Antibiotic Resistance: Facing the Challenges of Bacterial Infections

In 1928 Alexander Fleming made his groundbreaking discovery of penicillin. Antibiotics have since been our most powerful weapons against bacterial infections: The average life expectancy significantly increased and previously risky surgeries became standard medical interventions that revolutionized medicine. Nowadays resistance development casts its shadow on the once shiny drugs that saved millions of lives. Today more than 90% of pathogenic Staphylococcus aureus are resistant against penicillin. The full depth of the problem has long been obscured by the seemingly unlimited number of antibiotics. However, in the last years the number of new antibiotics has drastically decreased while the development and spread of resistances has dramatically increased.

The Resistance Problem
Bacterial resistance is a multifaceted problem with a broad range of reasons for their development, evolution, and distribution:

1) Only a relatively small number of molecular targets in bacterial cells is attacked by the majority of antibiotics [1]. For instance, β-lactams inhibit enzymes of the cell wall biosynthesis, aminoglycosides interrupt bacterial protein biosynthesis by inhibiting the 30S ribosomal subunit, and quinolones inhibit cell division by targeting the DNA gyrase complex (fig. 1).

2) While the number of antibacterial molecules seems to be enormous, the actual number of antibiotic classes is very small (fig. 1). The class of β-lactams for instance comprises various groups that taken together are dominating the market with approximately 65% of all antibiotics [2]. Antibiotics of one class frequently have the same molecular targets and thus resistance development against one antibiotic easily confers resistance to additional antibiotics.

3) Some resistance mechanisms apply for multiple antibiotics of various classes. Resistance development usually involves enzymatic inactivation of the antibiotic, alterations of the target enzyme, by-pass mechanisms, efflux pumps, and
permeability barriers [3]. A single drug efflux system for instance can pump out a variety of different antibiotic classes [4].

4) Resistance genes can be easily spread by horizontal gene transfer.

Bacterial resistance against antibiotics does not have to evolve de novo for every antibiotic in a strain or species. Horizontal gene transfer by conjugation, transformation, and transduction easily disseminates antibiotic resistances from one species to another [5].

5) Antibiotics have been over- and misused extensively for the treatment of simple self-resolving infections, prophylaxis, and household products. However, the by far most extensive use of antibiotics has been in livestock. In the US 80% of antibiotics are not for the treatment of human diseases but used in farm animals [6]. Thus, antibiotics are released in large quantities into the environment resulting in increasing resistance development.

6) Our bodies host 10-times as many bacterial cells as human cells. Many of these bacteria are facultative pathogens that may lead to severe infections when they accidentally get in the wrong place. Antibiotic treatment can result in the colonization by resistant facultative pathogens like MRSA strains and clearance of beneficial bacteria whose niches can be taken over by resistant strains [7].

The Antibiotic Crisis
Rapid evolution of antibiotic resistance continues to threaten the treatment of bacterial infections and requires the development of new antibiotics and alternative strategies. However, the development of new antibiotics has decreased over the last decades. In the years 2004 to 2014 a total of only eight new antibiotics were released to the market while in the years 1980 to 1990 it had been 46 new antibiotics and combination drugs. Among the antibiotics approved in the 80's were
blockbusters like ciprofloxacin and azithromycin as well as several of the drugs that are still today on the WHO list of essential medicines.

Multiple reasons contribute to why antibiotic development has been abandoned by many big players in the pharmaceutical industry. Resistance development has shortened the life span of antibiotics while development to market approval is a long and expensive process that often takes a decade or more. Developmental risks are high and 90% of drugs fail during the long path from preclinical studies to market approval [8]. Finally, developmental costs and risks have to be compensated by market returns which again are threatened by emergence of resistances and patent expiry.

Also, it has become hard to find entirely new classes of antibiotics and the antibiotics approved in the past ten years are mostly based on known structures.

We are thus facing the problem of a steadily decreasing number of new antibiotics while resistance development is speeding up and multi-drug resistant strains are spreading rapidly. If this development continues, high mortalities for simple bacterial infections and high risks for normal surgeries will mark the upcoming post-antibiotic era.

