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ONLINE APPENDIX

GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

UPDATED 2020

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GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

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This online Appendix contains background and supplementary material for the Global Initiative for Asthma (GINA) 2020 Global Strategy Report for Asthma Management and Prevention. The full GINA report and other GINA resources are available at www.ginasthma.com

This document is intended to provide background information for the full GINA 2020 report, as a general guide for health professionals and policy-makers. It is based, to the best of our knowledge, on current best evidence and medical knowledge and practice at the date of publication. When assessing and treating patients, health professionals are strongly advised to consult a variety of sources and to use their own professional judgment, and to take into account local or national regulations and guidelines. GINA cannot be held liable or responsible for inappropriate healthcare associated with the use of this document, including any use which is not in accordance with applicable local or national regulations or guidelines.

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Chapter 1.
The burden of asthma

PREVALENCE, MORBIDITY AND MORTALITY

Asthma is a problem worldwide, with an estimated 358 million affected individuals.[1] Despite hundreds of reports on the prevalence of asthma in widely differing populations, the lack of a precise and universally accepted definition of asthma makes reliable comparison of reported prevalence from different parts of the world problematic.[2] Nonetheless, based on standardized methods for assessing asthma symptoms, it appears that the global prevalence of asthma ranges from 1 to 22% of the population in different countries (Boxes A1-1, A1-2).[3-5] There are insufficient data to determine the likely causes of the described variations in prevalence within and between populations.

There is firm evidence that international differences in asthma symptom prevalence in children have decreased over recent decades; symptom prevalence has been decreasing in Western Europe and increasing in regions where prevalence was previously low.[6] Asthma symptom prevalence in Africa, Latin America, Eastern Europe and Asia continues to rise. The World Health Organization *Global Burden of Disease Study* estimated that in 2015, 26.2 million disability-adjusted life years (DALYs) were lost due to asthma, representing 1.1% of the total global disease burden.[1] It is estimated that asthma causes 495,000 deaths worldwide every year,[7] with widely varying case fatality rates that may reflect differences in management.[3]

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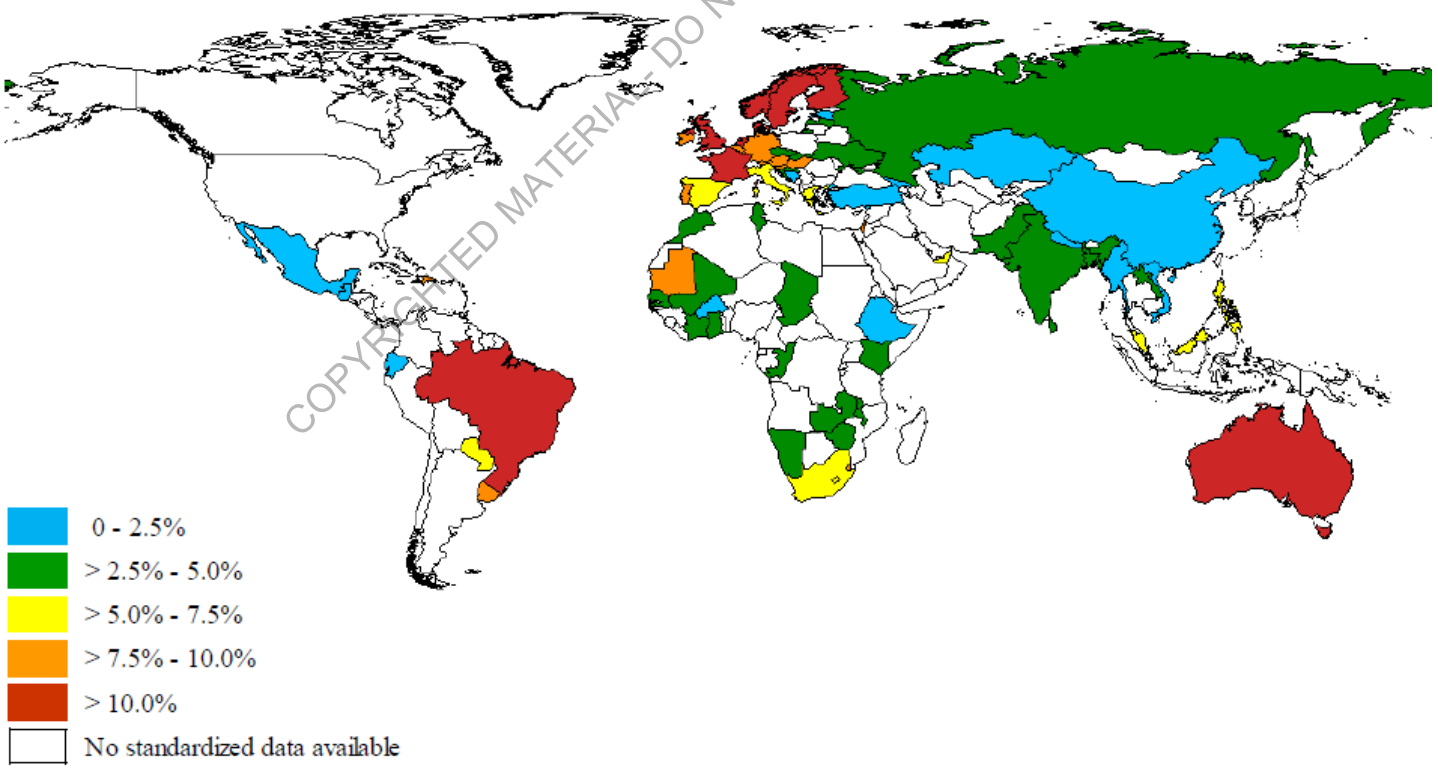
Box A1-1. World map of the prevalence of asthma in adults



Prevalence of 'clinical asthma' in adults from the World Asthma Survey, 2003-2005. Figure reproduced with permission from To et al, BMC Pul Med 2012; 12:204. Data based on doctor diagnosed asthma and/or ever treated for asthma and/or taking asthma medication in the last 2 weeks.

Box A1-2. Prevalence of current asthma in 2000–2003 in children aged 13–14 years (%)

Country	% asthma	Country	% asthma	Country	% asthma
Isle of Man	15.6	Austria	7.6	Ethiopia	4.6
El Salvador	15.4	Turkey*	7.4	Morocco	4.5
Australia	15.3	Malta	7.3	Malaysia	4.5
Vietnam	14.8	Ukraine	7.3	FYR Macedonia	4.4
Scotland	13.9	Tunisia	7.2	Algeria	4.4
Wales	13.8	Nicaragua	6.9	South Korea	4.4
Costa Rica	13.7	Canada	6.9	Mexico	4.4
New Zealand	13.4	France*	6.8	Hong Kong	4.3
Republic of Ireland	13.4	Norway*	6.8	Palestine	4.3
Channel Islands	13.3	Bolivia	6.8	Philippines	4.2
England	11.5	Trinidad and Tobago	6.6	Sultanate of Oman	4.2
Sri Lanka	11.5	Nigeria	6.5	Croatia	4.2
Panama	11.5	Niue	6.4	Belgium	4.2
Romania	11.4	Sudan	6.3	Bulgaria	4.1
United States of America	11.1	Argentina	6.3	New Caledonia	4.1
Honduras	11.0	United Arab Emirates*	6.2	Italy	4.1
Reunion Island	10.8	Jordan	6.2	Kyrgyzstan	3.9
Paraguay	10.5	Netherlands	6.1	Kuwait	3.8
Barbados	10.4	Colombia	5.9	Bangladesh*	3.8
Congo	9.9	Portugal	5.9	Democratic Republic of Congo	3.8
Tokelau	9.9	Singapore	5.7	Lithuania	3.7
Peru	9.8	French Polynesia	5.7	Occupied Territory of Palestine*	3.6
Ivory Coast	9.7	Russia	5.6	Egypt	3.5
South Africa	9.6	Iran	5.4	Taiwan	3.1
Finland	9.5	Pakistan	5.4	Denmark*	3.0
Brazil	9.4	Cook Islands	5.3	India	2.9
Guinéa	9.3	Spain	5.3	Hungary	2.9
Cuba	8.9	Latvia	5.3	Samoa	2.9
Germany	8.8	Fiji	5.2	Cameroon	2.9
Togo	8.4	Thailand	5.2	Syrian Arab Republic	2.6
Ecuador	8.3	Gabon	5.1	Indonesia	2.6
Uruguay	8.2	Poland	5.1	Georgia	2.6
Kingdom of Tonga	8.1	Japan	5.0	Switzerland*	2.3
Czech Republic*	8.0	Sweden	4.9	Greece*	1.9
Kenya	7.9	Serbia and Montenegro	4.8	China	1.8
Venezuela	7.7	Estonia	4.7	Albania	1.7
Chile	7.7	Uzbekistan*	4.6	Nepal*	1.5

Data are based on ISAAC III.[4] The prevalence of current asthma in the 13-14 year age group is estimated as 50% of the prevalence of self-reported wheezing in the previous 12 months.*No data available from ISAAC III, figures taken from Global Burden of Asthma Report[3]

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SOCIAL AND ECONOMIC BURDEN

Social and economic factors are integral to understanding asthma and its care, from the perspective of both the individual person with asthma and the health care provider. In addition, quantifying the socioeconomic burden of diseases is important as it provides critical information to decision makers to efficiently allocate scarce health care resources. Attention needs to be paid to both direct medical costs (identifiable health care services and goods used for asthma such as hospital admissions, physician visits and medications) and indirect costs (productivity loss and premature death).[8,9]

Direct costs

The monetary costs of asthma, as estimated in a variety of health care systems including those of the United States,[10,11] Canada,[12] Italy,[13] and the United Kingdom[14] are substantial. Few economic studies are conducted in non-western countries, but there is strong evidence that asthma imposes a significant burden in the developing world.[15] Exacerbations are major determinants of the direct cost of asthma, and preventing exacerbations should be an important consideration in asthma management.[16]

Indirect costs

Since asthma is a chronic health condition that affects individuals across all ages, productivity loss due to asthma is substantial.[17] Absence from school and days lost from work are reported as substantial social and economic consequences of asthma in studies from various regions of the world.[9,18] Productivity loss itself can be in the form of missed work time (absenteeism), and present at work but with reduced performance (presenteeism).[19] Very few comparisons are available, but productivity loss due to presenteeism seems to be a more important source of economic burden than absenteeism.[17]

REDUCING THE BURDEN OF ASTHMA

Poor asthma control is associated with higher medical costs, increased productivity loss, and substantial reductions in quality of life.[20] In closely controlled clinical trials, good asthma control can be achieved in the majority of patients.[21] Nevertheless, in practice there remains a substantial fraction of patients with poorly controlled asthma due to sub-optimal treatment. For example, a recent study of pharmacological treatment of asthma in adults from the European Community Respiratory Health Survey I, II and III found that, although ICS use had increased over 20 years, only one-third of patients with persistent asthma were taking ICS on a regular basis, and fewer than half had seen a doctor for their asthma in the previous year.[22] In low and middle income countries, there are substantial problems with access to even basic asthma medications.[23]

Such findings signify care gaps and potential for improvements in health and reductions in costs.[20] However, good management of asthma poses a challenge for individuals, health care professionals, health care organizations, and governments. Efforts are required to provide access to appropriate controller medications, and to ensure that they are prescribed appropriately by health care providers and used correctly by patients.[24]

Comparisons of the cost of asthma in different regions lead to the following conclusions.

- The costs of asthma depend on its prevalence, the individual patient's level of asthma control, the extent to which exacerbations are avoided, and the costs of medical care and medications.
- Emergency treatment is more expensive than planned treatment and preventing hospitalizations is an achievable goal for health services.
- The non-medical economic costs of asthma are substantial. Specifically, presenteeism seems to be particularly high in patients with asthma.
- The presence of many individuals with uncontrolled asthma signifies a preventable source of socioeconomic burden

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Additional information about the burden of asthma can be found in the 2018 *Global Asthma Report*[25] and from the World Health Organization *Global Burden of Disease* project (www.who.int/healthinfo/global_burden_disease). Ongoing audit and research on the social and economic burden of asthma and the cost-effectiveness of treatment are needed in both developed and developing countries.

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Chapter 2.
Factors affecting the development and expression of asthma

BACKGROUND

Factors that influence the risk of developing asthma include host and environmental factors (Box A2-1).[26] However, the mechanisms whereby these factors influence the development and expression of asthma are complex and interactive; for example, genes are likely to interact both with other genes and with environmental factors to determine asthma susceptibility.[27,28] In addition, developmental aspects such as the maturation of the immune response, development of atopy, and the timing of infectious exposures during the first years of life, are emerging as important factors that modify the risk of asthma in the genetically susceptible person. Strategies that may be useful to prevent the development of asthma are described in the *Global Strategy for Asthma Management and Prevention 2019,* Chapter 7.[29]

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Box A2-1. Factors influencing the development and expression of asthma

Host factors ⟷	Environmental factors

• Genetic (e.g. genes predisposing to atopy, airway hyperresponsiveness, airway inflammation and innate immunity)
• Obesity
• Sex
• Pre-term or with small size for gestational age
	• Allergens
	  ○ Indoor: domestic mites, furred animals (e.g. dogs, cats, mice), cockroaches, fungi
	  ○ Outdoor: pollen, molds
	• Occupational sensitizers and allergens (e.g. flour, laboratory rodents, paints)
	• Infections (predominantly viral)
	• Microbiome
	• Exposure to tobacco smoke
	  ○ Passive smoking
	  ○ Active smoking
	• Outdoor or indoor air pollution
	• Diet
	• Stress

Links between asthma and socioeconomic status, with a higher prevalence of asthma in developed than in developing nations; in poor compared with affluent populations in developed nations; and in affluent compared with poor populations in developing nations; are likely to reflect lifestyle differences such as exposure to allergens, infections, diet, and access to health care. Much of what is known about risk factors for the development of asthma comes from studies of young children; the risk factors in adults, particularly *de novo* in adults who did not have asthma in childhood, are less well defined.

The heterogeneity of asthma, the previous lack of a clear definition, and lack of a biological 'gold standard' marker for asthma present significant problems in studying the role of different risk factors in the development of this complex disease. Characteristics that are commonly found in patients with asthma (e.g. airway hyperresponsiveness, atopy and allergic sensitization) are themselves products of complex gene–environment interactions and are therefore both features of asthma and risk factors for the development of the disease.

HOST FACTORS

Genetic

Asthma has a complex heritable component. Current data show that multiple genes may be involved in the pathogenesis of asthma,[30] and different genes may be involved in different ethnic groups.[31] The search for genes linked to the development of asthma has previously focused on four major areas: production of allergen-specific immunoglobulin E (IgE) antibodies (atopy); expression of airway hyperresponsiveness; generation of inflammatory mediators such as cytokines, chemokines and growth factors; and determination of the ratio between T helper lymphocyte Th1 and Th2 immune responses (as relevant to the hygiene hypothesis of asthma).[32] Family studies and case-control association analyses have identified a number of chromosomal regions that are associated with asthma susceptibility. For example, a tendency to produce an elevated level of total serum IgE is co-inherited with airway hyperresponsiveness, and a gene (or genes) governing airway hyperresponsiveness is located near a major locus that regulates serum IgE levels on chromosome 5q.[33] Over the last 10-15 years asthma genetics has moved towards large scale genome-wide association studies and meta-analyses of these studies.

A meta-analysis of genome-wide association studies (GWAS) for IgE identified a variant near HLA-DQB1 as a predictor of total serum IgE levels in multiple race and ethnic groups.[34] Another GWAS study defined the potential importance of genes such as IL33, IL1RL1, IL18R1 and TSLP that are involved in epithelial cell danger signal pathways.[35] To further complicate the issue, researchers have found associations for variants in innate immunity genes with asthma and suggest that these may play a role, in conjunction with early-life viral exposures, in the development of asthma.[36] In the most recent, large meta-analysis of GWAS of asthma conducted by the Transatlantic Asthma Genetics Consortium (TAGC),[37] nine known asthma loci were confirmed and five new asthma loci were discovered. Several asthma susceptibility genes appear to code for proteins which are either epithelial alarmins (e.g. IL-33, TSLP), type 2 cytokines (e.g. IL-5, IL-13) or transcription factors (i.e. GATA3 and RORα) of type 2 lymphocytes (either T helper 2 CD4+ lymphocytes or innate lymphoid cells type 2 [ILC2]).To date most asthma genetics studies have focused on mild-to-moderate disease. The largest moderate-to-severe asthma GWAS has confirmed the importance of the same genes as described in milder disease but has demonstrated an additional association with the MUC5AC gene implicating a role for mucin production in more severe disease.[38]

In addition to genes that predispose to asthma there are genes that are associated with the response to asthma treatments. For example, variations in the gene encoding the beta$_2$-adrenoreceptor have been linked to differences in some subjects' responses to short-acting beta$_2$-agonists.[39] Other genes of interest modify the responsiveness to corticosteroids[40] and leukotriene receptor antagonists.[41] Genetic markers will likely become important, not only as risk factors in the pathogenesis of asthma, but also as determinants of responsiveness to treatment.

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Sex

In childhood, male sex is a risk factor for asthma. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls.[42] As children grow older, the difference in prevalence between the sexes narrows, and by adulthood the prevalence of asthma is greater in women than in men. The reasons for this sex-related difference are not clear;[43] one potential contributor is differences in lung and airway size, which are smaller in males than in females in infancy,[44] but larger in females in adulthood.[45]

Early growth characteristics

Early growth characteristics might persistently affect lung function and thereby contribute to the risk of obstructive respiratory diseases in later life. Younger gestational age, lower birth weight, and greater infant weight gain are independently associated with persistent changes in childhood lung function. Stratified analyses of birth cohorts have shown that children born very preterm with a relatively low birth weight had the lowest FEV_1 and FEV_1/FVC ratio. Preterm birth, low birth weight, and greater weight gain were all associated with an increased risk of childhood asthma.[46]

Obesity

The prevalence and incidence of asthma are increased in obese subjects (body mass index >30 kg/m^2), particularly in women with abdominal obesity.[47,48] Inappropriate attribution of shortness of breath may contribute to over-diagnosis, but one study found that over-diagnosis of asthma was no more common in obese than in non-obese patients.[49] It is not known why asthma develops more frequently in the obese. Potential contributing factors include changes in airway function due to the effects of obesity on lung mechanics; the development of a pro-inflammatory state in obesity; and an increased prevalence of comorbidities, genetic, developmental, hormonal or neurogenic influences.[48]

Depression

While depression is a common comorbidity of asthma, the temporal relationship between the two conditions has not been clear. A systematic review and meta-analysis of six prospective studies with follow-up of 8-20 years found that depression was associated with a 43% increased risk of developing adult-onset asthma, after adjustment for potential confounding factors such as age, sex, smoking and body mass index. On the other hand, the two studies examining the relationship between asthma and risk of subsequent depression found no significant association, but this may have been due to insufficient studies being available.[50]

ENVIRONMENTAL FACTORS

Allergens

Although indoor and outdoor inhalant allergens are well-known triggers of asthma exacerbations in people with established asthma, their specific role in the initial development of asthma is still not fully resolved. Birth cohort studies have shown that sensitization to house dust mite allergens, cat dander, dog dander,[51,52] and *Aspergillus* mold[53] are independent risk factors for asthma-like symptoms in children up to 3 years of age. For children at risk of asthma, dampness, visible mold and mold odor in the home environment are associated with increased risk of developing asthma.[54] However, the relationship between allergen exposure and sensitization in children is not straightforward, depending on interactions between the allergen, the dose, the time of exposure, the child's age, and genetics.

