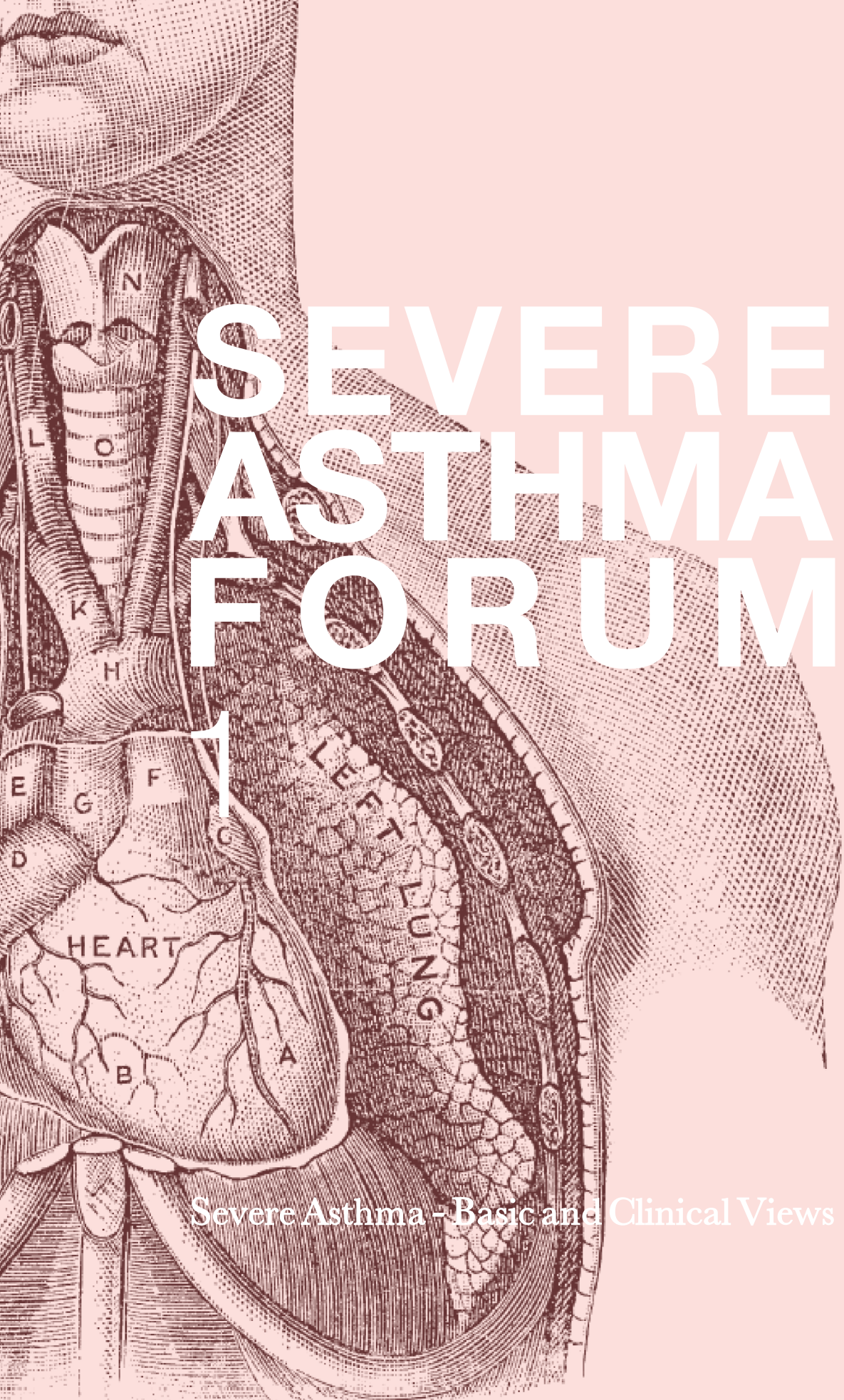

SEVERE ASTHMA FORUM

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Severe Asthma – Basic and Clinical Views

SEVERE ASTHMA FORUM
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The Severe Asthma Forum book series intends to publish scientific monographs based on papers at the annual scientific conference Severe Asthma Forum - SAF, South-eastern meeting (Slovenia, Croatia, Serbia). The monographs will be published during the annual SAF conference, and they will bring the latest research and reviews in the field of diagnosis and treatment of asthma.


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SEVERE ASTHMA FORUM

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Severe Asthma - Basic and Clinical Views

Edited by Sabina Škrgat

2022

moji mami
to my mother

Contents

Prvi monografiji o hudi astmi na pot
Predgovor

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Astma je bolezen dihalnih poti, ki v svojih hudih oblikah za bolnika predstavlja težko breme – zaradi potrebe po stalnem zdravljenju, zavoljo stranskih učinkov zdravil in pridruženih bolezni ter poslabšanj. In zaradi ves čas prisotne bojazni pred ponovnim »izbruhom«. Bolniki zato nimajo polnega življenja, kot bi ga želeli, in so tako v resnici prikrajšani za marsikatero lepo doživetje.

In zaradi astme se da še vedno umreti. Moji učitelji so zavoljo astme še videli umirati mlade ljudi na intenzivnih oddelkih. Imela sem to izjemno srečo, da sem kot zdravnica pričela delati v obdobju, ko je bilo zdravljenje z inhalacijskimi glukokortikoidi že vpeljano, čeprav vedenje o skrivnostih vdihovalnikov in inhalacijskih zdravil še daleč ni bilo tako pojasnjeno, kot je danes. To je bila prava revolucija pri zdravljenju te bolezni. Sedaj, v dobi bioloških zdravil, kot terapevti pravzaprav živimo zgodbo naslednje, morda druge revolucije v zdravljenju astme. In vendar vidimo, da vsemu znanju navkljub še vedno ni mogoče preprečiti občasnega ali rednega zdravljenja s sistemskimi glukokortikoidi, vsaj pri nekaterih bolnikih ne. Ti nosijo posebno breme stranskih učinkov in zapletov zdravljenja. So ranljivi in imajo dokazano povečano umrljivost, in prav na te bolnike sem posebej pozorna. Tovrstne bolnike je namreč treba obravnavati multidisciplinarno: zanje ni dovolj le zdravnik pulmolog, pač pa morajo sodelovati tudi gastroenterologi, endokrinologi, diabetologi, otorinolaringologi. Taki bolniki nedvomno potrebujejo psihološko podporo, ustrezno respiratorno fizioterapijo, nadzor nad prejemanjem zdravil, kliničnega farmacevta in dietetika ter izurjeno medicinsko sestro. Ko bolniki tak pristop začutijo in se odzovejo z ureditvijo astme, nemalokrat rečejo, da so redkokje deležni tako celovite obravnave. Moj odgovor njim v oči je enostaven: Skozi vrata ambulante niso vstopila pljuča, temveč vi kot človek. Navadno sledi trenutek prijetne tišine, droben nasmešek in trenutek ganjenosti. Pri bolniku in meni kot terapevtu. Ker je obema uspelo – bolniku in moji ekipi.

Menim, da je za dober izzid stroke, poleg odlično organiziranega »mikrookolja«, v katerem bolnike obravnavamo, potreben še strokovni konsenz na nacionalni ravni, kar pa smo na številnih področjih pravzaprav dosegli. Jagoda na smetani je zagotovo sodelovanje na mednarodni ravni, tako v širši regiji kot na ravni Evropskega respiratornega združenja. Zato se je leta 2018 rodil »Severe asthma forum – a joint Southeast European Meeting on Severe Asthma«. Ideja o ustanovitvi foruma je nastala v sodelovanju s profesorjem Petrom Koroščem, izjemnim poznavalcem bazičnih principov in zakonitosti astme. Sodelovanje z njim je bil privilegij in priložnost za odlične »brainstorminge«. Mednarodna sodelovanja ponujajo možnost preverjanja lastnega znanja, stroke in organiziranosti. So ogledalo kvalitete lastnega dela. Odličen

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primer tovrstnega dela je sodelovanje v iniciativi SHARP (Severe Heterogeneous Asthma Research collaborration, Patient-centered) pri Evropskem respiratornem združenju. Zahvaljujem se profesorju Ratku Djukanoviću za povabilo v to strokovno skupino.

In neznansko se veselim še nečesa – vedoželjnosti mladih, ki jih imam čast učiti, ki mi z lahkoto sledijo, ki opazijo kaj, česar jaz ne, in mi to spoštljivo povedo, ki imajo pogum za nove in težke začetke. In imajo občutek za te bolnike, ki so vendarle malo posebni.

Pričujoča monografija je nastajala dolgo in premišljeno. Ideja je bila pravzaprav izrečena v družbi mojih prijateljev, profesorjev Zvonke Zupanič Slavec in Jonatana Vinklerja. V tem varnem »duhu« je plula naprej. Uživala sem na poti njenega nastajanja zaradi odzivanja in truda avtorjev. In zaradi njihovega občutka odgovornosti, ki ga je bilo čutiti ves čas več kot enoletnega dela. Monografijo, ki je pred bralcem, tvori šest temeljnih poglavij. Osnovnim bazičnim principom patogeneze astme sledi poglavje o dolgi poti glukokortikoidov pri zdravljenju astme, ki povzema tako zgodovinski vidik in razvoj zdravljenja, kot tudi osvetljuje problem stranskih učinkov in breme oralnih glukokortikoidov. Zgodbo v monografiji nato razvijamo z multidisciplinarnim pristopom k zdravljenju, z diagnostičnimi in terapevtskimi izzivi in fenotipi astme ter zaključimo s protislovji in dilemami, ki še obstajajo. Na tem mestu se posebej zahvaljujem profesorjema Sanji Popović-Grle in Mitji Košniku za odlično opravljeno vlogo. Želeli smo zapisati strokovne tekste in jih pustiti v branje kolegom zdravnikom in njihovim timom, ki so v umetnosti astme že izurjeni, in tistim, ki bodo to šele postali. Če jim bo pričujoča monografija pri tem pomagala, je namen dosežen.

Ker obravnava bolnika s hudo astmo ni zgolj zdravljenje, je kanček umetnosti.

Srečno.

Preface

Sabina Škrgat[1,2]

Asthma is an airway disease which, in its severe forms, represents a serious burden for patients – due to continuous treatment and its side effects, comorbidities and asthma exacerbations. Many of them have a continuous fear of new exacerbations that might happen in future and a lower quality of life as they are deprived of many a fine experience.

It is still possible to die because of asthma. My teachers still saw young people die in intensive care units due to severe asthma exacerbations. I was exceptionally fortunate to become a medical doctor at a time when the basic therapy with inhaled glucocorticoids had already been introduced, although the knowledge about the mysteries of inhalers and inhalation techniques was far from being as clear as it is today. This was a proper revolution in asthma treatment. Now, in the area of biologics, we – the therapists – are probably in the middle of the second revolution in asthma treatment. But despite all these steps forward, we can see that it is still not possible to prevent, at least in some patients, a need for systemic glucocorticoids in maintenance or sporadic treatment. These patients might have a huge systemic glucocorticoid burden, they have greater mortality and they need a special care. They are vulnerable, and they have my special attention since they need a multidisciplinary approach: it means that they need not only a pulmonologist, but also gastroenterologist, endocrinologist, diabetologist and otorhinolaryngologist. Undoubtedly important and valuable partners in the team are also an experienced severe asthma nurse, psychologist, nutritionist, good respiratory physiotherapist and clinical pharmacist to provide support. When patients experience this approach which enables them to control their asthma, they often say that they are not often treated so comprehensively. My answer to them is simple and clear: "You are not merely the lungs that come through the door of our outpatient clinic, but you are a whole person." Many times this is followed by silence, a timid smile and a moment of happiness – both the patient's and mine in my role of a therapist. Because we have succeeded, both the patient and my team.

My belief is that in addition to a perfectly organized "micro-environment" in which the patients are treated, a good professional outcome also requires professional consensus at a national level, which has actually been achieved in numerous fields. The cherry on the cake is surely our participation at the international level, both regionally and at the level of the European Respiratory Society. The idea to launch the Severe asthma forum was born in cooperation with prof. Peter Korošec who is an exceptional authority on basic asthma principles. Our cooperation with him was a great privilege and the opportunity for excellent brainstorming debates. International cooperation provides opportunities

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for verification of our own knowledge, profession and organization. It also mirrors the quality of our work. The SHARP initiative (Severe Heterogeneous Asthma Research collaboration, Patient-centred) is an excellent example of this kind of work and I thank prof. Ratko Djukanović for invitation to this working group.

And I am really happy about something else – the inquisitiveness of young people that I have the honour to teach, who easily follow, who notice something that I do not and respectfully let me know, and who have the courage for new and difficult beginnings. They feel with these patients who are somehow specific nonetheless.

The present monograph has taken a long time and a lot of thought to emerge. As a matter of fact, the idea was first expressed in the company of my friends, prof. Zvonka Zupanič Slavec and prof. Jonatan Vinkler. In this safe "spirit" it sailed on. I enjoyed the course of its creation because of the responses and efforts of the authors. And because of their sense of responsibility which could be felt throughout the more than one year of our work. This monograph consists of six basic chapters. The basic principles of asthma pathogenesis are followed by a chapter on the long path of glucocorticoids in the treatment of asthma, which summarizes both the historical aspect and development of treatment, as well as highlights the problem of side effects and the burden of oral glucocorticoids. The story in the monograph then evolves with multidisciplinary approaches to the treatment, diagnostic and therapeutic challenges and asthma phenotypes, and ends with still existing contradictions and dilemmas. I would especially like to thank prof. Sanja Popović-Grle and prof. Mitja Košnik for their excellent performance. We wished to write professional texts and let them be read by fellow doctors and their teams who are already trained in the art of asthma, and those who are yet to become so. If the present monograph helps them in this, our purpose will be achieved.

Because treating a patient with severe asthma is not just a therapy, it is also a bit of art.

Good luck!

1

Basic Principles in Severe Asthma

Endotypes and Immune Cells in Severe Asthma

1.1

Matija Rijavec[1,2] and Peter Korošec[1,3]

Abstract

Severe asthma accounts for a small proportion of asthma prevalence, however due to high requirements for treatment the majority of medical resources are directed toward those patients. Asthma is a highly heterogeneous disease, an umbrella diagnosis for several diseases with variable clinical presentations (phenotypes) and distinct mechanistic pathways (endotypes), and its pathophysiology is not yet completely understood. Thus despite similar clinical symptoms, asthma patients may respond very differently to the same therapeutic interventions. Asthma endotypes are currently regarded as type 2 high (T2-high) or non-T2. Th2 cells, innate lymphoid cells, eosinophils and mast cells are the most important cell types associated with T2-high asthma, on the other hand neutrophils, Th1 and Th17 cells are involved in non-T2 asthma. As more and more innate and adaptive immune cell types and mediators are identified as important drivers of asthma, asthma endotype definitions are still fluid and continue to evolve. The identification and understanding of the molecular mechanisms of different asthma endotypes, that reflect a highly variable response to different treatments, will lead to more precise asthma management and better outcomes in patients.

Keywords: severe asthma, endotype, phenotype, immune cells, eosinophils, innate lymphoid cells, mast cells, basophils

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Introduction

Severe asthma remains a worldwide problem. Even though accounts for a small proportion of asthma prevalence affecting a minority of patients, it is characterized by high requirements for treatment to partly or completely control severe and frequent symptoms, and as a result, the majority of medical resources are directed toward those patients[9,12,14-19]. Asthma is a highly heterogeneous disease and its pathophysiology is not yet completely understood. Large asthma clinical heterogeneity and high variability in treatment response extend beyond clinical phenotypes, and over the last two decades several genetic, immunologic, and environmental factors that contribute to asthma risk, pathogenesis and underlying asthma endotypes have been determined[6,17,18]. The identification and understanding of the molecular mechanisms of different asthma endotypes, that reflect a highly variable response to different treatments (related to certain clinical phenotypes), will lead to more precise asthma management and better outcomes in patients[6,13,17,18].

Phenotypes and Endotypes in Severe Asthma

Asthma heterogeneity reflects different underlying mechanisms. Asthma is nowadays

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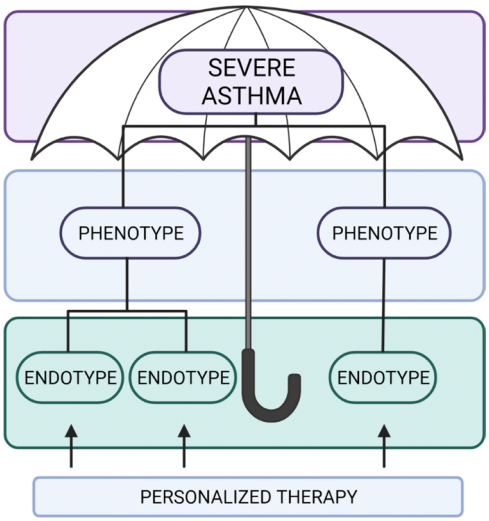

Figure 1. Association between phenotypes and endotypes in severe asthma. Severe asthma is considered an umbrella diagnosis linked to specific pathogenesis. There are many possible phenotypes (clinical presentations) and each phenotype is associated with distinct endotypes (distinct mechanistic pathways) that can be targeted with personalized therapy. Adapted from Fitzpatrick & Bacharier, 2019.

considered an umbrella diagnosis for several diseases with variable clinical presentations (phenotypes) and distinct mechanistic pathways (endotypes) (Figure 1)[13]. Hence, phenotypes are defined as „observable characteristics that result from a combination of hereditary and environmental influences" such as clinical presentation, symptoms, triggers and allergic features. However, the strategy was recently evolving to associate molecular mechanisms to phenotype and asthma endotypes describe these distinct pathobiological pathways at a cellular and molecular level. Thus despite similar clinical symptoms, asthma patients may respond very differently to the same therapeutic interventions. Why? Because of distinct endotypes (mechanistic pathways). Furthermore, the precise definition of these endotypes is central to asthma management due to inherent biological therapeutic implications[8,11,13].

As more and more innate and adaptive immune cell types and mediators are identified as important drivers of asthma, it is evident that asthma endotype definitions are still fluid and continue to evolve[13]. Asthma endotypes are currently regarded as type 2 high (T2-high) or non-T2. Why not adaptive Th2 high or non Th2 endotypes? Recently, a substantial body of evidence has proven that group 2 innate lymphoid cells (ILC2s) also play an equally critical role in type 2 immune responses. ILC2s are particularly high in airway tissues and produce large quantities of IL-5 and IL-13 in response to alarmins, mediators released from epithelial cells in response to stressors, such as infection or inflammation. In asthma, ILC2s appear to play an early and key role in augmenting the type 2 responses in the airway. Together, Th2 cells (adaptive) and ILC2s (innate) are the primary regulators of T2 immunity and express the master transcription factor GATA3. Therefore, Th2-high inflammation is labelled as type 2 (or T2) inflammation, to account for the role of both adaptive Th2 and innate ILC2 immune cells[5,7,11,13].

In T2-high asthma, there is an interplay of several individual pathways and cells (Figure 2). Alarmins, like TSLP, IL-25 and IL-33 are airway epithelial-derived mediators that respond to infection and inflammation. IL-33 and IL-25 mainly activate ILC2s, while TSLP also primes dendritic cells (DCs), and consequently B- and T-cells. Recent data suggest that IL-33 appears to be the most potential amplifier of T2-high asthma[1]. Alarmins serve to activate ILC2s. ILC2s are lineage-negative cells that lack lymphocyte surface markers and antigen-specific receptors and produce 10-fold more IL-5 and IL-13 compared with activated Th2 cells. On the other hand, adaptive pathways involve allergens-activated DCs that induce the expression of a Th2 pathogenic signature in the presence of the master

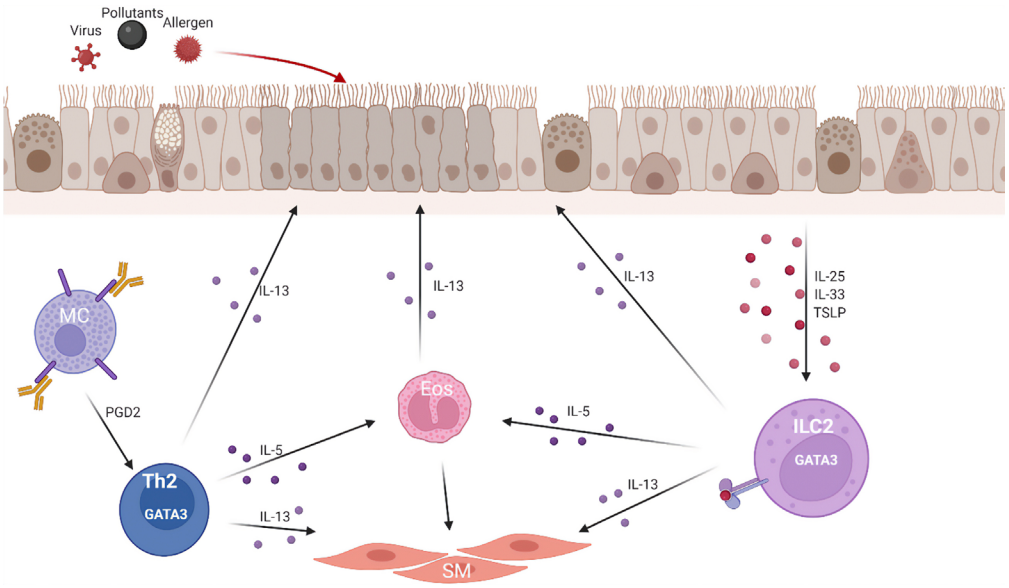

Figure 2. Mechanisms of T2-high asthma. Eos, Eosinophils; GATA3, GATA3 transcription factor; MC, mast cells/basophils; SM, smooth muscle cells; Th, T helper cells. Adapted from Corren, 2019.

transcription factor GATA-3. Th2 cells then stimulate type 2 immunity through the secretion of the cytokines IL-4, IL-5, and IL-13. Importantly, both IL-4, as well as IL-13, utilize a common IL-4Rα chain. IL-5 plays a pivotal role in promoting the differentiation and maturation of eosinophils, as well as their subsequent mobilization and survival. Furthermore, T2 cytokines have effects on goblet cells (mucus), fibrogenic functions (remodelling), and hyperresponsiveness[5,7,11].

Eosinophils are the hallmark cell type associated with T2-high asthma and have pleiotropic effects on various inflammatory cells. Upon stimulation, they release a myriad of inflammatory mediators chemokines, and cytokines including IL-5, IL-13, eotaxin, cysteinyl leukotriene (CysLT), major basic protein (MBP), eosinophil peroxidase (EPX), and eosinophil cationic protein (ECP). CysTL is a potent bronchoconstrictor that acts in synergy with IL-33 and further drives the self-amplifying loop that characterizes T2 inflammation. Eosinophils also activate bronchial fibroblasts. Very important from the therapeutic target, IL-5 plays a pivotal role for eosinophils (differentiation and survival)[5,7,11,13].

While the role of mast cells degranulation in acute asthma exacerbation is well established especially in allergen driven exacerbations, the functional significance of basophils in asthma has recently gained attention. Notably, it was shown that basophils have been recruited in the bronchial walls of T2-high asthma. Moreover, it is well known that in humans basophils are one of the major producers of IL-4 and can thus directly modulate T2 inflammation. IgEs, which on mast cells and basophils through FcεRI mediate immediate hypersensitivity response to allergens, can also facilitate and modulate antigen presentation by dendritic cells and response to viruses. Additionally, recent data strongly suggest that an altered functional subtype of mast cells may have greater potential to generate PGD2. These PGD2-high mast cells strongly predict poorly controlled T2-high

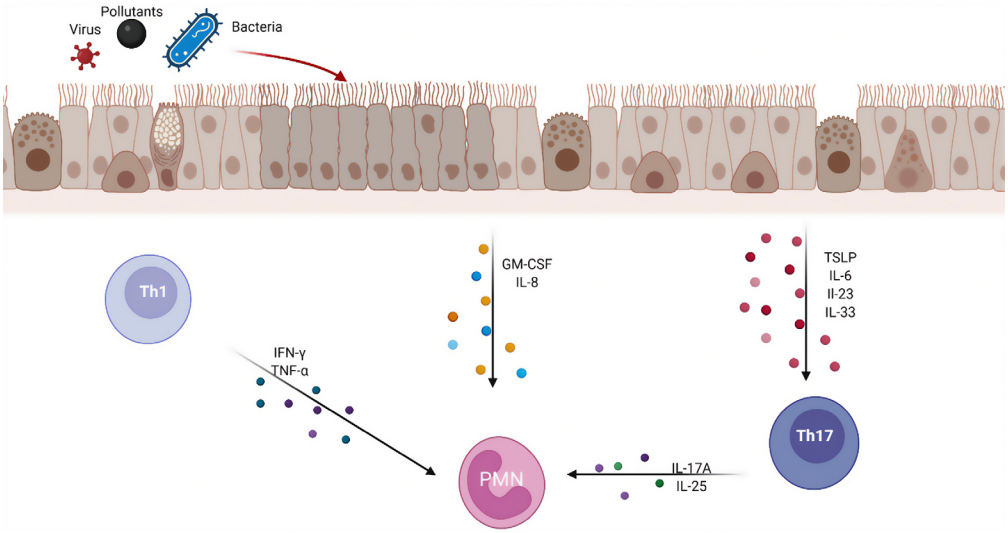

Figure 3. Mechanisms of non-T2 (T2-low) asthma. PMN, polymorphonuclear cell; Th, T helper cells. Adapted from Corren, 2019.

asthma and are associated with more severe disease (targeting CRTH2)[5,7,11,13].

Non-T2 (T2-low) asthma is typified by the absence of markers of T2-high disease. It is generally characterized by neutrophilic (sputum neutrophils > 40–60%) or paucigranulocytic (i.e., normal sputum levels of both eosinophils and neutrophils) inflammation and a lack of response to corticosteroid therapy. Mechanisms underlying recruitment and maintenance of neutrophilic airway inflammation are yet unknown: the role of the neutrophil itself is in debate. It has been linked with the Th1 and/or Th17 cells, cytokines IL-17A, IL-17F, IL-22, IFN-γ, TNF-α, IL-1β, IL-6, IL-8, and NLRP3 inflammasome. It is also possible that some non-T2 endotype are labelled as such only because steroid therapy has masked the T2 signature (Figure 3)[5,7,11,13].

High Th1 is marked by the production of IFN-γ. Elevated IFN-γ was associated with high airway resistance, increased inflammatory infiltrates, and corticosteroid refractoriness. Corticosteroids may not only be inefficacious in these patients but may exacerbate the underlying inflammatory state through increased Th1 recruitment. High Th17 is marked by increased levels of IL-17A, IL-17F, and IL-22 and IL-17F frequent exacerbator endotype has been recently described. Additionally, IL-6 has been recently shown to cause systemic inflammation in a subgroup of asthma patients with obesity and severe disease[5,7,11,13].

Currently, due to the availability of therapies targeted toward T2 cytokines, the approach is to divide patients into those with T2-high and non-T2 (T2-low) asthma. There continue to be critical unanswered questions in severe asthma, mainly since our understanding of the inflammatory microenvironment in the lower airway and the contributions to the clinical expression of the disease remains incomplete. Recent advances have provided further insight into molecular mechanisms underlying steroid resistance, tissue remodelling, and disease exacerbations. The accurate translation of discoveries from these studies will require careful clinical

characterization for the design of clinical trials and the development of new biologic therapies[13].

Immune Cells Drivers of Severe Asthma

Eosinophils

Eosinophils have been widely considered to play a prominent role in the pathogenesis of T2-high asthma and have pleiotropic effects on various inflammatory cells. Eosinophils are implicated in several pathologic processes including epithelial damage, smooth muscle hypertrophy, neural plasticity, and impaired tissue repair processes, promoting chronic airway remodelling and airflow obstruction. Additionally, blood eosinophilia or an increased number of eosinophils in blood positively correlated with increased disease severity, worse disease control, and increased risk of severe exacerbations. Eosinophilia results from the stimulation of eosinophil production from hematopoietic stem and progenitor cells. The differentiation and survival of eosinophils involve signalling by IL-3, IL-5, and GM-CSF. Of these three cytokines, IL-5 plays the most critical role, which is very important from a therapeutic view as a target. Tissue recruitment involves the activation of their surface integrins in response to chemotactic factors including eotaxins and lipid mediators. Once infiltrated, eosinophils may undergo activation. Upon stimulation and activation, eosinophils release a myriad of signature mediators, chemokines, cytokines and growth factors including ECP, eosinophil-derived neurotoxin (EDN), EPX, MBP, IL-5, IL-13, eotaxin, CysLT, and transforming growth factor (TGF)-β1. Among these factors are several key actors of T2 immunity and tissue remodelling, most notably IL-4, IL-13, and TGF-β1. Furthermore, CysTL is a potent bronchoconstrictor that acts in synergy with IL-33 and further drives the self-amplifying loop that characterizes T2 inflammation[13,20].

Innate Lymphoid Cells

It is 12 years since the discovery of innate lymphoid cells (ILCs)[3]. ILCs reside at barrier surfaces and regulate tissue homeostasis, immunity, and disease pathology. Cytokine-producing ILCs are divided into 3 groups, group 1 ILCs (ILC1s), group 2 ILCs (ILC2s), and group 3 ILC3 (ILC3s), based on their functional similarities to the main groups of adaptive T helper (Th) cells. ILC1s are the innate equivalents of Th1 cells and produce IFN-γ and TNF-α. ILC2s are the innate equivalents of adaptive Th2 cells. On activation, they secrete type 2 cytokines including Il-4, IL-5 IL-9, and IL-13. They also produce amphiregulin and IL-10. ILC3s are the innate equivalents of Th17 cells. ILC3s produce IL-17A/F and IL-22.

Recent data suggest that ILC2s might be highly important in the pathogenesis of asthma[3]. They respond rapidly to allergen exposure and environmental insults in mucosal organs, producing type 2 cytokines. It was shown that epithelium-derived cytokines IL-25, IL-33, and TSLP activate ILC2s resulting in eosinophilia, mucus hypersecretion, and remodelling of mucosal tissues. Increased ILC2s have been reported in blood and BAL from patients with asthma as compared with healthy controls, and in blood and induced sputum of patients with severe asthma in comparison with mild asthma. The number of circulating ILC2s correlated with eosinophil counts in induced sputum and blood and ILC2s frequencies were also increased in induced sputum of pediatric patients with severe asthma. Regarding the activation status of circulating ILC2s subjects with severe asthma or uncontrolled asthma had increased numbers of IL-5+ and IL-13+ ILC2s cells. Besides IL-25, IL-33, and TSLP cytokines eicosanoids likely play a critical role in promoting migration and activation of ILC2s in asthma. Involvement of ILC2s was also observed with viral triggers of asthma besides allergens, both in respiratory syncytial virus infection in mice and experimental rhinovirus

infection in humans. Recently, studies have been initiated to elucidate the effects of asthma treatment on ILC2s and to modulate ILC2s as a potential treatment option for asthma as ILC2s may contribute to steroid resistance and persistent airway pathology. Further studies using anti-IL5 and IL4/13 biologics likely will provide useful information to dissect the roles of ILC2s and innate type 2 responses in the pathophysiology of asthma and, at the same time, will help to develop novel treatment strategies for asthma by targeting ILC2s[3]. Further studies are also needed to elucidate the possible role of ILC1s and ILC3 responses in asthma.

