HISTORICAL REVIEW

Summing up 100 years of asthma

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Summary
In this review, we aim to lead the readers through the historical highlights of pathophysiological concepts and treatment of asthma. Understanding the nature and links of asthma has modeled our diagnostic, pathophysiological and therapeutic thinking and acting. The recognition of its heterogeneous nature in combination with several refined and sophisticated technologies will mark a new era of phenotype-specific approach and treatment of asthma.
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Introduction

With the centennial anniversary of Respiratory Medicine, this article summarizes some of the history of asthma. The journal started in 1907 as British Journal of Tuberculosis (1907–42), changed into the British Journal of Tuberculosis and Diseases of the Chest (1943–58) and subsequently into the British Journal of Diseases of the Chest (1959–88). As a result of the changing clinical and scientific interests based on disease prevalence and developing technologies, there has been a shift in the focus of topics. In the first 50 years of the journal, the number of published articles on asthma was around 20, mounting to over 700 in the past decade alone.

Apart from the increasing prevalence over the years, the definition, insights into and the understanding of pathophysiology and the associated treatment modalities of asthma changed due to methodological advances and controlled-randomized trials.

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Concepts on the aetiology of asthma throughout the centuries

In ancient times, asthma was already recognized in many cultures, including the Chineses', Hebrews', Greeks' and Romans'. The Greek physician Hippocrates (460–377 BC) first described asthma, which is derived from the Greek word "asthmaino" (αστημαινω) indicating "panting or gasping". The first aetiological link with bronchospasm was made by Galen (130–201 AD), who also described the association between upper and lower airways.[1,2]

From ancient times throughout the middle ages, there was little interest in asthma and the term was mainly applied for cardiac and pulmonary dyspnoeic disorders. At that time physicians considered the paradigms by Hippocrates and Galen as golden standard. Evidently, treating kings and nobility, inspired physicians to search for novel aetiological links and therapeutic options for asthma: largely derived from trial and error in single patients or based on personal conviction. In his *Treatise on asthma*, Maimonides (1135–1204), physician of sultan

Saladin, suggested to treat asthma with rest, avoidance of opium, good personal and environmental hygiene and emphasized the importance of dietary factors.[1,2]

In the 16th century, the German physician Georgius Agricola (formerly Georg Bauer; 1494–1555) described the association between environmental factors and airway symptoms and was possibly the first to report occupational asthma. He suggested to prevent asthma in miners with protective masks to avoid the inhalation of dust.[3] In the Renaissance period airway symptoms associated with exposure to seasonal allergens were already reported.[2,3] At that time, avoidance of some allergenic factors and cold baths (once in 14 days or once a month) were the mainstay of asthma therapy.[3]

Bronchial asthma in its modern definition dates back to the early 19th century, when it was recognized as a unique airways disorder characterized by bronchospasm following Rene Laennec's (1781–1826) invention of the stethoscope.[2,3] In addition, the familial clustering of asthma and allergy was appreciated.

In 1860, Henry Hyde Salter (1823–71) proposed a classification into extrinsic and intrinsic asthma, based on the nature and putative mechanism of various stimuli (e.g. animal dander or emotional stress) inducing episodes of bronchospasm.[4] Some 30 years later, William Osler (1849–1919) described the link between various (non)specific stimuli causing paroxysmal airways dysfunction in asthma—later recognized as bronchial hyperresponsiveness. Osler considered asthma as an inflammatory disease, based on several pathological changes within the asthmatic airways including oedema, gelatinous mucus, and Charcot–Leyden crystals ('asthma crystals') in the sputum.[5] The identification of the asthma crystals as eosinophil granulocytes came when Paul Ehrlich (1854–1915) discovered tetrabromofluorescein (eosin).[6] Using aniline stainings Ehrlich also identified mast cells and basophils.

In the beginning of the 20th century, the hereditary and heterogeneous nature of asthma, its relationship with several allergies and its neural, inflammatory, and vascular mechanisms gained interest.[7] An early letter in this journal reports on the controversies in these days: while a French group regarded asthma as "uracémie respiratoire" occurring on an "arthritic diathesis", contemporary physicians rather referred to a "colloidoclassic diathesis". And as the author states: "these views were largely based upon clinical experience"; and hence, it was felt that more experimental work was needed to fund these hypothesis.[8] Furthermore, during a long period of time, the neuro-psychogenic origin of asthma has been entertained.[9] This concept has gained renewed interest in recent years.[10,11] Others felt that "the sensitive nerves of the diaphragm are stretched and irritated, resulting in shortness of breath and a feeling of oppression which occurs especially during the night".[12] Although neuro-psychological aspects were still considered of pivotal importance, following the discovery of allergic mechanisms, the origin of asthma was largely regarded as allergic.

