

Microbes are Confronted Steadily by Numerous and Threatening Hazards. A Constant War! Another Point of View on Infective Microorganisms than that of Microbe Hunters.

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Introduction

Since the discovery of antimicrobial activities of arsphenamin (i.e. Salvarsan) in 1910 by Paul Ehrlich, of penicillin by Fleming in 1928 and the synthesis of a sulfonamide by Domagk in 1935 these drugs, called “antibiotics”, have revolutionized the therapy of bacterial infections¹. Actually, we witness, however, that these magic bullets tend to lose their protective effects² possibly due to overuse and misuse.

Indeed, the therapeutic as well as prophylactic use of antibiotics in medicine, veterinary medicine as well as in agriculture has changed dramatically the life of microorganisms. In addition, the vast use of disinfectants for hygienic purposes also contributes to the hard life of microorganisms. Whereas these aspects are in the focus of interest of medical doctors, from the point of view of bacteria, however, these issues are only of secondary importance, since they are exposed to other and even more relevant hazards.

In fact, bacteria are fighting permanently against each others, especially against related bugs by means of bacteriophages, bacteriocins and other antimicrobial peptides. By the way, some of these agents are not only directed against bacteria but also against other microorganisms which could compete with bacteria for their territory.

Furthermore, the antibacterial effects of the processes conferring the innate immunity of mammals acting topically on skin and mucosal surfaces as well as systematically within the body, which are known until now at least to a great extent, will threaten the life of bacteria once they dare to invade a host.

In this comment an unconventional look at the hard life of bacteria will be presented, and finally one could almost develop compassion with these tiny microorganisms exposed steadily to all these insidious challenges.

Hazards Faced by Microbes

Endolysins from Prophages

Certain viruses are adapted to bacteria; some of these bacteriophages are able to kill rapidly some bacterial species, for example by triggering the production of endolysins³.

Bacteriocins /Mycocins

Bacteriocins (sometimes called bacteriocines) are antimicrobial peptides or small proteins consisting of 30-60 aminoacids in general produced ribosomally by practically all bacteria. Most bacteria generate at least one bacteriocin. But some bacteria, especially lactobacilli, are equipped with an extended genetic repertoire to synthesize up to 100 different bacteriocins^{4!} (Lantibiotics used for food preservation represent a particular group of bacteriocins, which are characterized by the content of a special aminoacid, i.e. lanthionin). The genetic information of most of these antimicrobial compounds is coded on plasmids (except in *Pseudomonas*).

Whereas most of these bacteriocins exert their activities only towards a very small spectrum of bacteria, namely against closely related bacteria, some derivatives dispose of a broader range of susceptible microbes.

The ability to form bacteriocins will help the producer to cope with the environmental conditions where an ample flora of similar and different bacteria fight against each other. Hence, bacteriocins will represent one versatile weapon in the permanent struggle for survival. Since lactobacilli possess the genes for many bacteriocins⁴, they have an advantage to survive in settings like the vagina, which in principal can be colonized by various bacteria, for example originating from the gut flora. Indeed, the power of bacteriocins will contribute to the regulation of the vaginal flora and not only by means of reducing the pH due to lactate production or by virtue of antimicrobial peroxides⁵.

Fungi also strive permanently with neighbours by means of small peptides, the so-called mycocins (fig. 1). Yeasts in particular are prone to manufacture mycocins⁶.

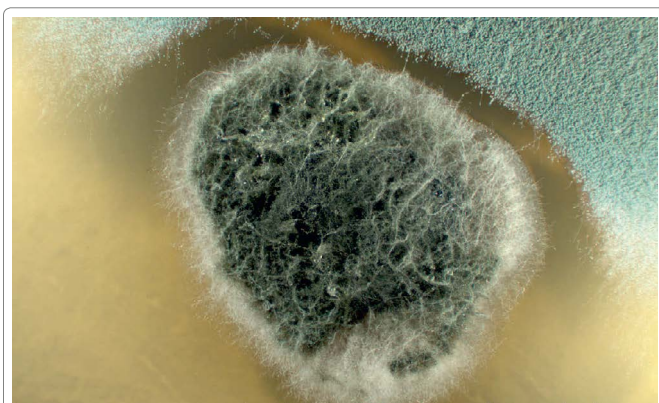


Figure 1: Fight for survival of the dematiaceous *Stachybotrys chartarum* (low) against *Aspergillus fumigatus* (above), presumably due to production of mycocins.

