

Carlos Agustí  
Antoni Torres

# Pulmonary Infection in the Immunocompromised Patient

STRATEGIES FOR MANAGEMENT

 WILEY-BLACKWELL

---

# PULMONARY INFECTION IN THE IMMUNOCOMPROMISED PATIENT

## STRATEGIES FOR MANAGEMENT

---

*Editors*

**Carlos Agustí and Antoni Torres**

*Cap de Servei de Pneumologia i Allèrgia Respiratòria Hospital Clínic de Barcelona,  
Barcelona, Spain*

 **WILEY-BLACKWELL**

A John Wiley & Sons, Ltd., Publication

This edition first published 2009  
© 2009 John Wiley & Sons, Ltd

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

*Registered office:* John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

*Other Editorial Offices:*

9600 Garsington Road, Oxford, OX4 2DQ, UK  
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at [www.wiley.com/wiley-blackwell](http://www.wiley.com/wiley-blackwell)

The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

*Library of Congress Cataloguing-in-Publication Data*

Pulmonary infection in the immuno-compromised patient: strategies for management/edited by Carlos Agusti and Antoni Torres.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-470-31957-4 (cloth)

1. Respiratory infections. 2. Lungs—Infections. 3. Immunosuppression—Complications. I. Agusti, Carlos. II. Torres Marti, A. (Antoni)

[DNLM: 1. Lung Diseases—complications. 2. Opportunistic Infections—complications. 3. Immunocompromised Host. 4. Lung Diseases—therapy. 5. Opportunistic Infections—therapy. WF 600 P983495 2009]

RC740.P83 2009

616.2'4—dc22

2008036179

ISBN 978-0-470-31957-4

A catalogue record for this book is available from the British Library.

Set in 10.5/12.5pt Times by Thomson Digital, Noida, India

Printed in Singapore by Markono Print Media Pte. Ltd.

First printing – 2009

---

# **PULMONARY INFECTION IN THE IMMUNOCOMPROMISED PATIENT**

---

# Preface

The number of immunocompromised patients has increased over the last decade. Improvements in solid-organ and haematopoietic stem cell transplantation techniques, the expanded use of chemotherapeutic treatments and glucocorticoids use, and the appearance of new immunomodulatory therapies are some of the reasons that justify this increase. The success of the different transplant techniques has generated a great deal of interest in the management of immunocompromised patients among clinicians and basic scientists. The recognition and management of pulmonary complications that result from immunosuppression is a challenging task. The lungs may be injured directly through an infectious or toxic insult. Conversely, lung disease may result as a secondary event. Pulmonary complications in these patients require a multidisciplinary approach that often involves different specialists. This includes an appreciation of the epidemiology of post-transplant pulmonary complications, the differential diagnoses for these processes, the appropriate diagnostic explorations, and the specific treatments and potential interactions.

Our goals in this book are to provide an integrated discussion of progress in a comprehensive fashion. The general aspects of the lung immune defences are reviewed by Drs Patel and Koziel. Microbiological diagnosis and respiratory sampling in this population are a very important issues, related to the adequacy of treatment and mortality. Dr Ieven and Dr Baughman have reviewed both chapters in depth. The radiological approach to the diagnosis of respiratory complications is of particular importance and Dr Franquet presents the different tools that we currently have in our hands.

The remaining chapters of the book are dedicated to the review of respiratory infections regarding different types of immunosuppression: HIV infected patients, neutropenia, haematopoietic stem cell transplantation and chronic steroid treatment. Finally, intensive care management, antibacterial, antifungal and antiviral treatments are updated by experts in these subjects.

As in any multi-author book, the success of the endeavour relates to the commitment and creativity of the collaborating authors; we are extremely thankful for the hard and careful work of each of our contributors. We would also like to thank our colleagues at John Wiley & Sons, Ltd who provided outstanding support for this project.

