Yong Chul Lee
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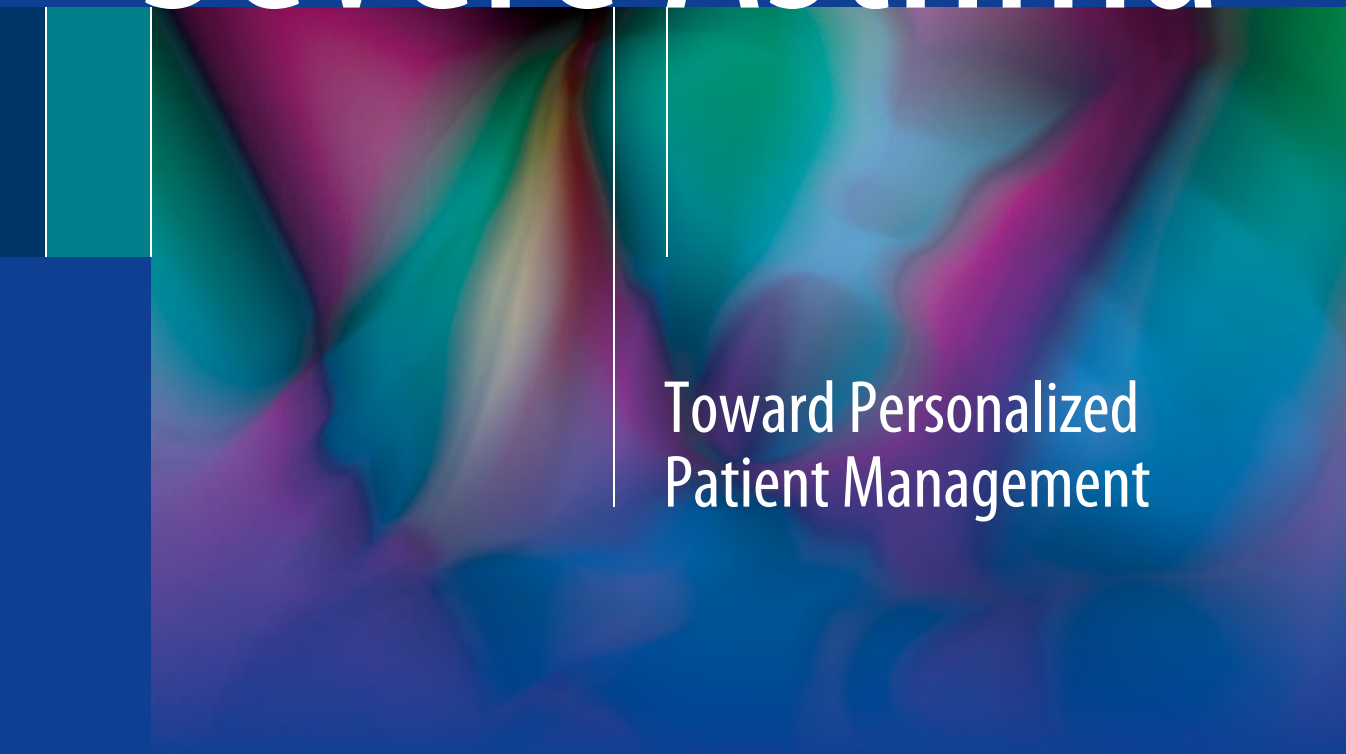
Editors