While at that time inhaled allergen provocation was the mainstay for diagnosis of allergic asthma, this changed with the discovery of IgE and the possibility to measure specific IgE antibodies. However, Francis Rackemann (1887–1973) described patients with asthma without any evidence of allergic triggering of their symptoms and hence coined the term 'intrinsic asthma'.[13] Similarly, attempting to classify asthma on the basis of provoking agents in 1971, Margaret Turner-Warwick concluded that 'there remains a group of patients in whom asthmatic symptoms are unrelated to any demonstrable agent and where prick skin tests remain negative even when challenged with a wide range of antigens'.[14]

Although previously reported by Osler, bronchial or airway hyperresponsiveness as a major pathophysiological characteristic of asthma was first quantified in 1946 by Curry, who examined the effects of increasing doses of inhaled histamine in subjects with and without asthma.[15] Eventually, these experiments resulted in one of the most reliable diagnostic tools for asthma.

The concept, that asthma is an inflammatory disorder was firmly established in the 20th century, which also marked the advent of interventional randomized control trials, the development of invasive and non-invasive methodologies and emerging immunological technologies, which increasingly replaced personal experience and observations. Airway remodelling, another important feature of asthma, has first been reported in this journal by Ellul-Micallef in 1973.[16] Applying flexible bronchoscopy, Laitinen and colleagues were amongst the first to report the structural changes within the airways of asthmatics.[17] From that time on, an expanding number of (interventional) studies applying submucosal and even transbronchial biopsies have been conducted that helped to define the immuno-histopathological changes within the asthmatic airways. Presently, there are 2 major hypothesis on airway remodelling: while the structural airway changes are mostly regarded as a consequence of chronic airway inflammation,[18] some view airway remodelling and chronic airway inflammation as parallel processes, since airway wall changes can be present even in the absence of a long-standing history of asthma (Fig. 1). Presently, it is debated whether airway remodelling may account for the accelerated decline in lung function in severe persistent asthma or whether structural changes within the airways may serve a protective purpose.[18,19] During the last decade of the 20th century, another long-standing concept, namely the systemic features of the allergic–asthmatic inflammation including the concept of unified airways, which was introduced by Galen almost 2000 years ago, were reinvented.[20]

Evolution of the current concepts on the pathophysiology and immunology of asthma

For many years asthma was considered to have a psychosomatic background; as a consequence psychopharmaca were used to "lessen emotional tension in asthma" in the 20th century.[21] Furthermore, the importance of airway smooth muscle in the pathophysiology of asthma has been entertained for centuries.[16] Therefore, early anti-asthma strategies mainly aimed at relieving bronchospasm with bronchodilator agents, such as coffee and tea. In the 20th century, their mechanism of action was confirmed by observations that asthmatic bronchi dilate in response to theophylline (derivates) and β2-agonists.[22,23] During the past decade, there has been renewed interest in the airway
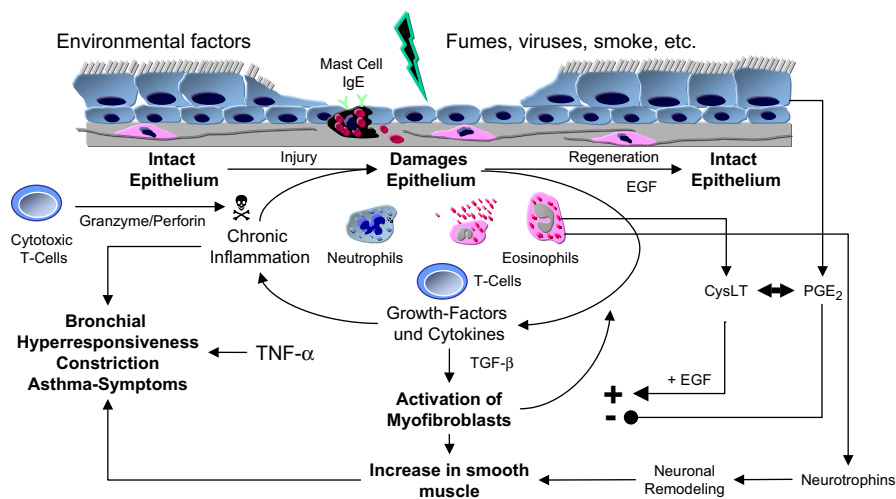
Pathophysiology of Airway-Remodeling

