Sumário *Content*

Editorial *Editorial*
Hisbello S. Campos — 1

Artigo original *Original Article*

Epidemiology of Asthma
Epidemiologia da Asma
Joan B Soriano, Hisbello da Silva Campos — 3

Asthma Pathogenesis
Patogênese da Asma
Michael C. Pynn, Catherine A. Thornton, Gwyneth A. Davies — 11

Asthma as a Cause of Death
Asma como Causa de Morte
Thais Mauad, Diogenes Seraphim Ferreira — 18

The Diagnosis of Asthma
O Diagnóstico da Asma
Julian M. Hopkin — 25

Fundamentals of Asthma Treatment
Os Fundamentos do Tratamento da Asma
Timothy Scialla, Adam Wanner — 33

The Pharmacogenetics of Asthma and the Road to Personalized Medicine
A Farmacogenética da Asma e o Caminho para a Medicina Personalizada
Victor E. Ortega, Eugene R. Bleecker — 41

Corticosteroid Therapy for Asthma
Corticoterapia no Tratamento da Asma
Peter J. Barnes — 53

Broncodilatadores
Bronchodilators
Hisbello S. Campos, Paulo A. M. Camargos — 60

Medicação anti-inflamatória alternativa aos glicocorticóides para o tratamento da asma: papel dos modificadores de leucotrienos, estabilizadores de mastócitos e outras perspectivas
Anti-inflammatory medication beyond glucocorticoids for asthma therapy: role of leukotriene modifiers, mast cell stabilizers and other perspectives
Priscilla Christina Olsen, Marco Aurélio Martins — 65

Asthma Guidelines in Day-to-day Practice
Diretrizes de Asma na Prática Diária
Sidney S. Braman — 70

Education of the Person with Asthma as a Fundamental Part of the Management Strategy
Educação do Indivíduo com Asma como Parte Fundamental da Estratégia de Manejo
Martyn R. Partridge — 76

Instrução para autores *Instructions for the authors* — 81

PULMÃO RJ ISSN 1415-4315

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Publicação oficial da Sociedade de Pneumologia e Tisiologia do Rio de Janeiro. Todos os direitos reservados. Indexada no banco de dados do LILACS (BIREME). **Contato:** pulmaorj@gmail.com. **Circulação**: Trimestral. **Distribuição:** assinantes e, gratuitamente, aos sócios da SOPTERJ, às sociedades regionais de pneumologia, a bibliotecas de faculdades e hospitais universitários do Brasil. **Capa:** Figura referente ao artigo Asthma as a Cause of Death.

Órgão Financiador: FAPERJ

EXPEDIENTE

Prefácio

Prefácio

Roberto Stirbulov[1,2]

A asma constitui-se em uma doença inflamatória crônica que, além dos sintomas, muitas vezes incapacitantes, resulta em alterações estruturais importantes das vias aéreas, decorrentes do remodelamento tecidual causado pela inflamação.

Estima-se que 11% da população brasileira sejam portadores de asma, estando sua grande maioria sem preencher os critérios de controle estabelecidos pelas diretrizes nacionais e internacionais. Isso se deve a diversos fatores, entre os quais, a dificuldade de acesso aos medicamentos, a falta de esclarecimento do paciente, a falta de adesão ao tratamento devido e, principalmente, a falta de informação, que deveria ser prestada pelo médico, de que a asma é uma doença crônica, incurável e portanto passível de tratamento prolongado, independentemente da existência de sintomas.

As recentes diretrizes nacionais e internacionais estabelecem critérios de obtenção e manutenção do controle da asma através de medidas medicamentosas e não medicamentosas, entre as quais se destacam o controle de exposição ambiental e a educação em asma, passando pelo importante processo de automanejo; infelizmente, essas medidas têm sido adotadas pela minoria dos médicos.

A consequência dos fatos descritos acima é a constatação de uma relativa falta de consideração em relação à morbidade e à potencial gravidade da asma, o que resulta em mortes desnecessárias e perfeitamente evitáveis que ainda constatamos em nosso meio. A mídia tem notificado casos dramáticos de morte por asma no último ano, em geral, vitimando pacientes jovens; grande parte dessas ocorrências se deve a inadequação de manejo e/ou desconhecimento da gravidade da asma.

Entre as várias estratégias importantes para a redução da morbidade e mortalidade da asma está a educação continuada do médico brasileiro, prerrogativa própria das escolas médicas, dos instrumentos de divulgação científica e das sociedades médicas envolvidas. Esse processo permanente de informação deve envolver desde o entendimento da doença, com dados sobre sua fisiopatologia e epidemiologia, a noções de definição, classificação, obtenção e manutenção do controle e manejo terapêutico dinâmico, escalonado e estruturado, feito de acordo com o

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estado de controle. Além disso, torna-se fundamental a divulgação do fato de que a asma não tem cura e que seu tratamento deve ter, levando-se em conta a constância, o mesmo padrão de tratamento do diabetes ou da hipertensão arterial.

A publicação do presente suplemento se reveste de extrema importância, não só pelos dados relatados acima, como também pela excelência dos temas e de seus respectivos autores, que estão entre os mais respeitados do mundo. Esses professores e pesquisadores são responsáveis pelas mais importantes publicações sobre o tema, como também pelas principais diretrizes sobre asma, cujas recomendações são largamente adotadas.

A Sociedade de Pneumologia e Tisiologia do Estado do Rio de Janeiro cumpre, com a presente obra, um papel de destaque na Pneumologia brasileira, com a disseminação de informações importantes, de alto teor científico e com aplicabilidade prática imediata para os profissionais de saúde que atuam no manejo da asma no Brasil.

Editorial

Palavras do Editor

Hisbello S. Campos[1,2]

Aquilo que chamamos de asma pode ser definido de forma simplista como o resultado da interação entre determinados genes e o meio ambiente. Desse encontro, resultam diferentes formas clínicas com mecanismos patogenéticos distintos, envolvendo uma grande variedade de citocinas, assim como todas as células funcionais e constitutivas do trato respiratório. A situação fica ainda mais complexa quando esse encontro se dá num cenário com outras morbidades, como alergia e obesidade, por exemplo. A interação entre genes, fatores ambientais, células, citocinas, mecanismos alergênicos, determinantes de comorbidades e fatores emocionais gera uma diversidade de mecanismos inflamatórios no pulmão e alterações nos componentes neurais das vias aéreas, que acarretam diferentes apresentações clínicas, respostas terapêuticas e prognósticos.

O asmático é único quando visto sob o prisma das alterações básicas do trato respiratório e dos sintomas cardeais. Certamente, todos os asmáticos compartilham características comuns: inflamação do trato respiratório, obstrução intermitente ao fluxo aéreo, hiper-responsividade brônquica, hipersecreção de muco, hipertrofia e hiperplasia da musculatura lisa peribrônquica. Praticamente todos os pacientes, em maior ou menor grau, em momentos distintos, referem dispneia, sibilo, tosse (geralmente seca e noturna) e sensação de opressão torácica. Entretanto, as diferentes apresentações clínicas, mecanismos patogenéticos, fatores desencadeantes, respostas terapêuticas e prognósticos não permitem que a asma seja vista como uma doença única, mas múltipla, tal qual uma síndrome.

Tradicionalmente, as diferentes formas de apresentação da asma são categorizadas em fenótipos, da seguinte forma:

• Agrupando asmáticos de acordo com a semelhança de apresentações clínicas

• Usando múltiplas variáveis, como características clínicas (idade de início, gravidade, limitação fixa do fluxo aéreo, etc.)

• Determinando fatores associados com ou desencadeantes de sintomas (por exemplo, alérgenos, aspirina e obesidade)

• Detectando aspectos patobiológicos (inflamação eosinofílica ou neutrofílica)

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Entretanto, a classificação por "tipos clínicos" de asmáticos visando definir a orientação terapêutica e a previsão prognóstica não parece ser adequada.

Muitas das características usadas para compor os fenótipos da asma são clinica e fisiopatologicamente inespecíficas, gerando numerosos subgrupos. Mais ainda, o fenótipo não está diretamente relacionado ao processo subjacente determinante da alteração, nem identifica o mecanismo patogenético específico. Por essa razão, vem sendo proposta uma nova maneira de classificar a asma, usando endotipos em lugar dos fenótipos. Por definição, endotipos compreendem um subtipo de uma determinada alteração, definido por um mecanismo funcional ou fisiopatológico distinto. Os mecanismos subjacentes em muitos dos endotipos propostos ainda não estão esclarecidos, mas, certamente, a compreensão deles permitirá identificar alvos terapêuticos e biomarcadores capazes de fornecer critérios diagnósticos e prognósticos formais. Só assim pode-se pensar em personalizar o tratamento, tornando-o mais efetivo, e apontar os perfis necessários para os novos desenvolvimentos farmacológicos. Além disso, será possível indicar a melhor maneira e momento de usar as alternativas terapêuticas atualmente disponíveis.

Olhar a asma como uma doença inflamatória crônica das vias aéreas, que se expressa por episódios repetidos de obstrução variável ao fluxo aéreo, fez com que a corticoterapia inalatória fosse considerada seu pilar terapêutico e que o broncodilatador fosse o instrumento ideal de resgate nos períodos sintomáticos. Entretanto, na medida em que o conhecimento sobre os mecanismos envolvidos na patogenia da asma vem crescendo, novos alvos terapêuticos e a necessidade de novos fármacos vêm sendo identificados.

Certamente estamos avançando, mas a estrada ainda é longa. É inegável que a terapia associada — corticosteroide e β2-agonista de longa duração inalatórios — é capaz de controlar a maioria dos asmáticos. Porém, uma fração dos nossos pacientes continua sintomática, sem possibilidade de conseguir reverter muitas das disfunções.

A resposta terapêutica e o prognóstico são variáveis e, por vezes, imprevisíveis. Por essa razão, o tratamento da asma não deveria ser padronizado, mas personalizado. Idealmente, a abordagem terapêutica deve ser direcionada para reverter o mecanismo patogênico específico em cada asmático. Isso só será possível quando os diferentes mecanismos e alvos terapêuticos envolvidos forem esclarecidos e, subsequentemente, as terapias ideais forem identificadas.

No presente suplemento de asma editado pela Sociedade de Pneumologia e Tisiologia do Estado do Rio de Janeiro, são apresentados e discutidos alguns dos aspectos mais relevantes na asma. Os autores compõem um grupo de renomados pesquisadores que aceitaram o convite para compartilhar seu saber conosco. Eles são responsáveis por grande parte dos avanços na compreensão dos mecanismos envolvidos na asma e na maneira de abordar os pacientes. A eles, o nosso muito obrigado.

Artigo original

Epidemiology of Asthma

Epidemiologia da Asma

Joan B Soriano[1], Hisbello da Silva Campos[2]

RESUMO

Quando comparadas às principais causas globais de doença e morte, as doenças respiratórias recebem menos atenção e financiamento. Particularmente na asma, todos os indicadores epidemiológicos sinalizam um grande e crescente problema de saúde pública.

Estima-se que 300 milhões de pessoas em todo o mundo sejam asmáticas e que 180.000 mortes anuais sejam causadas por asma. No Brasil, o estudo ISAAC identificou áreas com altas prevalências de asma, similares às do norte da Europa e da Oceania. Enquanto um estudo de mortalidade concluiu que a asma é responsável por mais de 2.000 mortes anuais no Brasil, ou seja, cerca de 6 por dia, com uma grande variação regional, outro estudo sobre morbidade quantificou cerca de mil hospitalizações diárias, representando um custo de R$100 milhões anuais para o Sistema Único de Saúde.

Pode-se concluir que, face às mudanças demográficas nas populações, no estilo de vida e à epidemia tabágica, a asma continuará sendo um peso crescente em vários países do mundo, incluindo o Brasil.

Descritores: Asma/economia; Asma/epidemiologia; Asma/mortalidade; Asma/prevenção & controle; Brasil.

ABSTRACT

Respiratory diseases in general receive little attention and funding in comparison with other major causes of morbidity and mortality. For asthma in particular, all epidemiological indicators suggest a huge and growing burden.

It is estimated that, worldwide, 300 million people suffer from asthma and that there are about 180,000 asthma-related deaths annually. In Brazil, the ISAAC surveys identified areas in which the prevalence of asthma is high, similar to that observed for Northern Europe and Oceania. Mortality studies have shown that, in Brazil, there are more than 2,000 asthma-related deaths per year, or approximately 6 per day, with considerable regional variability, whereas morbidity studies have demonstrated that there are approximately 1,000 hospital admissions for asthma every day, at an annual cost of 100 million Brazilian reals to the Brazilian Unified Health Care System.

We conclude that, as a result of changing demographics, lifestyle changes, and the smoking epidemic, the burden of asthma is and will be growing, worldwide and in Brazil.

Keywords: Asthma/economics; Asthma/epidemiology; Asthma/mortality; Asthma/prevention & control; Brazil.

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The authors declare that they do not have any potential conflict of interest.

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INTRODUCTION

Asthma is a serious health problem that affects people of all backgrounds and all ages. According to data published in the World Report on Asthma in 2004, an estimated 300 million people suffer from asthma (1). That estimate was later endorsed by the World Health Organization and the Global Alliance against Chronic Respiratory Diseases (2,3). Therefore, among respiratory diseases, asthma is only surpassed by rhinitis, from which 400 million suffer (Table 1). Taken together, chronic respiratory diseases affect approximately 1.15 billion (16.4%) of the 7 billion people in the world.

Table 1 - Estimated prevalence of chronic respiratory diseases worldwide.

Condition	Number of Individuals affected
Asthma	300 million
Chronic obstructive pulmonary disease	210 million
Rhinitis (excluding asthma)	400 million
Sleep-disordered breathing	100 million
Other	50 million
Total	1.15 billion

Source: Beasley (1).

In 2009, the Global Initiative for Asthma reported that the overall prevalence of asthma (in children and adults) was between 1% and 18%, depending on the country, with considerable heterogeneity when broken down by age, gender, and region. The report also identified a recent reduction in asthma prevalence among adolescents in 13-14 year age bracket living in North America or Western Europe, in contrast to what was reported for countries in which the prevalence of asthma had previously been lower (4,5). However, the overall proportion of children and adolescents with asthma increased, probably because of improvements in diagnostic techniques (1).

The asthma burden can be assessed in terms of prevalence, mortality, morbidity, and costs. Although incidence rates can be also considered, given the lifelong duration of asthma and the fact that the onset of asthma symptoms can occur at any age, the incidence rate is a less reliable metric by which to assess the epidemiology of asthma. Therefore, in this review, we briefly summarize the available data on the prevalence, mortality, morbidity, and costs of asthma.

PREVALENCE

Whatever the disease, prevalence estimates depend on the definition that is used for diagnosis. The asthma prevalence data currently available are the result of two major international epidemiological studies initiated in the early 1990s: the European Community Respiratory Health Survey (ECRHS), which studied the prevalence of asthma in young adults (6), and the International Study of Asthma and Allergies in Children (ISAAC), which analyzed the pediatric population (7).

After the first wave of data (for 1993 and 1994) had been analyzed (8), the ECRHS reported that the average prevalence of asthma among individuals between 20 and 44 years of age, across 22 countries, was 4.5%. It also showed that the prevalence rates were highly variable among different geographical areas (6). Subsequent ECRHS reports examined the population by age bracket and showed that there was a generational increase in asthma prevalence, an increase that was highly variable among countries (9), as can be seen in Figure 1. A reassessment of the cohort of young adults who had participated in the ECRHS (5-11 years after the initial assessment) showed an increase in the number of patients treated with medication to control their asthma, without an increase in the number of patients with asthma symptoms (10). This raised two hypotheses: either treatments had become more effective and were being used more widely; or more patients were being diagnosed with mild asthma.

In the first phase of the ISAAC study, conducted in 19 countries in 1994, it was found that the prevalence of asthma symptoms was higher in children and adolescents (14 years of age or younger) than in adults (7). In addition, the prevalence varied greatly among countries, from 2% in Indonesia to 32% in the United States. There was a good correlation between the ISAAC data and the ECRHS data, for the various countries (6,7). It is of note that, within the 17 countries evaluated in both studies, there was a strong correlation between the phase I ISAAC data and the phase I ECRHS in terms of the prevalence of "wheeze in the last 12 months", the former explaining 64% and 74% of the variation of the latter at the country level and at the facility level, respectively. There was also generally good agreement between the two surveys in terms of the international patterns observed for self-reported asthma (74% at the country level and 36% at the facility level), self-reported asthma before age 14 yrs (64 and 26%, respectively), hay fever (61 and 73%, respectively), and eczema (41 and 50%, respectively). Therefore, although there were differences in the absolute levels of prevalence observed in the two surveys, there was good overall agreement between the ECRHS and the ISAAC (11).

By integrating ECRHS and ISAAC data, together with other local studies and estimates (12), the geographic distribution of asthma can be depicted (Figure 2). As can be seen in Figure 2, there are still many regions of the world, particularly in Africa and Asia, for which there are no data. It can be also seen that the prevalence of asthma is highest (≥ 10%) not only in Australia, New Zealand, Western Europe,

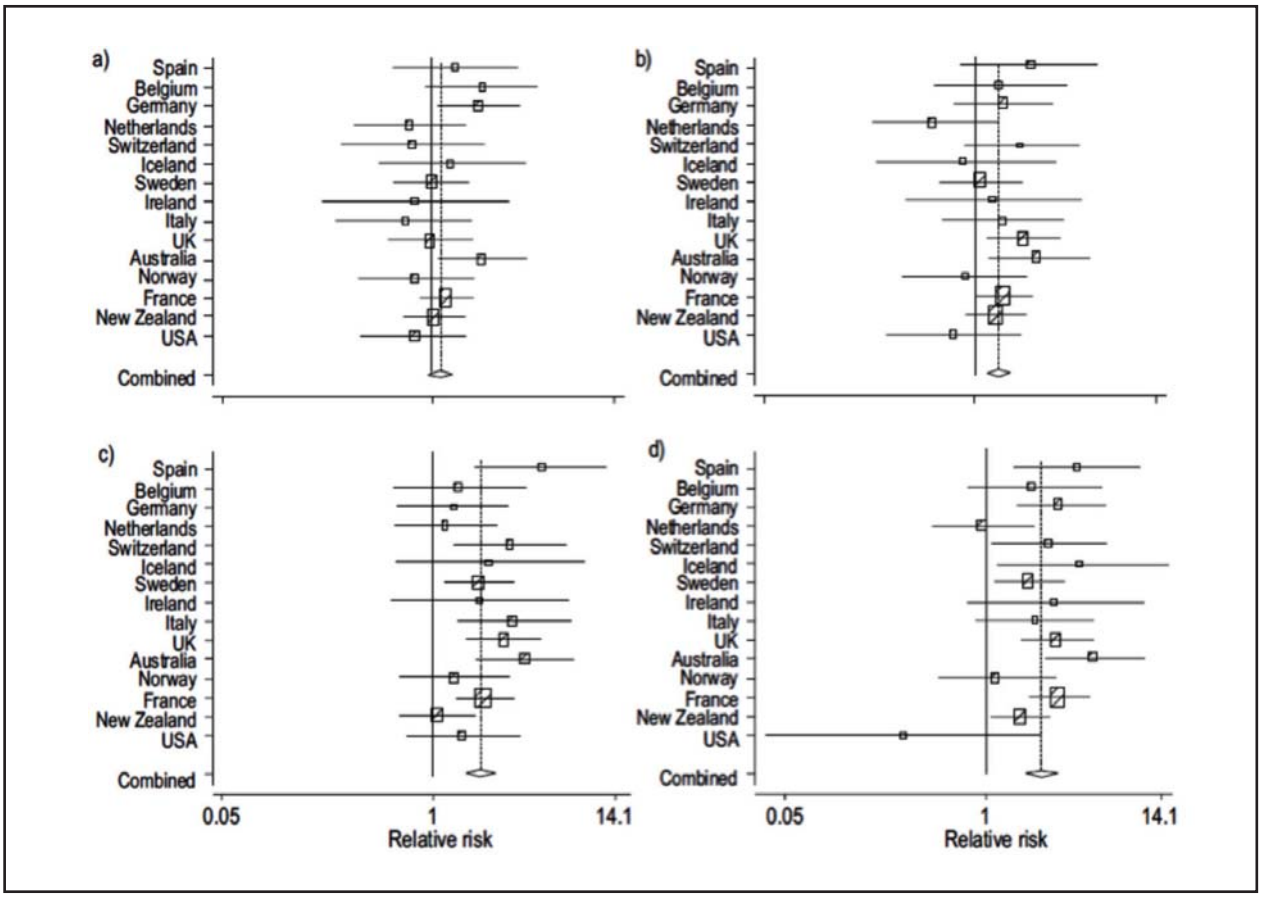

Figure 1 - Generational increase in the prevalence of asthma according to the ECRHS.

