gut, the authors found that levels of *C. difficile* were increased in these mice compared to infected germ-free mice. Notably, increased levels of *C. difficile* colonization is dependent on the ability of *B. thetaiotaomicron* to cleave host sialic acid, which is source of nutrition for *C. difficile.*

The significance of the microbiota in the context of this infection is underscored by findings which demonstrate that transplant of stool from healthy uninfected individuals can reduce colonization by diverse bacterial pathogens such as C. *difficile* or Vancomycin-resistant *enterococci* (VRE) [40–42]. A better understanding of the physiology of members of the gut microbiota will enable the rational selection of bacteria that best compete with specific enteric pathogens.

Host-microbiota-pathogen interactions: a systems approach to infection

While there is still much to be learned regarding the basic interactions within the gut microbiome itself, thinking about the microbiome in the context of infection can provide a more complete story in the study of host-pathogen interactions.

In many bacterial infections, such as those caused by VRE or *Citrobacter rodentium*, the cytokine IL-22 is protective [43,44]. Yet surprisingly, when comparing salmonella infection in wild-type versus IL-22 deficient mice, *S.* Typhimurium, colonization was enhanced in the presence of IL-22 [45••]. After exploring possible factors such as the pre-infection gut microbial community structure or post-infection levels of inflammation the authors found no major differences between the two strains of mice. However, the authors noticed that following *S.* Typhimurium infection, the intestine of IL-22 deficient mice experienced a ‘bloom’ of bacteria from the family Enterobacteriaceae. Further work demonstrated that commensal Enterobacteriacea were suppressed by antimicrobial peptides upregulated by IL-22, however in the absence of IL-22 the Enterobacteriacea were not suppressed and thus were able to compete with *S.* Typhimurium, reducing levels of colonization.

Concluding remarks

Gastrointestinal infections are more than host-pathogen interactions; rather they represent the culmination of dynamic exchanges between a host, its microbiome and a pathogen. The microbiota affects the outcome of infections both directly and indirectly. Studying the gastrointestinal microbiota within the framework of infectious diseases provides context to the narrative of an infection. Experiments cataloging structural differences in the microbiome during disease have paved the way for future studies, which should strive to understand the functional result of these changes.

Acknowledgments

This work was funded by NIH grants T32 AI007528 (JLL) U19 AI09871 AND P30 DK034933 (VBY).

References

1. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. Nature Reviews Microbiology. 2008; 6:776–788.
2. Chung H, Pamp SJ, Hill JA, Surana NK, Edelman SM, Troy EB, Reading NC, Villablanca EJ, Wang S, Mora JR, et al. Gut immune maturation depends on colonization with a host-specific microbiota. Cell. 2012; 149:1578–1593. [PubMed: 22726443]
3. Semova I, Carten JD, Stombaugh J, Mackey LC, Knight R, Farber SA, Rawls JF. Microbiota regulate intestinal absorption and metabolism of fatty acids in the zebrafish. Cell Host Microbe. 2012; 12:277–288. [PubMed: 22980325]
4. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Sci Transl Med. 2014; 6:237ra265.
5. Morris A, Beck JM, Schloss PD, Campbell TB, Crothers K, Curtis JL, Flores SC, Fontenot AP, Ghedin E, Huang L, et al. Comparison of the respiratory microbiome in healthy nonsmokers and smokers. Am J Respir Crit Care Med. 2013; 187:1067–1075. [PubMed: 23491408]
6. The Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486:207–214. [PubMed: 22699609]
•7. Vujkovic-Cvijin I, Dunham RM, Iwai S, Maher MC, Albright RG, Broadhurst MJ, Hernandez RD, Lederman MM, Huang Y, Somsouk M, et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci Transl Med. 2013; 5:193ra191. The authors show that the mucosal microbial community of untreated HIV infected patients is distinct from uninfected individuals. In addition, they found a correlation between disease progression and the presence of gut microbes capable of catabolizing tryptophan suggesting a link between this altered microbiome and the pathogenesis of HIV infection.
8. Erickson AR, Cantarel BL, Lamendella R, Darzi Y, Mongodin EF, Pan C, Shah M, Halfvarson J, Tysk C, Henrissat B, et al. Integrated metagenomics/metaproteomics reveals human host-microbiota signatures of Crohn's disease. PLoS One. 2012; 7:e49138. [PubMed: 23209564]
9. Cho I, Yamanishi S, Cox L, Methe BA, Zavadil J, Li K, Gao Z, Mahana D, Raju K, Teitler I, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012; 488:621–626. [PubMed: 22914093]
10. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, Kim SG, Li H, Gao Z, Mahana D, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell. 2014; 158:705–721. [PubMed: 25126780]
••11. Theriot CM, Koenigsknecht MJ, Carlson PE Jr, Hatton GE, Nelson AM, Li B, Huffnagle GB, JZL, Young VB. Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to *Clostridium difficile* infection. Nat Commun. 2014; 5:3114. The authors report that antibiotic induced changes in the microbiome shift the cecal metabolome to one that supports *C. difficile* colonization. Notably, they found that different microbial community structures could result in similar metabolic profiles. [PubMed: 24445449]
12. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol. 2014; 30:332–338. [PubMed: 24625896]
13. Francis MB, Allen CA, Shrestha R, Sorg JA. Bile acid recognition by the *Clostridium difficile* germinant receptor, CspC, is important for establishing infection. PLoS Pathog. 2013; 9:e1003356. [PubMed: 23675301]
14. Sorg JA, Sonenshein AL. Inhibiting the initiation of *Clostridium difficile* spore germination using analogs of chenodeoxycholic acid, a bile acid. J Bacteriol. 2010; 192:4983–4990. [PubMed: 20675492]
15. Buffie CG, Bucci V, Stein RR, McKenney PT, Ling L, Gobourne A, No D, Liu H, Kinnebrew M, Viale A, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. Nature. 2014 advance online publication.
16. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffer PJ, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013; 504:451–455. [PubMed: 24226773]

17. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013; 341:569–573. [PubMed: 23828891]

18. Johanns TM, Ertelt JM, Rowe JH, Way SS. Regulatory T cell suppressive potency dictates the balance between bacterial proliferation and clearance during persistent Salmonella infection. PLoS Pathog. 2010; 6:e1001043. [PubMed: 20714351]

•19. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature. 2013; 500:232–236. This work demonstrates the ability of members of the gut micorbiota to stimulate localized host immunity. [PubMed: 23842501]

20. Faith JJ, Ahern PP, Ridaura VK, Cheng J, Gordon JI. Identifying gut microbe-host phenotype relationships using combinatorial communities in gnotobiotic mice. Sci Transl Med. 2014; 6:220ra211.

•21. Khosravi A, Yanez A, Price JG, Chow A, Merad M, Goodridge HS, Mazmanian SK. Gut microbiota promote hematopoiesis to control bacterial infection. Cell Host Microbe. 2014; 15:374–381. This is the first report demonstrating that the micorbiota regulates systemic immunity via promotion of hematopoiesis. [PubMed: 24629343]

22. Uchiyama R, Chassaing B, Zhang B, Gewirtz AT. Antibiotic treatment suppresses rotavirus infection and enhances specific humoral immunity. J Infect Dis. 2014; 210:171–182. [PubMed: 24436449]

23. Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, Paley MA, Antenus M, Williams KL, Erikson J, et al. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity. 2012; 37:158–170. [PubMed: 22705104]

24. Stearns JC, Lynch MD, Senadheera DB, Tenenbaum HC, Goldberg MB, Cvitkovitch DG, Croitoru K, Moreno-Hagelsieb G, Neufeld JD. Bacterial biogeography of the human digestive tract. Sci Rep. 2011; 1:170. [PubMed: 22355685]

25. Marteyn B, West NP, Browning DF, Cole JA, Shaw JG, Palm F, Mounier J, Prevost MC, Sansonetti P, Tang CM. Modulation of *Shigella* virulence in response to available oxygen *in vivo*. Nature. 2010; 465:355–358. [PubMed: 20436458]

••26. Albenberg L, Esipova TV, Judge CP, Bittinger K, Chen J, Laughlin A, Grunberg S, Baldassano RN, Lewis JD, Li H, et al. Correlation Between Intraluminal Oxygen Gradient and Radial Partitioning of Intestinal Microbiota. Gastroenterology. 2014; 147:1055–1063. e1058. Using a novel approach to measure the oxygen in the murine gastrointestinal tract, the authors report that there is a radial oxygen gradient which correlates with microbial colonization. Furthermore, changes the host oxygen exposure results in alteration of the gut microbial community. [PubMed: 25046162]

27. Rivera-Chavez F, Winter SE, Lopez CA, Xavier MN, Winter MG, Nuccio SP, Russell JM, Laughlin RC, Lawhon SD, Sterzenbach T, et al. *Salmonella* uses energy taxis to benefit from intestinal inflammation. PLoS Pathog. 2013; 9:e1003267. [PubMed: 23637594]

28. Winter SE, Winter MG, Xavier MN, Thiennimitr P, Poon V, Keestra AM, Laughlin RC, Gomez G, Wu J, Lawhon SD, et al. Host-derived nitrate boosts growth of *E. coli* in the inflamed gut. Science. 2013; 339:708–711. [PubMed: 23393266]

29. Spees AM, Wangdi T, Lopez CA, Kingsbury DD, Xavier MN, Winter SE, Tsolis RM, Baumler AJ. Streptomycin-induced inflammation enhances *Escherichia coli* gut colonization through nitrate respiration. MBio. 2013:4.