Figure 1 Pathophysiological mechanisms of airway remodelling in asthma.

smooth muscle cells for their role in the pathophysiology of airway hyperresponsiveness and remodelling, and for their interaction with other (inflammatory) effector cells of asthma.[24–26]

In 1966, another milestone of pathophysiological evidence came with the discovery of (specific) IgE and its role in mast cell activation.[27] Histamine, one of the key pro-inflammatory mediators released from mast cells, had already been implicated in the pathophysiology of asthma since 1911, when Dale and Laidlaw induced anaphylaxis with histamine in laboratory animals.[28] Human experiments suggested a pivotal role for histamine in the asthmatic response and, hence, researchers determined histamine levels in blood.[28] Indeed, some authors claimed therapeutic effectivity of antihistamines in the treatment of (childhood) asthma.[29] After the initial hype, the interest in mast cells decreased again, mainly due to the limited potency of antihistamines in most asthmatics.[30] However, there is now renewed interest in the role of mast cells in airway hyperresponsiveness in asthma, as there is evidence that they might interact with airway smooth muscle cells within the airway wall.[24–26]

In the 1990s, flexible bronchoscopy helped to establish the concept of a skewed T-helper (TH) cell profile in asthma with a predominance of TH-2 cells and a related cytokine profile which is associated with both airway eosinophilia and IgE-production.[31] These findings led to a plethora of investigations into the role of T-cells and their products in the pathogenesis of asthma among which IL-5 and its regulatory role on eosinophils appeared to explain many features of the asthmatic inflammation.[31,32] However, IL-5 antibodies failed to abolish the features of asthma despite removing eosinophils,[33,34] which redefined the role of eosinophils in the pathophysiology of asthma: both the involvement in airway inflammation and in the process of airway remodelling.[35,36] Although eosinophilic inflammation was considered crucial in the pathophysiology of asthma, severe persistent asthma has increasingly been recognized as an immunologically different subset with a predominantly neutrophilic airway inflammation.[37]

In recent years, the role of growth factors, neurotrophins and genetic factors has become a focus of interest in the pathophysiological context of asthma.[11,38,39] Yet, none of these hypotheses has been able to fully explain the pathophysiology of asthma. Similarly, interventions targeting any of the mentioned substrates have only partially reversed the pathophysiological features with little impact on the overall asthma severity.

Triggering factors and clinical phenotypes and presentations of asthma

Clinically, there are several phenotypes of asthma. Worldwide, the atopic phenotype ("extrinsic asthma") seems to have a higher prevalence than the non-atopic phenotype ("intrinsic asthma").[40] Allergic asthma generally starts in childhood or adolescence, and thus has a high prevalence in mainly younger individuals suffering from airway symptoms in response to common aeroallergens but sometimes also in response to occupational agents. Most patients with allergic asthma have a positive family history of atopy or other allergic diseases. Alternatively, some patients develop asthma at a later age ("adult onset asthma"), often as a consequence of viral respiratory infections. Unlike in the allergic phenotype, in these patients total and specific serum IgE-concentrations are commonly not elevated and symptoms are not precipitated by environmental allergens ("intrinsic asthma"). Although sometimes referred to as 'infectious asthma' this has to be considered a misnomer since exacerbations in response to respiratory tract infections are common to both allergic and intrinsic asthma. Although some investigators tried to find allergies against infectious agents in intrinsic asthma, this has never been conclusively substantiated. There are a few studies reporting on clear immunological differences between allergic and intrinsic asthma. Apart from airway eosinophilia found in both subsets, Walker and colleagues reported distinct patterns of T-cell activation yielding different cytokines in peripheral blood and bronchoalveolar lavage of subjects with allergic and non-

allergic asthma.[41] Whether intrinsic asthma can actually progress to Churg Strauss Syndrome has been debated but early observations suggest a common clinical pathway between intrinsic asthma and asthma with polyarteritis nodosa, where "there is no family history of allergic disease; the onset is often later in life than in the case of allergic asthma; loss of weight may be considerable; high eosinophilia is general, and often exceeds 5000/mm; chest X-rays frequently show transient infiltrations and asthma can be successfully treated with oral corticosteroids".[42]

When the British Thoracic Society investigated asthma death in relation to their atopic status, they found that atopic asthmatics were more likely to die of acute asthma, most often in the months of May/June and September/October and mostly on weekends, whereas non-atopic asthmatics had a higher risk of suffering a fatal asthma attack in the months of January to April without a predilection during the week.[43] These findings again underscore the difference in trigger factors and mechanisms involving asthma attacks between allergic and non-allergic asthma. Although less common than allergic asthma, Ulrik and colleagues report non-atopic intrinsic asthma in children.[44] As was observed after 1 year in their study, this asthma subset appeared to have different predictors and outcome parameters and was, therefore, considered to have a different pathogenesis.[44]