**Carlos Agustí  
Antoni Torres**

# Contributors

## **Bekele Afessa**

Division of Pulmonary and Critical Care  
Medicine, Mayo Clinic College of Medicine,  
200 First ST, Rochester,  
MN 55905, USA  
Email: afessa.bekele@mayo.edu

## **José M. Aguado**

Unit of Infectious Diseases, University  
Hospital 12 de Octubre, Av. de Andalucía  
Km. 5,400. 28041 Madrid, Spain  
Email: jaguadog@medynet.com

## **Carlos Agustí**

Institut Clinic de Pneumologia ICPCT,  
Hospital Clinic, C/Villarroel, 170, 08036  
Barcelona, Spain  
Email: CAGUSTI@clinic.ub.es

## **Robert P. Baughman**

University of Cincinnati Medical Center,  
1001 Holmes, Eden Avenue, Cincinnati,  
OH 45267-0565, USA  
Email: baughmrp@ucmail.uc.edu

## **Natividad Benito**

Infectious Diseases Unit, Sant Pau Hospital,  
Sant Antoni Maria Claret 167, 08025  
Barcelona. Spain  
Email: nbenito@santpau.es

## **Oliver A. Cornely**

Uniklinik Köln, Klinik I für Innere Medizin,  
Klinisches Studienzentrum, Schwerpunkt  
Infektiologie II, Bachemer Strasse 86,  
50931 Köln, Germany  
Email: Oliver.Cornely@ctuc.de

## **Santiago Ewig**

Thoraxzentrum Ruhrgebiet, Kliniken für  
Pneumologie und Infektiologie,  
Evangelisches Krankenhaus Herne und  
Augusta-Kranken-Anstalt, Bergstrasse 26,  
44791 Bochum, Germany  
Email: ewig@augusta-bochum.de

## **Tomás Franquet**

Chief of Thoracic Imaging Section,  
Department of Radiology, Hospital de Sant  
Pau, St. Antoni Maria Claret, 167, 08025,  
Barcelona, Spain; and Department of  
Radiology, Universitat Autònoma of  
Barcelona, Barcelona, Spain  
Email: tfranquet@santpau.es

## **Mitchell Goldman**

Division of Infectious Diseases, Indiana  
University School of Medicine, Wishard  
Memorial Hospital (Room OPW 430),  
1001 W. 10th Street, IN 46202, USA  
Email: mgoldman@iupui.edu

## **Didier Gruson**

Division of Medical Intensive Care,  
University Hospital Bordeaux, Hôpital  
Pellegrin, Place Amelie Raba-Léon,  
F-33076 Bordeaux Cedex, France

## **Gilles Hilbert**

Division of Medical Intensive Care,  
University Hospital Bordeaux, Hôpital  
Pellegrin, Place Amelie Raba-Léon, F 33076  
Bordeaux Cedex, France  
Email: Gilles.hilbert@chu-bordeaux.fr

**Andy I.M. Hoepelman**

University Medical Center Utrecht,  
Division of Medicine, Department  
of Internal Medicine and Infectious  
Diseases, PO Box 85500,  
3508 GA Utrecht, The Netherlands  
Email: i.m.hoepelman@umcutrecht.nl

**Margareta Ieven**

Department of Medical Microbiology,  
Faculty of Medicine, University of Antwerp,  
Universiteitsplein 1 S3,  
B-2610, Wilrijk, Belgium  
Email: greet.ieven@uza.be

**Michael G. Ison**

Northwestern University Feinberg School  
of Medicine, Divisions of Infectious Diseases  
& Organ Transplantation, Transplant  
& Immunocompromised Host Infectious  
Diseases Service, 676 N. Street Clair  
Street Suite 200, Chicago, IL 60611, USA  
Email: mgison@northwestern.edu

**Henry Koziel**

Division of Pulmonary, Critical Care and  
Sleep Medicine, Kirstein Hall, Room E/KSB-  
23, Beth Israel Deaconess Medical Center  
and Harvard Medical School, 330 Brookline  
Avenue, Boston,  
MA 02215, USA  
Email: hkoziel@bidmc.harvard.edu

**Elyse E. Lower**

University of Cincinnati Medical Center,  
1001 Holmes, Eden Avenue, Cincinnati, OH  
45267-0565, USA