Source: Sunyer et al. (9).

Note: The relative risks and respective 95% confidence intervals are presented for each asthma cohort with respect to the baseline cohort (i.e., those born between 1946 and 1950) by country, and the relative risk combo. a) 1951-1955 cohort; b) 1956-1960 cohort; c) 1961-1965 cohort; and d) ≥ 1966 cohort. Countries are ranked according to the prevalence of asthma adjusted for age and sex in the 1946-1950 cohort: 2.2% in Spain; 3.5% in Belgium; 4.6% in Germany; 6.0% in the Netherlands; 6.1% in Switzerland; 7.8% in Iceland; 8.0% in Sweden; 8.2% in Ireland; 9.7% in Italy; 10.0% in the UK; 11.0% in Australia; 11.0% in Norway; 12.5% in France; 19.8% in New Zealand; and 20.2% in the U.S. The box size is inversely proportional to the variation of relative risk. The horizontal lines represent 95% confidence intervals.

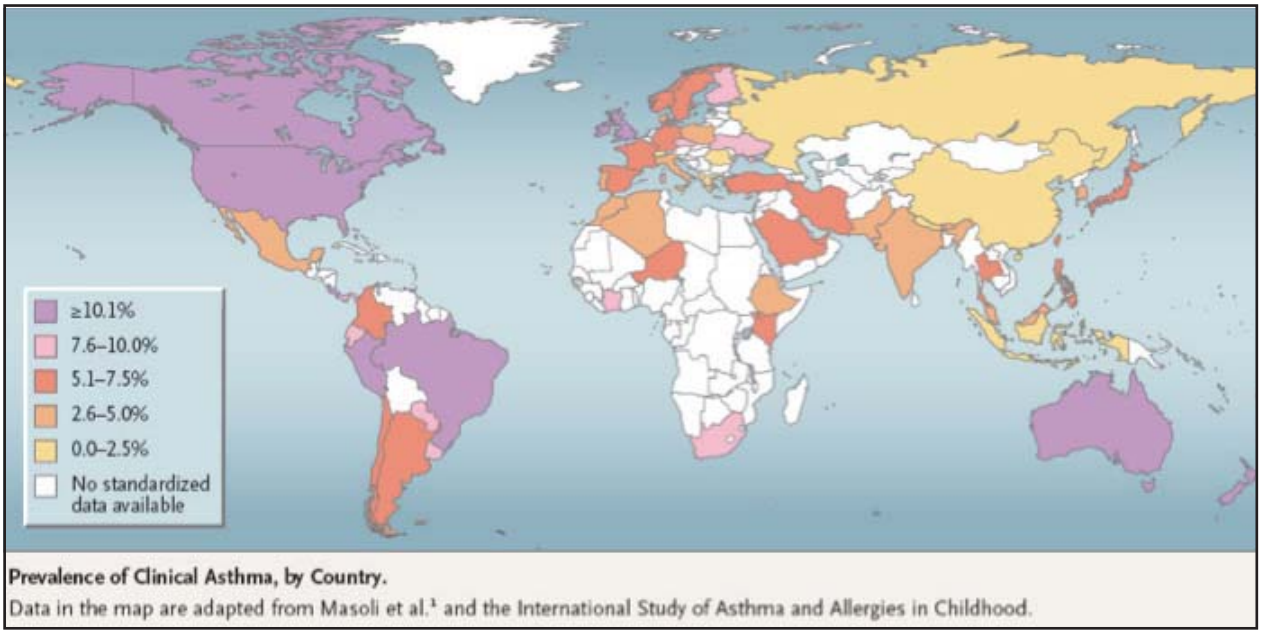

Figure 2 - Geographic distribution of asthma prevalence, where data are available.

Source: Mantzouranis (12).

North America and other English-speaking countries but also in Brazil and some other countries. In fact, the ISAAC showed that Brazil was within the top quartile for asthma prevalence, ranking slightly below Peru and Costa Rica, whereas it ranked slightly above Paraguay and Uruguay (Figure 3).

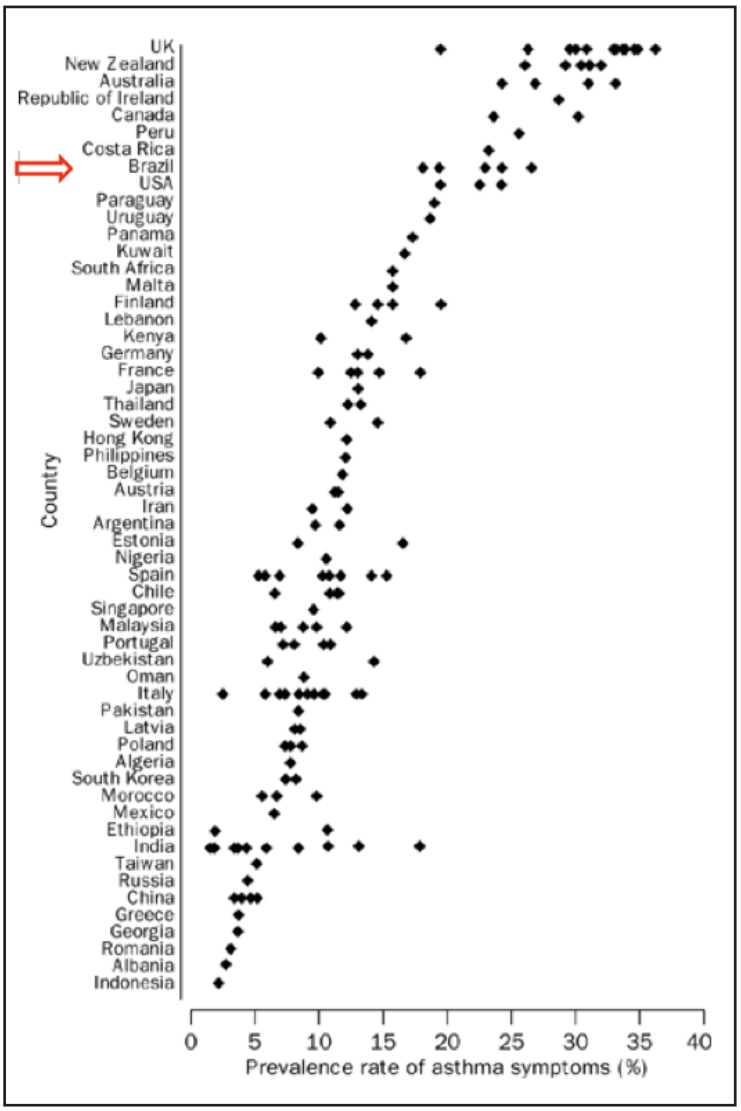

Figure 3 - ISAAC symptoms data
Source: ISAAC (7).

MORTALITY

The true number of asthma-related deaths is difficult to determine, particularly among adults and the elderly, even among those who die in the hospital. In addition, death from asthma is becoming a rare event. Accordingly, asthma mortality data have to be always interpreted with caution. However, although in absolute numbers they are relatively rare events, most fatal or near-fatal episodes could be prevented. It is estimated there are approximately 180,000 deaths annually due to asthma. The report published by Global Initiative for Asthma in 2004 stated that one in every 250 deaths worldwide is attributable to asthma (1). However, since the late 1980s, there has been a widespread and progressive decline in the asthma mortality rate, which fell to 0.23 per 100,000 population in the 2004-2005 period, with an average reduction of 63% between 1985 and 2005 (13).

Recently, asthma mortality in Brazil was revisited (14). Data were collected from the Brazilian National Mortality Database for two periods: 1980-1995, when the tenth revision of the International Classification of Diseases (ICD-9) code 493 was used; and 1996-2006, when the ICD-10 codes J45 and J46 were used. It was reported that during the 1980-2006 period, asthma was responsible for an average of 2,118 deaths per year in Brazil, or approximately 6 per day, with considerable regional variability (Figure 4). The overall asthma mortality rate was 1.5 per 100,000 habitants, and there were slightly more deaths among females than among males (1.7/100,000 vs. 1.3/100,000). For the period as a whole (1980-2006), the asthma mortality rate trended downward by 0.2% per year. Of all asthma-related deaths 16% occurred among children under 5 years of age and 58% occurred among individuals 55 years of age or older (Table 2). The fact that a high proportion of all asthma-related deaths (72%) occurred at health care clinics might indicate that there is a lack of efficient ambulatory care for the asthmatic population.

MORBIDITY AND COSTS

Morbidity assessment includes physician visits, emergency room visits, and hospital admissions. Because of the high prevalence of asthma and of the associated morbidity, together with the fact that most asthma patients live for many years with a chronic condition that does not reduce their life expectancy, therefore requiring drug treatment, as well as scheduled and unscheduled care, there is a significant economic burden associated with asthma. In developed countries, asthma care is thought to account for 1-2% of the total public health care budget (15).

In Brazil, there is a lack of national data on asthma morbidity. A recent report investigated hospital admissions during the 1998-2008 period (16). Data were obtained from the database of the Information Technology Department of the Brazilian Sistema Único de Saúde (SUS, Unified Health Care System), which includes all public (SUS-funded) hospitals. During the period studied, the ICD-10 codes J45 (asthma) and J46 (status asthmaticus)

were employed. The report concluded that asthma was responsible for 328,620 hospital admissions per year (900/day), corresponding to 177.4 such admissions per 100,000 population, being slightly higher among females. In most cases, the J45 diagnostic classification was used as the indication for hospitalization (88% vs. 12% for the J46 classification). Over the period studied, there was a downward trend of 5% per year (Figure 5) and hospital mortality rates were low (0.3%). Between 1998 and 2008, the annual average SUS expenditures related to hospital admissions for asthma, in Brazilian reals (R$), was R$103.5 million, having increased by 7% per year over the period. The highest hospitalization rate was among children under 5 years of age, followed by individuals 55 years of age or older, the latter possibly indicative of cases of chronic obstructive pulmonary disease misdiagnosed as asthma. In that same report (16), it was concluded that exacerbations of asthma resulted in approximately 1,000 hospital admissions per day during the period studied, at an annual cost to the SUS of R$100 million. The number of hospital admissions and the cost remained relatively stable over the period under study.

Table 2 - Asthma mortality rates (per 100,000 population) by age bracket. Brazil, 1980-2006.

	Age bracket (years)									
Year	< 1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	≥ 75
1980	7.94	2.43	0.22	0.22	0.51	1.08	2.02	6.32	12.23	28.23
1981			0.14	0.23	0.54	0.86	2.07	4.81	10.97	23.49
1982			0.16	0.22	0.52	0.98	2.01	4.96	10.35	21.78
1983			0.18	0.23	0.46	0.95	1.97	4.77	10.73	24.36
1984			0.16	0.25	0.50	0.80	1.95	3.78	9.21	20.33
1985			0.15	0.24	0.41	0.65	1.69	3.67	8.17	21.30
1986			0.17	0.19	0.39	0.90	1.99	4.26	9.47	19.06
1987			0.16	0.19	0.44	0.84	1.54	3.14	6.79	17.60
1988			0.16	0.17	0.34	0.64	1.76	3.30	8.37	19.35
1989			0.17	0.25	0.45	0.84	1.44	3.27	7.25	17.36
1990			0.14	0.21	0.37	0.73	1.66	3.53	8.17	19.88
1991	3.81	1.37	0.13	0.15	0.27	0.67	1.39	3.05	7.18	15.83
1992			0.19	0.21	0.34	0.67	1.50	3.87	7.49	18.62
1993	3.83	1.34	0.14	0.21	0.41	0.90	1.81	4.42	9.61	20.39
1994	3.62	1.51	0.25	0.22	0.37	0.90	2.14	3.91	9.58	19.76
1995	3.99	1.38	0.18	0.22	0.47	1.02	1.91	4.93	9.52	21.63
1996	2.57	0.97	0.16	0.24	0.40	0.69	1.75	4.06	8.62	17.95
1997	3.07	1.12	0.11	0.24	0.42	0.77	1.77	3.97	8.60	19.76
1998	2.31	1.04	0.11	0.17	0.36	0.88	1.88	4.05	8.34	20.16
1999	1.54	1.03	0.14	0.24	0.40	0.80	1.75	3.77	8.71	21.12
2000	1.96	0.88	0.14	0.14	0.32	0.71	1.48	3.16	7.67	17.91
2001	2.05	0.84	0.15	0.13	0.30	0.64	1.54	3.36	7.54	16.82
2002	1.75	0.78	0.09	0.16	0.31	0.61	1.24	3.15	6.66	16.70
2003	1.91	0.79	0.08	0.15	0.31	0.67	1.53	2.80	6.69	16.77
2004	1.24	0.59	0.09	0.13	0.32	0.57	1.44	3.44	6.23	18.26
2005	1.46	0.63	0.10	0.17	0.30	0.67	1.36	2.99	5.65	17.93
2006	1.41	0.61	0.12	0.13	0.38	0.77	1.69	3.15	7.48	23.26
Average	2.34	0.96	0.15	0.20	0.39	0.78	1.71	3.85	8.42	19.84

Source: Campos (14).

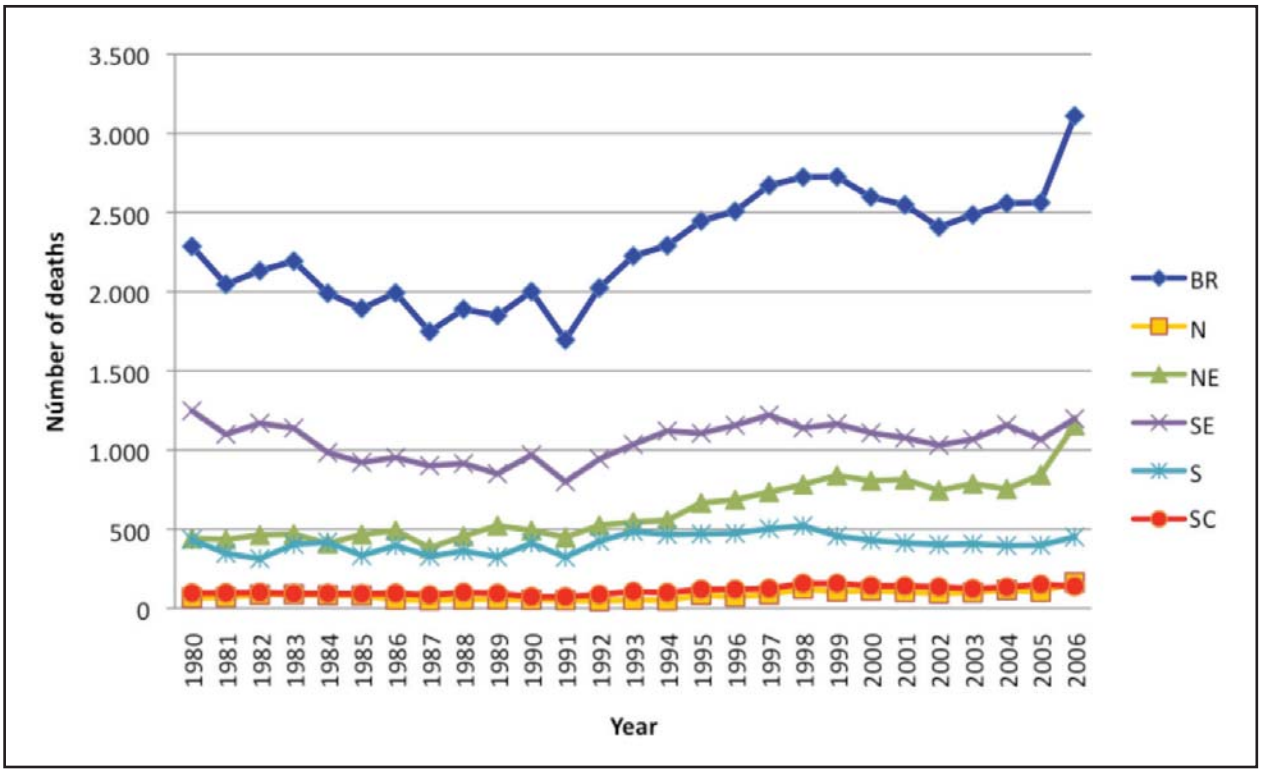

Figure 4 - Total annual number of asthma deaths by region. Brazil, 1980-2006.

BR: Brazil (nationwide); N: north; NE: northeast; SE: southeast; S: south; SC: south-central.
Source: Campos (14).

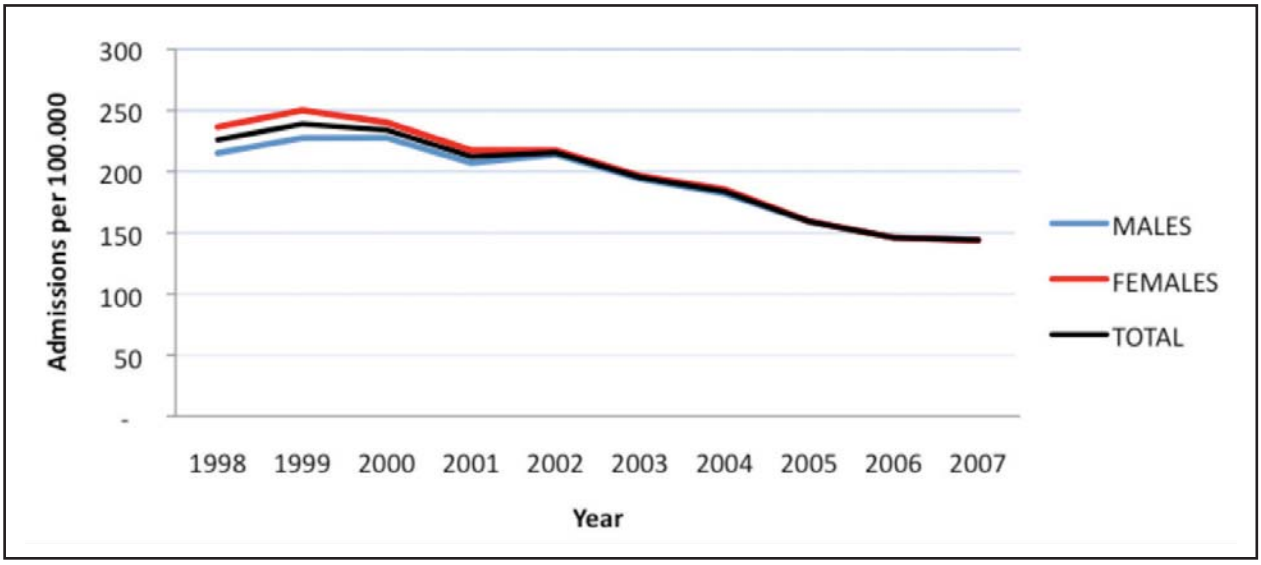

Figure 5 - Trends in asthma-related admissions to SUS-funded hospitals, by gender. Brazil, 1998-2007.

Source: National Institutes of Health (16).

INFERENCES AND FUTURE TRENDS

The many causes of asthma can be classified as host risk factors (most of them non-modifiable, such as genetic predisposition, atopy, airway hyperresponsiveness, gender, and ethnicity) or environmental risk factors (most of which are modifiable). Environmental risk factors can be further subdivided into susceptibility factors (indoor/outdoor allergens, occupational sensitizers, tobacco smoke, air pollution, respiratory infections, parasitic infections, socioeconomic status, overcrowding in homes, diet, drugs, and obesity) and precipitating factors (indoor/outdoor allergens, air pollutants, respiratory infections, exercise-induced hyperventilation, meteorological changes, pollutants such as sulfur dioxide, foods/food additives, drugs, high levels of expressed emotion at home, smoking in the home, and irritants). Such a myriad of risk factors produces multiple, varying effects in individuals and populations, thus making asthma a complex disease.

