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Petra Dersch *Editors*

How to Overcome the Antibiotic Crisis

Facts, Challenges, Technologies and Future Perspectives

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Preface

The worrying increase of nosocomial infections caused by multi-resistant pathogenic bacterial strains, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci (VRE), fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRPA) is generally regarded as one of the major global challenges in human medicine. Since the new threat has been caused by multiple factors, a multi-disciplinary collaborative approach will be imperative to keep these new super-bugs at bay. The current volume was compiled by the principal investigators of the Helmholtz Centre for Infection Research (Braunschweig, Germany) and the associated universities and research institutes, where expertise in all important fields, ranging from infection biology and microbiology to epidemiology, immunology and drug discovery is readily available.

The authors of this book have contributed articles that cover all core disciplines and a range of current topics and emerging approaches in infection and drug research at the centre and world-wide. They address several aspects of basic research, such as the evolution and spread of resistance in bacterial pathogens and the influence of currently used antibiotics on the gut microbiota. Contributions on the search for novel biochemical targets that block pathogenicity and the development of alternatives to the state of the art treatments, such as antivirulence therapies, combine basic and applied aspects, leading to our strategy in the search for new antibiotics and their preclinical and clinical development. Several papers are dedicated to this important topic, ranging from strategies to discover new drugs based on biodiversity and genome mining and the optimisation of novel lead structures. Others address the accessibility of anti-infectives by means of medicinal chemistry, total synthesis, and biotechnological technologies, and include aspects of drug delivery in an alternative approach to overcome the cell wall of gram-negative bacteria as an important biological barrier that prevents most antibiotics from reaching their target site in those pathogens. The development of vaccines as valid alternative therapeutic approach to antibiotics therapy is also outlined. Moreover, aspects of clinical research, such as epidemiological studies of important bacterial pathogens and the development of innovative technologies for detection and diagnostics of the “bad bugs” are also illustrated by articles in this ebook.

The following 17 contributions are from microbiologists, immunologists and natural product chemists of the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany, its two branches, the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken and the TWINCORE in Hannover, and neighboring partner universities (Leibniz Institute DSMZ, Veterinary School Hannover, Leibniz University Hannover). The HZI is one of the largest research centres world-wide that is dedicated to infection biology, immunology, and drug research. The institute, which was formerly known as the Gesellschaft für Biotechnologische Forschung (GBF), has recently celebrated its 50th anniversary. The GBF has become renowned for its biotechnological production facilities and above all, the accomplishments of its natural product chemistry departments. Those included the discovery and development of the anticancer drug, Ixabepilone, the antifungal soraphens and many other compounds derived from gliding bacteria. Ten years ago, the focus of the GBF has changed to infection research, followed by the renaming of the institute to HZI in 2006. Over the past years, the HZI has refined its research portfolio and strengthened its expertise amongst others by founding joint institutes with strong partner institutions. The HIPS in Saarbrücken was founded in 2009 with the Saarland University as a daughter institute of the HZI, and has significantly intensified HZI drug research, e.g. through recruitments with substantial industrial expertise. At the TWINCORE in Hannover, a joint institute with the Hannover Medical School, basic research scientist and clinicians work side by side since 2008 to transfer latest research findings to new therapies or diagnostic procedures for patients. With the translational scope in mind, the HZI's strategy combines basic research at all resolution levels with clinically oriented and pharmaceutical research, focusing on clinically relevant bacterial and viral pathogens, the immune system and immune interventions as well as anti-infectives. Antibiotics research is a field of topical significance due to multi-resistant bacteria increasingly challenging modern medicine. Thus, microbiologists, cell biologists, epidemiologists and immunologists of the HZI collaborate closely with the drug research departments, as well as with renowned scientists from the neighboring and international partner universities and research institutes to address this task. The current volume addresses the challenges afflicted with the threat of an antibiotic crisis and thus covers the important scientific activities of the HZI directed to combat bacterial pathogens, but not its excellent research on viral diseases and important host defense mechanisms.

