Microbiome and Infection: A Case for “Selective Depletion”

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Key Messages

- The microbiome is a virtual organ that should be protected in therapeutic interventions.
- Narrow-spectrum inhibitors can “selectively deplete” the pathogen while protecting the microbiome.
- The microbiome itself can be a valuable source of antimicrobials.

Abstract

In most instances where a pathogen has initiated an infection, the primary goal of the treating physician or pharmacist is to eliminate the pathogen. In the absence of knowledge of the precise identity of the problem-causing microbe, a broad-spectrum antimicrobial gives the best chance of success. This approach has saved many lives and is an invaluable tool in fighting infections. However, perhaps our current appreciation of the importance of the microbiome in human health should give us pause. We can regard the microbiome as a virtual organ within the human body, and we would surely hesitate to advance any therapeutic approach that would cause substantial damage to one of our organs. This is one consequence of many broad-spectrum antimicrobial therapies. There may be instances where a more precise approach would be useful. I have termed this “selective depletion”; a concept where pathogen numbers are curtailed by a narrow-spectrum inhibitor but the microbiome is protected and can play a role in restoring health and suppressing the outgrowth of the pathogen in the infected patient. It may well be that the best reservoir of microbiome-friendly antimicrobial agents is the microbiome itself, and I provide examples of where the microbiome has been mined for novel precision antimicrobials.

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Microbiome, Pathogens, and Host

As a rule, microbes are good for us. We interact with trillions of microbes every day, and almost all these interactions are mutually beneficial, or at the very least are benign. Our most important microbial interaction is that between us and our microbiome, our fellow travellers on our journey through life.
We are born into a microbial world, and as adults, all our exposed surfaces are colonised with thousands of microbial strains selected from the millions we have encountered since birth [1]. We provide our microbes with a somewhat protected, albeit highly competitive, environment. It is more correct to state that we provide hundreds of micro-environments or niches. We as hosts provide sustenance and permissive environmental conditions, while our microbial partners fulfil many functions important to human health. We share the same chemical language, and so there is constant communication between our microbes and our nervous system, our immune systems, and our mucosal surfaces. In a healthy human, these interactions with our microbial “virtual organ” [2] is important for maintaining health and preventing disease. The microbiome is a valuable partner and, as with any other organ, should be protected insofar as possible.

In this context, we can see microbial infections as an aberration where a specific microbe has broken with the normally benign or beneficial relationship between microbes and hosts. We call these microbes pathogens or opportunistic pathogens. Infection describes any interaction between a microbe and a host that results in damage that is severe enough to be manifested in the form of symptoms. Infection usually follows a very prescribed path, initiated by acquisition or exposure to the infectious microbe (pathogen), engagement between the pathogen and the host in terms of survival, colonisation, growth, and ultimately damage mediated by virulence factors such as invasive mechanisms and/or the production of toxins. The damage caused can result in mild symptoms or death depending on a myriad of factors. These factors include the identity of the pathogen, including the genus, species, and even the genetic complement of a given strain; the possession and expression of virulence factors; the dose; the circumstances surrounding the exposure in terms of food carriers or breach of barriers (skin or mucosal surface); the genetics of the host; the hosts immune status; and of course, the commensal microbes present at the site of infection (the microbiome).

There are many instances where the pathogen is not acquired but is already a member of our microbiome, for example, *Clostridioides difficile*, *Staphylococcus aureus*, or certain strains of *Escherichia coli*. These pathogens often only cause disease when the surrounding microbiome is compromised in some way, and the pathogen manages to grow and use its virulence factors to cause damage to the host. We can regard the microbiome as a barrier to infection (Fig. 1). Antibiotic treatment can be an effective solution to reduce or even eliminate a pathogen but can also lead to further damage to the microbiome. For *C. difficile*, this can result in recurring bouts of diarrhoea and even fatal outcomes. Most microbiomes will

![Fig. 1. A diverse abundant microbiome (left) can act as a barrier to infection through a variety of mechanisms, including direct inhibition, colonisation resistance, or educating the immune system. A damaged microbiome (right) may be more susceptible to infectious bacteria causing damage.](image-url)
recover from antibiotic exposure and will revert to a level of complexity and community structure that approximates the pre-treatment microbiome, but of course, there will also be an undesirable selection pressure for the emergence of antibiotic resistance in both target and nontarget species. A link between microbiome composition and sensitivity to viral infection in humans has also been reported recently [3].