In addition, there is a group of patients whose asthma initially starts with allergen-dependent symptoms but progresses to a less allergen-dependent subtype. Although skin test reactivity remains present in these individuals, their clinical response to allergen wanes. Consequently, these patients clinically often behave very similar to those with intrinsic asthma and hence are referred to as 'mixed type asthma'. Some 50 years ago, these patients have been clinically described as "having a characteristic story of intermittent asthma from childhood" … which … "at some point became complicated by persistent cough with sputum". Thus, continuous wheezing with breathlessness replaced the earlier intermittent asthmatic attacks and "recurrent winter colds on the chest" became a further regular complication.[45]

Occupational asthma has been often classified as a distinct asthma-subset, based on its various presentations with or without IgE-mediated symptoms. For example, bakers' asthma (induced by flour) is IgE-mediated and strongly resembles allergic asthma. Alternatively, low molecular weight sensitizers, such as isocyanates, may cause asthma without measurable IgE-antibodies with a number of features similar to non-allergic or intrinsic asthma. Meadway found no clear relationship between atopic status or skin rashes to resin and a fall in FEV1 in patients who presented with asthmatic symptoms following exposure to epoxy resins.[46]

Exercise-induced asthma has also gained much interest. Exercise-induced bronchoconstriction occurs in allergic as well as non-allergic asthma and is most likely due to thermal and osmotic changes in the hyperresponsive airways following hyperventilation during exercise. In this journal, Anderson and colleagues have written a comprehensive historical review on this topic.[47]

Viruses are important triggers of asthma attacks but possibly also causative agents in the pathogenesis of asthma in certain patients.[48]

In addition to phenotypes, asthma can be classified according to its severity, ranging from intermittent to (mild, moderate and severe) persistent.[49] Interestingly, mild to moderate persistent asthma is often associated with atopy, whereas the severe persistent or "refractory/difficult-to-treat" phenotype is a more heterogeneous disorder, that can be subdivided into different clinical or pathophysiological subsets with various comorbidities, requiring a customized therapeutic approach.[50,51]

Clinically, asthma and chronic bronchitis are sometimes difficult to separate. Nevertheless, is has been suggested that the "use of such a term as "asthmatic bronchitis" should be avoided" as it was deemed "inaccurate and likely to prove misleading".[52] In 1986, Wardman et al. reported that in a general practice, a clear differentiation between asthma and COPD was difficult in 1/3rd of the patients.[53] Currently, it is unclear whether this has improved.

Therapeutic options: past and present

Early anti-asthma regimens largely aimed at relief of symptoms or modification of external factors, applying plant extracts, life-style adaptations, surgery, or hypnosis for the relief of asthma.[12,54] Apart from these treatment options, in the pre-inhaler era, early pharmacotherapy consisted of inhaling the smoke of the so-called "asthma cigarettes", containing various relieving compounds including atropine, belladonna, menthol, morphine or cocaine.[55] Furthermore, since asthma was considered to have a psychological origin, psychopharmaca such as chlorpromazine were prescribed.[21] However, none of these "control"-aiming therapies proved effective, while some treatment options such as early immunotherapeutic vaccines and the use of opiates appeared hazardous.[55] While at that time asthma therapy was predominantly based on trial and error, targeting inflammatory mechanisms came in the course of mainly the second half of the 20th century with the discovery of pathological, pathophysiological and immunological substrates following the invention and/or refinement of spirometry, flexible bronchoscopy and immunological techniques.

Xanthines

For centuries, strong coffee and tea were recommended for the relief of dyspnoea due to bronchospasm. While at that time practitioners were most likely not aware of the pharmacological mechanism, i.e. bronchodilator effects through inhibition of phosphodiesterase (PDE); this was probably the first application of xanthines in the treatment of asthma. The anti-asthmatic effect of theophylline was first described by Hirsch in 1922.[56] Subsequently, theophylline followed by its more soluble derivate aminophylline in 1937, became the most widely prescribed drugs for asthma for about four decades.[57,58] However, in clinical practice, theophylline showed limited efficacy with serious side-effects at higher doses due to its narrow therapeutic window.[58,59] These disadvantages and the advent of the superior sympathicomimetics finally led to its relegation to second/third line anti-asthma treatment in developed countries during the 1980s.[49,60–62] In recent years, interest revived in xanthine-derivates due to their oral formulation and low cost. Moreover,