For some allergens, such as those derived from house dust mites and cockroaches, the prevalence of sensitization appears to be directly correlated to exposure.[52,55] However, while some data suggest that exposure to house dust mite allergens may be a causal factor in the development of asthma[56] other studies have questioned this interpretation.[57,58] Cockroach infestation has been shown to be an important cause of allergic sensitization, particularly in inner-city homes.[59]

Some epidemiological studies have found that early exposure to cats or dogs may protect a child against allergic sensitization or the development of asthma.[60-62] Conversely others suggest that such exposure may *increase* the risk of allergic sensitization.[61,63-65] A study of over 22,000 school-age children from 11 birth cohorts in Europe showed no association between pets in the home early in the child's life and higher or lower prevalence of asthma.[66]

Sensitization to ingestant allergens in early life remains a risk factor for subsequent asthma;[67] however, there are insufficient data to permit intervention, and no strategies can be recommended to prevent allergic sensitization pre-natally. In particular, there is no evidence that antenatal peanut or tree nut exposure increases the risk for subsequent asthma in children.[68]

Rhinitis in individuals without asthma is a risk factor for development of asthma both in adults and children. In adults, asthma development in individuals with rhinitis is often independent of allergy; in childhood, it is frequently associated with allergy.[69,70]

A meta-analysis of studies examining the effect of allergen immunotherapy concluded that allergen immunotherapy did not result in a statistically significant reduction in the risk of developing a first allergic disease, but that, among those with

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allergic rhinitis, there was evidence of a reduced short-term risk of developing asthma. However, it is unclear whether this benefit was maintained over the longer term.[71]

Occupational sensitizers

Occupational asthma is asthma caused by exposure to an agent encountered in the work environment.[72,73] Asthma is the most common occupational respiratory disorder in industrialized countries, and occupational agents are estimated to cause about 15% of cases of asthma among adults of working age.[74] Over 300 substances have been associated with occupational asthma, including highly reactive small molecules such as isocyanates; irritants that may cause an alteration in airway responsiveness; immunogens such as platinum salts; and complex plant and animal biological products that stimulate the production of IgE (e.g. flour, laboratory rodents, wood dust). Occupations associated with a high risk of occupational asthma include bakers, hair dressers, farming and agricultural work, laboratory animal facilities, painting (including vehicle spray painting), cleaning work, and plastic manufacturing.[73]

Most occupational asthma is immunologically mediated and has a latency period of months to years after the onset of exposure.[75] Both IgE-mediated allergic reactions and cell-mediated allergic reactions are involved.[76] Levels above which sensitization frequently occurs have been proposed for many occupational sensitizers; however, the factors that cause some people but not others to develop occupational asthma in response to exposure to the same agent are not well identified. Very high exposures to inhaled irritants may cause 'irritant-induced asthma' (including reactive airways dysfunctional syndrome (RADS)) even in non-atopic individuals.[77] Atopy and tobacco smoking may increase the risk of occupational sensitization, but screening individuals for atopy is of limited value in preventing occupational asthma.[72] The most important method of preventing occupational asthma is to eliminate or reduce exposure to occupational sensitizers. However, occupational asthma, once present, persists in most patients even after removal from exposure.[72]

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Infections

Infection with a number of viruses during infancy has been associated with the inception of the asthmatic phenotype. Respiratory syncytial virus (RSV), human rhinovirus (HRV) and parainfluenza virus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma.[78,79] Several long-term prospective studies of children admitted to hospital with documented RSV infection have shown that approximately 40% will continue to wheeze or have asthma into later childhood.[78,79] On the other hand, some respiratory infections early in life, including measles and sometimes even RSV, appear to protect against the development of asthma.[80] The data do not allow specific conclusions to be drawn. With the advent of improved molecular techniques for detecting viral pathogens, the important contributions of community-based wheezing illnesses due to HRV during infancy and early childhood with the subsequent development of asthma have now been well recognized.[81,82] Both allergic sensitization[83] and certain genetic loci[84] appear to interact with HRV wheezing illnesses in early life to increase the risk of developing asthma in childhood. Common bacterial pathogens may also be associated with wheezing illnesses in early life.[85] Parasitic infections do not in general protect against asthma, but infection with hookworm may reduce the risk.[86]

The 'hygiene hypothesis' proposes that exposure to infections early in life influences the development of a child's immune system along a 'non-allergic' pathway, and leads to a reduced risk of asthma and other allergic diseases.[32] This mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma. For example, young children with older siblings and those who attend day care are at increased risk of infections, but enjoy protection later in life against the development of allergic diseases, including asthma.[87-89] The hygiene hypothesis continues to be investigated.

Recent observations indicate that the microbiome (i.e. the collection of microorganisms and their genetic material), both within the host and in the host's surrounding environment, may contribute to the development and/or prevention of allergic diseases and asthma.[90] For example, delivery by cesarean section has been associated with an increased risk of asthma up to the age of 12 years compared with vaginal delivery.[91-93] In rural settings, the prevalence of childhood asthma is reduced and this has been linked to the presence of bacterial endotoxin in these environments.[94] In rural

settings, the diversity of microbial exposure in house dust has been correlated inversely with the risk of developing asthma.[95]

The interaction between atopy and viral infections appears to be complex in that the atopic state can influence the lower airway response to viral infections; viral infections can then influence the development of allergic sensitization; and interactions can occur when individuals are exposed simultaneously to both allergens and viruses.[96,97] However, allergic sensitization in the first 3 years of life is more likely to precede viral-associated wheezing illnesses and may actually be causal in nature.[81] In children with allergic asthma, anti-IgE therapy decreased the duration of rhinovirus infections, viral shedding, and the risk and severity of rhinoviral illnesses,[98] suggesting that in allergic patients, blocking IgE may limit rhinovirus replication.

Socioeconomic inequalities

In all communities, poverty is strongly related to ill health. This has not generally been the pattern for asthma, where the lifetime prevalence of symptoms was usually higher in more affluent societies.[99] However, in recent years, data from many studies have challenged this view. There have been consistent demonstrations of a positive association between lower socioeconomic status and risk of wheezing, both in high- and in low- and middle-income countries (LMIC), indicating a more complex interaction between factors, some protective and others causative. In children living in inner cities in the USA, the burden of asthma is high and appears to be independent of ethnicity and income.[100] In addition, the relationship between poverty and asthma may change over time. For example, a study from Sweden has shown a reversal of the association between socioeconomic status and asthma prevalence; military conscripts of low socioeconomic status who three decades ago had the lowest, now have the highest prevalence of asthma, with increasing prevalence in successive generations.[101] In a cohort of Brazilian children, symptoms of asthma have been associated with unhygienic living conditions and infections.[102,103]

Stress

Asthma prevalence is increased in low income, inner-city neighborhoods, where family stress levels are high.[104]. Parental stress, both in the first year of life[105] and from birth to early school age,[106] has been associated with increased risk of asthma in school-age children. Lower cortisol levels in response to acute stress are observed in such children, suggesting a mechanistic explanation for increased asthma prevalence.[107] Challenges may be faced by patients with asthma following large-scale disasters.

Tobacco smoke

Exposure to tobacco smoke, either pre-natally[108] or after birth,[108] is associated with harmful effects including a greater risk of developing asthma-like symptoms in early childhood. Distinguishing the independent contributions of pre-natal and post-natal maternal smoking is problematic.[109] However, maternal smoking during pregnancy has an influence on lung development,[44] and infants of smoking mothers are four times more likely to develop wheezing illnesses in the first year of life,[109] although there is little evidence that maternal smoking during pregnancy has an effect on allergic sensitization.[110] Exposure to environmental tobacco smoke (passive smoking) also increases the risk of lower respiratory tract illnesses in infancy[111] and childhood.[112]

In people with established asthma, tobacco smoking is associated with an accelerated decline in lung function;[113] may render patients less responsive to treatment with inhaled[114,115] and systemic[116] corticosteroids; and reduces the likelihood of asthma being well controlled.[117] In a study of patients with adult-onset asthma, frequent exacerbations in current or past smokers were associated with higher blood neutrophils, whereas in never-smokers, frequent exacerbations were associated with higher blood eosinophils.[118]

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Outdoor and indoor air pollution

Children raised in a polluted environment have diminished lung function,[119] and exposure to outdoor air pollutants has significant effects on asthma morbidity in children and adults.[120-122] Similar associations have been observed in relation to indoor pollutants (e.g. smoke and fumes from gas or biomass fuels that are used for heating and cooling, molds, and cockroach infestations).[123] Exposure to outdoor pollutants, such as living or attending schools near high-traffic density roads increased the incidence and prevalence of childhood asthma and wheeze.[124,125] Prenatal NO_2, SO_2, and PM10 exposures are associated with an increased risk of asthma in childhood,[126] but it is difficult to separate pre- and post-natal exposure.

Diet

For some time, the mother's diet during pregnancy has been a focus of concern relating to the development of allergy and asthma in the child. There is no firm evidence that ingestion of any specific foods during pregnancy increases the risk for asthma. However, a recent study of a pre-birth cohort observed that maternal intake of foods commonly considered allergenic (peanut and milk) was associated with a *decrease* in allergy and asthma in the offspring.[127] Similar data have been shown in a very large Danish National birth cohort, with an association between ingestion of peanuts, tree nuts and/or fish during pregnancy and a decreased risk of asthma in the offspring.[68,128]

Data suggest that maternal obesity and weight gain during pregnancy pose an increased risk for asthma in children. A recent meta-analysis of 14 studies[129] showed that maternal obesity in pregnancy was associated with higher odds of ever asthma or wheeze or current asthma or wheeze; each 1 kg/m2 increase in maternal BMI was associated with a 2% to 3% increase in the odd of childhood asthma. High gestational weight gain was associated with higher odds of ever asthma or wheeze. However, unguided weight loss in pregnancy should not be encouraged.

The role of post-natal diet, particularly breast-feeding, in relation to the development of asthma has been extensively studied and, in general, the data reveal that infants fed formulas of intact cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed breast milk.[130]

Some data also suggest that certain characteristics of Western diets, such as increased use of processed foods and decreased antioxidants (in the form of fruits and vegetables), increased omega-6 polyunsaturated fatty acid (found in margarine and vegetable oil), and decreased omega-3 polyunsaturated fatty acid (found in oily fish) intakes are associated with recent increases in asthma and atopic disease.[131] A systematic review of randomized controlled trials on maternal dietary intake of fish or long-chain polyunsaturated fatty acids during pregnancy showed no consistent effects on the risk of wheeze, asthma or atopy in the child.[132] One recent study demonstrated decreased wheeze/asthma in pre-school children at high risk for asthma when mothers were given a high dose fish oil supplement in the third trimester;[133] however 'fish oil' is not well defined, and the optimal dosing regimen has not been established.

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Vitamin D

There has been substantial interest in recent years in the role of vitamin D intake during pregnancy. A systematic review of cohort, case control and cross-sectional studies concluded that maternal intake of vitamin D, and of vitamin E, was associated with lower risk of wheezing illnesses in children.[134] This was not confirmed in randomized controlled trials of vitamin D supplementation during pregnancy, although a significant effect was not ruled out.[135,136] Evidence is still inconclusive, and further randomized controlled trials are needed. When the results from these two trials were combined, there was a 25% reduction of risk of asthma/recurrent wheeze at ages 0-3 years.[137] The effect was greatest among women who maintained 25(OH)vitamin D levels of at least 30ng/ml from the time of study entry through delivery, suggesting that sufficient levels of Vitamin D during early pregnancy may be important in decreasing risk for early life wheezing episodes.[137]

Paracetamol (acetaminophen)

Several epidemiological studies have shown a relationship between frequency of paracetamol use in children or in pregnancy,[138,139] and a diagnosis of asthma in children. Interpretation is confounded by the fact that in infancy, paracetamol is often administered for viral respiratory infections, which themselves may either contribute to the development of asthma or be an early manifestation of asthma. In a prospective cohort study, paracetamol use was not associated with diagnosis of asthma after adjusting for respiratory infections, or when paracetamol was used only for non-respiratory indications.[140] Frequent use of paracetamol by pregnant women has been associated with asthma in their children,[139] but non-causal associations have not been ruled out.[141,142]

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Chapter 3.
Mechanisms of asthma

Asthma is an inflammatory disorder of the airways, which involves multiple inflammatory cells and mediators that contribute to characteristic clinical and pathophysiological changes.[143] In ways that are still not well understood, this inflammation is strongly associated with early life exposures,[144] airway hyper-responsiveness and asthma symptoms. The underlying mechanisms driving these clinical phenotypes and the response to therapies is incompletely understood.[143,145,146] One major advance has been that biomarkers of type 2 inflammation (such as increased FeNO levels and blood or sputum eosinophilia), particularly in severe disease, have been shown to predict the therapeutic response to corticosteroids, monoclonal antibodies targeting type 2 cytokines (e.g. IL5) or their receptors (IL4Rα; IL5R).[145,147] There is a clear need to continue investigation into the root causes of asthma so that targeted diagnostics and therapeutics can be developed.[148]

AIRWAY INFLAMMATION IN ASTHMA

The clinical spectrum of asthma is highly variable and shows different sputum cellular patterns. Based upon eosinophil and neutrophil counts in sputum, four asthma inflammatory phenotypes can be discerned: eosinophilic asthma, neutrophilic asthma, mixed granulocytic asthma and pauci-granulocytic asthma. However, even in patients with pauci-granulocytic asthma, the eosinophil count in sputum is still significantly increased as compared with healthy subjects.[149] The prevalence of those with eosinophilic or mixed granulocytic is approximately 50-70% although there is variability between patients. Within patients the proportions change over time and are affected by exposures to allergens, infection and pollutants and in response to treatment.[145] Corticosteroids, even when given acutely for exacerbations, can change levels of eosinophil biomarkers.[150]

In addition to granulocytes other inflammatory cells play key roles in asthma summarized in (Box A3-1)[151,152] and their co-location with structural cells is important such as mast cell airway smooth muscle interactions in airway hyper-responsiveness.[145,153] Airway inflammation in asthma persists even when symptoms are episodic, and the relationship between the severity of asthma and the intensity of inflammation has not been clearly established.[154] The inflammation affects all airways, including the upper respiratory tract and nose in most patients, but its physiological effects are most pronounced in medium-sized bronchi.

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Box A3-1. Inflammatory cells in asthmatic airways

Cell type	Action
Mucosal mast cells	Release the bronchoconstrictor mediators histamine, cysteinyl leukotrienes and prostaglandin D2 when activated.[155] Mucosal mast cells are activated by allergens and immunoglobulin E (IgE) through high-affinity IgE receptors as well as by non-allergic mechanisms including innate immune mechanisms, neural connections and osmotic stimuli, which accounts for exercise-induced bronchoconstriction.[156]
Eosinophils	Usually present in increased numbers in asthmatic airways, eosinophils release basic proteins that may damage airway epithelial cells. They also produce cysteinyl leukotrienes and growth factors.[157] In rare cases of steroid-resistant severe asthma with (sputum or blood) eosinophilia, an anti-interleukin 5 (IL5) or anti-IL5 receptor antibody can reduce asthma exacerbations.[158-161]

Box A3-1. Inflammatory cells in asthmatic airways (continued)

Cell type	Action
Lymphocytes	Present in increased numbers in asthmatic airways; T helper 2 CD4+ lymphocytes release specific cytokines, including interkeukins (IL) 4, 5, 9, and 13, which orchestrate eosinophilic inflammation, mucus overproduction and IgE production by B lymphocytes.[162] An increase in Th2 cell activity may be due, in part, to a reduction in the regulatory T cells that normally inhibit Th2 cells. In severe eosinophilic asthma, there is also an increase in innate lymphoid cells type 2 (ILC2),[163] whereas Th1 and Th17 cells might be involved in neutrophilic and mixed granulocytic (severe) asthma.[162]
Dendritic cells	These professional antigen-presenting cells sample allergens from the airway surface and migrate to regional lymph nodes where they interact with naïve CD4+ T cells. In healthy subjects, this dendritic cell (DC) – T cell interaction will induce regulatory T cells (Treg cells) producing immunomodulatory cytokines such as IL10 and Transforming Growth Factor beta (TGFβ), whereas in asthmatic individuals the DC -T cell interaction will ultimately stimulate production of type 2 cytokines by T helper 2 (Th2) cells.[164,165] Upon secondary allergen exposure in sensitized subjects, dendritic cells can activate memory Th2 cells in the airway mucosa.
Macrophages	Present in increased numbers in asthmatic airways, macrophages may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response, especially in severe asthma.[166]
Neutrophils	These cells are increased in the airways and sputum of some patients with severe asthma and in smoking asthmatics. The pathophysiological role of these cells is uncertain and their increase may be elicited by microbial infection of the airways, or even be due to corticosteroid therapy.[167] In patients with severe asthma, neutrophil extracellular traps (NETs) and extracellular DNA in sputum have been associated with airway epithelial cell damage and inflammasome activation.[168]

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The characteristic pattern of inflammation that is found in other allergic diseases is also seen in allergic asthma,[169] with activated mast cells, increased numbers of activated eosinophils, and increased numbers of the T-cell receptor invariant, natural killer T cells and T helper 2 lymphocytes (Th2), which release mediators that contribute to symptoms (Box A3-1). However, asthma can occur in the absence of allergy to aero-allergens, especially in patients with adult-onset asthma.

Innate lymphoid cells type 2 (ILC2), regulated by epithelial cell mediators such as TSLP, interleukin (IL)-25 and IL-33, have also been implicated in airway inflammation in asthma.[170] Upon activation by these epithelial alarmins, ILC2 can produce high amounts of type 2 cytokines (especially IL5 and IL13), leading to eosinophilic airway inflammation (even in the absence of allergy).[171] In some cases (especially severe asthma) neutrophils may also contribute to this response.[152]

Structural cells of the airways also produce inflammatory mediators, and contribute to the persistence of inflammation in various ways, as outlined in Box A3-2.

Box A3-2. Structural cells in asthmatic airways

Cell type	Action
Airway epithelial cells	These cells sense their environment, express multiple inflammatory proteins, and release danger signals (alarmins), cytokines, chemokines, and lipid mediators in response to physical perturbation.[121] Viruses and air pollutants also interact with epithelial cells.
Airway smooth muscle cells	These cells show increased number (hyperplasia), in part due to proliferation and recruitment of progenitors (fibrocytes and myofibroblasts),[145,172] and size (hypertrophy) In addition to effects on airway caliber through bronchial dilatation and contraction airway smooth muscle express similar inflammatory proteins to epithelial cells. [169]
Endothelial cells	Endothelial cells of the bronchial circulation play a role in recruiting inflammatory cells from the circulation into the airway and vascularity is increased in the airway.[173]
Fibroblasts and myofibroblasts	These cells produce connective tissue components, such as collagens and proteoglycans that are involved in airway remodeling and are associated with the increased airway smooth muscle.
Airway nerves	Cholinergic nerves may be activated by reflex triggers in the airways and cause bronchoconstriction and mucus secretion. Sensory nerves that may be sensitized by inflammatory stimuli, including neurotrophins, cause reflex changes and symptoms such as cough and chest tightness, and may release inflammatory neuropeptides.

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Key cellular mediators of asthma

Over 100 different mediators are now recognized to be involved in asthma and mediate the complex inflammatory response in the airways (Box A3-3).

Box A3-3. Key cellular mediators in asthma

Mediators	Action
Chemokines	Important in the recruitment of inflammatory cells into the airways; mainly expressed in airway epithelial cells.[174] CCL11 (eotaxin), is relatively selective for eosinophils, whereas CCL17 and CCL22 recruit Th2 cells.
Cysteinyl leukotrienes	Potent bronchoconstrictors and pro-inflammatory mediators mainly derived from mast cells and eosinophils. They are the only mediators that, when inhibited, have been associated with an improvement in lung function and asthma symptoms.[175]

Cytokines	Orchestrate the inflammatory response in asthma and determine its severity.[176] Important cytokines include:
	• IL-1-beta and TNF-α, which amplify the inflammatory response
	• GM-CSF, which prolongs eosinophil survival in the airways
	• Th2-derived cytokines, which include
	  ○ IL-5, that is required for eosinophil differentiation and survival
	  ○ IL-4, that is important for Th2 cell differentiation and IgE expression by B cells
	  ○ IL-13, that is needed for IgE expression, stimulates mucus production by goblet cells, and induces the enzyme iNOS (inducible Nitric Oxide Synthase) in airway epithelial cells, leading to increased levels of FeNO (fraction of exhaled Nitric Oxide [NO]).

Histamine	Released from mast cells, histamine contributes to bronchoconstriction and to the inflammatory response. Antihistamines however, have little role in asthma treatment because of their limited efficacy, side-effects, and the apparent development of tolerance.[177]
Nitric oxide	A potent vasodilator produced predominantly from the action of inducible nitric oxide synthase (iNOS) in airway epithelial cells.[178]
Prostaglandin D2	A bronchoconstrictor derived predominantly from mast cells. It is involved in Th2 cell recruitment into the airways.

CCL: chemokine ligand; Th2: T helper 2 lymphocytes; IL: interleukin; TNF: tumor necrosis factor; GM-CSF: granulocyte macrophage colony-stimulating factor.

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STRUCTURAL CHANGES IN THE AIRWAYS

In addition to the inflammatory response, characteristic structural changes, often described as 'airway remodeling', are seen in the airways of asthma patients (Box A3-4). Some of these changes are related to the severity of the disease and may result in relatively irreversible narrowing of the airways.[179,180] These changes may represent repair in response to chronic inflammation, or may occur independently of inflammation.[143,181]

Box A3-4. Structural changes in asthmatic airways

Tissue	Changes in asthma
Subepithelial fibrosis	A deposition of collagen fibers and proteoglycans under the basement membrane that is seen in most asthmatic patients, even before the onset of symptoms, but there is a large overlap with normals. Fibrosis also occurs in other layers of the airway wall, with deposition of collagen and proteoglycans.[131]
Increased airway smooth muscle	A consequence of both hyperplasia and hypertrophy, which contributes to the increased thickness of the airway wall.[179] This process is related to disease severity, airway luminal narrowing and lung function impairment.
Increased blood vessels in airway walls	These amplify the influence of growth factors such as vascular endothelial growth factor, YKL-40 and tissue factor and may contribute to increased airway wall thickness[182] and luminal narrowing.[183]
Mucus hypersecretion	Results from increased numbers of goblet cells in the airway epithelium and increased size of sub-mucosal glands[184] and is assoaicated with intensity of T2 inflammation.[185]

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PATHOPHYSIOLOGY

Airway narrowing

Airway narrowing is the final common pathway leading to symptoms and physiological changes in asthma; with airway narrowing itself likely to be an additional stimulus for remodeling.[181] Several factors contributing to the development of airway narrowing in asthma are listed here.