**Asunción Moreno-Camacho**

Infectious Diseases Service,  
Hospital Clinic, Villarroel 170,  
08036-Barcelona, Spain  
Email: amoreno@clinic.ub.es

**Jan Jelrik Oosterheert**

University Medical Center Utrecht,  
Division of Medicine, Department  
of Internal Medicine and Infectious  
Diseases, PO Box 85500, 3508  
GA Utrecht, The Netherlands  
Email: j.j.oosterheert@umcutrecht.nl

**Naimish Patel**

Division of Pulmonary, Critical Care  
and Sleep Medicine, Kirstein Hall, Room  
E/KSB-23, Beth Israel Deaconess Medical  
Center and Harvard Medical  
School, 330 Brookline Avenue,  
Boston, MA 02215, USA

**Steve G. Peters**

Division of Pulmonary and Critical Care  
Medicine, Mayo Clinic College of Medicine,  
200 First St, Rochester,  
MN 55905, USA  
Email: peters.steve@mayo.edu

**Julio C. Medina Presentado**

Cátedra de Enfermedades Infecciosas,  
Universidad de la República,  
Uruguay

**Ana Rañó**

Institut Clinic de Pneumologia ICPCT,  
Hospital Clinic, C/ Villarroel, 170,  
08036 Barcelona, Spain

**Maria J. Rüping**

Uniklinik Köln, Klinik I für Innere Medizin,  
Klinisches Studienzentrum, Schwerpunkt  
Infektiologie II, Bachemer Strasse 86,  
50931 Köln, Germany  
Email: Maria.Rueping@ctuc.de

**George A. Sarosi**

Department of Medicine, Indiana University  
School of Medicine, Indianapolis VAMC,  
Room C-7-018, 1461 West 10th Street, IN  
46202, USA  
Email: george.sarosi@med.va.gov

**Andrew F. Shorr**

Pulmonary and Critical Care Medicine,  
Washington Hospital Center, Room 2D-38,  
110 Irving Street, NW, Washington, DC  
20010, USA  
Email: afshorr@dnamail.com

**Ayman O. Soubani**

Division of Pulmonary, Allergy, Critical Care  
and Sleep, Wayne State University School of  
Medicine, Harper University Hospital, 3990  
John R- 3 Hudson, Detroit, MI 48201, USA  
Email: asoubani@med.wayne.edu

**Antoni Torres**

Institut Clinic de Pneumologia ICPCT,  
Hospital Clinic, C/Villarroel, 170, 08036  
Barcelona, Spain  
Email: ATORRES@clinic.ub.es

**Frederic Vargas**

Division of Medical Intensive Care,  
University Hospital Bordeaux, Hôpital  
Pellegrin, Place Amelie Raba-Léon,  
F 33076 Bordeaux, Cedex, France

**Jörg J. Vehreschild**

Uniklinik Köln, Klinik I für Innere Medizin,  
Klinisches Studienzentrum, Schwerpunkt  
Infektiologie II, Bachemer Strasse 86, 50931  
Köln, Germany  
Email: Janne.Vehreschild@ctuc.de



# Contents

<b>Preface</b>	<b>ix</b>
<b>List of Contributors</b>	<b>xi</b>
<b>1 Lung Immune Defences in the Immunosuppressed Patient</b>	<b>1</b>
<i>Naimish Patel and Henry Koziel</i>	
1.1 Introduction	1
1.2 Host defence function in health	1
1.3 Host defence function in select immunocompromised patients	7
1.4 Summary and future directions for this field	17
<b>2 Microbiological Diagnosis of Respiratory Infections in the Immunocompromised</b>	<b>29</b>
<i>Margareta Ieven</i>	
2.1 Introduction	29
2.2 HIV infection and <i>Mycobacterium tuberculosis</i>	30
2.3 HIV infection and non tuberculous mycobacteria (NTM)	33
2.4 HIV and <i>Pneumocystis jirovecii</i>	34
2.5 Infections in transplant patients or other immunodeficiencies	35
2.6 Concluding remarks	45
<b>3 Diagnosis of Pneumonia in Immunocompromised Patient</b>	<b>53</b>
<i>Robert P. Baughman and Elyse E. Lower</i>	
3.1 Introduction	53
3.2 Clinical assessment	55
3.3 Blood cultures	60
3.4 Sputum	60
3.5 Endotracheal aspirate	61
3.6 Non bronchoscopic bronchoalveolar lavage	63
3.7 Protected brush sample (PBS)	64
3.8 Bronchoalveolar lavage (BAL)	65
3.9 Transbronchial biopsy (TBB)	71
3.10 Surgical lung biopsy (SLB)	73
3.11 Sample processing	74
3.12 Clinical approach to pulmonary infiltrates in immunosuppressed patient	76
3.13 Conclusion	80