circumstantial evidence pointed to some anti-inflammatory properties,[63,64] through the suppression of the inflammatory gene transcription by activation of histone deacetylase (HDAC), which is the key target for corticosteroids.[65] This mechanism may explain the beneficial effects on asthma control reported by several investigators when combining (low dose) theophylline with inhaled corticosteroids (ICS).[66,67] Recently, additional anti-inflammatory effects have been reported, including the acceleration in eosinophil apoptosis and the decrease in recruitment of lymphocytes and neutrophils into the airways.[64,68] These properties may be promising in the treatment of severe asthma or COPD.[64] Although initially classified as a PDE inhibitor, the pharmacological effects of theophylline appear much broader and largely not yet identified.

In parallel with the renewed interest in theophylline, there has been development of several more specific PDE-inhibitors in the last decade. Despite a better tolerability of these drugs, the gastrointestinal side effects are still substantial.[69] Targeting PDE-3 has been shown to produce bronchodilation.[70] Alternatively, targeting the major isoform within airway inflammatory cells, specific PDE-4 inhibitors (e.g. roflumilast and cilomilast) have been developed for the treatment of asthma and COPD, although with varying success.[71–73] Future studies in asthma applying combined PDE-3/4 inhibitors should demonstrate their putative superior effectivity.[70]

$\beta 2$ agonists

Although the use of adrenal substances in asthma dates back to 1900,[74] in the 1940s epinephrine (or adrenaline) became the standard bronchodilator therapy for the treatment of acute asthma.[75] However, due to its non-specific mechanism of action, the use of epinephrine was complicated by several—mostly cardiovascular—side effects.[76] A breakthrough came in the beginning of 1960s with the discovery of the adrenergic receptor subsets, yielding the α and β receptor, with a further subdivision into the $\beta 1$ receptor, mainly located in the heart and intestinal smooth muscle, and into the $\beta 2$ subset on bronchial and uterus smooth muscle.[77,78] Isoprenaline was the first agonist interacting with β adrenergic receptors, while salbutamol, and later on terbutaline, were the first agonists with a higher specificity for $\beta 2$ adrenergic receptors.[79,80] Soon after its development in 1968, salbutamol rapidly became—and still is—the most widely used fast-acting reliever for asthma.[49] The success of salbutamol initiated the development of several other short-acting $\beta 2$ agonists (SABAs), like carbuterol, clenbuterol and fenoterol, with a duration of action up to 6 h.[81,82] The final step for this class of drugs came in 1980s with the development of long-acting $\beta 2$ agonists (LABAs). Salmeterol was first launched with a duration of action up to 12 h,[83] followed by formoterol. The latter drug combines long-lasting bronchodilatator effects ($>$12 h) with a fast onset of action, similar to salbutamol (Fig. 2).[84] Currently, several novel LABAs are being developed with a duration of action up to 24 h, creating the possibility of once daily dosing.[85]

