Perspectives on and Need to Develop New Infection Control Strategies

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Abstract Bacterial infections by antimicrobial-resistant pathogens threaten to become the number one cause of death in 2050. Therewith the optimism about infection control that arose after the discovery of antibiotics has come to an end and new infection control strategies are direly needed. Development of new antibiotics is generally considered unlikely. In this chapter, a likelihood perspective is given, for the possibilities offered by combination and smart encapsulation of existing antibiotics, use of probiotics and phage therapy, antimicrobial peptides and nanotechnology-based antimicrobials. Combination of existing antibiotics with probiotics, antimicrobial peptides, or nanotechnology-based antimicrobials may also have good perspectives for clinical infection control, also when caused by antimicrobial-resistant strains. Therewith, existing antibiotics may still be useful for several decades to come despite the occurrence of antibiotic resistance, provided further research and development of the above strategies are focused on their downward clinical translation, carried out collaboratively within academia and industry, rather than on developing and publishing yet another, new antimicrobial compound.

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Introduction: Historical Perspective and Outlook

Long before the first microscopic observation of infectious bacteria, mankind has been struggling to effectively combat bacterial infections. Infection control strategies have for many centuries consisted of low potency antimicrobials, such as herbs, honey, old bread, and heavy metal salts, which were already used in ancient Roman, Chinese, and Egyptian cultures to cure infections. In 1640, Parkington found that molds were effective in curing wound infection (in: Wainwright [1]), while around the same time Van Leeuwenhoek [2] described the "*small animals on our teeth*" that we now call bacteria. In 1877, Pasteur found *Penicillium notatum* is harmful for the growth of *Bacillus anthracis*. Lactic acid producing bacteria were suggested by Döderlein [3] as early as in 1892 for the control of urogenital infections in women, while others made similar suggestions for intestinal infections [4–6].

In 1908, Nobel prize laureate Metchnikov proposed that longevity of Caucasian peasants was related to the high intake of fermented milk products. In his landmark paper "*On the prolongation of life*," Metchnikov described that ageing was caused by toxic bacteria in the gut and that the consumption of lactic acid bacteria in sour milk could elongate life. He was the first to allude to "*probiotic*" bacteria, by suggesting that harmful intestinal bacteria could be replaced by useful ones. In 2013, the World Health Organization recognized probiotics as "*live microorganisms that, when administered in adequate amounts, confer a health benefit on the host*" (in: Hill et al. [7]).

Around the same period that Metchnikov published his groundbreaking work on probiotics, Twort in 1915 demonstrated that bacteriophages could be targeted to and kill specific bacteria (in: Levin and Bull [8]). The first therapeutic use of phages by d'Herelle was reported in 1919, approximately a decade before Fleming's discovery of penicillin (in: Chan et al. [9]). In the 1940s, phages were marketed in the USA by Eli Lilly to treat a range of bacterial infections. However, further development of both probiotics and phage therapy for infection control were arrested by the hopeful discovery of penicillin by Fleming, except in the former Soviet Union where phage therapy was continued to be further developed and successfully applied during WWII to the aid of wounded soldiers (in: Wittebole et al. [10]).

Fleming incidentally observed the antibiotic effects of penicillin in 1923 [11]. Penicillin was first isolated in 1939 and its potency was unprecedented at the time. Penicillin was brought to clinical application in a record time, as accelerated by the need to help the many wounded soldiers in WWII. In 1943, penicillin was first tested on soldiers and in 1945 more than seven billion units were produced for

military use, in which year Flemming the name is Fleming was also awarded the Nobel Prize.

Many new antibiotics have been developed since and for several decades there was great optimism with respect to the control of bacterial infections: "*One day we could not save lives, or hardly any lives; on the very next day we could do so across a wide spectrum of diseases*" (in: McDermott and Rogers [12]). Antibiotics saved millions of lives, but at the same time their abuse and overuse stimulated the development of resistant bacteria. Although the first reports on bacterial resistance stem from the early 1940s [13, 14], it was still foreseen by some in 1986 that "*a manpower reduction of 36% in the number of fellows in infectious disease may be just about right*" (in: Petersdorf [15]).