<b>4</b>	<b>Pulmonary Imaging in Immunocompromised Patients</b>	<b>95</b>
	<i>Tomás Franquet</i>	
4.1	Pulmonary infections in immunocompromised patient	95
4.2	Respiratory infections	100
4.3	Interventional procedures in patients with pneumonia	111
4.4	Summary	113
<b>5</b>	<b>Pulmonary Infections in HIV Patients in the Highly Active Antiretroviral Therapy Era</b>	<b>117</b>
	<i>Natividad Benito and Asunción Moreno-Camacho</i>	
5.1	Introduction	117
5.2	Epidemiology and etiology	118
5.3	Diagnosis	128
5.4	Prognosis	131
5.5	Conclusions	132
<b>6</b>	<b>Neutropenia</b>	<b>143</b>
	<i>Maria J. Rüping, Jörg J. Vehreschild, Santiago Ewig and Oliver A. Cornely</i>	
6.1	Introduction	143
6.2	Management of the neutropenic patient	149
6.3	Specific infectious diseases	160
<b>7</b>	<b>General Management of Suspected Pneumonia in the Solid Organ Transplant Patient</b>	<b>197</b>
	<i>Andrew F. Shorr</i>	
7.1	Introduction	197
7.2	Epidemiology	197
7.3	Differential diagnosis and non-infectious complications	199
7.4	Diagnostic approach	201
7.5	Conclusion	210
<b>8</b>	<b>Respiratory Infections Following Haematopoietic Stem Cell Transplantation</b>	<b>213</b>
	<i>Ayman O. Soubani</i>	
8.1	Immune system recovery after HSCT	215
8.2	Bacterial pneumonia	217
8.3	Invasive pulmonary aspergillosis	222
8.4	Cytomegalovirus	232
8.5	Community respiratory viruses	235
8.6	Non-infectious pulmonary complications	239
8.7	Conclusion	241

<b>9</b>	<b>Chronic Non-infectious Pulmonary Complications in Haematopoietic Stem Cell Transplantation</b>	<b>257</b>
	<i>Bekele Afessa and Steve G. Peters</i>	
9.1	Introduction	257
9.2	Bronchiolitis Obliterans (BO)	260
9.3	Bronchiolitis Obliterans organizing pneumonia (BOOP)	263
9.4	Idiopathic pneumonia syndrome (IPS)	265
9.5	Diffuse alveolar haemorrhage (DAH)	267
9.6	Peri-engraftment respiratory distress syndrome (PERDS)	269
9.7	Delayed pulmonary toxicity syndrome (DPTS)	270
9.8	Pulmonary cytolytic thrombi (PCT)	271
9.9	Other non-infectious pulmonary complications	272
9.10	Summary	274
 <b>10</b>	 <b>Pulmonary Infections in Patients on Chronic Glucocorticoid Treatment</b>	 <b>283</b>
	<i>Ana Rañó and Carlos Agustí</i>	
10.1	Introduction	283
10.2	Associated inflammatory response in pneumonia	283
10.3	Glucocorticoids: Mechanisms of action	284
10.4	Glucocorticoid therapy in clinical practice	286
10.5	Diagnostic approach	296
10.6	Empirical treatment of suspected pneumonia in patients receiving chronic GC therapy	298
10.7	Prognosis	298
10.8	Conclusions	299
 <b>11</b>	 <b>Intensive Care Management in the Immunocompromised Patient with Pulmonary Infiltrates</b>	 <b>305</b>
	<i>Gilles Hilbert, Didier Gruson and Frederic Vargas</i>	
11.1	Introduction	305
11.2	Invasive ventilation	306
11.3	Rationale for NIV	307
11.4	Mechanisms of improvement with NIV in immunocompromised patients with acute respiratory failure	308
11.5	Clinical studies	309
11.6	Equipment and techniques: particularities in immunocompromised patients	316
11.7	Predictive factors of NIV outcome	319
11.8	Conclusions	320

