



ERS | *monograph*

Respiratory Diseases of the Newborn Infant

Edited by Ian P. Sinha,
Jayesh Mahendra Bhatt,
Alex Cleator and
Helen Wallace

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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*.

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Preface

John R. Hurst 

“For in every adult there dwells the child that was, and in every child there lies the adult that will be”.



This quote from *The Book of Lost Things* by John Connolly seems an apt way to start this book, or rather *Monograph*, addressing Respiratory Diseases of the Newborn Infant. Whether you are a neonatal clinician managing respiratory diseases, a scientist researching these areas or an adult clinician managing lungs that have been shaped by early life influences, this topic is of relevance to you.

I am therefore pleased to see publication of this *Monograph*, which will educate and inform you about both the development of the human lung in health, and respiratory diseases in the newborn. I warmly congratulate the Guest Editors Ian P. Sinha, Jayesh Mahendra Bhatt, Alex Cleator and Helen Wallace on proposing, commissioning and collating a comprehensive collection of review articles from a diverse group of authors. Sincere appreciation too, to the individual chapter authors for their valuable and authoritative contributions.

Included here are sections on structure and function of the newborn respiratory system, neonatal lung disease in preterm infants, and the developmental, structural and functional diseases of the respiratory system. You will also find important discussion about the socioeconomic determinants of early years respiratory health, newborn lung disease in low- and middle-income countries, the ethics of neonatal resuscitation and prophylaxis against RSV in high-risk infants.

I hope you enjoy the collection.

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

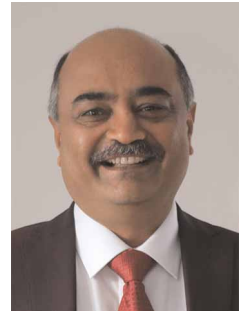
Ian P. Sinha

Ian P. Sinha is a consultant respiratory paediatrician at Alder Hey Children's Hospital (Liverpool, UK) and an Honorary Associate Clinical Professor at the University of Liverpool (Liverpool, UK). He is clinical lead for the National Asthma and COPD audit programme in the UK. His main clinical interests are neonatal lung disease and asthma, and his academic work relates to evidence-based medicine, clinical trials and health inequalities. He conducts clinics in BPD, structural lung disease and CDH.



Jayesh Mahendra Bhatt

Jayesh Mahendra Bhatt is a Consultant in Respiratory Paediatrics in a busy regional centre – Nottingham Children's Hospital (Nottingham, UK). He looks after children with a wide variety of respiratory problems, but his special interests are children with BPD, orphan lung diseases, CF, asthma, pre-school wheeze and chronic cough.



Jayesh established the BPD service in Nottingham. Since it was established, over 350 patients have been discharged on home oxygen.

Jayesh provides respiratory expertise for the nationally funded ataxia telangiectasia (A-T) clinic in Nottingham, which receives referrals from international centres. He chaired a European task force and produced a statement on multidisciplinary respiratory management in A-T. He is a member of the task force that produced the European Respiratory Society (ERS) statement on tracheobronchomalacia in children.

Jayesh is the immediate Past President of the British Paediatric Respiratory Society (2016–2019). He serves as paediatric respiratory specialist for the Paediatric Medicines Expert Advisory Group, part of the Commission on Human Medicines. He has also held various teaching and training roles nationally (previous Chair of the College Specialist Advisory Committee,

active Senior Examiner for the Royal College of Paediatrics and Child Health (RCPCH) clinical examination) and internationally for the ERS. He is a member of the paediatric HERMES exam committee for the ERS.



Alex Cleator

Alex Cleator is a senior neonatal subspeciality trainee. He is completing his training in tertiary neonatal intensive care units across Liverpool and Manchester (UK). His interests include neonatal echocardiography, quality improvement and medical education. He is passionate about teaching and sits on the Paediatric Trainee Education Committee in the UK's North West. He has recently set up a national virtual neonatal teaching programme for senior trainees and also directs the annual 4-day Pre-ST1 course at Alder Hey Children's Hospital (Liverpool, UK). Alex has found it a privilege to read, review and edit a *Monograph* of this calibre and is sure it will bring much joy to those who read it.





Helen Wallace

Helen Wallace is a Senior Lecturer in Physiology (teaching focused), specialising in respiratory physiology education, at the University of Liverpool (Liverpool, UK). She is the Physiology Curriculum Lead, and Research and Scholarship Lead for the Undergraduate Medicine Programme at the University of Liverpool. Her research interests include CF and smooth muscle physiology.