Part I Antibiotic Resistance: Problems and New Opportunities

The first part of this two-part volume includes some of the most recent aspects and developments in infection biology, antibiotic resistance and host defense. E. Medina and D. Pieper [1] highlight current problems emerging multidrug resistant pathogens with a special focus on methicillin-resistant *Staphylococcus aureus*, MDR- and XDR-resistant *Mycobacterium tuberculosis* and ESBL-producing gram-negative pathogens. They discuss new possibilities to prevent and control infections of these dangerous pathogens, reduce the emergence of antibiotic resistance and develop new drugs. The following article by Nübel et al.

[2] emphasizes the importance to address emergence and spread of antimicrobial resistance using bacterial population genomics. Recent progress in DNA sequencing technologies and genomic studies now allows us to follow the evolution of antibiotic resistances. This approach not only illustrated that global populations of certain drug-resistant bacterial pathogens are dominated by a few clones, it also revealed features that were crucial for their spreading success. Most studies on the epidemiology of multidrug-resistant variants of clinically important pathogens such as methicillin-resistant *S. aureus* (MRSA) were focused on the emergence and spread in hospitals and other health care settings. The contribution by Mehraj et al. [3] presents more recent epidemiological studies, which analyzed carriage patterns in community settings, providing new insights on risk factors for colonization and new ideas for strategies to prevent infections. The high and increasing rate of antibiotic resistance hinders conventional use of antibiotics and increases morbidity and mortality due to ineffective treatments of infections. This situation demands fast and precise diagnostics of pathogens and their antibiotic resistance profile. Hornischer and Häußler [4] highlight new approaches and possibilities implementing modern omics technologies for the development of biomarker-driven molecular test systems for early diagnostics and resistance profiling for targeted therapy and a more effective stewardship of antibiotic agents. Use of antimicrobial agents in veterinary medicine is essential to control infectious diseases in domestic animals, but it also increases emergence of antimicrobial resistance. Seitz et al. [5] outline current aspects and problems related to the use of antimicrobial agents in animal farms, in particular swine husbandries with emphasis on resistance in *Streptococcus suis*, a major pathogen in swine. Current research on the intestinal microbiome revealed that a consequence of antibiotic treatment is a drastic change of the composition of the microbiota. The article by Thiemann et al. [6] provides current information about how this can be associated with an enhanced susceptibility towards gastrointestinal infections and metabolic disorders, and how it can also increase abundance of antibiotic resistance genes with bacterial commensals. To successfully combat against antibiotic resistance, novel treatment options and alternative antimicrobial therapies are urgently required. One novel strategy is to target and interfere with crucial bacterial pathogenicity factors or virulence-associated traits to bypass the evolutional pressure on the bacterium to develop resistance. Numerous potential drug targets for antivirulence therapies which have been identified over the last years, as well as structure-based tailoring of intervention strategies and established screening assays for small molecule inhibitors of such pathways are presented in the article by Mühlen and Dersch [7]. More specific approaches to block pathogenesis by interference with the flagella apparatus and the associated chemosensory system are highlighted in the contribution by Erhardt [8]. Finally, Schulze and colleagues [9] outline the importance of vaccination to control infectious diseases and emphasize a new immunization strategy using a non-invasive mucosal and transdermal application system to increase vaccination efficacy.