Mast Cells and Basophils

The evidence that mast cells degranulation followed by the release of various mediators represent important contributors to the pathogenesis of asthma is strong. Mast cells normally reside in the lungs, and on activation by IgE-dependent or other mechanisms, they can release a diverse spectrum of mediators that in turn can rapidly induce local effects on blood vessels, nerves, and mucous glands, as well as on epithelial cells, airway smooth muscle cells, and immune cells[4]. Among the mast cells secreted mediators histamine, prostaglandin (PG) D2, and leukotriene (LT) C4 are capable of inducing bronchoconstriction, mucus secretion, and mucosal oedema, all asthma characteristics. Additionally, recent data strongly suggest that an altered functional subtype of mast cells may have greater potential to generate PGD2. These PGD2-high mast cells strongly predict poorly controlled T2-high asthma and are associated with more severe disease (targeting CRTH2)[5,7,11,13]. Besides, mast cells also synthesize and secrete a large number of proinflammatory cytokines (including IL-4, IL-5, and IL-13), which regulate both IgE synthesis and the development of eosinophilic inflammation, and several profibrogenic cytokines, including TGF-β. Furthermore, major mast cells' secretory products, serine proteases tryptase, chymase, and carboxy-peptidase, can interact with various cell types and direct their activity via protease-activated receptors and other processes[4]. On the other hand, the functional significance of basophils in the pathogenesis of asthma has gained attention only recently. Similarly, as mast cells, IgEs on basophils through FcεRI mediate immediate hypersensitivity in response to allergens, and can also facilitate and modulate antigen presentation by dendritic cells and response to viruses. Basophils are recruited in the bronchial walls of T2-high asthma. Basophils and eosinophils appear to be closely linked by directly or indirectly influencing each other since they are responsive to similar cytokines and chemokines[10]. Basophils activation leads to the release of immunoregulatory and effector mediators, including IL-4 and IL-13, histamine, and LTC4. Moreover, it is well known that human basophils are one of the major producers of IL-4 and can thus directly modulate T2 inflammation[4,5,7,11,13].

The pathophysiologic mechanisms driving corticosteroid insensitivity and severe asthma are still unclear and evidence suggests that mast cells and basophils might have a role in it. *In vitro* studies using various cell types showed that different mediators produced by activated mast cells and/or basophils, including cytokines, can interfere with the therapeutic action of corticosteroids. Mediators released by activated mast cells have been shown to decrease the anti-inflammatory action of glucocorticoids in airway smooth muscle cells by reducing the expression of anti-inflammatory genes. Mast cells infiltration and interactions have been described in different compartments of the airways, including epithelium, submucosa and airway smooth muscle. Therefore, mast cells' airway infiltration, release of mediators and interaction with lung structural cells may contribute to the corticosteroid insensitivity in severe asthma[2,4].

Conclusion

For many years, severe asthma has been recognized as a subset of asthma that is poorly managed by standard therapy for asthma. Nowadays asthma is considered an umbrella diagnosis for several diseases with variable clinical presentations (phenotypes) and distinct mechanistic pathways (endotype). The precise definition of these endotypes and deciphering the complex interplay of several individual pathways and immune cells is central to asthma management due to inherent biological therapeutic implications. The identification and understanding of the molecular mechanisms of different asthma endotypes, that reflect a highly variable response to different treatments, will lead to more precise asthma management and better outcomes in patients.

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2

Long Journey of Corticosteroids

The Story of Corticosteroids in Asthma

2.1

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Abstract

Asthma is a common respiratory disease affecting patients of all ages and races. Up to the middle of the 20th century there was scarce knowledge regarding the biology of the disease and asthma was a potentially lethal disease with very limited therapeutic options. The introduction of corticosteroids revolutionized the management of asthma and improved the lives of millions of patients. Parental and later oral administration was the first treatment with remarkable effects on asthma symptoms and exacerbations but led to serious systemic effects. The invention of inhaled forms of corticosteroids that had minimal systemic absorption and adverse reactions, the enhancement of their efficacy by LABAs and the understanding of asthma pathophysiology were only a few of the significant advances in asthma management over the last 60 years. In this review we present these life-changing advances in asthma treatment, focusing on the evolutionary role of corticosteroids.

Keywords: asthma history, asthma treatment, OCS, ICS, LABA

Introduction: Historical Overview

Asthma is a chronic inflammatory airway disease affecting patients of all ages and races. It is characterized by heterogeneity which is defined by different underlying disease processes and pathophysiological characteristics (phenotypes).[1] This heterogeneity is reflected in therapeutic interventions that have been extensively evaluated during the last 20 years or so.

The term asthma is a Greek noun, άσθμα, which derives from the verb ασθμαίνω meaning to exhale with open mouth, to pant. The first written record of asthma appears around 2700 years ago in Homer's Iliad. The earliest text where the word asthma is found as a medical term is in the writings of the school of Hippocrates of Kos (460-360 B.C.).[2] In the writings of Hippocrates, however, the term probably refers to asthma as a symptom and not to the disease we know today. In the beginning of the 19th century, asthma was defined as an airway disease characterized by bronchospasm following invention of the stethoscope by Laennec (1781-1826).[3] The first reports of asthma as an extrinsic or intrinsic disorder caused by stress or animal dander are attributed to Henry Hyde Salter in 1860. In his treatise "On Asthma: its Pathology and Treatment", Salter describes asthma as a disease in which the airways narrow as a result of contraction of their smooth muscle.[4] A few years later Paul Ehrlich (1854-1915) described eosinophils and mast cells in asthmatic sputum using eosin and toluidine blue staining.[5] Sir William Osler (1849-1919),

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often mentioned as the Father of Modern Medicine, made a more precise definition of asthma connecting pathology, physiology, symptoms, and clinical findings, in the first edition of his Textbook Principles and Practice of Medicine.[6] Thus, it was in the 19th century that asthma was described as a distinct lung disease with specific etiology, clinical findings, and treatment.

Early Therapeutic Interventions

Therapeutic options for asthma were limited until the middle of 20th century and asthma was treated largely as a disease of bronchospasm.[7] Regimens containing *anticholinergics* were the first aetiologic treatment administered for asthma. Paul Ehrlich proposed black coffee for the treatment of bronchospasm, as this beverage contains theophylline and its derivative theobromine.[8] Henry Hyde Salter discusses "Asthma cigarettes" containing dried leaves and flowering of D. Stramonium as a treatment for asthma in his 19th century work.[9] Datura Stramonium contains alkaloids of belladonna which has anticholinergic action. William Osler in his eight edition of his textbook in 1914 suggests hypodermic injections of pilocarpine for asthma treatment.[10] *Adrenergic bronchodilators* were introduced as treatment for asthma in the beginning of 20th century. Initially both adrenaline and ephedrine were used subcutaneously at repeated intervals during asthma attacks.[11] In 1947, in Cecil's Textbook of Medicine, Rackemann presented the inhaled administration of ephedrine to relieve asthma symptoms.[12] Since then, inhalers were widely available for asthma and bronchodilators such as isoprenaline and orciprenaline.[13,14] The widespread use of those nonselective bronchodilators led to an increased ratio of deaths among asthmatics in England and Wales in the 1960s, possibly due to their cardiovascular adverse effects or as a result of inadequately treated asthma. In the 1970s, salbutamol[15] and terbutaline[16], relatively more selective β2- bronchodilators, were developed for inhaled use. Long-acting beta-agonists (LABAs - e.g., formoterol, salmeterol), introduced in middle '90s as an important drug in asthma management. They demonstrate a clear benefit in reducing asthma-related symptoms and improving lung function but only when used in combination with an anti-inflammatory agent.[17]

The Introduction of Corticosteroids on Asthma Management

The story of corticosteroids in asthma begins in the early 1950s, when cortisone was first administered to treat asthma successfully. Case series reporting the benefits of *parenteral administration* of cortisone in patients with allergic asthma were published: In 1950, Carryer presented 3 patients with seasonal asthma and hay fever who received sequentially 100 mg cortisone or cholesterol suspension daily over a 4-week period in a blinded manner. All three patients experienced prompt relief from symptoms of asthma and hay fever, which lasted a few days post administration.[18] In 1953, Burrage W. presented 14 cases of severe bronchial asthma treated with a mean daily dose of 50mg cortisone for a prolonged period. The author mentioned that "the use of cortisone in severe asthma involves a treatment of an as yet imperfectly understood disease with a potent hormone, whose mode of action remains a mystery" and that "no patient has remained asthma free on less than 25mg of cortisone daily".[19] Several other reports of parenteral administration of cortisone in patients with asthma were published over the following years.[20-22]

The difficulties of parenteral administration and the relapse of symptoms following discontinuation of treatment were extinguished with the initiation of *oral therapy*. In January 1951, Scwartz E. reported 3 cases of "intractable" asthma successfully treated with cortisone acetate tablets at initial doses of 50-100mg with gradual tapering

to maintenance dose of 25mg daily.[23] Sidney and Alex Friedlaender described a series of 12 patients who received an average daily dose of 150 to 200mg oral cortisone which produced a comparable effect to that obtained with intramuscular administration. Interestingly they mentioned reduction in eosinophil counts.[24] Savidge R. and Brockcbank studied 24 asthmatics with remarkable limitation in their daily activities in 1954: Using a partially blinded methodology, they started with an initial dose of 100mg cortisone daily or placebo, gradually tapering by 12.5mg every four to six weeks in an effort to avoid side effects. In all patients, there was remarkable improvement in symptoms and patient could return to their daily activities.[25] At that period, oral cortisone for asthma treatment was administered as long-term or intermittent basis with an effort to use the minimal needed doses.[26]

The following years, several forms of steroids such as hydrocortisone, prednisolone, triamcinolone and dexamethasone were used, providing an effective management for a disease that previous to their use, had been life threatening and had detrimental effect on patients' lives.[27,28] Unfortunately, oral steroids also have side effects. So, in asthma steroids have always been a double-edged sword, due to their systemic adverse reactions.[29] By 1960 all the systemic toxic effects of oral and parenteral treatment of corticoids had been described and OCS-sparing efforts were made in nearly every disease where OCS were used, not only due to safety issues but also to improve outcomes.[27,30–34] This effort was reflected in many published works on the administration of cortisone *by inhalation* which started shortly after intramuscular treatment was made an established choice for severe asthma. In 1951, Maxwell Gelfand reported 5 cases of bronchial asthma treated for two weeks with 5mg nebulized cortisone inhaled every hour for a period of ten hours daily. Discontinuation of treatment led to relapses, which though, were successfully treated with re-initiation of treatment. The medical community had not yet linked asthma with inflammation of the airways, so the author discusses a probable mechanism of cortisone action as follows: "*The direct application of cortisone to the bronchial mucosa may either interfere with the union of antigen and antibody or inhibit the liberation of histamine in the site of shock organ* (lung)".[35] Inhaled dexamethasone in a study of 64 patients resulted in withdrawal of oral steroids in 29 of these patients for a period from 2 to 120 months.[36] In the early 60s, the first studies evaluating the effects of inhaled steroids in lung function with the use of spirometry were published.[36] *Unfortunately, despite these advances, the systemic absorption of agents such as dexamethasone, even when administered by inhalation proved an insuperable problem.*[37]

The Break-through of ICS in Asthma Treatment

A milestone in asthma treatment was the invention of Beclomethasone dipropionate (BDP) which was patented in 1962 and was the first inhaled corticosteroid (ICS) marketed for use in the treatment of chronic asthma.[38] In 1972 Brown H.M, Storey G. and George W.H.S published the results of a study involving 60 asthmatic patients who received *Beclomethasone dipropionate* by means of a metered aerosol delivering 50 μg of micronized powder per puff.[39] (37 of these patients had been oral steroid dependent for up to 16 years). Two puffs four times daily, giving a total of 400 μg, was the usual dose, occasionally increased to three puffs four times a day. In 56 cases 400 μg was the optimum dose but four remained well controlled on 150 to 200 μg daily. In 28 out of 37 steroid-depended cases there was complete withdrawal of OCS. Besides, 19 out of 23 other asthmatics not dependent on steroids were also completely controlled. In that study Beclomethasone was the first inhaled steroid that had no biochemical

evidence of adrenal suppression. In other studies Beclomethasone dipropionate proved a safe and effective alternative to oral Prednisolone by means of patients' preference, use of rescue medications and lung function (PEFR, FEV1).[37,40]

Budesonide, the second broadly used inhaled ICS, was patented in 1973.[41] The first studies on asthmatic patients showed a comparable action with beclomethasone in asthma control in both adults and children.[42,43] In vivo studies have shown different pharmacodynamic properties and although beclomethasone has higher receptor affinity, Budesonide has higher in vitro potency.[44] Like Beclomethasone, the introduction of Budesonide in corticosteroid dependent patients with severe asthma seemed to offer an improvement, allowing substantial reduction or withdrawal of oral prednisolone without systemic absorbsion.[45] *Fluticasone propionate* was patented in 1980 and approved for medical use in 1990.[46] In a large international study fluticasone propionate 1mg/day was as effective as 2mg/day beclomethasone dipropionate in the control of severe asthma, better effect on lung function with less effect on adrenal function.[47,48] The results were similar in lower doses of both medications.[49] Other studies also demonstrated that both the dry powder and aerosolized formulations of fluticasone propionate had twice the efficacy of beclomethasone dipropionate via a pressurized inhaler, introducing an alternative dry powder device (Diskhaler) for asthma drug delivery.[50]

In the last 30 years, three more inhaled steroid agents were introduced: Mometasone Furoate, Ciclesonide, and Fluticasone Furoate. *Mometasone furoate* is a highly potent synthetic glucocorticoid initially used as a topical dermatologic agent proved to be an effective treatment for patients with mild-to-moderate persistent asthma previously taking only inhaled β2-adrenergic agonists when administered either as a once daily or twice daily regimen.[51,52] *Ciclesonide* is a prodrug glucocorticosteroid which itself is inactive and needs to be cleaved by esterases in the lung to bind to the glucocorticoid receptor. In the majority of clinical trials, it was administered as a single dose.[53–55] *Fluticasone Furoate* is the newest discovered inhaled corticosteroid that demonstrates prolonged action up to 26 h in asthma patients.[56]

Pilot Studies on Asthma Pathophysiology: The Role of Inflammation

Understanding the pathophysiology and *inflammatory triggers and processes* of asthma *as well as the effects of ICS* on the control of inflammation and bronchial mucosal infiltration was a milestone in asthma management. Laboratory and clinical studies *established inhaled steroid treatment as the main therapeutic option for asthma, dethroning bronchodilator monotherapy*. In 1991 Laitinen LA and coworkers compared the effect of budesonide and terbutaline, on clinical symptoms, lung function, and airway epithelium (on biopsies obtained with bronchoscopy) in 14 adult patients with newly diagnosed asthma. Budesonide improved lung function and bronchial hyperreactivity but most importantly was more effective in *ameliorating abnormalities of the bronchial epithelium and decreasing inflammation in the airways.*[57] One year earlier Haahtela and coworkers had shown that early anti-inflammatory treatment with ICS in newly detected asthma resulted in greater improvement of symptoms and lung function than treatment with terbutaline and that the improvement lasted through the entire two-year study period.[58] In a follow-up study, patients who had been assigned to terbutaline were assigned to ICS and experienced less improvement than those who had started on ICS, suggesting that *early treatment was more effective than delayed treatmen, ie treatment later into the course of asthma.*[59,60]

Despite these advances, the information on whether *inhaled corticosteroids prevent deaths from asthma* remained sparse and inconclusive. Suissa S. and coworkers conducted a population-based epidemiologic study to determine whether and to what extent the use of inhaled corticosteroids prevents death from asthma. The cohort consisted of 30596 subjects who were followed from 1975 through 1997 and the results were published in 2000. Authors concluded that regular use of low dose inhaled corticosteroids was associated with a decreased risk of death from asthma and that the rate of death from asthma decreased by 21 percent with each additional canister of inhaled corticosteroids used in the previous year.[61] Unfortunately, to this day, we see patients receiving bronchodilators only and deaths associated with excessive bronchodilator use.

Enhancing Efficacy of ICS with LABA: Past and Present

A major advance in asthma management was *also the discovery that LABAs enhance the clinical efficacy of inhaled corticosteroids in asthma*[62]. In 1997 Pauwels R A and coworkers in the game-changing *FACET study,* evaluated the effects of adding inhaled formoterol to both lower and higher doses of the inhaled glucocorticoid budesonide and showed that combining ICS and LABAs, resulted in better outcomes, required lower doses of ICS and resulted in better lung function, less activity limitation and better quality of life. In short, 852 patients treated with glucocorticoids were randomly assigned to one of four treatments (low or high ICS with or without LABA) given twice daily for one year. The study showed that, in patients who have persistent symptoms of asthma despite treatment with inhaled glucocorticoids, the addition of formoterol to either the lower or the higher dose of budesonide also improved asthma-symptom scores and lung function and reduced exacerbations and the need for rescue medications.[63]

During the first decade of 21st century, effort was made to achieve control of asthma symptoms and exacerbations with the use of ICS and LABA combinations. *In the Gaining Optimal Asthma Control (GOAL) study*, Bateman and colleagues have assessed how frequently total asthma control or well controlled asthma control can be achieved. Stepping up the treatment to higher doses of Fluticasone alone or Fluticasone/Salmeterol resulted in a higher proportion of patients with controlled asthma. Similarly to the FACET study, more patients rapidly achieved totally or well-controlled asthma with the combination of inhaled salmeterol/fluticasone and at a lower dose of corticosteroid than with inhaled fluticasone alone.[64] Another option for gaining asthma control was the use of fixed Budesonide/Formoterol combination both for maintenance and relief, the *Symbicort Maintenance And Reliever Therapy (SMART) approach*. In 2007 Bousquet J and colleagues showed that in the treatment of uncontrolled asthma, budesonide/formoterol maintenance and reliever therapy reduced the incidence of severe asthma exacerbations and hospitalization/ER treatment with similar daily symptom control compared to sustained high-dose salmeterol/fluticasone plus SABA. This benefit war achieved with substantially less ICS exposure.[65] Over the following years several studies supported the MART strategy in asthma treatment.

Over the last 20 years the combination of LABA with ICS remained the main option for the treatment of moderate to severe asthma.[66] On the contrary, guidelines recommended, until recently, that most adults and adolescents with mild asthma use regular daily low dose ICS as maintenance treatment to reduce airway inflammation, symptoms, and the risk of exacerbations.[67] However, in clinical practice patients show poor adherence to asthma medications, particularly inhaled

glucocorticoids and rely on SABAs for symptom relief, a phenomenon more intense in mild asthma. However, SABAs do not address the underlying inflammatory process and they do not protect against exacerbations. On the contrary *SABA overuse* is related to high asthma mortality.[68,69]

SYGMA 1 and SYGMA2 are both multicenter, phase III, randomized, double-blind, 52-week, placebo-controlled studies, involving asthma patients who were assessed as needing GINA step 2 treatment. In the SYGMA 1 study, patients were randomly separated into three subgroups: i) terbutaline as needed group, ii) budesonide-formoterol as needed group, and iii) budesonide-formoterol regular maintenance group.[70] This study showed that, budesonide-formoterol as needed treatment was superior to terbutaline in outcomes as asthma control and severe exacerbations and equivalent to maintenance budesonide, but with an 83% lower median daily ICS dose. In SYGMA 2, the regular use of low dose ICS budesonide plus SABA as needed was tested against low dose budesonide-formoterol as needed in asthmatics with mild asthma. In this study, BUD/FORM as needed was non-inferior to BUD alone for reducing severe asthma exacerbations but resulted in 75% lower median daily ICS dose.[71] These data resulted in fundamental changes in the treatment of intermittent and mild asthma, the biggest changes since the initial development of GINA recommendations almost three decades ago (1995): The 2019 guidelines proposed that adults and adolescents with *mild asthma should preferably be treated with ICS-containing regimens: as-needed low-dose ICS-formoterol in Step 1 and as needed low-dose ICS plus as-needed SABA or as-needed low-dose ICS-formoterol in* Step 2. And this was the last major advance in asthma treatment confirming the essential role of ICS in treatment even in mild stages of the disease.[72]

Summary

The long journey of corticosteroids in asthma started in early 1950s. Despite their severe adverse effects, the parenteral and oral forms of these agents were a life changing medication for asthmatics, whose treatment options were almost non-existent until then. Twenty years later, the first inhaled steroids proved to be effective and safer, limiting the use of oral agents to more severe stages of disease and during asthma exacerbations. Personalized, phenotype-based treatment approaches using combinations of ICS with LABA, newer inhalation devices and, when needed, biologics for severe asthma are the new reality for all asthma patients. For the majority of patients, the target is to obtain control of asthma with the least (optimal) dose of ICS that each patient requires. ICSs combined with LABAs remain the cornerstone of asthma therapy.

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Challenges of Systemic Glucocorticoids Taper in the Treatment of Severe Asthma

2.2

Sabina Škrgat[1,2], Peter Kopač,[3] Natalija Edelbaher[4] and Tomaž Kocjan[2,5]

Abstract

Asthma is a chronic airway inflammatory disease, characterized by reversible airway obstruction and airway hyperresponsiveness. It affects 1-18% of population in different countries and approximately 5–10% of the overall asthma population has severe asthma. Systemic glucocorticoids still represent a significant burden due to treatment of asthma exacerbations and severe forms of asthma. Monoclonal antibodies are powerful anti-inflammatory agents with glucocorticoid-sparing properties. With the increasing use of biologics, tapering and cessation of maintenance systemic glucocorticoids have become much more common. Personalized approach to tapering and careful assessment for adrenal insufficiency in all patients are recommended by the experts.

Keywords: severe asthma, glucocorticoids, side effects, adrenal insufficiency

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Introduction

Asthma is a chronic airway inflammatory disease, characterized by reversible airway obstruction and airway hyperresponsiveness[1]. It affects 1-18% of population in different countries[2]. Approximately 5–10% of the patients have severe asthma[3], which remains uncontrolled despite adherence to maximal optimized therapy and treatment of contributory factors and comorbidities[2].

Systemic glucocorticoids (GC) became available in 1956 and they have provided effective treatment of asthma ever since[4]. Their widespread use led to the recognition that long-term systemic GC use is associated with significant adverse events[5] and to introduction of inhaled GC in 1972 as maintenance treatment for asthma[4]. However, there is still a significant burden of systemic GC due to treatment of asthma exacerbations and of severe asthma[4,6].

The many systemic effects associated with long-term systemic GC use have been well studied and described[7]. The most common serious systemic GC-associated comorbidities include osteoporotic fractures, diabetes, obesity, cardiovascular disorders, and hypothalamic-pituitary-adrenal (HPA) axis suppression. In addition, use of systemic GC has been associated with psychiatric symptoms such as insomnia, mania, depression, anxiety, or aggressive behavior. Dyspepsia, hypertension, dyslipidemia, opportunistic infections, muscle atrophy, cataracts, glaucoma, bruising, cushingoid appearance, skin striae and change in appetite can also occur[5,8,9]. Moreover, there is published evidence suggesting that even brief (3–7 days), but repetitive courses of systemic GC can provoke

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significant negative outcomes for patients, such as bone density loss, hypertension, gastrointestinal bleeding, and have negative impact on mental health[7].

Evidence from European Registries

The European Respiratory Society (ERS) Severe Heterogeneous Asthma Research collaboration (SHARP) was set up in 2018 to harmonize severe asthma management across Europe and to unravel underlying heterogeneity in a patient-centered way[10]. The current project involves the first structured assessment and comparison of national severe asthma registries that are part of SHARP to discover strengths/weaknesses in those registries and to evaluate severe asthma and its treatment across Europe.

Across-sectional retrospective analysis of aggregated patients' characteristics and their treatments before starting biologicals from 11 national SHARP affiliated severe asthma registries showed that patients were treated differently between countries. Their mean inhaled GC daily dose (fluticasone equivalent) ranged from 700 µg in Slovenia to 1335 µg in Poland when starting anti-interleukin (IL)-5 antibody and from 772 µg in Slovenia to 1344 µg in Spain in those starting anti-IgE, respectively. Maintenance oral GC use ranged from 21.0% (Belgium) to 63.0% (Sweden) and from 9.1% (Denmark) to 56.1% (the UK) in patients starting anti-IL-5 and anti-IgE, respectively[11]. The reasons for these differences are not entirely clear. Potential explanations, which would require a focused study by the SHARP clinical research collaboration, might include the cost of treatment and the fear of high-dose treatment-related side-effects[11].

Indeed, a recent systematic review and meta-analysis has suggested that the majority of oral GC-sparing effect of high-dose inhaled GC was likely to be due to their systemic effects[12]. Regarding the effects on HPA axis, 1000 µg of fluticasone propionate might have similar systemic effects to 5 mg of prednisone[13], which might be also true for 2500 µg of budesonide[14]. Therefore, high doses of inhaled GC should potentially be considered as harmful as low doses of systemic GC[15] and their effects are accumulative on top of systemic GC[7].

Approaches to Systemic GC Taper After Introduction of Monoclonal Antibodies

Monoclonal antibodies are powerful anti-inflammatory agents with GC-sparing properties[16-19]. Their availability represents a cornerstone for systemic GC taper and withdrawal in severe asthma, which is becoming a common scenario in clinical practice with the increasing use of biologics. However, a specific guidance on how to proceed is lacking[20].

Accordingly, over 130 international experts employed a modified Delphi method to develop a consensus statement on appropriate systemic GC use and tapering in patients with asthma, adverse effects, patient–physician shared decision-making, and future research domains[21]. The paper provided a broader guidance on when and how to taper systemic GC in patients with asthma, regardless of whether biological therapy has been initiated. According to consensus, tapering should be individualized and attempted in all patients with asthma receiving maintenance systemic GC therapy, regardless of comorbidities. The recommendations generated support for minimizing systemic GC use as much as possible. Global Initiative for Asthma (GINA) recommendations restrict systemic GC use to those patients who are ineligible for biologic treatment and define the lowest acceptable systemic GC maintenance daily dose at less than 7.5 mg of prednisolone[2]. On the other hand, the Delphi expert consensus considered a daily dose of less than 5 mg of prednisolone as acceptable, if no alternative treatment is available[21]. However, even merely 5 mg of prednisolone a day contributes to a cumulative dose of more than 1.8 g per year. Additional

awareness is therefore needed, if we consider the evidence that a lifetime cumulative systemic GC load of 0.5-1 g was associated with diabetes, while most other adverse effects emerged at 1 to less than 2.5 g[5].

Therefore, a routine screening using a minimal checklist for adverse effects and comorbidities is recommended in all patients with asthma on systemic GC treatment (Table 1).

Table 1. Minimal checklist for glucocorticoid adverse effects screening[21]

Glycemic control
Bone mineral density
Blood pressure
Cataracts and glaucoma
Weight change
Fracture risk assessment (e.g., FRAX)

Definition of abbreviation: FRAX=Fracture Risk Assessment Tool.

According to the expert consensus systemic GC tapering should be initiated only when it is considered appropriate for the clinical situation and asthma phenotype.

Three common baseline clinical scenarios were provided[21]:

1. *Do not attempt tapering* in EGPA (eosinophilic granulomatosis with polyangiitis) and ABPA (allergic bronchopulmonary aspergillosis) that relapses during tapering and no other changes can be proposed.
2. *Tapering with caution* in cases with:
   - history of life-threatening attacks,
   - systemic GC dependence for extended period (e.g., more than 6 months),
   - in patients with comorbidities that respond to systemic GC.
3. *Tapering should be done if:*
   - systemic GC result in no asthma improvement and/or side effects,
   - dose or duration of systemic GC treatment is cause for concern,
   - asthma control is achieved (especially with biologics),
   - there is a reasonable likelihood of HPA axis recovery.

Table 2. Consensus information on systemic GC tapering and suggested tapering speeds according to current systemic GC (methylprednisolone) dose[21]

Daily dose ≥ 16 mg	Daily dose 8-16 mg	Daily dose 4-8 mg
Faster pace	Medium pace	Slower pace
Reduce by 8 mg/ week or 30-50 % every 2-4-weeks	Reduce 2-4 mg every 1-2 weeks	Reduce by 1-2 mg every 1-2 weeks

During systemic GC tapering patients should be continuously evaluated for adrenal insufficiency (AI), comorbidities, and asthma symptoms. If GC taper is intolerable, tapering attempts should be stopped and postponed to a later date. Return to previous efficacious dose is also recommended. When symptoms are mild, current GC dose should be maintained and tapering speed should be reduced.

Proceeding toward GC cessation is suggested when:

- daily systemic GC dose is ≤ 4 mg of methylprednisolone,
- a sparing strategy has been initiated,
- the patient has agreed to cessation,
- there is no evidence of EGPA/ABPA,
- there is no evidence of adrenal insufficiency.

