



ERS | *monograph*

# Anti-infectives and the Lung

Edited by Stefano Aliberti,  
James D. Chalmers  
and Mathias W. Pletz

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and Mathias W. Pletz

Editor in Chief  
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Published by European Respiratory Society ©2017

March 2017

Print ISBN: 978-1-84984-083-5

Online ISBN: 978-1-84984-084-2

Print ISSN: 2312-508X

Online ISSN: 2312-5098

Typesetting by Nova Techset Private Limited

Printed by Ashford Colour Press Limited

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# Preface

Robert Bals

The use and prescription of antibiotics is an area of discussion, insecurities, a multitude of guidelines, a number of novel drugs and one of the most frequent medical interventions. The clinical spectrum of patients with infections of the respiratory tract is wide, and covers disease entities such as viral infections presenting as a common cold, “standard” CAP and pneumogenic sepsis with multiresistant microorganisms. While respiratory infections are among the most frequent diseases in pulmonary medicine, a number of problem areas are obvious: 1) there is often a lack of evidence-based approaches to therapy; 2) the role of novel antibiotics is not well defined; 3) the number of resistant microorganisms is increasing for a variety of reasons, from false application in patients to misuse in animal husbandry; and 4) the inadequate use of anti-infectives can cause significant harm.



With this *ERS Monograph*, we provide the reader with a broad and detailed overview on anti-infective drugs in pulmonary care. Several chapters focus on the pharmacology and clinical use of specific antibiotics or antifungals. Other chapters go into more detail on specific disease entities, such as asthma, COPD, pleural infections, TB and CAP. In addition, the book discusses current topics that cover subjects of broad importance, including resistance mechanisms, inhaled application of antibiotics, antibiotic stewardship, long-term treatment and novel drug developments.

The Guest Editors, Stefano Aliberti, James D. Chalmers and Mathias W. Pletz, have worked very successfully to select these topics and to integrate these aspects into this *ERS Monograph* that summarises our current knowledge. I thank the Guest Editors and all of the authors for their excellent work. Together, they have produced a practice-guideline publication that comprises information on the scientific background and the application at the patient’s bedside. I am sure that this comprehensive overview will be useful for the clinical practice of

a broad range of respiratory physicians and improve the care for patients with pulmonary infections.

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**Disclosures:** R. Bals has received grants from the German Research Ministerium and the Deutsche Forschungsgemeinschaft. He has also received personal fees from GSK, AstraZeneca, Boehringer Ingelheim and CSL Behring.



# Guest Editors

## Stefano Aliberti

Stefano Aliberti is Associate Professor in Respiratory Medicine at the University of Milan and consultant at the Policlinico Hospital in Milan (Italy). His major clinical and research interests are in chronic and acute respiratory infections. He started working on CAP in the mid-2000s at the University of Louisville (KY, USA) as an investigator of the Community-Acquired Pneumonia Organization (CAPO) and member of the Community-Acquired Pneumonia Inflammatory Study Group (CAPISG). He has extensively published clinical and translational research papers on CAP, especially in the field of antimicrobial resistance, and was awarded the Young Researcher Award in Respiratory Infections from the European Respiratory Society (ERS) in 2007.



In recent years he has been heavily involved in bronchiectasis research, leading the largest non-cystic fibrosis bronchiectasis clinic in Italy. He co-founded the European Bronchiectasis Registry (EMBARC), and is the Director of the Italian Bronchiectasis Registry and the Italian Registry of Pulmonary Non-tuberculous Mycobacteria.

Stefano Aliberti has published over 130 articles on respiratory infections over the past 10 years. He is an Associate Editor of *ERJ Open Research* and *BMC Pulmonary Medicine*. He has been involved in the ERS, as Secretary of the Respiratory Infections Group, and Secretary and now Head of the Respiratory Infections Assembly.

## James D. Chalmers

James D. Chalmers is Clinical Senior Lecturer and Honorary Consultant at the University of Dundee (UK). He trained in Glasgow and Edinburgh (UK), performing his PhD studies at the Medical Research Council (MRC) Centre for Inflammation Research studying the immunology of bronchiectasis. His research and clinical interests are in respiratory infections, including bronchiectasis, COPD and CAP.