Severe Asthma



Toward Personalized Patient Management

Springer

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Preface

Considerable efforts of clinicians and researchers have been concentrated to define the concept of severe asthma and to understand its pathogenesis through a multifaceted approach. Nowadays, asthma is accepted as a heterogeneous disease; is defined as a clinical syndrome of intermittent respiratory symptoms triggered by viral upper respiratory infections, environmental allergens, or other stimuli; and is characterized by nonspecific bronchial hyperresponsiveness and airway inflammation. In addition, the term "severe asthma" is based on the characteristic of resistance to the current standard treatment including inhaled steroid. Asthma heterogeneity is most easily recognized in severe asthma, where patients have diverse symptom profiles and altered responses to medications. Thus, identification of various phenotypes of severe asthma and understanding their pathogenesis are expected to provide a cornerstone to develop novel therapeutics, fulfilling the unmet needs of patients suffering from severe asthma. This book presents state-of-the-art knowledge on severe asthma, covering general information, clinical significance, pathogenesis, diagnostic modalities, and therapeutics. In particular, for readers to grasp the content easily, basic experimental data and clinical information are simultaneously provided with intuitive schematic figures. Tips on management as well as cutting-edge preclinical and clinical data of severe asthma will be very helpful for medical students, researchers, general physicians, specialists, and related paramedical staff. We hope this book can be a useful guide for your research and medical practice and understanding the changes of concept of asthma and its pathophysiology.

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Part I

Overview of Severe Asthma

Basics of Severe Asthma in Clinical Practice

1

Jae Seok Jeong and Yong Chul Lee

1.1 Definition of Severe Asthma

Bronchial asthma is now widely recognized as a heterogeneous clinical syndrome consisting of various disease phenotypes. Each asthma phenotype may have distinct observable molecular, cellular, morphological, functional, and clinical features [1, 2], all of which can be possibly integrated into specific biological mechanisms, called as endotypes [3]. Although differentiating asthma into various phenotypes/endotypes remains speculative so far, these concepts of separation may be useful in characterizing and predicting disease severity, progression, and response to general and specific therapies including biologic medications [4]. This is particularly important for severe asthma patients who are refractory to current standard therapies including inhaled and systemic corticosteroids (CS) and bronchodilators. Because these patients account for a significant proportion of health-care expenditure of asthma [5], recognizing the heterogeneous nature of asthma, especially severe asthma, may enable us to develop safe and effective phenotype-targeted biological therapies.

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Importantly, appropriate clinical phenotyping of severe asthma patients, in turn, inevitably requires standardized definition of severe asthma which can be applied to a wide range of populations all over the world. There have been numerous proposed definitions for severe asthma in association with several respiratory and medical societies. It has been also referred as difficult, therapy-resistant, as well as refractory asthma. Firstly, to properly define the clinical situation of severe asthma, a prior diagnosis of asthma should be made. Then, clinical symptoms of bronchial asthma should persist despite the maximal treatment of current therapies. In general, previous studies have suggested that failure of controlling asthma symptoms despite the prescription of high-dose inhaled corticosteroids (ICS) may be a minimum requirement of definition for severe asthma, and numerous recent works have also stipulated the therapeutic level of severe asthma as those equivalent to high-dose therapies [6] (*see* Table 1.1).

The first definitions of severe asthma were proposed in 1999 and in 2000 by European Respiratory Society (ERS) [7] and American Thoracic Society (ATS) [8], respectively (*see* Table 1.1). These definitions of severe, difficult-to-treatment, or therapy-resistant asthma then were incorporated into several US and European severe asthma cohorts to further understand the pathophysiology, to improve management, and to develop novel therapy for the disease. These cohorts include Severe Asthma Research Program

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Table 1.1 Definitions for severe asthma in various medical and respiratory societies