Part II Natural Compound Research and Anti-infective Development

The second part of this volume mainly focuses on various aspects that relate to the discovery and development of antibiotics. As outlined by Mohr [10], this field of research has been historically dominated by natural products, since the vast majority of the molecules that were turned into therapeutically useful antibiotics have been derived from fermentation of bacteria and fungi. The chapter by Landwehr et al. [11] accordingly treats the most important groups of bacterial secondary metabolite producers, i.e., Actinobacteria and Myxobacteria, and describes the current scenario that is being employed to screen these organisms using sophisticated methodologies that are dominated by state-of-the art techniques, including the development of special isolation protocols, e.g. for organisms from extreme habitats. The following chapter by Karwehl and Stadler [12] is dedicated to fungi, emphasizing the importance of combining biodiversity-driven approaches to identify producer organisms of novel lead compounds. An immense diversity has recently been recognized in fungi since modern methods of molecular phylogenetics have become available, and these organisms are highly likely to yield further innovative lead compounds. The chapter by Hermann et al. [13] focuses on three case studies involving highly promising current exploratory research projects on new antibiotics that are derived from bacteria. The utility of synthetic biotechnology, structural biology and genomics research for optimising natural lead structures and discovery of their mode-of-action is amply illustrated, based on the model compounds, griselimycin, aminochelocardin and cytobactamid. The outcome of these projects gives some hope that it will finally be possible to overcome the void in antibiotics discovery, using a combination of rational methods of lead structure generation that could not be imagined even ten years previously. However, these compounds will still need to be adopted by industrial partners since the resources of a public research institute are insufficient to cover the high costs involved with clinical drug development. Klahn and Brönstrup [14] have added to this approach, emphasizing on the importance of molecular target evaluation and give various examples for developmental candidates and investigational drugs mostly based on natural scaffolds but also give some examples for synthetic compounds that are now under development. Kalesse et al. [15] illustrate the utility of total synthesis of antibiotics, using selected "historical" examples. This approach will continue to provide a valid alternative to the biotechnological production of natural antibiotics, especially for less complex molecules that can easily be built up and modified synthetically but are produced by the microbes at rather low titers. An overview on the current status of the global pipeline of antibiotics in clinical trials is given by Hesterkamp [16]. Finally, a strategy to tackle one of the greatest challenge of the 21th century in novel antibiotics discovery, i.e. the improvement of pharmaceutical properties of such antibiotic drugs to overcome the barrier of the cell wall of the gram-negative pathogens by employing sophisticated drug delivery technologies, is presented by Graef et al. [17].

We dedicate this volume to two esteemed colleagues who have been instrumental in the implementation of the aforementioned strategic re-orientation of the GBF: Jürgen Wehland, the former Scientific Director, and Gursharan Singh Chhatwal, the former head of department of Microbial Pathogenicity who passed away recently.

That the HZI has now developed to one of the global strongholds of infection biology and anti-infective research is without doubt due to their great efforts. We are very thankful to all authors for their contribution in this special volume and hope that it will increase interest in antibacterial research and stimulate work on antibacterial drug discovery that is urgently needed.

1. Medina EI, Pieper DH (2016) Tackling threats and future problems of multidrug-resistant bacteria.
2. Nübel U (2016) Emergence and spread of antimicrobial resistance: recent insights from bacterial population genomics.
3. Mehraj J, Witte W, Akmatov MK, Layer F, Werner G, Krause G (2016) Epidemiology of *Staphylococcus aureus* nasal carriage patterns in the community.
4. Hornischer K, Häußler S (2016) Diagnostics and resistance profiling of bacterial pathogens.
5. Seitz M, Valentin-Weigand P, Willenborg J (2016) Use of antibiotics and antimicrobial resistance in veterinary medicine as exemplified by the swine pathogen *Streptococcus suis*.
6. Thiemann S, Smit N, Strowig T (2016) Antibiotics and the intestinal microbiome: individual responses, resilience of the ecosystem and the susceptibility to infections.
7. Mühlen S, Dersch P (2016) Anti-virulence strategies to target bacterial infections.
8. Erhardt M (2016) Strategies to block bacterial pathogenesis by interference with motility and chemotaxis.
9. Schulze K, Ebensen T, Riese P, Prochnow B, Lehr CM, Guzman CA (2016) New horizons in the development of novel needle-free immunization strategies to increase vaccination efficacy
10. Mohr KI (2016) History of antibiotics research.
11. Landwehr W, Wolf C, Wink C (2016) Actinobacteria and Myxobacteria – Two of the most important bacterial resources for novel antibiotics.
12. Karwehl S, Stadler M (2016) Exploitation of fungal biodiversity for discovery of novel antibiotics.
13. Herrmann J, Lukežič T, Kling A, Baumann S, Hüttel S, Petković H, Müller R (2016) Strategies for the discovery and development of new antibiotics from natural products: Three Case Studies.
14. Klahn P, Brönstrup M (2016) New structural templates for clinically validated and novel targets in antimicrobial drug research and development.
15. Kalesse M, Böhm A, Kipper A, Wandelt V (2016) Synthesis of antibiotics.
16. Hesterkamp T (2016) Antibiotics clinical development and pipeline.
17. Graef F Gordon S, Lehr CM (2016) Anti-infectives in drug delivery—overcoming the Gram-negative bacterial cell envelope.