- *Airway smooth muscle contraction:* this occurs in response to multiple bronchoconstrictor mediators and neurotransmitters and is one of the predominant mechanisms of airway narrowing. It is largely reversed by bronchodilators.
- *Airway edema*: this is due to increased microvascular leakage in response to inflammatory mediators. Airway edema may be particularly important during acute exacerbations.
- *Airway thickening*: this results from structural changes, often termed 'remodeling'. Airway thickening is not fully reversible using current therapies and may be important in more severe disease.
- *Mucus hypersecretion*: a product of increased mucus secretion and inflammatory exudates, mucus hypersecretion may lead to luminal occlusion ('mucus plugging'). Charcot-Leyden crystals (CLCs)[186] are formed from the eosinophil granule protein galectin-10 and might contribute to mucus plugging in (severe) eosinophilic asthma.

Airway hyperresponsiveness

Airway hyperresponsiveness, a characteristic functional abnormality of asthma, results in airway narrowing in a patient with asthma in response to a stimulus that would be innocuous in a healthy person. This airway narrowing leads to variable airflow limitation and intermittent symptoms. Airway hyperresponsiveness is linked to both inflammation and to the repair of the airways, and is partially reversible with therapy. The mechanisms of airway hyperresponsiveness are incompletely understood but include the following.

- *Excessive contraction of airway smooth muscle*: this may result from increased volume and/or contractility of airway smooth muscle cells[187,188] amplified by co-location of inflammatory cells, in particular mast cells.[153,173]
- *Uncoupling of airway contraction*: a result of inflammatory changes in the airway wall that may lead to excessive narrowing of the airways, and a loss of the maximum plateau of contraction that is found in normal airways when bronchoconstrictor substances are inhaled.
- *Thickening of the airway wall*: edema and structural changes amplifies airway narrowing due to contraction of airway smooth muscle for geometric reasons.[179]
- *Sensory nerves*: these may be sensitized by inflammation, leading to exaggerated bronchoconstriction in response to sensory stimuli.[187]

SPECIAL MECHANISMS IN SPECIFIC CONTEXTS

Exacerbations

Short-term worsening of asthma may occur as a result of exposure to 'triggers' (e.g. exercise, cold air, air pollutants),[189] and even certain weather conditions such as thunderstorms in association with grass pollen.[190,191] More severe worsening of asthma usually occurs with viral infections of the upper respiratory tract (particularly rhinovirus and respiratory syncytial virus)[192] and/or allergen exposure.[96,97] Infections and allergen exposure increase inflammation in the lower airways (acute or chronic inflammation) that may persist for several days or weeks.

Nocturnal asthma

The mechanisms accounting for the worsening of asthma at night are not completely understood, but may be driven by circadian rhythms of circulating hormones such as epinephrine, cortisol and melatonin, and neural mechanisms such as cholinergic tone. The reported nocturnal increase in airway inflammation may reflect a reduction in endogenous anti-inflammatory mechanisms.[193]

Persistent airflow limitation

Some patients with severe or long-standing asthma develop progressive airflow limitation that is not fully reversible with currently available therapy. This may reflect changes in airway structure or mucus plugging (Box A3-4).[185,194] These patients may be described as having asthma-COPD overlap, or more appropriately as chronic asthma with persistent airflow limitation. Mechanisms are likely to be heterogeneous. For example, long-term studies suggest that about half of patients with persistent airflow limitation in adult life reached this position by rapid decline from normal lung function in early adulthood, whereas the other half had a normal rate of decline from low initial lung function in early adulthood.[195]

Difficult-to-treat asthma

The reasons why some patients develop asthma that is difficult to manage and relatively insensitive to the effects of corticosteroids are not well understood.[196] Common associations are poor adherence with treatment, incorrect inhaler technique, (passive or active) smoking and psychological and psychiatric disorders. More information on the management of difficult-to-treat asthma is provided in the *GINA Pocket Guide on Difficult-to-treat & Severe Asthma in adolescent and adult patients* (first version in November 2018; second version in April 2019).[197]

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Probably, genetic factors may contribute in some cases as many of these patients have difficult-to-treat asthma from the onset of the disease, rather than progressing from milder asthma. In these patients, there may be inflammation of peripheral airways that leads to airway closure, air trapping and hyperinflation. Although the pathology appears broadly similar to other forms of asthma, there are more neutrophils, more involvement of small airways, and more structural changes than in other patients.[198]

Smoking and asthma

Asthma patients who smoke tobacco have asthma that is more difficult to control, have more frequent exacerbations and hospital admissions, and experience a more rapid decline in lung function and an increased risk of death than asthma patients who are non-smokers.[199] Asthma patients who smoke may have a neutrophil-predominant inflammation or a mixed granulocytic inflammation in their airways and are poorly responsive to corticosteroids.[114,116]

Obesity and asthma

Multiple factors may contribute to the increased incidence and prevalence of asthma in obesity,[48] including:

- Mechanical changes
- The development of a pro-inflammatory state, with increased production of pro-inflammatory cytokines and chemokines (e.g. IL6),[200] increased oxidative stress, increased leptin and reduced adiponectin levels
- An increased prevalence of comorbidities such as gastroesophageal reflux disease, obstructive sleep apnea and metabolic syndrome[200]
- Shared etiological factors such as common genetic and *in utero* influences
- Dietary and environmental factors.

The use of systemic corticosteroids and a sedentary lifestyle may promote obesity in patients with severe asthma, but in most instances, obesity precedes the development of asthma.[47]

Exercise-induced asthma

The increased ventilation of exercise results in increased osmolality in airway lining fluid. This triggers surface mast cells to release mediators such as leukotriene D_4, resulting in bronchoconstriction.[201] In elite athletes, the long-term effects of environmental exposures during training may also contribute to the development of airway hyperresponsiveness and asthma, due to airway epithelium injury, airway inflammatory and structural changes (remodeling). These features have been observed in elite athletes, even without asthma or airway hyperresponsiveness.[201]

Aspirin-exacerbated respiratory disease

This distinct asthma phenotype is associated with intolerance to cyclooxygenase-1 inhibition and increased release of cysteinyl-leukotrienes due to increased expression of leukotriene C4 synthase in mast cells and eosinophils.[202] More detail is provided in the *Global Strategy for Asthma Management and Prevention 2019,* Chapter 3, '*Managing asthma in specific populations or settings'.*[29]

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Chapter 4.
Tests for diagnosis and monitoring of asthma

MEASURING LUNG FUNCTION

The diagnosis of asthma is based on the history of characteristic respiratory symptoms and the demonstration of variable expiratory airflow limitation (see *Global Strategy for Asthma Management and Prevention 2019*, Box 1-2).[29] A number of methods are available to assess airflow limitation, but two methods have gained widespread acceptance for use in patients over 5 years of age. These are spirometry, particularly the measurement of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) and their ratio (FEV_1/FVC), and the measurement of peak expiratory flow (PEF).

Although measurements of lung function do not correlate strongly with symptoms or other measures of asthma control in either adults[203] or children,[204] these measures provide complementary information about different aspects of asthma control. Patients with asthma frequently have poor perception of the severity of their airflow limitation, especially if their asthma is long standing.[205]

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Spirometry

Spirometry is the recommended method of measuring airflow limitation and reversibility (the latter now also called bronchodilator responsiveness[206]) to establish a diagnosis of asthma. Measurements of FEV_1 and FVC are made during a forced expiratory maneuver using a spirometer. Recommendations for the standardization of spirometry have been published.[206] The degree of *reversibility in FEV_1*, that exceeds the variation in a healthy population and is consistent with a diagnosis of asthma in patients with typical symptoms, is generally accepted as 12% and 200 mL from the pre-bronchodilator value.[45] However most asthma patients, particularly those already on controller treatment, will not exhibit reversibility at each assessment, and the test therefore lacks sensitivity.[207] Repeated testing at different visits, or after withholding of bronchodilator medications, is advised if confirmation of the diagnosis of asthma is needed. Recommendations for withholding of bronchodilator medications include 4 hours for SABA, 12 hours for twice-daily LABA or ICS-LABA, and 24hours for once-daily LABA or ICS-LABA.[206]

Between-visit variability in FEV_1 of >12% and >200mL has high specificity but poor sensitivity for diagnosis of asthma,[208] but it may be more accessible than a bronchial provocation test. Spirometry is effort-dependent, so proper instructions on how to perform the forced expiratory maneuver must be given to patients in order to obtain reproducible results. The highest value of three recordings is taken.

A reduced FEV_1 may be found with many other lung diseases (or with poor spirometric technique), but a reduced ratio of FEV_1 to FVC (FEV_1/FVC) compared with the lower limit of normal indicates expiratory airflow limitation. In respiratory literature, the terms ‘airflow limitation’ and ‘airway obstruction’ are often used interchangeably when lung function test results are being described. Many spirometers now include multi-ethnic age-specific predicted values together with the lower limit of normal.[209] I

Predicted values of FEV_1, FVC, and PEF based on age, sex and height have been obtained from population studies. These are being continually revised, and with the exception of PEF, for which the range of predicted values is too wide, they are useful for judging whether a given value is likely to be ‘abnormal’ or not. Multi-ethnic reference values have recently been published for ages 3–95 years.[209] The normal range of values is wider in young people (younger than 20 years) and in the elderly (older than 70 years).[209]

A ‘normal’ or near-normal FEV_1 in a patient with frequent respiratory symptoms (especially when symptomatic):

Prompts consideration of alternative causes for the symptoms; e.g. cardiac disease, or cough due to post-nasal drip or gastroesophageal reflux disease

In children, FEV_1 may be insensitive for diagnosis of mild obstructive disorders. In a meta-analysis of pediatric data, although isolated lung function measurements were not associated with risk of exacerbations, a decrease in FEV_1 of >10% over a period of 3 months (even within the range of 80% to 120% which is commonly considered as "normal") was associated with an increased risk of subsequent exacerbation.[210]

Peak expiratory flow

PEF measurements are made using a peak flow meter and can be an important aid in both the diagnosis and monitoring of asthma. Modern PEF meters are relatively inexpensive, portable, and ideal for patients to use in home settings for day-to-day measurements of airflow limitation. However, measurements of PEF are not interchangeable with other measurements of lung function such as FEV_1 in either adults or children,[211] and FEV_1 and PEF expressed as a percentage of predicted are not equivalent. PEF can underestimate the degree of airflow limitation, particularly as airflow limitation and gas trapping worsen. Because values for PEF obtained with different peak flow meters vary and the range of predicted values is wide, PEF measurements should be compared to the patient's own previous best ('personal best') measurement[212] using the same peak flow meter. The personal best measurement is usually obtained while patients are asymptomatic or on full treatment, and it serves as a reference value for monitoring the effects of changes in treatment.

Careful instruction is required to reliably measure PEF because PEF measurements are effort-dependent. Most commonly, PEF is measured first thing in the morning before treatment when values are often close to their lowest, and then in the afternoon or evening when values are usually higher. On each occasion, the highest of three PEF measurements should be recorded. Various calculations of PEF variability have been used, including the following:[213]

- For diurnal variability the upper limit of normal with twice-daily PEF measurement is 8% in adults, 9.3% in adolescents, and 12.3% in healthy children. Diurnal variability is calculated as follows: for each day, calculate the diurnal variability as [day's highest PEF minus day's lowest PEF], divided by the mean of these two values; then average these daily variability results over 1 week.[214]
- The minimum morning pre-bronchodilator PEF over 1 week, expressed as a percent of the patient's recent best (Min%Max) is a simple index for clinical practice (Box A4-1).[215]

Which patients should carry out PEF monitoring?

Short-term PEF monitoring

Monitoring of PEF twice daily for 2–4 weeks may be useful in the following contexts:

- To confirm the diagnosis of asthma. Although spirometry is the preferred method of documenting variable expiratory airflow limitation, the following PEF measurements suggest a diagnosis of asthma:
    - Improvement in PEF after inhalation of a bronchodilator by 60 L/min or ≥20% from the pre-bronchodilator value,[216] or
    - Diurnal variation in PEF of >10% from twice daily readings[217] (>20% if calculated from more frequent daily readings).[218]
- To assess response to treatment
- To establish a baseline for management of exacerbations. After starting ICS treatment, personal best PEF (from twice daily readings) is reached on average within 2 weeks.[90] Average PEF continues to increase, and diurnal PEF variability to decrease, for about 3 months.[76,90]

Long-term PEF monitoring

Ongoing monitoring of PEF is valuable in a sub-set of patients:

- To assist in managing the patient's asthma. This is useful for patients who have limited ability to perceive airflow limitation,[205] or for some patients with severe asthma or frequent or sudden exacerbations. For PEF-based written asthma action plans, those based on personal best PEF improve asthma outcomes, whereas those based on predicted PEF do not.[219]

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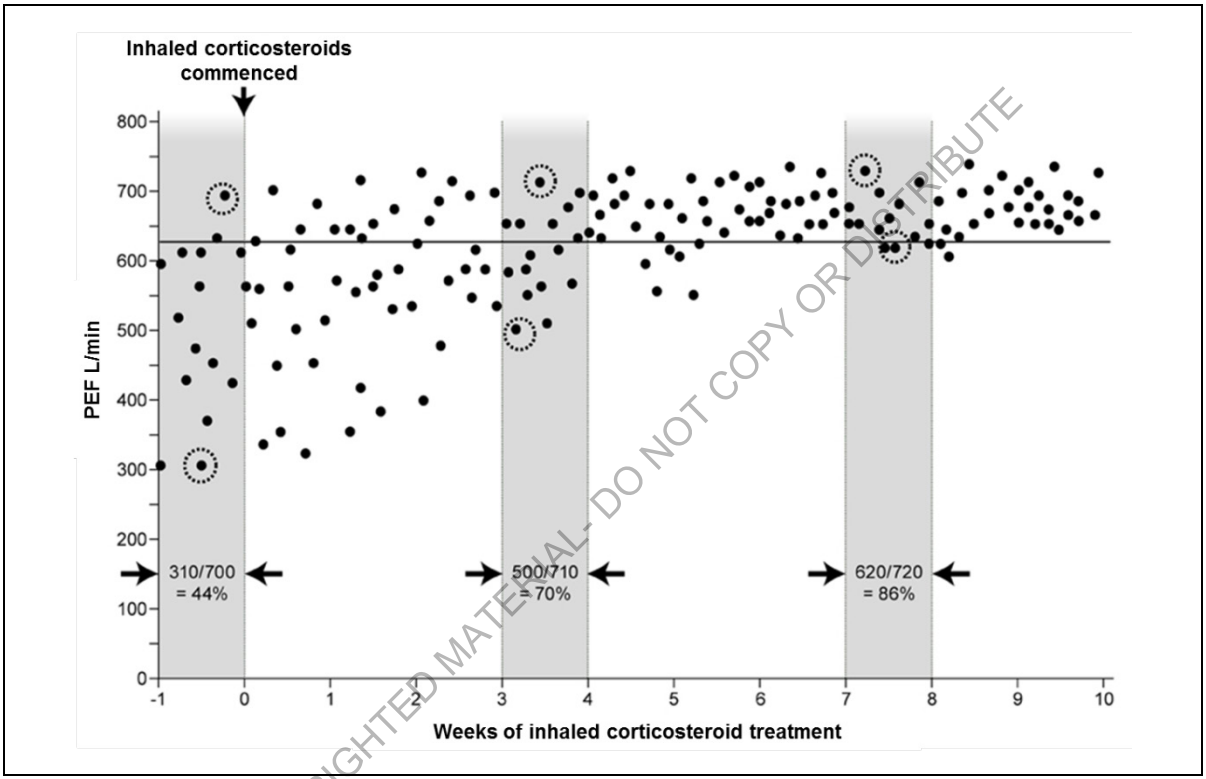
- To identify environmental (including occupational) causes of asthma symptoms: this involves the patient monitoring PEF several times each day over periods of suspected exposure to risk factors in the home or workplace, or during exercise or other activities that may cause symptoms, and also during periods in which they have no exposure to the suspected agent.

Displaying PEF results on a standardized laterally compressed chart (showing 2 months on a landscape format page) may improve the accuracy of identification of exacerbations.[158] A suitable chart is available to download from www.woolcock.org.au/moreinfo/.

Box A4-1. Measuring PEF variability



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The figure shows PEF data of a 27-year old man with long-standing poorly controlled asthma, before and after the start of inhaled corticosteroid treatment. With inhaled corticosteroid treatment, PEF levels increased, and PEF variability decreased, as seen by the increase in Min%Max (lowest morning PEF over 1 week/highest PEF over the same week, %).

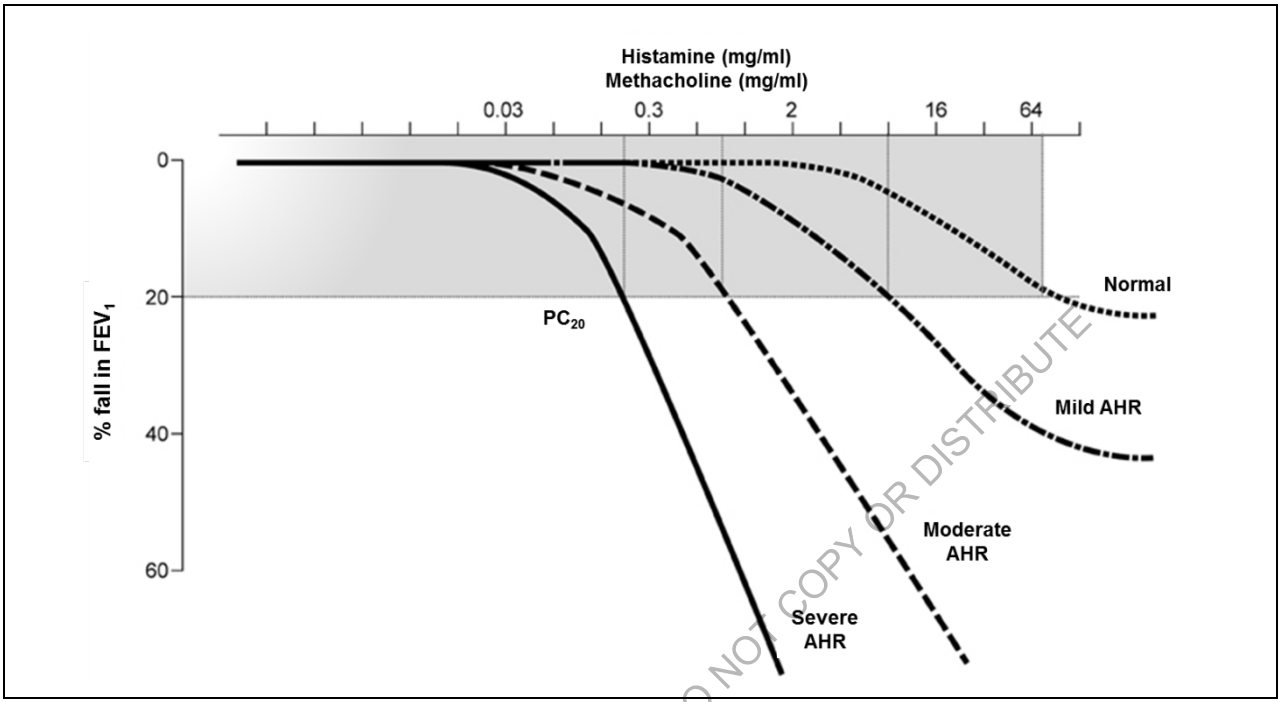
Measurement of airway responsiveness

For patients who have symptoms consistent with asthma but normal lung function, measuring airway responsiveness to direct airway challenges (e.g. inhaled methacholine or histamine) or indirect airway challenges (e.g. inhaled mannitol or an exercise challenge) may help establish a diagnosis of asthma.[220] The test results are usually expressed as the provocative concentration (or dose) of the agonist causing a given fall (often 15% or 20%) in FEV_1 (Box A4-2). Recent guidelines on exercise-induced bronchoconstriction recommend 10% fall in FEV1 as the criterion for a positive exercise challenge; the authors also noted that a criterion of 15% would provide greater specificity.[221]

These tests are sensitive for a diagnosis of asthma but have limited specificity; airway hyperresponsiveness has been described in patients with allergic rhinitis, and in those with airflow limitation caused by conditions other than asthma, such as cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease (COPD).[220] Consequently, a negative

test can be useful to exclude a diagnosis of asthma in a patient who is not taking ICS treatment, but a positive test does not always mean that a patient has asthma.[222]

Box A4-2. Measuring airway responsiveness



This graph shows airway responsiveness to inhaled methacholine or histamine in a healthy subject, and in a person with asthma who has mild, moderate or severe airway hyperresponsiveness. People with asthma have both an increased sensitivity to the agonist (as indicated by FEV_1 falling at a lower concentration of agonist), and an increased maximal bronchoconstrictor response to the agonist (as indicated by a greater fall in FEV_1 at a given concentration), compared with those without asthma. Asthma is also characterized by the loss of the plateau in the response-dose curve that is seen in normal healthy subjects. With direct challenges, the response to the agonist is usually expressed as the provocative concentration or dose of agonist causing a 20% decrease in FEV_1 (PC_{20} and PD_{20} respectively).