30. Majeed H, Lampert A, Ghazaryan L, Gillor O. The weak shall inherit: bacteriocin-mediated interactions in bacterial populations. PLoS One. 2013; 8:e63837. [PubMed: 23704942]

31. Wang BY, Kuramitsu HK. Interactions between oral bacteria: inhibition of *Streptococcus mutans* bacteriocin production by *Streptococcus gordonii*. Appl Environ Microbiol. 2005; 71:354–362. [PubMed: 15640209]

32. Cotter PD, Ross RP, Hill C. Bacteriocins - a viable alternative to antibiotics? Nat Rev Microbiol. 2013; 11:95–105. [PubMed: 23268227]

33. Birri DJ, Brede DA, Tessema GT, Nes IF. Bacteriocin production, antibiotic susceptibility and prevalence of haemolytic and gelatinase activity in faecal lactic acid bacteria isolated from healthy Ethiopian infants. Microb Ecol. 2013; 65:504–516. [PubMed: 23184155]

34. Lakshminarayanan B, Guinane CM, O'Connor PM, Coakley M, Hill C, Stanton C, O'Toole PW, Ross RP. Isolation and characterization of bacteriocin-producing bacteria from the intestinal microbiota of elderly Irish subjects. J Appl Microbiol. 2013; 114:886–898. [PubMed: 23181509]

35. Rea MC, Alemayehu D, Casey PG, O'Connor PM, Lawlor PG, Walsh M, Shanahan F, Kiely B, Ross RP, Hill C. Bioavailability of the anti-clostridial bacteriocin thuricin CD in gastrointestinal tract. Microbiology. 2014; 160:439–445. [PubMed: 24287693]

36. Crost EH, Pujol A, Ladire M, Dabard J, Raibaud P, Carlier JP, Fons M. Production of an antibacterial substance in the digestive tract involved in colonization-resistance against *Clostridium perfringens*. Anaerobe. 2010; 16:597–603. [PubMed: 20603221]

•37. Deriu E, Liu JZ, Pezeshki M, Edwards RA, Ochoa RJ, Contreras H, Libby SJ, Fang FC, Raffatellu M. Probiotic bacteria reduce *Salmonella* typhimurium intestinal colonization by competing for iron. Cell Host Microbe. 2013; 14:26–37. This sudy reveals one method by which bacteria provide colonization resistance to invading pathogens via competition for limited nutirents. [PubMed: 23870311]

38. Maier L, Vyas R, Cordova CD, Lindsay H, Schmidt TS, Brugiroux S, Periaswamy B, Bauer R, Sturm A, Schreiber F, et al. Microbiota-derived hydrogen fuels *Salmonella* typhimurium invasion of the gut ecosystem. Cell Host Microbe. 2013; 14:641–651. [PubMed: 24331462]

39. Ng KM, Ferreyra JA, Higginbottom SK, Lynch JB, Kashyap PC, Gopinath S, Naidu N, Choudhury B, Weimer BC, Monack DM, et al. Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. Nature. 2013; 502:96–99. [PubMed: 23995682]

40. Lawley TD, Clare S, Walker AW, Stares MD, Connor TR, Raisen C, Goulding D, Rad R, Schreiber F, Brandt C, et al. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. PLoS Pathog. 2012; 8:e1002995. [PubMed: 23133377]

41. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013; 368:407–415. [PubMed: 23323867]

42. Ubeda C, Bucci V, Caballero S, Djukovic A, Toussaint NC, Equinda M, Lipuma L, Ling L, Gobourne A, No D, et al. Intestinal microbiota containing *Barnesiella* species cures vancomycin-resistant *Enterococcus faecium* colonization. Infect Immun. 2013; 81:965–973. [PubMed: 23319552]

43. Kinnebrew MA, Ubeda C, Zenewicz LA, Smith N, Flavell RA, Pamer EG. Bacterial flagellin stimulates Toll-like receptor 5-dependent defense against vancomycin-resistant *Enterococcus* infection. J Infect Dis. 2010; 201:534–543. [PubMed: 20064069]

44. Zheng Y, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, et al. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat Med. 2008; 14:282–289. [PubMed: 18264109]

••45. Behnsen J, Jellbauer S, Wong CP, Edwards RA, George MD, Ouyang W, Raffatellu M. The cytokine IL-22 promotes pathogen colonization by suppressing related commensal bacteria. Immunity. 2014; 40:262–273. The authors find that in the context of *Salmonella* infection, IL-22 induction of anti-microbials suppresses related commensals allowing for inhanced *Salmonella* colonization. [PubMed: 24508234]

Highlights

- The gut microbiome is a critical component in many gastrointestinal infections.
- The microbiota modulates infections through both direct and indirect interactions.
- Appropriate development of host immunity is dependent on the microbiome.
- Dissimilar microbial communities may provide similar functions.

Table 1

The Effect of the Microbiome on Infection

Type of Interaction	Pathogen	Outcome of Infection	Reference
Direct			
Production of bacteriocins	*C. perfringens* *C. difficile*	Decreased colonization	[35] [36]
Competition for nutrients	*S.* Typhimurium	Decreased colonization	[37]
Cross-feeding (eg. H_2, Salic acid)	*S.* Typhimurium *C. difficile*	Increased colonization	[38] [39]
Conversion of host derived metabolites (eg. Bile acids)	*C. difficile*	Decreased colonization	[11••]
Indirect			
Production of immunomodulatory molecules (e.g. butyrate)	---	---	[16] [17] [19•]
Stimulation of hematopoiesis	*L. monocytogenes*	Increased myelopoiesis and protection from systemic infection	[21•]