He runs a translational research group primarily focused on developing novel diagnostics and treatments for respiratory infections, with current major programmes looking at neutrophilic inflammation and the microbiome in bronchiectasis, COPD and severe asthma. He is a co-founder and Chair of EMBARC.

James D. Chalmers has published over 120 papers in peer-reviewed journals since 2008, and has received prestigious research and teaching awards from the British Thoracic Society, ERS and Royal College of Physicians. He is an Associate Editor of the *European Respiratory Journal*, a member of the International Advisory Board of *Lancet Respiratory Medicine*, Secretary of the European Board for Accreditation in Pneumology, Chair of the British Thoracic Society Respiratory Infections Speciality Advisory Group and holds a number of other major society/committee appointments.

## Mathias W. Pletz



Mathias W. Pletz, Professor for Infectious Diseases, is a board-certified physician for internal medicine, pulmonology and infectious diseases, and the Head of the Center for Infectious Diseases and Infection Control of the University Hospital in Jena (Germany). He also leads a clinical research group focusing on novel diagnostic and therapeutic strategies against MDR bacterial pathogens, funded by the German Ministry for Science and Education.

Mathias W. Pletz received his PhD in Virology at the University of Leipzig (Germany). During his thesis he worked as a guest researcher at the Food and Drug Administration Laboratory of Parasitic Pathology and Biochemistry (Bethesda, MD, USA). After his medical training at the University of Leipzig, Baylor College of Medicine (Houston, TX, USA) and the University of Basel (Switzerland), he started his residency at the Chest Hospital in Berlin (Germany). Subsequently, he spent 2 years as a postdoctoral researcher at Emory University (Atlanta, GA, USA) working with Keith Klugman's group on the spread of multiresistant pneumococci. In addition, he served as a guest researcher at the Centers for Disease Control and Prevention (CDC) in Atlanta, exploring the severe acute respiratory syndrome (SARS) epidemics. After his return to Germany, he finished his medical training at the Dept of Respiratory Medicine at the Hannover Medical School.

Mathias W. Pletz is the Deputy Director of the German Competence Network for Community-Acquired Pneumonia (CAPNETZ), a member of the Board of Directors of the German Society for Infectious Diseases (DGI) and scientific

advisor for the German Robert Koch Institute. He has published more than 180 papers on pneumonia, pneumococcal vaccines, respiratory infections, antimicrobial resistance and pharmacokinetics of antibiotics in the critically ill. He has also received numerous scientific awards, *e.g.* the Honor Award Certificate from the CDC, the Kass Award of the Infectious Diseases Society of America and the Respiratory Infections Award from the ERS.



# Introduction

Stefano Aliberti<sup>1</sup>, James D. Chalmers<sup>2</sup> and Mathias W. Pletz<sup>3,4,5</sup>

On returning from holiday to St Mary's Hospital in London in 1928, Alexander Fleming discovered something unexpected on a Petri dish containing *Staphylococcus*. Contamination of the plate with a rare *Penicillium* fungus led to a zone of bacterial killing, demonstrating that the fungus was secreting a factor that killed staphylococci.

Fleming observed that an extract from this fungus could kill a wide range of bacteria, particularly Gram-positive bacteria. Subsequent work confirmed that some organisms were susceptible to the *Penicillium* extract, while many, particularly Gram-negative organisms, were not. Indeed the initial application of penicillin published in the *British Journal of Experimental Pathology* in June 1929 appeared to be as a method to differentiate between different bacteria in the laboratory [1]. However, in his Nobel Lecture on December 11, 1945, Fleming had already foreseen the “antibiotic resistance crisis” caused by overuse and underdosing [2]:

*But I would like to sound one note of warning. ... It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.*

Thus, through a remarkable accident, one of the greatest medical advances in history was made, *i.e.* the ability to cure disease through antibiotic treatment, and simultaneously the threat of antibiotic resistance was also discovered.

These competing opportunities and threats continue in parallel to this day.