AI is very common among users of systemic GC after tapering[22] and experts[21] agreed that this condition is insufficiently assessed or underrecognized. Risk factors for development of GC-induced AI include the duration of GC therapy, mode of administration (e.g., oral vs. inhaled), GC dose and potency, concomitant drugs that interfere with GC metabolism, and individual susceptibility. Importantly, the risk of developing GC-induced AI is difficult to predict on an individual basis

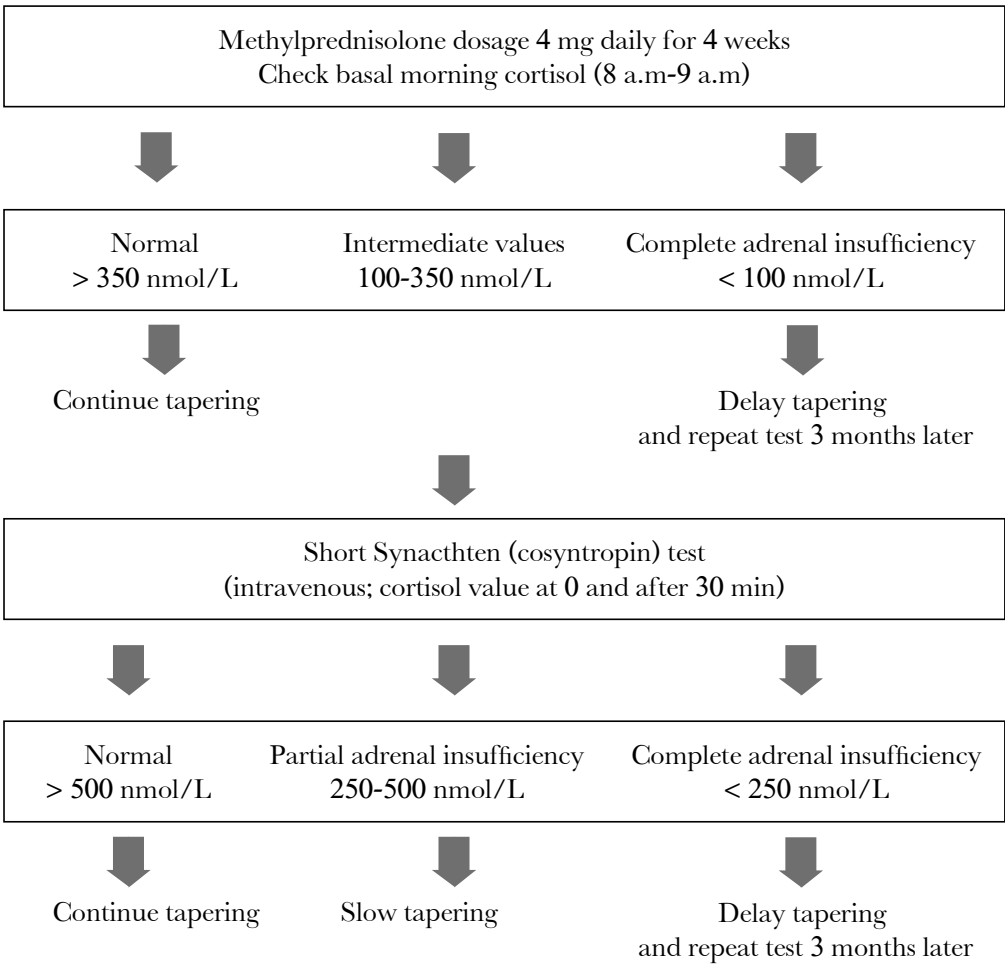

Figure 1. Recommended evaluation for adrenal insufficiency in severe asthma patients, previously treated with systemic GC (adapted from Menzies-Gow et al., 2021)

and low threshold for HPA axis evaluation is advised if clinical suspicion of AI exists. Use of basal morning cortisol is generally recommended for this purpose with short Synacthen (cosyntropin) testing to follow in the case of intermediate results[23].

Successful systemic GC dose reduction in patients with severe asthma after initiation of biological therapies, using preset tapering protocols, has been recently demonstrated. Specifically, the PONENTE study[24] has successfully authenticated a personalized systemic GC reduction algorithm with incorporated HPA axis integrity assessment . The investigators recommended evaluation for AI after patients had been receiving 5 mg of prednisolone (equivalent to 4 mg of methylprednisolone) daily for 4 weeks, as shown in Figure 1.

Clinicians should be aware that such protocols can serve as a guide only and that real-life management should be tailored on an individual basis. Moreover, cut-offs vary

according to the cortisol assay used and local practices. For example, basal morning cortisol that excluded AI varied between 336 and 506 nmol/L when measured by three different immunoassays. Therefore, the cut-offs proposed here should be seen as a direction only. Additionally, patients should be tested at least 24 h after the last dose of exogenous GC, because (methyl) prednisolone can interfere with immunoassays and cause falsely elevated cortisol values. To completely exclude this possibility, patients could be also switched to a replacement dose of hydrocortisone, a short-acting GC, before testing serum cortisol[23].

In the case of AI, the switch to hydrocortisone replacement therapy was generally preferred by the experts to continued prednisolone, but the consensus was not reached[25,21]. Theoretically, its shorter half-life might accelerate the recovery of HPA axis by negative feedback, especially when avoiding late afternoon exposure to hydrocortisone[23]. Switch to hydrocortisone is also recommended from practical reasons, for instance when low-strength GC tablets, such as (methyl) prednisolone 1 mg tablet, are not available.

Conclusions

Modern anti-inflammatory treatment with biologics is changing lives of many patients with severe asthma who had to rely on systemic GC and cope with their potentially serious side effects in the past. However, clinicians should be aware that life-threatening AI is common among systemic GC users and should familiarize themselves with correct GC tapering and cessation.

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3

Multidisciplinary Approach in Severe Asthma

The Multi-Disciplinary Team Approach to Specialist Adult Difficult Asthma Care

3.1

Ramesh J Kurukulaaratchy[1,2,3,4] and Chellan Eames[4]

Abstract

Difficult-to-treat (or difficult) asthma presents a challenging multidimensional model of chronic disease that imposes a significant burden at both individual patient and wider societal levels. Within that model of disease there is increasing understanding of the diverse range of asthma phenotypes that might be encountered. There is also the growing realisation that these do not occur in isolation but exist within a wider multimorbidity disease framework. Identifying these other treatable traits that exist within the setting of difficult asthma has shown capability to improve patient outcomes. In that context, application of structured approaches to patient assessment have shown good efficacy, both at more general as well as specialist care levels. So too have multidisciplinary team approaches to difficult asthma care. The combined roles of the Asthma Specialist Physician, Asthma Nurse Specialist, Asthma Pharmacist, Speech & Language Therapist and Asthma Dietitian in that regard are evolving rapidly. In this chapter we review the multimorbidity model of difficult asthma and how best to approach that via multi-disciplinary team working approaches when undertaking specialist management of adult difficult asthma in clinical practice.

Keywords: difficult asthma, multi-disciplinary team, multimorbidity, treatable traits

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Introduction – Burden, Disease Mechanisms, and Definitions of Difficult-to-Treat Asthma

Asthma is a common but heterogeneous chronic inflammatory airway disease responsible for associated symptoms of breathlessness, chest tightness, wheeze and cough. It is estimated to affect over 300 million people globally across the life course[1]. Most people with asthma can attain good disease control with standard inhaled therapies administered in line with conventional guideline-based approaches[2]. However, around 5-10% of people with asthma have more complex and difficult-to-control disease that is associated with greater disease morbidity, healthcare dependency, higher treatment needs and potential mortality risk. Though representing a small proportion of the asthma population, subjects with more severe disease account for a disproportionate burden imposed by this disease. They are estimated to account for at least 50% of asthma-associated healthcare costs[3]. Therefore there has been a concerted effort in recent years to better understand the nature and driving mechanisms behind more severe asthma and develop effective treatments for it.

Our current pharmacotherapeutic approach to asthma is moulded to the Type 2 (T2) inflammation pathophysiological paradigm of asthmatic disease. This concept of "T2-high" and "T2-low" asthma inflammatory

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endotypes[4] defined by the presence or absence of T2 inflammatory processes has become the central polarizing lens through which we view asthma pathophysiology. T2 inflammation may be driven by either (CD4+) Type 2 helper (Th2) lymphocytes or innate lymphoid cells group 2 (ILC2).[5] Th2 lymphocytes produce critical "asthma-genic" cytokines including interleukin (IL)-4, IL-5 and IL-13. IL-4 promotes IgE production by B lymphocytes, increases low-affinity CD23 ($F_{C\varepsilon}RII$) IgE receptor expression on B lymphocytes and macrophages while directing class switching of naïve CD4 T-helper lymphocytes to the T2 type.[6] IL-13 shares a common receptor (IL-4Rα) with IL-4 and shows similar effects including promoting IgE production and CD23 expression.[7,8] IL-4 and IL-13 also induce goblet cell metaplasia and MUC5AC production, driving mucus production too.[8] IL-5 is a key driver of eosinophilic processes, responsible for eosinophil migration into the asthmatic airway where they are a predominant cell type in T2 disease.[9] Eosinophils are now commonly regarded as the prime target for a range of evolving asthma treatment options from newer inhaled corticosteroids (ICS) and other prophylactic medications to monoclonal antibody biologic treatments. The last 5-years have seen a proliferation of higher level biologic asthma treatments enter clinical practice globally with undoubted improvements in patient outcomes. These include agents such as Omalizumab, Mepolizumab, Reslizumab, Benralizumab and Dupilumab. Yet not all patients respond well to biologic treatments[10]. Furthermore, recent studies have also shown that following a thorough characterization, most patients with more problematic asthma fall into the T2 category of disease suggesting the need to look beyond that simple pathophysiological paradigm in the future[11,12].

As our understanding of the pathophysiology of more severe asthma has grown, so has our recognition of the context in which that disease exists in patients encountered in daily clinical practice. Thus there is also a growing understanding that problematic asthma is seldom purely severe asthma in isolation but often part of a wider constellation of adverse health issues. Attempts to highlight this by adoption of specific terminology with discrete definitions for "difficult-to-treat (or difficult) asthma" and "severe asthma" have been proposed as outlined by the Global Initiative for the management of Asthma (GINA)[13]. Using that perspective, difficult asthma describes asthma in which aggravating co-morbidities, inadequate treatment, suboptimal inhaler technique and/or poor adherence may individually or collectively impede good asthma control. This broad definition also encompasses the subset of patients with truly severe asthma that remain sub-optimally controlled despite optimised treatment of both asthma and contributory factors[13-17]. Severe asthma has been defined by the ERS/ATS as asthma which requires treatment with guideline suggested medications for GINA steps 4–5 asthma (high dose ICS & long acting beta agonist (LABA) or leukotriene modifier/theophylline) for the previous year *or* systemic steroids for > 50% of the previous year *to* prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy[18]. For this definition, uncontrolled asthma was defined as at least one of: poor symptom control (as measured by standard measures such as Asthma Control Questionnaire or Asthma Control Test), frequent severe exacerbations (2 or more bursts of systemic steroids for at least 3 days at a time in the past year), serious exacerbation (at least 1 asthma hospitalisation in the past year), or airflow limitation (pre-bronchodilator FEV_1, Forced Expiratory Volume in 1 second <80% predicted alongside reduced FEV_1/FVC [Forced Vital Capacity] defined as less than the lower limit of normal). In parallel there is increasing emphasis on thorough and holistic assessment of patients with more difficult asthma. With such approaches it is becoming evident that

following comprehensive assessment, a large proportion of patients with more problematic asthma actually fall into the category of difficult rather than severe asthma. Two recent European studies have highlighted this point. In a study of 1034 asthma patients attending 4 respiratory clinics in Denmark, 17% were classified as having difficult asthma following application of ERS/ATS criteria for difficult asthma based on treatment levels. In those subjects after a systematic assessment process, only 12% fulfilled the stringent criteria for severe asthma in isolation, while 56% fell into the category of difficult asthma and 32% had overlapping features of both[19]. In a Dutch pharmacy database study of adult asthma patients, 17.4% met criteria for having difficult asthma. Following an Innovative Medicine Initiative (IMI) definition based on adherence and good inhaler technique to distinguish those with severe refractory asthma, only 20.5% of these difficult asthmatics were deemed to have severe asthma[20]. These findings collectively signal the point that most patients with problematic asthma have potentially modifiable treatable factors if those are identified through an appropriate comprehensive and holistic assessment process.

Difficult Asthma as a Multimorbidity Difficult Breathing Syndrome – The Concept of Treatable Traits

Clinicians readily acknowledge that a proportion of patients with asthma do not attain good asthma control despite full optimisation with currently available asthma treatments. This concerning fact was the focus of a Lancet 2017 Commission "After asthma: redefining airways disease".[21] In addition the realisation is dawning that poorly controlled asthma seldom occurs as an isolated health problem. In particular at the more "difficult-to-control" end of the spectrum asthma often constitutes part of a multimorbidity constellation of conditions best regarded as a "Difficult Breathing Syndrome" rather than "severe asthma" alone (Figure 1). This has led to the need to adopt a more holistic perspective

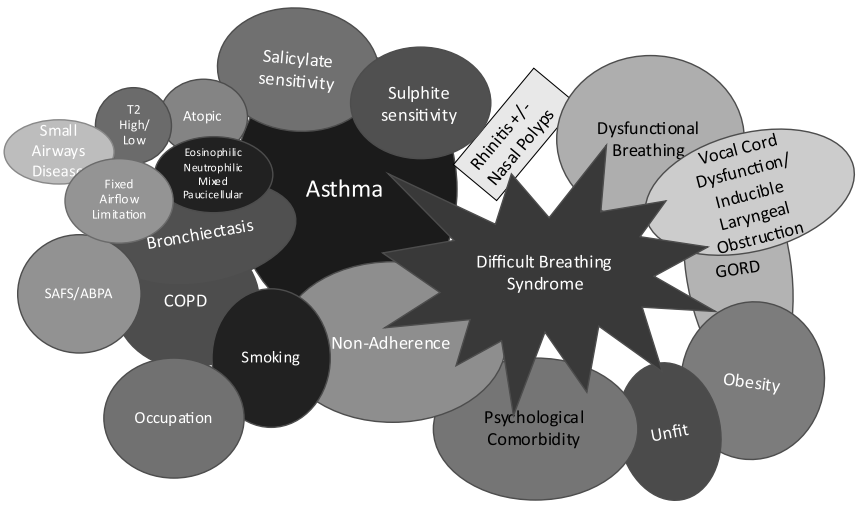

Figure 1. The "Difficult breathing syndrome" in difficult asthma.
Abbreviations: T2 – Type 2 inflammation, ABPA – Allergic Bronchopulmonary Aspergillosis, SAFS – Severe Asthma with Fungal Sensitisation, COPD – Chronic Obstructive Pulmonary Disease, GORD – Gastro-oesophageal reflux disease.

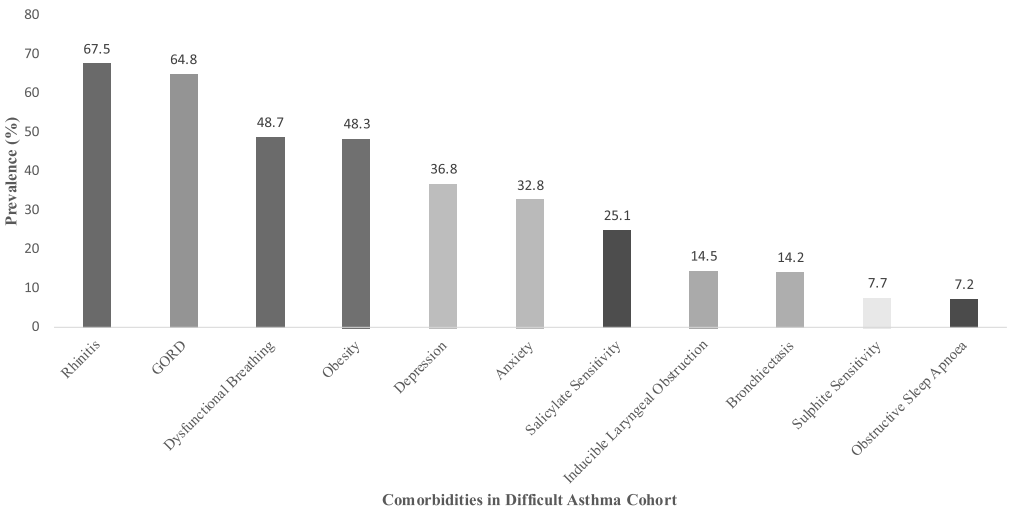

Figure 2. Comorbidities in the Wessex AsThma CoHort of difficult asthma (WATCH) study.
Abbreviations: GORD – Gastro-oesophageal reflux disease.

to understand the numerous challenges faced by patients with problematic asthma.

Real-world studies clearly demonstrate the significant level of ongoing comorbidity seen in patients with difficult asthma. For example in the Wessex AsThma CoHort of difficult asthma (WATCH) study based in the tertiary referral Difficult Asthma Clinic at Southampton, United Kingdom (UK), high prevalence of physical comorbidities like rhinitis and gastro-oesophageal reflux disease (GORD) were noted. But so too were psychophysiologic comorbidities like anxiety, depression, dysfunctional breathing patterns and inducible laryngeal obstruction/vocal cord dysfunction (Figure 2). Recent findings from the WATCH study have also demonstrated differing associations of these various comorbidities with difficult asthma phenotypes based on age of asthma onset/sex which merit wider understanding.[22] In particular, psychophysiologic comorbidities and obesity tended to be commoner in females with difficult asthma in that study highlighting other treatment options beyond asthma pharmacotherapy for particular subgroups.[22]

An important new taxonomic approach to airways disease based on identifying and managing component factors rather than generic disease labels such as asthma was recently proposed by Augusti et al to provide structure to this understanding of multimorbidity in airways diseases like difficult asthma.[23] Such potentially modifiable factors, known as "treatable traits" are broadly categorised as pulmonary, extrapulmonary and behavioural in nature and occur concurrently in combinations that may be specific to an individual patient. Pulmonary traits might include fixed airflow limitation, small airways disease, pattern of airway inflammation (eosinophilic, neutrophilic, mixed inflammatory, paucicellular), allergic fungal airways disease, aspirin exacerbated respiratory disease, bronchiectasis, airway infections and dual COPD. Extrapulmonary traits could include rhinitis, chronic rhinosinusitis (with or without polyps), gastro-oesophageal reflux disease, obesity, obstructive sleep apnoea, physical deconditioning, dysfunctional breathing, inducible laryngeal obstruction (ILO)/vocal cord dysfunction (VCD), anxiety, and depression.

Behavioural traits include poor inhaler technique, poor treatment adherence, distorted symptom perception and smoking. A core purpose of this structured approach of identifying treatable traits is to acknowledge the underlying complexity of clinical presentation in a manner that facilitates more precise asthma management which is personalised and holistic. This a notable shift from the "one size fits all" approach encouraged by traditional guideline-based management strategies that have been the mainstay of clinical management in recent decades.

Treatable traits are common in difficult asthma where they may cluster to variable degrees in individual patients.[16,17,24-26] One study indicated a median number of 3 comorbidities per patient attending a specialist-referral difficult asthma clinic in Melbourne, Australia.[27] Of note, the burden of treatable traits appears to align with worse asthma outcomes such as exacerbations, asthma control and quality of life.[17,23,25] Conversely systematic clinical approaches that incorporate addressing treatable traits in asthma has also recently shown clinical effectiveness in improving outcomes for this patient group.[27,28] This model of difficult asthma as a Difficult Breathing Syndrome with numerous treatable traits further stimulates the need to engage a systematic approach to assess and manage such patients and take into account multi-disciplinary approaches based on individual patient need.

Structured Multi-Disciplinary Team Approaches to Difficult Asthma Care

The recognition of difficult asthma as typically constituting a multimorbidity disease model alongside the growing portfolio of higher level biologic medications has led to a growing consensus that there is a need to adopt an increasingly structured and holistic approach to care for patients with difficult asthma.[13,29] A key advancement that has accompanied that consensus has been to both address the asthmatic component as well as relevant aggravating comorbidities in such patients. That in turn has been accompanied by an increasing focus on multidisciplinary team (MDT) models of care centred around a systematic assessment process in order to meet the diverse support needs of this patient group. Such structured models of care will inevitably vary according to healthcare system and available resource. This structured approach lends itself particularly well to implementation via specialist care centres for patients with difficult asthma. In countries such as the UK this approach has been further aligned to a process of regional specialist centres for difficult asthma supporting regional networks of care[29]. These centres must meet specified resource requirements and are subject to quality benchmarking on core outcomes. While the UK specialist commissioned framework offers one systematic approach, data has consistently shown that comprehensive assessment within more specialised difficult asthma care realises improvements in patient asthma status regardless of geography or healthcare system.[27,30,31] Thus a 3 step systematic approach to difficult asthma specialist care based on diagnostic confirmation, comorbidity detection and inflammatory phenotyping was assessed in Melbourne, Australia.[30] This resulted in significant improvements in comorbid conditions like chronic rhinosinusitis and dysfunctional breathing. It also resulted in significant parallel improvements in asthma related outcomes such as asthma control, asthma related quality of life and exacerbation frequency. Further work from the same research group has more closely focused on asthma patient-related outcome measures.[31] This found that a systematic assessment framework in difficult asthma specialist care realized significant improvements across multiple asthma domains. These included a halving of maintenance oral corticosteroid dose (regardless of biologic co-administration) and achievement of minimally important differences for asthma symptom control and quality of life

in over 50% patients. Reduced exacerbations were found in 64% patients while 40% patients improved their FEV_1 by ≥ 100ml. Improvement in at least domain was found in 87% of patients undergoing that systematic assessment. Of note, the improvements demonstrated in this study were independent of biologic treatment initiation, highlighting the value of early adoption of such approaches in the patient care pathway to ensure focusing the right treatments on the right patients, at the right time. In that context, structured assessment can be applied at different points along the asthma care pathway, not just in a specialist centre environment. SIMPLES was introduced as a tool for use in primary care to support management of patients with poorly controlled asthma.[32] The SIMPLES approach encompassed self-management, education, monitoring, lifestyle (with emphasis on smoking status) in addition to pharmacotherapy. The specific assessment domains in SIMPLES comprised smoking status, inhaler technique, monitoring, pharmacotherapy, lifestyle, education and support. Often ignored facets such as regular review and accessibility were also recognised and given prominence. This was coupled to guidance on when to refer from primary to specialist care. Another important component to SIMPLES was the early adoption of digital technologies with web-based access to both the SIMPLES framework and relevant assessment tools. More recently the Severe Asthma Toolkit was developed as a holistic resource to support structured multidisciplinary care for patients with severe asthma across the healthcare spectrum.[33] Developed by a consortium of multidisciplinary experts with patient and advocate codesign, this resource was established in the format of an easily accessible website. Content included background information about severe asthma, diagnosis and assessment, management, medications, comorbidities, living with severe asthma, information on establishing a clinical service, specifics to paediatric and adolescent care, advice on specific population needs, registries and access to relevant supporting resources. A structured electronic template to guide severe asthma systematic evaluation has also been recently created in the form of SAGE (Severe Asthma Global Evaluation) to encourage consistency in the systematic assessment process[34]. It contains up to 282 input fields but utilises auto-calculations and decision making tools to streamline the process.

The case to base difficult asthma care on a systematic multidisciplinary assessment framework seems entirely logical and well supported by an emerging evidence base as discussed above. However, that approach is not without potential difficulties at multiple levels as recently highlighted by Majellano et al.[35] These problems might be down to the physician with poor adherence to guidelines and checklists, alongside underuse of diagnostic tests and available referral pathways. They may also reflect issues of communication and different perceptions of management goals between physician and patient. A recent US study further emphasized the potential discordance in recognition of asthma control between physician and patient. Of note it demonstrated a tendency for under perception of symptoms and asthma control by patients when assessed by parameters such as Asthma Control Test or GINA asthma control criteria.[36] Other critical barriers to optimal multidisciplinary assessment and care may also occur at an organisational/resource level with inadequate clinical staffing, clinical space and capacity. Such factors may place limitations on access to both assess, review and treat patients in a timely and ideal fashion.

The MDT Components of Specialist Difficult Asthma Care in a Specialist Clinic

In a Specialist clinic setting, the assembled MDT typically will include a range of healthcare professionals including Consultant Respiratory Physicians, Consultant Allergists, Asthma Nurse Specialists, Asthma Physiotherapists,

Asthma Psychologists, Asthma Pharmacists, Speech & Language Therapists and Dietitians. Patients referred into such services will generally undergo comprehensive assessment at the point of referral followed by appropriate pharmacotherapeutic treatment changes. They then have regular follow-up with appropriate members of the MDT as dictated by individual need. Such MDT's typically review cases on a regular (often weekly) basis in a meeting setting to achieve group consensus on appropriate treatment steps culminating in approval for higher level biologic treatments once the MDT is satisfied that other appropriate actions have been addressed. This structured pathway meets the important goal of ensuring that all other facets of patient need are met rather than simply escalating to higher and higher asthma therapies in the hope of improving refractory breathing difficulties. It should therefore maximise the chances of improving healthcare status and facilitate rational use of higher-level costly biologic medications where they are truly indicated.

In the following sections we review the roles of different MDT members involved in difficult asthma care.

The Asthma Specialist Physician

In the Specialist clinic setting, a Consultant (or equivalently experienced) Respiratory Physician with subspecialist expertise and experience in managing difficult asthma plays a central role in directing patient treatment and overseeing an individualized approach to multidisciplinary patient care. In simple terms they might be viewed as the conductor of the MDT orchestra. Their role will initially focus on establishing that the patient does indeed have asthma. This basic step is important as it has been shown that after a thorough evaluation process a not insubstantial minority of patients (5-12%) may be deemed to not have a diagnosis of asthma.[37,38] If asthma seems probable, the Physician then must determine patient asthma phenotype and/or endotype to define the core type of asthma that is present. In parallel, they need to assess factors such as adherence to treatments and issues of inhaler technique to identify if such treatment related factors explain why that patient's asthma is not well controlled. Their assessment must also search for all possible aggravating comorbidities that might a) negatively impact on asthma control or b) themselves drive symptoms of breathing difficulty that lead to a misperception of those symptoms as being driven by asthma when they are not. In order to achieve this understanding they will need to undertake and interpret a range of objective measures to aid asthma characterization including blood tests (full blood count, Total IgE, aspergillus serology), allergy skin prick tests to a standard aeroallergen panel appropriate for that locality, lung function testing (spirometry with bronchodilator reversibility plus gas transfers), measures of airway inflammation (Fractional Exhaled Nitric Oxide [FeNO] +/- induced sputum differential counts) plus radiological imaging (chest radiography +/- High Resolution Computed Tomography [HRCT] chest). They will also need to undertake a range of screening assessments for comorbid conditions and their severity using standardised disease monitoring tools such as the Nijmegen Questionnaire (to assess breathing pattern disorder), HADS (Hospital Anxiety and Depression) score (to assess psychological comorbidity status), Epworth score (to assess for sleep apnoea) and SNOT-22 (to assess for rhinitis).[39-42] The use of such questionnaires as a standard component of the assessment process has been associated with significantly better identification of asthma-related comorbidities though it can be time consuming and onerous for the patient in the short-term.[43]

Following the initial comprehensive evaluation process, the Specialist Asthma Physician needs to determine appropriate asthma focused pharmacotherapeutic strategies and establish potential timelines to consider higher level biologic asthma therapies should

conventional approaches meet with limited success. At the same time they have to appropriately consider the need to involve other core members of the MDT in patient care including Nurse Specialist, Physiotherapist, Psychologist, Dietitian and Speech Therapist. Furthermore, they need to consider any need to refer to other specialists to address particular comorbidities (e.g. Gastroenterologists and Otolaryngologists for example).

In addition to a good understanding of asthma management, the Specialist Asthma Physician must have a good working knowledge of managing relevant comorbidities. A difficult asthma MDT would also benefit from having multiple Specialist Asthma Physicians in order to ensure resilient capacity to meet the demands placed on that service. That also offers the opportunity to create a Specialist team with a diversity of overlapping clinical expertise which can then prove helpful in complex case management. In that context having Physicians within the difficult asthma MDT who have added expertise in Allergy, Bronchiectasis, COPD, Sleep Medicine and ILO/VCD can significantly enhance the effectiveness of that MDT.

The Asthma Nurse Specialist

Asthma Nurse Specialists sit at the core of any difficult asthma MDT where they fulfil a variety of key roles at different stages of the patient journey as outlined in Figure 3.

When a patient is first assessed in a difficult asthma service, the Specialist Nurse may undertake a supportive role with many of the initial objective assessments. These might include performing aeroallergen skin prick testing, blood sampling and FeNO testing to inform asthma characterization as well as administering a range of questionnaires related to both asthma control and relevant aggravating comorbidities. These actions are time consuming. However, that time spent by a Nurse Specialist with a new patient at the outset of their Specialist Care can provide invaluable opportunity to establish a rapport with the patient, gain understanding of their hopes and fears and gain their confidence. A further important nursing role, both initially and then longer term, is to support patient understanding of their condition and the relevant aggravating factors that need to be addressed to aid their asthma management. These might include education on aeroallergen avoidance, smoking cessation, mitigating exposures to other irritants and measures such as weight loss and improved physical activity. Another important function of the Specialist Nurse is to support patient management by interlinking with other members of the MDT including the Consultant, Physiotherapist, Psychologist, Speech Therapist, Dietitian and Pharmacist as well as the patient during the course of the patient journey.

Ensuring optimal inhaler technique, developing sustainable self-management plans and achieving good adherence to both medications and other aspects of that management plan are all activities that Specialist Nurses also are well placed to deliver. These should be addressed at the outset but need regular reassessment and reinforcement over time as improvements in these areas may wane over time. In that regard, poor inhaler technique is commonplace among asthma patients, potentially present to some degree in most patients at some point, and remains an ongoing issue that facilitates poor asthma control.[44-47] A Cochrane database review of studies assessing impact of strategies to improve inhaler technique found some benefit for asthma control and quality of life but generally did not result in consistent or important clinical benefits.[48] This may in part reflect the heterogeneity and inherent biases of studies assessed in that review. Conversely a recent systematic review of critical inhaler errors and their impact on health outcomes did identify some studies that found beneficial impact of strategies to improve inhaler technique in relation to asthma outcomes.[49] There is also a major role for the Asthma Nurse Specialist in assessing

and addressing issues with suboptimal adherence to inhaler treatments in conjunction with Asthma Specialist Physician, Pharmacist and sometimes the Psychologist.

Self-management is a multicomponent approach that gives patients the confidence to deal with medical management, role management and emotional management of their chronic health conditions. Use of an asthma self-management plan, including regular monitoring of asthma symptoms and lung function, plus clear guidance on appropriate management strategies can significantly empower patients to take more effective control of their asthma. Specialist Nurses have a crucial role in guiding such strategies. A core value of self-management in a variable state like asthma is recognising worsening features and guiding early action. Thus self-management strategies have been shown to improve asthma control, quality of life while reducing exacerbations and acute healthcare usage without increasing healthcare costs.[50] Though self-management should be a core component of asthma care it is poorly implemented in routine clinical care despite an unacceptable burden of poor asthma outcomes.[51] Numerous barriers to effective use of self-management strategies in asthma are becoming increasingly understood.[52] Building on that, development of more versatile and user-friendly asthma self-management platforms to aid patients and healthcare professionals is attracting growing interest and Asthma Nurse Specialists could be integral to their oversight and coordination. In particular, interest on harnessing interactive technologies using patient-friendly digital platforms is growing. Studies have reported promising potential, good patient engagement, usability and satisfaction with some approaches.[53,54,55] Therefore, in the future Asthma Nurse Specialists are likely to need to be able to engage with such new technologies and approaches to undertake their roles within the MDT.

As Specialist difficult asthma care evolves with the emergence of a wide portfolio of T2 targeting biologic asthma therapies, so another significant role for the Asthma Nurse Specialist is taking form. This is to supervise the administration of these new agents and often coordinate that with new modalities of treatment delivery such as homecare and self-injection. In addition the Asthma Nurse Specialist is central to monitoring of treatment response during the initial treatment trial and for assessing continued response thereafter, with surveillance of need for a switch of biological therapy should response to the initial biologic drug wane over time. These new biologic agents deliver significant improvements in patient outcome for a majority of patients.[56-59] One area of opportunity in biologic responders is to significantly reduce maintenance oral corticosteroid (OCS) burden in a proportion of previously OCS dependent patients. This has highlighted another important role for the Asthma Nurse Specialist in guiding safe OCS weaning while remaining observant for features of secondary adrenocortical insufficiency.