A number of hypotheses have been proposed in order to explain the worldwide increase in the prevalence of asthma: the hygiene hypothesis (17), which suggests that there is an inverse association between increased exposure to other children during childhood and allergen sensitization; the westernization hypothesis (18), which posits that exposure to new types of foods can trigger asthma; and the lesser-known physiological hypothesis (19), in which obesity, a sedentary lifestyle, and a lack of aerobic activity are though to predispose children to asthma. The last merits further consideration, given that an "indoor" lifestyle includes at least three elements related to the development of asthma: greater exposure to indoor allergens, the potential for overeating, and the lack of physical activity. One can argue that obesity itself increases lung inflammation. However, we could also argue that the lack of physical activity (particularly that involved in normal outdoor play) has removed a form of protection that previously acted to control wheezing. All three of these hypotheses are applicable, at least in part, to the current situation in Brazil, as well as in many other countries, in Latin America and elsewhere. Should we expect an asthma epidemic in Brazil? The change to a more westernized lifestyle, including diet changes, less time spent outdoors, and architectural modifications of houses (including double-glazing, more carpeting, central heating, and air conditioning, and therefore less home ventilation and more recirculation of dust and allergens) has been relatively swift in Brazil. In addition, asthmogenic factors at the population level, such as urban overcrowding, smaller family sizes, universal vaccination, reductions in the numbers of parasites, exposure to pets, smoking, and the abovementioned more sedentary lifestyle have become more predominant. Therefore, all signs point to the possibility that the already high asthma prevalence rates reported in the ISAAC and other studies conducted in Brazil are set to increase in the near future. To quantify the asthma problem and to allocate health resources to tackle the individual and population burden, with the objective of minimizing the impact of chronic respiratory disease, close monitoring of epidemiological trends is warranted. Interventions aimed at reducing the underdiagnosis and undertreatment of asthma should be coupled with those aimed at reducing misdiagnosis and overtreatment. Learning and applying lessons from countries where the problem of asthma was pronounced might be considered (20), with an action program focused on the dissemination of new knowledge, especially in the primary care sphere. The focus might be on screening symptomatic children and adults, as well as on treatment with anti-inflammatory drugs from the outset. For example, such a program in Finland reported that, over a 10-year period (21), there was a 54% reduction in the number of days spent in the hospital, at the national level, as well as a 36% reduction in the annual per-patient costs (21). Not only was the incidence of asthma-related death near zero but even hospital admissions for asthma were nearly abolished in the country. Similar asthma projects and programs have been implemented in Argentina, Australia, China, Japan, Mexico, the Philippines, Russia, South Africa, and Turkey. A recent panel discussion identified low rates of dissemination and implementation of national and international treatment guidelines, low levels of continuing medical education and training of primary health care professionals, as well as limited access to and distribution of inhaled corticosteroids, all of which are considered major barriers to the overall success of a national asthma management program. In the less developed asthma programs, under-recognition and undertreatment further limited the success of the programs. Evidence from well-established national asthma management programs suggests that establishment of a successful program entails a logical progression through specific developmental stages, starting with the endorsement and commitment of politicians and stakeholders, followed by epidemiological evaluation, evaluation of the disease burden, and evaluation of access to care and best treatment practices, as well as the optimization of care and maintenance therapy for individual patients (22).

FINAL CONSIDERATIONS

In conclusion, asthma is and will be a huge and growing burden worldwide. This is no less true in Brazil, where changing demographics, lifestyle changes, and the smoking epidemic continue be significant risk factors for asthma.

REFERÊNCIAS

1. Beasley R. The Global Burden of Asthma Report, Global Initiative for Asthma (GINA). Available at: http://www.ginasthma.org 2004.
2. Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. www.who.int/gard/publications/GARD%20Book%202007.pdf Date last updated: 2007.
3. Bousquet J, Kiley J, Bateman ED, Viegi G, Cruz AA, Khaltaev N, Aït Khaled N, Baena-Cagnani CE, Barreto ML, Billo N, Canonica GW, Carlsen KH, Chavannes N, Chuchalin A, Drazen J, Fabbri LM, Gerbase MW, Humbert M, Joos G, Masjedi MR, Makino S, Rabe K, To T, Zhi L. Prioritised research agenda for prevention and control of chronic respiratory diseases. Eur Respir J 2010;36:995-1001.
4. Global Initiative for Asthma. Global strategy for management and prevention. NHLBI/WHO workshop report 2009. Disponible en http://www.ginasthma.com.
5. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality.

Pediatrics 2002;110:315-322.
6. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community respiratory health survey (ECRHS). Eur Respir J 1996;9:687-695.
7. The international study of asthma and allergies in childhood (ISAAC) steering committee. Worldwide variations in the prevalence of asthma symptoms: the international study of asthma and allergies in childhood (ISAAC). Eur Respir J 1998;12:315-335.
8. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community respiratory health survey (ECRHS). Eur Respir J 1996;9:687-695.
9. Sunyer J, Antó JM, Tobias A, Burney P. Generational increase of self-reported first attack of asthma in fifteen industrialized countries. European Community Respiratory Health Study (ECRHS). Eur Respir J 1999;14:885-91.
10. Chinn S, Jarvis D, Burney P, Luczynska C, Ackermann-Liebrich U, Anto JM et al. Increase in diagnosed asthma but not in symptoms in the European Community respiratory health survey. Thorax 2004;59:646-651.
11. Pearce N, Sunyer J, Cheng S, Chinn S, Björkstén B, Burr M, Keil U, Anderson HR, Burney P. Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. Eur Respir J 2000;16:420-6.
12. Mantzouranis EC. Taking your child's breath away--the extension of asthma's global reach. N Engl J Med. 2008 Mar 20;358(12):1211-3.
13. Wijesinghe M, Weatherall M, Perrin K, Crane J, Beasley R. International trends in asthma mortality rates in the 5- to 34-year age group: a call for closer surveillance. Chest. 2009;135(4):1045-9.
14. Campos HS. Asthma mortality in Brazil, 1980-2006.
15. National Institutes of Health. Global strategy for asthma management and prevention. Publication No. 02-3659. Bethesda, MD: National Heart, Lung and Blood Institute; 2002.
16. Campos HS. Asthma as a cause of hospitalization in public hospitals. Brazil, 1998-2008.
17. Strachan DP. Family size, infection and atopy: the first decade of the 'hygiene hypothesis'. Thorax 2000; 55(Suppl 1): S2–S10.
18. Von Mutius E. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994;149:358-364
19. Crater SE, Platts-Mills TAE. Searching for the cause of the increase in asthma. Curr Opin Pediatr 1998.
20. Haahtela T, Klaukka T, Koskela K, Erhola M, Laitinen LA; Working Group of the Asthma Programme in Finland 1994-2004. Asthma programme in Finland: a community problem needs community solutions. Thorax 2001;56:806-14.
21. Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, Nieminen MM, Kontula E, Laitinen LA. A 10 year asthma programme in Finland: major change for the better. Thorax 2006;61:663-70.
22. Lalloo UG, Walters RD, Adachi M, de Guia T, Emelyanov A, Fritscher CC, Hong J, Jimenez C, King GG, Lin J, Loaiza A, Nadeau G, Neffen H, Sekerel BE, Yorgancioğlu A, Zar HJ. Asthma programmes in diverse regions of the world: challenges, successes and lessons learnt. Int J Tuberc Lung Dis 2011;15:1574-87.

Artigo original

Asthma Pathogenesis

Patogênese da Asma

Michael C. Pynn, Catherine A. Thornton, Gwyneth A. Davies[1]

RESUMO

A asma resulta de uma interação complexa entre genes e meio ambiente que leva à tríade característica de obstrução variável do fluxo aéreo, hiper-responsividade e inflamação da via aérea.

Estímulos ambientais, como alérgenos e vírus, agindo em estágios críticos do desenvolvimento, promovem o início e a progressão da doença em pessoas geneticamente suscetíveis. O epitélio, ao interagir com estímulos ambientais e sinalizar para o mesênquima subjacente, direciona para o remodelamento da via aérea. Interações complexas entre subclasses de células T CD4+ efetoras, incluindo as tradicionais Th2 e as mais recentemente descobertas Th9 e Th17, células imunes e estruturais, desencadeiam inflamação e remodelamento da via aérea e são cruciais para a compreensão dos diversos fenótipos de asma. Novos fenótipos, como o de obesidade, podem ajudar a esclarecer mecanismos patogenéticos recentemente descritos na asma.

A patogênese de fenótipos distintos de asma está começando a ser descoberta; esse esclarecimento será crucial para a compreensão dessa doença complexa. O desenvolvimento de uma abordagem biológica e sistemática, integrando biologia molecular e características clínicas, poderá levar a definição de alvos terapêuticos, especialmente na asma grave, e também avançar em busca de um tratamento personalizado na asma.

Descritores: Asma/patologia; Asma/genética; Inflamação/patologia; Remodelação das vias aéreas; Interação gene-ambiente.

ABSTRACT

Asthma arises from complex gene-environment interactions that drive the characteristic triad of variable airway obstruction, airway hyper-responsiveness, and airway inflammation.

Environmental stimuli (e.g., allergens and viruses), acting at critical stages of development, lead to the initiation and progression of disease in genetically susceptible individuals. The epithelium, by interacting with environmental stimuli and with the underlying mesenchyme, directs airway remodelling. Complex interactions between subsets of CD4+ effector T cells, including classical Th2 cells and the more recently discovered Th9 and Th17 cells, as well as immune and structural cells, drive airway inflammation and remodelling. Understanding such interactions is crucial to our understanding of the various asthma phenotypes. Descriptions of newer asthma phenotypes, such as the obesity phenotype, might clarify novel pathogenetic pathways in asthma.

The pathogenetic mechanisms of distinct asthma phenotypes are beginning to be unravelled; clarification will be crucial to our understanding of this complex disease. A systems biology approach integrating genetics, molecular biology, and clinical assessment is needed in order to develop targeted therapeutics, especially for patients with severe asthma, and advance toward tailored treatment of this disease.

Keywords: Asthma/pathology; Asthma/genetics; Inflammation/pathology; Airway remodeling; Gene-environment interaction.

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The authors declare that they do not have any potential conflict of interest.

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INTRODUCTION

Asthma is a chronic inflammatory disease characterised by variable airway obstruction, inflammation, and airway hyper-responsiveness (AHR). The evolutionary origins of asthma are likely to lie in the advantage conferred by a vigorous Th2-cell mediated inflammatory response to parasites, which in asthma is directed against otherwise innocuous agents such as allergens (1). Complex gene-environment interactions underlie the pathogenesis of asthma, and genetic susceptibility interacts with particular environmental stimuli (e.g., allergens and viruses) at critical phases in early life.

In individuals between 5 and 25 years of age, the main predictor of asthma is atopy, which is defined as a genetic predisposition toward the development of IgE-mediated immediate hypersensitivity reactions against common environmental antigens (allergens). However, asthma is not synonymous with atopy, and the population attributable fraction for aeroallergen sensitisation in adults is estimated at 30% (2). In fact, in late-onset, "intrinsic" asthma, certain types of occupational asthma (e.g., isocyanate-induced asthma), and non-allergic asthma in children, Th2 inflammation can occur without elevating circulating levels of IgE (3). Viral infections are major factors in asthma exacerbations, and emerging evidence suggests that such infections play a role in the origins of this heterogenous disease, including the programming of dendritic cells to direct Th2 responses (4,5).

The pathogenesis of airway obstruction in asthma is characterised by the following:

- airway hyper-responsiveness (AHR), resulting in excessive smooth-muscle contraction in response to environmental stimuli
- airway inflammation, involving mast cells, eosinophils, and Th2 cells

Once asthma has become established, the airway remodelling process begins, as evidenced by goblet cell hyperplasia, reticular basement membrane thickening, and smooth-muscle hypertrophy (Figure 1).

Airway Inflammation

It has been postulated that epithelial dysfunction renders the airways susceptible to damage inflicted by viruses, allergens, pollutants, and other insults (6,7). Bidirectional interaction between epithelial and dendritic cells is pivotal to the development of immunological tolerance or inflammation resulting from exposure of the airways to antigens (8). The sub-populations of effector T cells thus generated propagate the inflammatory response in the airways of asthma sufferers. Subsets of CD4+ effector T cells are defined by the arsenal of cytokines they secrete, which reflect the signature expression of transcription factor profiles.

The Th1/Th2 paradigm has underpinned research into the contribution of T cells to airway inflammation for many years. Consequently, the roles that IL-4, IL-5, and IL-13 play in atopy and asthma are well documented: IL-4 promotes allergic sensitisation and IgE production; IL-5 influences the differentiation, maturation, and survival of eosinophils; and IL-13 mediates mucus production, remodelling, and AHR. However, a more extensive array of effector T-cell subsets has emerged (9).

A third major subset of CD4+ effector T cells is that composed of Th17 cells, which play roles in host defence and auto-immunity. The characteristic Th17 cytokines are IL-17A and IL-17F, and Th17 cells primarily influence neutrophil recruitment and activation (10). Interest in Th9 cells, characterised by IL-9 secretion, is also growing. Although IL-9 is considered a Th2 cytokine, a distinct population of IL-9-producing Th9 cells can arise in chronic diseases. The contribution of Th9 cells to chronic airway inflammation has only begun to be elucidated (11,12). The emergent hypothesis is that CD4+ effector T-cell subpopulations differentially contribute to asthma phenotypes. For example, Th17 cells might be more involved in neutrophilic rather than eosinophilic asthma (10).

Other key T-cell subsets postulated to play a role in airway inflammation are regulatory T (Treg) cells, including the naturally occurring CD4+CD25+FoxP3+ subset and induced adaptive CD4+ Treg cells (13,14). In

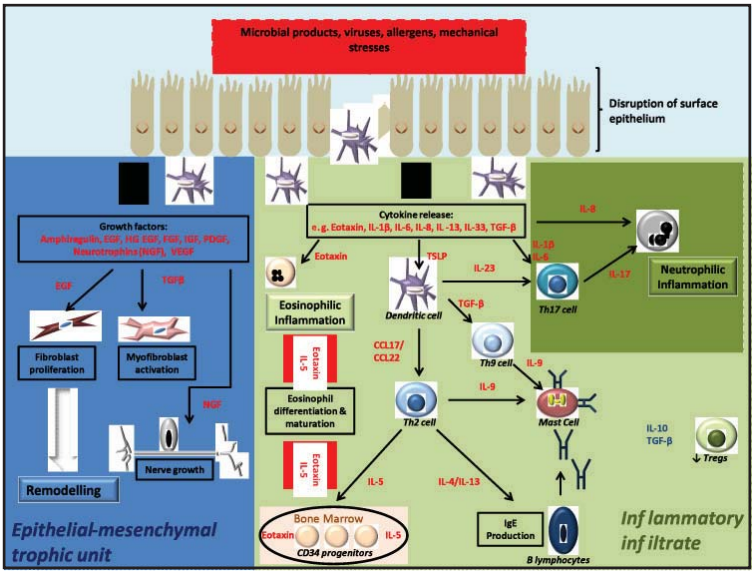

Figure 1 - Schematic representation of the epithelial-mesenchymal trophic unit and inflammatory cells that play important roles in the pathogenesis of asthma.

HB-EGF: heparin-binding EGF; CCL: chemokine (C-C motif) ligand

Note: The epithelium releases a number of growth factors important to the coordination of airway remodelling. The cytokines released promote migration and activation of various inflammatory cells. Th2 cells are pivotal to orchestrating eosinophilic inflammation and IgE production; Th9 cells might play a role in local IL-9 generation. IL-17 (produced by Th17 cells) and IL-8 could play roles in the development of neutrophilic disease. The numbers of Treg cells, which promote immunological tolerance, are decreased, as is their functionality, in asthma sufferers.

individuals without asthma, Treg cells promote immunological tolerance to aeroallergens. Changes in the number, phenotype, or function of Treg cells, including those present in the lungs, have been described in upper and lower airway disease (13,14). Early life events seem to be critical in programming immunoregulatory pathways that underpin immune homeostasis in the airways and other tissues (15,16). Immunoregulatory invariant natural killer T cells, which are reactive to CD1d-presented glycolipids, are also of interest. Such cells are found in human airways where they are relatively rare, but numbers are similar between mild/moderately severe asthma, COPD and controls (17). Additional T-cells subsets implicated in airways inflammation and asthma include CD8+ T cells and gamma-delta T cells (9).

Effector CD4+ T-cell subsets mediate their effects via the release of cytokines that then modulate, either directly or indirectly, the activity of other cell types—including eosinophils, neutrophils, and mast cells, all of which in turn augment the inflammatory response. High numbers of eosinophils are observed in the airways of many asthma patients. However, non-eosinophilic asthma occurs across a range of asthma severity, and there is particular interest in the role of neutrophils in severe asthma. The release of bioactive molecules such as histamines and leukotrienes from degranulated mast cells contributes to airway inflammation and the clinical symptoms of asthma.

The prime function of a barrier is to discriminate between relatively innocuous environmental antigens (including allergens) and infectious pathogens. Various stimuli drive cytokine production at barriers and this creates a local cytokine milieu that further informs the innate immune response and educates the adaptive immune response. Pattern recognition receptors, including Toll-like receptors (TLRs), nucleotide-binding oligomerisation domain-like receptors, and retinoic acid-inducible gene I-like receptors, are critical to that process. The repertoire of pattern recognition receptor expression differs by cell type, is developmentally programmed, and is further influenced by genetic variation and the local microenvironment. Dendritic cells are exquisitely placed, both physically and functionally, to bridge innate and adaptive immunity: they are in intimate contact with the epithelium where they can interact with environmental cues that shape the repertoire of cytokines, chemokines, and co-stimulatory molecules, which they express during antigen-specific priming of the immune response. This determines the nature of the allergen-specific CD4+ effector T-cell response generated.

Epithelium-derived cytokines and chemokines orchestrate the recruitment and activity of multiple cell types. Epithelium-derived eotaxin and IL-8 direct the recruitment of eosinophils and neutrophils, respectively, to the airways. Currently, there is much focus on IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), all of which have been implicated in allergic airway disease (and anti-helminth immune responses) but are not alone in demonstrating such properties (18). Models of airway over-expression are typically used to reveal their role but immunohistochemical and other analyses demonstrate the relevance of IL-25, IL-33, and TSLP to airway inflammation in humans. It has been shown that IL-25 plays a role in regulating IL-9 expression by CD4+ T cells (19), and IL-33 is a chromatin binding nuclear cytokine of the IL-1 family, implicated in classical Th2 cell- and mast cell-mediated asthma and anaphylaxis (20). However, IL-33 is an alarmin released by necrotic cells to recruit and activate immune cells, i.e., to signal damage and amplify the innate immune response (21). Given the recent identification of neutrophil-derived enzymes as critical to the generation of mature bioactive IL-33 (22), neutrophil infiltrates might amplify IL-33 bioavailability in the airways. For its part, TSLP can promote Th2 cytokine-associated inflammation, modulate activity of granulocyte populations, limit the expression of dendritic cell-derived proinflammatory cytokines, and promote Treg responses (23). The recently identified natural helper cells have also been shown to play a role in Th2-dependent immune response. Natural helper cells are non-B, non-T innate effector cells that are activated via IL-25 or IL-33 to promote Th2 cytokine responses and might represent an ancient evolutionary conserved pathway (24,25).

Neuro-effector mechanisms have also been implicated in airway inflammation, with loss of pre-ganglionic, auto-regulatory muscarinic 2 receptors observed after exposure to allergens and viruses. These receptors normally limit the release of the neurotransmitter acetylcholine, which causes bronchoconstriction. Non-adrenergic, non-cholinergic systems might also play a role in airway bronchoconstriction, with substance P and tachykinins causing bronchoconstriction via the natural killer cell receptors 1 and 2, respectively (18).

The Epithelium and Remodelling

There is compelling evidence to support a fundamental role for the airway epithelium and the underlying mesenchyme (the epithelial-mesenchymal trophic unit) in the pathogenesis of asthma. It has been suggested that genetically susceptible individuals have impaired epithelial barrier function with disrupted tight junctions and defective anti-oxidant and innate immune defences (7,26). The epithelium is therefore vulnerable to viral infection in early life, conditioning immature dendritic cells to drive a Th2 "allergic" phenotype. A dysfunctional epithelium is susceptible to allergen sensitisation, and further environmental insults (e.g., exposure to viruses or pollutants), acting in concert with a susceptible genotype during the critical stages of immune system development, are critical to the development and persistence of asthma. In asthma sufferers, bronchial epithelial cells are more

susceptible to rhinovirus infection due to reduced IFN-β production and defences are restored by exogenous IFN-β (27). Susceptibility to recurrent exacerbations is associated with an O-secretor mucin glycan phenotype (28). The concept of epithelial dysfunction provides an explanation for certain aetiological factors in asthma (Table 1) and of exacerbation in response to environmental insults such as exposure to pollutants.

Table 1 - Summary of the main environmental factors (exposures) implicated in the aetiology of asthma.