European Respiratory Society (ERS) task force in [7]	*Difficult/therapy-resistant asthma* can be defined as follows: Poorly controlled asthma with continuous requirement for short-acting β2-agonists despite delivery of a reasonable dose of inhaled corticosteroids (ICS); diagnosis on the basis of this definition can be established by means of follow-up of and care for the patient by a respiratory specialist for a period of ≥6 months
American Thoracic Society (ATS) workshop in [8]	Definition of *refractory asthma* requires one or both major criteria and two minor criteria: *Major characteristics*: 1. Treatment with continuous or near-continuous (≥50% of year) oral corticosteroids (CS) 2. Requirement for treatment with high-dose ICS *Minor characteristics*: 1. Requirement for daily treatment with a controller medication in addition to ICS 2. Asthma symptoms requiring short-acting β-agonist use on a daily or near-daily basis 3. Persistent airway obstruction 4. One or more urgent care visits for asthma per year 5. Three or more oral steroid "bursts" per year 6. Prompt deterioration with ≤25% reduction in oral or ICS dose 7. Near-fatal asthma event in the past
World Health Organization (WHO) in [14]	*Severe asthma* can be defined as follows: Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children) *Severe asthma* includes three groups, each carrying different public health messages and challenges: 1. Untreated severe asthma 2. Difficult-to-treat severe asthma 3. Treatment-resistant severe asthma. This group includes the following: • Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and CS-resistant asthma • Asthma for which control can be maintained only with the highest level of recommended treatment
ERS/ATS guidelines in [2]	Definition of *severe asthma* for patients aged ≥6 years: Asthma which requires high-dose ICS and long-acting β2-agonists [LABA] or leukotriene modifier/theophylline for the previous year or systemic CS for≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy Uncontrolled asthma defined as at least one of the following: • Poor symptom control: asthma control questionnaire (ACQ) consistently >1.5, asthma control test (ACT) <20 (or "not well controlled" by National Asthma Education and prevention program (NAEPP)/global initiative for asthma (GINA) guidelines) • Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year • Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year • Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal) Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)
British Thoracic Society (BTS)/Scottish intercollegiate guidelines network (SIGN) guideline in [6]	*Difficult asthma* is defined as follows: Persistent symptoms and/or frequent asthma attacks despite treatment with high-dose therapies or continuous or frequent use of oral steroids High-dose therapies include (for inadequately controlled asthma on a combination of short-acting β2-agonists as required, medium-dose ICS, and an additional drug usually a LABA): • Increase the inhaled corticosteroids to high dose (adults) *or* • Add a leukotriene receptor antagonist *or* • Add a theophylline *or* • Add slow-release β2 agonist tablets, although caution needs to be used in patients already on long-acting β2 agonists *or* • Add tiotropium (adults)

(SARP) [9] initiated by National Heart, Lung, and Blood Institute (NHLBI) and a European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) [10]. Although there were numerous differences regarding national health-care system, races, and socioeconomic status among each study population, clinical phenotypes of patients with severe asthma were quite similar in those studies. Subject with severe asthma were less atopic, had persistent symptoms despite high-dose controller and reliever medications, and had lower lung function with incomplete reversibility after bronchodilation [9–11]. Furthermore, diverse approaches on asthma phenotyping using more statistical methods (e.g., cluster analysis) [12] emphasized the heterogeneity of severe asthma phenotypes in these cohort populations [13].

Meanwhile, with the increasing needs of a definition of asthma severity that can be applied worldwide, the World Health Organization (WHO) published document on uniform definition of asthma severity, control, and exacerbation in 2010 [14]. In the document, it was described that components of asthma severity comprises four components: *level of control* (including current clinical control over previous 2–4 weeks and exacerbation over previous 6–12 months), *level of current treatment* (including inhalation technique and compliance), *responsiveness to treatment* (including relative insensitivity to CS and CS dependency), and *risk* (including likelihood of exacerbations, development of chronic morbidity such as progressive decline in lung function, and risk of adverse reactions from asthma medication). According to the document, severe asthma can be defined by the *level of clinical control* and *risks* as "uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)." The significance of the uniform definition of WHO is that it is applicable in all countries regardless of the availability to the current asthma medication and socioeconomic status, thereby allowing appropriate epidemiologic assessment of severe asthma worldwide (*see* Table 1.1).

