



ERS | *monograph*

α_1 -Antitrypsin Deficiency

Edited by Pavel Strnad,
Mark L. Brantly and
Robert Bals

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Editor in Chief
John R. Hurst

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Preface

John R. Hurst

This is an exciting time for those interested in AATD, and for those caring for people affected by AATD. A greater understanding of the science underpinning pathophysiological mechanisms is now directly translating into trials of innovative therapies, whilst our understanding of the role of augmentation therapy is changing with the recent publication of well-conducted trials using novel CT imaging end-points. Consequently, a *Monograph* addressing AAT is timely, and I congratulate the Guest Editors and authors for their excellent contributions; this should be essential reading and the “go to” reference work on the topic for many years to come.



AAT is a fascinating condition, affecting people at all ages, from neonates through to the elderly, and with protean manifestations that demand that the AAT specialist be aware not just of the respiratory manifestations of this condition, but also the assessment and management of liver disease and rarer manifestations, such as panniculitis and vasculitis. The diagnosis of AATD is all too often delayed and it is therefore essential that general pulmonologists and the wider multi-professional respiratory community are aware of when to suspect AATD, and how to test for it. Our patients deserve nothing less.

Finally, and in addition to thanking the Guest Editors and authors, I'd like to take this opportunity to thank the *Monograph* staff who work “behind the scenes” at the ERS Publications Office.

I warmly recommend this *Monograph* to you.

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Guest Editors

Pavel Strnad

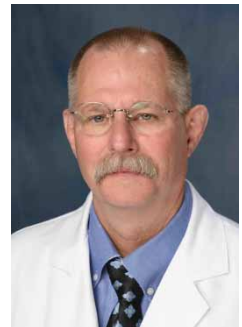
Pavel Strnad is an Associate Professor and Senior Physician at the University Hospital Aachen, Aachen, Germany. He received his medical and research training at the University of Mainz, Mainz, Germany, and at Stanford University, Stanford, CA, USA. His research interests include clinical and experimental hepatology, with a focus on intermediate filaments, iron metabolism and AATD. In 2016, he was named a Rising Star by United European Gastroenterology (UEG).



Pavel Strnad currently leads a European initiative for the study of AATD-associated liver disease. He is a member of the editorial boards of several journals, including *Gastroenterology*, *PLoS ONE* and *Digestive Diseases and Sciences*. He is also reviewer of rare diseases for the the European Association for the Study of the Liver.

Mark L. Brantly

Mark L. Brantly is a Professor of Medicine and Chief of Molecular Genetics and Microbiology in the Division of Pulmonary, Critical Care and Sleep Medicine at the University of Florida College of Medicine in Gainesville (FL, USA), where he is also the Alpha-1 Foundation Research Professor.



Mark L. Brantly earned his medical degree from the University of Florida College of Medicine. He completed a residency in internal medicine at Eastern Virginia Medical School in Norfolk (VA, USA), where he was also Chief Medical Resident, and a research fellowship in pulmonary disease at the National Institutes of Health (NIH) in Bethesda (MD, USA). Mark L. Brantly was a senior scientist at NIH for 13 years in the National Institute of Child Health and Human Development (NICHD) Human Genetics Branch and the National Heart, Lung, and Blood Institute (NHLBI) Pulmonary Branch.

Mark L. Brantly's clinical and research interests include AATD and lung inflammation and the molecular basis of lung and

liver disease. He has published more than 160 papers and book chapters. He is a member of the American Thoracic Society (ATS) and the American Society for Cell Biology (ASCB); an editor of *Genetic Testing and Molecular Biomarkers* and a former editor of *CHEST*; and is a reviewer for many journals, including *CHEST*, the *American Journal of Respiratory and Molecular Cell Biology*, *Hepatology*, the *New England Journal of Medicine*, the *Journal of Clinical Investigation* and the *American Journal of Respiratory and Critical Care Medicine*.

Robert Bals



Robert Bals studied medicine and biology at the Ludwig-Maximilian University Munich (Munich, Germany). He obtained doctoral degrees in both areas and worked as a post-doctoral fellow at the University of Pennsylvania (Philadelphia, PA, USA). Back in Germany, he continued his career as physician–scientist with board certifications in internal medicine, pulmonology, intensive care medicine, allergology, emergency medicine and sleep medicine. After spending 10 years at the Philipps University Marburg (Marburg, Germany), he was appointed director of the Saarland University’s Department of Pulmonology, where he focuses on teaching, research and patient care. In the research area, he covers preclinical and clinical research, and has contributed to 250 papers and several books. His research areas are inflammatory lung disease, asthma, COPD and infection. In the basic science laboratory, Robert Bals and his team investigate how the lung interacts with the environment, including smoke, allergens and microorganisms, with a focus on stem cell biology and regeneration. In clinical research, he performs investigations in COPD, asthma, pneumonia and cystic fibrosis.

Robert Bals established and manages the German AAT Registry and is member of the steering committee of COSYCONET.

Robert Bals is a former Chief Editor of the *ERS Monograph*.