Nowadays, the timeline of antibiotic discovery to observation of antibiotic resistance shows that in general antibiotic resistance occurs faster and faster after first discovery (Fig. 1). It is estimated that at least 700,000 people per year die from infections caused by antimicrobial-resistant pathogens and this number will rise to 10 million per year by 2050 (Fig. 2), overwhelming the current number of deaths caused by cancers [16].

Therewith, now that available antibiotics seem to reach their end-phase of efficacy, infection control is back to square one and the tide has changed again to pessimism, following the optimism stimulated by the discoveries of probiotics and phage therapy, both left largely unexplored. This somber outlook can only be reverted to a favorable change of the tides by rapid development and clinical translation of new infection control strategies, that we here briefly summarize and place in a likelihood perspective.

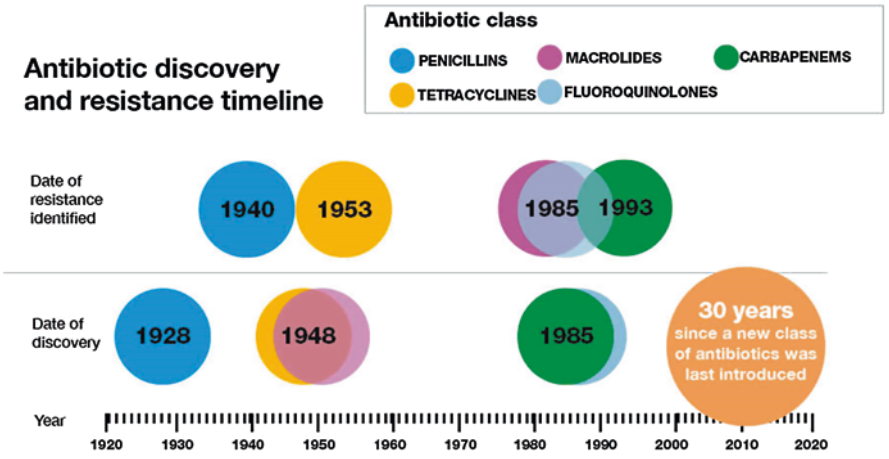

Fig. 1 Timeline of antibiotic discovery to observation of antibiotic resistance. (Downloaded on 10 Jan 2019 from: https://desdaughter.com/2016/02/14/antibiotic-discovery-and-resistance-timeline/)

New Strategies for Infection Control: A Likelihood Perspective

The timeline of antibiotic discovery to observation of antimicrobial resistance (Fig. 1) has greatly discouraged development of new antibiotics [17, 18]: "*Low hanging fruits have been plucked, economically it is not a good investment and research and development is too risky and expensive due to regulatory requirements*." Yet, with the outlook of the numbers of death by antimicrobial-resistant bacterial infections overwhelming the number of deaths caused by cancer in 2050 (Fig. 2 and [16]), new strategies for bacterial infection control are direly needed. As a consequence, "*old-fashioned*" strategies like probiotic and phage therapies are currently experiencing renewed interest. Biomimetic strategies, including application of antimicrobial peptides, are considered as well, while hopes are high with respect to nanotechnology-based antimicrobial strategies. In this section, we will briefly summarize new strategies considered nowadays and place them in a likelihood perspective.

Antibiotics

Whereas development of new antibiotics is considered unlikely for reasons mentioned above, this does not necessarily imply that the "age of antibiotics" has definitely come to a halt. Since the first reports on antibiotic resistance, many mechanisms of bacterial recalcitrance to antibiotic treatment have been revealed