Introduction

Ian P. Sinha^{1,2}, Jayesh Mahendra Bhatt ³, Alex Cleator⁴ and Helen Wallace⁵

 @ERSpublications

The early years are crucial for lung health through the life course. This *Monograph* comprises state-of-the-art reviews about neonatal respiratory problems. <https://bit.ly/3h2V7pd>

Those of us lucky enough to work with babies know that our decisions and actions – whether right or wrong – have a lifelong impact for our patients and their families. This is profoundly evident with the respiratory system. Cramped within the thorax of adults reading this *Monograph* is a beautifully intricate respiratory system with an alveolar surface area the same as Wimbledon’s Centre Court, and capillaries that, end-to-end, would stretch from Liverpool to Rome. It is delicate enough to enable gas exchange that keeps us alive, yet robust enough to withstand all the adverse exposures thrown at it. This system begins to develop only a few weeks after conception, and continues to grow into adulthood. In this *Monograph*, we consider the respiratory system in the neonatal phase of this lifelong journey.

We begin with summaries of the structure and function of the respiratory system, and how it develops [1, 2]. We felt this would be an appropriate manner in which to start a *Monograph* about diseases of the newborn lung: without understanding how the respiratory system should work, we do not know how to support and protect it.

We move on to discuss the problems the respiratory system faces when babies are born prematurely [3–10]. One in 10 babies is born too early, and the limits of viability are moving earlier and earlier. In medical speciality terms, neonatology is still itself just a baby, but progress has been staggering – BPD was only described 50 years ago, and since then NICUs around the world have helped millions of premature babies, who are some of the most vulnerable and clinically unstable people imaginable. This has only been made possible by excellent research, service development, audit, education and collaboration. The goals of neonatal care are now not just to keep babies alive but to do so with the least possible damage, so that they can go on to live happy, healthy lives. We aimed to reflect that in this section of the *Monograph*, with chapters describing the respiratory care of preterm infants at birth and in the neonatal unit [3], and in clinic after they are discharged [4–10]. We also recognise that it is not always appropriate to keep babies alive at all costs;

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later in the *Monograph*, we have included a chapter around the ethics of neonatal resuscitation, which is a crucial topic to ensure our clinical actions are in the best interests of babies [11].

Of course, not all lung disease in the neonatal period relates to prematurity. In the next section of the *Monograph*, the chapters describe disorders of all aspects of the respiratory system in the neonatal period, including infections [12], and congenital and acquired problems affecting central drive, the large airways, lung parenchyma, the lymphatic system [13], the interstitium, and the diaphragm [14]. These are rare but significant diseases, which carry substantial morbidity and mortality, and necessitate close working between neonatologists and paediatricians. We have also included a chapter on CF in the neonatal period which, in keeping with this *Monograph*, describes a condition that is worlds apart from the condition we saw 20 years ago, and in which the goal is to get the early years right in order to enable a long and healthy life [15]. The chapters discussing radiological [16] and histological [17] investigations are included because these tests are so crucial to making the right diagnosis and helping guide treatment.

We finish with a broader view of some of the wider considerations around neonatal lung disease. Socioeconomic determinants of health in the neonatal period are an area in which we are developing a greater understanding, and this is a timely chapter given that health inequalities have been brought so sharply into focus during the coronavirus disease 2019 (COVID-19) pandemic [18]. We are also conscious of the fact that much discussion around health and neonatal care focusses on high-income settings, so we are delighted to share some insights into these problems in low- and middle-income countries [19]. The burden of preterm birth is no less profound here, and it is heartening to see collaborations and networks forming to help develop effective and cost-effective approaches in low- and middle-income countries.

We extend our immense thanks to the authors of these chapters, who we feel have done a stellar job. The authorship includes world-leading authorities, and up-and-coming stars in the field. We have convened a mixture of healthcare professionals and scientists, from around the world, and this has brought a diversity to the *Monograph* that is appropriate, given the global nature of the problems of neonatal lungs. We are grateful to the all the expert reviewers who gave up so much of their time to help us. The *Monograph* was compiled during the COVID-19 pandemic, and the efforts that our authors and reviewers have made during these challenging times is hugely appreciated. We are also very indebted to the excellent team at the *ERS Monograph*, comprising John R. Hurst (Editor in Chief), Rachel Gozzard (ERS Monograph Managing Editor) and Caroline Ashford-Bentley (ERS Editorial and Library Services Coordinator). Their enthusiasm and experience has kept this project on track, and their desire to develop a *Monograph* for babies has been inspiring. We have really enjoyed commissioning, reading, reviewing and editing the chapters, and we sincerely hope you find them as useful and interesting as we did.