Factor	Example(s)	Study type	Findings
Allergens	House dust mite	Prospective	Sensitisation increases asthma risk
			Early childhood exposure increases asthma risk
			Minimal threshold level of allergen exposure
	Cockroach allergens	Case control	Increased sensitisation in asthmatics
	Animal allergens: cat/dog	Prospective cohort	Exposure decreases sensitisation to other aeroallergens
			No protective effect on asthma
Pollutants	Nitrogen dioxide (NO_2)	Cross-sectional, prospective	High NO_2 - increased asthma prevalence
			Indoor gas stove use associated with asthma symptoms
			Proximity to roads/elevated NO_2 - increased asthma risk
	Diesel exhaust particles	Mechanistic	Diesel exhaust particles promote dendritic cell maturation
			Diesel exhaust particles cause airway epithelial activation and pro-inflammatory cytokine release
Viral infections		Prospective cohort	High number of viral infections in infancy - reduced risk of asthma and atopy
Smoking	Active smoking	Prospective cohort	Smoking increases risk of asthma development
	Second hand smoking	Cross-sectional	Pre-natal maternal smoking - increased asthma risk
			Post-natal maternal smoking - increased asthma risk
			Adult passive smoking - increased physician-diagnosed asthma
Medication use	Antibiotic use in childhood	Meta-analysis of prospective and retrospective studies	Antibiotic use in first year of life - increased asthma risk
	Hormone replacement therapy (HRT)	Cross-sectional, prospective	HRT use - increased asthma incidence
Obesity		Prospective	Dose-dependent association between body mass index and asthma risk
			Weight loss studies improve disease control
Early menarche		Cross-sectional, longitudinal	Early menarche - higher asthma risk
Peri-natal	Maternal diet	Prospective cohort	↑ Maternal vitamin E - ↓ childhood asthma risk
			↓ Maternal vitamin D - ↑ childhood asthma risk
	Prematurity	Retrospective meta-analyses	Prematurity - higher asthma risk
	Breastfeeding	Prospective cohort	Breastfeeding for 3-6 months - reduced wheeze

Sustained epithelial injury leads to disordered communication with the underlying mesenchyme, thereby triggering airway remodelling (29). The inhibition of epithelial repair results in the release of growth factors, including TGF-β2, which activate subepithelial fibroblasts to form myofibroblasts and promote mucous metaplasia. Myofibroblasts deposit extracellular matrix, thickening the epithelial *lamina reticularis*, and secrete mitogens causing smooth-muscle hypertrophy. Remodelling, including angiogenesis, can occur in childhood asthma, even before a clinical diagnosis of asthma has been made (30-32).

Airway remodelling represents a crucial part of AHR in established asthma and is a major cause of fixed airflow obstruction and declining lung function in more severe asthma. Repeated airway exposure to environmental insults promotes a milieu of persistent inflammation and remodelling associated with progressive disease. Targeting therapeutics toward enhancing epithelial barrier function, as well as exploring novel

anti-inflammatory targets, presents an opportunity to advance asthma treatment.

NEW INSIGHTS – ASTHMA PHENOTYPES AND "ENDOTYPES"

The heterogeneity of asthma is evidenced by the identification of distinct phenotypes, including the early-onset "extrinsic" allergic phenotype, the late-onset "intrinsic" eosinophilic phenotype, and the late-onset, non-eosinophilic female version of the obesity phenotype (33). Despite sharing the common defining feature of variable airflow obstruction, the underlying pathophysiology is likely to differ. Recently, there has been a move toward describing asthma "endotypes", subtypes defined by distinct pathophysiological mechanisms. Several asthma endotypes have been described, including aspirin-sensitive asthma, allergic bronchopulmonary aspergillosis, allergic adult asthma, predictive indices of asthma in childhood, late-onset eosinophilic asthma, and asthma in cross-country skiers (34).

SEVERE ASTHMA

Severe asthma encompasses the early-onset, eosinophilic, neutrophilic, and obesity phenotypes (35). Neutrophilic asthma with no evidence of eosinophilic inflammation is often seen in individuals with severe disease on high-dose steroids. Neutrophilic asthma shows features of innate immune activation within the airways, including upregulation of TLR2 and TLR4 and soluble CD14, as well as enhanced expression of proinflammatory cytokines such as IL-1β and IL-8 (36). This asthma phenotype might also involve systemic changes in innate immune function with upregulation of genes promoting neutrophil survival observed in peripheral blood (37). Upregulation of TNF-α within the airways has also been implicated and identified as a potential therapeutic target (38). Although early studies in steroid-resistant disease, using the anti-TNF-α drug etanercept, have produced promising results (39), those results have not been replicated in larger multi-centre studies (40). Adaptive immune mechanisms, including neutrophil inflammation promoted by Th17 cells, have also been implicated (10).

ASTHMA IN THE OBESE – A NEW ASTHMA PHENOTYPE?

The increasingly prevalent obesity phenotype of severe asthma is characterised by the absence of eosinophilic inflammation, a predominance of females, and late onset (35). Corticosteroid therapy is poorly effective in this group (41,42), which shows a dramatic improvement with weight loss measures, including bariatric surgery (43). Neutrophilic inflammation might explain the relative corticosteroid resistance observed (44). The underlying pathophysiology of the obesity phenotype is currently unknown, although several mechanisms have been suggested (Figure 2). Obesity enhances systemic inflammation through the release of pro-inflammatory cytokines (45), by increasing oxidative stress (46), or via adipocyte-derived hormones (adipokines), which have immunomodulatory effects (47). Although there is much interest in the impact that these mechanisms have on the airways, studies of the topic have produced inconsistent results. Further studies examining the interactions among obesity, asthma, and innate immune function are warranted.

The elucidation of asthma phenotypes and their pathogenesis is crucial to our understanding of this complex disease. A systems biology approach integrating genetics, molecular biology, and clinical assessment is needed in order to develop targeted therapeutics, especially for patients with severe asthma.

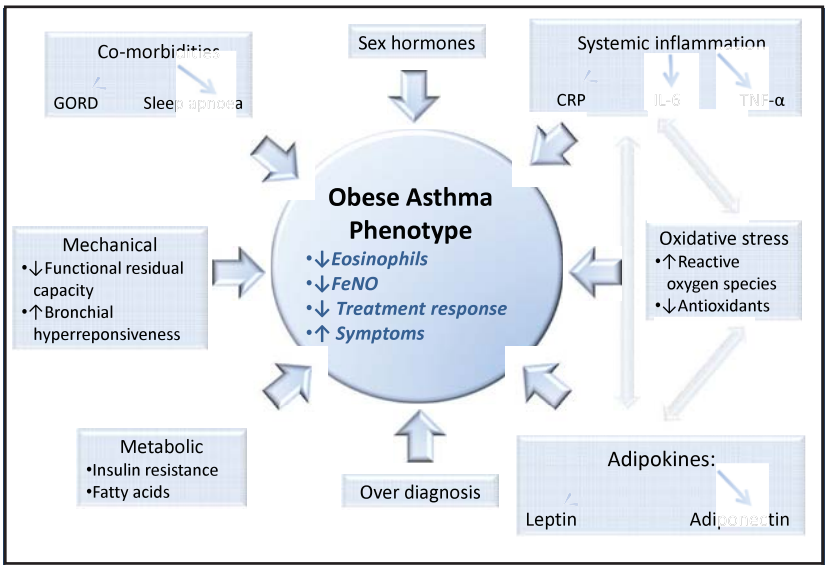

Figure 2 - Diagram illustrating the mechanisms that might link obesity and asthma.

GORD: gastro-oesophageal reflux disease; CRP: C-reactive protein.

Note: Some of these factors could interact with each other: adipokines are known to have many immunomodulatory effects and might promote reactive oxygen species generation; metabolic factors such as insulin resistance might play a role in systemic inflammation; and fatty acids might moderate inflammation via Toll-like receptor signalling.

REFERÊNCIAS

1. Hopkin J. Immune and genetic aspects of asthma, allergy and parasitic worm infections: evolutionary links. Parasite Immunol. 2009;31(5):267-73.
2. Jaakkola MS, Ieromnimon A, Jaakkola JJ. Are atopy and specific IgE to mites and molds important for adult asthma? J Allergy Clin Immunol. 2006;117(3):642-8.
3. Mapp CE, Boschetto P, Miotto D, De Rosa E. Asthma induced by isocyanates: a model of IgE-independent asthma. Acta Biomed 2005;76(Suppl):15–19.
4. Walton RP, Johnston SL. Role of respiratory viral

infections in the development of atopic conditions. Curr Opin Allergy Clin Immunol. 2008;8(2):150-3. Review.
5. Strickland, D. H., J. W. Upham, et al. Epithelial-dendritic cell interactions in allergic disorders. Current Opinion in Immunology 2010;22(6): 789-794.
6. Xiao, C., S. M. Puddicombe, et al. Defective epithelial barrier function in asthma. Journal of Allergy and Clinical Immunology. 2011;128(3):549-556.
7. Holgate ST. The sentinel role of the airway epithelium in asthma pathogenesis. Immunol Rev. 2011;242(1):205-19.
8. Lambrecht BN, Hammad H. The role of dendritic and epithelial cells as master regulators of allergic airway inflammation. Lancet. 2010 Sep 4;376(9743):835-43.
9. Lloyd, C. M. and E. M. Hessel. Functions of T cells in asthma: more than just TH2 cells. Nat Rev Immunol. 2010;10(12):838-848.
10. Cosmi, L., F. Liotta, et al. Th17 cells: new players in asthma pathogenesis. Allergy 2011;66(8): 989-998.
11. Soroosh, P. and T. A. Doherty. Th9 and allergic disease. Immunology 2009;127(4): 450-458.
12. Stassen, M., E. Schmitt, et al. From interleukin-9 to T helper 9 cells. Annals of the New York Academy of Sciences 2011;1247(1): 56-68.
13. Lloyd, C. M. and C. M. Hawrylowicz. Regulatory T Cells in Asthma. Immunity 2009;31(3): 438-449.
14. Robinson, D. S. Regulatory T cells and asthma. Clinical & Experimental Allergy 2009;39(9): 1314-1323.
15. Smith, M., M. R. Tourigny, et al. Children with egg allergy have evidence of reduced neonatal CD4+CD25+CD127lo/- regulatory T cell function. Journal of Allergy and Clinical Immunology 2008;121(6): 1460-1466.
16. Strickland, D. H. and P. G. Holt. T regulatory cells in childhood asthma. Trends in Immunology 2011;32(9): 420-427.
17. Vijayanand, P., G. g. Seumois, et al. Invariant Natural Killer T Cells in Asthma and Chronic Obstructive Pulmonary Disease. New England Journal of Medicine 2007;356(14): 1410-1422.
18. Finkelman, F. D., S. P. Hogan, et al. Importance of Cytokines in Murine Allergic Airway Disease and Human Asthma. The Journal of Immunology 2010;184(4): 1663-1674.
19. Angkasekwinai, P., S. H. Chang, et al. Regulation of IL-9 expression by IL-25 signaling. Nat Immunol 2010;11(3): 250-256.
20. Liew, F. Y., N. I. Pitman, et al. Disease-associated functions of IL-33: the new kid in the IL-1 family. Nat Rev Immunol 2010;10(2): 103-110.
21. Moussion, C., N. Ortega, et al. The IL-1-Like Cytokine IL-33 Is Constitutively Expressed in the Nucleus of Endothelial Cells and Epithelial Cells In Vivo: A Novel 'Alarmin'? PLoS ONE 2008;3(10): e3331.
22. Lefrancais, E., S. Roga, et al. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. Proceedings of the National Academy of Sciences 2012;109(5): 1673-1678.
23. Ziegler, S. F. and D. Artis. Sensing the outside world: TSLP regulates barrier immunity. Nat Immunol 2010;11(4): 289-293.
24. Neill, D. R., S. H. Wong, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature 2010;464(7293): 1367-1370.
25. Saenz, S. A., M. Noti, et al. Innate immune cell populations function as initiators and effectors in Th2 cytokine responses. Trends in Immunology 2010;31(11): 407-413.
26. Message SD, Johnston SL. Host defense function of the airway epithelium in health and disease: clinical background. J Leukoc Biol. 2004 Jan;75(1):5-17.
27. Cakebread JA, Xu Y, Grainge C et al. Exogenous IFN-β has antiviral and anti-inflammatory properties in primary bronchial epithelial cells from asthmatic subjects exposed to rhinovirus. J Allergy Clin Immunol. 2011;127(5):1148-54.
28. Innes AL, McGrath KW, Dougherty RH et al. The H antigen at epithelial surfaces is associated with susceptibility to asthma exacerbation. Am J Respir Crit Care Med. 2011;183(2):189-94.
29. Holgate ST, Davies DE, Lackie PM, et al. Epithelial-mesenchymal interactions in the pathogenesis of asthma. J Allergy Clin Immunol. 2000 Feb;105(2 Pt 1):193-204. Review.
30. Baena-Cagnani C, Rossi GA, Canonica GW Airway remodelling in children: when does it start? Curr Opin Allergy Clin Immunol. 2007 Apr;7(2):196-200..
31. Barbato A, Turato G, Baraldo S, et al. Epithelial damage and angiogenesis in the airways of children with asthma. Am J Respir Crit Care Med. 2006;174(9):975-81.
32. Malmström K, Pelkonen AS, Malmberg LP, et al. Lung function, airway remodelling and inflammation in symptomatic infants: outcome at 3 years. Thorax. 2011;66(2):157-62.
33. Haldar P, Pavord D, Shaw DE, Berry MA, et al. Cluster analysis and clinical asthma phenotypes. American Journal of Respiratory and Critical Care Medicine, 2008;178:218-224.
34. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, et al. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. Journal of Allergy and Clinical Immunology, 2011;127: 355-360.
35. Wenzel S, Severe asthma: from characteristics to phenotypes to endotypes. Clinical and Experimental Allergy, 2012 Jan 18. doi: 10.1111/j.1365-2222.2011.03929.x.
36. Simpson JL, Grissell TV, Douwes J et al. Innate immune activation in neutrophilic asthma and bronchiectasis. Thorax 2007;(62):211-218.
37. Baines KJ, Simpson JL, Bowden NA et al. Differential gene expression and cytokine production from neutrophils in asthma phenotypes. European Respiratory Journal, 2010;35: 522-531.
38. Howarth PH, Babu KS, Arshad HS et al. Tumour necrosis factor (TNFalpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. Thorax, 2005;60(12): 1012-1018.
39. Morjaria JB, Chauhan AJ, Babu KS, et al. The role of a soluble TNFalpha receptor fushion protein (etanercept) in corticosteroid refractory asthma: a double blind randomised placebo-controlled trial. Thorax, 2008;63:584-591.
40. Holgate ST, Noonan M, Chanez P et al. Efficacy and safety of etanercept in moderate-to-severe asthma: a randomised controlled trial. European Respiratory Journal, 2011; 37(6):1352-1359.
41. Boulet LP, Franssen E Influence of obesity on response to fluticasone with or without salmeterol in moderate

asthma. Respiratory Medicine, 2007;101: 2240-2247.
42. Peters-Golden M, Swern A, Bird SS et al. Influence of body mass index on the response to asthma controller agents. European Respiratory Journal, 2006;27:495-503.
43. Dixon AE, Prately RE, Forgione PM et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. Journal of Allergy and Clinical Immunology, 2011;128(3):508-515.
44. Scott HA, Gibson PG, Garg ML et al. Airway inflammation is augmented by obesity and fatty acids in asthma. European Respiratory Journal, 2011. Sep;38(3):594-602.
45. Yudkin JS, Stehouwer CD, Emeis JJ et al. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol, 1999;19: 972-978.
46. Kearney JF, Larson MG, Vasan RS et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham study. Arteriorsclerosis, Thrombosis and Vacular Biology, 2003;23: 434-439.
47. La Cava A, Maltrese G. The weight of leptin on immunity. Nature Reviews Immunology, 2004;4: 371-379.

Artigo original

Asthma as a Cause of Death

Asma como Causa de Morte

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RESUMO

Mortes causadas por asma são incomuns, mas, mesmo assim, respondem por cerca de 287.000 óbitos anuais mundialmente. Embora as taxas de mortalidade por asma venham diminuindo em diversos países, há grande disparidade na mortalidade por asma no mundo. A maior parte das mortes está relacionada ao manejo clinico subótimo.

Fatores frequentemente envolvidos com asma quase fatal e fatal incluem história prévia de crises quase fatais, intubação/ventilação mecânica prévia, hospitalização ou admissão em UTI, falta de adesão ao tratamento, percepção falha de dispneia, distúrbios psicológicos e nível socioeconômico baixo. Na autópsia, os pulmões de pacientes que morreram de asma estão geralmente hiperinflados e os brônquios maiores e menores ocluídos por muco. Os achados histológicos incluem descolamento epitelial, espessamento da lâmina *reticularis* da membrana basal, glândulas submucosas e músculo liso aumentados e composição alterada da matriz extracelular nas vias aéreas grandes e pequenas. A inflamação brônquica é generalizada, sendo proeminente na camada adventícia das pequenas vias.

Os mecanismos que levam à morte na asma não estão claros. O espasmo potente da musculatura lisa e a produção excessiva de muco parecem ser os eventos chave que culminam em morte. Uma exacerbação aguda pode ser mortal em pacientes com asma mal controlada e subtratada e que tenham alterações estruturais nas vias aéreas pré-existentes.

Descritores: Asma/mortalidade; Asma/patologia; Asma/prevenção & controle.

ABSTRACT

Death attributable to asthma is considered uncommon. However, worldwide, there are approximately 287,000 such deaths every year. Although asthma mortality rates are decreasing in many countries, there is a great disparity among countries in terms of asthma mortality in the world. Most asthma deaths are related to suboptimal disease management.

Factors frequently associated with near-fatal and fatal asthma include a previous near-fatal asthma exacerbation, previous intubation/mechanical ventilation, asthma-related admission to the hospital or ICU, lack of treatment adherence, poor perception of dyspnea, psychological disorders and low socioeconomic status. At autopsy, the lungs from patients who died of asthma are usually hyperinflated. The large and small bronchi are occluded with mucus. Histological findings include epithelial detachment, thickening of the *lamina reticularis* of the basement membrane, enlarged submucosal glands, greater airway smooth muscle area, and altered extracellular matrix composition in the large and small airways. Bronchial inflammation is present throughout, with prominent inflammation in the adventitial layer of the small airways.

The mechanisms of death from asthma remain unclear. Pronounced airway smooth muscle constriction and excessive mucous discharge are likely to be key events. In patients with poorly controlled, undertreated, severe asthma, with pre-existing structural alterations in the airways, an acute exacerbation can be deadly.

Keywords: Asthma/mortality; Asthma/pathology; Fatal asthma.

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The authors declare that they do not have any potential conflict of interest.

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INTRODUCTION

Fatal asthma is defined as a severe asthma exacerbation resulting in death (1). Near-fatal and fatal asthma may be seen as a continuum of a very severe asthma exacerbation, which would likely result in fatality if appropriate and timely management were not available.

Many countries have experienced decreases in asthma mortality in the last two decades, especially countries where the use of inhaled corticosteroids increased. Nevertheless, it was estimated that, in 2004, asthma accounted for about 287,000 deaths yearly worldwide (2). Data from the World Health Organization show large discrepancies in asthma mortality among countries, the rates being lower in Europe and North America, whereas rates are higher in Africa, Central Asia, and Central (3).

EPIDEMIOLOGY

Although the mechanisms leading to death from asthma have been not fully elucidated, fatal asthma is frequently associated with suboptimal management and delays in obtaining treatment during the final attack (3).

Asthma mortality risk increases with age, and the mortality rate is approximately 10 times higher among persons over 65 years of age than among those under 34 years of age (4). However, there has been inaccurate reporting of mortality data for the older age groups, because of confusion with other respiratory ailments or concurrent medical conditions (5). In contrast, the rate of false-positive asthma diagnosis is quite low for individuals in the 5- to 34-year age bracket. Therefore, comparisons are typically made relative to the population of asthma sufferers with that age bracket.

Since the 1960s, there have been two epidemics of fatal asthma. During the 1960s, asthma mortality spiked in England, Wales, Scotland, Ireland, Norway, New Zealand, and Australia (6-8). Between 1959 and 1966, the age-adjusted mortality rate (for 5- to 34-year age group) rose from 0.7 to 2.2 per 100,000 population, a threefold increase, in England and Wales (6). This epidemic of fatal asthma was attributed to the use of high doses of the poorly selective beta-agonist isoprenaline (7). The increase in sales of this bronchodilator coincided with the increase in deaths observed in the countries where it was sold. Countries where highly concentrated isoprenaline was not available during that decade—the United States and West Germany—were spared (7). However, there is controversy over this claim, and other factors have been proposed as contributors to the increased deaths, such as undertreatment of asthma and increased prevalence or increased severity of the disease (9,10).

A second epidemic was observed in New Zealand in the second half of the 1970s. The age-adjusted asthma mortality rate in New Zealand was 1.4/100,000 population in 1975 and rose to 4.1/100,000 population in 1979 (11). The increase in asthma mortality was attributed to the use of fenoterol (12). As safety warnings were issued and fenoterol sales dropped, the number of asthma deaths in the country also fell (13).

