



ERS | *monograph*

# Pleural Disease

Edited by Nick A. Maskell,  
Christian B. Laursen,  
Y.C. Gary Lee and  
Najib M. Rahman

# Pleural Disease

---

Edited by  
Nick A. Maskell, Christian B. Laursen,  
Y.C. Gary Lee and Najib M. Rahman

Editor in Chief  
John R. Hurst

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*.

*ERS Monographs* are available online at [www.books.ersjournals.com](http://www.books.ersjournals.com) and print copies are available from [www.ersbookshop.com](http://www.ersbookshop.com)

Editorial Board: Mohammed AlAhmari (Dammam, Saudi Arabia), Sinthia Bosnic-Anticevich (Sydney, Australia), Sonye Danoff (Baltimore, MD, USA), Randeep Guleria (New Delhi, India), Bruce Kirenga (Kampala, Uganda), Silke Meiners (Munich, Germany) and Sheila Ramjug (Manchester, UK).

Managing Editor: Rachel Gozzard  
European Respiratory Society, 442 Glossop Road, Sheffield, S10 2PX, UK  
Tel: 44 114 2672860 | E-mail: [monograph@ersnet.org](mailto:monograph@ersnet.org)

Production and editing: Caroline Ashford-Bentley, Alyson Cann, Jonathan Hansen, Claire Marchant, Catherine Pumphrey, Kay Sharpe and Ben Watson

Published by European Respiratory Society ©2020  
March 2020

Print ISBN: 978-1-84984-115-3

Online ISBN: 978-1-84984-116-0

Print ISSN: 2312-508X

Online ISSN: 2312-5098

Typesetting by Nova Techset Private Limited

Printed by Bell & Bain Ltd, Glasgow, UK

All material is copyright to European Respiratory Society. It may not be reproduced in any way including electronic means without the express permission of the company.

Statements in the volume reflect the views of the authors, and not necessarily those of the European Respiratory Society, editors or publishers.



# Contents

---

Pleural Disease	Number 87 March 2020
Preface	v
Guest Editors	vi
Introduction	viii
List of abbreviations	xii
1. Epidemiology: why is pleural disease becoming more common? <i>Uffe Bodtger and Robert J. Hallifax</i>	1
2. The pathophysiology of breathlessness and other symptoms associated with pleural effusions <i>Rajesh Thomas, Y.C. Gary Lee and Eleanor K. Mishra</i>	13
3. <i>In vitro</i> and <i>in vivo</i> laboratory models <i>Xuan Yao and Nikolaos I. Kanellakis</i>	29
4. Radiology: what is the role of chest radiographs, CT and PET in modern management? <i>Laura Duerden, Rachel Benamore and Anthony Edey</i>	48
5. Thoracic ultrasound: a key tool beyond procedure guidance <i>Radhika A. Banka, Søren H. Skaarup, Rachel M. Mercer and Christian B. Laursen</i>	73
6. Pleural interventions: less is more? <i>Maged Hassan, Mohammed Munavvar and John P. Corcoran</i>	90
7. Pleural physiology: what do we understand and what should we measure in clinical practice? <i>Michael Gregory Lester, David Feller-Kopman and Fabien Maldonado</i>	105
8. Medical thoracoscopy in 2020: essential and future techniques <i>Valentina Pinelli and Amelia O. Clive</i>	120
9. Optimal diagnosis and treatment of malignant disease: challenging the guidelines <i>David T. Arnold, Mark Roberts, Momen Wahidi and Rahul Bhatnagar</i>	138
10. Pleural infection: moving from treatment to prevention <i>Eihab O. Bedawi and Najib M. Rahman</i>	155

11. Effusions related to TB	172
<i>Jane Alexandra Shaw, Liju Ahmed and Coenraad F.N. Koegelenberg</i>	
12. Pneumothorax: how to predict, prevent and cure	193
<i>Robert J. Hallifax, Steven Walker and Stefan J. Marciniak</i>	
13. Nonspecific pleuritis	211
<i>Christopher Kapp, Julius Janssen, Fabien Maldonado and Lonny Yarmus</i>	
14. Nonmalignant pleural effusions: are they as benign as we think?	218
<i>Steven Walker and Samira Shojaee</i>	
15. Mesothelioma: is chemotherapy alone a thing of the past?	232
<i>Anna C. Bibby, Kevin G. Blyth, Daniel H. Sterman and Arnaud Scherpereel</i>	
16. Novel technology: more than just indwelling pleural catheters	250
<i>Rachel M. Mercer, Robert J. Hallifax and Nick A. Maskell</i>	
17. The role of surgery	263
<i>Elizabeth Belcher and John G. Edwards</i>	
18. The specialist pleural service: when, why and who?	282
<i>Vineeth George and Matthew Evison</i>	