A further activity that an experienced Asthma Nurse Specialist can undertake is to provide a parallel nurse-led channel of care with rapid access for designated patients under a difficult asthma MDT. There is limited definitive evidence on such activity in the setting of difficult asthma. The role of Asthma Nurse Specialists for asthma in general was highlighted in a comprehensive review which found no significant differences in asthma exacerbations, subsequent asthma severity or quality of life between Nurse-led or Physician-led care.[60] That concluded that Nurse-led care was potentially appropriate for well-controlled asthma but suggested the need to establish the evidence base in those with other levels of asthma control/severity. An Asthma Nurse Specialist can provide interim review for patients in between their Physician appointments during periods of clinical instability or where closer observation

is warranted, as in the case of a pregnant difficult asthma patient. Such channels can also interlink with acute care pathways and follow-up patients who have had an acute asthma admission to ensure optimised post-discharge care that seamlessly interlinks with the difficult asthma MDT. An early study of such post-discharge support identified improvements in patient knowledge about their asthma and relevant actions to take which was accompanied by reduced emergency GP call-outs in the following 4 months but no reduction in hospitalisations for acute asthma.[61] That mixed outcome might in part reflect the nature of the applied intervention. A subsequent study in our own Institution assessed impact of Asthma Nurse Specialist patient management as part of a Respiratory Physician-led pathway for patients with acute asthma in the Acute Medical Assessment Unit.[62] This intervention led to significant improvements in achieving safe discharge criteria and reduction in 30-day readmission, but at the expense of an extra day in hospital for the index admission. The role of an Asthma Nurse Specialist in such post-discharge pathways has also been demonstrated in a UK randomised controlled trial comparing nurse-delivered and physician-delivered post discharge outcomes.[63] That showed no significant differences in exacerbations or quality of life between the 2 intervention arms, though exacerbations remained relatively common in both. As our own group have subsequently shown, a combined MDT approach that links in with the difficult asthma MDT may deliver the best results for such post-discharge asthma care pathways (see section; *Impact of Combined Difficult Asthma MDT Approaches*).[64]

It can be readily appreciated that, as with the Asthma Specialist Physician, the Asthma Nurse Specialist needs to have well developed understanding of the nature, assessment and management of difficult asthma and relevant comorbidities. Overlapping experience in other areas of Respiratory Medicine and in Allergy are desirable to facilitate these requirements. They also need expertise in patient education allied to good communication skills, the ability to interact with a range of healthcare professionals and to apply new technologies as they emerge.

The Asthma Specialist Pharmacist

As the portfolio and complexity of available asthma pharmacotherapies expands, the Asthma Specialist Pharmacist has become an increasingly important member of the Asthma

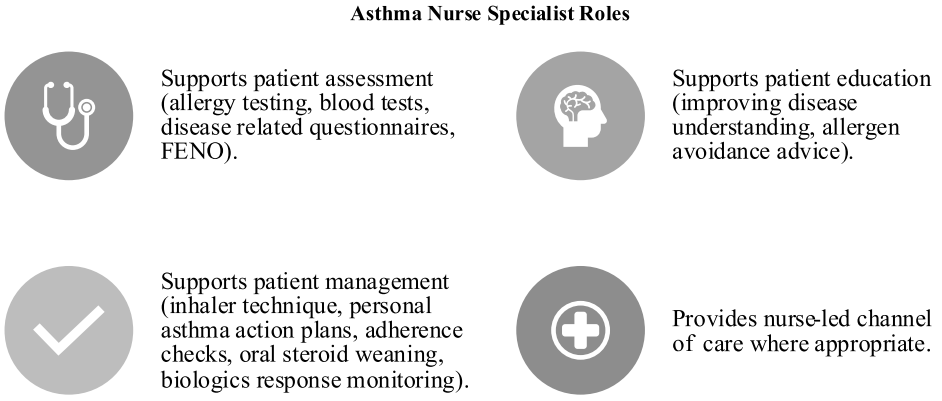

Figure 3. The Multidimensional Role of an Asthma Nurse Specialist.
Abbreviations: FENO = Fractional Exhaled Nitric Oxide.

MDT. Their role is potentially multidimensional with focused activities including assessment of inhaler adherence, optimisation of inhaler technique, undertaking patient consultations within the clinical pathway and input to providing governance oversight to biologics treatment pathways.

Suboptimal adherence to asthma therapies has long been recognised among patients with difficult asthma. A UK study over a decade ago identified that over one third of such patients had obtained less than 50% of their prescribed ICS while nearly half of those prescribed maintenance OCS were found to be non-adherent to that medication.[65] Another contemporaneous UK study demonstrated that 65% of patients in a difficult asthma clinic were non-adherent to their asthma medications defined by less than 80% pick up of prescribed medications.[66] In this study, non-adherence was a predictor of poor asthma outcome including history of needing ventilation for acute severe asthma. A more recent Australian study identified that nearly 50% of patients assessed in a difficult asthma clinic setting using electronic monitoring devices were found to have suboptimal inhaler adherence defined as taking less than 75% of prescribed doses. That study also noted that around half of those eligible for costly biologic therapies met non-adherence criteria for their conventional preventer treatment regime.[67] These studies collectively highlight a significant problem with non-adherence in this patient population which an Asthma Specialist Pharmacist would be well suited to identifying and addressing. However, subjective patient reporting is unreliable and simple clinical assessment has been shown to be inaccurate too.[67] Tools such as prescription pick up data and calculation of the medicines possession ratio have gained widespread use.[65] These probably work best in healthcare settings with well-constructed electronic health record systems clearly documenting prescription issues that can be readily accessed and easily interpreted by the Asthma Specialist Pharmacist. One obvious drawback of this approach is that prescription refill does not always equate to actual medication usage. An alternative adherence assessment is the FeNO suppression test used in patients with high baseline FeNO, whereby they undergo daily FeNO measurement alongside monitored inhaler usage.[68,69] This has accurately identified patients with poor adherence who showed greater falls in FeNO during the course of the test. Increasing adoption of electronic technologies in healthcare offers opportunities with respect to adherence assessment in asthma too. Numerous electronic add-on devices can yield useful insight into inhaler usage.[67,70] These tools can offer a foundation for discussions with patients on then improving adherence to inhaled medications. Blood monitoring for adherence to OCS has also seen increasing uptake with development of paired prednisolone and cortisol assays for use in clinical practice for patients on maintenance OCS.[71,72]

There are also multiple dimensions to non-adherence which might be either a considered intentional act by the patient or a non-intentional outcome associated with other demographic patient factors that influence poor medication usage.[73] Therefore individualised approaches to addressing adherence may be needed dependent on the specific patient. An Asthma Specialist Pharmacist may be well placed to deliver such activity in the difficult asthma MDT setting, coupled to actions such as inhaler training consultations. Pharmacist delivered asthma inhaler training has been shown to improve both adherence and asthma control at a general asthma population level.[74] Systematic reviews have demonstrated positive impact of Pharmacist delivered interventions on both asthma adherence and a range of outcomes.[75,76] However, improved asthma medication adherence may not always be followed by improved clinical status in a multimorbid disease model such

as difficult asthma. Nevertheless as we traverse an era of new biologic asthma therapies, formal assessment of adherence to conventional asthma therapy and optimisation has become a mandated prerequisite to accessing biologic therapies in many healthcare systems such as the UK.[29] In such systems, the Asthma Specialist Pharmacist often assumes a central gatekeeping role.

The Asthma Physiotherapist

An Asthma Specialist Physiotherapist can deliver 3 important roles in the context of a difficult asthma MDT; chest clearance support, breathing control training and physical exercise training.

Asthma is a chronic inflammatory disease associated with airway epithelial goblet cell hyperplasia and consequent potential for mucus hypersecretion. Some difficult asthma patients may show a hypersecretory pattern of airways disease with excessive mucus production that is associated with airflow obstruction and worse asthma control.[77] Furthermore, it is increasingly recognised that overlap airway disease states may arise with features of dual asthma, COPD and bronchiectasis. Much debate has focused on the concept of an Asthma-COPD-Overlap-Syndrome that may show bronchitic clinical features.[78] Bronchiectasis, while complicating distinct asthma phenotypes such as allergic fungal airways disease is estimated to occur in about 1/3 of asthma patients and align with more severe asthma.[79,80,81] Chest clearance may be a helpful adjunct tool in the setting of such dual disease phenotypes. An Asthma Specialist Physiotherapist may facilitate that by teaching patients techniques such as active cycle of breathing approaches centred on core components of breath control, thoracic expansion exercises and forced exhalation techniques augmented by use of Positive Expiratory Pressure (PEP) devices where appropriate[82]. There is minimal formal evidence to demonstrate the efficacy of such methods in difficult asthma.

Dysfunctional breathing (or breathing pattern disorder) describes an aberrant breathing pattern which results in breathing difficulty that is often accompanied by other symptoms including palpitations, chest pain, light-headedness, paraesthesia and anxiety. It is commonplace among patients with difficult asthma, affecting nearly 50% of subjects in some studies.[22,83] Furthermore it may link with other detrimental comorbidities in difficult asthma including psychological comorbidities and inducible laryngeal obstruction/vocal cord dysfunction.[83,84] An Asthma Specialist Physiotherapist is central to addressing this through breathing retraining techniques. These have shown benefit in the setting of asthma in general, as well as in difficult asthma.[85-88] The high burden of dysfunctional breathing in difficult asthma has potential to impose significant workload pressures on an Asthma Specialist Physiotherapist. It is therefore encouraging that a digital self-guided breathing retraining intervention has shown equivalent beneficial impact compared to face-to-face Physiotherapist delivered training in incompletely controlled asthma.[89]

Physical deconditioning and weight gain are recognised features of difficult asthma. Exercise interventions have potential to improve asthma control, fitness levels and quality of life.[90,91] While the evidence base for Pulmonary Rehabilitation in COPD is well established, that remains limited in asthma. However, a recent study demonstrated positive effects of such an approach in severe asthma with respect to exercise capacity and symptoms.[92] An Asthma Specialist Physiotherapist would be well placed to support these types of intervention. However, high perceived barriers to exercise have been documented in difficult asthma in conjunction with associated comorbidities and airways disease status that can make such management options challenging.[93]

It can be seen that the Asthma Specialist Physiotherapist may effectively support a variety of needs for the difficult asthma patient. A recent systematic review has supported that concept demonstrating the benefits of a range of physiotherapy inputs to asthma care.[94]

Speech & Language Therapist

Inducible laryngeal obstruction/ vocal cord dysfunction (ILO/VCD) is a "middle airway" disorder characterised by involuntary narrowing of the vocal folds predominantly during inspiration. It gives rise to symptoms of breathing difficulty including breathlessness, voice change, and may be associated with the phenomenon of upper airway or glottic wheeze. It may act as a mimic for asthma symptoms but has been demonstrated to be present as an aggravating comorbidity in 15-30% of difficult asthma patients.[22,37] Diagnosis ideally requires an MDT approach with input from Asthma Specialist Physician, Asthma Nurse Specialist, Asthma Specialist Physiotherapist, Otolaryngologist plus Speech and Language Therapist. Clinical assessment alone might miss the diagnosis which ideally rests on objective visualisation of the dynamic laryngeal abnormalities at laryngoscopy.[95] An alternative empirical diagnostic pathway based around MDT consensus has been proposed due to restrictions around undertaking laryngoscopy during the Covid-19 pandemic.[96] Management approaches remain to be validated for ILO in the setting of difficult asthma. MDT approaches revolving around the input of a speech and language therapist nevertheless show efficacy and are often the mainstay of treatment in centres specialising in this condition.[97] These typically employ a multicomponent approach that includes patient education, strategies to reduce laryngeal irritation and tension plus elements of psychological and physiotherapy support where appropriate.

The Asthma Psychologist

Psychological comorbidity such as depression and anxiety affects at least 1/3 of patients with difficult asthma.[22] Psychological comorbidity in asthma has been shown to associate with worse asthma and psychological outcomes as well as impaired quality of life.[98-103] Clear understanding of the impact of such health issues upon the multimorbid disease model of difficult asthma remains to be defined. That it is likely to have significant impact is suggested by previous findings from our Institution.[104] In a retrospective study of patients repeatedly hospitalised with acute asthma in a 12 month period, 69.4% had a known psychiatric diagnosis alongside frequent other comorbidities including dysfunctional breathing and obesity. Such patients accounted for a disproportionately high number of bed days and associated healthcare costs.

The Asthma Psychologist can create a personalised approach to support the psychological needs of the difficult asthma patient. A variety of processes might be utilised including mindfulness therapies and cognitive behavioural therapies. Mindfulness practice is centred on non-judgemental acknowledgement of experiences in order to reduce anxiety and depression.[105] A randomised control trial (RCT) of mindfulness-based stress reduction, found improved quality of life and less perceived stress across 42 patients with mild, moderate and severe asthma (compared against a control intervention).[106] The feasibility and positive impact of delivering such interventions in a group setting has been shown in a recent pilot observational study.[107] Cognitive Behavioural Therapy (CBT) provides another avenue for the Asthma Psychologist to support patients with difficult asthma. This focuses on stopping negative thought cycles associated with an overwhelming complex issue such as difficult asthma by breaking that down into smaller parts that be more readily addressed. A Cochrane review of CBT in persistent asthma demonstrated some

improvements in quality of life, asthma control and anxiety levels, though wider effects could not be discerned. Additionally inconsistent study methodology reduced the degree to which these results could be interpreted.[108] A case series from UK difficult asthma centres illustrated the potential individual patient benefits that can be obtained using CBT interventions.[109]

A potential role for the Asthma Psychologist within a multidimensional intervention is indicated by the recent demonstration of a clustering of extrapulmonary comorbidities in difficult asthma patients with very poor asthma control. These included psychological factors such as depression and anxiety plus obesity and physical inactivity.[24] Adequate Psychologist resource and time to support the mental wellbeing needs of patients under specialist services with difficult asthma is likely to become a pressing need within difficult asthma MDT's.

The Asthma Dietitian

Obesity is a common finding among patients with difficult asthma. For example, in the WATCH study the average BMI of patients was 31, while the prevalence of obesity was 48%.[22] The presence of obesity is associated with worse asthma outcomes and greater disease severity. [110] Weight loss strategies can improve asthma outcomes particularly when combined with other behavioural interventions targeting exercise and/ or mental wellbeing.[111] The input of a dietitian to support such interventions could be very impactful but there is little evidence base in the literature on which to guide that role. Another role of the dietitian may be in those asthma patients who have significant food allergies. The combination of food allergy and asthma is mutually detrimental and the role of a skilled dietitian to establish safe food practices is invaluable in that setting.[112] The role of dietitians in allergy practice is well-established and may provide a framework that can be adapted for future pathways in difficult asthma.[113]

Impact of Combined Difficult Asthma MDT Approaches

The multimorbid nature of difficult asthma ideally requires an integrated MDT approach to properly address the constituent parts. Significant benefits from such an approach have recently been demonstrated utilising a structured assessment to identify treatable traits, aligned with appropriate MDT involvement that was coordinated by a nurse case manager.[28] These included improvements in quality of life, asthma control and acute primary care asthma visits. Previously an integrated MDT approach was established by our Institution when initiating a tertiary care outreach difficult asthma clinic on the Isle of Wight, UK.[114] That involved an Asthma/ Allergy Specialist Physician, Asthma Specialist Nurse, and Allergy Dietitian alongside access to Respiratory Physiotherapist and Clinical Psychologist. Within 18 months of being under that care pathway, difficult asthma patients showed significant reductions in maintenance OCS use and dosing requirement. In addition significant reductions in asthma healthcare utilisation were observed with respect to GP visits, Emergency Department visits, Hospital bed days and Intensive Care Unit bed days. None of the patients in that study received biologic therapies during the study period. Integrating such MDT approaches to link acute inpatient care and outpatient care can also deliver significant benefits for difficult asthma patients.[64] An MDT was implemented comprising Asthma Specialist Physician, Asthma Specialist Nurse, Respiratory Physiotherapist and Clinical Psychologist spanned the patient journey from inpatient to outpatient care. Over the course of 2-years this intervention reduced repeated asthma admissions by 33%, associated bed-days by 52% and associated repeat admission costs by 35%.

Conclusions

Difficult asthma represents a complex multimorbid disease model with many aspects of need that require a well-structured and highly coordinated multidisciplinary team approach. MDT's are therefore central to the management of difficult asthma with key roles for the Asthma Specialist Physician, Asthma Nurse Specialist, Asthma Physiotherapist, Asthma Pharmacist, Speech & Language Therapist and Dietitian. There is growing evidence that coordinated MDT-based management of difficult asthma can deliver significant patient benefits.

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The Characteristics of Upper Respiratory Tract in the Patients with Asthma and the Patients with Episodic Laryngeal Obstruction

3.2

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Abstract

Background. Asthma and some other diseases of the upper respiratory tract have similar symptoms and signs. The signs and symptoms of rhinitis and laryngitis are not unusual in patients with allergic asthma. Attacks of dyspnea are not characteristic only for asthma but also for some other diseases with pathogenesis in the larynx.

Methods. The recent papers on upper respiratory tract characteristics in the patients with asthma and the patients with episodic laryngeal obstruction were reviewed.

Results. The connections between the nasal signs and symptoms and asthma are well established what is not the case for laryngeal problems. The laryngeal symptoms and signs in patients with asthma can be caused by the same triggers as asthma. However, they can also be merely the consequences of the asthma signs and symptoms or the asthma treatment. The pathogenesis of the episodic laryngeal obstruction includes a variety of causes which dictate the mode of treatment. In some cases, asthma and episodic laryngeal obstruction can coexist.

Conclusions. In order to find the correct diagnosis and proper treatment of the upper respiratory tract problems in patients with dyspnea attacks, a team of different specialists is necessary.

Keywords: asthma, rhinitis, laryngitis, allergy, dyspnea, diagnostics, treatment

Upper Respiratory Tract Problems in the Patients with Asthma

Nasal Disorders

The upper and lower respiratory tract share the same anatomical, functional, pathogenic, clinical, and immunological features. The airborne allergens activate the similar effector cells in the respiratory tract. Therefore, a term »the united airway disease« was introduced[18]. It is well known that asthma and allergic rhinitis appear together in a considerable number of patients. In a large study in China, it was confirmed a 29.4% prevalence of allergic rhinitis in asthmatic patients, and a 20.6% prevalence of asthma in patients with allergic rhinitis[27]. The association between asthma and allergic rhinitis was extensively studied. It is very likely that it is a disease occurring simultaneously in both parts of the respiratory tract[11,24,17]. In a recent study on molecular mechanisms causing asthma, rhinitis and eczema, 15 pathways involved in this multi-morbidity were found[2]. There are limited studies on the risk factors responsible for the progression of allergic rhinitis to asthma. However, recent data suggest that it is possible to prevent asthma onset by allergen immunotherapy in the patients with allergic rhinitis[30].

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Laryngeal Disorders

In terms of unified respiratory path (nose, middle ear, larynx, lungs), a mediator response in one organ can trigger similar responses along the rest of respiratory tract. There is a paucity of research on allergic laryngitis. Some authors even doubt that such entity really exists. The diagnosis of allergic laryngitis is a diagnosis of exclusion after all other possible diagnoses (laryngopharyngeal reflux, retronasal drip as a consequence of sinusitis, laryngeal symptoms due to irritation at working place, etc) are ruled out[47]. Most patients with suspicion of allergic laryngitis complain because of cough, throat clearing, sensation of a foreign body and excessive mucous in the throat, postnasal drip, and different voice disorders. When the researchers studied reaction of laryngeal mucosa to various antigen exposures thick-viscous endolaryngeal mucous and transient or chronic reactive vocal folds oedema and hyperaemia was noticed in a great majority of the cases[39,6]. There are several studies showing a link between allergic rhinitis and vocal symptoms which can improve with increased duration of immunotherapy treatment[31,44].

Voice disorders are not unusual in the patients with asthma. Deteriorated voice quality was noticed in asthma patients when compared to healthy controls with the use of objective and subjective evaluation methods[14]. There are several different mechanisms through which the voice quality in asthma patients can be affected. According to the theory of the unified respiratory disease, the vocal fold mucosa may be affected by allergic inflammation thus altering the mass of the vocal folds and their vibrating characteristics. The mucous on the vocal folds can give the characteristic of »wet voice« but also forces the patient to cough. As a matter of fact, cough is one of the most prominent symptoms of asthma. During cough the vocal folds violently strike together causing mechanical trauma, oedema, erythema and even the occurrence of some benign laryngeal lesions[46]. The third possible way is though the reduction of air flow coming from the lungs of the asthmatic patient to the vocal folds. Consequently, the available subglottic pressure does not suffice for good voice quality and causes the speaker to change the activity of laryngeal muscles during phonation in order to compensate for the insufficient subglottic pressure[46].

The fourth possible mechanism of affecting voice quality is through the influence of asthma treatment on larynx. Dysphonia is the most common side effect of inhaled corticosteroids treatment. After inhaled steroids exposure the laryngeal findings range from vocal fold oedema, erythema, and atrophy to irregularities of the vocal fold edges, interarytenoid thickening, and supraglottic hyperactivity[19]. The vocal fold atrophy results in vocal folds' bowing and incomplete vocal folds closure during phonation. Ozbilen Acar et al. proved corticosteroid-associated myopathy after inhaled corticosteroids treatment by performing EMG and stroboscopy during therapy and after its cessation. The glottis gap and voice disorders improved in several weeks after the end of therapy[35].

Inhaled corticosteroids produce their affects mostly by local immunosuppression secondary to reduced mRNA synthesis[35]. Localized laryngopharyngeal candidiasis is the most frequently documented infection after the use of inhaled corticosteroids. The incidence of laryngeal candidiasis associated with dysphonia was estimated at 20% in those taking inhaled steroid therapy[50]. As a matter of fact, the entire microflora of the larynx changes after regular inhalation of corticosteroids, and potentially lead to the occurrence of rare opportunistic laryngeal infections[49].

Episodic Laryngeal Obstruction

Attacks of dyspnea and wheezing are not only the typical symptoms of asthma. Sudden airway obstruction at the level of the larynx was first described as a disturbance in the

functioning of the laryngeal muscles in 1842 and was called "hysterical croup"[15]. Since then, more than 70 different names have been used for the problem described. Recently, the terms periodic occurrence of laryngeal obstruction or episodic laryngeal obstruction (ELO) have been used, which include the possibility of pathological events both at the level of the vocal folds and at the level of the supraglottis[9].

Etiology

The etiology is not entirely clear. Among the possible causes for inducible laryngeal obstruction with breathing disorders many different factors and situations are mentioned: the aerodynamic principles possibly connected with age, gender and physical capacity[20,45,29,40]; alteration of the laryngeal sensibility after stimulation of the supraglottis mucosa or direct stimulation of the superior laryngeal nerve by laryngopharyngeal reflux, allergy, infections[36,25,40], irritants, temperature and humidity of the air in the surroundings[26]; and psychological aspects[42,23].

Morrison hypothesized that the cause for abnormal laryngeal obstruction during inspiration is a change in the central nervous system resulting in hyper-irritable state of the sensory and motor pathways. Various pathophysiological processes lead to chronic irritation of the laryngeal nerves, and due to the plasticity of the nervous system, the way the central neurons respond to an incoming stimulus may change. Thus, the event triggers a sensory stimulus, and airway obstruction occurs due to the hyperexcitable state of the neural network in the brainstem that controls the functioning of the larynx[32]. Ayres and Gabbott believe that the altered balance of the autonomic nervous system maintained by structures in the central nervous system plays a role in abnormal vocal folds movement in patients with ELO[5]. Frequent prevalence of symptoms of laryngopharyngeal reflux and decreased laryngeal sensitivity have been reported among individuals with ELO. The authors thought that sudden laryngeal closure could be triggered by poorer laryngeal sensitivity or inflammation of the laryngeal mucosa. Another possible explanation could be that the threshold of excitability is lowered, but when it is reached, it triggers a very strong reaction in the sense of "all or nothing"[13,22]. Some believe that the cause of mainly supraglottic approximation of structures is the negative inspiratory pressure during rapid deep breathing which attracts tissues into the lumen of the larynx. They call it „bottle neck" theory based on special laryngeal anatomy with narrow laryngeal inlet[41,40]. In the case of coexisting laryngopharyngeal reflux from the oesophagus, the characteristic oedema of the laryngeal inlet makes it even more pliable and the approximation of aryepiglottic folds is more likely[22].

Classification

The ELO is divided into three categories according to the triggering factor:

1. ELO due to irritation (substances from the environment, laryngopharyngeal reflux),
2. exercise-induced laryngeal obstruction (EILO),
3. psychogenic ELO.

In fact, all three forms of ELO can be intertwined. Airway obstruction can occur at the level of the vocal folds or supraglottis, or at both levels at the same time. In some patients, vocal folds' approach occurs not only during inspiration but also during expiration. Between dyspnea attacks, the patient has no breathing problems[9].

Epidemiology

There are no accurate data on the prevalence of ELO in the population. ELO is thought to be the real cause of breathing problems in 10% of patients who are unsuccessfully treated for asthma. It is often the cause of breathing

problems in patients with certain psychiatric disorders (e.g. depression, childhood sexual abuse, obsessive-compulsive disorders)[16,4]. Women predominate among ELO patients, with a 3:1 ratio in their favour as reported in the professional literature. Problems most commonly occur between the ages of 20 and 40, but patients aged 6 to 83 years have also been described[9,23].

More information is available for EILO, one of the subtypes of ELO. EILO occurs mostly in adolescent or young adult women, often top athletes at maximum exercise. Among randomly selected young people in Denmark, at least 7.5% of people with EILO were identified, and among adolescents with upper respiratory hyperexcitability, as many as 26.1% of people with EILO[42,8].

Symptoms and Signs

Especially in EILO, shortness of breath occurs and very often also inspiratory stridor during physical exertion, so these patients are initially treated for exercise-induced asthma[33,43]. Other symptoms include dysphonia, dysphagia, cough, and some patients also report a foreign body sensation in the throat or a feeling of discomfort in the chest and throat[9]. Problems can occur at rest or during physical exertion, either during the day or at night. Symptoms of shortness of breath and inspiratory stridor can be triggered by an identified trigger (e.g. strong odour, irritants in the air, emotional stress), or they can occur without any obvious reason. Problems usually pass within seconds, minutes rarely lasting longer[32]. Occlusion at the level of the supraglottis occurs more frequently. The arytenoids descend forward above the entrance to the larynx, the aryepiglottic folds approach the median line, leaving little room for breathing between them and the epiglottis. In the case of glottis closure, the vocal folds come very close together, they can even be practically compressed, leaving only a tiny space for breathing between the two vocal processes of the arytenoid cartilages[9,12].

Diagnostic Procedures

A group of different specialists should be involved in the diagnostics of ELO (otorhinolaryngologist, pulmonologist, gastroenterologist, neurologist, psychiatrist, psychologist, speech therapist and others according to the clinical picture). The gold standard in ELO diagnostics is a larynx examination using a flexible nasolaryngoscope during the attack of dyspnea. In most cases it is impossible to have the opportunity to perform the examination and to have the necessary equipment on site. Only in EILO, the diagnostic procedure can be planned and carried out. Flexible nasolaryngoscopy is performed during exercise on a bicycle or treadmill while monitoring ECG, lung function, blood oxygen saturation, and blood pressure fluctuations[21,48,40]. At rest or in the period without problems, the laryngoscopic picture is usually normal.

In the differential diagnosis of ELO, asthma, especially stress-induced asthma, anaphylactic and other allergic reactions, foreign body in the respiratory tract, angioedema, laryngospasm, epiglottitis, other upper respiratory infections, unilateral and bilateral paralysis of the larynx from other causes, adductor-respiratory congenital anomalies and benign and malignant changes in the larynx, stenosis of the larynx and upper trachea must be mentioned. To exclude other diseases that can also cause occasional breathing problems and audible breathing, it is advisable to take a measurement of lung function. The flow-volume curve shows a typical decrease in the curve during inspiration during an ELO attack. A methacholine test is required to rule out asthma. Positive allergy tests, detection of peripheral blood eosinophils, C1 inhibitor concentrations, and C4 levels distinguish ELO from allergic manifestations and angioedema[9]. It is possible that exercise-induced asthma and EILO coexist.

Among the youth with airway hyperresponsiveness, the prevalence of EILO was 26.1%[8].

Treatment

Team approach is necessary to treat patients with ELO problems. When the correct diagnosis is established with appropriate procedures, we can explain the events to the patient in the acute phase and calm him down. In some patients, rapid "dog breathing" is successful, in others a slow long breath through the nose, in others an attempt to smell or phonate a high voice / s / or a combination of these two manoeuvres. Some patients are helped by speaking quickly, loudly, coughing, or holding their breath[1]. Some authors report the success of diazepine therapy, while other authors are not in favour of this method of treating acute dyspnea[1,9]. Christopher and colleagues were the first to describe the immediate beneficial effect of inhaling a mixture of helium and oxygen during an attack, and the effect of the treatment was not only acute but also long-lasting[10]. Although ELO is benign in nature and difficulty breathing ceases after a period of time, cases have been described where intubation or even tracheotomy was required due to severe respiratory distress during the attack[9].

So far, quite a few methods have been used in the treatment of recurrent problems with varying degrees of success. Speech therapy treatment is based on breathing exercises, exhalation against resistance, strengthening of inspiratory muscles and relaxation of vocal cords[9,7]. Psychotherapy and counselling help in 30% to 90% of cases, greater successes are of course in the psychogenic form of ELO. There are some reports of successful use of hypnosis in the paediatric population[3,9].

Until a few years ago, experts believed that gastroesophageal reflux to the level of the larynx and pharynx was the main cause of ELO. This is the case in certain patients. There are studies that have demonstrated the presence of reflux in patients with ELO, so it was logical to use proton pump inhibitors, ranitidine, and antacids in those patients. The success of such treatment is very good in those patients in whom reflux has been demonstrated[38,34].

Surgical treatment also gives good results, but only in selected patients. The most commonly used method is to cut the aryepiglottic folds closer to the epiglottis and to remove the mucosa and cuneiform cartilage from the aryepiglottic fold with the help of a laser (supraglottoplasty). The use of a suture that pulls the epiglottis towards the root of the tongue and lateralization of one vocal cord with a suture is also described[28,51].

Pinder and co-workers used a questionnaire to determine the long-term course of the disease. After 15 years of ELO onset, none of the patients reported deterioration. The condition improved or completely recovered in 68% of included subjects[37].

Conclusions

Respiratory tract acts as a whole. The same causes can induce asthma, rhinitis and laryngitis in some individuals. Some of the laryngeal characteristics of the asthma patients can be just the result of asthma symptoms or asthma treatment. In others, there are different diseases manifesting the same symptoms of the upper respiratory tract. In some patients, different pathologies coexist. Therefore, a team of different specialists must be involved in the diagnostic procedures and the treatment of asthma, asthma – caused conditions, asthma-accompanying diseases, and asthma-like diseases of the upper respiratory tract.