**Strategies for the Future**

What can we do about this imminent threat and how can Chemistry and Biology contribute to alternative solutions? First of all I do not think that we will be able to completely replace antibiotics any time in the near future. Antibiotics are too important as last resort for the treatment of highly progressed and life threatening bacterial infections like sepsis, where rapid clearance of the infective agent is required to prevent death of the patient. We thus need to take action to save these valuable drugs:

The use of antibiotics should be limited to the treatment of actual infections and banned from use in household products and as growth enhancers for livestock. Over-the-counter sales in pharmacies should be restricted worldwide and limited to controlled applications in hospitals. Hospitals in turn have to take more responsibility for the resistance problematic, i.e. limiting application of antibiotics to the absolute necessary and establishing strict policies using the model of the Dutch MRSA search-and-destroy policy [9].

Advanced diagnostic techniques have become available that allow the rapid identification of pathogens and resistance markers before treatment so that customized narrow spectrum drugs can be applied. While broad spectrum antibiotics easily lead to resistance development of commensal bacteria and
colonization with resistant strains, narrow spectrum drugs could prevent the disruption of the beneficial human microbiome. Combination therapies with different antibiotics and combinations of antibiotics with drugs that target resistance like β-lactamase inhibitors have been already applied for years and may become the predominant antibiotic strategy in the future to combat resistant pathogens.

For the majority of infectious diseases, however, antibiotics would actually not be necessary if alternatives were available. Such alternatives could be anti-virulence strategies that do not kill but disarm bacteria. The concept is simple: small molecules inhibit enzymes that are essential for infection rendering the bacterium disarmed [10]. Such infection related functions can be virulence factors like toxins and extracellular enzymes, proteins for adhesion to eukaryotic cells, type III secretion systems, or central regulators of virulence. Anti-virulence strategies also include inhibiting population behavior like biofilm formation or bacterial coordination by quorum sensing. Once the bacteria are disarmed the host immune response eventually will clear the intruders. It is proposed that some anti-virulence strategies would be less prone to resistance development, as they don't exert direct selective pressure. Anti-virulence strategies are in development and have already proven successful in animal models [11]. Applications could be preventive care after surgeries, treatment of chronic and recurrent infections, as well as most other not immediately life-threatening diseases.

Strategies of the future also may involve lytic bacteriophages as narrow spectrum agents against certain pathogens [12]. Phage therapy may have several advantages over antibiotics like the reproduction of the therapeutic agent in the host body and accumulation at the site of infection [13]. Further strategies may involve vaccinations against key pathogens which, however, can only be used for prophylaxis and not for treatment of an ongoing infection [14]. Vaccines against multi-drug resistant Staphylococcus aureus (MRSA) are currently under development. In contrast to vaccines, antibodies can be even used therapeutically as narrow spectrum drugs [15].

Further preventive methods may include material modifications such as impregnating catheters and implants with anti-biofilm agents or antibacterial nanoparticles [16]. Emerging physical treatment technologies like non-thermal gas plasmas -ionized gas generated by electric discharge - are currently in clinical trial and could be used for efficient treatment of wound infections [17]. Finally, supporting and controlling our beneficial microbial flora could be a major strategy for the prevention of infections in the future. Commensal bacteria are the first line of defense that physically occupy the existing niches of the human body, compete
with intruding microbes, and produce a diversity of anti-bacterial and anti-fungal compounds and thereby prevent the invasion of pathogenic strains. Understanding the complex interactions in the microbiome and its importance for human health may help us in the future to preserve and directly control the composition of beneficial bacteria in our microbiome that strengthen our immune system and protect us from bacterial infections.

Conclusions
Antibiotic resistance poses a serious threat to our society and has led to an unfolding crisis for healthcare. Immediate actions should be taken to reduce the development and spreading of resistance to save antibiotics for the treatment of life-threatening infections. Alternatives to antibiotics are urgently needed and instead of a single strategy we will have to develop a broad mixture and combinations of narrow spectrum drugs and therapies that along with faster and more specific diagnostic methods can be applied to effectively treat infections. These strategies should simultaneously preserve the beneficial bacteria of the human microbiome and reduce the risk of resistance development and colonization with resistant strains.

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Literature

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