The Sabouraud agar plate inoculated with *A. fumigatus* was accidentally contaminated by *S. chartarum*. After 2 days of incubation at 26°C an inhibition zone around the colony of *S. chartarum* was clearly delineated.

Antimicrobial Peptides (AMPs) – a part of the innate immunity

Once bacteria have survived in their hostile families and inimical neighbourhood, they are confronted inevitably to other deleterious challenges; for example antimicrobial peptides (AMPs) represent a major threat.

There are numerous antimicrobial peptides in nature, namely more than 400 agents described so far, with variable chemical composition. In general, they consist of short chains of aminoacids, mostly with less than 60 members, either in lineal or helical forms. Sometimes they possess sidechains, for example composed of lipids (i.e. lipopeptides). The majority of AMPs is cationic but a few anionic compounds also exist. Typically these molecules are characterized by an enrichment with a few, particular aminoacids, for example proline or cysteine. They may exert antiviral, antibacterial, antifungal and/or antiparasitic activities (some show even antitumor effects^{7, 8}). Their modes of action can be quite different, namely inhibition of cell division, interference with membrane stability, arrest of protein or nucleic acid synthesis or disturbance of protease activities. They act either systematically in various organs or only locally after secretion onto mucosal surfaces or skins^{9, 10}.

Indeed, practically all beings in nature, i.e. plants, insects, amphibians, fishes, mammals as well as humans, produce large amounts of such antimicrobial peptides (Fig 2).

a) AMPs produced by bacteria

A series of AMPs is produced by bacteria some of which have achieved a practical role in therapy of bacterial infections (tab. 1).

b) AMPs produced by plants

Plants are exposed to a large scale of phytopathogenic microorganisms and have developed various survival mechanisms among them the AMPs¹². A particular role play

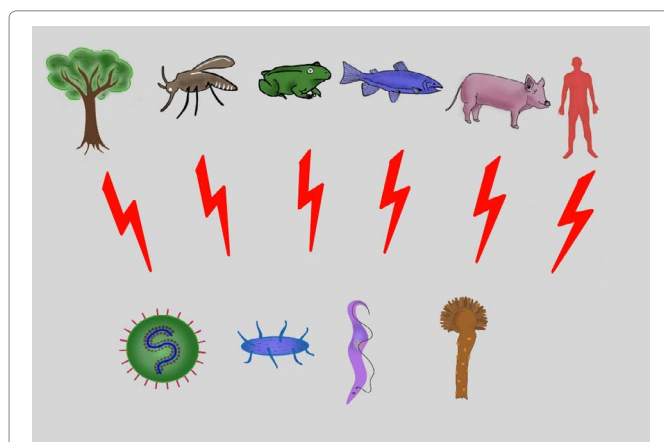
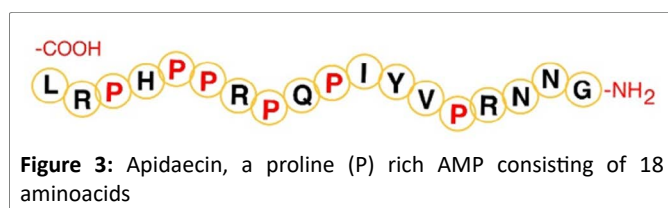


Figure 2: Antimicrobial peptides from plants, insects, amphibians, fishes, mammals and humans are directed against viruses, bacteria, parasites and fungi (9, 10).