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NON-INVASIVE MARKERS OF AIRWAY INFLAMMATION

Sputum analysis

Airway inflammation may be evaluated by examining spontaneously produced or hypertonic saline-induced sputum for eosinophilic or neutrophilic inflammation.[223,224] Sputum analysis does not assist in the diagnosis of asthma, as sputum eosinophilia may also be found in eosinophilic bronchitis, COPD and hypereosinophilic syndromes, and asthma may also have a neutrophilic or mixed inflammatory pattern.[167,224] In the 'future risk' domain of asthma control, sputum eosinophilia is associated with an increased risk of exacerbations during corticosteroid reduction or cessation.[225-227] In clinical trials in patients most of whom had moderate to severe asthma, exacerbations were reduced when treatment was guided by sputum eosinophil percentage.[228] However, this test is generally only available in specialized centers, and careful standardization and training of staff for both sputum induction and cell counting are required for reliable results.[224] There are insufficient data available in children to assess this approach.[229]

Fractional concentration of exhaled nitric oxide

Diagnosis of asthma

Measurement of fractional concentration of exhaled nitric oxide is becoming more widely available. There is a modest association between blood and sputum eosinophils and FeNO in asthma patients[230] and the relationship may vary over time.[231,232] FeNO is usually elevated in non-smokers with eosinophilic asthma who are not taking ICS, and in many patients with asthma who are taking ICS. Elevated FeNO may also be found in conditions such as allergic rhinitis, eosinophilic bronchitis and hypersensitivity pneumonitis,[233] making it important to consider the context and differential diagnosis when an elevated FeNO is found. There is ethnic variability in FeNO levels, particularly in children.[234] Unlike sputum eosinophilia, elevated FeNO is generally not predictive of asthma exacerbations during ICS reduction or cessation.[233]

Assessment of need for ICS?

In studies mainly limited to non-smoking patients, FeNO >50 parts per billion (ppb) has been associated with a good short-term response to ICS.[233,235] However, these studies did not examine the longer-term risk of exacerbations. Such evidence therefore does not mean that it is safe with regard to exacerbations to withhold ICS in patients with low initial FeNO. More recently, in two 12-month studies in mild asthma, severe exacerbations were reduced with as-needed ICS-formoterol versus as-needed SABA and versus maintenance ICS, independent of baseline inflammatory characteristics including FeNO.[236,237]

Consequently, in patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS, but cannot be used to decide against treatment with ICS. Based on past and current evidence, GINA recommends treatment with daily low-dose ICS or as-needed low dose ICS-formoterol for all patients with mild asthma, to reduce the risk of serious exacerbations.[238]

FeNO-guided ICS dose-titration studies

In children and young adults with asthma, FeNO-guided treatment was associated with a significant reduction in the number of patients with ≥1 exacerbation (OR 0.67 [95% CI 0.51-0.90]) and in exacerbation rate (mean difference -0.27 [-0.49- -0.06] per year) compared with guidelines-based treatment (Evidence A); similar differences were seen in comparisons with non-guidelines-based algorithms.[239] However, in non-smoking adults with asthma, no significant reduction was seen in the risk of exacerbations, or in exacerbation rates, with FeNO-guided treatment compared with guidelines-based treatment.[240] In several studies of FeNO-guided treatment, problems with the design of the intervention and/or control algorithms make comparisons and conclusions difficult.[241] Results of FeNO measurement at a single point in time should be interpreted with caution.[233,242]

At present, neither sputum- nor FeNO-guided treatment is recommended for the general asthma population. Sputum-guided treatment is recommended for adult patients with moderate or severe asthma who are managed in centers experienced in this technique[243] (Evidence A). However, further studies are needed to identify the populations most likely to benefit from sputum-guided or FeNO-guided treatment,[239,240] and the optimal frequency of FeNO monitoring.

Measurements of allergic status

The presence of atopy or allergic disease such as eczema or allergic rhinitis increases the probability of a diagnosis of allergic asthma in patients with respiratory symptoms. The identification of specific allergic reactions by skin prick testing or measurement of a specific immunoglobulin E (IgE) in serum can help identify the factors responsible for triggering asthma symptoms in individual patients.

Allergy skin prick tests are the primary diagnostic tool for determining a patient's atopic status. They are simple and rapid to perform, and have a low cost and high sensitivity. Optimal results are dependent on the use of standardized allergen extracts and on the skill of the tester.[244] The choice of the allergen panel will depend on the local context.

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Measurement of allergen-specific IgE in serum is more expensive and generally less sensitive than skin prick testing for identifying sensitization to inhaled allergens.[244] Measurement of total IgE in serum has no value as a diagnostic test for atopy, and a normal total IgE does not exclude clinical allergy.[244]

Provocation of the airways with a suspected allergen or sensitizing agent may be helpful in the setting of occupational asthma but is not routinely recommended; it is rarely useful in establishing a diagnosis, requires considerable expertise, and can result in life-threatening bronchospasm.[244]

In patients with respiratory symptoms, the main limitation of allergy testing is that a positive test does not necessarily mean that the disease is allergic in nature or that allergy is causing the patient's asthma. The relevant exposure and its relationship to the patient's asthma symptoms must be confirmed by the patient's history.

TELEHEALTHCARE

Telehealthcare has been defined as "the provision of personalized healthcare over a distance" with the stipulation that it comprises of three essential components:[245]

- The patient/carer providing data such as the recording of asthma symptoms, peak flow readings or medication adherence;
- These data being transmitted electronically, whether synchronously or asynchronously, to a healthcare provider who is at some other location; and
- The healthcare provider then providing personalized feedback that is tailored to the individual.

Using the above definition, telehealthcare can be considered to encompass an array of technologies, ranging from a telephone call to short message service (SMS) to video-conferencing to smart peak expiratory flow meters or inhalers, which connect patients/carers with providers. Telehealthcare is distinct from telemedicine, which is defined as connecting healthcare providers to each other (e.g. primary care physician to respiratory physician).

There is increasing policy interest in telehealthcare as it offers the potential for continuous monitoring (as opposed to the current mainly episodic model of care) and the opportunity for patient-centered delivery of care at home or in an alternative location of the patient's choosing.[246] In the context of asthma, telehealthcare also offers the opportunity to support medication adherence, facilitate earlier detection of loss of asthma control and prevent asthma exacerbations.[247] However, its implementation and utility are subject to problems such as access and socio-economic disadvantage.[248]

There is a growing body of work investigating the effectiveness of telehealthcare interventions, particularly in the context of managing long-term conditions.[249] Much of this work is of relatively poor methodological quality with inconsistent evidence of impact on clinical or health economic outcomes. The available evidence suggests that simple telephone-based approaches are likely to confer as much benefit as more elaborate remote monitoring-based approaches, and that these benefits are most likely to be seen in those with moderate-to-severe disease.[249]

Focusing on asthma, there is evidence that telehealthcare-based approaches can increase the proportion of patients who are reviewed[250] or receive an action plan,[251] and can improve adherence,[252] but there is no consistent evidence that these lead to improvement in clinical outcomes such as reduction in symptoms or improvements in asthma-specific quality of life.[250] There is however some evidence from studies, at moderate-to-high risk of bias, that rates of hospitalization may be reduced over a 12-month period.[252] There is very little available evidence on the risks of telehealthcare or the cost-effectiveness of this approach in the context of managing patients with asthma.[253]

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Chapter 5.
Asthma pharmacotherapy

PART A. ASTHMA PHARMACOTHERAPY - ADULTS AND ADOLESCENTS

ROUTE OF ADMINISTRATION

Inhaled administration delivers drugs directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects. Inhaled medications for asthma are available as pressurized metered-dose inhalers (pMDIs), breath-actuated pMDIs, dry powder inhalers (DPIs), soft mist inhalers, and nebulized or "wet" aerosols. Inhaler devices differ in their efficiency of drug delivery to the lower respiratory tract, depending on the form of the device, formulation of medication, particle size, velocity of the aerosol cloud or plume (where applicable), and ease with which the device can be used by the majority of patients. Individual patient preference, convenience, and ease of use may influence not only the efficiency of drug delivery but also patient adherence to treatment. Problems with incorrect inhaler technique are common in community-based studies, regardless of the device, and are associated with worse asthma control. [254]

Pressurized MDIs (pMDIs) require training and skill to coordinate activation of the inhaler and inhalation. In the past, medications in pMDIs were dispensed as suspensions in chlorofluorocarbon propellants (CFCs), but most are now dispensed with hydrofluoroalkane (HFAs) propellant, either as suspensions or as solutions in ethanol. The aerosol plume of HFA inhalers is generally softer and warmer than that of CFC products.[255] For some corticosteroids, the particle size for HFA aerosols is smaller than for the corresponding CFC product, resulting in less oral deposition (with associated reduction in oral side effects), and greater lung deposition.[255] There are theoretical reasons why smaller particle ICS could be more effective than larger particle ICS, but methodologic issues with the available studies preclude a clear answer. A real-world study reported fewer exacerbations with extra-fine vs fine-particle ICS,[256] but the analysis was not adjusted for clustering or for physician characteristics that could have influenced not only the choice of ICS but also other management decisions relevant to exacerbation outcomes. A meta-analysis found no high-quality evidence of clinical benefit with fine vs standard particle size ICS.[257]

Pressurized MDIs may be used by patients with asthma of any severity, including during exacerbations. However, patients require training and skill to coordinate activation of the inhaler and inhalation, and this is often easier with use of a valved spacer. Breath-actuated aerosols may be helpful for patients who have difficulty using conventional pMDIs.[255] Dry powder inhalers are generally easier to use than pMDIs, but sufficient inspiratory flow (which varies between different DPI devices) is required to disaggregate the powder, and this may prove difficult for some patients to generate. DPIs differ with respect to the fraction of ex-actuator dose delivered to the lung. For some drugs, the dose may need to be adjusted when switching between different types of devices. Nebulized aerosols are rarely indicated for the treatment of chronic asthma in adults.[258]

Some inhaler devices and techniques for their use are illustrated on the GINA website (www.ginasthma.org) and the ADMIT website (www.inhalers4u.org/).

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CONTROLLER MEDICATIONS

Inhaled corticosteroids

Role in therapy

ICS are the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies have demonstrated their efficacy in reducing asthma symptoms, improving quality of life, improving lung function, reducing the frequency and severity of exacerbations and reducing asthma mortality,[259-265] as well as decreasing airway

hyperresponsiveness[260,266] and controlling airway inflammation.[267] However, they do not cure asthma, and when they are discontinued approximately 25% of patients experience an exacerbation within 6 months.[268] Patients not receiving ICS appear to be at increased risk of airway remodeling and loss of lung function.[269,270]

ICS differ in their potency and bioavailability,[271] but because of relatively flat dose-response relationships in asthma relatively few studies have been able to confirm the clinical relevance of these differences.[272]

Box A5-1 lists 'low', 'medium' and 'high' doses of different ICS. It is not a table of equivalence, but represents suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options. The efficacy of some products varies when administered via different inhaler devices.[273] Doses may be country-specific depending on labelling requirements.

Box A5-1. Low, medium and high daily doses of inhaled corticosteroids for adults and adolescents

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options for adults/adolescents, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Adults and adolescents (12 years and older)

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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Most of the clinical benefit from ICS is seen at low doses, and clear evidence of dose-response relationships is seldom available within the dose ranges evaluated for regulatory purposes. 'High' doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects.

For new preparations, including generic ICS, the manufacturer's information should be reviewed carefully; products containing the same molecule may not be clinically equivalent. For more detailed discussion see Raissy et al.[271]

Most of the benefit from ICS is achieved in adults at relatively low doses, equivalent to 400 mcg of budesonide per day.[274] *Post-hoc* analysis of a large 3-year randomized controlled trial in patients with mild recent-onset asthma[264] showed that the risk of serious exacerbations was halved with low dose ICS even in patients with infrequent symptoms at entry (0-1 days/week).[275] Increasing to higher doses provides little further benefit in terms of asthma control but increases the risk of side effects.[274,276] However, there is marked individual variability of responsiveness to ICS, at least partly due to heterogeneity of airway inflammation. Because of this and the recognized poor adherence to treatment with ICS, some patients will require higher ICS doses to achieve full therapeutic benefit.[21] Tobacco smoking reduces the responsiveness to ICS, so higher doses may be required in patients who smoke.[115]

For patients whose asthma is not well-controlled on ICS alone, despite good adherence and correct inhaler technique, add-on therapy with a long-acting beta$_2$-agonist (LABA, see below) is preferred over increasing the dose of ICS.[21,261,277,278] For maintenance treatment, there is a relationship between the dose of ICS and the prevention of severe exacerbations of asthma,[261] although there may be differences in response according to clinical or inflammatory phenotype.[279] Therefore, some patients with severe asthma may benefit from long-term treatment with higher doses of ICS.

Adherence with ICS in the community is very poor, exposing the patient to the risks of SABA-only treatment. The likelihood of good adherence should be checked before prescribing ICS with as-needed SABA.

Adverse effects

Local adverse effects from ICS include oropharyngeal candidiasis, dysphonia, and (occasionally) coughing from upper airway irritation.[280] For pressurized MDIs the prevalence of these effects may be reduced by using a spacer device.[281] Mouth washing (rinsing with water, gargling, and spitting out) after inhalation may reduce oral candidiasis.[281] The use of pro-drugs that are activated in the lungs but not in the pharynx (e.g. ciclesonide and HFA beclometasone) and new formulations and devices that reduce oropharyngeal deposition may reduce such effects. The use of ICS may be associated with periodontal disease, but effects may be confounded by comorbidities, asthma severity, and use of (highly acidic) salbutamol.[282] There is also a strong association between periodontal disease and emergency department visits and hospitalizations for asthma.[282]

ICS are absorbed from the lung, accounting for some degree of systemic bioavailability. The risk of systemic adverse effects from an ICS depends upon its dose and potency, the delivery system, systemic bioavailability, first-pass metabolism (conversion to inactive metabolites) in the liver, and the half-life of the fraction of systemically absorbed drug (from the lung and possibly gut).[271] Therefore, the systemic effects differ among the various ICS. Evidence suggests that in adults, systemic effects of ICS are not a problem at doses of 400 mcg or less of budesonide or equivalent daily.[283]

Use of a questionnaire for patient-reported symptoms provides evidence of many more, predominantly mild, dose-dependent effects of ICS use,[204,205] underlining the need to step down treatment to the lowest dose that maintains good symptom control and prevents exacerbations.[284-286]

The systemic side effects of long-term treatment with high doses of inhaled corticosteroids include easy bruising,[287] adrenal suppression[288-290] and decreased bone mineral density.[291] A meta-analysis indicated that, among patients with asthma, adrenal insufficiency was less common after use of ICS (6.8% of patients) than oral and other forms of corticosteroids (43.7% of patients). For ICS, the proportion of patients with adrenal insufficiency was higher with increasing dose (1.5% for low, 5.4% for medium, 18.5% for high dose) and with increasing duration (1.3% for short, 9.0% for medium and 20.3% for long duration treatment).[292] The threshold to test corticosteroid users for adrenal insufficiency should be low in clinical practice, especially for patients with nonspecific symptoms after cessation of corticosteroid treatment.[292] A meta-analysis of case-control studies of non-vertebral fractures in adults using ICS indicated that in older adults, the relative risk of non-vertebral fractures increased by about 12% for each 1000 mcg/day (BDP equivalent) increase in the dose, but that the magnitude of this risk was considerably less than other common risk factors for fracture in the older adult.[293] ICS have also been associated with cataracts in cross-sectional studies, [294-296] but there is no evidence of posterior-subcapsular cataracts in prospective studies.[297,298] Even at high doses, ICS do not appear to increase the risk of glaucoma.[295,299] One difficulty in establishing the clinical significance of such adverse

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effects lies in dissociating the effect of high dose ICS from the effect of courses of oral corticosteroids taken by patients with severe asthma.

Exposure to high doses of ICS may increase the risk of tuberculosis, particularly in regions with high prevalence of tuberculosis.[300,301] However ICS are not contraindicated in patients with active tuberculosis.[302] A recent case control study found that people with asthma using ICS have an increased risk of pneumonia or lower respiratory infection when compared with asthmatics who did not have a prescription for an ICS in the last three months.[303] The risk is greater at higher ICS doses, and may vary between different ICS.[303] In a meta-analysis of clinical trials, the risk of adverse or serious adverse events reported as pneumonia for people with asthma receiving budesonide was not increased compared with placebo.[304] A meta-analysis found no significant difference in the risk of pneumonia between children receiving ICS and placebo.[305]

ICS-LABA combinations

Role in therapy – Steps 1 and 2

Low dose ICS-formoterol, used as needed for symptom relief, is a preferred controller treatment in mild asthma. A large double-blind study in mild asthma found a 64% reduction in severe exacerbations compared with SABA-only treatment,[306] with a similar finding in an open-label study in patients with mild asthma previously taking SABA alone.[236] (Evidence A). Two large double-blind studies in mild asthma showed as-needed budesonide-formoterol was non-inferior for severe exacerbations compared with regular ICS.[306,307] In two open-label randomized controlled trials, representing the way that patients with mild asthma would use as-needed ICS-formoterol in real life, as-needed budesonide-formoterol was superior to maintenance ICS in reducing the risk of severe exacerbations[236,237] (Evidence A). In all four studies, the as-needed ICS-formoterol strategy was associated with a substantially lower average ICS dose than with maintenance low dose ICS. The existing data for as-needed ICS-formoterol are with budesonide-formoterol, but beclometasone-formoterol should be able to be used in a similar way, as its efficacy in maintenance and reliever therapy has been established.[308] The safety of as-needed ICS-formoterol has been well established in studies of maintenance and reliever therapy [309,310], and no new safety issues emerged during the recent studies in mild asthma.[236,237,306,307]

Role in therapy – Steps 3-5

In patients prescribed regular maintenance ICS, when a low dose of ICS alone fails to achieve good control of asthma, addition of LABA is the preferred option, preferably as a combination ICS-LABA inhaler. The addition of LABA to ICS improves clinical asthma outcomes and reduces the number of exacerbations in patients ≥12 years old.[261,311-320] In very large studies in adults and adolescents, severe exacerbations were reduced by 17-21% with maintenance ICS-LABA combination vs the same dose of ICS, but differences in symptom control and SABA use were small.[278,318,319]

Controlled studies have shown that delivering ICS and LABA in a combination inhaler is as effective as giving each drug separately.[321] Fixed combination inhalers are more convenient for patients, may increase adherence compared with using separate inhalers,[322] and ensure that the LABA is always accompanied by ICS. Severe exacerbations requiring hospitalization are more common in patients prescribed separate ICS and LABA inhalers than in those receiving combination ICS-LABA, likely because of differential adherence.[323]

Low dose combination inhalers containing the rapid-acting beta$_2$-agonist formoterol with either budesonide or beclometasone may be used for both **maintenance and reliever therapy**,[308,324,325] to further reduce the risk of exacerbations in at-risk adult and adolescent patients. When budesonide-formoterol was used as the reliever medication by patients receiving maintenance budesonide-formoterol, both components contributed to enhanced protection from severe exacerbations compared with SABA as reliever.[326] In patients with a history of one or more severe exacerbations in the previous year, this strategy provides a reduction in exacerbations and similar improvements in asthma control at relatively low doses of ICS compared with conventional maintenance therapy with ICS or ICS-LABA.[324] In open-label studies without a requirement for a history of exacerbations, maintenance and reliever therapy was associated with a similar risk of exacerbations as maintenance ICS-LABA plus as-needed SABA, with a lower average ICS dose.[327]

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A study by Papi et al supports maintenance ICS-LABA, rather than as-needed ICS-formoterol alone (without maintenance therapy) in Step 3.[328] In this study, patients with asthma were eligible if their asthma was either not controlled by low dose ICS (≤500 mcg BDP/day or equivalent) or if their asthma was controlled by twice-daily maintenance low-dose ICS+LABA over the previous 2 months. Study participants then entered a 6-week run-in period, during which they received twice daily open-label combination inhaled budesonide-formoterol 200/6 mcg plus as-needed inhaled 500 mcg terbutaline. Participants whose asthma was controlled during the final 14 days of the run-in were randomly allocated to receive either as-needed budesonide-formoterol 200/6 mcg or twice-daily budesonide-formoterol 200/6 mcg. The study found that as-needed ICS-formoterol was inferior to twice-daily ICS-formoterol when assessed by a composite endpoint of treatment failure. Nearly all of this difference was driven by lower risk of ≥2 nocturnal awakenings on 2 consecutive days (10% v 21%) with twice-daily therapy. Exacerbations requiring systemic corticosteroids or ICS for asthma worsening were not different between groups (13 vs. 14%).[328]

Currently approved combination ICS-LABA inhalers for maintenance treatment in asthma at Steps 3–5 include:

- Beclometasone-formoterol
- Budesonide-formoterol
- Fluticasone furoate-vilanterol trifenoate (once daily)
- Fluticasone propionate-formoterol.
- Fluticasone propionate-salmeterol
- Mometasone-formoterol.