The most recent definitions of severe asthma in several up-to-date guidelines resemble those of previous works in many ways (*see* Table 1.1). For instances, in the international ERS/ATS guidelines reported in 2014, severe asthma for patients aged ≥6 years is defined that asthma which requires high-dose ICS and long-acting β2-agonists [LABA] or leukotriene modifier/theophylline for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy [2]. In addition, British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guideline in 2016 defines difficult asthma as persistent symptoms and/or frequent asthma attacks despite treatment with high-dose therapies or continuous or frequent use of oral steroids [6]. Although there are still many different definitions for severe asthma available and difficulties in making an accurate definition for severe asthma, numerous data based on these definitions consistently demonstrate the heterogeneity of severe asthma in populations with asthma [15, 16]. Furthermore, with increasing appreciation on the heterogeneity of severe asthma, recent phenotyping of severe asthma in regard to natural history, clinical and physiological features, and underlying molecular pathobiology with predictable response to specific therapy have made the precision medicine possible. For example, newer guidelines recommend anti-interleukin (IL)-5 monoclonal antibody particularly in adults and adolescents (≥12 years) with severe eosinophilic asthma [2, 17]. Indeed, these conceptual advancements reflect the beginning of the new era in severe asthma management according to phenotype/endotype-driven approaches.

1.2 Epidemiology and Clinical Significance of Severe Asthma

Bronchial asthma is a major health problem all over the world, affecting 1–18% of the population in different countries [17]. It is estimated that approximately 300 million people have asthma

globally including nearly 26 million asthmatic patients in the USA [18]. In real life, bronchial asthma may be associated millions of lost school and work days, long-term controller medication, regular and urgent health-care utilization, and significant comorbidities. Accordingly, annual economic burden of the bronchial asthma is reported to be about 56 billion dollars in the USA [19]. In this regard, severe asthma has growingly become major concern as it accounts for a disproportionately large proportion of asthma-associated health-care expenditures, while representing only a minority of total patients with asthma.

The exact prevalence of severe asthma is still unclear partly owing to the inhomogeneity in the definition and patient characteristics with different age, sex, race, and regional profiles across many population studies. For example, whereas the prevalence of severe asthma, defined strictly as the disease remains uncontrolled despite addressing and removing all possible factors that might aggravate the underlying disease, was shown to be only 3.6% among total asthmatics in the population study from the Netherlands [20], the prevalence of severe asthma according to the definition from the Global Initiative for Asthma (GINA) guidelines in Sweden was reported to be as high as 17.8% of adult asthmatics [21]. Despite these inconclusive results from numerous population studies, experts generally regard that severe asthma is a rare disease entity and estimated prevalence of severe asthma might be up to 5–10% of adult patients with asthma.

Furthermore, there is limited information regarding the exact disease burden and health outcomes of severe asthma to date. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, initiated in 2001, was a multicenter observational cohort study which primarily aimed to collect data to evaluate the natural history of severe or difficult-to-treat asthma. In this study, inclusion of severe or difficult-to-treat asthma patients was based on the physician's assessment of asthma severity and additional criteria determined by the frequency of urgent care visits and/or the use of multiple controller medications [22]. Results of the TENOR study showed that severe or difficult-to-treat asthma, regardless of age, was associated with evidently high rates of health-care use despite the use of multiple long-term controller medications. For instance, at the time of enrollment, more than 50% of patients were on three or more long-term controller medications [23]. However, 52.8% of adults (≥18 years of age), 43.6% adolescents (13–17 years of age), and 53.4% of children (6–12 years of age) reported a corticosteroid burst (short courses of corticosteroid therapy) in the 3 months before the enrollment. In addition, 15.2% of adults, 19.1% of adolescent, and 25.5% of children reported an emergency department visit in the 3 months before the baseline [22]. Similarly, in the SARP, another large cohort of severe asthma in which primary goal was to characterize subject with severe asthma to understand pathophysiologic mechanisms of the disease, severe asthma patients were older with longer disease duration, more daily symptoms, urgent health-care utilization especially intensive care, and comorbidities such as sinopulmonary infections compared to non-severe asthma [9]. In fact, substantial differences exist between two studies. Firstly, the definition of severe or difficult-to-treat asthma differs from each other. While SARP adopted the definition of severe asthma from ATS Workshop in 2000 [8], physicians were not instructed to use specific guidelines and independently assessed severity of asthma in TENOR study. Secondly, SARP included all asthma severities, whereas approximately 96% of the cohort in TENOR study was considered to have difficult-to-treat asthma based on the need for multiple drugs, occurrence of frequent and severe exacerbations, inability to avoid triggers, and complex treatment regimens [24]. Nevertheless, the similar results from these two large cohorts emphasize the medical burden of severe asthma and thus the urgent need of novel therapeutic approaches.