What is it about the microbiome that keeps these pathogens in check, and can we develop effective therapies aimed at selectively depleting the pathogen during an infection? I use the term “selective depletion” to describe any treatment that causes minimal damage to the microbiome but reduces the pathogen to levels that do not lead to symptoms or cause long-term damage to the host. What kind of strategies would meet this objective of selective depletion? Perhaps the best place to start is the microbiome itself. Can we explore the microbiome for strategies that can prevent and even treat infections? I will draw upon some of our own work in this area to illustrate some of the possibilities of “mining the microbiome” for novel anti-infectives.

Mining the Microbiome

Microbiome-derived anti-infection strategies have ranged from using an entire intact microbiome or a microbial consortium to selecting single biological entities (bacteria, fungi, bacteriophage, or bacterial metabolites) (Fig. 2). In most instances, the objective is one of selective depletion, rather than the broad-spectrum approach typical of many antibiotic or antiviral strategies. Much of the data generated to date have been acquired from animal models since it can be difficult to design and perform experiments on humans with respect to infection.

**Faecal Microbiota Transplantation**

Faecal microbiota transplantation (FMT) is perhaps the most dramatic example of mining the microbiome for solutions to infections. A recent systematic review and meta-analysis concluded that there is high-quality evidence that FMT is effective in breaking the vicious cycle of recurring *C. difficile* infections [4], although a similar success rate has not been reported for non-infectious diseases such as irritable bowel syndrome [5]. Essentially, FMT involves collecting the entire microbiome from one individual in the form of a faecal donation and transplanting it with minimal processing to the colon of a patient with recurring *C. difficile* infections. The generally accepted opinion is that FMT “repairs” a microbiome that has been damaged by the antibiotic therapies used to try to control the initial infection(s) and allows the recipient to use this more diverse microbiome to suppress subsequent outgrowth of the pathogen. Another strategy linked to FMT is using an undefined microbial consortium composed of spores purified from a faecal sample and transferred to a patient with a similar objective of restoring diversity and suppressing pathogen-induced damage. This intervention had less successful results in published phase 2 clinical trials [6] but has the potential to be the platform for a range of microbiome-based intervention strategies.

**Probionts**

Probionts are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [7]. There is evidence that probiotics can be used to prevent and treat infection, and some of these data have been generated in humans. The strength of the data is not entirely consistent, since most meta-analyses and systematic reviews are performed across a range of different probiotic interventions, dose ranges, and disease outcomes. Nonetheless, there have been positive outcomes. A recent meta-analysis on the ability of probiotics to prevent necrotizing enterocolitis in preterm neonates concluded that there are “significant benefits of probiotic supplements in reducing death and disease in preterm neonates” [8]. A similar analysis for the use of probiotics in upper respiratory tract infections concluded that “low-quality evidence provides support that probiotics have potential efficacy for preventing upper respiratory tract infections in adults” [9]. Yet another meta-analysis conducted on the use of probiotics in children with acute diarrhoea “supports the potential beneficial roles of probiotics and synbionts for acute diarrhoea in children” [10]. There are also single clinical trials with impressive evidence, for example, a randomised clinical trial in India involving over 45,000 children using a symbiotic composed of *Lactiplantibacillus plantarum* together with fructooligosaccharides reported a...
significant reduction in sepsis and death in the treatment co-

Mechanistic insights have also been generated in animal
models. We were able to demonstrate that bacteriocin pro-
duction is responsible for the protective effect of Ligilactoba-
cillus salivarius UCC118 against deliberate infection of mice
with Listeria monocytogenes [12]. We showed that the bacte-
riocin was highly active against L. monocytogenes and that a
non-bacteriocin-producing genetic knockout had no protec-
tive effect against the pathogen in the same model. Other
anti-infective mechanisms could include interacting with the
immune system or improving barrier function [13]. Bacte-
ricins represent another example of the “selective depletion”
concept in that they are usually narrow spectrum and should
be rapidly broken down by proteases and peptidases in the
gut and therefore unlikely to select for resistance.