The lung is the key interface between the human body and the microbial world, with an average person with a normal breathing rate inhaling nearly 1 000 000 bacteria per day. It is therefore not surprising that respiratory tract infections are the most common reason for antibiotic prescribing in both primary and secondary care, and a leading cause of mortality worldwide. Despite advances in hygiene and the availability of antimicrobials, TB and pneumonia remain devastating on a global level, while bronchiectasis, cystic fibrosis, pleural

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infection and NTM disease represent some of the most complex and challenging infectious diseases in medicine.

The correct principles of antibiotic therapy are therefore a critical skill for all practising pulmonologists, primary care physicians, infectious disease specialists and allied health professionals with responsibility for respiratory patients.

It is for this reason we are delighted to introduce this *ERS Monograph* dedicated to understanding the pharmacology, administration, clinical role and stewardship of antibiotics in respiratory disease.

This was a challenging *Monograph* to write and edit. Unlike many aspects of respiratory disease, there are rarely large RCTs to guide our therapy, and respiratory infectious diseases are often neglected in terms of research funding and underestimated in terms of public importance.

In the absence of robust evidence, many antibiotic practices have evolved differently in different countries in Europe and worldwide. A patient presenting with severe CAP in Scandinavia may receive intravenous penicillin, while a patient with the same characteristics might receive piperacillin–tazobactam plus macrolide or vancomycin in the USA. Global antibiotic practices are determined by differences in common organisms and antibiotic resistance patterns, but also more obviously, by cultural attitudes toward the risk of missing a serious infection, perceptions of the importance of antibiotic resistance, concerns over litigation and organisation of healthcare.

We are especially pleased, therefore, that this *ERS Monograph* captures important perspectives from Northern, Southern and Eastern Europe as well as the USA and Japan, among others. The topics cover the major indications for antibiotic use, from LRTIs in the community through to severe infections in critical care. Inhaled delivery is extensively discussed, as is the role of antibiotic therapy in airways diseases such as asthma, COPD and bronchiectasis. Pleural infection, TB, NTM disease and respiratory infections in children are also some of the key highlights.

The first *ERS Monograph* on Antibiotics and the Lung was published in 2004 [3]. A key addition to the current book is that we address the emerging risk of antibiotic resistance with chapters on antimicrobial stewardship and the importance of looking to the future of new drug development to tackle this threat.

After a tumultuous 2016, the authors are writing this Introduction a few days before the inauguration of a new US President in January 2017. You will forgive us then, for paraphrasing from a former US President, from a simpler time, to introduce this new *ERS Monograph*:

*Ask not what your antibiotics can do for you, ask what you can do for (the responsible use of) antibiotics.*

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**Disclosures:** J.D. Chalmers has received grants from Aradigm, AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, GSK, Novartis and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Bayer Healthcare, Boehringer Ingelheim, Chiesi, Napp and Pfizer. M.W. Pletz has received grants from the German Research Foundation, the German Ministry for Science and Education, Biotest, InfectoPharm and Pfizer. He has also received personal fees from AstraZeneca, Basilea, Biotest, Clinigen, InfectoPharm, MSD, Pfizer and Thermo Fisher, and has a patent "Measuring antibiotic blood levels with Raman spectroscopy" pending. S. Aliberti has received grants from Bayer Healthcare, Aradigm Corporation, Griffols, European Respiratory Society and Chiesi. He has also received personal fees from Bayer Healthcare, Aradigm Corporation, European Respiratory Society, Griffols, AstraZeneca, Basilea, Zambon, Novartis, Raptor, Chiesi and Actavis UK Ltd.

# List of abbreviations

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AUC	area under the curve
BAL	bronchoalveolar lavage
CAP	community-acquired pneumonia
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
ESBL	extended-spectrum $\beta$ -lactamase
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
ICU	intensive care unit
IFN	interferon
IL	interleukin
LRTI	lower respiratory tract infection
MAC	<i>Mycobacterium avium</i> complex
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
NTM	nontuberculous mycobacteria
PCR	polymerase chain reaction
PCT	procalcitonin
RCT	randomised controlled trial
TB	tuberculosis
TNF	tumour necrosis factor
VAP	ventilator-associated pneumonia
XDR	extensively drug-resistant