# Preface

John R. Hurst

The aim of an *ERS Monograph* is to provide accessible, evidence-based and state-of-the-art reviews in a specific area of respiratory medicine, in order to guide clinicians, stimulate research and, ultimately, improve patient care. As such, it is a pleasure and a privilege to present and recommend to you this latest *Monograph* on Pleural Disease. The Guest Editors Nick Maskell, Christian Laursen, Gary Lee, and Najib Rahman are world-renowned in the field, and together with an impressive list of distinguished chapter authors, they have delivered a really exciting work.



The science underpinning our understanding of pleural disease, and the evidence base for treatment, is expanding rapidly. Indeed, with the increasing need for specialist intervention, pleural disease has rightly become a subspeciality of respiratory medicine. The need for a new *Monograph* in the area was therefore great.

Whether you are a generalist, a pleural specialist, a researcher investigating pleural disease or a specialist from another area of medicine in which pleural disease is common, there will be topics of interest here, written and edited with care and expertise. The edition covers epidemiology, models of pleural disease, physiology, radiology and intervention, in addition, of course, to the major pleural pathologies, including pleural effusions and pneumothorax.

I would like to take this opportunity to congratulate the Guest Editors and authors for their excellent contributions; this *Monograph* is essential reading and should be the “go to” reference work on the topic for many years to come.

---

**Disclosures:** J.R. Hurst reports receiving grants, personal fees and non-financial support from pharmaceutical companies that make medicines to treat respiratory disease. This includes reimbursement for educational activities and advisory work, and support to attend meetings.



# Guest Editors

Nick A. Maskell



Nick A. Maskell undertook his Doctor of Medicine thesis on pleural diseases in Oxford (UK) prior to taking up a consultant post at North Bristol NHS Trust (Bristol, UK) in 2003. His research interests include clinical trials in pleural disease, mesothelioma and patient safety during pleural procedures. He leads the pleural service at the North Bristol NHS Trust and the Bristol Pleural Clinical Trials Unit at the University of Bristol (Bristol, UK).

Nick Maskell is the chief investigator for a number of pleural randomised controlled trials. He was Co-Chair of the 2018 British Thoracic Society (BTS) mesothelioma guidelines and is one of the Chairs of the forthcoming BTS pleural disease guidelines.

Christian B. Laursen



Christian B. Laursen is Head of Research and Associate Professor at the Respiratory Research Unit in the Department of Clinical Research at the University of Southern Denmark (Odense, Denmark). In his clinical work, he is a consultant at the Department of Respiratory Medicine at Odense University Hospital (Odense, Denmark).

Christian Laursen has a PhD in point-of-care ultrasound and his main research interest has been in the use of TUS within the field of respiratory medicine.

At an international and organisational level, he is Chair of the European Respiratory Society (ERS) Ultrasound group, is Co-Chair of the ERS Task Force on TUS, and is part of the committee organising the ERS TUS Training Programme.

## Y.C. Gary Lee

Y.C. Gary Lee is a professor and clinician scientist, and leads a clinical and translational research programme in pleural medicine. The programme is patient-focussed and uniquely integrates clinical and lab research arms with the most active pleural service in Australasia, which he directs. He has built major platforms that have delivered research with clinical impact. These include the multicentre Australasian MPE (AMPLE) clinical trial network (with centres from Australia and Asia), an allied health pleural research group and a bench-to-bedside pipeline, bringing new therapeutic targets to human trials.



His programme has trained over 20 clinical pleural fellows worldwide and has 10 (current and graduated) PhD research students.

Gary Lee currently works as a Professor of Respiratory Medicine at the University of Western Australia (Perth, Australia), and directs Pleural Services at the Respiratory Department of Sir Charles Gairdner Hospital (Perth, Australia). He is also the Head of the Pleural Medicine Unit at the Institute for Respiratory Health (Nedlands, Australia).

Gary Lee has over 280 publications with a total citation of over 9000, and an H-index of 52. He has delivered more than 300 invited lectures on pleural diseases in 30 countries.