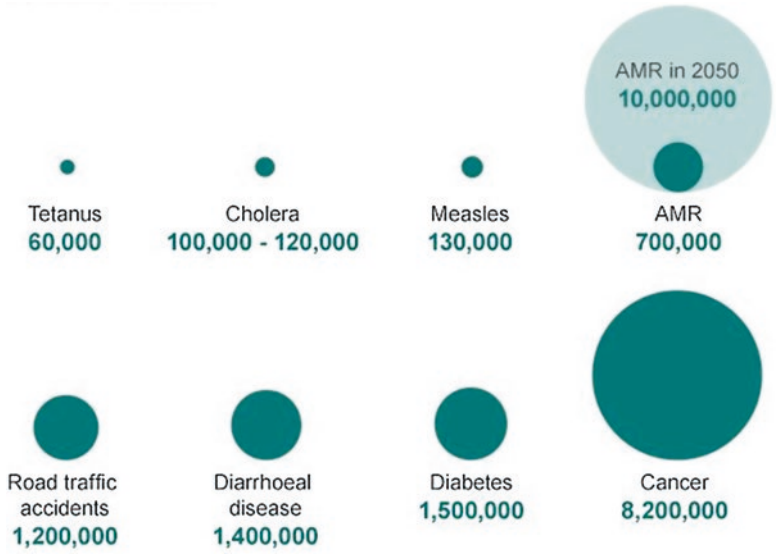

Fig. 2 Current annual numbers of deaths attributable to antimicrobial resistance and other diseases and the projected number of deaths attributable to antimicrobial-resistant (AMR) infection in the year 2050. (Downloaded on 10 Jan 2019 from: https://www.bbc.com/news/health-30416844)

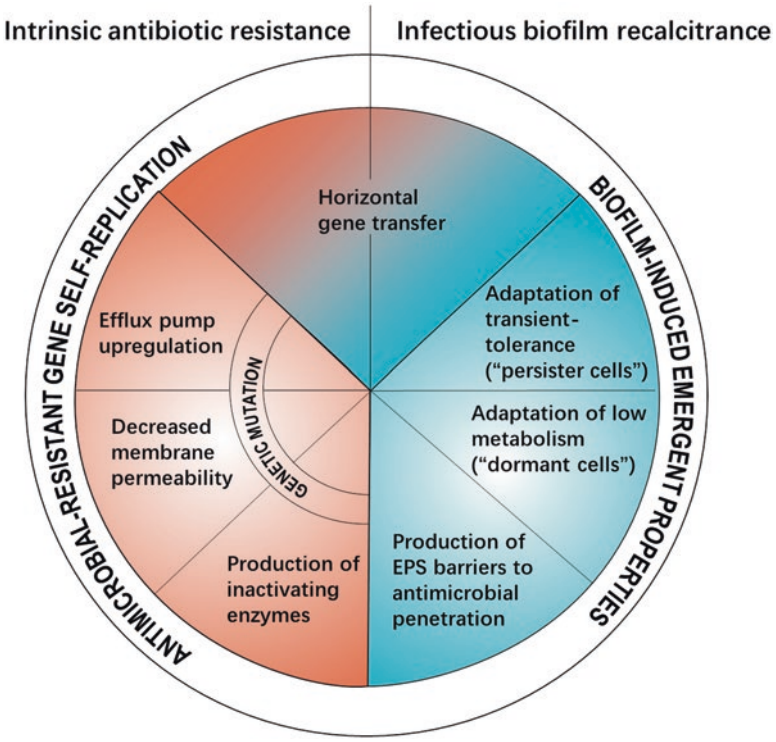

Fig. 3 Important mechanisms of bacterial recalcitrance to antimicrobial treatment, distinguishing factors related to intrinsic antibiotic resistance of the infecting bacterium and emergent properties of bacteria in their biofilm mode of growth, as is characteristic to the majority of bacterial infections [23]

(Fig. 3), that are either intrinsic [19–21] to the infecting bacterium or related to emergent properties [22] due to the biofilm mode of bacterial growth, in which the majority of bacterial infection present themselves [23]. In addition to the mechanisms summarized in Fig. 3, bacterial pathogens seek shelter in mammalian cells, that are difficult to penetrate by most existing antibiotics [24]. Despite these recalcitrance mechanisms, even intrinsically antibiotic-resistant bacteria have difficulties evading treatment by multiple, existing antibiotics at the same time and dual-antibiotic treatment can be effective against multidrug-resistant bacterial infections [25]. Alternatively, existing antibiotics can be administered together with protected (encapsulated, see below) probiotic bacteria or other new antimicrobial strategies for enhanced, synergistic action. Also, smart encapsulation of existing antibiotics with responsive and targeting features allows to establish higher local concentrations near or in an infection site than can be achieved through conventional administration (see also below). These developments imply that (existing) antibiotics when applied differently, may remain to be useful in bacterial infection control for several decades despite antibiotic resistance, even though the development of new antibiotics may have come to a halt.