Another significance of TENOR is that it involves quite a large number of populations over 4000 patients, and thus numerous subgroups having different clinical phenotypes can

be identified. For example, patients with aspirin sensitivity are associated with increased disease severity and, possibly, remodeling of the lower airways [25]. Moreover, one of TENOR analyses found that persistent airflow limitation (defined as post-bronchodilator FEV_1/FVC ratio of ≤70% at two annual consecutive visits) in patients with severe or difficult-to-treat asthma is highly prevalent up to 60% and is related to several clinical and demographic factors, including older age, male, black ethnicity, current or past smoking, aspirin sensitivity, and longer duration of asthma [26]. In another analysis, increased weight is associated with worse asthma-related outcomes (e.g., poorer disease control, worse quality of life, and greater need for oral corticosteroids bursts) [27], and female patients with IgE-mediated allergic asthma are worse than the disease of male in terms of disease severity, quality of life, health-care use, disease control, and allergic comorbidities [28]. Taken together, heterogeneous nature of severe or difficult-to-treat asthma demonstrated in TENOR study, along with the similar findings in SARP [16], highlight that identification of important severe asthma phenotypes may reduce the burden of the disease and improve severe asthma-related health outcomes through phenotype-targeted therapeutic approaches.

However, physicians should be aware of numerous comorbidities and confounders that can change asthma phenotypes before commencing phenotype-based approaches in severe asthma, although there has been substantial advancement in identifying phenotypes through less biased and more statistically based methodology [1] (*see* Table 1.2).

Current smoking or exposure to second-hand smoke may be associated with the corticosteroid-resistant inflammatory process in the lung, thereby making asthma more difficult-to-treatment [29]. Moreover, environmental tobacco smoke exposure on asthmatic individuals has been reported to be associated with lower lung function and quality of life and greater risk for exacerbation, health-care use, and airway hyperresponsiveness, thereby leading to adverse asthma-related outcomes [30].

Table 1.2 Comorbidities and confounders that may impact on phenotypes of severe asthma

History of smoking or second-hand smoke
Environmental exposures: molds, viruses, bacteria, and ozone
Occupational exposures
Hormonal influences: premenstrual, menarche, menopause, pregnancy, and thyroid disorders
Obesity
Obstructive sleep apnea
Rhinosinusitis/nasal polyps
Vocal cord dysfunction
Gastroesophageal reflux disease
Psychological factors: personality trait, symptom perception, anxiety, and depression
Drugs: nonsteroidal anti-inflammatory drugs, β-adrenergic blockers, and angiotensin-converting enzyme inhibitors
Nonadherence to treatment and poor inhaler technique

Early-life exposures to diverse pathogenic microbes including molds, viruses, and bacteria may also relate to severe asthma. Particularly, fungal exposure has been reported to be associated with the development [31] and exacerbation of bronchial asthma [32–35]. Furthermore, epidemiologic studies have shown that fungal sensitization is found more often in asthmatic patients with increasing severity, and fungal sensitivity is a possible precipitating factor for life-threatening asthma [36–38]. Based on these knowledges, severe asthma with fungal sensitization (SAFS) has been proposed to investigate a particular phenotype of severe asthma with therapeutic implications in clinical trials [39]. Notably, several recent guidelines of severe asthma recommend allergen testing to molds in patients with difficult asthma and recurrent hospital admission [6]. In addition, viral and bacterial exposure may predispose susceptible individuals to initiate and exacerbate allergic inflammation in the lung [40].