<b>12</b>	<b>Current Strategies and Future Directions in Antibacterial Treatment</b>	<b>325</b>
	<i>Jan Jelrik Oosterheert and Andy I.M. Hoepelman</i>	
12.1	Introduction	325
12.2	Farmacokinetics and pharmacodynamics	325
12.3	Antibacterial treatment options	331
12.4	Resistance	336
12.5	HIV related bacterial pulmonary infections	339
12.6	Length of treatment	342
12.7	Conclusions	343
<b>13</b>	<b>Current Strategies in the Treatment of Fungal Infections in the Intensive Care Unit Setting</b>	<b>349</b>
	<i>Mitchell Goldman and George A. Sarosi</i>	
13.1	Introduction	349
13.2	Antifungal therapies	350
13.3	The endemic fungi in the critical care unit	351
13.4	Other yeast infections in the critical care unit	358
13.5	Invasive mould infections in the critical care unit	363
13.6	Summary	375
<b>14</b>	<b>Current Strategies and Future Directions in Cytomegalovirus (CMV) Pneumonitis</b>	<b>383</b>
	<i>Julio C. Medina Presentado and José M. Aguado</i>	
14.1	Effects of CMV infection in immunocompromised patients	383
14.2	Pathophysiology of CMV pneumonitis	384
14.3	Risk factors for CMV pneumonitis	385
14.4	Pulmonary manifestations of CMV infection	386
14.5	Indirect respiratory effects of CMV infection	387
14.6	Diagnosis of CMV pneumonitis	387
14.7	Antiviral agents against CMV	388
14.8	Treatment of CMV pneumonia	390
14.9	Prevention of CMV pneumonia	393
<b>15</b>	<b>Antiviral Agents against Respiratory Viruses</b>	<b>401</b>
	<i>Michael G. Ison</i>	
15.1	M2 inhibitors	402
15.2	Neuraminidase inhibitors	407
15.3	Cidofovir	412
15.4	Ribavirin	414
15.5	Investigational agents	417