Since the late 1980s, there has been a consistent reduction in asthma mortality in many countries (14). Improved management of asthma is the most likely reason for this reduction, because the use of inhaled corticosteroid therapy is associated with a reduced risk of death from asthma (15,16) and the use of this medication has been associated with decreased asthma mortality in various countries (17,18).

FACTORS ASSOCIATED WITH NEAR-FATAL AND FATAL ASTHMA

Many factors associated with near-fatal and fatal exacerbations of asthma have been identified (Chart 1). The risk factors most often implicated in near-fatal asthma or fatal asthma include a history of mechanical ventilation, as well as admission to the hospital or ICU for an asthma attack (19-21).

Chart 1 - Risk factors for near-fatal and fatal asthma.

Previous near-fatal asthma exacerbation
Previous intubation and mechanical ventilation for asthma
Previous ICU admission for asthma
Previous hospital admission for asthma
Lack of adherence to asthma treatment
Poor perception of dyspnea
Psychological problems and psychiatric diseases
Low socioeconomic status
Allergen exposure (Alternaria, soybean)
Intolerance to aspirin and nonsteroidal anti-inflammatory drugs
Smoking

Concern about the safety of long-acting β_2 agonist therapy was raised in the 1990s when asthma-related death was found to be three times more likely among patients taking salmeterol than among those taking albuterol, despite the fact that the difference was not statistically significant (22). The Salmeterol Multicenter Asthma Research Trial (SMART) demonstrated a fourfold increase in asthma deaths associated with salmeterol use (23). A post hoc analysis suggested the risk was related to the lack of use of inhaled corticosteroids, which was also less common among African-Americans. This prompted the United States Food and Drug Administration to issue a public health advisory in 2005 stating that long-acting β_2 agonists can "increase the chance of severe asthma episodes and death when such episodes occur" (24). A second safety warning, issued in 2010, stated the ongoing concern regarding the safety of long-acting β_2 agonists (25). Various meta-analyses provided evi-

dence that the combination of inhaled corticosteroids and long-acting β_2 agonists can be used safely (26-28), which conforms to the recommendations of current asthma treatment guidelines (29,30).

Many factors related to treatment adherence have been identified in cases of near-fatal and fatal asthma. Such factors include the underuse of inhaled corticosteroids (20,31) and delay in initiating oral corticosteroids during an acute attack (20). Lack of appropriate medical care (32), limited use of primary care services (33), and failure to keep appointments (34) have also been identified in affected individuals. It has been also suggested that a blunted perception of dyspnea can predispose some asthma sufferers to a life-threatening attack. (35).

Adverse psychological factors have also been associated with near-fatal and fatal asthma. These include having been diagnosed with a psychiatric disorder, most commonly depression or a behavioral disorder, especially denial (36). However, in one systematic review of psychological risk factors associated with near-fatal and fatal asthma, it was not possible to conclude that such factors increased the risk of near-fatal asthma/fatal asthma, because of a lack of consistency across studies, in terms of the methodology employed in the psychological assessments (37).

Patients of lower socioeconomic status seem to be at increased risk of death from asthma (38). This association might be related to limited access to health care services and lower compliance with prescribed treatment regimens.

Intolerance to aspirin and nonsteroidal anti-inflammatory drugs can cause severe asthma exacerbations (39). Aspirin intolerance has been shown to be more common among patients with a history of near-fatal asthma attacks than among those without (40). In one study, Alternaria sensitivity was identified as a major risk factor for near-fatal asthma (41). In another investigation, high levels of exposure to mold spores were associated with an increased risk of death from asthma (42).

Smoking has been associated with near-fatal asthma and fatal asthma in some studies (32,43). However a systematic review (21) did not find a significant association between smoking and near-fatal asthma/fatal asthma.

PATHOLOGICAL ASPECTS OF FATAL ASTHMA

The lungs of patients that have died from asthma are hyperinflated and might not collapse when the chest cavity is opened at autopsy. The atelectatic areas observed on the pleural surface represent areas of collapse distal to bronchial obstruction by mucous plugs. Lung sections typically show occlusion of the larger and smaller bronchi by tenacious mucus or mucous plugs (Figure 1).

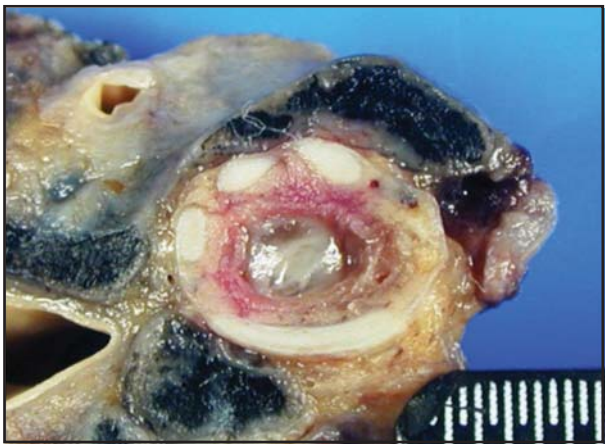

Figure 1 - Cross-section of a large, cartilaginous bronchus. The lumen is filled with a viscous mucous plug.

Scale bar = 0.5 cm.

Luminal obstruction by exudates composed of mucus and cells is a major contributing cause to a fatal event in most asthma patients. In cases of fatal asthma, Aikawa et al. reported an increase in the mucus occupying ratio, especially in the peripheral airways (44). The analysis of the mucus of a single patient that died of asthma showed a high mucin content, with proteins of extreme size and low charge density, which could explain the solidity of the plugs observed in status asthmaticus (45).

In fatal asthma, there is extensive sloughing of the epithelium to the airway lumen. Epithelial detachment can have deleterious consequences, such as increased exposure of the mucosal nerve endings to irritant factors, enhanced penetration of allergens, and reduced mucociliary clearance (44,46). In addition, the epithelial disruption observed in fatal asthma can lead to greater retention of mucus through impairment of mucociliary clearance, and the inflammatory cell debris can impair clearance by increasing mucus viscosity (47). Histological samples of large airways in fatal asthma are shown in Figures 2 and 3.

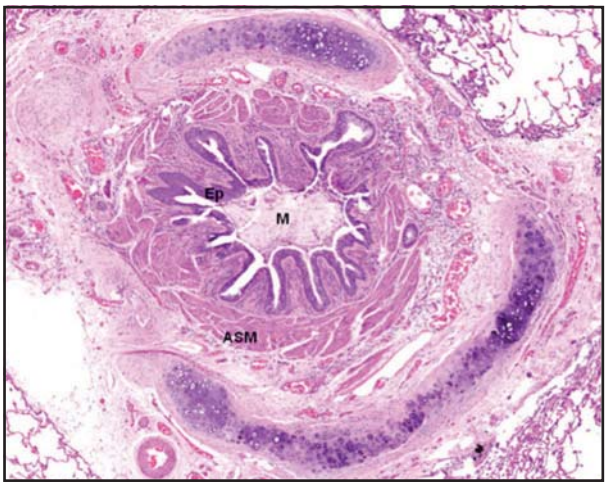

Figure 2 - Large airway of a patient who died from a fatal asthma attack, showing a mucous plug within the airway lumen, epithelial folding, and thickened ASM layer.

Hematoxylin and eosin staining. Ep, epithelium; and M, mucus. Scale bar = 500 µm.

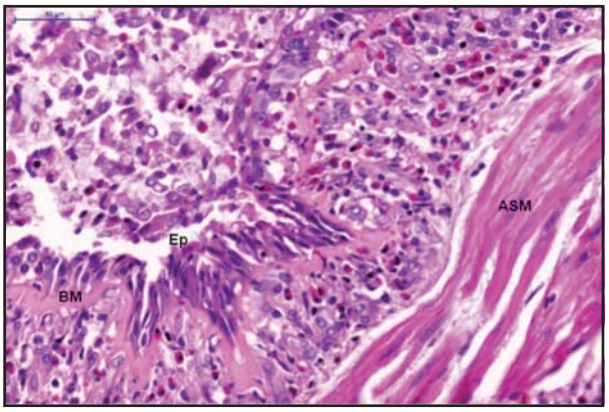

Figure 3 - Bronchial mucosa of a patient who died from a fatal asthma attack, showing epithelial damage and basement membrane thickening. The lamina propria is thickened with abundant inflammation, as is the ASM layer.
Hematoxylin and eosin staining. BM, basement membrane; Ep, epithelium. Scale bar = 50 µm.

Submucosal glands are enlarged in patients with asthma, contributing to a hypersecretory state (48). In cases of fatal asthma, there is a disproportionate increase in smooth muscle actin in the myoepithelial cells of the bronchial mucous glands, which could be at least partially responsible for the abundant mucous discharge that is characteristic of a fatal asthma attack (49).

Hyaline thickening of the basement membrane has been described in cases of fatal asthma (50). In such cases, there is thickening of the subepithelial *lamina reticularis* that underlies the true basal lamina of the bronchial epithelium, and this is therefore referred to as pseudo-thickening (46). This thickening is caused by the deposition of several extracellular matrix components. There have been no studies comparing the varying degrees of asthma severity in terms of basement membrane thickening. Due to its constant accessibility in bronchial biopsies, this airway compartment has been used as a marker of remodeling (46).

An increase in airway smooth muscle (ASM) area is the structural change that most consistently correlates with parameters of obstruction and disease severity. In addition, the role of the ASM as an immunomodulator, like that of the airway epithelium, has received considerable attention in recent years (46,51).

Patients with asthma have proportionally greater ASM area than do those without asthma and those with COPD (52). The increased ASM area observed in cases of fatal asthma is due to hyperplasia, hypertrophy, or increased extracellular matrix deposition (53,54). It occurs throughout the tracheobronchial tree and is the major contributor to the increased area of the inner airway wall in asthma (55).

An increase in the quantity of elastic fibers and fibronectin within the ASM has been described in the large airways of patients with fatal asthma and might contribute to altered muscle mechanics. In addition, an increase in the expression of matrix metalloproteinases 9 and 12 by ASM cells shows that the ASM participates in the remodeling process in asthma (56). James et al. analyzed the stereological properties of ASM thickness in a large number of autopsies and concluded that the ASM layers were thickest in the most severe cases of asthma (57). It is of note that neither ASM thickness nor the degree of ASM hyperplasia/hypertrophy was found to correlate with patient age or disease duration, suggesting that the structural alterations in the ASM layer occur early in the course of asthma (57).

The outer layer of the small airways is intimately connected to the alveolar parenchyma by the alveolar attachments. The elastic load provided by the lung parenchyma is transmitted to the airways through the alveolar attachments, resulting in a mechanical interdependence between airways and parenchyma. Studies on fatal asthma tissue have provided important information about this compartment. The quantity of altered alveolar attachments is increased in fatal asthma, and that increase is accompanied by a decrease in the number of elastic fibers and in the proteoglycans decorin/lumican, as well as by an increase in collagen type III content in the outer walls (58-60). These structural alterations could impair the tethering forces and could explain some functional abnormalities, such as the loss of the bronchodilator effect of deep breathing in spontaneous bronchoconstrictive episodes, the loss of elastic recoil, and the increased airway closure described in cases of severe asthma.

In fatal asthma, there is a marked congestion of the bronchial blood vessels. Two separate studies revealed that the larger blood vessels occupy a greater area in cases of fatal asthma than in other cases of asthma and control cases, although the total number of vessels was not increased (52,61).

Various studies have assessed the quantity and extent of inflammation in fatal asthma. Such studies have contributed to the notion that inflammation in asthma extends to the distal lung and to the upper respiratory tract (62-64). Inflammatory (and structural) alterations at this level could influence the mechanisms of airway parenchyma interdependence and could alter small airway function.

Innate immune stimuli, such as exposure to viruses or air pollution, might be involved in the pathogenesis of asthma exacerbations. Fregonese et al. found that the expression of the anaphylatoxin receptors C3ar and C5ar was higher in lung tissue obtained from patients who died from a fatal asthma attack than in biopsy samples obtained from patients with mild asthma and from controls, suggesting that triggers that activate the complement system are involved in the mechanisms of a fatal asthma attack (65).

A distinct phenotype of fatal asthma, related to the time of onset of the last crisis, has been recognized. Patients that died shortly after the onset of the attack (within the first 2-3 h) presented more neutrophils than eosinophils in the large and small airways

(66). Faul et al. studied five cases of sudden death from asphyxia during an asthma attack (< 1 h after the onset of the attack) and showed that all five patients had a high proportion of CD8+ T cells in the airways (64). Sudden-onset asthma attacks are most often triggered by nonsteroidal anti-inflammatory drugs and inhalation of fumes, whereas slow-onset asthma attacks are most often associated with suspected respiratory infections (1).

Viral infections are likely to be implicated in near-fatal/fatal asthma exacerbations. However, previous studies of tissue samples obtained from patients who died from a fatal asthma attack have shown that the levels of respiratory virus nucleic acids did not differ from that observed in control samples (67,68). However, it possible that, in fatal asthma, there is an aberrant T-cell response to viral infection. O'Sullivan et al. detected an aberrant T cell population with higher expression of perforin (a marker of cytotoxicity), interleukin 4, and interferon gamma in patients that have died from asthma (68).

In summary, the alterations observed in the lungs of patients that have died from asthma probably represent the adverse combination of a severe, acute exacerbation (triggered by any one of a number of factors) and a poorly controlled, undertreated, severe form of the disease with pre-existing structural alterations in the airways.

REFERÊNCIAS

1. Plaza V, Serrano J, Picado C, Sanchis J. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J 2002;19(5):846-52.
2. World Health Organization. The global burden of disease : 2004 update. Geneva: World Health Organization; 2008.
3. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59(5):469-78.
4. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma--United States, 1980-2004. MMWR Surveill Summ 2007;56(8):1-54.
5. Sears MR, Rea HH, de Boer G, Beaglehole R, Gillies AJ, Holst PE, et al. Accuracy of certification of deaths due to asthma. A national study. Am J Epidemiol 1986;124(6):1004-11.
6. Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. Br Med J 1968;1(5588):335-9.
7. Stolley PD. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972;105(6):883-90.
8. Gandevia B. The changing pattern of mortality from asthma in Australia. 2. Mortality and modern therapy. Med J Aust 1968;1(21):884-91.
9. Benatar SR. Fatal asthma. N Engl J Med 1986;314(7):423-9.
10. Buist AS. Is asthma mortality increasing? Chest 1988;93(3):449-50.
11. Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Mortality from asthma: a new epidemic in New Zealand. Br Med J (Clin Res Ed) 1982;285(6344):771-4.
12. Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. Lancet 1989;1(8644):917-22.
13. Crane J, Pearce N, Burgess C, Jackson R, Beasley R. End of New Zealand asthma epidemic. Lancet 1995;345(8955):984-5.
14. Wijesinghe M, Weatherall M, Perrin K, Crane J, Beasley R. International trends in asthma mortality rates in the 5- to 34-year age group: a call for closer surveillance. Chest 2009;135(4):1045-9.
15. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, et al. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. JAMA 1992;268(24):3462-4.
16. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343(5):332-6.
17. Melissinos CG, Gourgoulianis K, Adamidis SC. Inhaled drug consumption and asthma mortality in Greece. Chest 1995;107(6):1771-2.
18. Neffen H, Baena-Cagnani C, Passalacqua G, Canonica GW, Rocco D. Asthma mortality, inhaled steroids, and changing asthma therapy in Argentina (1990-1999). Respir Med 2006;100(8):1431-5.
19. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 1998;157(6 Pt 1):1804-9.
20. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: demographics, health care, and management of the acute attack. Thorax 2000;55(12):1007-15.
21. Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. Can Respir J 2005;12(5):265-70.
22. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306(6884):1034-7.
23. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129(1):15-26.
24. US Food and Drug Administration. FDA Public Health Advisory: Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol inhalation powder), Foradil Aerolizer (formoterol fumarate inhalation powder). www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm162678.htm. Date last updated: May, 2006. Date last accessed: March 30, 2012.
25. US Food and Drug Administration. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm. Date last updated: February, 2010. Date last accessed March 30, 2012.

26. Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. Cochrane Database Syst Rev;5:CD007891.
27. Jaeschke R, O'Byrne PM, Mejza F, Nair P, Lesniak W, Brozek J, et al. The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. Am J Respir Crit Care Med 2008;178(10):1009-16.
28. Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med 2008;149(1):33-42.
29. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2011. www.ginasthma.org. Date last updated: December, 2011. Date last accessed: March 30, 2012.
30. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma (EPR-3). www.nhlbi.nih.gov/guidelines/asthma/. Date last updated: July, 2007. Date last accessed: March 30, 2012.
31. Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM, et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. Clin Exp Allergy 2007;37(4):552-7.
32. Harrison B, Stephenson P, Mohan G, Nasser S. An ongoing Confidential Enquiry into asthma deaths in the Eastern Region of the UK, 2001-2003. Prim Care Respir J 2005;14(6):303-13.
33. Sturdy PM, Butland BK, Anderson HR, Ayres JG, Bland JM, Harrison BD, et al. Deaths certified as asthma and use of medical services: a national case-control study. Thorax 2005;60(11):909-15.
34. Burr ML, Davies BH, Hoare A, Jones A, Williamson IJ, Holgate SK, et al. A confidential inquiry into asthma deaths in Wales. Thorax 1999;54(11):985-9.
35. Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994;330(19):1329-34.
36. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: psychological factors. Thorax 2002;57(4):317-22.
37. Alvarez GG, Fitzgerald JM. A systematic review of the psychological risk factors associated with near fatal asthma or fatal asthma. Respiration 2007;74(2):228-36.
38. Grant EN, Lyttle CS, Weiss KB. The relation of socioeconomic factors and racial/ethnic differences in US asthma mortality. Am J Public Health 2000;90(12):1923-5.
39. Picado C, Castillo JA, Montserrat JM, Agusti-Vidal A. Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. Eur Respir J 1989;2(2):127-9.
40. Yoshimine F, Hasegawa T, Suzuki E, Terada M, Koya T, Kondoh A, et al. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. Respirology 2005;10(4):477-84.
41. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324(6):359-63.
42. Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. J Allergy Clin Immunol 1995;95(5 Pt 1):955-61.
43. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, et al. Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. Am Rev Respir Dis 1992;146(1):76-81.
44. Aikawa T, Shimura S, Sasaki H, Ebina M, Takishima T. Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack. Chest 1992;101(4):916-21.
45. Sheehan JK, Richardson PS, Fung DC, Howard M, Thornton DJ. Analysis of respiratory mucus glycoproteins in asthma: a detailed study from a patient who died in status asthmaticus. Am J Respir Cell Mol Biol 1995;13(6):748-56.
46. Mauad T, Bel EH, Sterk PJ. Asthma therapy and airway remodeling. J Allergy Clin Immunol 2007;120(5):997-1009; quiz 1010-1.
47. Kuyper LM, Pare PD, Hogg JC, Lambert RK, Ionescu D, Woods R, et al. Characterization of airway plugging in fatal asthma. Am J Med 2003;115(1):6-11.
48. Carroll NG, Mutavdzic S, James AL. Increased mast cells and neutrophils in submucosal mucous glands and mucus plugging in patients with asthma. Thorax 2002;57(8):677-82.
49. Green FH, Williams DJ, James A, McPhee LJ, Mitchell I, Mauad T. Increased myoepithelial cells of bronchial submucosal glands in fatal asthma. Thorax 2010;65(1):32-8.
50. Dunnill MS. The pathology of asthma, with special reference to changes in the bronchial mucosa. J Clin Pathol 1960;13:27-33.
51. An SS, Bai TR, Bates JH, Black JL, Brown RH, Brusasco V, et al. Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma. Eur Respir J 2007;29(5):834-60.
52. Kuwano K, Bosken CH, Pare PD, Bai TR, Wiggs BR, Hogg JC. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;148(5):1220-5.
53. Bai TR. Evidence for airway remodeling in chronic asthma. Curr Opin Allergy Clin Immunol 2010;10(1):82-6.
54. James AL, Elliot JG, Jones RL, Carroll ML, Mauad T, Bai TR, et al. Airway Smooth Muscle Hypertrophy and Hyperplasia in Asthma. Am J Respir Crit Care Med. Epub ahead of print March 8, 2012. doi:10.1164/rccm.201110-1849OC.
55. James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. Eur Respir J 2007;30(1):134-55.
56. Araujo BB, Dolhnikoff M, Silva LF, Elliot J, Lindeman JH, Ferreira DS, et al. Extracellular matrix components and regulators in the airway smooth muscle in asthma. Eur Respir J 2008;32(1):61-9.
57. James AL, Bai TR, Mauad T, Abramson MJ, Dolhnikoff M, McKay KO, et al. Airway smooth muscle thickness in asthma is related to severity but not duration of asthma. Eur Respir J 2009;34(5):1040-5.
58. Mauad T, Silva LF, Santos MA, Grinberg L, Bernardi FD, Martins MA, et al. Abnormal alveolar attachments with

decreased elastic fiber content in distal lung in fatal asthma. Am J Respir Crit Care Med 2004;170(8):857-62.
59. de Medeiros Matsushita M, da Silva LF, dos Santos MA, Fernezlian S, Schrumpf JA, Roughley P, et al. Airway proteoglycans are differentially altered in fatal asthma. J Pathol 2005;207(1):102-10.
60. Dolhnikoff M, da Silva LF, de Araujo BB, Gomes HA, Fernezlian S, Mulder A, et al. The outer wall of small airways is a major site of remodeling in fatal asthma. J Allergy Clin Immunol 2009;123(5):1090-7, 1097 e1.
61. Carroll NG, Cooke C, James AL. Bronchial blood vessel dimensions in asthma. Am J Respir Crit Care Med 1997;155(2):689-95.
62. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. Eur Respir J 1997;10(2):292-300.
63. de Magalhaes Simoes S, dos Santos MA, da Silva Oliveira M, Fontes ES, Fernezlian S, Garippo AL, et al. Inflammatory cell mapping of the respiratory tract in fatal asthma. Clin Exp Allergy 2005;35(5):602-11.
64. Faul JL, Tormey VJ, Leonard C, Burke CM, Farmer J, Horne SJ, et al. Lung immunopathology in cases of sudden asthma death. Eur Respir J 1997;10(2):301-7.
65. Fregonese L, Silvestri M, Sabatini F, Defilippi AC, Rossi GA. Severe and near-fatal asthma in children and adolescents. Monaldi Arch Chest Dis 2001;56(5):423-8.
66. Sur S, Hunt LW, Crotty TB, Gleich GJ. Sudden-onset fatal asthma. Mayo Clin Proc 1994;69(5):495-6.
67. Macek V, Dakhama A, Hogg JC, Green FH, Rubin BK, Hegele RG. PCR detection of viral nucleic acid in fatal asthma: is the lower respiratory tract a reservoir for common viruses? Can Respir J 1999;6(1):37-43.
68. O'Sullivan S, Cormican L, Faul JL, Ichinohe S, Johnston SL, Burke CM, et al. Activated, cytotoxic CD8(+) T lymphocytes contribute to the pathology of asthma death. Am J Respir Crit Care Med 2001;164(4):560-4.