The mechanism of action of $\beta 2$ agonists is predominantly bronchodilator through airway smooth muscle relaxation, despite modest anti-inflammatory activity encountered in some studies.[86,87] Formerly prescribed as "4–6 times daily" maintenance therapy, current guidelines now recommend SABAs on "as needed" basis.[49] This change of view came with the growing understanding that airway inflammation is
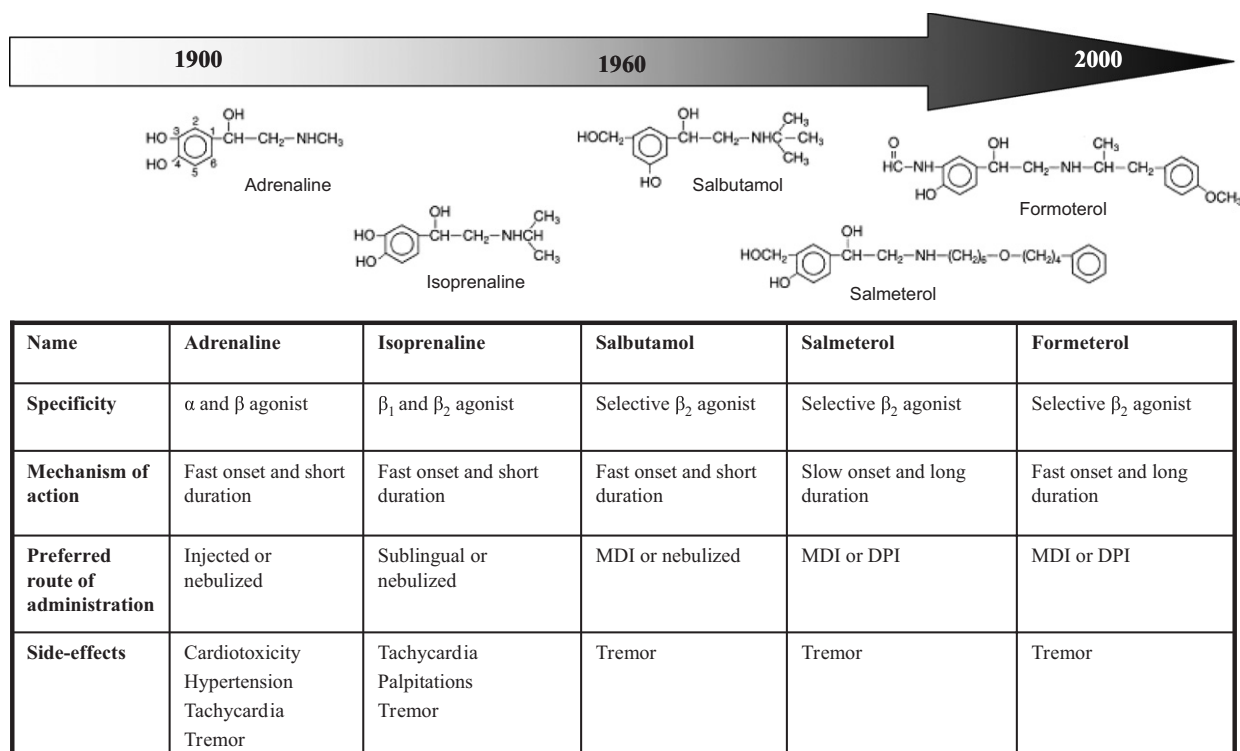

Name	Adrenaline	Isoprenaline	Salbutamol	Salmeterol	Formeterol
Specificity	α and β agonist	β_1 and β_2 agonist	Selective β_2 agonist	Selective β_2 agonist	Selective β_2 agonist
Mechanism of action	Fast onset and short duration	Fast onset and short duration	Fast onset and short duration	Slow onset and long duration	Fast onset and long duration
Preferred route of administration	Injected or nebulized	Sublingual or nebulized	MDI or nebulized	MDI or DPI	MDI or DPI
Side-effects	Cardiotoxicity Hypertension Tachycardia Tremor	Tachycardia Palpitations Tremor	Tremor	Tremor	Tremor

Figure 2 Structure and mechanism of action of the most widely used β-agonists developed in the last century.

a key feature of asthma and that targeting airway inflammation should be the primary goal of asthma treatment, as different from "symptoms control" only. Moreover, several studies in asthma provided evidence that maintenance therapy with both SABAs and LABAs — in or without combination with ICS — is associated with potential masking of the airway inflammation.[88,89] In addition, despite concomitant use of ICS, maintenance therapy with LABAs has been shown to induce tolerance to its bronchoprotective effects and cross-tolerance to the bronchodilator effects of SABAs.[90–93] Finally, data from several studies show that patients who are homozygous for arginine (Arg/Arg) as opposed to glycine (Gly/Gly) at the 16th amino acid position of the $\beta2$ adrenergic receptor have an impaired therapeutic response to $\beta2$ agonists.[94,95] In these patients, long-term treatment with albuterol has been found to be associated with significant decrease in lung function over time.[94] Some of these deleterious effects during long-term use of LABAs with or without an adequate dose of ICS may have resulted in an increased morbidity and even asthma deaths in the recently reported SMART study.[96] Present guidelines, therefore, favour maintenance therapy with LABAs only in combination with appropriate doses of corticosteroids in the more severe disease (treatment steps 3–5).[49,97]

Anticholinergics

During several centuries, the most controversial modality of asthma treatment has probably been the "asthma cigarette". The active ingredient of these cigarettes consisted of alkaloids from the Belladonna plant, delivered to the lung by smoking. This therapy has been advocated for the treatment of asthma until the middle of the 20th century. At that time empirically based, today we know that the mechanism of action was largely caused by the ingredients' anticholinergic properties. In the late 1970s, this knowledge resulted in the development of ipratropium, a synthetic anticholinergic, for the treatment of asthma. Ipratropium, and the later developed, long-acting tiotropium, both antagonize the effect of acetylcholine at the muscarinic M1 and M3 receptor. Despite still a limited role in the treatment of asthma, anticholinergics may benefit patients with genetically determined adverse responses to $\beta2$ agonists—up to 20% of the asthma population.[95] In addition, during an acute exacerbation when response to SABAs is poor, addition of an anticholinergic may provide a faster-onset relief.[98,99]