References

1. Swarr DT, Deshmukh H, Zacharias W. *In utero* and post-natal development of the human lung and its defence mechanisms. In: Sinha IP, Bhatt JM, Cleator A, *et al.*, eds. *Respiratory Diseases of the Newborn Infant* (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 1–20.
2. LoMauro A, Zannin E. Respiratory physiology. In: Sinha IP, Bhatt JM, Cleator A, *et al.*, eds. *Respiratory Diseases of the Newborn Infant* (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 21–37.

3. Stepanovich G, Donn SM. Respiratory support in the delivery suite and the NICU. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 38–49.
4. Mižikova I, Alejandre Alcazar MA, Thébaud B. Pathogenesis of BPD. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 50–67.
5. Dassios T, Greenough A. Long-term sequelae of BPD. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 68–78.
6. Rose K, Woodland C, Murphy G, *et al.* Management of BPD: strategies to prevent short- and long-term complications following discharge from the NICU. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 79–88.
7. Jones CB, Johns M. Pulmonary hypertension in preterm infants. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 89–103.
8. Dhannapuneni RRV, Kong S-L, Subedhar NV. When and how to close patent ductus arteriosus in a preterm infant. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 104–117.
9. Walker WT, Everitt LH. Primary ciliary dyskinesia. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 118–132.
10. Everitt LH, Bhatt JM, Evans HJ. Structured approach to monitoring and weaning off home oxygen therapy in neonatal respiratory disease. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 133–146.
11. Haward MF, Danziger PD, Wilson S, *et al.* The ethics of resuscitation. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 350–360.
12. Primhak S, Myttarakis E, Whittaker E. Congenital infections of the respiratory tract. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 245–258.
13. Bush A, Mayell S, Pabary R. Pulmonary lymphangiectasia. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 197–212.
14. Boonthai A, Losty PD. Congenital diaphragmatic hernia. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 179–196.
15. Sadlers V, Woodland C, Walsh A, *et al.* Managing cystic fibrosis. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 259–272.
16. Kaleem M, Harave S. Chest radiology. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 301–319.
17. Ashworth MT, Hutchinson JC, Haini M. Histopathology of newborn lung disease. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 287–300.
18. Busuulwa P, Sharp A. Socioeconomic determinants of early years respiratory health, and the impact on later life. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 336–342.
19. Tongo OO, Iman ZO. Low- and middle-income countries. *In: Sinha IP, Bhatt JM, Cleator A, et al.*, eds. *Respiratory Diseases of the Newborn Infant (ERS Monograph)*. Sheffield, European Respiratory Society, 2021; pp. 343–349.

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List of abbreviations

BAL	bronchoalveolar lavage
BPD	bronchopulmonary dysplasia
CDH	congenital diaphragmatic hernia
CF	cystic fibrosis
CHD	congenital heart disease
CPAM	congenital pulmonary airway malformation
CPAP	continuous positive airway pressure
CT	computed tomography
ECMO	extracorporeal membrane oxygenation
FEV₁	forced expiratory volume in 1 s
FRC	functional residual capacity
GOR	gastro-oesophageal reflux
HRCT	high-resolution computed tomography
IUGR	intra-uterine growth restriction
MAS	meconium aspiration syndrome
MRI	magnetic resonance imaging
NEHI	neuroendocrine cell hyperplasia of infancy
NICU	neonatal intensive care unit
NRD	neonatal respiratory distress
P_{aCO_2}	arterial carbon dioxide tension
P_{aO_2}	arterial oxygen tension
PCD	primary ciliary dyskinesia
P_{CO_2}	carbon dioxide tension
PEEP	positive end-expiratory pressure
PH	pulmonary hypertension
PPHN	persistent pulmonary hypertension of the newborn
PVR	pulmonary vascular resistance
RDS	respiratory distress syndrome
RSV	respiratory syncytial virus
S_{pO_2}	oxygen saturation measured by pulse oximetry
TTN	transient tachypnoea of the newborn
VEGF	vascular endothelial growth factor