Occupational exposure to various chemicals and compounds is also known to initiate and worsen asthma in susceptible patients [41], and changes in the level of female sex hormones and thyroid hormones may impact on clinical course of bronchial asthma [42]. Other common comorbidities of severe asthma include obesity, obstructive sleep apnea, rhinosinusitis/nasal polyps,

vocal cord dysfunction, gastroesophageal reflux disease, and psychologic problems such as anxiety and depression, all of which can change clinical manifestation of severe asthma. Lastly, patient's adherence to the treatment and concurrent use of other medications targeting coexisting disorders such as nonsteroidal anti-inflammatory drugs, β-adrenergic blockers, and angiotensin-converting enzyme inhibitors may modify the observable characteristics of severe asthma.

1.3 Specific Considerations in Severe Asthma

1.3.1 Fungal Sensitization/Allergy-Associated Clinical Conditions

Respiratory fungal exposure is constant in humans, and fungal spores constitute the largest proportion of aerobiological particles in usual air environment [43]. Similarly, impact of respiratory fungal exposure on the clinical courses of bronchial asthma has been widely reported in the literatures for a long time [39], and fungal exposure has long been regarded as a precipitating factor for severe asthma phenotype. For example, inhalation of environmental fungal spores also led to the exacerbation of bronchial asthma control illustrated by daily variation in the patient symptoms, aggravation of the underlying pulmonary function (e.g., variations in peak expiratory flow), and increased incidence for critical events such as hospital admission and asthma-related deaths [32–35].

Furthermore, fungi can colonize, actively germinate, and infect the human respiratory tract. Moreover, they can produce a wide array of enzymes and toxins closely implicated in pathologic process such as allergic inflammation [44]. Therefore, fungi can potently sensitize and induce host immune response, in contrast to other inhalable aeroallergens such as house dust mites (HDMs), animal dander, and grass pollen [39, 45]. Consistent with this knowledge, over 50% of patients with severe asthma may be sensitized to one or more fungi [46], and, particularly, *Aspergillus fumigatus* and *Alternaria alternata* are common airborne fungi implicated in severe asthma [39, 47]. Numerous epidemiologic studies have also demonstrated that fungal sensitization is found more often in asthmatic patients with increasing severity, and fungal sensitivity is a possible precipitating factor for life-threatening asthma [36–38].

In general, fungal sensitization/allergy-associated conditions refer to exaggerated immune responses against non-pathogenic fungi, which are mainly orchestrated by IgE and type 2 helper T (T_H2) cells. In contrast, the term of fungal infection can be applied when there is evidence of tissue dysfunction directly associated with the growth and invasion of pathogenic fungi in the host. There are several important disease entities that represent severe end of the fungal sensitization/allergy-associated conditions, including allergic bronchopulmonary aspergillosis (ABPA)/allergic bronchopulmonary mycosis (ABPM) and SAFS (*see* Table 1.3) [48]. Whereas ABPA was firstly reported in 1952, the definition of SAFS was introduced in 2006 [39] and has been used in clinical trial settings to demonstrate the possible role of antifungal therapy for treating a particular phenotype of severe asthma associated with fungi [49]. Historically, early data on fungal allergy were mainly derived from researches of ABPA/ABPM. However, ABPA/ABPM may be a severe end of the spectrum of allergic inflammation against fungi that are often associated with

Table 1.3 Definitions of ABPA/ABPM and SAFS

Disease entity	Definition
ABPA/ABPM	Asthma or cystic fibrosis (often that are not well controlled) Elevated total serum IgE (> 1000 IU/ml) Elevated IgE and/or IgG antibodies Immediate skin test positive Serum eosinophilia (> 1000 cells/μl) Presence of central (or proximal) bronchiectasis Radiographic pulmonary infiltrates
SAFS	Severe asthma Elevated total serum IgE (< 1000 IU/ml) Sensitization to any fungus by skin prick test or specific IgE