# Lung immune defences in the immunosuppressed patient

**Naimish Patel and Henry Koziel**

*Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA*

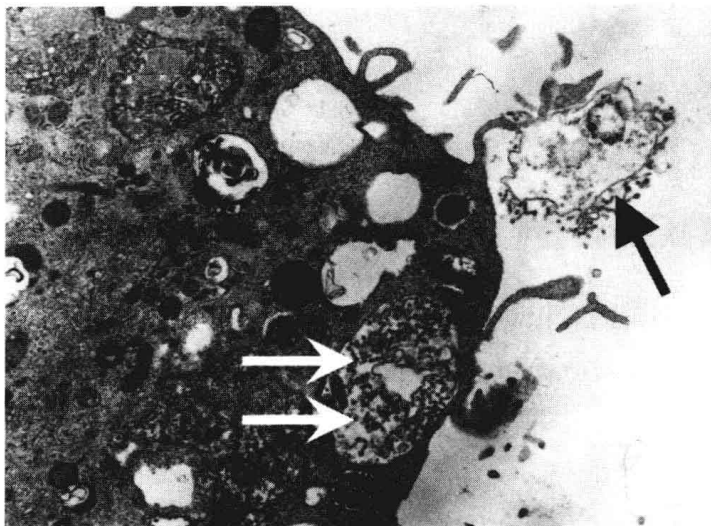
---

## 1.1 Introduction

The respiratory tract is constantly exposed to environmental elements and potential pathogens on a daily basis during the obligatory process of breathing or through subclinical aspiration. To avoid infectious disease pathogenesis in the respiratory tract, a number of elegant, complex and interdependent systems of host defence mechanisms are in place to prevent microorganism colonization of the respiratory epithelium, promote efficient microbe elimination, and maintain sterility of the lower respiratory tract in the healthy host. The layers of host defence mechanisms include physical barriers and secreted chemical factors (operant immediately), innate immune system (operant within minutes to hours), and the adaptive immune system (operant within days). Disruption of any of these components of lung host defence may lower critical threshold for microbial invasion and promote disease pathogenesis. Several acquired immunodeficiency states are associated with frequent and severe respiratory tract infections, and lung infections with opportunistic pathogens. This chapter will review the components of lung host defences in health with particular focus on human data, and discuss perturbations of host defences associated with select specific immunodeficiency states that may promote susceptibility and contribute to pathogenesis of respiratory tract infections.

## 1.2 Host defence function in health

In health, host defence function is provided by three critical integrated components, including (1) physical (or mechanical) and chemical mechanisms; (2) innate immunity; and (3) adaptive immunity. Physical and chemical mechanisms are present and operate continuously and serve as an immediate protective function to microbial challenge. For microbes that circumvent or bypass physical and chemical mechanisms, the innate



**Figure 1.1** Electron micrograph of human alveolar macrophage engaging pneumocystis organisms. Alveolar macrophages represent the predominant immune cells in the alveolar airspace, and critical effector cells in pathogen recognition and elimination. Pneumocystis trophic forms are seen in the process of engagement by macrophage pseudopodia (arrow) and ingested in the macrophage (arrows). *Pneumocystis* is a major opportunistic pathogen responsible for severe pneumonia in the immunocompromised host. (Electronphoromicrograph courtesy of Angeline Warner, Harvard School of Public Health, Boston, MA).

immune system represents another layer of the host defence response. Cellular and soluble components of innate immunity are constantly present, and are capable of recognizing, engaging and eliminating a broad array of microbes (through molecular recognition of conserved molecular patterns expressed by pathogens but not host cells) within minutes to hours of microbial challenge (Figure 1.1). Through a relatively limited number of secreted and host-cell associated recognition molecules, innate immunity can detect and generate an appropriate antimicrobial response to a broad range of bacteria, fungi and viruses. In health, the majority of daily microbial challenges are likely effectively cleared by these first two layers of host defences, as the majority of living creatures have only mechanical and chemical defences, and innate immunity. If clearance of microbes is not achieved despite activation of innate immune mechanisms, the adaptive immune system can be activated within days to provide an amplified and specific immune response. The adaptive immune response is composed predominantly of B-lymphocytes and T-lymphocytes that recognize specific antigen determinants on pathogens, and ultimately provide lifelong memory against repeated challenges with the same pathogen.

### Physical (mechanical) and chemical mechanisms of host defence

Physical barrier and mechanical host defence mechanisms, and chemical host defence mechanisms are constantly available for immediate action in the healthy host. Particle size in part determines fate, as particles and microbes generally exceeding  $5\text{ }\mu\text{m}$  can be entrapped as air flows through the tortuous channels of the nasopharynx and by nasal

hairs, and through inertial forces are impacted along the tonsillar pillars, glottis, trachea and branching bronchi and bronchioles. Entrapped particles and microbes may be expelled through coughing and sneezing mechanisms. The complex glycoprotein mucins lining the airway epithelial surfaces facilitate particle entrapment, and promote elimination by the cephalad respiratory epithelial cell ciliary movement that allows expectoration or swallowing of mucin-entrapped pathogens. In general, particles and potential pathogens smaller than 5  $\mu\text{m}$  can bypass these mechanical obstacles and gain access to the terminal bronchioles and alveoli. In addition, the respiratory epithelium serves as a critical barrier function. Similar to the function of the skin, the integrity of the mucosal surfaces including the respiratory epithelial cells and associated tight junctions remains critical to protective host defence function. The importance of these mechanisms, which operate constantly, is underscored by conditions that interfere with proper function such as mucociliary disease (dynein arm dyskinesia), bronchiectasis (anatomical distortion and scarring of epithelium), and neurological disorders or pharmacological agents that prevent effective cough reflexes.