**Bacteriocins**

Concentrated or purified bacteriocins have also been ex-
plored for their potential in preventing or treating infection
(reviewed by [14–16]). Bacteriocins have been largely tested
in laboratory animal models, although a broad-spectrum an-
tibiotic, nisin, has been used commercially to prevent mastitis
in dairy cattle [17, 18]. Some bacteriocins such as nisin are
relatively broad spectrum, but an attempt has also been made
to use narrow-spectrum bacteriocins for “selective depletion”
of specific pathogens. One example is the discovery of thuri-
cin CD, a very narrow-spectrum bacteriocin targeting C. dif-
icile [19, 20]. Thuricin CD is produced by a strain of Bacillus
thuringiensis that was mined from the human gut microbiome
in an extensive screening program. It was subsequently dem-
onstrated in improvised models of the human colon (faecal
fermentations) that thuricin CD could dramatically reduce C.
difficile levels in a highly complex microbiome without caus-
ing substantial collateral damage to the other members of
the community. Antibiotics or broad-spectrum bacteriocins de-
ployed in the same model also reduced levels of C. difficile
but also caused significant shifts in microbiome composition
[20]. While this approach has not been validated in humans or
animals, it provides a glimpse of future developments in this
exciting area.

Bacteriocins also have a potential as antimicrobials for
treating skin infections, some as broad-spectrum inhibitors
such as garvicin KS and micrococcin P1 [21, 22], but others as
potentially narrow-spectrum inhibitors that could be used in
selective depletion strategies. Because bacteriocins are gene
encoded, they can be engineered to improve their physico-
chemical characteristics and/or inhibition spectrum [23]. Bac-
teriocins can also be used in combination with other antiimi-
crobiotics for greater effect [24].

**Bacteriophage and Bacteriophage Lysins**

Bacteriophages (phages) are bacterial viruses that often have
a very narrow-spectrum of inhibition. There are several ad-
vantages and disadvantages to using bacteriocins to treat in-
fecions, a concept often referred to as phage therapy [25].
Disadvantages include the narrow host ranges, although, of
course, this could be regarded as an advantage in selective
depletion strategies. This disadvantage can be addressed by
using cocktails of phages to cover a wider spectrum of target
bacteria, or by carefully selecting the correct phage from an
existing phage bank to use against a specific pathogenic strain
infecting a patient. Another disadvantage is the ease with
which bacteria can develop resistance to the phage attack,
again an issue that may be overcome by using multiple phag-
es in cocktails. Advantages include their widespread distribu-
tion in nature and subsequent ease of isolation in many in-
stances, and, of course, their ability to multiply at the site of
infection. However, the clinical evidence is scarce. Phages
have been used for decades in eastern Europe, and it is logical
to assume they must have benefits in that they have survived
as frontline treatments for so many years [26]. In the West,
phages have been used in some high-profile instances in sin-
gle patients with infections that were recalcitrant to antibi-
otic therapies [27, 28]. Phages can potentially be applied on
the skin, by inhalation, or by ingestion [29].

Lysins are enzymes produced by bacteriophages that are
responsible for lysing the target bacterium following multipli-
cation of phage particles. Phage lysins target the cell wall and
can also act from outside the cell. Lysins can be broader spec-
trum than their carrying phages, but are still limited to the spe-
cies or genus level, making them good candidates for selec-
tive depletion strategies. There have been many attempts to
use phage lysins to target specific pathogens (reviewed by [30,
31], particularly on the skin [32] and in the respiratory tract [33].
As is the case for bacteriocins, these gene-encoded antimimi-
crobials can readily be engineered for greater efficacy [34].

**Conclusions**

The microbiome provides both a barrier to infection and a
source that can be mined for novel antimicrobials. While
these antimicrobials, including FMT, microbial consortia, pro-
biotics, bacteriocins, and bacteriophages (and their lysins),
have often been analysed for their solo impact on infection,
there is no reason why these could not be used as combina-
torial treatments. Perhaps the most attractive feature of these
microbiome-based inhibitors is their potential narrow spec-
trum of inhibition that would act to selectively deplete the
pathogen, while preserving the complexity of the surrounding
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microbiome. This might require precise identification of the pathogen before initiating treatment, but this is not a significant problem with chronic infections and is becoming less of a problem with speedy high-throughput bacterial identification becoming more accessible for acute infections [35]. The future of smart antimicrobial therapies may not involve pathogen elimination with collateral damage to the microbiome (broad-spectrum approaches) but may well lie in restricting the growth of pathogens to a point where they cannot cause disease while harnessing the power of the microbiome to ensure a return to a healthy state—a strategy I designate as selective depletion.

References


Statements of Ethics

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Conflict of Interest Statement

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