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4

Diagnostic and Therapeutic Chalenges in Severe Asthma

Lung Function Tests to be Used in Severe Asthma: Spirometry and Bronchodilator Test, Diffusion Capacity for CO, Induced Sputum, Body Plethysmography, Electronic PEF Measurements

4.1

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Abstract

Lung function tests are the cornerstone for asthma diagnostic procedure and patient follow-up and is complementary to other phenotyping tools used later for precision diagnosis. Spirometry and bronchodilator tests are used to define degree and reversibility of airway disease, diffusion capacity of the lung for CO is used as exclusion tool for comorbid diseases (particularly COPD), Body plethysmograph is used in small airway asthma to determine the degree of air trapping and hyperinflation, electronic PEF monitoring is used for work-related asthma characterization and targeted sputum examinations (induced sputum protocol) are used in immune phenotyping process. In hands of pulmonologist these tests (not all of them routinely used) are necessary to separate uncontrolled asthma from severe asthma phenotype.

Keywords: lung function tests, severe asthma, work related asthma, asthma phenotyping

Introduction

Asthma from lung function perspective is a disease detected by *smooth muscle hyperresponsiveness* and airway *obstruction,* which is *variable* and *reversible*. All these physiological hallmarks of the disease can be appropriately tested, although the results may vary over the course and intensity of the disease. If chosen in context of a clinical picture of a patient, they can provide most definite diagnostic confirmation of the disease[6].

Clinically used Tests and Physiological Background

Smooth Muscle Hyperresponsiveness

In case of normal spirometry (no obstruction) and pretest probability of asthma between 30 and 70%, a surrogate test to detect airway hyper responsiveness in non-specific or specific bronchial provocation test (methacholine or histamine vs. allergen test) BHR can be used to determine inducible airway constriction, seen in asthma, COPD, some normal persons, in children after childhood bronchiolitis, in smokers and in a course of acute bronchitis. The presence of BHR is linked to respiratory symptoms such as chronic cough, nocturnal cough, wheeze, dyspnea on exertion, periodic dyspnea at rest, inhalational allergy-related lower respiratory symptoms, etc.

In diagnostic procedure of asthma, assessment of BHR is in place if pre-test probability of asthma is at least 30% and not more than 70%. It is also not necessary if the patient present with completely reversible airway obstruction (normalization of flows, volumes and resolution of obstruction – normalization of FEV1/VC ratio) after 400mcg of inhaled short acting bronchodilator drug (e.g., salbutamol). Proper timing of the test

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is necessary because positive test during the acute bronchitis episode and 4-6 weeks after that could produce false positive result and lead physician to false conclusion, that the patient has asthma. Proper timing of the test is also important in elite sportsmen exercising in cold environments (e.g., biathlon runners) and in diagnostic procedure of work-related asthma.

BHR test has a high (over 95%) negative predictive value – to *exclude* asthma. The positive predictive value varies very much in relation to provocation dose of inhaled agent and has over 50% of »false positives« in a range above 2mg cumulative methacholine dose. Therefore, if the test is negative at the time when the patient has symptoms, we can be sure that the patient does *not* have asthma.

BHR is linked to different genetic loci on our chromosomes as is atopy. Current evidence suggests, that BHR has two components: »inducible« – linked to the level of airway inflammation (due to either IgE-mediated and/or neutrophilic-mediated) and »constitutive« – linked to the level of airway remodeling, hypertrophy of bronchial smooth muscles and intrinsic properties of smooth muscle cell. In that concept, it is understandable, that the first part of BHR could be diminished or even abolished by proper anti-inflammatory treatment of airway mucosa and the second being more inaccessible to treatment. In most of asthmatic patients their BHR exists over the entire lifetime, even though the level of BHR may vary significantly and is linked to expression of their symptoms.

Repeated test for BHR is not useful in clinical practice. If the first test is done in a proper time, its positive value can be considered significant. Repeated BHR is also not recommended to assess the success of medical treatment (e.g., inhalation drugs for asthma). However, the test could be repeated in certain circumstances:

1. Periodic asthma (allergen driven seasonal asthma): the test could be positive during pollen season and negative during wintertime; however, this is more an exemption as a rule.
2. Workplace-related asthma: the test could be repeated if new-onset respiratory symptoms appear in a patient working in asthma-risk workplace; 3-5 years after complete removal from workplace, if test was positive (e.g., in retirement).[1,8]

Repeatability of the test in the same person within a week is within two doubling concentrations of the provoking agent. However, inter-laboratory repeatability can reach up to 300% difference. That methodological issue makes the interpretation of repeated test even more difficult.

Bronchial Hyper Responsiveness vs. Bronchial Reversibility

Those terms could not be used interchangeably since they do not necessary represent the same process within the airways. However, many epidemiological studies, looking for population-based bronchial hyper responsiveness have used a significant BD response as a surrogate marker of BHR. Therefore, large population cohort data are hard to interpret. Some patients can have a positive BD test (defined by increase in FEV1 over 12% and 200mL) and negative broncho provocation test, while other with documented BHR could have negative BD response (e.g., COPD patients). As already stated, both BD response as BHR are dynamically changing variables over time, depending both on underlying airway inflammation and structural changes.

Structural Changes in Airways Linked to BHR

Airway Smooth Muscle (ASM)

Human studies in alternations of airway smooth muscle function require bronchial biopsy and are therefore limited. However, epithelial damage of any kind can result in altered smooth muscle function and thickening

of basal membrane. ASM hyperplasia (mediated through growth factors, epithelial inflammatory mediators, and extracellular matrix components) is a key mechanism, most probably irreversible with treatments available nowadays[5].

Epithelial Damage and Inflammation

Epithelial damage (e.g., in viral bronchitis)[10] can be a reason for dysfunction in airway smooth muscle innervation (particularly parasympathetic and NANC-non-cholinergic non-adrenergic) and consequently causing a transient BHR[9,11]. In COPD and smokers' airways that mechanisms are even more prominent. Repair process could lead to collagen deposition, basal membrane thickening and permanent airway narrowing[12].

Techniques to Measure Bronchial Hyper Responsiveness

Direct and Indirect Bronchial Challenge Tests

'Direct' BPTs measure airway smooth muscle function, whereas the 'indirect' tests reflect airway inflammation. Airway caliber is important in determining response to direct stimuli[2]. Therefore, the direct challenges function best to exclude current asthma when they are negative. By contrast, all the indirect challenges (exercise, eucapnic voluntary hyperpnoea, hypertonic saline, adenosine mono phosphate (AMP) and mannitol) critically depend on the presence of airway inflammatory cells[4]. Many of the indirect challenges are dose limited meaning that it is not possible to push the dose beyond a certain limit that is limited by physiology (exercise, eucapnic voluntary hyperpnoea) or solubility (AMP). Comparative studies have demonstrated that the indirect challenges are highly specific but have a relatively low sensitivity compared with methacholine[7]. Due to their high specificity (and low sensitivity), indirect challenge tests function best to confirm the presence of disease and are ideal tools for studying individuals who have or are suspected to have exercise-induced bronchoconstriction[3].

The response to bronchoprovocation agent is dose (or concentration) dependent. Since it is clinically not feasible to test both hyperreactivity and hypersensitivity (due to possibility to induce severe obstruction in former), arbitrary point of decease of FEV1 is chosen as 20% of drop of FEV1 comparing the FEV1 after inhalation of normal saline (0.9% NaCl). Patterns of response are shown on Figure 1.

Airway obstruction is a term that is derived from spirometric flow-volume curve and is defined as a decrease of Index Tiffeneau (FEV1/VC ratio) for 12% below lower limit of normal. Decrease of expiratory flows *per-se* (FEV1 or PEF) is not sufficient for confirmation of obstructive ventilatory defect but can be used (after we define obstruction) as a marker of degree of obstruction (mild, moderate, severe). Since in many cases asthma (as predominantly large/medium airway disease) can affect small airways too, impulse oscillometry and/or body plethysmography measurement are used to define the degree of bronchial system involvement.

Variability of airway obstruction usually (but not always i.e., in non-eosinophilic asthma) parallels the intensity of airway asthmatic inflammation. The variability should be assessed over time; the best tool is to use PEF measurements for at least 2 weeks, three times daily at home environment in the period, when the patient describes asthmatic symptoms. Diary of those measurements (best provided by electronic PEF meter, since compliance of a patient with ordinary PEF meter is less than 30%) is assessed day by day and excess variability is determined by more than 20% fluctuation of PEF.

Reversibility of obstruction is assessed by bronchodilator test. Improvement of airway obstruction after short-acting bronchodilator (in Slovenia standard is 400mcg of salbutamol) for at least 200ml increase on either FVC

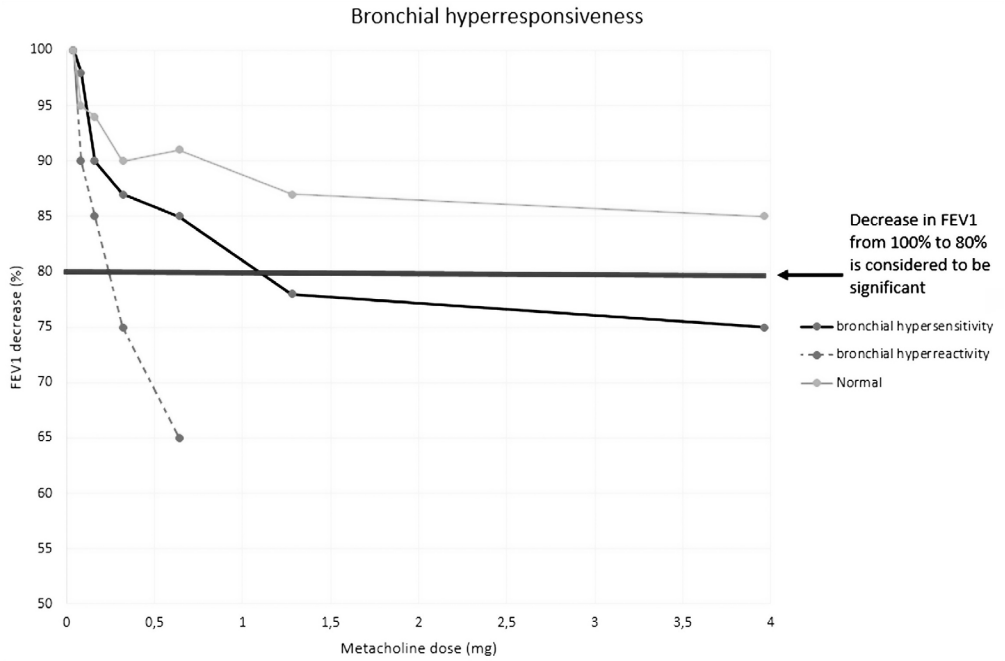

Figure 1. Patterns of response to Broncho provocation agent.

or FEV1 PLUS 12% of pre-bronchodilator value is considered positive. In some cases, both FVC and FEV1 increase simultaneously – in those patients we should think about small airway asthma (increase on FVC can be due to decrease in air trapping after BD and consequently more air available for expiration before airway close during expiration).

Conclusions

Intrinsic airway disease (smooth muscle and epithelial damage due to asthmatic inflammation) can be assessed using lung function measurements. The scope of test differs in respect of timing and activity of disease process (i.e., methacholine testing is used in stable disease, with normal spirometry; BD test is used in acute exacerbation, longitudinal PEF measurements are used in induced-variability environments (e.g., workplace)). Since the disease is very variable over time and place, most test scan be repeated, and dynamic changes are used as a support for diagnosis as for appropriate treatment. Pre BD spirometric measurement should always be used in outpatient follow-up; BD reversibility can detect degree of current airway inflammation. In latter case, exhaled FENO values are valuable in titrating anti-inflammatory treatment.

Workplace asthma can be either true occupational asthma (that developed due to allergens at workplace in a previously non-asthmatic person) or workplace-exacerbated asthma (usually in known asthmatic due to irritants at workplace – »dirty workplace« asthma). Long-term measurements of flows at workplace (electronic PEF) are necessary, best in a period on/off place when the patients are symptomatic[1].

Results of lung function tests should be reproducible. Therefore, standardization of procedure in lung function lab is necessary.

Screening results (done by spirometry on the field, e.g., GP office, etc.) should be confirmed and assessed further at the pulmological level.

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Biomarkers in Severe Asthma

4.2

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Abstract

Asthma is the most common chronic respiratory disease, affecting both children and adults. It is an umbrella term, encompassing multiple phenotypes. Asthma phenotypes may also be identified as clusters of measurements from different dimensions of the disease, and are partly genetically determined. The mechanisms leading to the disease are complex and it is still a challenge to choose suitable biomarkers, which have become especially important with the introduction of biological asthma treatment. Asthma can be broadly divided into T2-high and T2-low molecular endotypes. Early-onset asthma is typical of allergic phenotype and has so far been the most extensively investigated. The prevalence of adult-onset asthma i si increasing because of the ageing population. This asthma phenotype can be divided into two types considering the existence of eosinophilic inflammation. Various other asthma phenotypes, for instance, exercise-induced, and obesity or smoking-associated asthma, should be taken into account when evaluating the patient. Severe asthma,with the prevalence of 5-10% of all asthma patients, remains a clinical challenge. Various biomarkers are thus under investigation in the hope of helping researchers and clinicians in better disease evaluation since the individual approach and personalized medicine are imperative.

Keywords: asthma phenotype, clusters, biomarkers, eosinophils

Introduction

Asthma is the most frequent chronic respiratory disease[1], with almost 1 in 8 children and 1 in 12 adults affected[2]. Since 2016, the Global initiative for asthma (GINA) has stated that asthma is a heterogeneous disease[3]. Asthma phenotyping is needed for a more precise patient approach and a better understanding of asthma diversity. Asthma heterogeneity is seen in diverse clinical presentations, different responses to treatment, and different pathophysiological features and findings due to various pathogenic mechanisms, which lead to multiple asthma phenotypes.

Phenotype is by definition an observable disease characteristic which is the result of gene-environment interaction. These characteristics can be disease symptoms, triggers, body shape and weight, age of asthma onset, etiology, atopic status, response to the smoking habit, laboratory findings, biomarkers, lung function parameters and presence of chronic airflow obstruction, bronchodilator reversibility, reaction to drugs or substances, response to treatment, level of asthma control, number of exacerbations, severity and speed of asthma deterioration, need for hospitalization or intensive care unit treatment, including mechanical ventilation, duration

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of quiescent state of asthma, involvement of upper respiratory airways and/or nasal polyps etc. The topic concerning asthma phenotypes is very important as personalized, individually tailored treatment adjusted to the understanding of underlying phenotype mechanisms yields much better results in asthma patients[4,5].

Asthma phenotype description dates from the mid-20th century, with Rackeman's idea from 1947 about extrinsic and intrinsic asthma, emphasizing the triggering role of allergens in asthma[6]. After the enthusiasm for inhaled corticosteroid treatment in asthma in the'80s of the previous century, and the introduction of LABAs (long acting beta agonists) in asthma treatment in the '90s[7], with much better achievements in asthma control, the first decade of the new millennium brought a rise in the asthma heterogeneity awareness[8].

However, observable characteristics are not enough, because of many overlapping symptoms of the disease, so the common underlying pathophysiological mechanism in asthma is important. Due to these facts, a new term was developed - asthma endotypes[9].

Biomarkers are specific measurable disease characteristics. These are quantifiable factors distinguishing between physiological and pathological processes and could be used as a pathway for therapy selection and therapeutic response monitoring[10]. The mechanisms leading to the disease are complex and it is still a challenge to choose suitable biomarkers to adequately stratify patients, which became especially important with the introduction of biologicals in asthma treatment[11]. The key point is biomarkers for the endotypic (and phenotypic) criteria. The right combination of various biomarkers in different phenotypes is under investigation hoping to help researchers and clinicians in better disease evaluation since the individual approach and personalized medicine are imperative[11,12]. Today, defining a severe asthma phenotype is a process based on a biomarker-driven approach[10]. There is no perfect biomarker, and unlike for some other disorders, biomarkers for asthma are less precise, and still not completely known. Generally, based on these markers, asthma can be divided into two groups, T2-high asthma, and T2-low (or non-T2) asthma[11,10].

Continuous improvement of asthma phenotypes and their identification has led to an individualized, targeted approach in asthma therapy, especially in severe cases. Biomarkers are the key to understanding and recognizing phenotypes, and accordingly the key to therapy and treatment assessment.

Type 2 high-inflammation asthma is characterized by eosinophilic airway inflammation, while type 2 low-inflammation asthma includes neutrophilic and paucigranulocytic asthma. A larger proportion of cases of severe asthma are type 2-high asthma[17,18].

A high level of type 2 cytokines is characteristic of T2-high asthma, and those areIL-5, IL-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Biomarkers of type 2 inflammation have proven valuable for endotyping in asthma[17,18].

Biomarker: Type 2 Inflammation

Blood Eosinophils

Eosinophils are specialized leukocytes produced in the bone marrow, primarily found in tissues and in the respiratory system, airway mucosa, and airways, which promote inflammation by releasing an abundance of inflammatory mediators. These mediators, together with those released from T2 cells, cause eosinophilic inflammation, bronchoconstriction, and airway remodelling. Blood eosinophil counts are a potential surrogate biomarker for eosinophilic inflammation in asthma and are relatively easy to obtain. However, their levels depend on the time of sampling (highest at midnight, lowest at midday), time since eating, exercise, and therapy (corticosteroids reduce eosinophilia)[13]. Although studies of blood eosinophil count, as predictors of high

sputum eosinophils in eosinophilic asthma, have yielded somewhat mixed results, blood eosinophil counts have been useful in the selection of patients for eosinophil-targeting agents. The exact cut-off value is still debatable, but the cut-off used in the clinical trials to define high blood eosinophil counts has ranged between 150 and 300 cells/μL. Some studies showed that patients with eosinophil counts above 300 cells/_L have more frequent exacerbations and acute respiratory events[13].

Markers of Eosinophil Activation

The predominant mediators in the eosinophil granules are cytotoxic cationic proteins, such as eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN), major basic protein (MBP), and reactive oxygen species (ROS). Some of these mediators can be measured in blood and used as a guide in better asthma clustering, but also as a potential treatment target. High ECP levels are detected in the blood and sputum of severe asthma patients (mostly atopic), compared to those with non-severe asthma. ECP is associated with bronchospasm and airway resistance and is elevated in asthma exacerbation, and its levels are reduced after therapy induction. It is assumed that ECP can be used as a marker for corticosteroid induction and dosage, but this needs to be confirmed. EDN is another marker of eosinophilic disease and persistent airflow limitation in severe asthma patients; it can be measured in serum, urine, and other body fluids[14-16].

Periostin

Periostin is an extracellular matrix protein secreted by bronchial epithelial cells and lung fibroblasts in response to Th2 cytokines, IL-13, and IL-4.

In addition to its role in cell proliferation, invasion and angiogenesis, periostin also plays a significant role in the development of inflammatory processes, as well as the development of the T2 phenotype[19,20]. The exact mechanism and role of periostin in the pathophysiology of asthma are still unclear. Mouse models suggest that periostin plays a role in mucus production, eosinophil recruitment, and subepithelial fibrosis.

In a recent study conducted by Takahashi et al., it was presented that serum periostin levels were good predictors of blood eosinophilia (r = 0.36), which could mean that periostin levels serve as a biomarker of eosinophilic airway inflammation[21,22].

50 ng/L is considered the cut-off in most studies while values above 50 ng/L are considered high periostin levels. The limitation of periostin is that it is also secreted by osteoblasts and the levels can be elevated in some tumours (brain tumours, bony metastasis), and growing children[23].

Dipeptidyl Peptidase-4 - DPP4

Dipeptidyl peptidase-4 (DPP-4) is expressed in a variety of lung epithelial and endothelial cells and submucosal glands, however, the role in the pathophysiology of asthma is uncertain. DPP-4 can be found in bronchoalveolar lavage (BAL) and correlates with airway inflammation in rat models. Studies related to DPP-4 are limited; IL-13 is thought to stimulate DPP-4 production, and, like periostin, DPP-4 can be measured in serum and can be used as a guide to induce anti-IL-13 therapy[18,24].

Immunoglobulin E

An utterly important predominant biomarker in patients with asthma is allergen specific IgE. IgE is a product of B lymphocytes in reaction to a foreign antigen[25]. Serum IgE levels have been shown to correlate with the severity of asthma. In the case of severe asthma exacerbations, total IgE levels rise, after which they fall, and stable levels are reached within 1-1.5 months after the onset of severe exacerbations[26]. Different specific immunoglobulin E and their interactions may be an important causal mechanism in the development

of asthma[27]. Nevertheless, with the advent of targeted asthma therapy, it gained a key role in tailoring individual therapy as well as monitoring its effectiveness. Depending on blood levels, total IgE may also indicate other comorbidities (including allergic bronchopulmonary aspergillosis, certain primary immunodeficiencies, infections and infestations (parasites), inflammatory diseases, and malignancies)[28].

Fractional Exhaled Nitric Oxide Concentration (FeNO)

Fractional exhaled Nitric Oxide (FeNO) is used to detect active airway eosinophilic inflammation, measured by solely non-invasive tests[35].

Due to its immense importance in the differential diagnostic process, fractional exhaled nitric oxide concentration (FeNO) has a distinctive role among all biomarkers. Nitric oxide (NO) is normally found in exhaled breath while patients with asthma often exhibit higher levels of NO in their exhaled breath, which is thought to be due to the upregulation of inducible nitric oxide synthase (NOS2) in airway epithelial cells, the enzyme in charge of epithelial NO production[36]. Given that NO levels can be measured relatively easily, and the test itself is non-invasive and easily repeatable, FeNO has enormous potential in everyday clinical practice.

The American Thoracic Society recommends clinically significant cut-off points for FeNO: (1) <25 ppb (<20 ppb in children), and (2) >50 ppb (>35 ppb in children)[37].

FeNO is a biomarker of T2 response (or airway eosinophilia) but does not correlate with sputum eosinophils. A FeNO level >50 ppb suggests a steroid-responsive inflammation, while patients with a FeNO level around 25 ppb are less likely to respond to steroids[37].

A recent study by Price et al., found that people with a combination of high FeNO and high blood eosinophils were prone to a notably increased risk of severe exacerbations in the year preceding FeNO measurement[38].

A recent study by Brooks, Massanari, Hanania and Weiner found that the implementation of FeNO into pre-omalizumab treatment assessment decreases the expected per-patient cost by almost 50% from the moment of omalizumab initiation into therapy, and the same trend continues during the first year of the omalizumab treatment. Authors point to the obvious benefit of using FeNO for detecting omalizumab responders (prior to initiating a 12-week trial of omalizumab)[39].

Induced Sputum and Airway Inflammation

Studies have demonstrated the usefulness of induced sputum to guide asthma treatment and showed that normalizing airway eosinophilic inflammation allowed better control of asthma with reduced exacerbations and hospital admissions[29]. The technique of induced sputum that allows non-invasive collection of airway cells is considered the gold standard to identify inflammatory asthma phenotype[30]. In one study performed using induced sputum, it was shown that compared to the paucigranulocytic phenotype, eosinophilic, neutrophilic and mixed granulocytic phenotypes were characterised by a poorer lung function. Eosinophilic phenotype exhibited a higher frequency of atopy, higher levels of IgE, higher bronchial hyperresponsiveness to methacholine, higher FeNO levels and lower asthma control compared to paucigranulocytic. The mixed granulocytic phenotype had higher levels of fibrinogen, the lowest lung function and the highest degree of bronchial hyperresponsiveness to methacholine[31]. As far as the sputum neutrophilic phenotype is concerned, there was a weak correlation between sputum and blood neutrophil count taken in percentage. In a study conducted by Ntontsi et al., it was found that paucigranulocytic asthma was most likely to be a benign asthma type, related to good treatment response[32]. Smokers did not have a significantly

higher proportion of neutrophils in their sputum than ex-smokers or never smokers[30]. Independent predictors of sputum eosinophil count ≥3% were the percentage of blood eosinophils, low FEV1/FVC, and high FENO and IgE levels. A cut-off value of 220/mm3 or 3% for blood eosinophils performed equally to FeNO50 ppb to identify the presence of a sputum eosinophil count ≥3%. Independent predictors of sputum neutrophilia were advanced age and high FRC, while blood neutrophil count was not[31]. *Sputum eosinophils >3% can only distinguish eosinophilic vs neutrophilic, mixed or paucigranulocytes asthma phenotype*[33]. Using blood eosinophilia per se as a biomarker for eosinophilic asthma is difficult due to the daily fluctuations of blood eosinophils, with or without treatment[34]. In the study by Agache et al., serum IL-5 and IL-13 were identified as the best blood eosinophilia predictors, with a good reproducibility at repeated testing after 6 weeks[34].

Conclusion

Asthma is a complex heterogeneous condition, and under this broad term, severe asthma itself covers several subgroups with specific characteristics, symptom profiles and biochemical mechanisms of the disease. A biomarker is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In severe asthma, biomarkers could be used for diagnosis of phenotype or endotype, can also be predictive of clinical outcomes or response to therapy, and may be dynamic with time or therapy. Fully determining phenotype or endotype of severe asthma will require the interpretation of combinations of commercially available biomarkers. Today, defining a severe asthma endotype is a process based on a biomarker-driven approach. There is no perfect biomarker. Biomarkers for asthma are less precise, and still not completely known. With no perfect biomarkers, there is no perfect endotype classification. Multiple biomarkers are superior to a single biomarker. Despite significant improvement in asthma understanding, there is still a long way to go to resolve the asthma problem in most persons suffering from asthma syndrome.

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5

Asthma Phenotypes and Therapeutic Possibilities

Asthma and Aspirin Exacerbated Respiratory Disease

5.1

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Abstract

Aspirin exacerbated respiratory disease (AERD) is a disease characterized by the triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reaction to cyclooxygenase 1 inhibitors. The prevalence of AERD is estimated is reported to be: 7% in patients with asthma, 15% in patients with severe asthma, 24% in patients with life-threatening asthma, 10% in patients with nasal polyposis, and 9% in patients with unspecific chronic rhinosinusitis.

Aspirin and other nonsteroidal antiinflamatory drugs (NSAID) can cause hypersensitivity by different immunological mechanisms that can be classified into 5 categories: NSAID exacerbated cutaneous disease, NSAID induced urticaria or angioedema, single NSAID anaphylaxis, aspirin-exacerbated respiratory disease, single NSAID induced delayed reaction. The clinical picture, pattern of cross-reactivity, disease course, and course of desensitization may also be quite different. It is important to diagnose which disease phenotype is involved. This can be determined in most cases by history.

Due to distinctive symptoms, the diagnosis of AERD could often be based on reliable history. In patients with adult-onset asthma, recurrent nasal polyposis and multiple (two or more) reactions after a single NSAID or reactions after two different NSAIDs in the last 5 years the diagnosis could be based on history alone. However, in some cases, further diagnostic tests are necessary to avoid underdiagnosing or over-diagnosing the disease. Cross reactivity between NSAIDs in AERD is not associated with similarity of chemical structure, as it is in IgE mediated hypersensitivity, but it is associated with the strength of COX-1 inhibitions therefore the patient with AERD must avoid all the other drugs which are strong COX-1 inhibitors. Aspirin desensitization in AERD could be performed for two purposes: aspirin tolerance in cardiovascular indication or symptoms improvement in severe cases of chronic rhinosinusitis with nasal polyposis.

Keywords: aspirin, asthma, drug hypersensitivity, nonsteroidal antiinflamatory drugs

Introduction

Aspirin exacerbated respiratory disease (AERD) is a disease characterized by the triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reaction to cyclooxygenase 1 inhibitors. It was first described in the literature as a case report by French professors Widal and colleges in 1922[1]. Since then this condition has been given many different names from "Morbus Widal", "Samter's triad", "ASA induced asthma with nasal polyposis" and "NSAID-Exacerbated Respiratory Disease - NERD". Various specialists, including pulmonologists, otorhinolaryngologists, and allergists, treat patients with this condition.

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It is important to diagnose if the patient has an AERD, as NSAIDs are widely used as analgesic, antipyretic and cardio-protective drugs. NSAID asthma exacerbations in these patients may occur unexpectedly and may be severe[2]. Also, aspirin-associated asthma is a specific phenotype of eosinophilic asthma and with a different treatment decision. Asthma control can be improved by additional treatment with antileukotrienes and, in selected cases, by desensitization to aspirin. Therefore, it is important to define the tolerability of NSAIDs in all patients with asthma and nasal polyposis.

NSAID Hypersensitivity

Prevalence of hypersensitivity to NSAID is reported to be 1.6%[3]. Aspirin and other NSAIDs can cause hypersensitivity by different immunological mechanisms. Therefore, the clinical picture, cross-reactivity, disease course, and course of desensitization may also be quite different. It is important to diagnose which disease phenotype is involved. This can be determined in most cases by history.

NSAID hypersensitivity can be classified into 5 categories: NSAID exacerbated cutaneous disease (NECD), NSAID induced urticaria or angioedema (NIUA), single NSAID anaphylaxis, aspirin-exacerbated respiratory disease (AERD), single NSAID induced delayed reaction (SNIDR)[4-7]. Mixed pattern, called "blended reactions" represent the second most frequent entity in NSAID hypersensitivity simultaneously involving skin and airways[8] Immunological and clinical characteristics of various types of NSAID hypersensitivity are summarized in Table 1.

NSAID exacerbated cutaneous disease (NECD) occurs in patients who are suffering from chronic spontaneous urticaria. Approximately 12-30% of patients with chronic urticaria have worsening of their disease and occurrence of generalized hives and/or angioedema within 1-6 hours after application of NSAID. Skin symptoms may persist for several days. It is important to distinguish these symptoms from anaphylaxis. In NECD there are only cutaneous symptoms present, without systemic involvement. The intensity and the threshold dose for the reaction are changing through time and the course of the disease. The severity of the symptoms is also dose-dependent. Usually, NSAIDs are well tolerated when chronic spontaneous urticaria is in remission. Sometimes there are additional co-factors, such as viral disease, psychical or physical stress present, which aggravate the disease, and patients better tolerate NSAID without these co-factors. Therefore it is sometimes difficult to confirm the diagnosis with a drug provocation test, as results are not always replicable. Skin tests have no diagnostic value in NECD. NSAID exacerbated cutaneous disease is unpleasant, but it is not life threatening. Patients with NECD usually well tolerate selective COX-2 inhibitors and also the lower dose of aspirin (eg 100 mg as in antithrombotic treatment). However, desensitization to aspirin is rarely successful in NECD patients and patients should avoid all COX-1 inhibitors in therapeutic dose[5,6].