Currently approved low dose combination ICS-LABA inhalers for maintenance and reliever treatment in asthma include:

- Beclometasone-formoterol
- Budesonide-formoterol.

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Earlier studies showed that LABAs may provide longer protection for exercise-induced bronchoconstriction than SABAs, but the duration of effect wanes with long-term use in adults[329] and adolescents.[330] Salmeterol and formoterol provide a similar duration of bronchodilation and protection against bronchoconstrictor agents, but there are pharmacological differences between them: formoterol has a more rapid onset of action than salmeterol[331,332] which may make formoterol suitable for symptom relief as well as symptom prevention.[333] However, LABAs including formoterol and salmeterol, are indicated in asthma only when given in addition to ICS, preferably in a combination inhaler. For pre-exercise use in patients with mild asthma, a 6-week study showed that use of low dose budesonide-formoterol for symptom relief and before exercise reduced exercise-induced bronchoconstriction to a similar extent as regular daily low dose ICS with SABA for symptom relief and before exercise.[334] This suggests that patients with mild asthma who are prescribed as-needed ICS-formoterol do not need to also be prescribed a SABA puffer for pre-exercise use.

Based on product information, the maximum recommended dose of ICS-formoterol in a single day is a total of 48 mcg formoterol for beclometasone-formoterol (total 8 inhalations of 100/6 mcg beclometasone-formoterol), and 72 mcg formoterol for budesonide-formoterol (total 12 inhalations of 200/6 budesonide-formoterol by Turbuhaler). However, in the randomized controlled trials in mild asthma, such high usage was rarely seen, and average use of as-needed ICS-formoterol was around 3-4 doses per week.[236,237,306,307]

Adverse effects

Adverse effects of ICS are described on p.35. Therapy with LABAs may be associated with headache or cramps, but systemic adverse effects such as cardiovascular stimulation, skeletal muscle tremor, and hypokalemia, are less common than with oral beta-agonist therapy. The regular use of $beta_2$-agonists in both short- and long-acting forms may lead to relative refractoriness to $beta_2$-agonists.[335] Based on data indicating a possible increased risk of asthma-related death associated with the use of salmeterol in a small number of individuals,[336] and increased risk of exacerbations when LABA is used regularly as monotherapy,[337] LABAs should never be used as a substitute for inhaled or oral corticosteroids, and should only be used in combination with an appropriate dose of ICS as determined by a physician, preferably in a single inhaler.[338,339] In the past there had been concerns that using LABA alone or in combination with

ICS might increase asthma mortality.[340,341] However, large randomized controlled trials with ICS-LABA combination maintenance treatment showed no inferiority to ICS alone for serious adverse events (death, intubation and hospitalization due to asthma).[278,318-320] Based on these studies[278,318-320], systematic reviews of randomized controlled trials[338,339] and observational studies,[342] LABA is considered safe when used in combination with ICS.[343].

No influence of beta$_2$-adrenergic receptor phenotypes upon the efficacy or safety of ICS-LABA therapy has been observed in adults whether by the single inhaler for maintenance and reliever regimen or at a regular fixed dose.[344,345]

Leukotriene modifiers

Role in therapy

Leukotriene modifiers include cysteinyl-leukotriene 1 (CysLT1) receptor antagonists (LTRA) (montelukast, pranlukast, and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). Clinical studies have demonstrated that leukotriene modifiers have a small and variable bronchodilator effect, reduce symptoms including cough,[346] improve lung function, and reduce airway inflammation and asthma exacerbations.[347] They may be used as an alternative treatment for adult patients with mild persistent asthma,[348-350] and some patients with aspirin-sensitive asthma respond well to leukotriene modifiers.[351] However, when used alone as controller therapy, the effect of leukotriene modifiers are generally less than that of low doses of ICS, and, in patients already on ICS, leukotriene modifiers cannot substitute for this treatment without risking the loss of asthma control.[352]

Leukotriene modifiers used as add-on therapy may reduce the dose of ICS required by patients with moderate to severe asthma.[353] For patients with persistent asthma and with suboptimal asthma control with daily use of ICS, the addition of anti-leukotrienes is beneficial for reducing moderate and severe asthma exacerbations and for improving lung function and asthma control compared with the same dose of ICS.[354] However, leukotriene modifiers are less effective than LABA as add-on therapy.[355]

Adverse effects

Leukotriene modifiers are well tolerated, and few if any class-related effects have so far been recognized. Zileuton has been associated with liver toxicity[356] and monitoring of liver tests is recommended during treatment with this medication. Prescribing information for the use of zileuton should be consulted. No association has been found between Churg-Strauss syndrome and the use of leukotriene modifiers after controlling for asthma drug use, although it is not possible to rule out an association given that Churg-Strauss syndrome is very rare and highly correlated with asthma severity.[357] Post-marketing surveillance reports have led to concerns about a possible association between leukotriene receptor antagonist use and suicide risk in young adults, but a case-control study found no association after adjustment for potential confounding factors.[358] Patients should be counselled about the risk of neuropsychiatric events with montelukast and health professionals should consider the benefits and risks of mental health side effects before prescribing. (ref https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug).

Chromones: sodium cromoglycate and nedocromil sodium

Role in therapy

The role of sodium cromoglycate and nedocromil sodium in long-term treatment of asthma in adults is limited. Their anti-inflammatory effect is weak and they are less effective than low-dose ICS.[359] Meticulous daily cleaning of the inhalers is required to avoid blockage.

Adverse effects

Side effects are uncommon and include cough upon inhalation and pharyngeal discomfort. Some patients find the taste of nedocromil sodium unpleasant.

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ADD-ON CONTROLLER MEDICATIONS

Long-acting anticholinergics (also called long-acting antimuscarinics, LAMA)

Role in therapy

The long-acting anticholinergic, tiotropium has been studied in adolescents and adults with uncontrolled asthma in a variety of contexts: added to ICS compared with doubling the dose of ICS or adding salmeterol,[360] and added to ICS[361] or to ICS-LABA with or without other controllers[362,363] compared with adding placebo[362,363].[364] Comparable bronchodilator effects to salmeterol have been shown in patients with the B16-Arg/Arg genotype, with no significant changes in asthma control.[365] In an open-label genotype-stratified study comparing the addition of LABA or tiotropium in African American patients receiving ICS, no differences were seen in time to first asthma exacerbation or measures of asthma control regardless of B16 genotype.[345] A Phase II study showed that adding tiotropium to patients with asthma not well-controlled on ICS and LABA improved lung function but not symptoms.[362] Two large one-year replicate trials in patients with at least one severe exacerbation in the previous year confirmed improvements in lung function, and also showed a 21% reduction in the risk of a severe exacerbation and 31% reduction in risk of asthma worsening, but inconsistent improvement were seen in symptom control and quality of life.[363] Direct evidence of LAMA versus LABA as add-on therapy to low dose ICS for Step 3 or medium dose ICS for Step 4 is currently limited to studies of less than six months' duration comparing tiotropium (Respimat) to salmeterol. Given the much larger evidence base for adding LABA vs placebo when asthma is not well-controlled on ICS alone, the current evidence is not strong enough to say that LAMA can be substituted for LABA as add-on therapy; but it may be an alternative option in patients with LABA side-effects.[366,367]

Adverse effects

The safety of tiotropium in these studies, with all patients also taking ICS, was similar to that of salmeterol.[360,362,363] Dry mouth, a characteristic side effect of this class of medication, was reported by fewer than 2% of the patients. There are no published long-term data (>1 year) on tiotropium safety in asthma.

Anti-IgE

Role in therapy

Anti-immunoglobulin E (anti-IgE, omalizumab) is a treatment option for patients aged ≥6 years with severe persistent allergic asthma, with typical criteria including that asthma is uncontrolled on treatment with corticosteroids (moderate/high dose inhaled and/or oral) and LABA.[368,369] The dose of omalizumab is based on serum IgE and patient weight, with the criteria for dose and eligibility varying between regulatory authorities.

Anti-IgE therapy is expensive and requires regular subcutaneous injections every 2-4 weeks, and observation after each injection. Therefore, it should only be considered when common causes of uncontrolled asthma, including incorrect inhaler technique and poor adherence, have been checked and addressed, and the contribution of comorbidities and modifiable risk factors to respiratory symptoms and exacerbations has been identified and minimized. For more details, see GINA Pocket Guide on Difficult-to-Treat and Severe Asthma in Adults and Adolescents.[197]

Asthma outcomes

Patients may benefit by having fewer exacerbations and need for lower doses of OCS, with modest improvement in quality of life and in asthma symptom control as reflected by fewer symptoms and less need for reliever medications.[368] The efficacy of omalizumab is supported by evidence from many real-life studies.[370] A meta-analysis of treatment outcomes in 25 uncontrolled non-randomized real-life studies examined outcomes at 4-6, 12 and 24 months of treatment in patients who were symptomatic on ICS plus LABA. Despite marked heterogeneity of patients and clinical sites, the analysis found improvements in symptom control (ACQ), quality of life (AQLQ), lung function, exacerbations and hospitalizations, reductions in doses of ICS, and overall assessment of benefit (Global Evaluation of Treatment

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Effectiveness score).[370] A long-term prospective cohort study showed improvements in symptom control and work, school and activity impairment over 5 years.[371]

In one study, the reduction in severe exacerbations with omalizumab compared with placebo was greatest in patients with higher baseline blood eosinophil levels (≥260 eosinophils/μL), higher baseline FeNO (≥24 ppb), or higher baseline periostin level (≥53 ng/mL) while taking high dose ICS.[372,373] If a patient does not respond clinically within 4 months of initiating treatment, it is considered unlikely that further administration of omalizumab will be beneficial.[243] Of patients with a good clinical response to omalizumab, about half relapse if it is discontinued, at a median of 13 months after discontinuation.[374] One placebo-controlled withdrawal study suggested that a high blood eosinophil count prior to omalizumab withdrawal or an increase in FeNO at 12 weeks after withdrawal may be associated with greater risk of post-withdrawal exacerbation.[375] Studies are needed to evaluate stretching the interval between doses.

Other outcomes

Nasal polyposis is not a specific indication for therapy with omalizumab, but patients with severe allergic asthma with concomitant chronic rhinosinusitis with nasal polyposis (CRSwNP) demonstrated a moderate improvement in nasal polyp score with add-on treatment with omalizumab.[376]

In one study in children and adolescents, add-on omalizumab started 4-6 weeks prior to return to school was associated with fewer fall-time exacerbations than with add-on placebo; there was no difference between omalizumab and ICS boost.[377,378] Analysis demonstrated a reduction in the duration and peak level of viral shedding during rhinoviral infection, and had a modest impact on frequency and severity of rhinovurus illnesses.[98]

Adverse effects

Anti-IgE appears to be safe as add-on therapy,[368] including in inner-city children generally considered to be at high risk for exacerbations.[379] Injection site reactions are more common with omalizumab than placebo.[368] In a systematic review and meta-analysis of 12 studies, there was no significant increase in risk of malignancy with omalizumab treatment.[380] Monitoring of patients receiving omalizumab showed no significant difference in cardiovascular or cerebrovascular events over 5 years compared with patients not receiving omalizumab, after adjustment for known confounding factors including OCS use.[381] Withdrawal of corticosteroids facilitated by anti-IgE therapy has led to unmasking the presence of Churg-Strauss syndrome in a small number of case reports.[382] Clinicians should be aware of the potential for this to occur and monitor patients closely.

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Anti-IL5/5R treatments

Role in therapy

Interleukin 5 (IL-5) is a Type 2 cytokine that is required for eosinophil maturation and survival. Antibody therapies directed at IL-5 or its receptor are a treatment option for patients with severe eosinophilic asthma whose asthma is uncontrolled on treatment with corticosteroids (moderate/high dose inhaled +/- oral) and LABA (or another controller). Three therapies have been approved by one or more major regulators for patients with severe eosinophilic asthma: mepolizumab and reslizumab, which are monoclonal anti-IL5 antibodies, and benralizumab, which is a monoclonal anti-IL5 receptor α antibody.

These medications are expensive, so they should only be considered when common causes of uncontrolled asthma, including incorrect inhaler technique and poor adherence, have been checked and addressed, and the contribution of comorbidities and modifiable risk factors to respiratory symptoms and exacerbations has been identified and minimized. There is debate over the optimal blood eosinophil criterion for patient selection. This report does not state specific criteria for eligibility for biologic therapies, as these vary between countries and jurisdictions. For more details, see GINA Pocket Guide on Difficult-to-Treat and Severe Asthma in Adults and Adolescents.[197]

Asthma outcomes

Mepolizumab: for patients aged ≥12 years, administered monthly (100 mg) by subcutaneous injection. In clinical trials of patients with severe eosinophilic asthma and two or more severe exacerbations in the previous year, mepolizumab reduced exacerbations by ~55% compared with placebo.[383,384] The reduction in exacerbations was greater with increasing baseline blood eosinophil count and increasing number of exacerbations in the previous year; no significant reduction in exacerbations was seen with baseline blood eosinophils <150/μL.[385] Modest improvements were seen in lung function and asthma symptom control.[383,384] In patients requiring maintenance OCS, mepolizumab allowed a reduction in median OCS dose by ~50% compared with placebo, with reduced exacerbations and improved symptom control.[160]

Reslizumab: for patients aged ≥18 years, administered monthly (3 mg/kg body weight) by intravenous infusion. In clinical trials of patients with uncontrolled asthma symptoms despite moderate-high dose ICS, at least one severe exacerbation in the previous year, and baseline blood eosinophils of ≥400/μL, reslizumab led to ~50% reduction in moderate or severe exacerbations compared with placebo, with a modest improvement in lung function and small improvement in symptom control.[386] Reslizumab produced greater reductions in asthma exacerbations and larger improvements in lung function in patients with late versus early-onset asthma.[387]

Benralizumab: for patients aged ≥12 years, administered 8-weekly (30mg, first 3 doses 4-weekly) by subcutaneous injection. In clinical trials of patients with severe eosinophilic asthma, with blood eosinophils ≥300/μL in the previous 12 months while taking high dose ICS+LABA, and ≥2 severe exacerbations in the previous year, benralizumab reduced exacerbations by ~35-50% and improved lung function, compared with placebo.[388] Modest improvements in asthma symptoms were seen in some groups.[388] In patients requiring maintenance oral corticosteroids, benralizumab allowed a significant reduction in OCS dose compared with placebo, while also reducing exacerbations.[161] In patients with mild to moderate persistent asthma receiving low/medium dose ICS or low dose ICS-LABA, there was no clinically-important benefit for pre-bronchodilator FEV_1 with add-on benralizumab over 12 weeks compared with placebo.[389]

Other outcomes

Nasal polyposis is not a specific indication for therapy with anti-IL5/5R, but patients with severe allergic asthma with concomitant chronic rhinosinusitis with nasal polyposis (CRSwNP) demonstrated a moderate improvement in nasal polyp score with add-on treatment with reslizumab or high dose mepolizumab.[376]

Adverse effects

Adverse effects are infrequent; they include injection site reactions for mepolizumab, myalgia with reslizumab and headache with benralizumab. Anaphylactic reactions have been rare with these therapies. A small number of cases of herpes zoster have been reported in patients receiving mepolizumab. Patients with known parasitic infections were excluded from clinical trials of these therapies; at-risk patients should be screened for parasitic infections and, if found, treated before commencing therapy aimed at reducing eosinophils. Safety extension studies with mepolizumab[390] and with benralizumab[391] have found no adverse consequences of long-term eosinophil depletion, nor evidence of increased risk of opportunistic infections.

Anti-IL4 receptor α

Role in therapy

Dupilumab binds to interleukin-4 (IL-4) receptor alpha, blocking both IL-4 and IL-13 signaling. It is a treatment option for patients aged ≥12 years with severe eosinophilic asthma whose asthma is uncontrolled on treatment with moderate-high dose ICS and LABA, and for patients requiring maintenance OCS therapy for severe asthma. It is also indicated for treatment of moderate-severe atopic dermatitis.[392]

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Dupilumab is currently approved for ages ≥12 years, as 200mg or 300mg administered by SC injection every 2 weeks for severe eosinophilic/Type 2 asthma, and 300mg by SC injection every 2 weeks for OCS-dependent severe asthma or if there is concomitant moderate/severe atopic dermatitis. Self-administration may be an option.

Like other biologic agents for severe asthma, this medication is expensive, so it should only be considered when common causes of uncontrolled asthma, including incorrect inhaler technique and poor adherence, have been checked and addressed, and the contribution of comorbidities and modifiable risk factors to respiratory symptoms and exacerbations has been identified and minimized. This report does not state specific criteria for eligibility for biologic therapies, as these vary between countries and jurisdictions. For more details, see GINA Pocket Guide on Difficult-to-Treat and Severe Asthma in Adults and Adolescents.[197]

Asthma outcomes

Randomized controlled trials in patients with uncontrolled severe asthma with at least one exacerbation in the last year was associated with~50% reduction in severe exacerbations, and significantly improved quality of life, symptom control and lung function.[393] In patients with OCS-dependent severe asthma, without minimum requirements of blood eosinophil count or FeNO, treatment with anti-IL4R reduced median OCS dose by 50% versus placebo.[394] In a meta-analysis of four randomized controlled trials representing 2,992 patients, pooled analyses demonstrated a significant reduction in the annualized rate of severe exacerbations in the dupilumab group compared to placebo (RR 0.44, 95% CI 0.35-0.06, p<0.01). Dupilumab also improved FEV1 by a mean of 0.14L (95% CI 0.12-0.17L, p<0.01).

Potential predictors of a good asthma response to anti-IL4R include higher blood eosinophils, which are strongly predictive,[393] and higher FeNO.[393]

Other outcomes

Nasal polyposis is not currently a specific indication for anti-IL4R therapy, but a randomized placebo-controlled trial showed improved symptoms and reduced nasal polyps on endoscopy at 16 weeks.[395]

Adverse effects

Adverse effects include injection-site reactions which are common but minor. In a meta-analysis of four randomized controlled trials, use of dupilumab had a two-fold higher incidence of injection site reactions compared with placebo, but was otherwise well-tolerated and there was no significant increase in adverse events or serious adverse events.[396] Transient blood eosinophilia occurs in 4-13% of patients.

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Systemic corticosteroids

Role in therapy

Long-term treatment with oral corticosteroids (OCS) (that is, for periods longer than two weeks) may be required for severely uncontrolled asthma, but its use is limited by the risk of significant adverse effects. The therapeutic index (effect/side effect) of long-term ICS is always more favorable than long-term systemic corticosteroids in asthma.[397,398] If OCS are to be administered on a long-term basis, attention must be paid to measures that minimize the systemic side effects. Oral preparations are preferred over parenteral (intramuscular or intravenous) for long-term therapy because of their lower mineralocorticoid effect, relatively short half-life, and lesser effects on striated muscle, as well as the greater flexibility of dosing that permits titration to the lowest acceptable dose that maintains control.

Short-term use of systemic corticosteroids is important in the treatment of severe acute exacerbations because they prevent progression of the exacerbation, reduce the need for referral to emergency departments and hospitalization, prevent early relapse after emergency treatment, and reduce morbidity. The main clinical effects of systemic corticosteroids in acute asthma are only evident after 4 to 6 hours. Oral therapy is preferred and is as effective as intravenous hydrocortisone.[399] A typical short course of OCS for an exacerbation is 40-50 mg prednisolone given daily for 5 to 10 days[399] depending on the severity of the exacerbation. When symptoms have subsided and lung function has improved, the OCS can be stopped abruptly[400] [400,401] (or tapered, if taken for >2 weeks), provided that treatment with ICS

continues. Intramuscular injection of corticosteroids has no advantage over a short course of OCS in preventing relapse.[402] In a randomized controlled trial, a single dose of dexamethasone was inferior to prednisone for 5 days in adult asthma patients presenting at ED with a moderate asthma exacerbation.[403]

Adverse effects

The systemic side effects of long-term oral or parenteral corticosteroid treatment include osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, obesity, cataracts, glaucoma, skin thinning leading to cutaneous striae and easy bruising, and muscle weakness. Patients with asthma who are on long-term systemic corticosteroids in any form should receive an assessment for osteoporosis risk and based on this assessment receive preventive treatment for osteoporosis, as recommended in 2010 guidelines from the American College of Rheumatology.[404] Factors increasing the risk of corticosteroid-induced osteoporosis include low body mass index (BMI), current smoking, parental history of hip fracture, >3 standard alcoholic drinks/day, and higher daily or cumulative corticosteroid treatment.[404] Withdrawal of oral corticosteroids can also (rarely) elicit adrenal failure or unmask underlying disease, such as Churg-Strauss Syndrome.[405] Caution and close medical supervision are recommended when considering the use of systemic corticosteroids.