Artigo original

The Diagnosis of Asthma

O Diagnóstico da Asma

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RESUMO

O diagnóstico de asma — como exposto em diversas diretrizes nacionais — é fundamentado na história clínica e corroborado pelo exame clínico e pela função pulmonar, que demonstra obstrução ao fluxo aéreo, reversível espontaneamente ou após o uso de broncodilatador ou corticosteroide.

Diversos diagnósticos diferenciais devem ser cuidadosamente excluídos na avaliação clínica — incluindo bronquiolite viral na infância e DPOC nos adultos. Neste artigo, consideramos que o diagnóstico de asma deve agora avançar com o reconhecimento de que a asma é uma síndrome clínica heterogênea (casos individuais têm evolução e resposta ao tratamento diversos).

Recomendamos que a broncoscopia e a biópsia brônquica devam participar do processo diagnóstico nos casos de pacientes que seguem o tratamento e, mesmo assim, não obtêm o controle da asma com doses moderadas de corticosteroides inalatórios. Desse modo, uma melhor caracterização da alteração clínica do paciente será obtida, visando o uso de terapias alternativas (disponíveis ou ainda a serem desenvolvidas).

Descritores: Asma/diagnóstico; Asma/patologia; Asma/terapia.

ABSTRACT

The diagnosis of asthma—as espoused in diverse national clinical guidelines—is founded on the clinical history and corroborated by the clinical examination and pulmonary function testing which demonstrate airflow obstruction, reversible spontaneously or after bronchodilator or corticosteroid administration.

A number of important confounder diagnoses need careful exclusion by clinical assessment—including viral bronchiolitis in children and COPD in adults. This article contends that the diagnosis of asthma now needs to advance through the practical acknowledgment that asthma is a heterogeneous clinical syndrome (individual cases vary in their course and response to treatment).

This article contends that bronchoscopy and bronchial biopsy should become part of the diagnostic process when compliant patients fail to settle on moderate dose inhaled corticosteroid—in order to properly characterise these patients' disorder, as a basis for alternative therapies (currently available or yet to be developed).

Keywords: Asthma/diagnosis; Asthma/pathology; Asthma/therapy.

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INTRODUCTION

Asthma remains a disorder that worldwide demands further advances in understanding, diagnostics, and therapeutics (1,2).

Currently, the diagnosis of asthma is founded on careful clinical enquiry and observation—supported by documentation of labile airflow obstruction (either natural or treatment induced) by pulmonary function testing. The second limb allows testable arithmetic limits for "significant" airflow obstruction and lability of airflow obstruction.

There is tacit acknowledgement that this diagnostic approach identifies a syndrome rather than one disease; matched by physicians' observations of variable natural history and of variable response to treatment across sets of asthma patients, and indeed within any asthma patient at different times. However, direct understanding of the bronchial changes (by bronchoscopic biopsy) across many patients (with asthma varying from mild to difficult asthma) is very limited—because the method (pace efforts such as the Severe Asthma Research program in the United States, and case series at other centres) has not been an integral part of clinical practice (3-6). In clinical practice, many cases of asthma are understood as allergic type disorder (eosinophilic inflammation and active Th2 immune actions, often underlying atopy, and responsive to corticosteroid); but other cases might be most honestly described as "different"—generated by smoking in later life, by occupational toxins, by viruses (7,8), through inflammation of innate immune or Th1 immune type (9),and some with no inflammation at biopsy (6,10).

Fundamental research in asthma is advancing impressively. Powerful genome-wide studies of large patient groups have delineated the principal loci where genetic variants promote asthma, emphasising heterogeneity (11). Thus, more realistic models of asthma are emerging and being studied in cellular and molecular detail (12), and there are rich descriptions of molecular elements underlying immune/inflammatory processes and of epithelial functions (12-15).

In respect of these research advances, the clinical position of absent bronchial pathology in asthma patients (especially patients not settling quickly and securely on inhaled corticosteroid therapy) is disadvantageous to physicians and to patients. It might be contended that we respiratory physicians are overdoing "lumping" rather than "splitting" in our practical diagnostics of asthma—and that we are too reluctant to obtain gold standard pathology and thus align the clinical science with the advancing fundamental science. It might be asked why, when we concede that asthma is heterogeneous, do we not obtain bronchial pathology. Our approach could be contrasted with the readiness of other specialist clinicians to secure biopsies for precise morphological and, increasingly, molecular studies—for example nephrologists who have regularly biopsied kidneys and thus allowed identification of distinctive immune/inflammatory diseases as subsets of broad entities such as glomerulonephritis, and which have been the basis for distinctive therapeutic approaches (16).

We in mainstream asthma practice work with only irregularly collected data on the "phenotype" of our patients' asthma. That was not enough for Dr. Morrow Brown some forty years ago, when he demonstrated efficacy of an inhaled corticosteroid in difficult cases of asthma (17); and when he demanded demonstrable excess eosinophils in sputum to characterise "allergic asthma". Is it therefore not timely for us to reconsider our position on directly identifying the bronchial pathology of our patients (18,19)? Would this not clarify the proper management of compliant patients with disappointing early responses to inhaled corticosteroids; is it not the necessary clinical platform for stepwise advances in asthma therapies?

This article attempts an overview of current diagnostic practice (including differential diagnosis) in asthma—but cannot aspire to the invaluable details found in the asthma guidelines developed by the United States National Institutes of Health (20) and by the British Thoracic Society (21). The article will also contentiously address the need for direct bronchial pathology in clinical practice.

THE FEATURES AND DIFFERENTIAL DIAGNOSES OF ASTHMA

In both paediatric and adult practice, the physician must remain alert to other possible diagnoses—knowing that asthma is remarkably common but acknowledging other important and treatable causes of noisy and difficult breathing. The diagnosis of asthma in children or adults has weighty implications. The details of the history and of the clinical examination are key—and hence the physician's approach must be thoughtful and critical. Charts 1 and 2 list the confounding diagnoses in adults and children, respectively.

Chart 1 - Differential diagnosis of asthma in adults

Alternative diagnosis
COPD
Left ventricular failure
Local large airway obstruction (neoplasm, foreign body)
Bronchiectasis
Pulmonary eosinophilia syndromes
Bronchiolitis obliterans
Churg-Strauss vasculitis
Allergic bronchopulmonary aspergillosis
Vocal cord dysfunction

Chart 2 - Differential diagnosis of asthma in children

Alternative diagnosis
Viral bronchiolitis
Atopic rhinitis
Inhaled foreign body
Cystic fibrosis
Bronchiectasis (including immotile cilia syndrome)
Tuberculosis
Compressed, deformed large airway
Recurrent aspiration (neuromuscular dysphagia)
Cardiac failure
Vocal cord dysfunction

The effective physician may firmly and quickly diagnose asthma (high probability of asthma), or make a firm alternative diagnosis (e.g., viral bronchiolitis in children or left ventricular failure in adults). However, the physician may concede doubt—regarding asthma of intermediate probability and focus investigations to confirm or refute the proposition, or regarding another diagnosis and focus his investigations there. Effective physicians know that two disorders can coexist—such as asthma and COPD in smokers. The pace of investigations and actions should reflect the severity and acuteness of the illness.

Clinical features of asthma

Lability of symptoms and signs, as well as of airflow obstruction, is characteristic of asthma—and is evident from the history at presentation in many cases. The patient or parent reports periods (of hours or days) of difficult breathing, of noisy breathing ("whistling" or "wheezing"), of "tightness" in the chest, of cough with or without the production of tenacious or sticky light-coloured sputum. There may be a plain report that these symptoms are worse in bed in the early morning (4:00-7:00 a.m.) The patient or parent may recognise swift-acting triggers of symptoms:- exposure to tobacco smoke or other types of smoke/fumes, strong odours (e.g., perfumes), cold air, exercise, laughter, "allergens" (e.g., animal exposures, or seasonal pollens or spores), or some occupational agent. Patients or parents may recognise periods of remission with change of geographical location or climate, or with periods away from their occupation. Asthma sufferers may have some symptoms, if mild, of upper respiratory disorder—with excess of nasal mucus and sneezing.

On many occasions, the findings on clinical examination are perfectly normal (with calm and comfortable breathing and clear auscultation of the lungs)—depending on the timing of the examination and reflecting the lability of asthma. At other times, there are typical findings of respiratory distress with mild tachypnoea; difficult and irritating cough; inflation of the thorax; and polyphonic wheezes in the chest (mainly on expiration, which is prolonged). In extremis, the patient is limp, tired, and cool, with struggling chest movement, an inflated chest, and silent auscultation—all indicative of severe airflow obstruction.

Clues to alternative diagnoses

The physician should be open-minded as to diagnosis, and be alert to the differential diagnoses. The following are useful pointers to diagnoses other than asthma:

• viral bronchiolitis (a very common disorder with bouts of childhood wheeze)—occurrence with febrile illness, onset in early childhood (under two years of age), prompt remissions and clearance of wheezing illness with age (22,23)

• aspirated foreign body—a history from the patient or parent of a choking event, very abrupt onset of a persistent cough, a localised region of silence on auscultation of the chest, radiographic abnormality (visible foreign body, regional loss of volume, inflated hemi-thorax due to ball-valve gas trapping at main bronchus); expert fibreoptic bronchoscopy is required.

• cystic fibrosis—present from birth, moist cough, regional crackles at times, chest radiograph abnormality, finger clubbing, steatorrhoea, low weight; any should prompt sweat sodium testing

• immune or ciliary defects—present from birth, severe upper respiratory tract infections, dextrocardia; detailed assessment of immune function or ciliary ultra-structure on nasal biopsy required

• cardiac failure with pulmonary oedema—cyanosis, hepatomegaly, or cardiac murmur in the child; repeated bouts of nocturnal breathless in the adult, basal pulmonary crackles, oedema with raised jugular venous pressure; electrocardiogram and echocardiogram are required

• COPD—smoking, industrial exposures; critical testing of reversibility of airflow obstruction required, also assay of α-1 antitrypsin (in asthma patients who smoke cigarettes, asthma and COPD may coexist and the outlook for those who continue to smoke is bleak)

• bronchial neoplasm—smoking, haemoptysis, stridor or local signs in lung, finger clubbing, chest radiograph abnormality; bronchoscopy is required

• Churg-Strauss vasculitis—extra-pulmonary disorder (peripheral nerves, gut, skin, cardiac) on a background of late-onset asthma, chest radiograph showing nodular abnormality, marked eosinophilia (positive serology for perinuclear antineutrophil cytoplasmic antibodies in most); biopsy of involved tissue is required

• Ilergic bronchopulmonary aspergillosis (a complication of allergic asthma)—late summer exacerbations, cough producing brownish plugs, fleeting pulmonary radiograph shadows, high blood eosinophil counts; serology (IgE and IgG antibodies to *Aspergillus fumigatus*) is required

• pulmonary eosinophilia syndromes (parasite and medication induced)—geographic and social factors are clues to parasite driven disorder; regular medications to possible drug induced pulmonary eosinophilia; clinical features include fever and pleuritic pain, the chest radiograph shows pulmonary abnormality (including reticular or miliary shadows), prominent eosinophilia; microscopy to demonstrate larvae in sputum or blood, or serology are required; drug-induced pulmonary eosinophilia is idiosyncratic, and diagnosis requires suspicion and trial of drug cessation

• bronchiolitis obliterans (constrictive)—irreversible airflow obstruction with prominent hyperinflation, exposure to inhaled industrial toxins, exposure to certain drugs (e.g., penicillamine), background of immune disorder such as rheumatoid disease

• vocal cord dysfunction (24)—dysphonia and variable stridor, typically in a young adult; expert laryngoscopy at time of stridor is diagnostic

• "cough variant asthma"—cough occurs as in asthma, but alone; the disorder is based on eosinophilic bronchitis and responds to inhaled corticosteroid therapy

The physician should also consider the following in the differential diagnosis: gastro-oesophageal reflux; para-nasal sinus disorder; angiotensin-converting enzyme inhibitor-induced cough; aspirated foreign body; and bronchial neoplasm. These factors may also exacerbate typical asthma, should routinely be addressed in the clinical history, and should be countered as needed in the management of the patient.

CURRENT DIAGNOSTIC PROCESS IN ASTHMA

The current diagnostic process entails two essential components (20): the clinical diagnosis (the delineation of a clinical picture of asthma and the exclusion of a confounding diagnosis), which is central; and pulmonary function testing (the demonstration of airflow limitation and reversibility, spontaneous or on trial of treatment), which supports the clinical diagnosis. These provide the basis on which management is planned, matching the patient's clinical disorder to the treatment. Further investigations into the phenotype of the patient's asthma are now only irregularly performed in clinical practice.

Diagnostics in the adult

The delineation of the clinical picture of asthma (as recorded above) at the first clinical encounter takes account of the variable completeness of and severity of the asthma across different patients, as well as the variable severity with time in any asthma patients. Therefore, clinical examination findings can range from normal to a medical emergency at the time of assessment. Acknowledging these factors—and properly addressing alternative diagnoses—allows the physician to formulate the probability of asthma.

The history must address exacerbating factors. They are important diagnostic factors. Also their recognition is the foundation for their later management. Thus, in patients with asthma, smoking cessation is vital (25). Patients may also part with pet cats and dogs when evidence of allergy is plain. Pre-exercise inhaled albuterol or cromolyn can be valuable adjuncts in exercise-induced asthma in elite athletes and others.

The identification of occupational asthma (26) is of special importance. It may identify one dominant influence on a patient's asthma and creates the opportunity for management through changing or modifying occupation or through encouraging special measures to limit exposure. In many countries the diagnosis of occupational asthma has legal implications—and creates an opportunity for preventing asthma in other workers.

The history-taking must also address and document the frequency of symptoms, their severity, and their impact on quality of life. The use of a validated symptom questionnaire for this purpose (27,28), as recommended in the American and British asthma guidelines, is also valuable for monitoring progress and response to treatments. Asthma severity may be classified by category (21,29)—intermittent or persistent; mild, moderate or severe—and according to symptoms—night-time awakenings, bronchodilator usage, and pulmonary function (FEV_1, PEF).

Demonstration of airflow limitation and reversibility.

PEF measurements

Measurements of PEF are effort dependent (and require a skilled technique ensuring that forced expiration follows full inspiration, and avoidance of coughed expiration); also PEF measurements have a broad range of normal values, and do not provide formal evidence of airway obstruction (30). Despite these cautions, serial PEF measurements (twice or preferably four times daily, over a number of weeks) can be valuable indicators of labile pulmonary function in the context of wheezy breathlessness. Serial PEF measurements are also useful in monitoring asthma and response to treatments over long periods. Proportionate variability (amplitude of values as a percentage of highest values, PEF A%H) or percentage improvement of values after trial of treatment are more valuable than are absolute values (L/min). Normal values of PEF A%H are < 8% for twice daily measurements and < 20% for four times measurements (higher values suggest asthma). In asthma patients, reversibility of the PEF response to treatment (bronchodilator or corticosteroid) is defined as a ≥ 15% increase over baseline values.

Spirometry

Because of spirometry's high reproducibility and well-defined normal ranges (31,32), it is the gold standard for documenting airflow obstruction (FEV_1/FVC ratio < 0.7), as well as for recording reversibility (>12%

increase in FEV_1), immediately after bronchodilator use or longer term with corticosteroid use. It is usual cornerstone physiological method for patients entered into formal clinical trials in asthma. In addition, Low FEV_1 is predictive of asthma exacerbations (33). High frequency serial testing by spirometry is not practical. Hence, if periodic spirometric values remain normal in a suspected asthma sufferer, serial PEF testing can be used test for labile airflow function; alternatively, spirometry with methacholine challenge can be used. The normal provocative concentration of methacholine that causes a 20% decline in FEV_1 is > 8 mg/ml, and concentrations lower than this have a sensitivity of ≥ 70% for detecting asthma.

Extension and refinement of the phenotype in asthma

The broadly recognised heterogeneity of asthma, and the recent research advances in the genetics of asthma and in the diverse mechanisms of bronchial disorder (for example the roles of immune/inflammatory signallers such as thymic stromal lymphopoietin, IL-33, IL-13, and IFN-γ) now together pose an interesting challenge to respiratory clinicians (10-12). The challenge is whether clinicians should not now commit to this line of research through systematic collection of bronchial pathology phenotypes of their individual asthma patients (and or indeed single patients at different times, since the bronchus' regular exposure to microbial or toxic agents that might distort that pathology). Indeed, the concept of translational medicine (and advancing clinical medicine through research) is expressly about bridging fundamental science and clinical science, begging the question of why respiratory physicians and pathologists should not make directly obtained bronchial pathology an essential diagnostic tool in asthma in clinical practice. Sporadic bronchial pathology case series in asthma already point to diverse and unpredictable changes in difficult asthma—including unresolved Th2 inflammation, inflammation of different subtypes, no inflammation, unexpected microbial infection, or other unexpected pathologies (4-6). Surely such data—and not surrogates—should guide the best care of asthma sufferers who do not settle early and securely on inhaled corticosteroid therapy. Surely such data are needed in order to make clinical sense of the advances in fundamental research, and allow radical advances in the prevention and therapeutics of asthma.

Fibreoptic bronchoscopy is an uncomfortable procedure for the patient. But it can be performed safely and swiftly with the proper expertise and protocols (18,19,34); bronchial pathology case series in asthma have prominently included children (4-6). Bronchoscopic diagnostics are an essential component of other areas in respiratory medicine, including very sick patients—as in the diagnosis of pneumonias of obscure origin in immunosuppressed organ transplant recipients (35).

This author believes that the time is ripe for debate of the formal addition of direct bronchial pathology into asthma's clinical care protocols. However, in advance of that, the following represent examples of some current tests used as surrogates for more precise typing of the bronchial disorder in asthma sufferers. Their use is sporadic.