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Contents

Part I
Antibiotic Resistance: Problems and New Opportunities

Tackling Threats and Future Problems of Multidrug-Resistant Bacteria

Eva Medina and Dietmar Helmut Pieper

Abstract With the advent of the antibiotic era, the overuse and inappropriate consumption and application of antibiotics have driven the rapid emergence of multidrug-resistant pathogens. Antimicrobial resistance increases the morbidity, mortality, length of hospitalization and healthcare costs. Among Gram-positive bacteria, *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) *Mycobacterium tuberculosis,* and among the Gram-negative bacteria, extended-spectrum beta-lactamase (ESBLs)-producing bacteria have become a major global healthcare problem in the 21st century. The pressure to use antibiotics guarantees that the spread and prevalence of these as well as of future emerging multidrug-resistant pathogens will be a persistent phenomenon. The unfeasibility of reversing antimicrobial resistance back towards susceptibility and the critical need to treat bacterial infection in modern medicine have burdened researchers and pharmaceutical companies to develop new antimicrobials effective against these difficult-to-treat multidrug-resistant pathogens. However, it can be anticipated that antibiotic resistance will continue to develop more rapidly than new agents to treat these infections become available and a better understanding of the molecular, evolutionary and ecological mechanisms governing the spread of antibiotic resistance is needed. The only way to curb the current crisis of antimicrobial resistance will be to develop entirely novel strategies to fight these pathogens such as combining antimicrobial drugs with other agents that counteract and obstruct the antibiotic resistant mechanisms expressed by the pathogen. Furthermore, as many antibiotics are often inappropriately prescribed, a more personalized approach based on precise diagnosis tools will ensure that proper treatments can be promptly

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applied leading to more targeted and effective therapies. However, in more general terms, also the overall use and release of antibiotics in the environment needs to be better controlled.

List of Abbreviations

CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CDC	Center for Disease Control and Prevention
CRE	Carbapenem-resistant *Enterobacteriacea*
DOTS	Direct Observed Treatment Short-Course
ESBL	Extended spectrum β-lactamase
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.
FDA	Food and Drug Administration
H-MRSA	Hospital-acquired methicillin-resistant *Staphylococcus aureus*
hVISA	Heterogeneous vancomycin-intermediate *Staphylococcus aureus*
IDSA	Infectious Diseases Society of America
IMP	Metallo-β-lactamase active on imipenem
KPC	*Klebsiella pneumoniae* carbapenemases
LPS	Lipopolysaccharide
MDR	Multidrug-resistant
MDR-TB	Multidrug-resistant tuberculosis
MIC	Minimum inhibitory concentration
MRAB	Multidrug-resistant *Acinetobacter baumannii*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MYSTIC	Meropenem Yearly Susceptibility Test Information Collection
NDM	New Delhi β-lactamase
PBP2a	Penicillin-binding protein 2a
PDR	Pandrug-resistant
SIM	Seoul imipenemase
SME	*Serratia marcescens* enzyme
TDR-TB	Totally drug-resistant tuberculosis
VIM	Verona integron-encoded metallo-β-lactamase
VISA	Vancomycin intermediate-resistant *Staphylococcus aureus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WHO	World Health Organization
XDR	Extensive drug resistant
XDR-TB	Extensive drug resistant tuberculosis