Adverse effects of short-term high dose systemic therapy (corticosteroid 'bursts') are uncommon but include reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face ('moon facies'), mood alteration, insomnia, hypertension, peptic ulcer, and aseptic necrosis of the femoral head.

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Macrolides

Role in therapy

The role of the long-term use of macrolides in asthma remains under study. A meta-analysis of randomized controlled trials of macrolides or placebo for more than three weeks in asthma found no significant difference in FEV_1 or decrease in exacerbations; evidence was limited by incomplete reporting and heterogeneous inclusion criteria and outcomes.[406]

Two longer-term studies have been conducted. In a study in adult patients with uncontrolled asthma despite high dose ICS and a history of ≥2 exacerbations requiring OCS or respiratory infections requiring antibiotics in the previous year, low-dose azithromycin 250mg three times per week improved quality of life; in the subset with non-eosinophilic severe asthma, azithromycin reduced severe exacerbations.[407] In another study of adult patients with uncontrolled persistent asthma on medium-to-high dose ICS plus a LABA, add-on maintenance treatment with azithromycin 500 mg three times per week reduced asthma exacerbations and improved asthma-related quality of life.[408] Treatment for at least 6 months is suggested, as a clear benefit was not seen by 3 months. There is no clear evidence about how long treatment should be continued.

Adverse effects

Gastro-intestinal symptoms (e.g. diarrhoea) were more common with the higher dose of azithromycin.[408] Since macrolides such as azithromycin can elicit ototoxicity and cardiac arrhythmia, asthma patients with hearing impairment[408] or abnormal prolongation of the corrected QT interval[407,408] were excluded from the studies. Before considering add-on therapy with azithromycin in adult patients with uncontrolled (severe) asthma, sputum should be checked for atypical mycobacteria, and the risk of increasing antimicrobial resistance at the patient and the population level should be taken into account.

RELIEVER MEDICATIONS

Short-acting inhaled beta$_2$-agonists (SABA)

Role in therapy

Inhaled SABAs are used for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction. They include salbutamol, terbutaline, levalbuterol HFA, reproterol, and pirbuterol. Formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, but it should not be used without concomitant ICS therapy.[409]

SABAs should be used only on an as-needed basis at the lowest dose and frequency required. Increased use, especially daily use, is a warning of deterioration of asthma control and indicates the need to reassess treatment. Similarly, failure to achieve a quick and sustained response to SABA treatment during an exacerbation mandates medical attention, and may indicate the need for short-term treatment with OCS. A population-based survey reported that one-quarter of the SABA-only population had needed urgent asthma healthcare in the previous year.[410]

From 2019, GINA no longer recommends SABA-only treatment of asthma in adults or adolescents. Because adherence with ICS is often extremely poor, particularly in patients with infrequent symptoms, and because a feasible alternative is now available, SABAs are no longer the preferred reliever of choice in mild asthma. Although SABAs are highly effective for the quick relief of asthma symptoms[411] (Evidence A), patients whose asthma is treated with SABA alone are at risk of asthma-related death[265] (Evidence A) and urgent asthma-related healthcare[412] (Evidence A), even if they have good symptom control.[410] One long-term study of regular SABA in patients with newly-diagnosed asthma showed worse outcomes and lower lung function than in patients who were treated with daily low dose ICS from the start.[413]

Adverse effects

Tremor and tachycardia are commonly reported with initial use of SABA, but tolerance to these effects usually develops rapidly. Dispensing of ≥3 SABA canisters per year (average ≥1.5 puffs per day) is associated with increased risk of ED visit or hospitalization, independent of asthma severity.[414] Heavy use of SABAs (e.g. averaging more than one canister per month) is associated with increased risk of asthma-related death.[415]

Low dose ICS-formoterol

Role in reliever therapy

Low dose ICS-formoterol, taken only as needed for symptom relief, is a preferred treatment option for adults and adolescents with mild asthma. This recommendation is supported by evidence from a large double-blind study showing a 64% reduction in severe exacerbations compared with SABA-only treatment,[306] and two large studies in mild asthma showing non-inferiority for severe exacerbations compared with regular ICS plus as-needed SABA.[306,307] The evidence to date is with low dose budesonide-formoterol, but low dose beclometasone-formoterol should also be suitable. These medications are well-established for as-needed use as part of maintenance and reliever therapy in GINA Steps 3-5,[309] and no new safety signals were seen in the large studies with as-needed budesonide-formoterol in mild asthma.[262,307]

In patients with mild asthma, low dose budesonide-formoterol taken as-needed for symptom relief and before exercise reduced exercise-induced bronchoconstriction to a similar extent over 6 weeks as regular daily low dose ICS plus SABA for symptom relief and before exercise.[334]

Low dose ICS-formoterol is also the preferred reliever for patients prescribed maintenance and reliever therapy, in which a low dose of budesonide-formoterol or beclometasone-formoterol is taken as both regular daily maintenance treatment and as the patient's reliever therapy. See section on *Controller medications* above for details. ICS-formoterol should not be used as the reliever medication for patients taking combination ICS-LABA medications with a different (non-formoterol) LABA.

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Adverse effects

In the large studies of as-needed budesonide-formoterol, no notable differences in adverse events were seen compared with those with daily low dose ICS plus as-needed SABA.

Short-acting anticholinergics

Role in therapy

Short-acting anticholinergic bronchodilators used in asthma include ipratropium bromide and oxitropium bromide. Inhaled ipratropium bromide is a less effective reliever medication in asthma than SABAs. A meta-analysis of trials of inhaled ipratropium bromide use added to SABA in acute asthma showed that the anticholinergic produced a statistically significant, albeit modest, improvement in pulmonary function, and significantly reduced the risk of hospital admission.[416,417]

The benefits of ipratropium bromide in the *long-term* management of asthma have not been established, although it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from rapid-acting beta$_2$-agonists.

Adverse effects

Inhalation of ipratropium or oxitropium can cause dryness of the mouth and a bitter taste.

OTHER MEDICATIONS

Theophylline

Role in therapy

Long-term therapy: Theophylline is a relatively weak bronchodilator and when given in a low dose, has modest anti-inflammatory properties.[418] It is available in sustained-release formulations that are suitable for once-or twice-daily administration. Theophylline is an add-on option for adult patients whose asthma is not well controlled with ICS or ICS-LABA.[419-421] In such patients, the withdrawal of sustained-release theophylline has been associated with deterioration of asthma control.[422] However, for patients taking ICS, theophylline is less effective as add-on therapy than LABA.[423]

Short term therapy: In patients with acute asthma treated with inhaled SABA, the addition of intravenous aminophylline compared with placebo did not result in significant additional bronchodilation. Moreover, for every hundred patients treated with aminophylline there were an additional 20 patients with vomiting and 15 with arrhythmias.[424]

Adverse effects

Side effects of theophylline, particularly at higher doses (10 mg/kg body weight/day or more), are significant and reduce its usefulness. Side effects can be reduced by careful dose selection and monitoring, and generally decrease or disappear with continued use. Adverse effects include gastrointestinal symptoms, diarrhea, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the most common early events. Monitoring of blood levels is advised when a high dose is started, if the patient develops an adverse effect on the usual dose, if expected therapeutic aims are not achieved, and when conditions known to alter theophylline metabolism exist. For example, febrile illness, pregnancy, and anti-tuberculosis medications[425] reduce blood levels of theophylline, while liver disease, congestive heart failure, and certain drugs including cimetidine, some quinolones, and some macrolides increase the risk of toxicity. Lower doses of theophylline, that have been demonstrated to provide the full anti-inflammatory benefit of this drug,[419] are associated with fewer side effects, and plasma theophylline levels in patients on low dose therapy need not be measured unless overdose is suspected.

During short-term treatment, theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. Short-acting theophylline should not be administered to patients

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already on long-term treatment with sustained-release theophylline unless the serum concentration of theophylline is known to be low and/or can be monitored.

Oral beta-agonists

Role in therapy

Short-acting oral beta-agonists may be considered in the few patients who are unable to use inhaled medication. However, their use is associated with a higher prevalence of adverse effects.

Long acting oral beta-agonists include slow release formulations of salbutamol, terbutaline, and bambuterol, a pro-drug that is converted to terbutaline. They are used only on rare occasions when additional bronchodilation is needed.

Adverse effects

The side effect profile of oral long-acting beta-agonists is higher than that of inhaled beta$_2$-agonists, and includes cardiovascular stimulation (tachycardia), anxiety, and skeletal muscle tremor. Adverse cardiovascular reactions may also occur with the combination of oral beta-agonists and theophylline. Regular use of long-acting oral beta-agonists as monotherapy is likely to be harmful and these medications must always be given in combination with ICS.

Oral anti-histamines

Oral anti-allergy compounds have been introduced in some countries for the treatment of mild to moderate allergic asthma. A meta-analysis of 19 studies on the effects of anti-histamines in adult asthma does not support the use of these medications in asthma treatment.[426] Sedation is a potential side effect of some of these medications. [426]

Immunosuppressants

Several steroid-sparing drugs have been proposed for patients with severe asthma. The data to support their use is weak and they should be used only in selected patients under expert supervision, as their potential steroid-sparing effects may not outweigh the risk of serious side effects. Two meta-analyses of the steroid-sparing effect of low dose methotrexate showed a small overall benefit, but a relatively high frequency of adverse effects.[427,428] This small potential to reduce the impact of corticosteroid side effects is probably insufficient to offset the adverse effects of methotrexate (gastrointestinal symptoms, and on rare occasions hepatic and diffuse pulmonary parenchymal disease, and hematological and teratogenic effects).[429] Cyclosporin[430] and gold[431,432] have also been shown to be effective in some patients. The use of intravenous immunoglobulin is not recommended for treatment of asthma.[433-435]

Vitamin D

Vitamin D supplementation may be effective in reducing asthma exacerbations requiring systemic corticosteroids in patients with low baseline serum levels of Vitamin D (high quality evidence), based on a meta-analysis of 7 RCTs in children and adults with asthma. No effect on time to first exacerbation or exacerbation rates was seen. In view of the low cost of this intervention and the economic burden associated with asthma exacerbations, vitamin D supplementation in patients with documented vitamin D deficiency may represent a potentially cost-effective strategy.[436]

In a placebo-controlled trial in 408 adults with mild-moderate asthma who underwent ICS dose reduction, add-on high dose cholecalciferol (100,000 IU load plus 4000 IU/day) for 28 weeks vs placebo did not reduce the risk of asthma exacerbations[437] or severity or frequency of colds.[438]

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COMPLEMENTARY AND ALTERNATIVE MEDICINES AND THERAPIES

Role in therapy

The roles of complementary and alternative medicine in adult asthma treatment are limited because these approaches have been insufficiently researched and their effectiveness is largely unproven, or has not been validated by conventional standards.[439] Although the psychotherapeutic role of the therapist forms part of the placebo effect of all treatments, this aspect is viewed as an integral part of the so-called holistic approach used by practitioners of complementary and alternative methods, and mitigates against performance of the large, multicenter, placebo-controlled randomized studies required to confirm efficacy. However, without these the relative efficacy of these alternative measures will remain unknown.

Complementary and alternative therapies include acupuncture, homeopathy, herbal medicine, ayurvedic medicine, ionizers, osteopathy and chiropractic manipulation, and speleotherapy among others. Apart from those mentioned below, there have been no satisfactory studies from which conclusions about their efficacy can be drawn.

Dietary supplements, including selenium therapy[440] are not of proven benefit and the use of a low sodium diet as an adjunctive therapy to normal treatment has no additional therapeutic benefit in adults with asthma. In addition, a low sodium diet has no effect on bronchial reactivity to methacholine.[441] Evidence from the most rigorous studies available to date indicates that spinal manipulation is not an effective treatment for asthma.[442] Systematic reviews indicate that homeopathic medicines have no effects beyond placebo.[443] A Cochrane review of yoga interventions for asthma (with or without breathing, posture or meditation) compared to usual care (or sham intervention)[444] found moderate quality evidence of benefit for quality of life; there was no benefit for lung function or medication use. Few studies were matched for contact with health professionals, and few data were available about adverse effects.[444]

A systematic review of studies of breathing and/or relaxation exercises for asthma and/or dysfunctional breathing, including the Buteyko method and the Papworth method, reported significant but small improvements in symptoms, quality of life and/or psychological measures, but not in physiological outcomes or risk of exacerbations.[445] A subsequent large pragmatic study of breathing training in patients with impaired asthma-related quality of life showed significant but small improvements in quality of life, but no difference in asthma symptom control or risk of exacerbations. Results with three face-to-face physiotherapy sessions and DVD-based training were similar.[446] Breathing exercises used in some of these studies are available for free download from www.breathestudy.co.uk [446] and www.woolcock.org.au/moreinfo.[447] In order for studies of non-pharmacological strategies such as breathing exercises to be considered high quality, control groups should be appropriately matched for level of contact with health professionals and for asthma education. A study of two physiologically contrasting breathing techniques, in which contact with health professionals and instructions about rescue inhaler use were matched, showed similar improvements in reliever and ICS use in both groups.[447] This suggests that perceived improvement with breathing exercises may be largely due to factors such as relaxation, voluntary reduction in use of SABA medication, or engagement of the patient in their own care. Breathing exercises may thus provide a useful supplement to conventional asthma management strategies, including in anxious patients or those habitually over-using rescue medication. The cost of some programs is a potential limitation.

Adverse effects

With acupuncture, adverse effects including hepatitis B, pneumothorax, and burns have been described. Side effects of other alternative and complementary medicines are largely unknown. However, some popular herbal medicines could potentially be dangerous, as exemplified by the occurrence of hepatic veno-occlusive disease associated with the consumption of the commercially available herb, comfrey. Comfrey products are sold as herbal teas and herbal root powders, and their toxicity is due to the presence of pyrrolizidine alkaloids.

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PART B. ASTHMA PHARMACOTHERAPY – CHILDREN 6–11 YEARS

ROUTE OF ADMINISTRATION

Inhaled therapy is the cornerstone of asthma treatment for children of all ages. Almost all children can be taught to effectively use inhaled therapy. Different age groups require different inhalers for effective therapy, so the choice of inhaler must be individualized. Information about the lung dose for a particular drug formulation is seldom available for children, and marked differences exist between the various inhalers. This should be considered whenever one inhaler device is substituted with another. In addition, the choice of inhaler device should include consideration of the efficacy of drug delivery, costs, safety, ease of use, convenience, and documentation of its use in the patient's age group.[258,448]

Many children with asthma do not use their inhalers correctly and consequently gain little or no therapeutic benefit from prescribed treatment.[448] Therefore, for each age group, a major focus of inhalation therapy should be on which inhalers are the easiest to use correctly, and how much training is required to achieve correct technique. More than 50 different inhaler/drug combinations are now available for the treatment of asthma. Although such a variety increases the likelihood of finding an appropriate inhaler for each individual patient, it also increases the complexity of inhaler choice, and it may also reduce the health care provider's experience with each device. Therefore, it may be better for the individual health care provider to focus on a limited number of inhalers to gain better experience with them.

Both initial training and repeated follow-ups are crucial for correct inhaler use in children.[449] Prescription of inhaled therapy to a child should always be accompanied by thorough training in correct inhaler use, and repeatedly checking that the child can demonstrate correct technique. The number of cycles of correction and demonstration of technique depend on age and the psychomotor skills of the child. Inhaler technique continues to improve when skills training is repeated at subsequent visits.[450]

Options for inhalers include pressurized metered dose inhaler (pMDI) with or without a spacer device, and dry powder inhaler (DPI), These differ with respect to construction, aerosol cloud generation, optimal inhalation technique and ease of use. For children, prescription of pMDI alone (without spacer) is not generally recommended as they are more difficult to use correctly than pMDI with spacer, DPI or breath-actuated pMDI. DPIs and breath-actuated pMDIs are often preferred for use outside the home, as they are more convenient to carry than pMDI and spacer.

Spacers retain large drug particles that would normally be deposited in the oropharynx; this reduces oral and gastrointestinal absorption and thus systemic availability of the inhaled drug. This is important for ICS that have low first-pass metabolism (beclometasone dipropionate, flunisolide, triamcinolone). Use of a spacer also reduces oropharyngeal side effects. During asthma exacerbations, a spacer should always be used with a pMDI, as in this situation a child may be unable to correctly coordinate inhalation with pMDI actuation. Nebulizers have rather imprecise dosing, are expensive, are time consuming to use and care for, and require maintenance. They are mainly reserved for children who cannot use other inhaler devices. In life-threatening asthma exacerbations a nebulizer is often used, although in mild or moderate exacerbations, pMDI with a spacer is equally effective.[451]

Common inhaler devices for use by children aged over 5 years, together with features of optimal inhalation technique, and some common problems with their use are summarized in Box A5-2.

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Box A5-2. Inhaler devices, optimal technique, and common problems for children

Device	Age group/context	Optimal technique	Common problems
pMDI with valved spacer	All ages	Slow deep inhalation (30 L/min.) followed by 5 second breath-hold	Static electricity reduces output* (output is reduced after cleaning unless rinsed with detergent and air-dried) Multiple actuations into spacer
	All ages with acute severe wheeze ICS with low first pass metabolism (see text)	Slow tidal breathing (5–10 cycles) starting immediately after actuation.	
pMDI	> 8 years	Exhalation away from device, then inhaler actuation early during a slow (30 L/min) deep inhalation, followed by 5 second breath-hold	Coordination of actuation and inhalation
Breath-actuated pMDI	> 7 years	Exhalation away from device followed by a slow (30 L/min) deep inhalation followed by 5 second breath-hold	Slow inhalation is difficult
Dry powder inhalers	> 5 years	Exhalation away from device followed by a deep, forceful inhalation (minimal effective flow varies between devices)	Dose lost if child exhales through the inhaler

* Device dependent

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CONTROLLER MEDICATIONS

Controller medications for children include inhaled corticosteroids (ICS), combination ICS/long-acting beta$_2$-agonists (ICS-LABA), leukotriene receptor antagonists (LTRA) and chromones.

Inhaled corticosteroids

Role in therapy – regular daily treatment

ICS are the most effective controller therapy, and are therefore the recommended maintenance treatment for asthma, including for children.[452] Box A5-3 lists low, medium and high doses of different ICS for children 6–11 years. Concerns around SABA-only treatment are relevant to children, as in adults, and should be considered when initiating Step 1 treatment.[414]

Dose-response studies and dose titration studies in children[453,454] demonstrate marked and rapid clinical improvements in symptoms and lung function at low doses of ICS,[272,455,456] and mild disease is well controlled by low doses in the majority of patients.[264] Some children require higher doses to achieve optimal asthma control and effective protection against exercise-induced asthma, but incorrect inhaler technique and poor adherence may contribute. Only a minority of patients require treatment with high doses of ICS.[272]

In children, as in adults, maintenance treatment with ICS controls asthma symptoms, reduces the frequency of acute exacerbations, the need for additional asthma medication and the number of hospital admissions, improves quality of life, lung function, and bronchial hyperresponsiveness, and reduces exercise-induced bronchoconstriction.[266] Symptom control and improvements in lung function occur rapidly (after 1–2 weeks), although longer treatment (over months) and sometimes higher doses may be required to achieve maximum improvements in airway hyperresponsiveness.[266] When corticosteroid treatment is discontinued, asthma control deteriorates within weeks to months.[268]

Box A5-3. Low, medium and high daily doses of ICS for children 6–11 years

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS treatment options for children 6-11 years, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need medium dose ICS if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). High dose ICS (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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Most of the clinical benefit from ICS is seen at low doses, and clear evidence of dose-response relationships is seldom available within the dose ranges evaluated for regulatory purposes. 'High' doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects.

For new preparations, including generic ICS, the manufacturer's information should be reviewed carefully; products containing the same molecule may not be clinically equivalent. For more detailed discussion see Raissy et al. [271]

Role in therapy - as-needed treatment

Meta-analyses of asthma treatment in school-age children have sometimes compared regular ICS with either intermittent ICS (episodic) or as-needed (prn) ICS, the latter taken whenever SABA was taken.[457458] However, these two regimens are likely to differ in their clinical effectiveness. Daily treatment was reported to be superior to intermittent or prn treatment in several indicators of lung function, airway inflammation, asthma control and reliever use. However, taking ICS whenever SABA was taken substantially reduced the risk of asthma exacerbations compared with SABA-only treatment.[459] Both treatments appeared safe, but growth was slower (0.4 cm/year) in the regular treatment group. None of the studies recorded lifestyle factors such as daily physical activity or changes in fitness, which have been found to be reduced in children when their asthma is not optimally controlled.[460] The authors concluded that there was low quality evidence that intermittent and daily ICS strategies were similarly effective in the use of rescue oral corticosteroids and the rate of severe adverse health events, but that equivalence between the two options could not be assumed.