Cromones, antihistamines and ketotifen

Since mast cells have been thought to play a key role in the pathophysiology of asthma, in the 1970s these cells and their pro-inflammatory products became major focus of anti-asthma pharmacotherapy.[100,101] Traditionally, cromones (Cromolyn and Nedocromil) have been termed "mast cell stabilizers". Their mechanism of action has been based on inhibiting the release of pro-inflammatory mediators from mast cells following IgE-cross linking. However, sodium cromoglycate caused only a modest inhibition (of 10–20%) of the mast cell mediator release accompanied by a rapid-onset tachyphylaxis in in vitro studies.[102,103] In clinical studies of asthma, the overall efficacy of cromones was only marginally better than placebo, although clearly inferior to ICS.[104–108] Presently, treatment with cromones is confined to very mild disease, as add-on therapy in severe chronic asthma or in special patient populations.[104,109,110]

Although an important pro-inflammatory mediator of asthma, allergy and anaphylactic shock, pharmacotherapy-targeting histamine, the major release product of mast-cells, has been shown to be of little if any effect on asthma control.[63,111,112] Ketotifen, a drug inhibiting the release of pro-inflammatory mediators (histamine and leukotrienes) from mast cells and basophils combined with H1-antagonistic activity, showed inferior anti-inflammatory effect in asthma when compared with cromoglycate and ICS.[108,113,114] Therefore, current evidence does not support a predominant role for this category of drugs in the mainstay treatment of asthma.[49]

Corticosteroids

The first reports of corticosteroids in the treatment of asthma date back some 50 years ago. At that time, these drugs were administered either intravenously or orally with good therapeutic results.[115,116] However, the initial enthusiasm was dampened by the serious side effects accompanying long-term use of systemic corticosteroids, confining their systemic application to severe cases and exacerbations only.[49] In the early 1970s, the first topically active, aerosolized corticosteroid, beclomethasone diproprionate (BDP), was introduced into clinical practice.[117,118] This ICS showed effectivity in the treatment of asthma without the adverse effects associated with prednisone.[119,120]

Interestingly, the widespread use of ICS started some 20 years later, most likely as a result of the increasing evidence that asthma is an inflammatory disease and the effect of this paradigm-switch on the concurrent guidelines for asthma treatment.[49,121,122]

Corticosteroids are currently the most effective anti-inflammatory drugs for the treatment of persistent asthma. Especially, prolonged treatment with ICS has been shown to result in sustained improvement of symptoms and lung function in combination with a decrease in rescue medications, exacerbations and airway hyperresponsiveness in adults and children.[123,124] These effects are mediated through the intracellular glucocorticoid receptor in a large variety of (inflammatory) cells, resulting in both suppression of inflammatory gene transcription and activation of anti-inflammatory gene transcription.[125,126]

In the past two decades, modification of the initial compounds and inhalers increased the potency and first-pass metabolism in combination with an improved lung deposition. Presently, available ICS differ little in clinical efficacy and side effects, fluticasone and budesonide being the most widely used alone or in combination with a LABA in one inhaler device (Fig. 3). Being a pro-drug, the recently launched ciclesonide combines the advantages of a prolonged activity (once daily use) with still less (local and systemic) side effects[127–129] (Fig. 3).

However, despite their established clinical effectivity, even prolonged treatment with high doses of ICS can neither fully reverse all chronic aspects of the airway inflammation nor cure the disease.[130,131]
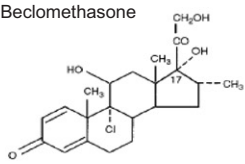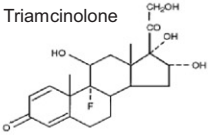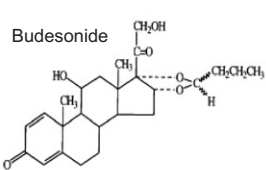
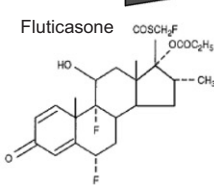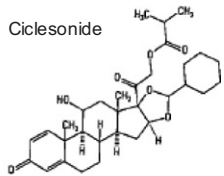| Name	Beclomethasone	Triamcinolone	Budesonide	Fluticasone	Ciclesonide
Preferred administration	2-4 dd via MDI/DPI	2-4 dd via MDI/DPI	1-2 dd via MDI/DPI	1-2 dd via MDI/DPI	1 dd via MDI
Advantages	-Proven clinical efficacy -Low-priced -Moderate oral bioavailability	-Proven clinical efficacy -Low-priced	-Proven clinical efficacy -Moderate oral bioavailability -Available as combination therapy	-Proven clinical efficacy -Low oral bioavailability -Available as combination therapy -Most potent	-Low oral bioavailability -On site activation -Once daily dosing
Disadvantages	-Not available as combination therapy	-High oral bioavailability -Not available as combination therapy -Least potent	-Short lung residence time	-Greatest risk of HPA axis suppression	-Limited clinical experience -Not available as combination therapy

Figure 3 Structure and major advantages and disadvantages of the most widely used corticosteroids.