NSAID induced urticaria or angioedema (NIUA) occurs in patients without the underlying cutaneous disease, but similar to NECD patients develop isolated skin symptoms up to 24 hours after ingestion of at least two chemical unrelated NSAIDs. Again, there is no systemic involvement, in contrast to IgE mediated anaphylaxis. Sometimes NIUA occurs in patients several years before they develop chronic spontaneous urticarial, but this is not always the case. Cross reactivity is associated with the strength of COX-1 inhibitions and not with the chemical structure of NSAID. Also these patients tolerate well selective COX-2 inhibitors. In contrast to NECD patients, desensitization with aspirin is rarely successful in NIUA patients. When desensitized to aspirin, patients do tolerate also other NSAIDs[5,6].

Single NSAID anaphylaxis is different from both phenotypes of NSAID

Table 1. Immunological and clinical characteristics of various types of NSAID hypersensitivity.

Terminology	Aspirin-exacerbated respiratory disease (AERD)	NSAID exacerbated cutaneous disease (NECD)	NSAID induced urticaria or angioedema (NIUA)	Single NSAID anaphylaxis	Single NSAID induced delayed reaction (SNIDR)
Pathophysiology	COX-1 inhibition	COX-1 inhibition	Unknown, probably COX-1 inhibition	IgE mediated	T-cell mediated
Underlying disease	Asthma, nasal polyposis	Chronic urticaria	none	none	none
Cross reactivity	NSAID Cross reactive	NSAID Cross reactive	NSAID Cross reactive	selective	selective
Timing	30-180 min	1-6 h	up to 24h	immediate (up to 1h)	delayed
Symptoms	Bronchial obstruction, nasal congestion and/or rhinorrhea, wheezing, coughing, dyspnea	Urticaria and/or angioedema	Urticaria and/or angioedema	Anaphylaxis	Various delayed reactions
Desensitization	Successful	Rarely successful	Rarely successful	Successful	Contraindicated in most cases

hypersensitivity described above. The mechanism is IgE mediated immediate allergy. Therefore classical symptoms of anaphylaxis, with pruritus, flush, hives, angioedema, and systemic involvement with bronchospasm, hypotension, and gastrointestinal symptoms occur immediate, or within 1 hour after exposure to NSAID. The severity of the disease is usually not dose dependent. Patients usually react to other NSAIDs with similar chemical structures (and not with similar strength of COX-1 inhibition). Skin tests and also basophil activation tests may be useful in diagnosing this disease. Drug provocation test can confirm the diagnosis of allergy to culprit drug, but it is contraindicated in case of a very severe reaction. Drug provocation test is useful to confirm tolerance of alternative NSAID. Desensitization to culprit NSAID is possible, but usually not recommended as there are many alternatives on the market[5,6].

Single NSAID induced delayed reaction is rare. It occurs in patients with no underlying skin or respiratory disease. The onset of the disease is delayed, usually more than 1 day up to weeks after exposure to the NSAID. It has various clinical manifestations and various organ involvement such as maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug reaction, Steven Johnson syndrome, toxic epidermal necrolysis, drug induced nephritis, pneumonitis, etc. The pathomechanism include specific T cell stimulation. Diagnostic tests are specific and different for each clinical manifestation. Desensitization to aspirin is contraindicated in case of a severe delayed reaction[5,6].

Clinical Characteristics of AERD

The symptoms of AERD do not develop immediately after taking NSAIDs, but somewhat later, on average 30-180 min after administration[9]. This can sometimes make it difficult to identify the culprit of the reaction. The reaction starts with upper respiratory tract symptoms like nasal congestion and/or rhinorrhea, followed by lower airway symptoms like wheezing, coughing, and shortness of breath. In patients with not, well controlled asthma symptoms usually occur much quicker with more severe bronchospasm which may even lead to a fatal outcome[10-12]. The onset and severity are dose-related, lowest dose provoking a reaction for individual patients vary between 100-300 mg ASA[11-13].

Patients also frequently have chronic symptoms such as recurrent nasal polyposis with the need for frequent surgery, loss

of smell, and also similar upper and lower respiratory symptoms after intake of alcohol[11,12]. Symptoms usually appear 1-5 years before asthma develops[14].

Epidemiology

The prevalence of AERD is estimated is reported to be: 7% in patients with asthma, 15% in patients with severe asthma, 24% in patients with life-threatening asthma, 10% in patients with nasal polyposis, and 9% in patients with unspecific chronic rhinosinusitis[5,15,16]. Reported prevalence is likely to be underestimated due to low awareness of the disease.

Symptoms of AERD usually appears in patients with adult onset asthma between the age of 20-40 years[17,18]. AERD in children is rare. The ratio of male to female patients is 1:2[17]. AERD was previously not associated with atopy or any other respiratory allergy, although some newer studies report a higher prevalence of atopy in these patients[19,20]. Non steroidal anti-inflammatory drugs that most common cause respiratory reactions are: aspirin (80%), ibuprofen (41%), naproxen (4%)[13].

Pathophysiology

NSAIDs inhibit cyclooxygenase 1, increasing leukotriene production and decreasing the production of anti-inflammatory prostaglandins. Patients with AERD have higher levels of leukotrienes due to inflammation mediated by neutrophils, monocytes, and basophils, eosinophils, and mast cells. Increased leukotriene production with NSAID ingestion leads to bronchoconstriction, eosinophilic inflammation, increased mucus production in the bronchi. Also in nasal polyps tissue, there are elevated concentrations of leukotrienes[21,22].

Diagnostics

Due to distinctive symptoms, the diagnosis could be often based on reliable history. In patients with adult-onset asthma, recurrent nasal polyposis and multiple (two or more) reactions after a single NSAID or reactions after two different NSAIDs in the last 5 years the diagnosis could be based on history alone[11,12]. However, in some cases, further diagnostic tests are necessary to avoid underdiagnosing or over diagnosing the disease.

As the disease is not IgE mediated skin tests or measurements of specific IgE are not applicable. Several other approaches have been proposed and researched (like sulfidoleukotrienes release assay, 15-HETE test, basophil activation test) but are not used in clinical practice[25-25]. Therefore, unfortunately, there is currently no other clinically applicable in vitro test available to confirm the diagnosis. This means that the only testing available is drug provocation testing, which is time-consuming, complicated, and potentially dangerous, and should therefore only be carried out in experienced centers by experienced physician and trained nurse. Emergency treatment equipment should be at hand. Indications for performing drug provocation test with aspirin in suspected AERD are confirmation of AERD in patients with unreliable history and assessment of provocation dose before oral desensitization procedure[12,26]. Absolute contraindication for drug provocation tests are the history of severe anaphylactic reaction after any NSAID, unstable asthma, FEV1 ≤ 70%, recent respiratory infection, pregnancy, severe underlying disease such as cardiovascular, renal or liver disease[12,26]. There are different routes of aspirin administration for provocation tests: inhaled intranasal, oral and intravenous. Most commonly used are nasal and oral provocation tests[27]. Both have their advantages and disadvantages. Nasal inhalation of lysine-aspirin is safer and less time consuming in comparison to standard oral provocation tests. The nasal provocation test has a lower sensitivity (80-87%) compared to the oral test, which has a sensitivity of 89-90%. However, the specificity of both tests is high (93-100%)[12,26 28-32]. Inhalation challenge with

lysine-aspirin is as sensitive as oral one, but safer and faster to perform[11].

Nasal provocation is useful in patients with severe and unstable asthma and is at higher risk for severe obstruction. On the other hand, it is not useful in patients with severe nasal obstruction due to massive nasal polyposis as this reduces the sensitivity of the test[26]. At first, the test should be done with intranasal saline to exclude unspecific hypersensitivity. Then lysine aspirin up to 80 uL is installed into each nostril[33]. Assessment of the reaction includes a combination of objective symptoms such as rhinorrhea, sneezing, nasal congestion, and objective reduction of nasal flow measured with acoustic rhinometry, active anterior rhinomanometry, and peak nasal inspiratory flow[33]. As the sensitivity of nasal provocation is low, negative test should be followed by oral provocation. Oral provocation test is considered the gold standard in drug hypersensitivity. Although it has a high specificity, it still does not have 100% sensitivity, so in some cases, even a negative provocation test cannot completely rule out drug hypersensitivity. Drug provocation test is time-consuming, complicated, and potentially dangerous. It needs to be performed in a situation where emergency treatment is available, as well as intensive care unit. Medications for anaphylaxis, adrenaline, and antihistamines should be available on site. It should be performed under the supervision of experienced and trained personnel. When selecting an appropriate protocol for drug testing, it should be borne in mind that inadvertent desensitization to the drug may occur during the test, resulting in a false-negative result. Therefore, the doses and the interval between doses should be carefully selected. Ideally, the interval between doses of an oral drug provocation test should be 60 min and the amount of drug administered should be at least 2 times, but preferably 10x the previous dose.

Vital parameters, blood pressure, pulse, and saturation should be carefully monitored during provocation testing. It is also recommended that if AERD is suspected, spirometry or at least a PEF measurement should be performed before the next dose. The test is positive if at least one or more objective symptoms are present, such as upper respiratory tract reaction (rhinorrhoea, nasal congestion, sneezing, lacrimation), bronchospasm (dyspnoea, wheezing), laryngospasm, a drop of 20% in FEV1 or PEF. At the slightest symptom onset, the test should be stopped immediately and treated aggressively with antihistamines, nasal decongestants, bronchodilators, and adrenaline. There are several different protocols for oral aspirin provocation. The initial dose is typically 10-20 mg. The number of steps also varies, mostly in 5-8 steps. When AERD is suspected, it is important to remember that a reaction can occur up to 3 hours after the aspirin dose and therefore a longer observation period is required. In contrast to immediate IgE-mediated hypersensitivity testing where reactions usually occur immediately or within the first hour after drug administration, so observation up to 2 hours after the last dose is usually sufficient. Therefore, most protocols provide for a 2-day provocation protocol with aspirin. The median cumulative dose at which symptoms occur is 68-157 mg[34,35]. Upper respiratory tract symptoms and lacrimation are usually the first to occur. Bronchospasm is described in 35-90%. In addition to these, gastrointestinal symptoms (abdominal pain, nausea, vomiting), skin signs (erythema, pruritus, urticaria), and even hypotension have been described[26,36].

Risk factors predicting a more severe bronchial reaction include: patients not receiving additional anti leukotriene therapy, AERD symptoms lasting less than 10 years, reduced FEV1 already before the start of testing, history of asthma exacerbations requiring an emergency room visit[37]. There are also patients with a high clinical pretest probability of AERD but in whom the aspirin challenge test is negative. According to some studies, the

sensitivity of the provocation test is only 90%. In these patients, it is reasonable to repeat testing with a higher cumulative dose of aspirin at the time of discontinuation of antileukotriene therapy and systemic steroids.

Management of AERD

Cross reactivity between NSAIDs in AERD is not associated with similarity of chemical structure, as it is in IgE mediated hypersensitivity, but it is associated with the strength of COX-1 inhibitions. A patient must avoid all the other drugs which are strong COX-1 inhibitors: acetylsalicylic acid, piroxicam, sulindac, fenoprofen, oxazopirin, mefenamic acid indomethacin, ibuprofen, naproxen, ketoprofen, diclofenac, ketorolac, etodolac, nabumetone. Metamizole (dipyrone) is considered as week COX-1 inhibitor[8]. But majority of patients with AERD develop respiratory exacerbation with metamizole[38]. Patients should carry with them information about their drug hypersensitivity.

Weak COX-1 inhibitors such as paracetamol, meloxicam, and selective COX-2 inhibitors (celecoxib, etoricoxib, parecoxib) are well tolerated by most AERD patients. Central analgetics such as tramadol and opiates are also safe alternative[12,39]. Some patients also have respiratory symptoms after alcohol ingestion so alcohol avoidance should be advised to AERD patients[40]. Some patients even report respiratory symptoms after using spearmint flavored food like chewing gum or toothpaste, cows milk, and salicylate rich diet[41]. Patients with AERD do benefit with additional antileukotriens for asthma symptoms[42].

Aspirin Desensitization in AERD

Drug desensitization is a method of inducing a temporary tolerance and safely administering the drug to a patient who is allergic to it. The procedure is potentially dangerous and time-consuming and it is suitable for the selected patient in which there are no other equivalent alternatives. It can be used for IgE-induced hypersensitivity (eg anaphylaxis after antibiotics, monoclonal antibodies, or chemotherapeutics), for non-immune-mediated hypersensitivity (eg aspirin angioedema), or infusion reactions (eg chemotherapy or monoclonal antibodies). Desensitization is also possible for mild delayed reactions (eg maculopapular rash after antibiotics)[43,44].

The exact mechanism of action of desensitization is not yet fully understood. In vitro studies have shown that during desensitization both basophils and mast cells are temporarily unresponsive to desensitized antigen, while these cells may still respond to another antigen.

It has been suggested that aspirin desesnitization followed by maintenance of a daily dose of aspirin improves deregulation of arachidonic acid metabolism which leads to decreased airway inflammation and to clinical improvement[45]. The state of anergy to an antigen is temporary, the cells are responding after about two half-lives of the allergen. Desensitization can be performed in all patients with immediate hypersensitivity to the drug that have no alternative choice. It can theoretically be administered for any drug. The relative contraindications for desensitization are: unstable patient, uncontrolled asthma, severe heart failure, pregnancy. In these cases, it is necessary to evaluate risks and benefits. Desensitization is also not recommended when proper patient supervision and safety cannot be ensured[43,44].

Different protocols exist for performing desensitization, but all include the administration of ascending doses of aspirin at intervals of 90-120 minutes until a reaction or the target dose is reached within 1-3 days[46]. An example of desensitization protocol used in University Clinic Golnik is presented in Table 2. Aspirin desensitization in AERD could be performed for two purposes: aspirin tolerance in cardiovascular indication or symptoms improvement in severe cases of chronic

Table 2. Aspirin desensitization protocol used in University Clinic Golnik.

Step	Interval (min)	Aspirin dose
1	0	1 mg
2	30	2 mg
3	60	4 mg
4	90	8 mg
5	120	16 mg
6	150	32 mg
7	180	64 mg
8	210	100 mg

rhinosinusitis with nasal polyposis. In the first case is the target dose of 100 mg of aspirin, in the second case, the target dose varies from 325 mg up to 1300 mg[47,48]. In both cases, the selected aspirin dose must be taken daily to maintain tolerance. If the dose is missed for more than 48 hours, desensitization must be carried out again. In the majority of the patients, desensitization is successful, although up to one-quarter of the patients have reactions during the procedure[47]. Factors associated with successful desensitization are female sex, high blood eosinophil count, low sputum neutrophils, severe nasal symptoms[49]. If the reaction occurs, the patient should be treated, and then the desensitization process can be continued. The most common long term adverse effect is gastric irritation.

Aspirin desensitization in AERD is associated with beneficial effects mainly in symptoms of chronic rhinosinusitis. Use of intranasal corticosteroid and recurrence of nasal polyps are reduced, and there is also less need for revision surgery in these patients. Aspirin desensitization is less effective in reducing asthma symptoms, although one study did confirm minor improvement in FEV1, symptom and medication score[46,50].

There are several studies researching the effect of biological therapies on AERD with various outcomes. Omalizumab, anti-IL5 treatment, and dupilumab do have clinical effects on nasal polyposis, reducing the need for surgeries and nasal steroid use, however, there was no effect on NSAID hypersensitivity[17,52].

Summary

Aspirin, NSAIDs and pyrazolones should be avoided in patients with history of reaction after any of these drugs until allergy workup. Safe alternatives are paracetamol and opioids. Most patients tolerate COX-2 inhibitors, but this should be confirmed with drug provocation test.

In patients with asthma, nasal polyposis or chronic rhinosinusitis and convincing history of multiple reactions to Aspirin, NSAIDs or pyrazolones, no further diagnostic procedures are needed and strict avoidance is necessary. In patients with chronic urticaria, diagnostic provocation tests should only be performed in patients with indication for anti-inflammatory effects of NSAID as in rheumatologic diseases.

Aspirin is the drug of choice in some emergency situations (e.g. acute myocardial infarction). Patients with history of reaction after single NSAID and no history of asthma and/or chronic urticaria, should be offered Aspirin provocation test. If Aspirin is tolerated, patient could be offered further provocation tests with alternative NSAID. In patients with ischemic heart disease and NSAIH hypersensitivity, confirmation of tolerance or desensitization up to 100 mg is usually possible also in patients with asthma or chronic urticaria.

Patients with asthma, especially severe asthma and concomitant nasal symptoms and unknown tolerance to Aspirin, NSAID and pyrazolones should be warned of the potential for development of AERD later in life.

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T2-low Asthma

5.2

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Abstract

T2-low asthma represents between 30-40% of severe asthma patients. It is less well defined compared to the allergic and eosinophilic asthma (T2-high asthma). There are no specific biomarkers for T2-low asthma but is often connected with the smoking, air pollution and obesity. Most of the patients have late onset asthma with more symptoms that are induced by exercise and cold exposure with frequent infective exacerbations and bronchiectasis. The responce to inhaled steroid treatment is poor, so the available therapeutic options and the targeted therapies effective in both T2-high and T2-low asthma like new anti-TSLP monoclonal antibody tezepelumab are discussed. Ongoing trials with sophisticated transcriptomic and proteomic characterisations of different T2-low asthma patients should provide us tools to better characterise these patients and choose the precise therapeutic approaches.

Keywords: T2-low asthma, neutrophylic asthma, paucigranulocytic asthma

Introduction

Non-eosinophilic (T2-low) severe asthma is somewhat an „orphan" entity in the severe asthma spectrum[1]. Severe asthma is a heterogeneous disease involving diverse pathobiological mechanisms (endotypes) with different clinical presentations (phenotypes). While the allergic asthma and non-allergic eosinophilic asthma (T2-high asthma) are better defined and their pathobiology is better described with increasing number of specific treatment options, non-eosinophillic (T2-low asthma) is less defined, different mechanisms are involved in its pathobiology. The pathways are likely different in individual patients, vary over time and circumstances, and are more complex than a simple division into arbitrary groups: T (Type) 2 and non-T2 inflammation. More likely, the end product of airway inflammation will be a mixture of both pathways with either T2 or the non-T2 being dominant, and possibly reflecting a therapeutic target for greater disease control[2].

Clinical Characteristics

T2-low asthma represents between 30-40% of severe asthma patients. Persistently non-eosinophilic asthma prevalence has been reported up to 47% but most patients (>90%) considered to have neutrophilic bronchitis may have a re-emergence of sputum eosinophils when their steroid doses are tapered for long enough[3].

T2-low asthma is more frequent in the late-onset asthma patients, obese females and high symptomatic patients and has a poor responce to inhaled steroid treatment. Neutrophilic inflammation is frequently associated

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with smoking, air pollution, obesity, very late onset (>50 or > 65 years of age), exercise and cold induced asthma, infective asthma exacerbations and bronchiectasis[1,4].

Pathophysiology

Non-type 2 inflammation (T2-low) mediated asthma is difficult to define due to lack of signature biomarkers. It exists in the absence of T2-high or eosinophilic inflammation and includes neutrophilic and paucigranulocytic subtypes. Several cell types and cytokines, including Th1, Th17, IL-6, and IL-17, contribute to mechanisms of non-T2 asthma[5].

In response to industrial pollutants, infectious agents, tobacco smoke, and other nonspecific stimuli, injured airway epithelial cells release a multitude of factors that initiate innate and adaptive immunity with subsequent release of toll-like receptors (TLRs). TLR2 and TLR4 are innate immune receptors that are inducing the shift toward Th1 and Th17 response so the dominant T cells in T2-low asthma are Th1 and Th17 that generate pro-inflammatory cytokines as IL-8, IFN-γ, IL-6, IL-17A/F, TNF-α and IL-1ß. T helper 17 (Th17) cell-derived cytokines and immune factors mediate neutrophilic influx to the airways. Th17-secreted interleukin-17A (IL-17A) is an independent risk factor for severe asthma that impacts airway smooth muscle (ASM) remodeling. Transforming growth factor-β1 (TGF-β1) correlates with enhanced Th17 activity and is essential to Th17 differentiation and IL-17A production. Vice versa, IL-17A enhance activation of TGF-β1 signaling pathways augmenting the immune response[6].

The application of cluster analysis in asthma has gained increasing attention as a departure from traditional hypothesis-based approaches to phenotyping asthma. This analysis is accomplished through "omics" methods, which refers to a large dataset derived from a single sample to gain insight into previously unrecognized molecular host-environment interactions and mechanisms of disease (RNA Transcriptomics - study of gene expression and metabolomics - measurement of mediators or metabolic products). Minimally invasive analytic tools have been reported for asthma, using blood, sputum, or bronchial brushings[1]. The omics approach has been helpful in understanding the molecular mechanisms of T2-low asthma. The potential chemosensory and remodeling signatures recently described in asthmatic airways may point to new endotypes relevant in T2-low patients[7-9].

Beside the inflammation, some structural abnormalities of the airway smooth muscles and heightened neuronal dysfunction can lead to the increased cough reflex sensitivity connected with the poor asthma control[10].

There is a negative correlation between airway cytotoxic T cells (CD8+) and body mass index in severe asthma patients. Desreased expression of CD8+ cytotoxic T cell network in individuals with T2-low asthma[11] is strongly related to obesity and systemic inflammation. A primary function of CD8+ T cells is host defense against viral infection and an impaired immune response to viral infections could be a mechanism of exacerbations in T2-low asthma.

Airway mucus hypersecretion is associated with greater asthma severity, reduced lung function, increased number of exacerbation and is a predictor of a poorer response to anti-inflammatory treatment with glucocorticoids. Mutations or polymorphisms in the cystic fibrosis transmembrane conductance regulator (CFTR) gene were detected in hypersecreting patients with neutrophilic asthma, bronchiectasis, pansinusitis and recurrent respiratory infections[12].

Depending on the cellularity, T2-low asthma can be further classified into neutrophilic and paucigranulocytic but there are no strict borders between those groups.

Neutrophylic Asthma

Key cytokine involved in T2-low asthma, IL-17, promotes neutrophil migration by inducing IL-6 and IL-8 release from bronchial epithelial cells. IL-8 (CXCL8) is the most potent chemoattractant in the lung that correlates with both increased neutrophil percentage and absolute neutrophil counts. Moreover, neutrophils have also been demonstrated to secrete IL-8 creating a positive feedback loop that promotes further neutrophilic inflammation.

Receptor for advanced glycation endproducts (RAGE) is a pattern-recognition receptor that interacts with various endogenous ligands involved in host response to injury, infection, and inflammation. Asthmatics with neutrophilic inflammation have a deficiency in soluble form of RAGE (sRAGE). sRAGE serves as a decoy receptor by sequestering RAGE ligands and thus inhibiting RAGE dependent cellular responses. It is not known whether that deficiency is causative factor or the result of neutrophilic inflammation[13].

It is wrong to consider neutrophils as only negative cells in asthma. Activated neutrophils can eliminate pathogens by phagocytosis, degranulation or formation of neutrophil extracellular traps (NETs). Because of their role in mediating persistent inflammation and causing airway damage, they have been thought of as primitive killers. However, they can have immunomodulatory effects and play a role in tissue repair and healing through production of anti-inflammatory cytokines like IL-1RA, IL-10, TGFß1 and TGFß2. High extracellular DNA concentrations in sputum mark a subset of patients with more severe asthma who have NETs and markers of inflammasome activation in their airways[14,15].

The particular effect of the neutrophils is dependent on location of the cells, comorbidities and surrounding inflammatory milieu and nowadays we can recognise multiple neutrophil phenotypes with distinct morphological and functional characteristics. They can either activate a pro-inflammatory cascade or differentiate into immunomodulatory role. This knowledge is crucial in programming the treatment strategies because the treatment not adapted to the specific underlying pathobiology may lead to undue adverse effects[16].

Impact of Corticosteroids on Sputum Neutrophilia

Th1 cell activation leads to production of IFN-γ which in combination with the low secretory leukocyte protease inhibitor (SLPI) expression leads to high airway resistance and corticosteroid refractoriness. Use of corticosteroids (ICS and OCS) has been even shown to contribute to sputum neutrophilia[17] because the corticosteroids, while they promote apoptosis of eosinophils, have been demonstrated to inhibit neutrophil apoptosis. Sputum neutrophil count was higher in patients receiving moderate-to-high dose ICS than those receiving low-dose ICS.

Paucigranulocytic Asthma

Paucigranulocytic asthma encompasses patients with absence of airway inflammation (eosinophilia and neutrophilia) with persistent symptoms and evidence of AHR[5]. Activation of Type 1 ILCs with excessive IFN-γ production leads to reduced numbers of eosinophils and neutrophils resulting in paucigranulocytic inflammation. Mechanisms of this endotype can be changes in ASM or inflammation not reflected in the bronchial lumen.

Numerous stimuli, including inflammatory cytokines, pollutants, altered airway microbiome and mechanical strains, can predispose ASM to become nonspecifically hyper-responsive.

AHR independent of inflammation can be caused by the altered neuronal control of ASM contractility. Nerve growth factor (NGF) can induce AHR, activate inflammatory cells and cause airway remodeling. Neuroimmune cross-link dysregulation of critical

signaling molecules, including G protein-coupled receptors, transmembrane proteins, and growth transcriptional factors, can be possible mechanisms promoting AHR independent of airway inflammation.

Secretion of mast cell mediators could lead to bronchial obstruction, airway remodeling and AHR so the mast cell infiltration in ASM can play a role in the pathogenesis of this asthma phenotype.

Some patients may show both Th17 and Th2 mediated inflammation and mixed granulocytic inflammation might be a transition between neutrophilic and eosinophilic phenotypes.

Management of T2-low Asthma

No specific therapies have shown any clinical benefits in patients with asthma that is associated with a non-T2 inflammatory process. It remains to be seen if such an endotype truly exists and to identify treatments to target that endotype. There is a high unmet need in the endotype-driven approach for the T2-low asthma[1].

Meanwhile, identifying intense airway neutrophilia as an indicator of airway infection and airway hyperresponsiveness as an indicator of smooth muscle dysfunction, and treating them appropriately, and not increasing glucocorticosteroids in patients who do not have obvious T2 inflammation, seem reasonable[3].

First, we should confirm the T2-low nature of asthma with documented AHR and the absence of T2 inflammation (normal blood or sputum eosinophils, serum IgE or FeNO) or high sputum neutrophil. This is important because most of such patients (with the exception of mast-cell mediated disease) may not benefit from increasing the dosage of maintenance ICS.

Neutrophilic bronchitis can mask the underlying eosinophillic component so it is important to recheck the cell counts after the blood neutrophilia has resolved. In unresolved cases, investigations of transcriptome and proteome in sputum may lead to the better differentiation of T2 high and T2 low asthma.

Non-pharmacological Treatment

Active or passive smoking can induce neutrophilic inflammation, so the first measure in those patients is to promote smoking cessation.

Low-fat diet should be tried especially in obese patients. The high-calorie and high-fat meal can increase the neutrophil recruitment in the airways. Because of that, in obese patients weight reduction program with weight loss can lead to significant improvement in asthma control and forced vital capacity, reduction in symptom days, rescue-medication use and emergency room visits[18].

Bariatric surgery can be considered in morbid obese patients If there is no effect of weight reduction programs.

Bronchial thermoplasty (BT) can improve asthma control, peak expiratory flow, quality of life, symptom-free days and decrease the rescue medication use, severe exacerbations, emergency department visits and days missed from work/school. BT should be reserved for uncontrolled asthmatics with persistent symptoms, frequent exacerbations and severe AHR[19]. One limitation of bronchial thermoplasty is the difficulty of predicting clinical responders, so the discussion with experts about the feasibility and necessity of bronchial thermoplasty is adviced[20].

Mucus clearance procedures: In the patients with mucus hypersecretion, smoking cessation, physiotherapy in different body positions with high-frequency chest wall oscillation and eduaction about deep breathing with effective coughing can improve mucus clearance and alleviate the symptoms. In addition, intermittent positive end-expiratory pressure (PEEP) can dilate the small airway, reduce small airway obstruction, promote the sputum drainage and accelerate

mucus clearance. Inhalation therapies should be prefferentialy administered via humidified inhalation or aerosol inhalation in order to moisturize the airway, dilute sputum and facilitate expectoration[21].

Pharmacological Treatment

ICS could be discontinued or reduced in two thirds of non-eosinophilic asthma patients with no worsening of asthma control or exacerbation. Sometimes that reduction can reveal an eosinophilic inflammation and lead to the change in patient classification and treatment[22].

Tezepelumab is an anti-TSLP monoclonal antibody that binds human TSLP, prevents interaction with its receptor and, consequently, inhibits multiple downstream inflammatory pathways. Blocking of this pathways can improwe the severe asthma control in both T2 and non-T2 asthma[23].

Long acting bronchodilators (LAMA and LABA) can be effective in increasing the time to first exacerbation and improving lung function and symptoms[24].

Antibiotic treatment can be effective in patients with recurrent infective exacerbations. Molecular microbiology and mycology with extended cultures, including 16s deep sequencing, may be considered to direct the treatment.

Immunoglobulin replacement may improve asthma control in patients with infective exacerbations and immunoglobulin deficiency[25].

Azithromycin in long-term non-antibiotic doses of (250 mg daily three times per week) can result in decrease of severe asthma exacerbations frequency, improvement of the quality of life and reduced frequency of respiratory infections with no significant adverse events[26].

Selective antagonists of cysteinyl leukotrienes receptors in vitro can inhibit superoxide generation, production of LTB4 and release of elastase by activated neutrophils[27,28].

Theophylline in vitro promotes apoptosis of neutrophils, inhibits neutrophils from generating reactive oxygen species and causes a decline in neutrophil chemotaxis[29].

Roflumilast, a phosphodiesterase-4 inhibitor, can cause the reduction of neutrophil counts and TNF-α levels and can improve FEV1 in mild to moderate asthmatics when added to ICS[30].

Antifungal treatment should be considered in the patients with the persistent presence of Aspergillus in the respiratory tract[31,32].

Immunoglobulin replacement therapy: Patients with severe asthma and recurrent respiratory infections should be screened and (if appropriate) treated for immunoglobulin deficiency since that can improve asthma outcomes[33].

A proposal of algorithm to T2 low asthma approach is shown in the Figure 1.

Investigational Products

Because of an unmet need for new therapeutic agents in T2-low asthma, there are plenty of investigational products in development for that indication[3,34].

CXCR2 antagonists in preliminary studies showed significantly reduced sputum and blood neutrophilia in patients with severe neutrophilic asthma and decreased number of mild exacerbations.

Etanercept blocks TNF and in a small study demonstrated improvement in AHR, FEV1, and symptoms. Other investigated anti-TNF-α compounds showed unacceptable toxicity, mainly increased risk of infections.

Antibody against IL-17 receptor did not result in any statistically significant benefit uptill now.