A number of secreted airway products also contribute to antimicrobial functions by several mechanisms including direct antimicrobial activity, opsonization and agglutination (Table 1.1). Microbes that pass the physical and mechanical barriers may be eliminated by a range of chemical mediators that are constantly expressed and may be further induced. These mediators include molecules capable of direct antimicrobial effect (ex. lysozyme, lactoferrin, SLPI, complement,  $\alpha$ -,  $\beta$ - and  $\theta$ -defensins and cathelicidins), agents that inhibit microbial growth (ex. transferrin), and molecules that serve as opsonins that facilitate host cell recognition (ex. complement, fibronectin, collectins, SP-A, SP-D, IgA and IgG) or modulate host cell response to pathogens (ex. LPS-binding protein) (Crouch, 1998; Shepherd, 2002; Zhang and Koziel, 2002; McCormack and Whitsett, 2002). Lung collectins, such as surfactant components

**Table 1.1** Secreted antimicrobial factors in the airways.

---

Cathelicidin
Collectins
SP-A
SP-D
mannose binding protein (MBP), or mannose binding lectin (MBL)
Complement
Defensins ( $\alpha$ and $\beta$ )
Fibronectin, vitronectin
Ficolins
Immunoglobulins
IgA (predominant in upper airways)
IgG (predominant in lower airways)
Lactoferrin
LPS binding protein (LBP)
Lysozyme
Transferrin

---

SP-A and SP-D can serve as opsonins and enhanced phagocytosis, agglutination of microbes, and increased bacterial membrane permeability promoting pathogen elimination (Shepherd, 2002). Classical pathway complement proteins C3, C4, C1q and alternative complement pathway component factor B are expressed in the lung alveolar fluid (Watford, Ghio and Wright, 2000), and can provide opsonization of microbes in the respiratory tract.

### Innate immunity in the lungs

Innate immunity is an evolutionarily conserved ancient defence mechanism that comprised components that are constantly expressed and available, can be activated within minutes to hours, and can engage potential pathogens upon initial encounter (Martin and Frevert, 2005; Zaas and Schwartz, 2005). The principal cellular components of lung innate immunity include alveolar macrophages, neutrophils, NK cells, dendritic cells and eosinophils. Alveolar macrophages represent the predominant immune cell in the alveolar airspace, accounting for >85% of mobile cells in the alveoli. Neutrophils and eosinophils are generally not present in the alveoli but are recruited in response to chemotactic signals. Natural killer (NK) cells participate in early innate defence through cytotoxic activity against pathogen-infected cells and secretion of cytokines and chemokines that modulate subsequent steps in the adaptive immune response (Biron *et al.*, 1999). Recognition of microbial products by dendritic cells triggers functional dendritic cell maturation and leads to initiation of antigen-specific adaptive immune responses.