Probiotics

Ever since Metchnikov suggested the use of probiotics for replacement of toxic bacteria in the gut and prolongation of life, mechanisms of probiotic action have become more clear (Fig. 4). The idea of establishing a healthy oral, gastrointestinal, urogenital, or skin microbiome, in which recognized probiotic bacteria like lactobacilli or bifidobacteria play a dominant role, is large scale applied in over-the-counter or web-order products as lifestyle drugs to prevent infection. Scientifically founded, benefit demonstration of prevention efficacy by probiotics is cumbersome, while in vitro the relatively low bactericidal potency of probiotics compared with the one of antibiotics impedes extensive downward clinical translation for therapeutic use. Moreover, many probiotics have difficulties surviving and permanently installing themselves in their host target site. Encapsulation of probiotic bacteria by functionalized, nano-engineered shells to enhance installation and protect them against the often, hostile environment of their host target site, constitutes a possible route to solve this problem [26, 27]. Importantly, protective biofilm-inspired alginate shells have been demonstrated to allow survival of probiotic lactobacilli in the presence of tobramycin, while encapsulated lactobacilli applied in combination with tobramycin

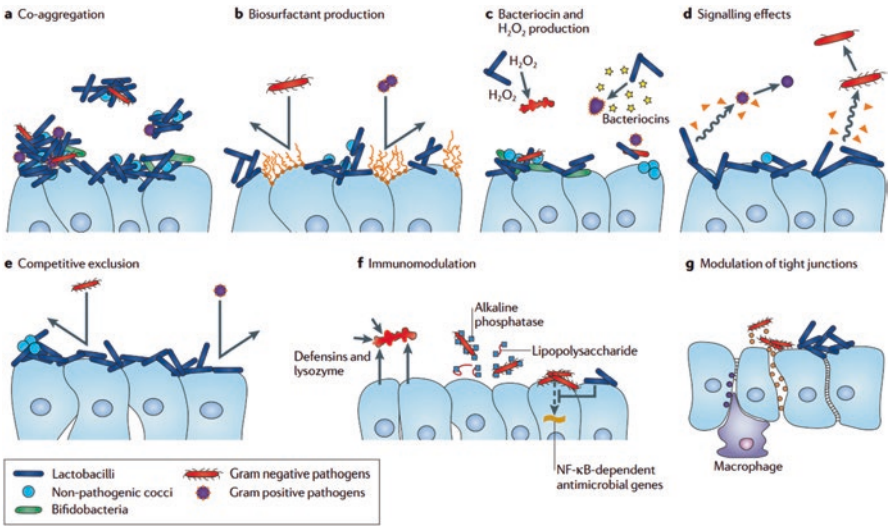

Fig. 4 Mechanisms of the restoration of the microbiota. (**a**) Co-aggregation of probiotic bacteria and pathogens interferes with the ability of the pathogenic species to infect the host. (**b**) Biosurfactants produced by probiotic bacteria help prevent pathogen adhesion to host surfaces. (**c**) Bacteriocins and hydrogen peroxide produced by probiotic bacteria can inhibit or kill pathogens. (**d**) Signaling between bacteria can lead to downregulation of toxin production in pathogens. (**e**) Probiotic bacteria can competitively exclude pathogens from host surfaces. (**f**) Probiotic bacteria can regulate immune responses, resulting production of, e.g., antimicrobial peptides. (**g**) Upregulation of tight junction proteins to limit the damage caused to host epithelia by pathogenic bacteria. (Reprinted with permission from [29], copyright at Nature Publishing Group)

had the ability to eradicate methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in vitro [28]. These new developments warrant research investments in probiotic use, of which the likelihood of dual administration of encapsulated probiotics combined with existing antibiotics to become clinically applied, may be considered quite large.