Anakinra (IL-1 receptor antagonist) in healthy volunteers significantly reduced sputum neutrophilia and caused the rise of sputum IL-1β, IL-6, and IL-8 levels.

*Anti-IL6 b*locking might be a potential therapeutic target in T2-low asthma, but

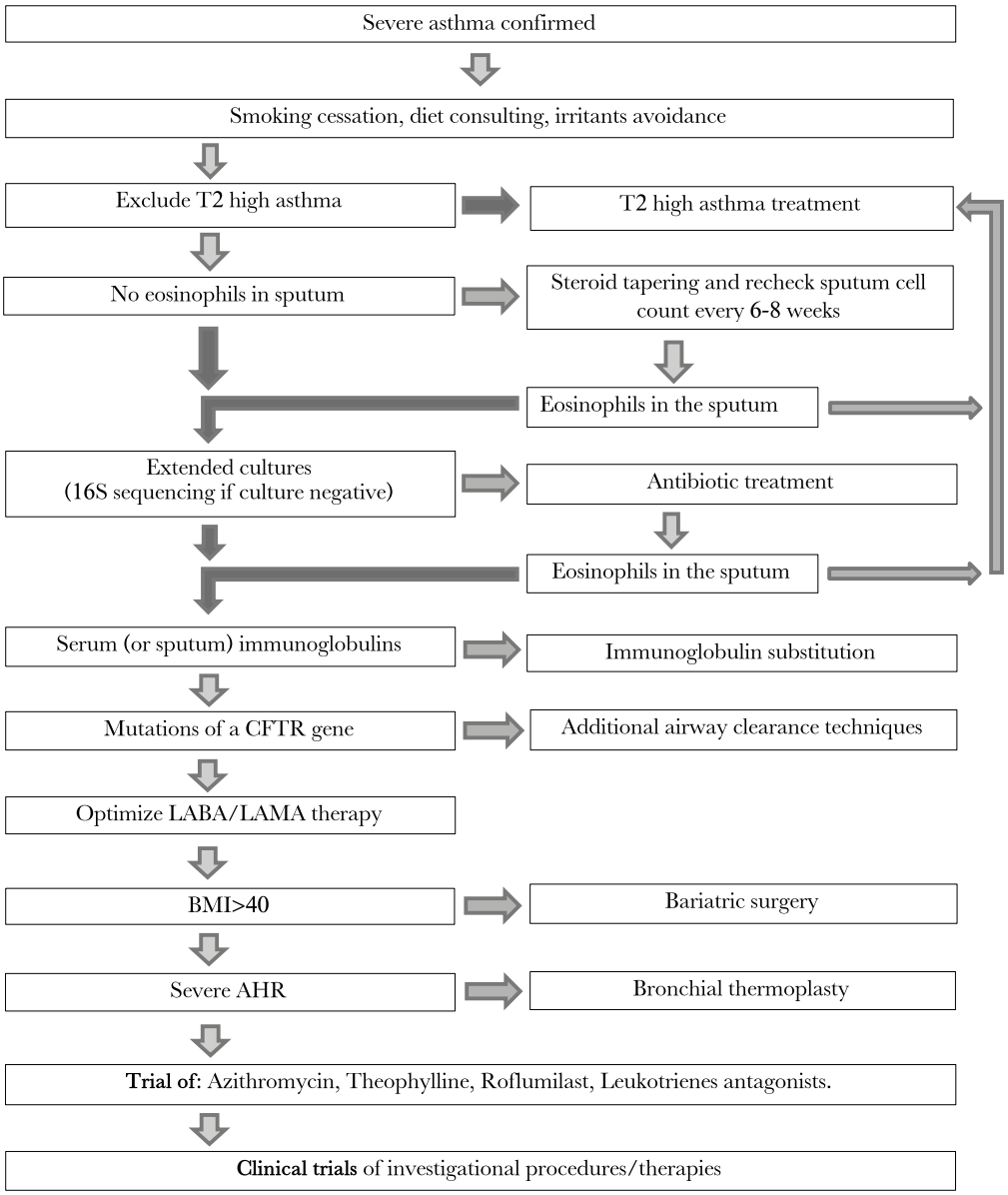

Figure 1. A proposal of algorithm to T2low asthma approach.
16S sequencing: 16S rRNA gene (DNA sequence corresponding to rRNA encoding bacteria, which exists in the genome of all bacteria)
CFTR gene: gene for a Cystic Fibrosis Transmembrane conductance Regulator protein
LABA: Long-Acting Beta Agonists
LAMA: Long-Acting Muscarinic Antagonists
BMI: Body Mass Index
AHR: Airway Hyperresponsiveness

there is no clinical trial data available for intervention in asthma.

Nebulized IFN-β treatment at the onset of viral upper respiratory tract infections shown to improve morning peak flow, increase in serum CXCR10 and reduced sputum CCL4 concentrations which suggested this treatment might improve outcomes of URTI induced asthma exacerbations.

Imatinib inhibits tyrosine kinase of KIT, induces mast cell apoptosis and reduces bone marrow mast cell burden. It can reduce airway mast cell burden and improve AHR in severe asthma.

5-lipoxygenase-activating protein (FLAP) inhibitors can reduce the sputum LTB4 levels but there are no significant effects on sputum neutrophil counts.

Modification of airway dysbiosis: Several novel approaches beyond antibiotics that may modify dysbiosis, including phage therapies, prebiotic nutrients, microbe-derived products (bacterial extracts, immune stimulants), and specific live microbial species (probiotics) may represent novel therapeutic avenues[35].

Targeting Mucus Hypersecretion: Quantitative imaging has been applied using computed tomography to develop validated mucus plugging scores in severe asthma. Novel inhaled and oral mucolytics and biologics that target IL-13–driven goblet cell metaplasia could help solve that problem.

Treating Comorbidities

A number of comorbid diseases, including rhinitis, rhinosinusitis, gastroesophageal reflux, and obstructive sleep apnea, are associated with severe or difficult-to-treat T2-low asthma. If present and untreated, these conditions may adversely affect asthma control, quality of life, and/or lung function, despite adequate treatment with step-up asthma controller therapy. Failure to recognize these comorbidities may divert appropriate care and increase disease burden. Assessment and management of these risk factors may contribute to improved asthma outcome[36].

Conclusion

Lately, the heterogeneity of asthma phenotypes is recognised and the treatment options are tailored according to those differences. T2-low asthma is still less well defined with different subtypes characterized by the low expression of T2 inflammatory markers and normal to low eosinophils.

Several treatment options for T2-high asthma have been developed and some of those treatments like new anti-TSLP monoclonal antibody tezepelumab are effective also in T2-low asthma. The results of ongoing trials with sophisticated transcriptomic and proteomic characterisations of different T2-low asthma patients will provide us tools to better characterise these patients and choose the precise therapeutic approaches.

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Eosinophilic and Allergic Asthma Phenotype and Therapeutic Possibilities

5.3

Ljiljana Bulat Kardum[1,2]

Abstract

Despite optimal treatment according to GINA guidelines, some patients with asthma have an uncontrolled, severe disease with significantly reduced lung function, an increased risk of exacerbations and disproportionate use of asthma-related health resources. The identification of specific phenotypes of asthma with unique pathophysiologic mechanisms such as T2-high and T2-low immunological pathways and clinical characteristics enabled the discovery of new and more effective treatments for severe asthma. The emergence of novel biologic treatments, including monoclonal antibodies as anti-IgE, anti IL-5/anti IL-5Rα and anti IL-4/IL-13 are has led to an enhanced understanding of the pathogenesis of asthma and highlighted the importance of patient-specific treatment dependent on phenotypic characteristics.

Keywords: severe asthma, phenotypes, T2 asthma, non-T2 asthma, biologic treatment, anti-IgE, anti IL-5/anti IL-5Rα, anti IL-4/IL-13

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More than 300 million people worldwide suffer from asthma and it is estimated that 400 million people will suffer from asthma by 2025. It is present in all regions of the world regardless of their socioeconomic level, although its prevalence varies. In the United States, the prevalence of asthma is 7.6% and 8.4% for adults and children, respectively; in the European Union the prevalence is about 8.2% and 9.4%, respectively.[1,2,3] Most patients can achieve good disease control and a satisfactory quality of life with conventional treatment according to international guidelines such as the Global Asthma Initiative (GINA)[3].

How Common is Severe Asthma?

Despite optimal treatment, some patients with asthma have uncontrolled severe asthma with an increased risk of exacerbations and overuse of asthma-related health resources including frequent hospital care and significantly reduced lung function with a risk of further deterioration over time.[3] In this group of patients, it is necessary to identify those who manifest uncontrolled asthma and in whom accurate diagnosis or adequate treatment will significantly improve the current control of the disease ("difficult-to-treat asthma"). It is estimated that about 24% of asthma patients have GINA treatment of 4th or 5th step, 17% of all asthma patients have "difficult to treat asthma", while 3.7% of asthma patients have severe asthma.[4]. The systematic review of 195 articles reporting on severe asthma studies found the prevalence of severe uncontrolled asthma to be as high as 87.4%.[5]

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Evolving Concepts of Severe Asthma: Personalized Asthma Management

Asthma is a complex respiratory disorder characterized by pronounced heterogeneity in disease triggers and individual responses to therapy. It is a heterogeneous disease with different phenotypic characteristics that arise from the complex interrelationship of genotypic characteristics and environmental factors. Therefore, a standard therapeutic approach is not as effective as unique pathophysiological mechanisms underlying a particular disease subtype which alter the response to conventional therapy.[8-10]

Severe asthma is defined as an asthma that requires treatment of level 4 or 5 according to GINA guidelines (high doses of ICS/LABA and/or tiotropium, leukotrienes or theophylline) in the previous year or treatment with systemic corticosteroids (CS) 50% of the previous year to prevent the development of "uncontrolled" disease or it remains uncontrolled despite this therapy. The next therapeutic step is to consider the indication for biological therapy, while oral corticosteroids according to the latest GINA guidelines revision are a backup therapeutic option to consider.[3,9]

Treating asthma with biological agents is the first step towards personalized therapy. Such approach is made possible by an increase in the understanding of the pathophysiological pathways in asthma and paved the way for new asthma treatments based mainly on T2-high pathway cytokines and associated certain phenotypes of severe asthma. Therefore, with the help of better identification of asthma phenotypes, we can select an effective targeted therapy (biological) that will allow us to achieve disease control in patients with severe asthma, in whom standard therapy has not been effective.[10-13]

Two Different Pathways Lead to Eosinophilic Airway Inflammation in Asthma

In the same time as the recognition of phenotypes of severe asthma, new knowledge about the pathophysiological and inflammatory mechanisms in asthma has advanced, which has further contributed to the differentiation of certain phenotypes and endotypes of asthma.[13] Two separate pathophysiological pathways cause eosinophilic inflammation in asthma:

1. In *allergic asthma*, dendritic cells after a contact with the allergen as well as alarmins IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) from exposed epithelial cells of the airway mucosa, present antigen to Th0-naive CD4 + lymphocytes and induce their transformation into activated Th2 cells, which produce IL-4, IL-5 and IL -13. In this process, B lymphocytes were also activated to produce IgE antibodies, airway eosinophilia, and hypersecretion of mucus.[13-15]
2. In *nonallergic eosinophilic asthma*, air pollution, microbes, and glycolipids induce the release of cytokines from epithelial cells, including alarmins IL-25, IL-33 and TSLP, which activate naive lymphoid cells (ILC2) in an antigen-independent manner. Activated ILC2 cells produce high amounts of IL-5 and IL-13 causing eosinophilia, mucosal hypersecretion and airway hyperreactivity. The importance of Th2 lymphocytes in this process was highlighted through the cytokines IL-4, IL-5 and IL-13 involved in eosinophilic inflammation and IgE production, in an asthma phenotype called T2-asthma (T2-high asthma).[15-17]

Th17 cells with cytokines IL-17, IL-8 and growth factor participate in neutrophilic inflammation in non-T2 asthma (T2-low asthma).[14]

Implications of T2-High and T2-Low Pathway on Asthma Phenotypes

Several strategies have been proposed for the identification of severe asthma phenotypes, based on different clinical characteristics or

in relation to the types of cellular airway infiltration. Although the stratification of asthma phenotypes by blood eosinophils is relatively easy, it does not allow a deeper/more detailed identification of clinical phenotypes. Therefore, cluster analysis is used to identify groups of patients with asthma who share specific clinical characteristics, e.g., cluster analysis using clinical characteristics of patients such as asthma onset age, lung function value, bronchodilator reversibility and demographics. The Severe Asthma Research Program (SARP) identified five clinical groups of asthma in adults, in which four groups showed eosinophilia of varying degrees.[18]

In order to identify severe asthma phenotypes, ADEPT study[19] was conducted and identified four clusters of asthma, which were also present in the UBIOPRED study.[20] Three of these four asthma clusters were associated with eosinophilia.

In the evolution of knowledge of clinical phenotypes, Saly Wenzel and her co-workers have made a definition as follows: early-onset allergic, late-onset eosinophilic and exercise-induced phenotype, all identified by biomarkers of Th2 asthma; and three phenotypes of non-Th2 asthma, obesity- related, neutrophilic and asthma in smokers. No biomarkers of non-Th2 asthma have been identified so far as a basis for new biologics and markers of a positive response to that treatment.[21,15] This is due to the lack of knowledge of the non-T2-High (T2-Low) immune response associated with the activation of Th1 and/or Th17 cells and IL-17, IL-8 cytokines and the mechanisms underlying the recruitment and maintenance of neutrophilic inflammation.[22]

Biological Agents Targeting Airway Inflammation in Asthma: The Rational Choice

Biomarkers can warn of the severity of the disease and predict the response to a particular treatment. Some of the biomarkers, alone or in combination, will be useful in identifying patients for targeted type 2 asthma treatment. Blood eosinophils due to its high predictive value of ≥300/μL is used as an initial biomarker to predict treatment responses targeting IL-4, IL-5, and IL-13.[15,23]

Consistent with its central role in the development of allergic asthma, serum value of IgE is a good biomarker of an atopic status. Serum IgE levels are positively correlated with the severity of asthma in adults and children. Serum total IgE is used to predict responses to anti-IgE therapy, but is not useful for monitoring responses.[15,24]

The role of periostin and FENO in tailoring the biologic therapy targeting type 2 asthma is less clear. Periostin is an extracellular matrix protein secreted from IL-4 and IL-13-induced airway epithelial cells, but has not been shown to be a good biomarker in routine use. Changes in FENO after dupilumab therapy (anti IL-13/IL-4) correlate well with improvement in FEV1.[25-27]

Allergic and Eosinophilic Asthma Phenotype

The decision to choose biological therapy is preceded by a process of asthma phenotyping based on the identification of clinical characteristics and driving mechanisms of inflammation. Biomarkers help us in the rational choice of biological and predict a positive response of patients to the selected treatment:

1. The "Early-onset allergic asthma" phenotype usually begins before the age of 12. Triggers are allergens and other allergic diseases, and/or a positive family history is associated too. Specific biomarkers are elevated total IgE, specific IgE and cytokines of T2 inflammation.[9,10,13, 21]
2. In the "Late-onset persistent eosinophilic asthma" phenotype, symptoms begin in adulthood, often are associated with chronic sinusitis and nasal polyposis. Biomarkers of this phenotype are elevated eosinophils of peripheral blood and

sputum. In some patients, "aspirin exacerbated respiratory disease" is also present.[21,28,29]

While IgE is involved early in the inflammatory cascade and can be considered a cause of allergic asthma, eosinophilia can be considered a consequence of the whole process. Hence the different roles of the IgE pathway and the IL-5 eosinophil pathway in the pathogenic mechanisms of airway inflammation occurring in asthma, and thus the reason for choosing anti-IgE monoclonal antibody or anti-IL-5/IL-5Rα treatment.[30]

Mechanisms of Action of Anti-IgE Treatment in Allergic Asthma Phenotype

Omalizumab is an anti-IgE treatment. It binds to free IgE and thus reduces the binding of IgE to mast cells, basophils and eosinophils. In addition, omalizumab reduces the expression of high-affinity FcεRI receptors for IgE on these cells, thereby further reducing IgE binding to them. This reduces the release of mediators from the cells, reduces allergic inflammation, prevents the exacerbation of asthma and reduces symptoms.[31,32] Omalizumab is indicated for adults and children over six years of age with uncontrolled moderate to severe allergic asthma with elevated total IgE antibodies, a positive skin allergy test, or specific IgE antibodies to perennial allergens.[33A]

Omalizumab statistically significantly reduced daily symptoms, reduced exacerbations, and the dose of inhaled corticosteroids. Omalizumab has improved asthma control and reduced the need for other asthma medications. All these effects are visible after 12 weeks of therapy.[32,34,35] In the STELLAIR study, the rate of exacerbation reduction was similar in patients with severe allergic asthma with high (≥ 300 cells/μL) and low (< 300 cells/μL) eosinophils. Patients with higher serum IgE levels, shorter disease duration and higher blood eosinophils may benefit from delayed omalizumab therapy.[33,36]

Mechanism of Action of Anti IL-5/Anti IL-5Rα and Anti IL-4/IL-13 Treatments in Eosinophilic Asthma Phenotype

IL-5 is a key factor in the eosinophil maturation, mediates eosinophil mobilisation, activation and survival. It achieves its effects by binding to a specific subunit of the IL-5 receptor, which is IL-5Rα. The IL-5Rα subunit binds only IL-5. Eosinophils express up to three times more IL-5Rα on their cell membrane than basophils. Th2 cells, mast cells, innate lymphoid cells (ILC 2), CD34 + progenitor cells, natural killer (NK) T cells and eosinophils themselves are the main cellular source of IL-5[37] Therefore, targeting IL-5 or IL-5Rα is a logical approach to treat patients with severe eosinophilic asthma.

Two different anti-IL-5 monoclonal antibodies, mepolizumab and reslizumab, bind to different epitopes of IL-5 by interfering with its binding to IL-5R expressed on the eosinophil membrane by reducing the IL-5 signaling pathway that impairs eosinophil maturation and survival.

Mepolizumab is a humanized monoclonal IgG4 antibody, administered subcutaneously at a dose of 100 mg every 4 weeks. Criteria for introducing mepolizumab into treatment are: forced expiratory volume in 1 second (FEV1) less than 80% of predicted value, at least two exacerbations of asthma in the previous year treated with systemic glucocorticoids while the patient was treated with high doses of inhaled corticosteroids with a long-acting beta2-agonist, and at least with an additional controller and an eosinophil count of at least 150 cells per microliter in peripheral blood at screening or at least 300 cells per microliter at some point during the previous year. Mepolizumab reduces the rate of exacerbations by 53% compared to placebo (P<0.001), reduces exacerbations requiring an emergency visit and hospitalization

by 61%. It also improves the quality of life and lung function, which is reflected in the average increase in FEV1 compared to placebo (P=0.03).[33,34,38]

Reslizumab is also a humanized monoclonal IgG4 antibody, administered intravenously at a dose of 3 mg/kg body weight every four weeks. Reslizumab is indicated in patients with uncontrolled severe asthma despite treatment with high doses of inhaled corticosteroids with a long-acting beta2-agonist, with the addition of one or more controllers and/or with additional OCS therapy. The blood eosinophil counts of ≥150 cells/μL at screening or ≥ 300 cells/μL within 12 months prior to treatment of ≥300 cells/μl i had to be present. Reslizumab reduces the incidence of asthma exacerbations compared to those receiving placebo, In two studies of Castro et al, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations - in study 1. exacerbation rate was reduced by 50%; in study 2 exacerbation rate reduced by 59%; both p<0·0001) compared with those receiving placebo. Lung function (FEV1) , asthma control (ACQ) and quality of life (AQLQ) have been improved over placebo.[32-34,39]

Benralizumab has a dual effect: it is a blocker of the IL-5Rα receptor on the eosinophil membrane and thus prevents the binding of activated IL-5, while binding NK cells that cause accelerated eosinophil apoptosis. This effect is associated with a rapid reduction in eosinophilia in the blood. It is administered subcutaneously at a dose of 30 mg every four weeks for the first three doses and then every eight weeks. Benralizumab significantly reduced asthma exacerbations and consequently progressively reduced daily OCS intake, improved ACT questionnaire value and an increase in lung function.[33,34,40]. Benralizumab is indicated in patients 12 years or older and in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists, with baseline blood eosinophil counts ≥300 cells/μL.

Dupilumab is the only biologic that has dual inhibitory activity; inhibits the signaling pathways of IL-4 and IL-13 by blocking the alpha chain of the IL-4 receptor, thus acting on two separate pathophysiological pathways cause eosinophilic inflammation in asthma:allergic and non-alergic eosinophilic patways. So, effects are not limited to those patients who have eosinophilia[28]. Dupilumab improved lung function and reduced severe exacerbations in patients with an uncontrolled severe asthma, regardless of the initial number of eosinophils and had a favorable safety profile, and therefore with inhaled corticosteroids and long-term therapy with β2-agonists could improve the life of patients with uncontrolled asthma in standard treatment.[34,41,42] Therefore, dupilumab is indicated in adults and adolescents 12 years and older with severe asthma characterised by blood eosinophil count of >150 cells/μL and/or raised fraction of exhaled nitric oxide (FeNO) >25 ppb, inadequately controlled with high dose ICS and one of more controlers.

Looking into the Near Future: Anti-epithelial Cytokine Antibodies

The epithelial cytokines: thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 are released from the airway epithelium in response to allergens, air pollution, and viruses triggering an inflammatory cascade in asthma. It has been hypothesized that the blockade of these cytokines, compared with biological agents aimed at T2-inflammation, could improve severe asthma outcomes in a much wider patient population. The results of recent RCTs have shown the efficiency of tezepelumab, a human monoclonal antibody which targets TSLP; itepekimab, an anti IL-33 human monoclonal antibody; and astegolimab, a human monoclonal antibody with an IL-33 receptor blockade effect in patients with severe asthma.[45-48]

In phase 3, RCT tezepelumab as add-one therapy in uncontrolled severe asthma at a dose of 230 mg administered subcutaneously every 4 weeks in adolescents and adults, has reduced the annual exacerbation rate by 56%, and among patients with blood eosinophil counts less than 300 cells/μL reduced exacerbation rate by 41%. In addition, tezepelumab has improved lung function, asthma control and the quality of life in the T2-high asthma group, but also in the T2-low asthma group. A rapid decline in blood eosinophil counts, a decrease in FeNO, a gradual reduction in serum total IgE and a reduction in bronchial hyperreactivity were observed. Safety profile of tezepelumab was similar to placebo.[45,46]

Itepekimab (anti IL-33) in phase 2 RCT at a dose of 300 mg sc every 2 weeks has reduced exacerbations and improved lung function in patients with moderate to severe uncontrolled asthma[45,47], while astegolimab (anti IL-33R) in phase 2 RCT was administered subcutaneously every 4 weeks in patients with severe asthma, including those with low peripheral blood eosinophils, reduced the rate of exacerbations, but did not improve lung function.[45,48] Positive results of phase 3 RCTs of monoclonal antibodies efficacy against epithelial cytokines are expected, especially for T2-low asthma.

Numerous elements contribute to the response to biologic treatment and individual patient responses will vary. The monitoring of lung function, the presence of symptoms, number of exacerbations and quality of life may help in early clinical assessment of response to treatment. Identifying patients with a therapeutic response and those who do not respond to biologic therapy is not easy. Suggested approach to the treatment of severe asthma beyond standard therapies involves the treatment omalizumab in case of elevated IgE and positive perennial antigen. After 4-6 months, an assessment follows and if treatment has no effect, switch to anti-IL-5 therapy in those patients with elevated eosinophils while IgE is in the reference values. If there is no effect of IL-5 therapy, bronchial thermoplasty should be considered as in those patients with low IgE and low eosinophils.[22] Patients who have an intermediate response to therapy either need to continue treatment for one year to assess response or consider switching to alternative biologic therapy if a therapeutic effect is absent. Clinical experience and new research may identify a panel of new biomarkers that will better predict a positive response to biological therapy and facilitate our therapeutic option.[43]

Unfortunately, none of the biological agents can meet the needs of patients whose asthma is not mediated by a T2 response (T2-low asthma). Due to our limited understanding of the immune response of in T2 low asthma, our therapeutic options are very limited and are a reflection of unmet needs in severe uncontrolled asthma.[22,44]

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6

A View Toward Controversies and Dilemmas

Controversies and Dilemmas in Severe Asthma

6.1

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Abstract

As severe asthma is a rather common respiratory disease, with a heavy burden for the patient, the health system and society, it is important to recognize it and apply modern biological therapy if indicated. As in today's approach to asthma management, we tend no more to "me too medicine", but to individual therapy in personalised and precise medicine. This article is dealing with some controversies and dilemmas in the field. After introducing biological therapy in the early 2000s, systemic glucocorticoids became the second option for patients with severe asthma. Starting with the controversy about accurate asthma diagnosis, then the question of where patients with severe asthma are hiding, thirdly, are we treating those patients appropriately and comprehensively, and finally, are we emphasising enough the necessity of smoking cessation? After reviewing the facts, and considering the extensive discussion exposed in controversies, a similar analysis brought up a few dilemmas, i.e. how could we precisely define severe asthma phenotypes, how should we distinguish asthma from COPD in middle-aged smoking patients, and how to make the right personalized choice of biologicals. There is also the dilemma about age - how old (or young) should the patient be for the indication for biologicals, and lastly, the length of treatment which is appropriate to assess a patient's response to biologicals ("responder" or "non-responders").

Keywords: asthma, diagnostics, precision medicine, smoking cessation, response to therapy assessment

Introduction

Asthma is the most frequent chronic respiratory disease[1], with almost 1 in 8 children and 1 in 12 adults affected[2]. Asthma has a great impact on the person, the health system and society. Therefore, investigating asthma from different angles is important, as is dealing with controversies and dilemmas in the field.

The First Controversy in Asthma Always Starts with Asthma Diagnosis

There is a substantial number of patients with an *incorrect diagnosis* of asthma. Around 2% of *misdiagnosed* patients were thought to have asthma, but instead, they had other serious diseases (like tracheal stenosis, and coronary artery disease...). A significant part of these patients was *frequently diagnosed with asthma without sufficient evidence, which is not beneficial for the patient (over-diagnosis)*- around 33% of patients had innocent diseases (i.e. rhinitis, GERB, anxiety etc.)[3]. Some of the patients also had a *failure of recognising asthma* (*underdiagnosis)*. In the general population of younger subjects < 44 years who on a questionnaire reported respiratory symptoms

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compatible with asthma, around 32% of the asthma was confirmed by further examination i.e. methacholine challenge testing, skin prick tests and serum IgE measurement (4). Although in older patients >65 years, a lower percentage of underdiagnosed asthma was found - in 15% of them. This fact is very important, because, in older patients with typical asthma symptoms, asthma is a rarely perceived physician-diagnosed disease, even in those patients who had< 10 pack-years of smoking or no history of congestive heart failure[5]. Independent risk factors for asthma misdiagnosis are spirometry underutilization and missing data on pack-years of smoking[6].

An even bigger problem is the diagnosis of severe asthma. There is a significant delay in some severe asthma patients until the right diagnosis of severe asthma is established. The most logical possible explanations are twofold: the appearance of disease with atypical presentations of asthma in persons with parallel conditions (like obesity), and secondly - some patients are "poor perceivers" (although there are also medical professionals failing to recognize the disease). There are asthma patients that never have wheezing, some never cough, but most of them have dyspnea. As dyspnea can be a manifestation of many diseases, the most often from cardiac origin, it is not surprising that some patients for many years do not perform any pulmonary diagnostics. Of course, heart diseases are the most common pathology in the elderly, so they are often present as a comorbidity, but are not necessarily the leading etiology. As many patients smoke and their obstructive disease is presented for the first time during an exacerbation, they immediately receive a COPD diagnosis, which has been going on for years. From personal experience, a certain number of "COPD" patients disclosed their asthma features after usage of a single or dual bronchodilator therapy in COPD became more regular, and somewhat earlier patients were advised to discontinue ICS from their therapy. The fact is that in most of those patients careful medical history should determine asthma immediately. Respiratory symptoms were present from childhood, they had sensitisation to perennial allergens, they were treated for asthma in youth, or have eosinophilia etc. "Lack of careful history taking is intellectually lazy, it is too expensive, so should be condemned."[7]

"Poor perceivers" are those patients with asthma who do not report symptoms when their FEV_1 dropped by 20%[8]. In the group with an established asthma diagnosis in this study of 1155 subjects, 6% were poor perceivers of dyspnea, while in the group which did not have physician-diagnosed asthma despite verified airways obstruction, 26% were poor perceivers. Both under and overdiagnosis of asthma lead to significant risks to patients, and every effort should be undertaken to establish a proper diagnosis[9].

It is usually stated that 5-10% of all asthma patients have severe asthma[10]. Since 2016, the Global initiative for asthma (GINA) has stated that asthma is a heterogeneous disease[11]. Asthma heterogeneity can be seen in diverse clinical presentations, different responses to treatment, and different pathophysiological features and findings due to various pathogenic mechanisms, which lead to multiple asthma phenotypes.

Here Comes the Second Controversy: Where are Those Patients With Severe Asthma Hiding?

There is an unmet need for standardisation of the referral pathway leading to early identification of patients with severe or difficult-to-treat asthma[12]. A possible solution for better referral to asthma specialists is better communication with emergency departments (ER).Patients discharged from the emergency departments after an acute asthma exacerbation episode should be referred to an asthma specialist, either a pulmonologist, allergist or pediatrician. Another possibility is also better access to the general practitioner's (GP's) pool of "problematic" asthma patients. Patients are

often put on a short course of OCS, without an individualised strategy for the patient during the high-risk period after an emergency room or hospital visit. Around 29% of asthma patients, who are using high doses of ICS, also take harmfully high doses of oral steroids of more than 0.429 per year[13]. Oral steroids have devastating effects on a person's health – an annual cumulative dose of 2 grams of oral steroids is associated with adverse side effects, like diabetes, osteoporosis, arterial hypertension, cataracts, depression, but also adrenal insufficiency - the side effect of which we are thinking the least[14].

There are also obstacles and barriers to diagnosing severe asthma patients. Here I refer to all kinds of medical doctors, GPs' and all different specialists, including pulmonologists. We have to ask ourselves: are we appropriately listening to our patients? Are we asking the right questions? Do we perform objective measurements, like questionnaires, PEF or other lung function measurements, do we detect airflow variability, FeNO, blood and sputum eosinophilia, skin prick tests etc. Are we actively looking for other diseases similar to severe asthma from a differential diagnosis (ANCA test, total and specific IgE to *Aspergillus fumigatus,* computed tomography HRCT, nasal polyps, drug sensitivities etc)? There is a lot of room for improvement in this area.