The innate immune response is mediated through interactions of microbes or microbial products with the germline-encoded host cell receptors. Innate immune cells such as alveolar macrophages recognize potential pathogens through surface recognition receptors such as mannose receptors,  $\beta$ -glucan receptors, scavenger receptors and Toll-like receptors (TLRs). The family of mammalian TLRs serves a critical role in the early host defence response through recognition of conserved molecules derived from microbial pathogens (Imler and Hossmann, 2001), leading to activation of NF- $\kappa$ B (Beutler, 2000) and MAP kinases (Barton and Medzhitov, 2003), and subsequent transcription and translation of host defence genes (Medzhitov, 2001; Aggarwal, 2003). Expressed on cells near mucosal portals of entry including macrophages (Jones *et al.*, 2001) dendritic cells (Muzio *et al.*, 2000) and lung epithelial cells (Armstrong *et al.*, 2004), mammalian TLR1 through TLR9 represent critical molecules in the first line of host defence to microbes in the lungs. Functional deficiency or genetic deletion of TLR4 increase susceptibility to *H. Influenza*, *S. pneumoniae*, and *K. pneumoniae* respiratory tract infection in murine models (Wang *et al.*, 2002; Branger *et al.*, 2004). Humans with TLR4 mutations are hyporesponsive to inhaled LPS (Arbour *et al.*, 2000). Alveolar macrophage and alveolar epithelial cells exhibit limited responsiveness to TLR4 stimulation due to relatively low membrane expression of the adaptor molecule MD-2 (Jia *et al.*, 2004; Kajikawa *et al.*, 2005). TLR5 polymorphism (TLR5<sup>392stop</sup>) in the ligand binding domain increases susceptibility of humans to *Legionella pneumonia* (Hawn *et al.*, 2003).



### *Regulation of activating pattern recognition receptors*

Control of inflammatory responses to infectious challenge is of particular importance for the continued normal gas exchange function of the lungs. In general innate receptor activation promotes proinflammatory responses, and cellular innate immune responses (such as macrophages) to antigenic challenge can result in enhanced innate immune response upon future rechallenge by the same antigen (Bowdish *et al.*, 2007). However, concurrent with innate surface membrane and intracellular receptor activation to promote proinflammatory responses, a number of counter regulatory molecules are also activated that likely limit the proinflammatory response to maintain homeostasis and limit collateral damage. Examples of these regulatory molecules for TLRs include: TOLLIP, IRAK-M, sMyD88, ST2, SIGIRR, SOCS-1, NOD2, MIF, PR105 and TAM receptor family (TYRO3, AXL and MER) (Rothlin *et al.*, 2007; Liew *et al.*, 2005). Whether these molecules are modulated by immunosuppressive agents or medical conditions associated with immune suppression is not completely understood.

### *Regulation of innate immunity by secreted products*

In addition to serving antimicrobial functions, soluble products can also serve to modulate cellular innate immune response in the lungs. For example, lung collectins such as SP-A can modulate the innate immune response, such as regulating macrophage pattern recognition receptor expression (Beharka *et al.*, 2002) and regulating the generation of macrophage reactive oxygen species (Crowther *et al.*, 2004). SP-A and SP-D bind LPS and prevent interaction with LBP and TLR4-CD14 complex on alveolar macrophages (Borron *et al.*, 2000; Sano *et al.*, 2000) and thus limit activating responses. In addition to hepatic production as an acute phase reactant, LBP is expressed by pulmonary artery smooth muscle cells (Wong *et al.*, 1995) and type-II alveolar epithelial cells (Wong *et al.*, 1995; Dentener *et al.*, 2000). Alveolar lining fluids contain high concentrations of sCD14 and LBP (Martin *et al.*, 1992; Martin *et al.*, 1997b) and thus can modulate TLR4-mediated signaling.

### *Epithelial cells*

Alveolar epithelial cells, in addition to providing a physical barrier function, also contribute to the innate immune response in the lungs. Epithelial cells express defensins HBD-1 and HBD-2 (McCray and Bentley, 1997; Hiratsuka and Al, 1998), and defensins also stimulate IL-8 production by epithelial cells (van Wetering *et al.*, 1997). Epithelial cells express TLRs and CD14, and can thus respond to microbial products analogous to TLR signaling in leukocytes, with release of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-8 and RANTES, GM-CSF, and TGF- $\beta$  (Diamond, Legarda and Ryan, 2000). Microbes and microbial components (such as lipopolysaccharide, peptidoglycan and flagella) can interact with innate receptors (such as TLR2) expressed on the apical surface of epithelial cells (often in the context of lipid rafts) (Soong *et al.*, 2004), which in turn can promote Ca<sup>2+</sup> release (Chun, Soong and Prince, 2006) and activate epithelial cell transcription factors such as