Antileukotrienes

In parallel with the discovery of other components of the airway inflammation in asthma, in 1940 Kellaway and Trethewie discovered the "slow reacting substance of anaphylaxis", which appeared to constitute of leukotrienes.[132,133] In the last two decades of the 20th century, a large array of studies on leukotrienes have been conducted both in healthy volunteers and in patients with asthma. Apart from their bronchoactive properties, leukotrienes appeared to mimic several other features of asthma, including airway hyperresponsiveness, airway inflammation and airway remodelling.[134] The discovery of leukotrienes introduced a new focus in asthma research and the subsequent development of anti-mediator drugs. Unlike other anti-mediator drugs (including antihistamines, platelet activating factor- and prostaglandin inhibitors), potent anti-leukotrienes effectively reduced several features of asthma in both adults and children.[135,136] In the second half of the 1990s, the leukotriene synthesis inhibitor, zileuton, and the leukotriene receptor antagonists (LTRAs), pranlukast, zafirlukast and montelukast entered into clinical practice: a novel class of anti-asthma therapy since 25 years.[136] Although not quite as potent as corticosteroids, LTRAs combine anti-inflammatory—mainly anti-eosinophilic—activity with mild, bronchodilator properties, based on antagonism of cysteinyl leukotrienes (CysLTs) at the CysLT1-receptor within the airways and on inflammatory cells.[134–137] Presently, application of LTRA has been approved for both adults and children in most steps of the asthma management plan, mainly as add-on medication, with a recent extension to virally induced bronchoconstriction and asthma with allergic rhinitis.[49,138–141] Another—more specific—application for LTRA is aspirin-induced asthma, recently referred to as Aspirin-Exacerbated Airway Disease—AERD.[137] Interestingly, in this journal Szczeklik and Nizankowska reported not only patients with an increased sensitivity to aspirin (aspirin-induced asthma), but also a small number of patients with asthma who had a bronchodilator response to aspirin.[142]

Specific, novel and future therapies

In the past two decades, controlled randomized trials in conjunction with modern technologies have greatly expanded our knowledge of the immunology of asthma and its systemic links. Although interfering with the inflammatory cascade dates back to the early experiments with immunotherapy,[55] increased understanding of the immunological basis initiated the development of several targeted therapies for asthma and related syndromes.

Recently, subcutaneous Omalizumab (a humanized monoclonal antibody, RhuMab-E25, directed against IgE) has been registered as add on therapy for the treatment of therapy resistant, severe allergic asthma. The mechanism of action is based on reducing serum levels of free circulating IgE and down-regulating the high-affinity IgE-receptors (FcεRI) on basophils and mast cells.[143] When combined with regular maintenance therapy, Omalizumab effectively improved disease control allowing reduction of the daily ICS dose in two-thirds of patients with allergic asthma and/or allergic

rhinitis.[144,145] The major drawbacks are its subcutaneous administration (every 2–4 weeks) and the high costs.

Another promising biological for the treatment of asthma is Etanercept, a soluble TNF-α receptor. Anti-TNF-α therapy has been shown to be effective in severe persistent asthma, possessing a predominant TH-1 cell profile. A recent study by Berry and colleagues reported marked improvement in airway hyperresponsiveness, QoL and post-bronchodilator FEV1 in patients with severe persistent asthma following 10 weeks of treatment with subcutaneous Etanercept compared to placebo.[146] Another study in severe asthmatics showed similar results after 12 weeks of open label treatment.[147] Not unexpectedly, Etanercept failed to protect against allergen-induced airway inflammation and airway hyperresponsiveness in patients with mild to moderate asthma.[148]

And although not all targeted therapies can modulate the asthmatic airway inflammation,[34,135,149] this specific approach has greatly contributed to our understanding of the immunology of asthma and the therapeutic options. In the next century, emerging biotechnologies including genomics, proteonomics, pharmacogenetics and molecular pharmacology will mark the future developments for customized or phenotype-related therapy for asthma and related syndromes.

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