## Najib M. Rahman

Najib M. Rahman runs the Oxford Pleural Unit (Oxford Centre for Respiratory Medicine, Oxford, UK), directs the Oxford Respiratory Trials Unit (Churchill Hospital, Oxford, UK) and conducts research in pleural disease at the Oxford Centre for Respiratory Medicine. Having qualified in Oxford, he underwent his medical senior house officer rotation at Queen's Medical Centre (Nottingham, UK), and re-joined Oxford as a Specialist Registrar in 2003. He undertook a DPhil and MSc in this period and was appointed Senior Lecturer and Director of the Oxford Respiratory Trials Unit, Consultant and Lead for Pleural Disease in Oxford in 2011. He was appointed as Associate Professor in 2014 and Professor of Respiratory Medicine in 2018.



Najib Rahman is currently involved in randomised and observational studies in pleural infection, pneumothorax and MPE intervention.

He is trained in thoracoscopy, TUS and clinical trials methodology, and has published over 180 papers with citations of >6000.



# Introduction

Nick A. Maskell<sup>1</sup>, Christian B. Laursen<sup>2,3</sup>, Y.C. Gary Lee<sup>4,5</sup> and  
Najib M. Rahman<sup>6,7,8,9</sup>



@ERSpublications

**Pleural diseases are common and associated with specialist procedures and a growing evidence base. This book, written by experts in the field, summarises up-to-date knowledge of the investigation, management and future directions of this exciting field.** <http://bit.ly/2uFiDCO>

Pleural diseases have been recognised since ancient times, with Imhotep providing the first known written description of pleural infection in 2700 BCE, and Hippocrates credited with the first descriptions of pleurisy and its treatment over 2000 years ago. These diseases are common, presenting as entities in themselves or as part of a wide-ranging number of other medical and surgical conditions. Pleural disease may therefore present to specialist respiratory physicians or to many other healthcare professionals, including surgery, general internal medicine, oncology, infectious diseases and oncology. There are currently over 65 recognised causes of pleural effusion, and in addition, other pleural conditions such as pleural thickening and pneumothorax represent a significant burden to the healthcare system and to patients. Largely due to the increasing evidence base and the provision of highly specialist procedures, pleural disease is now considered a distinct subspecialty, with a particular requirement for good liaison with the many other specialties it touches.

Given this vast array of causes and presentations, a thorough knowledge of the most up-to-date evidence in the diagnosis, investigation and management of patients with pleural conditions is essential for good medical practice. Historically, many patients with pleural effusion were simply drained to achieve some symptom benefit; the field is now far more nuanced, and understanding the evidence behind pathway-based management has become essential in order to provide accurate diagnosis and timely care to patient benefit. Perhaps uniquely, the last 20 years has seen a huge increase in our understanding of the mechanisms of pleural disease, and a significant number of studies have been published that bring high-quality evidence to the field, improving the diagnostic and treatment pathway on the basis of randomised trials that inform practice.

---

<sup>1</sup>Dept of Respiratory Medicine, Academic Respiratory Unit, University of Bristol, Bristol, UK. <sup>2</sup>Dept of Respiratory Medicine, Odense University Hospital, Odense, Denmark. <sup>3</sup>Dept of Clinical Research, Faculty of Health Science, University of Southern Denmark, Odense, Denmark. <sup>4</sup>Dept of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Australia. <sup>5</sup>Centre for Respiratory Health, School of Medicine, University of Western Australia, Perth, Australia. <sup>6</sup>Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. <sup>7</sup>Laboratory of Pleural and Lung Cancer Translational Research, Nuffield Dept of Medicine, University of Oxford, Oxford, UK. <sup>8</sup>Oxford Respiratory Trials Unit, Nuffield Dept of Medicine, University of Oxford, Oxford, UK. <sup>9</sup>National Institute for Health Research, Oxford Biomedical Research Centre, University of Oxford, Oxford, UK.

Correspondence: Najib M. Rahman, Oxford Pleural Unit, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE, UK. E-mail: [najib.rahman@ouh.nhs.uk](mailto:najib.rahman@ouh.nhs.uk)

Copyright ©ERS 2020. Print ISBN: 978-1-84984-115-3. Online ISBN: 978-1-84984-116-0. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Navigating this ever-changing field is the major purpose of this *ERS Monograph*, through summarised information on all major pleural diseases, written by experts in the field who have often contributed directly to the evidence base. The *Monograph* therefore covers aspects of background and investigation, including epidemiology [1], physiology and its relationship to symptoms and management [2], basic science and animal models of pleural disease [3], the role of radiology [4] and ultrasound [5], which is now considered an essential tool for pleural disease management. We have also included chapters on the major pleural entities including pleural infection [6], MPE [7], mesothelioma [8], pneumothorax [9], TB [10] and non-specific pleuritis [11]. Finally, liaison with other specialities and delivery of a pleural service has been addressed through chapters on surgery for pleural disease [12] and the key components of an active pleural service [13].