Extrapolation of results from the database to the general Dutch population: there are about 6000 patients with severe asthma who are candidates for biologic treatment – 1.5% of the entire asthma patient population (13). If we try to estimate the situation for Croatia, with 4,087,843 inhabitants (according to the mid-2018 estimate by the Croatian Bureau of Statistics) the asthma prevalence is 5.28%, as it was shown to be a European prevalence[15] (although there are epidemiological data that the asthma prevalence in schoolchildren in Croatia is higher - 6.02%–6.9%[16,17]), there are 215,838 asthmatics; among them there should be at least 5% of severe asthmatics, which is 10,792 patients. Not all of them are candidates for biological therapy; eligible are only those asthma patients who are prone to exacerbations or who need oral steroids for treatment.

In the entire asthma population, one-quarter of the patients are prone to exacerbations, not all of them, but 10% have severe asthma[18]. Prone to asthma exacerbations means more than two or three (some authors count four - still there is no consensus on the number of asthma exacerbations per year). A patient is said to have suffered from a severe exacerbation if any of the following are present: either systemic steroids had been used to treat the attack, the maintenance dose was required to be escalated for at least 3 days; or an emergency visit due to asthma had to be made to a health-care facility, during which systemic steroids were administered[19]. The same severe asthma population revealed that more than a third of those patients do not have asthma exacerbation at all. The most important risk factors for asthma exacerbations were BMI, gastroesophageal reflux, rhinosinusitis and blood eosinophils. Expenses for the 5% of patients prone to exacerbation make up almost 50% of the total exacerbation burden[20]. Until now, different cohort analyses did not reveal a single phenotype of patients prone to exacerbations[21]. It seems that patients became prone to exacerbations when having an increased underlying biological risk, and when he or she is exposed to a certain environment with allergens, pollution or stress[22].

There are 30% of patients with severe asthma who need oral steroids for their treatment to prevent their asthma from becoming uncontrolled, or for improvement in symptoms and prevention of exacerbations[23].

If we account for these facts, and if this is a similar situation in Croatia (we do not have solid statistical data about severe asthma) there are around 3500 patients with severe asthma who are prone to exacerbations

or are permanently on oral steroid therapy. As half of them have type 2 inflammation[24], then it is reasonable to assume that there are 1780 patients in Croatia eligible for some kind of biological therapy.

If we consider a different count, parallelly, in Croatia as in the Netherlands, where 1.5% of all asthma patients are eligible for biologicals, we get similar numbers. In Croatia, 1.5% of all asthma patients consist of 3237 individuals. Half of those patients are 1618 patients with severe asthma who are allergic or have eosinophilic asthma, or have asthma with type 2 inflammation - all of them are eligible for either anti-IgE, antiIL-5 or anti-IL-4/IL-13 biological therapy.

We investigated Croatian pulmonologists' attitudes toward the prescription of biologicals in severe asthma patients, to identify reasons for the discrepancy between the number of eligible severe asthma patients and proper biological treatment. Biologics can be prescribed only by a pulmonologist following specific guidelines proclaimed by the National Health Insurance (Croatian Health Insurance Fund, CHIF) and has to be approved by the Hospital Medicines Committee (HMC). We found that regular treatment with systemic glucocorticoids and frequent acute exacerbations were the most frequent major indications for biologics in severe asthma patients, 91.7% and 82.1%, respectively, followed by frequent ER visits or hospitalizations (53.6%). The average period from establishing the indication for biologic therapy until the actual application was estimated to be 2 months, significantly shorter in university hospitals (58 vs. 105 days, $z=2.255$, $p=0.024$) but without a difference between regions ($p=0.561$). A significant number of pulmonologists reported that some of their patients did not receive biological treatment for their severe asthma during the last 12 months even though they needed it: due to inappropriate diagnosis (64.3%), strict administrative directions for the reimbursement by the Croatian Health Insurance Fund (70.2%), and limited hospital resources (57.1%). Croatian pulmonologists also identified the problem of financial restrictions at the level of hospitals. When we examine the guidelines prescribed by CHIF, poor lung function (FEV1 <60% expected) is for all biologics one of the key criteria that had to be fulfilled. In international guidelines, poor lung function is not mentioned for indications for biologicals or it is restricted to FEV1 ≤80%. Therefore, negotiations with CHIF based on pharmaco-economic and health-related quality of life (HRQoL) criteria should be initiated to implement less stringent criteria for the reimbursement of biologics according to internationally recommended guidelines[25].

Third controversy: Are we Emphasizing the Necessity of Smoking Cessation Enough?

Asthma is not considered a disease of high mortality. Still, each day there are 3-6 deaths from asthma, as reported in Brazil[26]. Investigations have proven that decreasing the number of smokers also decreases the prevalence of respiratory deaths[27].

Tobacco smoke from cigarettes has many toxic compounds such as acrolein, acetaldehyde, and formaldehyde, which contribute to respiratory irritation[28]. Tobacco can increase the prevalence of allergic diseases, like asthma, allergic rhinitis and atopic dermatitis. It could precipitate allergic sensitization directly – by affecting the IgE production on a cellular level, or indirectly – by increasing the permeability of respiratory epithelium[29]. In the research conducted on Croatian citizens, we have found a statistically significant increased prevalence of allergic diseases and increased level of total IgE, both in active and passive smokers as opposed to non-smokers[30]. Active smoking increases the inflammatory process with cell infiltrations, especially eosinophils[31]. The clinical picture of asthma in smokers is more severe in terms of symptoms, with more frequent exacerbations than in asthmatic non-smokers[7]. Secondhand smoking leads to

more severe airway obstruction and greater hyper-responsiveness[32].

It is obvious that smoking negatively influences asthma -it aggravates symptoms and treatments for exacerbation, increases inflammation and decreases the possibility of asthma control. That is why physicians and all other health care professionals should exert the greatest effort to bring the awareness about harmful effects of tobacco smoking to our patients.

It is important to build a national capacity for smoking cessation policy, which the World Health Organization (WHO) summarizes in a document[33]. There are enumerated measures influencing the demand for tobacco products (like taxation and legislation) and other interventions directly targeted to facilitate the changes in tobacco user attitudes and behaviour (like Quit and Win competition, mass media communications campaign, telephone help-line etc.). At the individual level the most recommended is the 5A strategy[34]:

1. *Ask*: Identify and document the tobacco-use status of every patient at every visit.
2. *Advis*: In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. *Assess*: Is the tobacco user willing to make a quit attempt at this time?
4. *Assist*: For the patient willing to make a quit attempt, use counselling and pharmacotherapy to help him or her quit.
5. *Arrange*: Schedule follow-up contact, preferably within the first week after the quit date, in person or by telephone.

It would take only a few minutes to speak to patients and learn about their tobacco use and habits. We should help the smoker to understand the health risks of smoking. Tobacco is the single greatest preventable cause of disease and premature death. Stop smoking is the best thing one could do for his or her health.

Dilemmas in Severe Asthma

First Dilemma: How Could we Precisely Define a Severe Asthma Phenotype?

The real-world situation in medical praxis is concerning. Around half (1/2) of the physicians in the world do not have an approach to diagnostic tools satisfying for establishing an accurate diagnosis. Around one third (1/3) of the patients in the world receive inappropriate treatment, and around one quarter (¼) of patients have potential life-threatening side-effects because of inappropriate treatment.

Today, defining severe asthma phenotypes is a process based on a biomarker-driven approach[35]. Asthma phenotypes with underlying mechanisms became the centre of asthma research as there are efficient phenotype-driven therapies available. This therapy is usually biological[36, 37], but also includes macrolides, which are a successful therapy in uncontrolled asthma[38] (although the immunomodulatory effect of azithromycin was proven more than a decade ago in healthy persons[39]) and other airways diseases such as chronic obstructive pulmonary disease.

Precisiondefinition of severe asthma phenotype is crucial for applying personalized medicine[40].

For that purpose, we should combine medical history, physical examination, biomarkers and imaging methods. In medical history the most important is the age when an asthma diagnosis was established. Other factors to take into consideration are: whether it is childhood or adulthood asthma (early-onset or late-onset asthma), if there are allergies or any drug sensitivities, is there a family history of allergies, is there a smoking habit or obesity present, which comorbidities does the patient have, especially nasal polyps, and carefully monitoring of a steroid side effect, like arterial hypertension, diabetes mellitus, depression, adrenal insufficiency or cataracts. Among biomarkers for clinical praxis, the most important are total and specific

immunoglobulin E (IgE), eosinophils in blood and (induced) sputum, alsofractional exhaled nitric oxide (FeNO). It is important to find fungi in sputum if they are present and to distinguish if it is just sensitisation (SAFS - severe asthma fungal sensitisation), or colonisation and/or invasion (like ABA – allergic bronchopulmonary aspergillosis). Imaging like radiography or computed tomography (CT scan) will disclose bronchiectasis, eosinophilic infiltrates, also eosinophilic granulomatosis with polyangiitis (EGPA), as well as signs of bronchiolitis or mucoid impactions. In some cases, it will be necessary to perform bronchoscopy for a differential diagnosis or to remove thick and sticky eosinophilic secretion in the airways.

Second Dilemma: How Should we Distinguish Asthma From COPD in Middle-aged Smoking Patients?

The answer to this question at the beginning lies in detailed anamnesis, which no single diagnostic test could replace. A connection of symptoms to certain triggers, like allergen exposure worsening respiratory symptoms, or coexistence of respiratory symptoms with comorbidities like eosinophilic lung infiltrate, rhinosinusitis with or without nasal polyps, urticaria, atopic dermatitis, psoriasis, fungi sensitisation, etc., should be associated to asthma. Also, an allergy should always be looked for, or an aspirin sensitivity, as well as multiple episodes of respiratory symptoms during childhood and family history of allergies, whether in predecessors or descendants.

Another important factor, after medical history data, is lung function variability. The situation is not so clear when there is fixed airway obstruction (FAO) or persistent airflow limitation (PAL). Asthma and COPD are syndromes consisting of several endotypes and phenotypes, consequently comprising a spectrum of diseases[41].

It is very difficult to distinguish whether chronic airflow limitation is due to asthma or a CD, especially in smokers and the older population. Prevalence of FAO is higher in more severe degrees of asthma, in severe or difficult-to-treat asthma there are 55% to 60% of patients with FAO; of them fulfiling the criteria for COPD (42).When we compare asthma patients with asthma with and without FAO, those with FAO are more likely to be male and to have a longer asthma duration[43]. Mannino et al. found that up to 30% of subjects with airflow obstruction have a history of asthma rather than COPD, but reversibility was not assessed in this epidemiologic survey, which could make this number even higher[44].

Third Dilemma: How to Make the Right Personalized Choice of Biologicals?

As phenotype may or may not be associated with underlying disease mechanisms, clinical phenotypes alone are not precise enough to guide targeted immune-modulator therapy without a "biologic" marker to reveal underlying biologic heterogeneity[45].This means that the mandatory choice of biologicals is biomarkers, total and specific immunoglobulin E (IgE), eosinophils in blood and (induced) sputum, as well as fractional exhaled nitric oxide (FeNO). When we take everything into account, clinical and laboratory aspects, together with functional tests and imaging, we can make a responsible choice.

Still, there are a few problems to be resolved. We need to develop biomarkers, which could lead us to a more precise choice of which biological therapy to start with, which will have a better predictive value for responsiveness to biologics. Also, those biomarkers should be predictive for effective monitoring, or to give a signal when to stop biologics. Not to mention how important it is to find new biomarkers for the T2-low asthma phenotype (or non-T2 endotype), after which a search for an effective treatment could become a more realistic option for such patients.

Fourth Dilemma: Age. How Old (or Young) Should Our Patients be for Indication for Biologicals?

Allergic asthma is usually an early-onset (during childhood, before the age of 12 years), but not necessarily, while eosinophilic asthma is usually a late-onset, but also not necessarily. In children, after the age of 6 years, omalizumab showed good tolerability and safety, while anti-IL-5 treatment mepolizumab and benralizumab are recommended after the age of 12 years (reslizumab after the age of 18), as well as dupilumab with the indication for severe asthma[46]. Registries of severe asthma patients show that the average age of severe asthma patients receiving biologicals is older than 50 years, with a median of 56 years (with the oldest patient at the age of 83 years)[47]. In the group of late-onset severe asthma, there is also a group of patients with a "Non-T2 high" phenotype. They have neutrophils in induced sputum and are steroid-resistant. At this moment of medical science development, this group will not benefit from any of today's known biologicals[45]. Once again, the most important factor is to distinguish and properly define the asthma phenotype, to identify all comorbidities, the level of symptoms with the quality of life achieved with standard asthma treatment and good adherence, and to assess the potential benefit of biologic therapy. This should be done in a precise medical manner, personally in just that patient, with defined goals in asthma treatment by the patient himself[48], while chronological age is the least important factor.

Of course, our goal is also to find younger patients, able to work, or to improve their education, to ensure them a full life, by preventing exacerbations and airway remodelling with the least damage and side effects of medical treatment of their asthma.

Fifth Dilemma: Length of Treatment Appropriate to Assess a Patient's Response to Biologicals ("Responder" or "Non-responders")

We do not have a universally accepted definition of response to biologicals in severe asthma. There is no one parameter most important in an evaluation. Most experts agree that it is necessary to assess different asthma elements during follow-up, from the clinical point (frequency of exacerbations, symptom score), lung function, therapy dosages that patients need to control asthma symptoms, as well as inflammatory biomarkers values[49]. In the present-day perspective, it is also essential to have shared decision making. The importance of a conversation should be emphasized, which will define the patient's goals in biological treatment–that together,the patient and his physician should decide what the asthmatic person would like to improve with his asthma[48].

Responses to biological drugs in severe asthma are defined as super responders, partially responders and non-responders[50]. In this group of 114 Dutch patients with severe asthma treated with antiIL-5 therapy, it was established that 14% of super responders, after two years of follow-up had no residual manifestation of asthma. The majority consisted of partial responders, 69%, who have some asthma symptoms occasionally, while the smallest group were non-responders, 11% of patients whose asthma showed clinical worsening. Amongthe experienced residual manifestations of the disease most often were uncontrolled asthma symptoms, impaired lung function, and uncontrolled sinonasal symptoms.

A reasonable period for assessment of biological treatment response in severe asthma patients is one (the first) year of treatment (12 months), enough to count the number of exacerbations, oral steroid dosage, asthma control, eosinophilia, and estimate trends in lung function.

Different health care providers and insurance companies have different indications as well as rules for assessing the efficacy of biological therapy in severe asthma, sometimes even medically and scientifically non-logical and not correct. An example is that in some countries if a patient during omalizumab treatment for the first 4 months could not stop oral steroids, he or she is considered a non-responder, which is wrong. Many studies conducted with any biological treatment have revealed that more than a third of patients with severe asthma could not stop their steroid treatment (51), despite step 5 GINA treatment, good adherence and proper inhaler technique applied, with administered biologicals in concordance with asthma phenotype and type 2 inflammation (although 80% of patients significantly reduce steroid dosage[52]). Although patients could not stop steroids, they experience other benefits from biologicals, like less frequent exacerbations and overall quality of life, so it is an injustice to withdraw omalizumab after such a short period of treatment. GINA strategy suggests that 4 months should be adequate for assessment of mepolizumab response, but NICE guidelines indicated 12 months of treatment of mepolizumab[53].

The next question is about the duration of biological treatment when a person has at least a partial response. Some countries have the rule to quit biologicals after 2 years of treatment, despite good response, which is considered too short in the asthma scientific community. There are not many studies published on the length of biological treatment, as well as what happens after the discontinuation of biological therapy. Results from the Spanish severe asthma registry have shown that the effects of 6 years of omalizumab may persist after discontinuation of therapy in 60% of patients for at least 4 years[54]. There are no published data with results for other biologicals because they are of a shorter time in real life praxis with severe asthma patients' therapy. It is of utter importance to assess the duration of therapy seriously, with all sides and on a multidisciplinary basis, i.e. clinically, functional measurements, and laboratory biomarkers, as well as to discuss with the patient, and only then the proper decision should be made.

Sixth Dilemma: Should we Treat a Patient With Severe Asthma and Another Significant Disease, Like Allergic Broncho-pulmonary Aspergillosis (ABPA), or Eosinophilic Granulomatosis with Polyangiitis (EGPA)?

Biologics have been used in recent years to treat ABPA and EGPA in patients with severe asthma. However, robust clinical evidence of biological therapy efficacy in severe asthma with allergic broncho-pulmonary aspergillosis (ABPA) is lacking and still out of the label[55]. ABPA develops in susceptible patients whose airways are colonized with *Aspergillus fumigatus*. ABPA develops in 1-5% of asthmatic patients or 2-15% of patients with cystic fibrosis.

Biologics are used in patients with severe asthma and ABPA who have frequent acute exacerbations, who did not have a response to antifungal medication and in patients with stage IV ABPA (steroid-dependent asthma). All biologicals available for severe asthma have been applied, anti-IgE (omalizumab), anti-IL-5 (mepolizumab and benralizumab), and anti IL4/13(dupilumab). In all treated groups an improvement has been shown, with fewer exacerbations and symptoms with a steroid-sparing effect. The best improvement was found in lung function measured by FEV_1 in the vast majority of patients, where an improvement of more than 10% has been considered clinically relevant based on patient perception[56]. With the purpose to avoid hyper-eosinophilia, dupilumabwas introduced simultaneously with oral steroids[57].

EGPA became an indication for targeted biological anti-IL-5 treatment, with the

first FDA approval in 2017 for mepolizumab, but in a higher dose of 300 mg subcutaneously (sc.), while in Europe it is still not approved for this indication of EGPA, and not in this higher dose (just in a dose of 100 mg for severe asthma[58]). EGPA is always connected with asthma, hyper-eosinophilic syndrome, often rhinosinusitis with nasal polyps, as well as damage to two or more organs due to necrotising vasculitis of small vessels (heart, lung, skin, kidneys, gastrointestinal or nervous system). With the purpose of induction or maintenance of remission or preventing relapse or refractory EGPA, higher dosages of mepolizumab were applied. Further studies of EGPA treatment with "asthma-tailored" dosages (100 mg sc. every 4 weeks (q4 w) instead of 300 mg sc.q4w) have shown an improvement also clinically and in reducing steroid burden. It has been proven that anti-IL-5 treatment (besides mepolizumab, also benralizumab[59] and reslizumab is not approved for routine usage for patients yet, but a promising clinical trial has been published[60]) improves sinonasal scores, reduces asthma symptoms, improves lung function, decreases blood eosinophil count, and significantly decreases steroid dosage.

Conclusion

Severe asthma often has anatypical presentation, so first, we have to be sure which disease we are treating, and with which comorbidities. Efforts should be addressed to adherence, proper inhaler technique, and then the right treatment to the right patient at the right time. Due to the heterogeneity of asthma, and the fact that some biomarkers do not differ between clinical phenotypes, clinical phenotypes alone are not precise enough to guide targeted biological therapy. Mandatory for the choice of biologicals are biomarkers values, total and specific immunoglobulinE (IgE), eosinophils in blood and (induced) sputum, as well as fractional exhaled nitric oxide (FeNO). When we take everything into consideration, including clinical and laboratory aspects, together with functional tests and imaging, we can make a personalized choice of treatment, with a reasonable chance for significant improvement for our severe asthma patients. Still, there are many controversies and dilemmas in the field.

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His current research programme combines recent developments within the field of immunology and genetics. This effort enabled the discovery of novel pathogenesis pathways in anaphylaxis and severe asthma, and helped identify phenotype-specific immunological and genetic risk factors. He has supervised 13 PhD students to completion.

Prof. Mitja Košnik MD, PhD

He graduated at the Medical Faculty, University of Ljubljana in 1987. In 1992 he finished a specialisation of the internal medicine, latter he was nominated as a specialist in pulmonology and allergology. He earned a Ph.D. degree in 1998. In 2012 he was nominated as a full professor of internal medicine. He is a medical doctor and a head of the Department of Clinical Research at the University Clinic of Respiratory and Allergic Diseases Golnik and a head of the Chair of Internal medicine at the Medical Faculty, University of Ljubljana. His research interests are anaphylaxis, venom and drug allergy. He is a project manager of a national research project P3 – 0360: Slovenian network of allergy and asthma: from epidemiology to genetics. He was a mentor of 8 Ph. D. students. He is a president of Slovenian Association of Allergology and Clinical Immunology and od Slovenian Respiratory Society, a member of State expert body of internal medicine and a member of UEMS, section allergology. He published over 150 articles in journals with impact factor, his H-index is 42 and has 10.000 pure citations.

Marina Lampalo MD, PhD

Marina Lampalo graduated from University of Zagreb, Medical school in 2001. Since March 2008 she has been working as internal medicine physician, and since 2010 as subspecialist pulmonologist, at the Clinic for Lung Diseases Jordanovac - Department for Obstructive and Allergic Diseases. In March 2019, she acquired the title of primarius.

Marina Lampalo, MD, PhD, became a doctor of science in the field of natural sciences, scientific field of biology, 2017. at the Faculty of Science, University of Zagreb, defending her dissertation entitled "The effect of ABO blood genotypes and tissue plasminogen activator inhibitor on lung ventilation in asthma".

She is an active member of the Croatian Thoracic Society, the Croatian Respiratory Society, the European Respiratory Society, the Croatian Medical Association and the Croatian Medical Chamber. She has actively participated in numerous domestic and international scientific and professional conferences.

In 2018, she participated in the ERS spirometry training programme, and obtained a European license for an educator in the field of respiratory function.

So far, she has published several scientific and professional papers, 4 indexed in Current Contents, 9 in international indexed publications and 7 in other publications. She has participated in numerous domestic and international scientific and professional conferences, especially in the field of pulmonology and allergology. So far, she has actively participated in congresses and gatherings organized by the Croatian Thoracic Society (2014, 2016, 2017, 2018, 2019), International Congress of the European Respiratory Society (2018, 2019) European Academy of Allergy and Clinical Immunology Congress (2019).

She has 24 conference papers published in proceedings. She is the winner of "Toraks" Award for Best Scientific Paper in 2016. Since 2019 she has been a research associate at the School of medicine, University of Zagreb, and since October 2020 she has been elected as a senior lecturer at the Faculty of Medicine, University of Rijeka. The narrower area she has been dealing with for many years are obstructive lung diseases - primarily asthma, chronic obstructive pulmonary disease and lung function and allergic diseases.

Prof. Sanja Popović-Grle MD, PhD

Sanja Popović-Grle is a Professor of Respiratory Medicine at University of Zagreb, Croatia, and Chief of Clinical Department for allergic and obstructive pulmonary diseases at University Hospital Centre Zagreb.

After qualifying in medicine and obtaining her Doctor of Medicine degree from the University of Zagreb in 1983., prof. Grle started her professional career in the central state Pulmonary hospital Jordanovac in Zagreb, as an employee from the Medical faculty, after obligatory praxis for 2 years as a general practitioner.

Prof. Grle main research interest is in the field of asthma, allergy, and COPD, especially in clinical diagnostic methods and management. She has published papers in peer-reviewed journals and book chapters for students, residents, specialists or patients. In addition to the clinical duties, prof. Grle has lectured extensively on topics. She is a reviewer of various international journals. She has been Member of Organizing and Scientific Committees.

Assist. Prof. Matija Rijavec PhD

After graduating from the Biotechnical Faculty, University of Ljubljana (2004), he earned his PhD degree in the field of Biomedicine at the University of Ljubljana (2010). Since 2015 Matija is also Assistant Professor in the field of Immunology at the Biotechnical Faculty, University of Ljubljana. Matija is involved in different fields of clinical research, mainly studying immunology and genetics of complex diseases, allergy/anaphylaxis, hereditary angioedema, asthma, COPD, atopic dermatitis, sarcoidosis, cystic fibrosis, and alpha-1-antitrypsin deficiency. A

great proportion of his research activities represent the use of different techniques in molecular biology to study DNA (sequencing, PCR, qPCR, MLPA, NGS, ddPCR), expression profiles of mRNA, miRNA (RT-qPCR, NGS), proteins (flow cytometry, ELISA) in various disease entities, in an attempt to decipher disease mechanisms and finding novel biomarkers for diagnosis and prognosis/prediction. Currently, his research is focused on hereditary angioedema, asthma, and anaphylaxis mechanisms, genetics and pharmacogenetics, as evident from the summary of our latest publications in this field. He published 51 original scientific papers, and 6 review scientific papers, and has an H-index of 17.

Assist. Prof. Sabina Škrgat MD, PhD

Sabina Škrgat, MD, graduated from the Faculty of Medicine at the University of Ljubljana (1996). She is a specialist of internal medicine (2004) and pneumonology (2011). She got her PhD degree at the University of Ljubljana (2009) with the topic of investigation, related to angiogenesis and complement activation in asthma and chronic obstructive pulmonary disease.

Her main clinical work consists of management of patients with severe asthma and other obstructive lung diseases. She is an Assistant professor at Medical Faculty of Ljubljana and she curently has a leading position in Slovenian National recommendations for asthma management. She is the clinical lead of Severe asthma Clinic at University Medical Centre Ljubljana, Slovenia.

Beside clinical work, she is active in research of severe asthma by PhD mentoring. She is also the ERS SHARP (Severe Heterogenous Asthma Research Collaboration) National lead.

Dr. Škrgat is a member of Slovenian Respiratory Society steering committee and a member of SHARP steering committee since 2021.

She launched the first Severe asthma forum-joint meeting of South East Europe which was held in Bled, Slovenia in 2018.

Stylianos Vittorakis MD, PhD

Stylianos K. Vittorakis MD, PhD, received his medical education and his PhD from National and Kapodistrial University of Athens. He completed his residency in Pulmonary Medicine at "Sotiria" Athens Chest Hospital, Greece and obtained the European Diploma in Adult Respiratory Medicine E.R.S – H.E.R.M.E.S in 2011. He has conducted research in Cellular Immunology and Asthma at Biomedical Research Foundation (Academy of Athens) and Asthma Research Center-7th Respiratory Medicine Department (Sotiria Hospital). His research is mainly focused on asthma as an active member of Hellenic Thoracic Society Asthma and COPD working groups. Currently he is a private consultant Pulmonologist in Chania/Greece, and he is Coordinator in Hellenic Thoracic Society Primary Health Care Group.

Prim. Žarko Vrbica MD, MS

Dr. Žarko Vrbica graduated from the Faculty of Medicine at the University of Belgrade (1988). He is a specialist in internal medicine (1999 – UHC Zagreb) and pneumonology (2003 – UHC Zagreb). Dr. Vrbica earned his MS degree at the University of Zagreb (2003) with the topic of psycho-neuro-immunology of lung

cancer. He is a head of the Ward for pneumology and immunology in Dubrovnik County Hospital. His main clinical interest are obstructive lung diseases and is an active member of the Croatian GOLD and GINA initiative. He is a senior lecturer at the University of Dubrovnik.

Assist. Prof. Mihaela Zidarn MD, PhD

Mihaela Zidarn graduated from the Faculty of Medicine at the University of Ljubljana (1997). She is a specialist in internal medicine (2005), pneumology (2012) and allergy (2013). She got her PhD degree at the University of Ljubljana (2014) on the topic of allergen immunotherapy. Her main clinical work consists of the management of patients with allergic diseases and asthma. She is an Assistant professor at the Medical Faculty of Ljubljana. Besides clinical work, she is active in research on allergic rhinitis, anaphylaxis and hereditary angioedema. She is an author/co-author of 58 papers with an H-index of 24.

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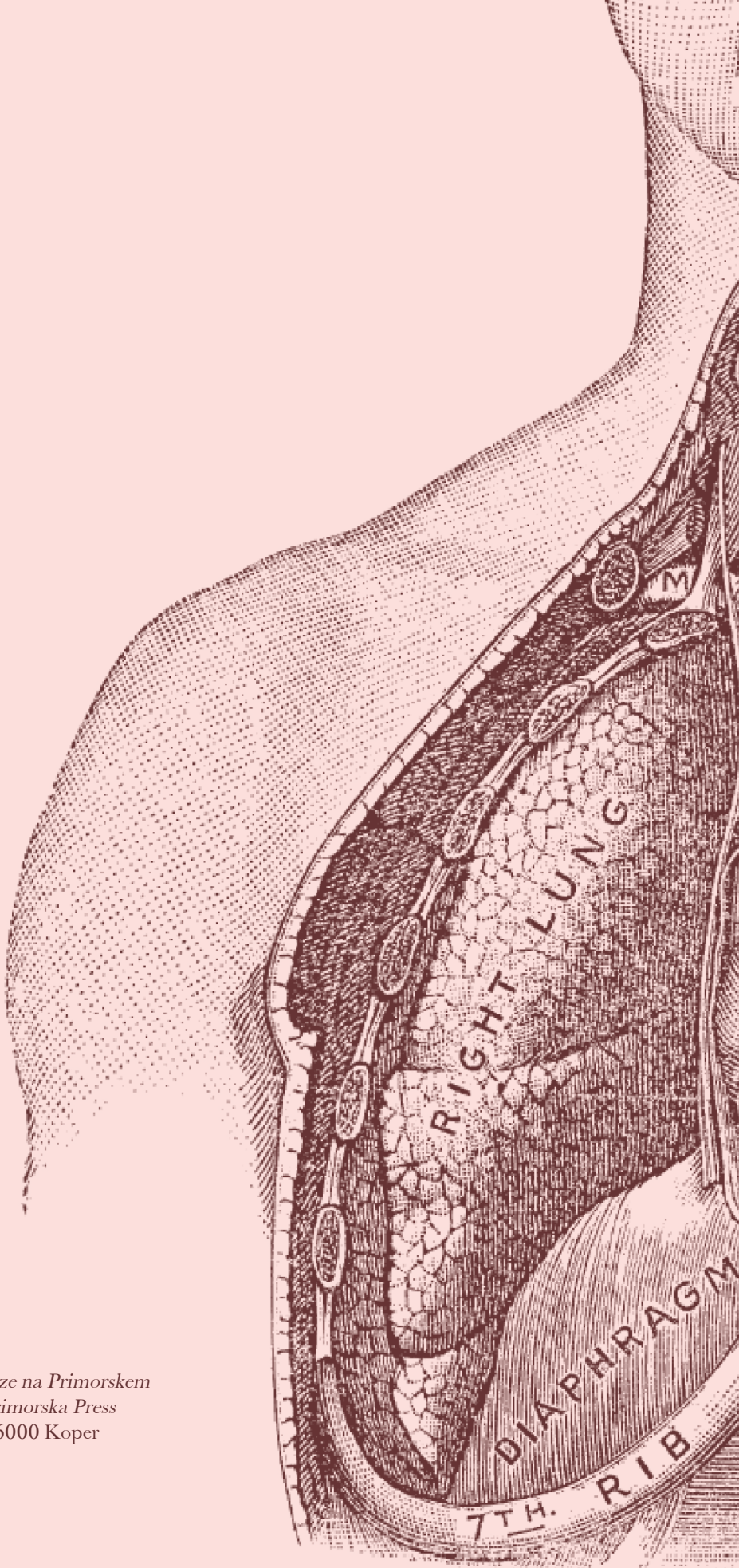

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