A further study in which patients were instructed to take ICS whenever SABA is taken was conducted in African-American children aged 6-17 years, using separate ICS and SABA inhalers. This study found similar outcomes as

physician-adjusted treatment but with lower average ICS dose[461] Interviews with parents indicated that those whose children were randomized to as-needed ICS+SABA felt more in control of their child's asthma than those whose children were randomized to physician-based adjustment.[461]

Adverse effects

Growth. When assessing the effects of ICS on growth in children with asthma, it is important to remember that uncontrolled or severe asthma adversely affects growth and final adult height.[462] Potential confounding factors also affect interpretation. For example, many children with asthma, especially severe asthma, experience a reduction in growth rate toward the end of the first decade of life. This continues into the mid-teens and is associated with a delay in the onset of puberty. This deceleration of growth velocity resembles growth retardation, but is also associated with a delay in skeletal maturation, so that the child's bone age corresponds to his or her height. Ultimately, adult height is not decreased, although it is reached at a later than normal age.[462,463] One study suggested that 400 mcg inhaled budesonide or equivalent per day to control asthma has less impact on growth than a low socioeconomic status.[463] A summary of the findings of studies on ICS and growth is provided in Box A5-4.[462,464,465]

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Box A5-4. Corticosteroids and growth in children

- Uncontrolled or severe asthma adversely affects growth and final adult height.[462]
- Daily use of 100–200 mcg ICS is generally considered to be without any clinically important adverse effects on growth.
- Growth retardation in both short- and medium-term studies is dose dependent. Growth retardation may be seen with moderate or high doses of all ICS.
- Important differences seem to exist between the growth-retarding effects of different ICS and different devices.
- Corticosteroid-induced changes in growth rate during the first year of treatment are not progressive or cumulative.
- In several studies, children with asthma treated with ICS for several years have been found to attain normal adult height.[264,462,463] However, one randomized, controlled trial of 5 years treatment with inhaled budesonide 400 mcg/day found that the initial 1.2 cm reduction in height was still detectable in adulthood (<1% of adult height), particularly in children who started treatment before 10 years of age.[464] Evidence favors the use of low dose ICS where possible.[466]

Bones. Several cross-sectional and longitudinal epidemiologic studies have assessed whether long-term ICS treatment is associated with osteoporosis and fractures.[467-473]. The conclusions are summarized in Box A5-5.

Box A5-5. Corticosteroids and bones in children

- No studies have reported an increased risk of fractures in children taking ICS.
- Use of oral or systemic corticosteroids increases the risk of fracture. The risk increases with the number of treatments, with a 32% increase after four courses (lifetime). ICS reduce the need for systemic corticosteroid courses.
- Controlled longitudinal studies of 2–5 years' duration, and several cross-sectional studies, found no adverse effects of ICS on bone mineral density.
- ICS use has the potential for reducing bone mineral accretion in male children progressing through puberty, but this risk is likely to be outweighed by the ability to reduce the amount of oral corticosteroids used in these children.[474]

Hypothalamic-pituitary-adrenal (HPA) axis: Although differences exist between different ICS and inhaler devices, treatment with ICS doses of less than 200 mcg budesonide or equivalent daily is not normally associated with any significant suppression of the HPA axis in children.[266] At higher doses, small changes in HPA axis function can be detected with sensitive methods.[471] The clinical relevance of these findings is not known, since there have been no reports of adrenal crisis in clinical trials of ICS in children. However, adrenal crisis has been reported in children treated in clinical practice with excessively high ICS doses.[475]

Cataracts: ICS have not been associated with an increased occurrence of cataract development in children.[297,476]

Central nervous system effects: Although isolated case reports have suggested that hyperactive behavior, aggressiveness, insomnia, uninhibited behavior, and impaired concentration may be seen with ICS treatment, no increase in such effects has been found in two long-term controlled trials of inhaled budesonide involving more than 10,000 treatment years.[264,266]

Oral candidiasis, hoarseness, and bruising: Clinical thrush is seldom a problem in children treated with ICS or oral corticosteroids. This side effect seems to be related to concomitant use of antibiotics, high daily doses, dose frequency, and inhaler device. Spacers reduce the incidence of oral candidiasis.[477] Mouth rinsing is beneficial.[478] The occurrence of hoarseness or other noticeable voice changes during budesonide treatment is similar to placebo.[297] Treatment with an average daily dose of 500 mcg budesonide for 3–6 years is not associated with an increased tendency to bruise.[297]

Dental side effects: ICS treatment is not associated with increased incidence of caries. However, the increased level of dental erosion reported in children with asthma[479] may be due to a reduction in oral pH from inhalation of beta$_2$-agonists.[480]

Other local side effects: The long-term use of ICS in children is not associated with an increased incidence of lower respiratory tract infections, including tuberculosis.

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Combination ICS-LABAs

Role in therapy

In children 6 years and older, LABAs are primarily used as add-on therapy for those whose asthma is insufficiently controlled by medium doses of ICS. Combination ICS-LABA products are preferred to use of separate inhalers, to ensure that the LABA is always accompanied by ICS. With add-on LABA, significant improvements in peak flow and other lung function measurements have been found in most studies.[481-483] However, the effects on other outcomes such as symptoms and need for reliever medication have been less consistent, and only observed in about half of the trials conducted. A cross-over study in children whose asthma was uncontrolled despite good adherence with low-dose ICS (n=182) found that adding LABA was most likely to produce the best clinical response over 16 weeks for a composite measure including lung function, compared with adding a LTRA or doubling the ICS dose.[484]

For exacerbations in children, by contrast with findings in adults, meta-analyses of randomized controlled trials showed no significant difference in exacerbations requiring systemic corticosteroids, when LABA was added to current treatment (which may or may not have included ICS),[485] when LABA was added to ICS,[486] or when ICS-LABA was compared with double dose ICS.[487] A large (n=6,208) study in children 4-11 years found no significant difference in serious exacerbations requiring hospitalization, or in severe exacerbations requiring oral corticosteroids, between fluticasone propionate and same dose combination fluticasone propionate/salmeterol.[488]

A single study of maintenance and reliever therapy with low dose budesonide-formoterol in children showed a large reduction in exacerbations compared with the same dose of budesonide-formoterol with SABA reliever, or compared with higher dose ICS.[489]

Not all combination ICS-LABA medications and devices are approved for use in children.

Adverse effects

There have been concerns that using LABA might increase asthma risks including mortality.[490] However, a large randomized controlled trial with fluticasone propionate/salmeterol combination inhaler in children 4-11 years showed no inferiority to fluticasone propionate alone for serious adverse events (death, intubation and hospitalization due to asthma).[343,488] Based on this study[488] and a systematic review[490] there is no apparent increase in risk for serious exacerbations in children with LABA when it is used in a combination inhaler with ICS.

Leukotriene receptor antagonists

Role in therapy

LTRAs provide clinical benefit in this age group at all levels of severity,[352,491-493] but the benefit is generally less than that of low dose ICS.[452] LTRAs provide partial protection against exercise-induced bronchoconstriction within hours after administration with no loss of bronchoprotective effect over time.[221,494] A systematic review of LTRAs as add-on treatment in children whose asthma was insufficiently controlled by low doses of ICS showed no significant improvement in outcomes, including in exacerbations.[495] Add-on therapy with montelukast was less effective in controlling asthma in children with uncontrolled persistent asthma than increasing ICS to moderate dose.[496] Montelukast has not been demonstrated to be an effective ICS-sparing alternative in children with moderate-to-severe persistent asthma.[497]

Adverse effects

No safety concerns have been demonstrated from the use of LTRA in children in clinical trials. Post-marketing surveillance reports suggested a slight increase in the rate of (rare) neuropsychiatric disorders potentially associated with use of leukotriene receptor antagonists in children and young adults, but no evidence was found in a case-control study.[358] Patients should be counselled about the risk of neuropsychiatric events with montelukast and health professionals consider the benefits and risks of mental health side effects before prescribing. (ref https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug)

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Chromones: sodium cromoglycate and nedocromil sodium

Role in therapy

Sodium cromoglycate and nedocromil sodium have a limited role in the long-term treatment of asthma in children. One meta-analysis concluded that long-term treatment with sodium cromoglycate is not significantly better than placebo for management of asthma in children.[498] Another meta-analysis confirmed superiority of low-dose ICS over sodium cromoglycate in persistent asthma; no difference between treatments was seen in safety.[359]

Nedocromil sodium has been shown to reduce exacerbations, but its effect on other asthma outcomes is not superior to placebo.[266] A single dose of sodium cromoglycate or nedocromil sodium attenuates bronchospasm induced by exercise or cold air.[499]

Sodium cromoglycate and nedocromil sodium inhalers require daily washing to prevent blockage.

Adverse effects

Cough, throat irritation, and bronchoconstriction occur in a small proportion of patients treated with sodium cromoglycate. A bad taste, headache, and nausea are the most common side effects of nedocromil.[500]

ADD-ON CONTROLLER MEDICATIONS

Long-acting anticholinergics (also called long-acting antimuscarinics, LAMA)

Role in therapy

A meta-analysis of over 900 patients 6-11 years showed the addition of tiotropium to medium or high dose ICS with or without a second controller was associated with significant improvements in FEV1 and Asthma Control Questionnaire responders, and reduced the number of patients with one or more exacerbations, but with no differences in reliever use. The approved dose for children varies between regulatory authorities.[501]

Anti-IgE

Role in therapy

Anti-IgE (omalizumab) has proven effect in children aged ≥6 years with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma. The efficacy of anti-IgE in children and adolescents is supported by the findings of effectiveness studies.[502] A 28-week, randomized, placebo-controlled study[503] included 334 children aged 6–12 years with moderate to severe allergic asthma, whose asthma was well controlled on ICS doses equivalent to 200–500 mcg/day of beclometasone. There were no differences in clinical effects between placebo and anti-IgE during a 16-week stable ICS dose period. During a 12-week tapering period, urgent unscheduled physician visits were significantly reduced by 30.3% in the anti-IgE group compared with placebo (12.9%) group,[503] and there were significant improvements in quality of life in the patients receiving anti-IgE, both during stable ICS dosing and during tapering.[504] The remaining outcomes were similar in the two treatment groups.

A one-year study evaluated the efficacy and safety of anti-IgE in 627 children aged 6–11 years with IgE-mediated asthma inadequately controlled on ICS at doses equivalent to or higher than 200 mcg/day fluticasone propionate (mean dose 500 mcg/day).[505] Anti-IgE treatment was associated with a significantly lower exacerbation rate, and the overall incidence of serious adverse events was significantly lower in the children receiving anti-IgE than placebo.

A 60-week study in 419 inner-city patients aged 6-20 years found that omalizumab significantly reduced symptoms and exacerbations, including seasonal exacerbations, compared with placebo.[379]

A substantial number of children with difficult asthma have higher IgE levels than the upper limit of IgE recommended for therapy (1,300 IU).[506] It is unknown if these patients will still benefit from omalizumab therapy.

The recent ERS/ATS Task Force on Severe Asthma recommended that 'Those adults and children aged 6 and above, with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance if their total serum IgE level is 30 to 700 IU/mL (in 3 studies the range was wider – 30–1300 IU/mL). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilisation, and improvement in quality of life. If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial.'[243]

Adverse effects

Drug-related adverse events in anti-IgE treated patients are mild to moderate in severity and include injection site pain, urticaria, rash, flushing, and pruritus.[503] The long-term (beyond one year) safety and efficacy have not yet been studied in children.

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Anti-IL5

Mepolizumab is approved in Europe for children 6 years and older with severe eosinophilic asthma. However, efficacy data in this population are limited to one very small open label uncontrolled study.[507]

Systemic corticosteroids

Because of the side effects of prolonged use, oral corticosteroids in children with asthma should be restricted to the treatment of acute severe exacerbations, whether viral-induced or otherwise. Even short-courses of oral corticosteroids, if used repeatedly, increase the risk of side-effects. In a prospective study, short courses of oral corticosteroids were associated with reduced bone density in boys.[474] In an epidemiological study, risk of fracture was increased with ≥4 courses of oral corticosteroids, although the contribution of disease severity could not be estimated.[470]

RELIEVER MEDICATIONS

Short-acting beta-agonists (SABA)

Role in therapy

SABAs are the most effective bronchodilators approved for this agegroup, and therefore the preferred treatment for acute asthma in children of all ages. The inhaled route results in more rapid bronchodilation at a lower dose and with fewer side effects than oral or intravenous administration.[508] Furthermore, inhaled therapy offers significant protection against exercise-induced bronchoconstriction and other challenges for 0.5 to 2 hours.[221] This is not seen after systemic administration.[509] Oral therapy is rarely needed and is reserved mainly for the small proportion of young children who cannot use inhaled therapy.

Adverse effects

Skeletal muscle tremor, headache, palpitations, and some agitation are the most common complaints associated with high doses of beta-agonists in children. These complaints are more common after systemic administration and disappear with continued treatment.

As-needed ICS-formoterol

There is only one study of maintenance and reliever therapy with low dose ICS-formoterol in this age-group. It showed a large reduction in risk of severe exacerbations compared with maintenance-only treatment with ICS-formoterol plus as-needed SABA.[489]

Anticholinergics

Role in therapy

Inhaled anticholinergics such as ipratropium bromide are not recommended for long-term management of asthma in children.[510] They may be tried in patients who are very sensitive to the side effects of SABAs, but their onset of action and maximum effect are generally lower than those of SABAs.

OTHER MEDICATIONS, NOT RECOMMENDED FOR USE IN CHILDREN

Theophylline (not recommended)

Role in therapy

Due to its high toxicity, theophylline is not recommended for use in children. Theophylline has only modest effects as monotherapy compared with placebo,[511] and as add-on treatment to inhaled or oral corticosteroids in children with severe asthma.[512,513] It has a marginal protective effect against exercise-induced bronchoconstriction.[514] Most clinical evidence in children has been obtained from studies in which plasma theophylline levels were maintained within the

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therapeutic range of 55–110 umol/L (5–10 mcg/ml). Theophylline elimination may vary up to tenfold between individuals, and measurement of plasma theophylline levels is recommended in otherwise healthy children when daily doses exceed 10 mg/kg/day.

Adverse effects

The most common side effects of theophylline are anorexia, nausea, vomiting, and headache,[515] mainly seen at doses higher than 10 mg/kg/day. The risk of adverse effects is reduced if treatment is initiated with daily doses around 5 mg/kg/day and then gradually increased to 10 mg/ kg/day. More serious side effects such as epileptic seizures may occur, and severe overdosing with theophylline can be fatal.

Long-acting oral beta-agonists (not recommended)

Treatment with long-acting oral beta-agonists such as slow release formulations of salbutamol, terbutaline, and bambuterol reduces nocturnal symptoms of asthma.[516,517] However, due to their potential side effects of cardiovascular stimulation, anxiety, and skeletal muscle tremor, their use is not encouraged. Oral long-acting beta$_2$-agonist therapy offers little or no protection against exercise-induced bronchoconstriction.

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PART C. ASTHMA PHARMACOTHERAPY – CHILDREN 5 YEARS AND YOUNGER

CONTROLLER MEDICATIONS

Inhaled corticosteroids

Role in therapy

Regular ICS treatment. A meta-analysis of 29 randomized controlled trials of ≥4 weeks' duration in children aged 1 month to 5 years, with a clinical diagnosis of wheezing or asthma for at least 6 months before study entry, found that those who received maintenance ICS had significantly less wheezing, fewer asthma exacerbations, fewer withdrawals caused by wheezing or asthma exacerbations, less albuterol use and more clinical and functional improvement than those on placebo[518] (Evidence A). A meta-analysis of 8 studies in children with persistent asthma showed reduced exacerbations with daily ICS compared with placebo, and in one study, with daily ICS compared with montelukast.[519]

Dose-response relationships have been less well studied in this age group. The clinical response may differ depending on the specific device used for delivery and the child's ability to use it correctly. For children whose asthma is not well-controlled with low dose ICS (Box A5-6), near-maximum benefits are achieved in the majority of patients with twice these doses, when given as regular, long-term treatment and with correct use of a spacer device.[520,521] Use of ICS for children up to 2 years of age has not been found to induce remission of asthma; symptoms almost always return when treatment is stopped[522] (Evidence B).

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Box A5-6. Low daily doses of inhaled corticosteroids for children 5 years and younger

***This is not a table of equivalence*,** but instead, suggestions for 'low' total daily doses for the ICS treatment recommendations for children aged 5 years and younger, based on available studies and product information. Data on comparative potency are not readily available, particularly for children, and this table does NOT imply potency equivalence. The doses listed here are the lowest approved doses for which safety and effectiveness have been adequately studied in this age group.

Low dose ICS provides most of the clinical benefit for most children with asthma. Higher doses are associated with an increased risk of local and systemic side-effects, which must be balanced against potential benefits.

Inhaled corticosteroid	Low total daily dose (mcg) (age-group with adequate safety and effectiveness data)
BDP (pMDI, standard particle, HFA)	100 (ages 5 years and older)
BDP (pMDI, extrafine particle, HFA)	50 (ages 5 years and older)
Budesonide nebulized	500 (ages 1 year and older)
Fluticasone propionate (pMDI, standard particle, HFA)	50 (ages 4 years and older)
Fluticasone furoate (DPI)	Not sufficiently studied in children 5 years and younger)
Mometasone furoate (pMDI, standard particle, HFA)	100 (ages 4 years and older)
Ciclesonide (pMDI, extrafine particle, HFA)	Not sufficiently studied in children 5 years and younger

BDP: beclometasone dipropionate; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); in children, pMDI should always be used with a spacer

Episodic ICS treatment versus placebo. In children with intermittent asthma or viral-induced wheeze, meta-analysis of 5 studies (422 children) found that the preemptive use of high-dose episodic ICS compared with placebo resulted in reduced risk of exacerbation.[519] Because of the potential for side-effects, this option should be considered only where the physician is confident that the medications will be used appropriately. In children aged 2–12 years with acute

asthma, adding a single dose of nebulized ICS to an initial dose of prednisolone was no better than adding placebo in preventing admission.[523]

Episodic ICS treatment versus regular ICS. The MIST study recruited pre-schoolers with recurrent wheeze, a positive asthma predictive index (API), and wheezing episodes on an average of one third of days, with two-thirds of the children taking ICS prior to entry. This study compared regular daily low-dose nebulized budesonide with episodic high-dose nebulized budesonide given each night for seven days with respiratory tract illnesses.[524]. This study showed similar outcomes for regular and intermittent ICS. Cumulative ICS dose was higher with regular versus episodic treatment.

As-needed ICS treatment (taken when SABA is required) versus regular ICS or placebo. The 'BEST for Children' study was a 3 month placebo-controlled study in 276 pre-schoolers with frequent wheeze comparing regular twice-daily nebulized beclometasone, as-needed nebulized beclometasone/salbutamol (given for symptom relief), and as-needed salbutamol alone.[525] This study showed similar clinical outcomes for regular vs as-needed ICS, but regular ICS was better than placebo for the primary outcome measure of symptom-free days. Cumulative ICS dose was lower with as-needed versus regular ICS.

The choice between regular, intermittent and as-needed controller treatment in clinical practice in pre-school children is still under discussion. A meta-analysis found strong evidence to support daily ICS for preventing exacerbations in preschool children with recurrent wheeze, specifically in children with persistent asthma.[519] For pre-school children with frequent viral-induced wheezing and interval asthma symptoms, as-needed (prn)[525] or episodic ICS[526] may be considered, but a trial of regular daily low dose ICS should be undertaken first. The effect on exacerbation risk seems similar for regular daily low dose and episodic high dose ICS.[519]

Adverse effects

The majority of studies evaluating the systemic effects of ICS have been undertaken in children older than 5 years. However, the available data in children 5 years and younger suggest that, as in older children, clinically effective doses of ICS are safe and the potential risks are well balanced by the clinical benefits.[522,527,528] Generally, low doses of ICS (Box A5-6**)** have not been associated with any clinically serious adverse systemic effects in clinical trials and are considered safe[520,521,527-535] (Evidence A). However, higher doses have been associated with detectable systemic effects on growth particularly in the first year of treatment and on the hypothalamic-pituitary-adrenal (HPA) axis.[520-522,527-535] These effects are similar to those reported in studies of older children that find no evidence that the initial effect on growth is accumulated with continued long term treatment.[462-464] The effects of the early reduction in growth on adult height has not been studied in children who started ICS before the age of 5 years. In children who had been treated with fluticasone propionate for 2 years from the age of 2 or 3 years,[522] catch-up in growth was seen at 2 years after cessation of ICS; however, in a *post hoc* analysis no catch-up was seen in children who at study entry were <2 years old and weighed <15 kg.[536]

Local side effects, such as hoarseness and candidiasis, are rare in children 5 years and younger.[271,533]

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Combination ICS/long-acting beta$_2$-agonists (ICS-LABA)

A short term (8 weeks) placebo-controlled study did not show any significant difference in symptoms between fluticasone propionate-salmeterol vs fluticasone propionate alone; no additional safety signals were noted in the group receiving LABA.[537] There are insufficient data about the efficacy and safety of ICS-LABA in children 4 years and younger to recommend their use in this age-group.