Eosinophils counts

Elevated eosinophil counts in blood (> 0.4×10^9 cells/L) provide only indirect evidence that a patient's asthma is driven by Th2-mediated bronchial inflammation—and has only moderate sensitivity in that respect (36,37). It has already been noted that very high eosinophil counts should heighten the physician's suspicion of confounding diagnoses such as pulmonary eosinophilic syndromes (parasite or medication driven) or Churg-Strauss vasculitis. Eosinophil counts in sputum (> 2% of cells present regarded as raised) are currently enjoying some interest through recollection of Dr. Morrow Brown's use of them as an essential diagnostic in the first trial demonstrating the efficacy of inhaled beclomethasone for troublesome asthma (17). If they are used, serial induced samples are best, given that observed eosinophil numbers vary according to corticosteroid exposure and other factors not yet identified.

Exhaled nitric oxide

The measurement of exhaled nitric oxide is an expensive mode (currently not widely available) that has attracted attention as a non-invasive surrogate assay for bronchial eosinophilic inflammation and prediction of corticosteroid response (38,39). Trial data, however, indicate that its utility is severely limited by its low sensitivity and specificity.

Testing for atopy

Atopy (allergen sensitisation) is a significant predictor of asthma, and is a pathogenic mechanism in many younger patients (40). Skin prick tests or allergen specific IgE titres in serum allow testing for IgE mediated allergic responses to, for example, *Dermatophagoides pteronyssinus*, grass pollens, fungi, and pet (dog and cat) dander. Positive results increase the probability of asthma when the diagnosis is uncertain (see asthma diagnosis in the child). They can also help guide management of asthma. If further research can advance the efficacy and safety of allergen specific immunotherapy (hyposensitisation) in asthma, then IgE assays may become an essential norm of best practice. High total serum IgE levels have been an entry requirement for trials of omalizumab therapy in asthma (41).

Bronchial provocation testing

Bronchial provocation testing is based on spirometry before and after inhaled challenge with a putative promoter/cause of asthma. It requires exacting safety

standards. Its utility is currently limited to occupational asthma (26) where there may be need for precise identification of one dominant influence on asthma, of import to individual patients and to public health.

Genetic variants and gene expression profiles

There are as yet no genetic variants or gene expression profiles that fit into clinical practice. However, recent progress on relating genome-wide common genetic variants to asthma in large and diverse populations of asthma has been striking (42). Moreover methodological advances in assaying diverse gene expression profiles have allowed the launch of studies of this type in asthma (11). These approaches provide hope of unravelling the heterogeneity of disorders underlying asthma.

Diagnostics in the child

Much that has been described for the diagnostic process in adults with asthma pertains also to the child. However, there are special considerations in the assessment of a child who is wheezing. First, the paediatrician acknowledges the very common difficulty in firmly differentiating between wheezing caused by viral bronchiolitis (which is often recurrent) and that caused by asthma (22,23). Second, it is difficult to measure pulmonary function in children ≤ 5 years of age. Valuable FEV_1 measurements become possible in many children after that age (32). However, it should be borne in mind that FEV_1 can be normal in children with persistent asthma. Although PEF measurements are methodologically less robust in children, the physician may use them in older children, similarly to how they are used in adults. To date, pulmonary function measurements that are more easily obtained (e.g., specific airway resistance, impulse oscillometry, and residual volume) have shown unclear relationships with childhood asthma. Other types of tests also remain unproven. Eosinophil counts in induced sputum—possible but time consuming in 75% of children over 5 years of age at specialist centres (43)—are so far uncertainly related to childhood asthma. Skin prick testing and IgE serology (total levels and allergen specific titres) can identify the common syndrome of atopy (40), the presence of which increases the probability of wheeze being asthma in children (22,23). As previously mentioned there have also been informative bronchial pathology case series studies of difficult asthma in childhood (4-6).

Empirical treatment with inhaled corticosteroids is a valid and important part of the diagnostic process in childhood—assessing clinical response, which is best recorded by validated questionnaire (21), accompanied by spirometric recordings when possible (32). Spontaneous remissions of bronchiolitis may coincide with the empirical use of a corticosteroid, thus causing diagnostic confusion. Hence the clinical picture is central in the diagnosis of asthma in child. Currently, observations over time are often paramount in allowing the characteristics of the illness to clarify.

Features in the history that increase the probability of asthma are frequent, recurrent wheeze; occurrence of bouts after exercise, laughter, change of ambient air (e.g., damp), or exposure to pets; coexistent atopic disorder (eczema or rhinitis); family history of asthma or atopy; and response to empirical asthma treatment. Features that lower the probability of asthma are cough only; moist cough; normal examination when symptomatic; and no response to empirical asthma treatment. It is important to make the differential diagnosis (Chart 2).

The British Thoracic Society Asthma Guidelines (21), which emphasise recording of symptoms by validated asthma questionnaire in children, acknowledge the often difficult diagnostics of asthma in childhood, and summarise the possible conclusions of the physician (and fitting actions) regarding the probability of asthma as follows:

a. highly probability → proceed to empirical treatment with documentation of response by validated questionnaire

b. intermediate probability → further careful observation of the child's progress ("watchful waiting") OR → consider pulmonary function testing by spirometry (response to bronchodilator; response to exercise; or response to methacholine challenge)—consider testing for atopy: if positive, manage as for high probability; if negative, manage as for low probability

c. low probability → address diagnostics and treatments of alternative disorders

FINAL CONSIDERATIONS

Clinical skills are and will remain the foundation of effective diagnostics for asthma and its confounder diagnoses. Validated symptom questionnaires provide added reliability and are valuable in assessing progress, as well as the response to treatments. Robust pulmonary function testing is an essential complement to the clinical diagnosis. Such testing is valuable in monitoring disease and assessing response to treatments, alongside clinical assessments.

This author contends that the diagnosis of asthma in clinical practice now needs stepwise advances. The clinical protocols for asthma assessment should include direct bronchial pathology for precise morphological and molecular characterisation. This change would complement and capitalise on the emerging progress on the fundamental science of asthma—and improve the care of patients now and in the future.

CONFLICT OF INTEREST STATEMENT

The author has been a member of the Board of Directors of Allerna Therapeutics Ltd and has an on-going interest in developing anti-signal transducer and activator of transcription 6 agents as potential therapeutics in asthma.

REFERENCES

1. Fiori NS, Gonçalves H, Dumith SC, Cesar MA, Menezes AM, Macedo SE. Ten-year trends in prevalence of asthma in adults in southern Brazil: comparison of two population-based studies. Cad Saude Publica. 2012;28(1):135-44
2. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med 2006;355(21):2226–2235.
3. Wenzel SE, Busse WW; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Severe asthma: lessons from the Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119(1):14-21.
4. Fitzpatrick AM, Higgins M, Holguin F, Brown LA, Teague WG; National Institutes of Health/National Heart, Lung, and Blood Institute's Severe Asthma Research Program. The molecular phenotype of severe asthma in children. J Allergy Clin Immunol. 2010;125(4):851-857.
5. Bossley CJ, Saglani S, Kavanagh C, Payne DN, Wilson N, Tsartsali L, Rosenthal M, Balfour-Lynn IM, Nicholson AG, Bush A. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. Eur Respir J. 2009;34(5):1052-9.
6. Jenkins HA, Cool C, Szefler SJ, Covar R, Brugman S, Gelfand EW, Spahn JD. Histopathology of severe childhood asthma: a case series. Chest. 2003;124(1):32-41.
7. Gern JE, Busse WW. Relationship of viral infections to wheezing illnesses and asthma. Nat Rev Immunol 2002;2(2):132–8.
8. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354(9178):541–5
9. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. J Allergy Clin Immunol 1995;95(4):843–52
10. Holgate ST. Pathophysiology of asthma: what has our current understanding taught us about new therapeutic approaches? J Allergy Clin Immunol. 2011;128(3):495-505.
11. Zhang Y, Moffatt MF, Cookson WO. Genetic and genomic approaches to asthma: new insights for the origins. Curr Opin Pulm Med. 2012;18(1):6-13.
12. Kearley J, Buckland KF, Mathie SA, Lloyd CM. Resolution of allergic inflammation and airway hyperreactivity is dependent upon disruption of the T1/ST2-IL-33 pathway. Am J Respir Crit Care Med. 2009;179(9):772-81.
13. Barnes PJ. Cytokine modulators as novel therapies for asthma. Annu Rev Pharmacol Toxicol 2002;42:81–98.
14. Gelfand EW, Dakhama A. CD8+ T lymphocytes and leukotriene B4: novel interactions in the persistence and progression of asthma. J Allergy Clin Immunol 2006;117(3):577–82.
15. Holgate ST. The sentinel role of the airway epithelium in asthma pathogenesis. Immunol Rev. 2011;242(1):205-19.
16. Warrell DA, Cox TM, Firth JD (eds) Glomeruloneohritis (pp3971-4001), The Oxford Textbook of Medicine (5th Ed), Oxford University Press, Oxford / New York, 2010
17. Brown HM, Storey G, George WH. Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. Br Med J. 1972;1(5800):585-90.
18. Wenzel SE, Szefler SJ, Leung DY, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. Am J Respir Crit Care Med 1997;156(3 Pt 1):737–43.
19. Du Rand IA, Barber PV, Goldring J, Lewis RA, Mandal S, Munavvar M, Rintoul RC, Shah PL, Singh S, Slade MG, Woolley A; BTS Interventional Bronchoscopy Guideline Group. Summary of the British Thoracic Society guidelines for advanced diagnostic and therapeutic flexible bronchoscopy in adults. Thorax. 2011;66(11):1014-5.
20. EPR Update 2002. "Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002 (EPR Update 2002)". NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003.
21. Stout JW, Visness CM, Enright P, Lamm C, Shapiro G, Gan VN, Adams GK III, Mitchell HE. Classification of asthma severity in children: the contribution of pulmonary function testing. Arch Pediatr Adolesc Med 2006;160(8):844–50.
22. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133–8.
23. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, Taussig LM, Wright AL, Martinez FD. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med 2005;172(10):1253–8.
24. Christopher KL, Wood RP, Eckert RC, Blager FB, Raney RA, Souhrada JF. Vocal-cord dysfunction presenting as asthma. N Engl J Med 1983;308(26):1566–70.
25. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 1998b;53(3):204–12.
26. Malo JL, Lemiere C, Gautrin D, Labrecque M. Occupational asthma. Curr Opin Pulm Med 2004;10(1):57–61
27. Bayliss MS, Espindle DM, Buchner D, Blaiss MS, Ware JE. A new tool for monitoring asthma outcomes: the ITG Asthma Short Form. Qual Life Res 2000;9(4):451–66.
28. Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. Eur Respir J 2004;23(2):287–91.
29. Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Relationships among quality of life, severity, and control measures in asthma: an evaluation using factor analysis. J Allergy Clin Immunol 2005b;115(5):1049–55.
30. Llewellin P, Sawyer G, Lewis S, Cheng S, Weatherall M, Fitzharris P, Beasley R. The relationship between FEV1 and PEF in the assessment of the severity of airways obstruction. Respirology 2002;7(4):333–7.
31. Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE. Spirometric criteria for asthma: adding further evidence to the debate. J Allergy Clin Immunol 2005;116(5):976–82.
32. Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma.

Pediatrics 2006;118(2):e347–e355.
33. Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. Chest 2004;126(6):1875–82.
34. Moore WC, Evans MD, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, Erzurum SC, Curran-Everett D, Dweik RA, Gaston B, Hew M, Israel E, Mayse ML, Pascual RM, Peters SP, Silveira L, Wenzel SE, Jarjour NN; National Heart, Lung, and Blood Institute's Severe Asthma Research Group. Safety of investigative bronchoscopy in the Severe Asthma Research Program. J Allergy Clin Immunol. 2011 Aug;128(2):328-336
35. Hopkin JM, Turney JH, Adu D, Michael J. Rapid diagnosis of obscure pneumonia in immunosuppressed renal transplant patients by cytology of alveolar lavage fluid. Lancet 1983; 2, 299-301
36. Deykin A, Lazarus SC, Fahy JV, Wechsler ME, Boushey HA, Chinchilli VM, Craig TJ, DiMango E, Kraft M, Leone F, et al.; Asthma Clinical Research Network, National Heart, Lung, and Blood Institute/NIH. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. J Allergy Clin Immunol 2005;115(4):720–7.
37. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360(9347):1715–21.
38. Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. Chest 2003;123(3):751–6.
39. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med 2004;169(4):473–78.
40. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, Bauer CP, Guggenmoos-Holzmann I. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. J Allergy Clin Immunol 1997;99(6 Pt 1):763–9
41. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest 2004;125(4):1378–86.
42. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, von Mutius E, Farrall M, Lathrop M, Cookson WO; GABRIEL Consortium. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010;363(13):1211-21.
43. Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J, Szefler SJ. Safety and application of induced sputum analysis in childhood asthma. J Allergy Clin Immunol 2004;114(3):575–82.

Artigo original

Fundamentals of Asthma Treatment

Os Fundamentos do Tratamento da Asma

Timothy Scialla, Adam Wanner[1]

RESUMO

A asma é uma doença complexa. Sua característica cardial é a inflamação crônica que leva a hiper-responsividade brônquica. Como nenhum tratamento é capaz de modificar a história natural da asma, todas as abordagens terapêuticas disponíveis devem ser consideradas com a finalidade de se atingir o controle da asma e não sua cura.

O principal objetivo do controle é o tratamento efetivo da inflamação da via aérea. Na maior parte dos casos, são necessários agentes farmacológicos para obter o controle. Os β_2-agonistas de curta duração são os medicamentos preferidos para o alívio, graças a seu início rápido de ação. Os corticosteroides inalatórios são o tratamento mais efetivo para o controle dos sintomas asmáticos em longo prazo. Entretanto, em pacientes com asma persistente moderada a grave, é necessária terapia coadjuvante. Adicionar um β_2-agonista de longa duração é mais efetivo na melhora dos sintomas do que agregar um antagonista dos receptores de leucotrienos. A teofilina continua a ter um papel específico em pacientes com pouca resposta aos corticosteroides inalatórios. O papel dos anticolinérgicos está evoluindo.

Aproximadamente 10% dos asmáticos têm sintomas refratários mesmo com a combinação de tratamentos de controle. A imunoterapia surge como uma alternativa potencial no tratamento desse grupo heterogêneo de alto risco.

Descritores: Asma/tratamento; Asma/prevenção & controle; Asma/imunologia.

ABSTRACT

Asthma is a complex disease. Its cardinal feature is chronic airway inflammation that leads to bronchial hyperresponsiveness. Because no therapies have been shown to influence the natural history of asthma, all currently available treatments must be viewed in the context of achieving asthma control and not as disease-modifying therapies.

The major target of control remains the effective treatment of airway inflammation. In most cases, pharmacological agents are needed in order to obtain control. Short-acting β_2 agonists are the preferred agents for quick relief because of their rapid onset of action, and inhaled corticosteroids are the most effective therapy for long-term control of asthma symptoms. However, for patients with moderate-to-severe persistent asthma, adjuvant therapy is needed. Adding a long-acting β_2 agonist is more effective at improving symptoms than is adding a leukotriene modifier. Theophylline continues to have a role, especially in patients who respond poorly to inhaled corticosteroid therapy, and the role of long-acting anticholinergic agents is evolving.

Approximately 10% of all asthma sufferers will have refractory symptoms despite the use of combination controller therapies. Immunotherapy has emerged as a potential alternative in the treatment of this heterogeneous, high-risk population.

Keywords: Asthma/treatment; Asthma/prevention & control; Asthma/immunology.

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INTRODUCTION

Asthma is a complex and heterogeneous disease. Clinically, it is characterized by episodic and reversible symptoms of wheezing, chest tightness, cough, and shortness of breath. Worldwide, it affects approximately 300 million people (1). Despite the many advances in our understanding of this chronic disease at both the genomic and the cellular level, its prevalence continues to increase. In the United States, the proportion of persons with asthma, in relation to the general population, increased from 7.3% (20.3 million persons) to 8.2% (24.6 million persons) between 2001 and 2009 (2). Fortunately, over the past decade, morbidity and mortality related to asthma have been declining because of the use of more effective asthma treatments (3). Nevertheless, there remain substantial challenges in managing patients with asthma. Responses to asthma treatment show high individual variability. While some patients receive substantial benefits from the standard asthma therapies, others seem to derive very little benefit and still have uncontrolled symptoms.

A broad and general understanding of the "fundamentals of asthma" is necessary for clinicians to make informed treatment decisions for their patients. Therefore, this review will begin with an overview of asthma pathophysiology. We will discuss the singular importance of achieving control of asthma. The clinicians' major arsenal in this regard includes patient education, trigger avoidance, and drug therapy. We will then discuss the agents currently available as treatments and how those agents can be used synergistically. As the title of this article suggest, our goal is to stress the fundamentals of managing asthma sufferers with a range of symptoms. The framework we present is expanded upon in the subsequent chapters.

PATHOPHYSIOLOGY

Chronic airway inflammation is the cardinal feature of asthma. It is associated with development of airway obstruction and airway hyperresponsiveness, which lead to recurrent symptoms of wheezing, chest tightness, shortness of breath, and cough. These symptoms are reversible, either spontaneously or with treatment. Airway inflammation involves many different cells and inflammatory mediators. The cells include mast cells, eosinophils, T lymphocytes, neutrophils, macrophages, and epithelial cells, as well as, possibly, autonomic neurons and airway vascular endothelial cells (4). The inflammatory mediators include chemokines, cytokines (IL-4, IL-5, and IL-13), cysteinyl leukotrienes, nitric oxide, growth factors, and IgE (5). In the acute phase of an asthma exacerbation, airway smooth muscle constriction and bronchoconstriction can occur quickly in response to various stimuli. In allergen-induced asthma, this bronchoconstriction develops in response to IgE-dependent release of histamine, leukotrienes and prostaglandins (6). The β_2 agonists, which are the mainstay of "acute/quick relief" of airflow limitation, work by relaxing bronchial smooth muscle and reversing bronchoconstriction.

When the inflammatory signals persist, edema (mucosal and submucosal), mucous cell hyperplasia, hypersecretion of mucus, and infiltration by effector cells ensue, as do changes in the airway smooth muscle (hypertrophy and hyperplasia). In addition, there are pronounced alterations in the tracheobronchial vasculature—proliferation of blood vessels and increased blood flow (7). The effect of this ongoing inflammatory process is bronchial hyperresponsiveness (exaggerated bronchoconstriction to a variety of stimuli). In some patients, airflow limitation becomes resistant to therapy. Airway remodeling (hypersecretion of mucus, subepithelial fibrosis, airway smooth muscle hypertrophy, and angiogenesis) has been associated with progressive loss of lung function, although a causal relationship between the two remains controversial (8). Corticosteroids are our most effective treatment option for this ongoing airway inflammation, because they downregulate these pro-inflammatory proteins through genomic mechanisms (gene transcription). They also have more rapid non-genomic effects, including decreased blood flow in the respiratory mucosa (7).

ACHIEVING ASTHMA CONTROL

Cohort studies of individuals with asthma have suggested that asthma sufferers lose lung function at a faster rate than do individuals without asthma (9-12). Unfortunately, identifying patients most at risk for accelerated loss of lung function has been elusive. In addition, trials that have examined whether inhaled corticosteroids can influence the natural history of asthma have not shown them to modify the disease process (13-15).

All currently available treatments for asthma must be viewed in the context of achieving disease control and not as disease-modifying therapies. The major target of control remains the effective treatment of airway inflammation. Asthma guidelines also stress that control be evaluated in two distinct domains (16): impairment and risk. Impairment describes the current physical limitations of patients attributable to active asthma symptoms and the need for frequent use of quick-relief medications (on > 2 days/week). Risk describes the number and severity of asthma exacerbations in the past year, as well as medication side effects. Assessing risk is meant to emphasize the importance of limiting future exacerbations, with the aim of preventing progressive loss of lung function. However, the two domains are not mutually exclusive. The current level of asthma control has been shown to significantly affect the future risk of exacerbations (17).

COMPONENTS OF EFFECTIVE ASTHMA MANAGEMENT

Treating patients with asthma requires a long-term commitment on the part of patients and providers alike. It requires continual reassessment of symptoms and lung function to ensure that control is maintained. It requires ongoing patient education and control of environmental factors. It requires treatment of comorbid conditions that affect asthma and, in almost all cases, the use of pharmacological agents, the goal of latter being to achieve asthma control with the fewest adverse effects.

As clinicians, we tend to emphasize medical therapy often at the expense of the other components of asthma management. Chart 1 summarizes the options available for control of environmental factors while Chart 2 lists the comorbid conditions that can make asthma control difficult. The remainder of this review addresses the medications currently prescribed for asthma treatment.

Chart 1 - Inhalant irritants/allergens and avoidance recommendations.