Table 1: Some AMPS are produced by bacteria.
They play a certain role in the therapy of infections⁷.

agent	produced by	composition
bacitracin	Bacillus subtilis	12 aminoacids
colistin=polymyxin E	Bacillus colistinus	mixture of at least 30 variants
daptomycin	Streptomyces roseosporus	13 aminoacids (lipopeptide)
gramicidin	Bacillus brevis	15 aminoacids
polymyxin B	Bacillus polymyxa	10 aminoacids
teicoplanin	Actinoplanes teichomyceticus	7 aminoacids
tyrocidine	Bacillus brevis	mixture of several variants
vancomycin	Streptomyces orientalis	7 aminoacids

Furthermore, some bacteria produce antifungal AMPs¹¹.



thionins in seeds, roots as well as leaves which will protect them against predators. These small peptides consisting of 45-48 aminoacids are characterized by three to four intramolecular disulfide bridges. They are active against fungi and bacteria.

c) AMPs produced by insects

Since insects display only of a primitive adaptive immune system, they particularly rely on their innate immunity supported by AMPs.

Among other AMPs cecropins, a large family, consisting of 31-37 aminoacids are present in various organs of the insects for example in moths and act against a broad spectrum of microorganisms including bacteria, fungi and viruses. It should be mentioned that these molecules act even against microorganisms in biofilms where they could find a safe habitat¹³.

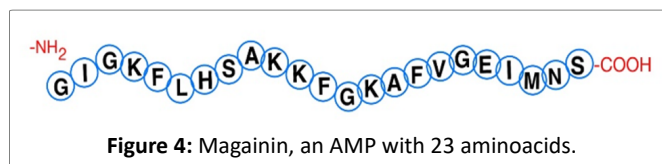
Honey bees for example are protected by apidaecin (fig. 3; 14). A queen bee will try to inhibit a deleterious infection of the bee larvae in the honeycomb by adding royalisin.

d) AMPs produced by amphibians

A frog is sitting in the water and goes not mouldy! On his neck he possesses two glands producing magainins (fig. 4), which are secreted on the skin and exert a broad antimicrobial activity against bacteria as well as fungi even in rather low concentrations¹⁵. Only few pathogenic bacteria, among them Listeriae, are resistant¹⁶.

e) AMPs produced by fishes

Fishes are able to produce all of the major classes



of AMPs, including defensins, cathelicidins, hepcidins, histone-derived peptides; in addition they generate a fish-specific class of the cecropin family, called piscidins¹⁷.

f) AMPs produced by mammals

Mammalians are able to manufacture a large scale of AMPs such as lysozyme, lactoferrin, histatins, defensins, cecropins¹⁸ and last but not least cathelicidins¹⁹. These AMPs will, for example, contribute substantially to the defense of pigs known to be highly resistant to microbes²⁰.

Cathelicidins are found within granulocytes. Their production is upregulated in case of bacterial infections. In addition, one effective expression inducer of cathelicidine genes is the active form of vitamin D. The direct antimicrobial mechanisms of action of cathelicidins against bacterial infection include damage of the bacterial cell membrane as well as neutralization of LPS produced by bacteria. Indirectly, this AMP works by inducing autophagy process of macrophages and chemotactic activities for PMNs, monocytes and lymphocytes²¹.

g) AMPs produced by humans

Many of those AMPs, also called „endogenous antibiotics“, are also present in humans.

Only 1 single cathelicidin, namely LL37 with 37 aminoacids, is present in granulocytes of humans.

A central role in the innate immunity of humans play various defensins with varying length being rich in cysteine forming intramolecular bridges. They are synthesized in various cell types and display a broad spectrum of antibacterial activities (tab. 2).

The group of α -defensins are produced mainly by neutrophilic granulocytes, wherefore they are called **hnp** (**human neutrophil proteins**). But also macrophages and NK-cells are able to synthesize these compounds from which 6 variants are known. The α -defensins 1-4, are stored in the azurophilic granula also called lysosomes (tab. 2).