Introduction

Pavel Strnad ^{1,2}, Mark Brantly³ and Robert Bals ⁴

 @ERSpublications

AATD is an inherited condition that primarily affects the lung and liver. This *ERS Monograph* provides a comprehensive guide to AATD, ranging from basic biology, diagnostics and clinical presentation to reports from affected patients. <http://bit.ly/2OeVD6H>

AAT is the most abundant serum antiprotease [1]. It is produced predominantly by liver hepatocytes that release it into the bloodstream and subsequently into other body compartments, where it exerts its function. The AAT gene has a number of mutations and as a consequence, one in 10 Caucasians carries an AAT variant giving rise to AATD [2]. To date, >120 AAT variants have been described and among them, Pi*Z is the most clinically relevant. Consequently, a homozygous carriage of the Pi*Z variant (Pi*ZZ genotype) is the characteristic cause of severe AATD. As Pi*Z mutation leads to the retention of AAT in hepatocytes, it is characterised by strongly diminished serum AAT levels [3, 4]. While severe AATD is a rare condition (with a frequency of 1:3000 in Caucasians), some AATD genotypes are more common, have modest reduction serum AAT levels and/or even AAT levels within a normal range [2, 3].

The resulting imbalance of antiprotease activity predisposes AATD individuals to proteolytic tissue damage and thereby to premature emphysema and COPD [5, 6]. In contrast, the accumulation of misfolded/polymerised AAT may lead to neonatal hepatitis and/or development of chronic liver disease, liver cirrhosis and HCC in adults [4, 7, 8]. While lung and the liver disease constitute the major causes of mortality in AATD, AAT is also a potent immunomodulatory protein and because of that, AATD subjects are predisposed to immune disorders such as panniculitis and granulomatous vasculitis [9].

More than 50 years after its initial description and despite the fact that it is fairly common, AATD remains a highly challenging condition. Although severe AATD can be easily recognised due to a five-fold reduction in serum AAT levels, only 10–15% of individuals are detected and it often takes many years and several physicians before the correct diagnosis is established [10]. To make things more difficult, many patients report symptoms that overlap with common respiratory diseases, such as asthma and bronchitis [6]. While the

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efficacy of AAT augmentation therapy in patients with a rapid decline in lung function has been supported by several randomised clinical trials, it is not reimbursed in many countries and an uncertainty prevails as to which AATD patient needs treatment and when the treatment should start [11]. The multiplicity of genotypes and the variable clinical presentation makes the counselling of AATD individuals challenging [12] and may result in both under- and overtreatment. Compared to lung involvement, liver affection has been studied even less and the burden of liver disease in AATD is only recently being appreciated [7, 8]. On the bright side, strong multinational registries have emerged and are likely to become particularly useful in uncovering the relevance of rare AATD genotypes as well as rare disease manifestations [13].

While liver transplantation still constitutes the only curative treatment option in end-stage liver disease related to AATD, multiple clinical studies are underway and use either RNA silencing or small molecules to counteract proteotoxic liver injury [8]. Moreover, the usefulness of AAT as an immunomodulatory protein is receiving more and more attention, and AAT augmentation therapy shows promise in the treatment of various immune-mediated disorders such as graft-versus-host disease [14].

Whether associated with severe deficiency alleles as a homozygous or heterozygous combination, AATD can be viewed both as a frequent condition and a rare disease. As a result, physicians of multiple disciplines, who systematically test for the presence of AATD, are confronted with many different genotypes as well as a highly variable clinical presentation. In addition, patients are often waiting for a correct diagnosis and are in need of evidence-based counselling explaining both the typical disease manifestations and the disease course [10, 12]. The knowledge and the standards of treatment also vary substantially between countries. With all this in mind, the goal of this *Monograph* is to provide a comprehensive and up-to-date overview, that covers most aspects of AATD. We have tailored the information to the physician taking care of lung and liver patients in daily practice, but have also included useful information for general practitioners who are responsible for the medical guidance of these patients. The book covers basic biology [1, 4, 5], genetics [2, 12], laboratory diagnostics [3] and the major organ manifestations. It describes the clinical presentation of AATD in both adults and children [6–9, 11], and includes chapters on genetic counselling, patient views and future therapies [10, 12, 14].

The authors of the individual chapters have produced a practice-guideline publication that comprises information on scientific background as well as application at the patient's bedside. We would like to thank all authors for their hard work and involvement in the writing of this publication. We hope that this book will raise awareness about this underdiagnosed condition and improve the everyday life of individuals with AATD.

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List of abbreviations

6MWT	6-min walk test
AAT	α_1 -antitrypsin
AATD	α_1 -antitrypsin deficiency
ALT	alanine aminotransferase
AST	aspartate aminotransferase
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
ELF	epithelial lining fluid
ER	endoplasmic reticulum
ERAD	endoplasmic reticulum-associated degradation
FEV₁	forced expiratory volume in 1 s
GGT	γ -glutamyltransferase
HCC	hepatocellular carcinoma
NE	neutrophil elastase
NF-κB	nuclear factor- κ B
TACE	tumour necrosis factor- α -converting enzyme
TNF	tumour necrosis factor
UPR	unfolded protein response

Common genotypes

Pi*M	wild-type AAT allele
Pi*MM	normal AAT genotype
Pi*SZ	genotype with compound heterozygous AAT mutation
Pi*Z/Pi*S	mutated AAT alleles
Pi*ZZ	classic, severe AATD genotype