Leukotriene receptor antagonists (LTRA)

Role in therapy

LTRA versus placebo: In a three-month placebo-controlled study of 689 children with persistent wheeze, montelukast reduced days with symptoms and days with rescue beta$_2$-agonist use by approximately 6 percentage points. The proportion of children experiencing an asthma 'attack' was not significantly reduced, but the proportion needing a course

of prednisolone was reduced from 28% to 19%.[538] In a 12-month placebo-controlled study of 549 young children with recurrent viral-induced wheezing, regular montelukast improved some asthma outcomes compared with placebo, but did not reduce the frequency of hospitalizations, courses of prednisone, or symptom-free days.[539] These findings were confirmed by a further study in children with intermittent wheezing.[540] Montelukast has also been shown to reduce airway hyperresponsiveness to methacholine[541] or hyperventilation with cold dry air.[542]

Regular LTRA versus regular ICS: A recent systematic review concluded that in pre-schoolers with asthma or recurrent wheezing, daily ICS was more effective in improving symptom control and reducing exacerbations than regular LRTA monotherapy.[543]

Episodic LTRA treatment versus placebo. In a 12-month placebo-controlled study in children with intermittent asthma that included 162 children aged 2–5 years, parent-initiated montelukast for 7–14 days had a modest effect on health care utilization.[544]. In a placebo-controlled study of 979 children aged 3 months to 2 years, and hospitalized with RSV bronchiolitis, montelukast had no effect on post-bronchiolitic wheeze or cough.[545] A large 12-month study comparing daily and intermittent montelukast with placebo showed no significant difference in health care utilization. There were numerical differences in symptoms and reliever use during respiratory infections with regular and episodic montelukast compared with placebo.[540]

A placebo-controlled trial of the addition of montelukast to usual asthma therapy for 45 days in the fall, including 42 children aged 2–5[546] found that this treatment reduced the number of days with worsening of asthma symptoms in boys but not in girls.

In summary, LTRAs improve some asthma outcomes in young children with intermittent wheezing or persistent asthma, but to a lesser extent than daily ICS (Evidence A). However, the role of LTRAs as add-on therapy in children 5 years and younger whose asthma is uncontrolled on ICS has not been sufficiently evaluated.

Adverse effects

No safety concerns have been demonstrated in clinical trials of LTRAs in young children. Product information for montelukast describes (rare) adverse effects such as nightmares in this age group. Parents should be counselled about the risk of the impact on sleep and behavior with montelukast and health professionals should consider the benefits and risks of side effects before prescribing; the FDA has required a boxed warning about these problems.[547]

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Chromones (sodium cromoglycate and nedocromil sodium)

A Cochrane review concluded that there was no beneficial effect of inhaled sodium cromoglycate compared with placebo in preschool children [548] (Evidence A). Two studies of nearly 1,000 children in this age group[549,550] have confirmed the superiority of ICS over chromones for almost all endpoints assessing asthma control (Evidence A). Nedocromil sodium has not been studied in preschool children. Chromones cannot be recommended in this age group.

Oral and other systemic corticosteroids

Because of the side effects associated with prolonged use, oral corticosteroids in young children with asthma should be restricted to the treatment of severe exacerbations, whether viral-induced or otherwise[551] (Evidence D), and their use minimized because of the potential for long-term adverse effects.

Azithromycin

Antibiotics are not currently recommended for treatment of asthma exacerbations in adults or children, but they are commonly used in clinical practice. Two studies have examined the effect of azithromycin in selected children with a history of severe wheezing with respiratory infections. In a large study, children 1-5 years were randomized to receive 5 days of azithromycin or placebo for respiratory infections; this study showed a significant reduction in the risk of more severe lower respiratory episodes.[552] In a smaller study in children 1-3 years, each respiratory infection lasting ≥3 days was randomly allocated to treatment with azithromycin or placebo for 3 days, with most children also receiving ICS; this

study showed a significant reduction in symptom duration with azithromycin.[553] Neither study found a difference in need for urgent health care (which was uncommon in both studies), or an increase in time to subsequent respiratory infections. Development of antibiotic resistance was slightly increased when examined in a small number of subjects.[552] It is still unclear which children should be considered for azithromycin treatment, and there is concern about the potential for greater antibiotic resistance in broader populations where adherence may be lower; more clinical trials are needed, using standardized outcome measures, before any recommendations can be made.

RELIEVER MEDICATIONS

Inhaled short-acting beta$_2$-agonists (SABA)

Inhaled SABA are the preferred reliever treatment for asthma in children 5 years and younger (Evidence A). In most cases, a pMDI with spacer is an effective way for delivering reliever therapy for as-needed use or in acute exacerbations.[451,554] (Evidence A). A face mask is added for children under 4 years. When delivery is not optimal because of lack of cooperation or distress, or when the child is hypoxic, nebulizer therapy is also an option.

Other bronchodilators

There is no evidence to support the use of anticholinergic agents such as inhaled ipratropium bromide in the routine daily management of asthma in children 5 years and younger.[555] (Evidence A) However, there is increasing evidence that ipratropium is effective when added to other therapy in patients with severe exacerbations.[556]

Oral bronchodilator therapy is not recommended due to its slower onset of action and the higher rate of side effects.

Other therapies

Theophylline (not recommended)

Theophylline is not recommended for use in children. Although a few studies in children 5 years and younger suggest clinical benefit from regular use of theophylline, the effects are small and mostly non-significant.[511] The efficacy of theophylline as initial therapy is less than that of low dose ICS, and side effects are more common.[511]

Allergen immunotherapy

Immunotherapy is not recommended for the treatment or prophylaxis of asthma in children 5 years and younger (Evidence D).

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Chapter 6.
Implementing asthma management strategies in health systems

KEY POINTS

- In order to improve asthma care and patient outcomes, evidence-based recommendations must be not only developed, but also adequately disseminated and implemented at a national and local level, and integrated into current practice.
- Implementation requires an evidence-based strategy involving professional groups and stakeholders, and should take into account local cultural and socioeconomic conditions and cost-effectiveness, so a decision can be made to pursue or modify them.
- GINA aims to guide implementation of its recommendations, provide examples of current implementation strategies, and offer a series of tools to help achieve this goal worldwide.

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INTRODUCTION

Due to the exponential increase in medical research publications, practical syntheses are needed to guide health care providers in delivering evidence-based care. Where asthma care is consistent with evidence-based recommendations, outcomes improve.[557-559] Strategy documents such as the *Global Strategy for Asthma Management and Prevention* provide a common template for health professionals to identify the main goals of treatment and the actions required to ensure their fulfilment in their own health system, as well as to facilitate the establishment of standards of care.

Guidelines and clinical practice recommendations now generally utilize specific methodology for evaluating and adapting evidence, ensuring development of unbiased, well-adapted recommendations.[560,561] However, increasing effort should be devoted to dissemination of recommendations and, most importantly, to their implementation at different levels so that integration into care is promoted and facilitated.

The recent adoption of rigorous methodologies such as GRADE[560] for the development of clinical practice recommendations, and the ADAPTE and similar approaches for assisting the adaptation of recommendations for local country and regional conditions, has assisted in reducing biased opinion as the basis for asthma programs worldwide. However, use of the GRADE method is costly and often requires expertise that is not available locally, and regular revision to remain abreast of developments (drug availability and new evidence) is not easily achieved [560,561] In addition, there is generally very limited high quality evidence addressing the many decision nodes in comprehensive clinical practice guidelines, particularly in developing countries.

GINA provides assistance for the processes of adaptation and implementation through provision of the *Global Strategy for Asthma Management and Prevention* report,[29] which contains evidence relevant to asthma diagnosis, management and prevention that may be used in the formulation and adaptation of local guidelines; where evidence is lacking, the GINA report provides approaches for consideration. An implementation 'toolkit' is also being developed, to provide a guide to local adaptation and implementation, with materials and advice from successful examples of asthma clinical practice guideline development and implementation in different settings.

Many barriers to, and facilitators of, implementation procedures have been described.[562-565]. Some of these are related to delivery of care, while others relate to patients' attitudes and behaviors (Box A6-1). Cultural and economic barriers can particularly affect the application of recommendations.

Box A6-1 Examples of barriers to the implementation of evidence-based recommendations

Health care providers	Patients
• Insufficient knowledge of recommendations • Lack of agreement with recommendations or expectation that they will be effective • Resistance to change • External barriers (organizational, health policies, financial constraints) • Lack of time and resources • Medico-legal issues	• Low health literacy • Insufficient understanding of asthma and its management • Lack of agreement with recommendations • Cultural and economic barriers • Peer influence • Attitudes, beliefs, preferences, fears and misconceptions

PLANNING AN IMPLEMENTATION STRATEGY

Implementation of asthma management strategies can be carried out at national, regional or local levels.[566] Ideally, this should be a multidisciplinary effort involving many stakeholders, and using methods of knowledge translation that are considered cost effective.[565-567] Any implementation initiative needs to consider the structure and function of the relevant health network and its components. Moreover, goals and implementation strategies will vary from country to country and within countries based on economics, culture and the physical and social environment.

The essential elements required to implement a health-related strategy are summarized in Box A6-2. The goals and processes for each of these components are summarized in the paragraphs that follow.

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Box A6-2. Essential elements required to implement a health-related strategy

1. Develop a multidisciplinary working group
2. Assess the current status of asthma care delivery, care gaps and current needs
3. Select the material to be implemented, agree on main goals, identify key recommendations for diagnosis and treatment, and adapt them to the local context or environment
4. Identify barriers to, and facilitators of, implementation
5. Select an implementation framework and its component strategies
6. Develop a step-by-step implementation plan:
   - Select target populations and evaluable outcomes
   - Identify local resources to support implementation
   - Set timelines
   - Distribute tasks to members
   - Evaluate outcomes
7. Continuously review progress and results to determine if the strategy requires modification

1. Develop a multidisciplinary working group

From its initiation, the working group should ideally include representation from diverse professional groups including primary and secondary care health professionals and their associations, public health officials, non-governmental associations, patients, asthma advocacy groups, and the general public. Each member will contribute according to his or her expertise, resources and contacts. This may be done under the umbrella of national or local health societies or professional or scientific organizations, or through initiatives such as the Global Initiative for Asthma (GINA) and the Global Alliance against Chronic Respiratory Diseases (GARD).[568] Knowledge translation specialists can be consulted to ensure optimal evidence-based implementation methods. Ideally, a project coordinator should be involved.

Public health strategies involving a broad coalition of stakeholders in asthma care, including medical societies, health care professionals, patient support groups, government, and the private sector, have been implemented in Australia,[569] in the United States,[570] and other countries.

2. Assess the current status of care delivery, care gaps and current needs in the target area

The working group should assess the current status of asthma care in the target country/region in terms of mortality and morbidity, indicators of delivery of quality care and available resources for implementation. Processes for referral, current care facilities and access to asthma medications, as well as the degree of understanding of the management recommendations by practitioners/caregivers also need to be evaluated. Current 'care gaps' and their determinants[565,571] should be identified and their respective consequences estimated. This will aid in setting priorities (Box A6-3) and planning strategies that can fill the care gaps.

3. Select the material to be implemented, agree on main goals, identify key recommendations, and adapt them to the local context or environment

Once the material to be implemented has been selected (e.g. specific management recommendations from the GINA report), the working group should determine if any of the material requires adaptation to the local/regional context and environment. The working group should agree on realistic goals, and set priorities. Instruments such as the ADAPTE[572] tool are available to guide the process of adaptation, including recommendations on planning and set-up, the adaptation process, and the production of the final document.

4. Identify barriers to, and facilitators of, implementation

The next step is to identify barriers to, and facilitators of, implementation in the target country/region, and develop appropriate strategies around this. In some areas, particularly in low-income countries, asthma may not be considered a high priority health concern in comparison to other respiratory diseases like tuberculosis and pneumonia. In such areas, practical asthma management strategies could include a simple algorithm for separating non-infectious from infectious respiratory illnesses; simple objective measurements for diagnosis and management such as peak flow variability; available, affordable and low-risk medications for achieving good asthma control; a simple process for recognizing severe asthma; and simple diagnosis and management approaches relevant to the facilities and limited resources available. Other local barriers such as the lack of availability of resources/medications, organizational problems, or communication issues between caregivers should also be addressed (Box A6-3).

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Box A6-3. Common asthma management care gaps

Management care gap	Barriers to reducing the gap (examples)	Possible implementation strategy	Process and outcome measures
Over/under-diagnosis of asthma	Lack of availability of lung function tests	Identification of nearby lung function facilities	% patients having lung function tests
Inadequate assessment of asthma control	Lack of knowledge of criteria	Education/continuing medical eduction (CME)	Survey of use of criteria
Lack of assessment of SABA use	Lack of direct questioning	Automated letter based on pharmacy dispensing	Number of canisters dispensed per year
Insufficient environmental or preventative measures	Lack of time to explain	Increase access to educators; involve patients as educators	Survey implementation of intervention
Lack of individualized pharmacotherapy	Insufficient knowledge of guideline	Education/CME	Assessment of treatment (e.g. audit)
Lack of education and guided self-management	Lack of availability of educators	Increase access to educators; involve patients as educators	% patients offered education
Absence of an asthma action plan, or failure by patients to use their action plan	Not enough time to produce and explain the plan	Increase access to educators; involve patients as educators; provide clinicians with templates	% patients receiving written asthma action plan
No assessment of patients' skills with inhalers, PEF	Lack of time or knowledge	Systematic assessment at visits; provide device-specific checklists	% patients in whom technique is checked
No assessment of adherence to therapy	Not integrated into practice	Reminders; sample wording (see GINA report, Box 2-4); automated pharmacy letter	% patients in whom adherence is checked
No regular follow up; discontinuity of care	Lack of follow-up arrangements	Improved management	% patients having follow-up visit
Variable/insufficient access to care; lack of availability of asthma controllers	Insufficient resources	Increase resources; revise process	Assess continuity of care
Poor communication between various groups of health care providers	Lack of willingness to change	Organize joint sessions on asthma care	Focus group assessing this aspect of care

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Based on Boulet et al. *A guide to the translation of the Global Initiative for Asthma (GINA) strategy into improved care*.[566]

NOTE: These are considered important care gaps according to current guidelines and consensus, but for some, specific evidence of improvement in asthma outcomes following their application is not yet available.

5. Select an implementation framework and its component strategies

The *Knowledge to action* model has been proposed as a framework for guideline implementation but other models can also be considered.[573] This framework allows a continuing circle of improvement and the integration of new evidence/guidelines updates into the intervention process. Using this framework, a series of strategies can be proposed based on their ability to address the previously identified care gaps and barriers. Box A6-4 lists examples of high-impact interventions for asthma management. Quality of care improvements are made in progressive steps with regular assessment of their performance.

Ideally, interventions should be conducted at the level of both the patient and the health care provider. Studies of the most effective means of medical education show that it may be difficult to induce changes in clinical practice. However, among the most effective methods are:

- Reminders at the point of care
- Automated letter to patient and/or prescriber based on pharmacy dispensing[574,575]
- Interactive workshops
- Audit and feedback
- Multifaceted interventions. These include methods such as medical audit and feedback, reminders, local consensus processes, marketing, and use of practice facilitators.[576-580]
- Publications in journals that are associated with multidisciplinary symposia, workshops or conferences involving national and local experts, along with involvement of the professional and mass media can help to communicate key messages.
- Embedding guidelines into electronic health records is promising,[581,582] but a recent review showed the challenges of developing integrated care pathways.[583]

A useful resource for choosing the best implementation strategy is provided in the recommendations of the Cochrane Effective Practice and Organization of Care Review Group.[584]

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Box A6-4 Examples of high-impact interventions in asthma management

- Optimized ICS use for patients with a recent hospital admission and/or severe asthma[585]
- Early treatment with ICS, guided self-management, reduction in exposure to tobacco smoke, improved access to asthma education[558]
- Self-inking stamp prompting assessment of asthma control and treatment strategies[586]
- Use of individualized written asthma action plans as part of self-management education[219]
- An evidence-based care process model for acute and chronic pediatric asthma management, implemented at multiple hospitals[587]

ICS: inhaled corticosteroids

According to the *Knowledge to action* conceptual framework, the implementation process should include:

- *A planning phase*: in which key recommendations are prioritized for the targeted population, and key messages, main outcomes and actions to be taken are determined.
- *An assessment phase*: to review uptake by the target group and the impact of interventions.
- *A monitoring and adjustment phase*: in which outcomes selected for determination of the impact and sustainability of the intervention are assessed, and interventions are adjusted based on the findings.

Potential new tools for implementation include internet-based programs, social networks and electronic tools, although their effectiveness remains to be determined. In all cases, the messages must be simple, easily understood, practical and implementable.

6. Develop a step-by-step implementation plan

Select target populations and outcomes

Efforts should be devoted to the entire asthma population, but particularly to 'at-risk' or 'high-morbidity' populations. This includes patients with poor adherence to treatment or follow up; those who experience frequent exacerbations or frequently use the health care system; adolescents; elderly patients; and those with socioeconomic, psychological, psychosocial and economic problems.[588-590] An alternative approach is to select a particular intervention and implement

this in a population that is already under care; for example, patients attending for another clinical problem could be offered an asthma control assessment at that time.

Key outcomes and realistic targets should be identified, and the expected degree of change estimated (Box A6-5).

Box A6-5 Potential key outcomes and targets to consider for implementation programs

- Reduce asthma-related hospital admissions by 50% in the next 3 years[16]
- Reduce emergency attendances (hospital and primary care) by 50% in the next 3 years
- Reduce asthma mortality rates by 80% in the next 5 years
- Have asthma control assessed in >80% of patients in the targeted population
- Achieve good asthma control in >80% of the patient population
- Ensure that >80% of patients with poor asthma control have had their medication optimized
- Have written asthma action plans provided to >80% of patients with diagnosed asthma
- Reduce acute health care costs related to asthma by 50%

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Identify resources

Local support of implementation initiatives is essential, and funding should be identified at the level of governments, funding agencies, medical or professional societies and industry.

Set timelines

A specific agenda should be established, with timelines for roll-out and assessment of interventions.

Distribute tasks to members

Participants should understand their assigned tasks and agree with the agenda. The process could start on a small scale with the most motivated people. Successes are a source of motivation for all, so it is helpful to initially select interventions with the highest chance of success and with an achievable timeframe for their implementation (e.g. 3–6 months). Involvement of participants and their performance should be monitored.

Evaluate outcomes

An important part of the implementation process is to establish a means of evaluating the effectiveness of the program and any improvements in quality of care. The Cochrane Effective Practice and Organization of Care Group (EPOC) offers suggestions on how to assess the effectiveness of interventions.[584]

Evaluation involves surveillance of traditional epidemiological parameters, such as morbidity and mortality, as well as specific audits of both process and outcome within different sectors of the health care system. Each country should determine its own minimum sets of data to audit health outcomes.

A variety of assessment tools are available to facilitate consistent and objective assessment of asthma morbidity and asthma control in the target population.[214] Recording the results of these assessments at each clinical visit can provide the clinician with a long-term record of a patient's response to their treatment. This type of direct feedback has several benefits. It is a means for the patient and health care provider to become familiar with good versus poor control of asthma (and to start to aim for the former); an indicator of changes in asthma control in response to changes in treatment; and a reference point against which deteriorating asthma can be evaluated. Use of administrative datasets (e.g. dispensing records) or urgent health care utilization can help to identify at-risk patients or to audit the quality of health care. A strategy that includes providing health care providers with direct feedback about specific health care results of their patients may be particularly important for general practitioners, who treat many diseases in addition to asthma, and thus could not be expected to know every guideline in detail.

7. Continuously review progress and results to determine if the strategy requires modification

Following the initial evaluation of outcomes of the implementation program, the working party should determine whether the strategies or initiatives need to be changed or improved. Methods should be established for ensuring that the intervention can be sustained, and individuals who will be responsible for ensuring its continuity should be identified, especially in terms of on-going financial and organizational support. Regular communications on the project's impact on asthma outcomes may help to maintain interest in the project and ensure continued resources.

ECONOMIC VALUE OF IMPLEMENTING MANAGEMENT RECOMMENDATIONS FOR ASTHMA CARE

Cost is recognized as an important barrier to the delivery of optimal evidence-based health care in almost every country, although its impact on patients' access to treatment varies widely both between and within countries. At the country or local level, health authorities make resource availability and allocation decisions that affect populations of asthma patients by considering the balance and trade-offs between costs and clinical outcomes (benefits and harms), often in the context of competing public health and medical needs. Treatment costs must also be explicitly considered at each consultation between health care provider and patient to assure that cost does not present a barrier to achieving good asthma control.[585] Thus, those involved in the adaptation and implementation of asthma guidelines require an understanding of both the cost and cost effectiveness of various management recommendations in asthma care.

GINA DISSEMINATION AND IMPLEMENTATION RESOURCES

Educational materials based on the *Global Strategy for Asthma Management and Prevention* are available in several forms and can be found on the GINA Website (www.ginasthma.org).

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