The phagocytic cells present receptors (such as TOLL-like receptors or CD14) on their cell surface specific for several PAMPs (**pathogen associated microbial patterns**) in the cell wall of bacteria such as LPS, teichoic acids, lipoteichoic acids and peptidoglycan. In case that a pathogen will come into contact with these receptors phagocytosis will be triggered leading to an internalisation. Within the host cells they are surrounded by a unit-membrane separating the phagocytic vacuole from the cytoplasm. This process activates immediately certain

Table 2: The role of defensins.

Designation	Site of production	Chemical structure	Mechanism of action
α -defensins 1-4 (hNP=human neutrophil proteins) 1-4	granulocytes (stored in azurophilic granula)	oligopeptides with 30-50 aminoacids	bactericidal for grampositive and gramnegative bacteria
α -defensins 5 and 6 (cryptdins)	Paneth cells (secreted on the surface of the duodenal mucosa)		
β -defensin 1	epithelial cells	oligopeptide with 47 aminoacids	bactericidal for grampositive and gramnegative bacteria
β -defensin 2	epithelial cells (and granulocytes)	oligopeptide with 64 aminoacids	baktericidal for gramnegative bacteria

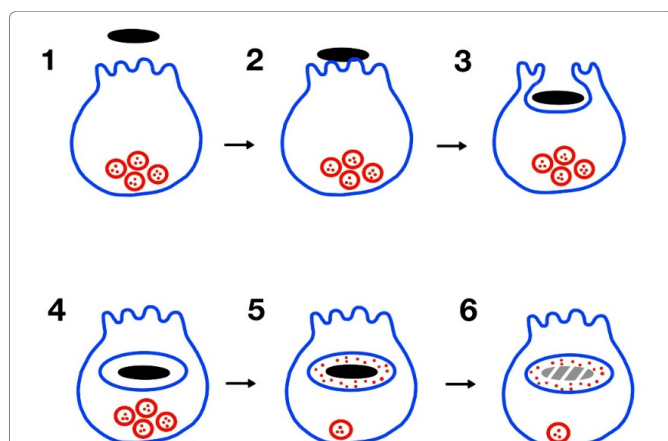


Figure 5: Schematic depiction of the phases of phagocytosis and the intracellular degradation of bacteria in granulocytes.

1. bacterium (black) meets a granulocyte (cell membrane blue; several intracellular granula (lysosomes) red).
2. adhesion of the bacterium to the surface of the granulocyte.
3. phagocytosis: the cell wall of the granulocyte engulfed the bacterium.
4. now the bacterium is internalised, i.e. located in phagocytic vacuole (an enclave) totally enclosed by the unit-membrane of the granulocyte.
5. fusion of some lysosomes with the phagocytic vacuole; now the bacterium is exposed to the aggressive components, among them AMPs.
6. the phagocytosed bacterium will be killed and degraded.

defense properties of the host cells. The contents of the lysosomes with the prepared AMPs, such as α -defensins 1-4, cathelicidin, lysozyme and lactoferrin, are transmitted into the vacuole when the lysosomes fuse with the vacuolar membrane. The antibacterial effects of AMPs are further supported by the generation of H^+ ions lowering the pH in the vacuole dramatically. The phagocytosed and killed bacteria are degraded (fig.5). Only few specialized bacteria, the so-called intracellular generating bacteria, among them *Listeria monocytogenes*²², are able to survive, since they have developed various mechanisms to withstand these hostile conditions.

Antibiotics

The availability of a huge arsenal of antibiotics, antimycotics and of antiparasitic and anthelmintic agents has worsened the survival conditions of microorganisms.