Phage Therapy

Phage therapy was never truly abandoned in former Soviet Union countries and rediscovered worldwide in the 1980s, in order to face the rising threat of antibiotic resistance [10]. Phage therapy is especially applied in Georgia, part of the former Soviet Union, for the treatment of antibiotic-resistant infections. A drawback of phage therapy is the high specificity of phages applied for a specific bacterial strain, which sometimes necessitates culturing of effective phages or the use of "phage cocktails" [9]. Phage therapy is not without risks and patients may suffer a septic shock due to bacterial endotoxins released from bacteria when they are broken up by phages [30]. Thus although in certain patients, phage therapy may have demonstrated efficacy in eradicating bacterial infection, including infections due to antibiotic-resistant strains [10], poorly understood complications [31] have obstructed regulatory approval in many countries worldwide. Nevertheless, its likelihood perspective is not to be underestimated as a strategy for infection control.

Antimicrobial Peptides

Antimicrobial peptides are part of the innate immune system and have emerged in synthetic form as novel antimicrobials to treat bacterial infections [32]. Antimicrobial peptides are positively charged, amphiphilic molecules that kill bacteria through membrane disruption and pore formation, but are prone to hydrolytic and proteolytic breakdown [32]. Antimicrobial peptides have been around since the onset of human existence without stimulating bacterial resistance and therefore, natural development of bacterial resistance against antimicrobial peptides seems unlikely [33]. Yet, others anticipate bacterial strategies of resistance to antimicrobial peptides to arise, especially if and when used large scale in clinical infection treatment [34, 35]. So far, clinical application of antimicrobial peptides is limited to address surface infections such as in chronic wound healing, as antimicrobial peptides do not specifically target bacterial cell membranes, but possibly also mammalian ones. Use of low concentration administration of antimicrobial peptides may prevent mammalian cell membrane damage, but lowers antimicrobial efficacy, which stimulated dual administration with existing antibiotics. Also specific targeting of bacterial cell membranes by in-tandem administration with nanoparticles might solve this problem [36–39].

While peptides may be synthesized in the future that effectively address these problems, manufacturing is expensive (around $100–$600 per gram using solid-phase chemical synthesis [40]). Therewith, the likelihood perspective of antimicrobial peptides to present a clinical alternative to antibiotics is hard to estimate.

Nanotechnology-Based Strategies

Intrinsic antibiotic resistance and poor penetration of antimicrobials into infectious biofilms form the two main reasons for the recalcitrance of infection to antimicrobial treatment (Fig. 3). Metal-based nanoparticles either on their own or in synergy with existing antibiotics can kill multidrug-resistant bacterial strains through ion release, (photoactivated) release of reactive-oxygen species, damage to intracellular proteins and DNA, membrane puncture or photothermal effects. Existing antibiotics can also be encapsulated to allow targeting and stealth penetration in infectious biofilms, while pH responsive features of such nanocarriers can create electrostatic double-layer attraction with bacteria inside infectious biofilms to prevent their washout. Magnetic nanoparticles are also investigated for their potential to become targeted in infectious biofilms. In this way, higher concentrations of existing antibiotics can be achieved in biofilms than with the use of antibiotics on their own.

Nanotechnology-based antimicrobial strategies closely follow developments in tumor treatment, that have further advanced to clinical application than antimicrobial strategies [41]. Likelihood perspectives of nanotechnology-based antimicrobials are good, as they may offer the possibility to make longer use of existing antibiotics and at the same time provide bacterial killing based on mechanisms to which bacteria may not be easily able to build up resistance mechanisms.

Conclusion

The war of mankind against antimicrobial-resistant pathogens may go on forever, with chances of winning fluctuating over the times from one side to the other. With the increasing number of bacterial strains and species resistant against all known antibiotics, bacterial pathogens appear on the winning side, for the first time since the discovery of antibiotics. Human defeat is well possible, since the likelihood of developing new antibiotics is low. Yet, existing antibiotics have not become useless, and combinations of existing antibiotics with probiotics, antimicrobial peptides, or nanotechnology-based antimicrobials yield good perspectives for clinical infection control, also when caused by antimicrobial-resistant strains. However, the complex regulatory landscape and need for commercially feasible strategies requires close collaboration between academia and industry in order to bring new strategies to clinical application. The need to develop yet another, new antimicrobial compound may be less urgent than the need to focus on downward clinical translation of available strategies, so far only published upon in scientific journals.

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