We hope that this *Monograph* will serve as an up-to-date resource for clinicians wishing to understand how to investigate and manage an array of pleural disease on the basis of evidence, thereby improving delivery of care, and expanding awareness of the development, biology and progression of pleural conditions. As a highly active research field, we also hope that this *Monograph* will inspire further studies and research programmes, and we have asked our authors to highlight areas in which evidence is lacking to promote this important goal.

It has been a privilege to edit this *Monograph*; the many contributing authors are leaders in their respective fields, and we feel this has created a highly focussed and relevant piece of work that will improve practice. We would like to thank the contributors for their input in the context of busy clinical and academic practices, and the European Respiratory Society for taking forward this much needed work.

## References

1. Boddart U, Hallifax RJ. Epidemiology: why is pleural disease becoming more common? *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 1–12.*
2. Thomas R, Lee YCG, Mishra EK. The pathophysiology of breathlessness and other symptoms associated with pleural effusions. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 13–28.*
3. Yao X, Kanellakis NI. *In vitro* and *in vivo* laboratory models. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 29–47.*
4. Duerden L, Benamore R, Edey A. Radiology: what is the role of chest radiographs, CT and PET in modern management? *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 48–72.*
5. Banka RA, Skaarup SH, Mercer RM, et al. Thoracic ultrasound: a key tool beyond procedure guidance. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 73–89.*
6. Bedawi EO, Rahman NM. Pleural infection: moving from treatment to prevention. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 155–171.*
7. Arnold DT, Roberts M, Wahidi M, et al. Optimal diagnosis and treatment of malignant disease: challenging the guidelines. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 138–154.*
8. Bibby AC, Blyth KG, Sterman DH, et al. Mesothelioma: is chemotherapy alone a thing of the past? *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 232–249.*
9. Hallifax RJ, Walker S, Marciniak SJ. Pneumothorax: how to predict, prevent and cure. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 193–210.*
10. Shaw JA, Ahmed L, Koegelenberg CFN. Effusions related to TB. *In: Maskell NA, Laursen CB, Lee YCG, et al. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 172–192.*

11. Kapp C, Janssen J, Maldonado F, *et al.* Nonspecific pleuritis. *In: Maskell NA, Laursen CB, Lee YCG, et al.* Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 211–217.
12. Belcher E, Edwards JG. The role of surgery. *In: Maskell NA, Laursen CB, Lee YCG, et al.* Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 263–281.
13. George V, Evison M. The specialist pleural service: when, why and who? *In: Maskell NA, Laursen CB, Lee YCG, et al.* Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 282–294.

---

**Disclosures:** N.A. Maskell reports receiving unrestricted research grants from Rocket and Becton Dickinson for the IPC plus HiSPEC and REDUCE studies. N.A. Maskell sat on the advisory board for Cook Medical. Y.C.G. Lee has received the following, outside the submitted work: support for acting as an advisory board member for BD/CareFusion; support for acting as an honorary advisor for Lung Therapeutic Inc.; drainage kits from Rocket Med Plc, provided without charge; and an unrestricted educational grant from Rocket Med Plc for multicentre clinical trials led by Y.C.G. Lee. N.M. Rahman reports receiving unrestricted research grants from Rocket and Becton Dickinson, sits on the advisory board of Biocube and acts as an external consultant to Lung Therapeutic Inc.

**Support statement:** Y.C.G. Lee is an Australian Medical Research Future Fund Practitioner Fellow. He has received research grant funding from the National Health and Medical Research Council of Australia, New South Wales iCARE Dust Disease Board, Sir Charles Gairdner Research Advisory Committee and the Cancer Council of Western Australia.



# List of abbreviations

---

ADA	adenosine deaminase
CT	computed tomography
IPC	indwelling pleural catheter
LDH	lactate dehydrogenase
MPE	malignant pleural effusion
MPM	malignant pleural mesothelioma
NEL	nonexpandable lung
NMPE	nonmalignant pleural effusion
PET	positron emission tomography
PSP	primary spontaneous pneumothorax
RCT	randomised control trial
SSP	secondary spontaneous pneumothorax
TB	tuberculosis
TGF	transforming growth factor
TUS	thoracic ultrasound
VATS	video-assisted thoracoscopic surgery