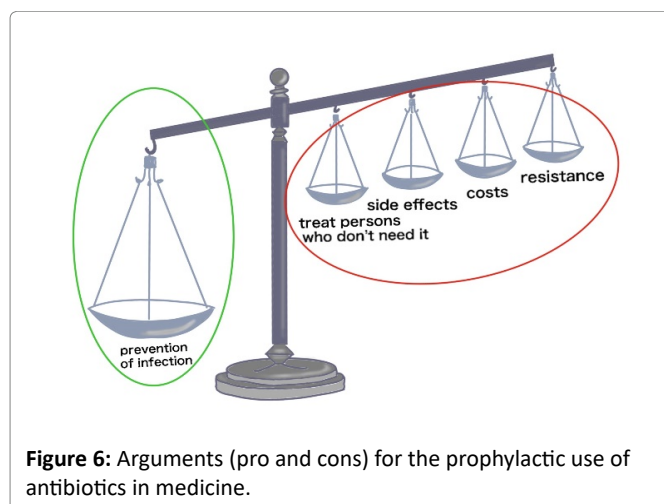


Figure 6: Arguments (pro and cons) for the prophylactic use of antibiotics in medicine.

These pathogens have only a chance to survive, if they rapidly develop resistance mechanisms. Especially, multidrug resistant microbes display the potency to fight against these menacing weapons.

Indeed, bacteria, for example, have developed and implemented quite various mechanisms of resistance:

- 1) The inactivation of antimicrobial agents by enzymes ("enzymatic barrier").
- 2) The interference with the in- and efflux of drugs through the walls or membranes, respectively, for example by activating efflux pumps ("membrane barrier").
- 3) The alteration of the drug targets by mutation.

Fungi, on the other hand, do not dispose of degrading enzymes; hence the resistance development is definitely lower than in bacteria^{23,24}.

Furthermore, the microorganisms have generated several pathways to expand resistance traits. In particular extrachromsomal coded properties on plasmids play a prominent role, since these mobile genetic elements can be distributed horizontally into offsprings or even vertically into other, more or less related species. The chromosomally coded transposons are equally mobile and can spread horizontally or vertically. Until now, neither plasmids nor transposons contribute to resistance propagation in fungi.

In both human and veterinary medicine antimicrobial agents are not always used judiciously, since they are not only given strictly in indicated and approved conditions to treat susceptible pathogens but also in ill-defined situations for which there are no reliable reasons, when for example no prove of microbial causes of symptoms is given.

One has to keep in mind, that most antimicrobial agents are used for prophylaxis of bacterial infections, which may be rational and appropriate in certain circumstances (fig. 6).

But the prophylactic use of large amounts of agents especially in agriculture, in animal husbandry or crop cultivation, has to be critically assessed²⁵, since the risk of resistance development in bacteria as well as fungi is pertinent²⁶. Hence, the danger arises that these weapons become blunt.

Disinfection

Highly effective agents are available to disinfect surfaces²⁷ and hands²⁸, so that microbes are easily eliminated by these hygienic measurements in the surroundings.

Discussion

Microbe hunters, hygienists, medical doctors and many people of other professions threaten microorganisms living in close proximity to humans. Antibiotics as well as antimicrobial chemotherapeutics are their powerful weapons for therapy or even prophylaxis (fig. 6) of infections. Disinfectants for hands and surfaces are used commonly. In addition, microbes in nature live in a constant battle for survival, as practically all living organisms (fig. 3 and 4), produce a battery of potent arms against adjacent competing microbes, for example an abundance of AMPs (fig. 2). Not only bacteria but fungi also compete with each others (Fig. 1).

Once they have invaded a host, they are confronted to a number of precarious defense systems, such as AMPS and immune cells (tab. 2, fig. 5), so that only microbes adapted the best are more likely to survive. In addition their eternal fratricidal wars for example mediated by bacteriocins pose a constant risk for their life. Last but not least special viruses adapted to a certain range of bacteria will infect and attack them. In a microbial community like the gut microbiome a permanent contest between microorganisms competing for the best settings takes place, and the local players displaying the best equipment with those inimical weapons will benefit the most.

Finally, one is tempted to feel sorry with these tiny creatures exposed at many instances to a lot of risks for their lives! Hence, microbe hunters, too, should avoid biased opinions and be more open-minded and more restrict an excessive use of antimicrobial agents to a more rational extent.

Anyway, if potential pathogens leave their natural habitats and become aggressive and induce infections, they have to be tackled relentlessly according to the general opinion of infectiologists.

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