Type of irritant	Avoidance recommendations and considerations
Indoor inhalant allergens*	
Animal allergens (including pet and rodent allergens)	Treatment of choice is removal of exposure If removal of pet not acceptable, then: - Keep pet out of patient's bedroom - Keep bedroom door closed - Remove upholstered furniture and carpets Consider weekly bathing of pet to remove large quantities of dander and dried saliva, although role in allergen avoidance is not established
House dust mite allergen	Encase mattress in an allergen-impermeable cover Encase pillow in an allergen-impermeable cover or wash weekly Wash sheets and blankets on patient's bed weekly in hot water
Cockroach allergen	Avoid leaving food or garbage exposed Consider use of poison baits, boric acid, and traps in houses with cockroach infestation Professional extermination with chemical agents not preferred as can be irritating to some patients
Indoor fungi (molds)	Controlling dampness and fungal growth in home can be beneficial
Outdoor inhalant allergens	
Trees, grass, weeds, and seasonal mold	Consider staying indoors during peak pollen times; particularly midday and afternoon Keep windows closed in an air-conditioned environment Outside activity shortly after sunrise results in less pollen exposure
Indoor/outdoor irritants	
Environmental tobacco smoke	Avoid smoking and exposure to environmental tobacco smoke
Air pollutants (particulate matter, nitrogen dioxide, ozone)	Avoid exertion or outdoor exercise when levels of air pollution are high
Formaldehyde and volatile organic compounds (sources include new linoleum flooring, synthetic carpeting, particle board, furniture, and recent painting)	Patient education on the potential irritating affects of newly installed furnishings and finishes
Gas stoves, wood-burning appliances, and fireplaces	Avoid exposure or make sure appliances vented to the outside
Occupational irritants	Avoidance of exposure recommended Referral to an occupational specialist

*Vacuuming carpets once or twice weekly can reduce house dust. Patients known to be sensitive to house dust should avoid rooms that are being or have just been vacuumed. If patients vacuum, they should wear a dust mask, use a cleaner fitted with a high-efficiency particulate air filter, or use a cleaner fitted with a double bag.

Source: U.S. Department of Health and Human Services (16).

Chart 2 - Comorbid conditions that can worsen asthma symptoms, with treatment recommendations.

Comorbid condition	Recommended treatment
Allergic bronchopulmonary aspergillosis	Prednisone 0.5 mg/kg with gradual tapering Evaluate progress by repeat chest imaging and determination of serum IgE
Gastroesophageal reflux disease*	Avoid heavy meals, fried food, caffeine, alcohol intake Avozzzzzzzid food or drink within 3 hours before bedtime Elevate the head of bed on 6- to 8-inch blocks Institute appropriate pharmacotherapy
Obesity	Weight loss has been shown to reduce asthma exacerbations and improve pulmonary function and quality of life
Obstructive sleep apnea	Expert panels have recommended screening patients with poorly controlled asthma for obstructive sleep apnea, especially if they are overweight or obese.
Rhinitis/sinusitis	Intranasal corticosteroids First- and second-generation antihistamines Immunotherapy can be considered in refractory cases
Stress and depression	Clinical trials still needed to determine role of stress reduction and asthma symptoms Observational studies show an association between chronic stress and worsening of asthma symptoms

*Asthma sufferers with asymptomatic reflux do not appear to benefit from acid suppression therapy.

Source: U.S. Department of Health and Human Services (16).

DRUG THERAPY

In a recent excellent review of drug therapy in asthma (3), Fanta stressed the importance of categorizing medical therapy on the basis of its role in treatment (quick relief versus long-term control), rather than on the basis of its specific molecular action (bronchodilation versus anti-inflammation). We will build on this concept by discussing the use of monotherapy and combination therapy in regards to long-term control. We will also discuss the challenge of severe asthma that is refractory to treatment.

For quick relief of asthma symptoms, the preferred agents are short-acting β_2 agonists (SABAs). They offer the fastest onset of action for bronchodilation and do not lose their potency with an increased number of daily treatments (18). Recent studies have shown that the use of an inhaled corticosteroid-SABA combination is clinical efficacious as rescue medication (19,20). This is appealing because it combines an acute bronchodilator with an anti-inflammatory agent at a time when inflammation is most active and control is not being achieved with the standard dose of the corticosteroid. However, the use of the inhaled corticosteroid-SABA combination has not been universally recommended (16). Although the combined use of a long-acting β_2 agonist (LABA) with a rapid onset of action and an inhaled corticosteroid (specifically the formoterol-budesonide combination) has shown favorable results as quick-relief therapy, its safety has not been extensively studied (3,21,22).

SINGLE-AGENT CONTROLLER THERAPY

Inhaled corticosteroids

Inhaled corticosteroids are the most effective therapy for long-term control of asthma symptoms. They consistently reduce asthma symptoms and airway hyperresponsiveness, improve peak expiratory flow, and prevent exacerbations (23-25). Their mechanisms of action (genomic and non-genomic) have broad effects on asthma inflammation. They are effective as monotherapy in patients with mild-to-moderate persistent asthma. In low-to-moderate doses, they tend to have very few systemic effects. However, at higher doses, their therapeutic efficacy tends to flatten, while the systemic absorption and side effects continue to increase. Therefore, the goal of effective treatment is to find the lowest dose possible to achieve control. This is done either by adding a second agent or by reducing the dose once control has been achieved and sustained for 3 to 6 months.

Leukotriene modifiers

Leukotriene modifiers are effective at treating mild persistent asthma. They are considered an alternative therapy in patients who cannot tolerate or do not wish to take inhaled corticosteroids. Because adherence to pills is often better than is adherence to inhalers, pragmatism suggests that these agents should be considered more frequently. In addition, as these agent come off patent, their cost-effectiveness might sway clinicians to use them as single-agent controller therapy in patients with adequate asthma control. Finally, due to their mechanism of action, these agents have salutatory effects on patients with associated allergic rhinitis or aspirin intolerance.

COMBINATION CONTROLLER THERAPY

For patients with moderate-to-severe persistent asthma, achieving symptom control can be very challenging and often requires inhaled corticosteroids plus adjuvant therapy (26).

inhaled corticosteroids/LABAs

For patients in whom asthma is not effectively controlled by inhaled corticosteroid therapy alone, adding a LABA is effective at improving asthma symptoms, decreasing future exacerbations, and lowering the total dose of inhaled corticosteroids (26-29). A LABA should never be used as monotherapy in the treatment of asthma, because they have been associated with an increased risk of fatal and near fatal asthma attacks (30). The use of an inhaled corticosteroid-LABA combination is believed to have synergistic effects by which the inhaled corticosteroid improves the efficacy of the LABA and vice versa (31). The LABAs are thought to facilitate transcription of anti-inflammatory genes, whereas inhaled corticosteroids potentiate the action of the β_2 agonist either by inhibiting its local deposition or by enhancing β_2 receptor signaling in the lung (31-33). Combined with an inhaled corticosteroid, the use of a LABA is considered safe and is recommended as the initial adjuvant for achieving asthma control (34).

Inhaled corticosteroids, LABAs, and leukotriene modifiers

In asthma patients on inhaled corticosteroid therapy, adding a leukotriene modifier is less effective than is adding a LABA (35). Combining a leukotriene modifier with a LABA (without an inhaled corticosteroid) is also less effective (36). Therefore, leukotriene modifiers are often used as a third agent to limit the total dose of inhaled corticosteroid in patients with difficult-to-control asthma.

Theophylline

Theophylline is a weak bronchodilator at the suggested plasma concentration (5-15 mg/L). Its potency is limited by side effects that can develop at a plasma concentration > 20 mg/L. The anti-inflammatory effects of theophylline have recently been re-examined. At a lower concentration (5 mg/L), theophylline activates histone deacetylases, which inhibit the expression of inflammatory genes such as nuclear factor kappa B (37). At lower doses, theophylline might have synergistic effects as an adjuvant to inhaled corticosteroid therapy (activated glucocorticoid receptors recruit histone deacetylases to inflammatory genes). In one study, low-dose theophylline was found to be as effective as are leukotriene modifiers in controlling mild-to-moderate asthma (38). Theophylline might have a role in patients who are poor responders to inhaled corticosteroids (smokers and obese patients).

inhaled corticosteroids and tiotropium

Short-acting anticholinergic agents are not currently recommended in the usual treatment of asthma. The long-acting anticholinergic tiotropium has been shown to be an effective bronchodilator and to reduce exacerbations in patients with COPD (39). It was only a matter of time before its potential role in asthma was closely examined. In a recent, large, double-blind, randomized control trial, patients already on an inhaled corticosteroid were randomized to the addition of tiotropium, the addition of a LABA, or the doubling of the inhaled corticosteroid dose (40). The primary endpoint was peak expiratory flow. Adding tiotropium was more effective than was doubling the inhaled corticosteroid dose and was equally as effective as was adding a LABA. Although further studies are pending to clarify the future role of tiotropium, its use can now be considered in patients who are intolerant to LABAs and are already on an inhaled corticosteroid.

SEVERE ASTHMA REFRACTORY TO COMBINATION THERAPY

Approximately 10% of asthma sufferers will have refractory symptoms despite a combination of controller therapies (41). This is a heterogeneous group of patients who often require either continuous oral corticosteroids or frequents corticosteroid "bursts" every year. Among such patients, there is greater morbidity and use of health care services. Although managing asthma in this population is challenging, there are now several novel treatment options to help these patients achieve better asthma control (42). In addition, patients with severe asthma display a number of asthma phenotypes that can help clinicians determine which of these therapies to pursue.

Immunotherapy

Omalizumab is an anti-IgE monoclonal antibody that is used in asthma sufferers whose symptoms are uncontrolled on triple therapy (an inhaled corticosteroid-LABA-leukotriene modifier combination). Omalizumab has been proven to decrease asthma exacerbations and emergency room visits, as well as improving quality of life in patients with moderate-to-severe allergic asthma (43). The prototypical patient in whom such treatment is considered has an asthma phenotype that includes a documented sensitization to a perennial aeroallergen (dust mite, animal dander, mold, or cockroach) as well as a serum IgE level of 30-700 IU/mL. Unfortunately, even with these parameters in place, it is difficult to predict which patients will respond to omalizumab therapy. In one study, the prescribing physician's overall assessment of the benefit of treatment after 16 weeks was found to predict who did best with this treatment in the long run (44). Finally, in those patients already requiring oral corticosteroids on a daily basis, omalizumab neither allows reduction in the dose of oral corticosteroids nor significantly decreases asthma exacerbations (43).

Two other biologics have received additional attention more recently. Mepolizumab is an anti-IL-5 monoclonal antibody. It is effective in reducing the

number of eosinophils in the airway and blood. In earlier trials, its effects on patients with mild-to-moderate asthma were disappointing (45,46). However, two small randomized trials recently showed that mepolizumab can reduce asthma exacerbations while reducing oral corticosteroid doses in a highly selected group of patients (47,48). Their phenotype included refractory asthma with persistent airway eosinophilia (> 3% eosinophils in induced sputum), despite treatment with oral corticosteroids or high-dose inhaled corticosteroids. The responders tended to have late-onset asthma (symptom onset in their late 20s) and less atopy than expected for the observed degree of eosinophilia. Despite reducing the frequency/severity of exacerbations, the addition of intravenous mepolizumab did not improve lung function.

Lebrikizumab is anti IL-13 monoclonal antibody. IL-13 is elevated in some patients with refractory asthma despite the use of inhaled and systemic corticosteroids. It has been proposed that IL-13 induces periostin secretion from bronchial epithelial cells with subsequent fibroblast activation and airway remodeling (49). In a recent trial, asthma patients treated with lebrikizumab had greater improvements in lung function than did those receiving a placebo, at 12 weeks but not at 24 weeks (50). Rates of exacerbations were not improved with treatment. In that study, the patients designated as having "high periostin levels" (above the median for the 212 patients studied) seemed to derive the most benefit from lebrikizumab, suggesting the existence of another asthma phenotype for specific therapy in the future.

Bronchial thermoplasty (BT)

Bronchial thermoplasty (BT) has recently been approved for the treatment of severe asthma. It involves performing three bronchoscopies in which thermal energy is delivered to the airway wall with the goal of reducing smooth muscle mass. The largest trial to date, which included a control sham bronchoscopy group, showed statistical improvement in a quality of life score in the intervention group, although the control group also showed greater than expected improvement (51). Secondary outcomes did note a benefit to BT in regards to severe exacerbation, emergency room visits, and days missed from work or school. Although the results were not uniform in those who underwent BT, no specific responder phenotype was evident. Some have suggested that patients with more prominent proximal airway inflammation and obstruction gain greater benefit from BT (52). In addition, it use was found to be safe in patients with an FEV1 as low as 60% of predicted, which might also constitute a target group. However, the long-term side effects of BT and the durability of its clinical benefits remain unknown.

Macrolide therapy

The phenotype of non-eosinophilic (neutrophilic) asthma has emerged as a challenging form to manage (41). Patients with neutrophilic asthma are more likely to be smokers and do not respond as well to inhaled corticosteroid therapy. Evidence of the benefits of macrolide therapy in chronic asthma is not conclusive, although macrolides do decrease neutrophil numbers and levels of associated cytokines in the airways (53,54).

FINAL CONSIDERATIONS

The key goal of asthma treatment is to achieve control. Mechanistically, this is achieved by combating ongoing airway inflammation. The approach to poorly controlled asthma is multifaceted. It involves patient education on allergen avoidance, as well as treatment of any comorbid conditions that can exacerbate asthma symptoms. Medical therapy in poorly controlled asthma begins with the use of inhaled corticosteroids. The most frequent adjuvant treatment associated with the best patient outcomes is the addition of a LABA. In patients who cannot tolerate the inhaled corticosteroid-LABA combination or in who asthma remains uncontrolled, there are additional roles for leukotriene modifiers, theophylline, and even long-acting anticholinergic bronchodilators. For patients with severe asthma that is refractory to treatment, a heterogeneous, high-risk group, novel therapies continue to emerge.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-78.
2. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stat Report:1-14.
3. Fanta CH. Asthma. N Engl J Med 2009;360:1002-14.
4. Robinson D, Hamid Q, Bentley A, Ying S, Kay AB, Durham SR. Activation of CD4+ T cells, increased TH2-type cytokine mRNA expression, and eosinophil recruitment in bronchoalveolar lavage after allergen inhalation challenge in patients with atopic asthma. J Allergy Clin Immunol 1993;92:313-24.
5. Barnes PJ, Chung KF, Page CP. Inflammatory mediators of asthma: an update. Pharmacol Rev 1998;50:515-96.
6. Busse WW, Lemanske RF, Jr. Asthma. N Engl J Med 2001;344:350-62.
7. Horvath G, Wanner A. Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma. Eur Respir J 2006;27:172-87.
8. Bousquet J, Chanez P, Lacoste JY, et al. Asthma: a disease remodeling the airways. Allergy 1992;47:3-11.
9. Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the childhood asthma management program. Am J Respir Crit Care Med 2004;170:234-41.
10. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1194-200.

11. Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. Eur J Respir Dis 1987;70:171-9.
12. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.
13. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med 2000;343:1054-63.
14. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006;354:1985-97.
15. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361:1071-6.
16. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120:S94-138.
17. Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol;125:600-8, 8 e1-8 e6.
18. Repsher LH, Anderson JA, Bush RK, et al. Assessment of tachyphylaxis following prolonged therapy of asthma with inhaled albuterol aerosol. Chest 1984;85:34-8.
19. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 2005;352:1519-28.
20. Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52.
21. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171:129-36.
22. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368:744-53.
23. Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL. A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. International Study Group. Eur Respir J 1993;6:877-85.
24. Dahl R, Lundback B, Malo JL, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. International Study Group. Chest 1993;104:1352-8.
25. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. Am Rev Respir Dis 1992;146:547-54.
26. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004;170:836-44.
27. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med 1997;337:1405-11.
28. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996;153:1481-8.
29. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet 1994;344:219-24.
30. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.
31. Giembycz MA, Kaur M, Leigh R, Newton R. A Holy Grail of asthma management: toward understanding how long-acting beta(2)-adrenoceptor agonists enhance the clinical efficacy of inhaled corticosteroids. Br J Pharmacol 2008;153:1090-104.
32. Horvath G, Mendes ES, Schmid N, et al. The effect of corticosteroids on the disposal of long-acting beta2-agonists by airway smooth muscle cells. J Allergy Clin Immunol 2007;120:1103-9.
33. Mendes ES, Horvath G, Campos M, Wanner A. Rapid corticosteroid effect on beta(2)-adrenergic airway and airway vascular reactivity in patients with mild asthma. J Allergy Clin Immunol 2008;121:700-4.
34. Jaeschke R, O'Byrne PM, Mejza F, et al. The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. Am J Respir Crit Care Med 2008;178:1009-16.
35. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev 2006:CD003137.
36. Deykin A, Wechsler ME, Boushey HA, et al. Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. Am J Respir Crit Care Med 2007;175:228-34.
37. Barnes PJ. Theophylline: new perspectives for an old drug. Am J Respir Crit Care Med 2003;167:813-8.
38. ALAACRC. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med 2007;175:235-42.
39. Keating GM. Tiotropium Bromide Inhalation Powder: A Review of its Use in the Management of Chronic Obstructive Pulmonary Disease. Drugs.
40. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med;363:1715-26.
41. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. In: Lancet. 2006/08/29 ed; 2006:780-93.
42. Firszt R, Kraft M. Pharmacotherapy of severe asthma. Curr Opin Pharmacol;10:266-71.
43. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. Cochrane Database Syst Rev 2006:CD003559.
44. Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. Respir Med 2007;101:1483-92.
45. Flood-Page P, Swenson C, Faiferman I, et al. A study to

evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007;176:1062-71.
46. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000;356:2144-8.
47. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360:973-84.
48. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009;360:985-93.
49. Sidhu SS, Yuan S, Innes AL, et al. Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. Proc Natl Acad Sci U S A;107:14170-5.
50. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med;365:1088-98.
51. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med;181:116-24.
52. Wahidi MM, Kraft M. Bronchial Thermoplasty for Severe Asthma. Am J Respir Crit Care Med.
53. Richeldi L, Ferrara G, Fabbri LM, Lasserson TJ, Gibson PG. Macrolides for chronic asthma. Cochrane Database Syst Rev 2005:CD002997.
54. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. Am J Respir Crit Care Med 2008;177:148-55.

Artigo original

The Pharmacogenetics of Asthma and the Road to Personalized Medicine

A Farmacogenética da Asma e o Caminho para a Medicina Personalizada

Victor E. Ortega, Eugene R. Bleecker[1]

RESUMO

A asma é uma doença frequente e heterogênea, tanto em termos de expressão fenotípica, como de resposta aos diferentes tratamentos medicamentosos.

Até o momento, os estudos farmacogenéticos investigaram o papel da variação genética na resposta farmacológica em três classes principais de medicamentos: agonistas dos receptores β_2-adrenérgicos (β_2-agonistas), corticosteroides e modificadores de leucotrienos. Essas análises contribuíram para a compreensão dos determinantes da resposta clínica às diferentes terapias contra asma; porém, a maioria dessas análises é limitada, pois são análises retrospectivas de pequenos grupos populacionais, feitas com base numa abordagem de identificação do gene candidato sujeita a vieses, o que pode requerer replicação em coortes maiores. Estudos farmacogenéticos também vêm investigando determinantes genéticos da resposta a terapias biológicas, tais como a inibição de citocinas por anticorpo.

Abordagens futuras deveriam utilizar ensaios clínicos com abordagens sem vieses, com genomas amplos em grandes populações. Na investigação de eventos incomuns, o ressequenciamento de genes candidatos ou de todo o genoma deveria ser usado para identificar variações genéticas raras com potencial na identificação de efeitos genéticos raros em fenótipos baseados na resposta ao tratamento. Algumas das variantes genéticas que determinam a resposta ao fármaco têm frequência baixa, embora não raras, e deveriam ser validadas através de estudos prospectivos com desenho estratificado por genótipo.

Descritores: Asma/terapia; Asma/genética; Farmacogenética.

ABSTRACT

Asthma is a common disease that is a heterogeneous disorder both in terms of phenotypic expression and its response to different drug therapies.

Asthma pharmacogenetic studies to date have investigated the role of genetic variation in drug response for three major drug classes: the β_2-adrenergic receptor agonists (beta agonists), corticosteroids, and leukotriene modifiers. These analyses have contributed to our understanding of the determinants of clinical response to different asthma therapies but are limited in that, for the most part, they are retrospective analyses of smaller clinical trial populations using what might be a more biased candidate gene approach that requires replication in larger cohorts. Pharmacogenetic studies have also investigated genetic determinants of drug response to biologic therapies such as antibody inhibition of cytokines.

Future approaches should utilize unbiased, genome-wide approaches in larger clinical trial populations. In the investigation of uncommon events, resequencing of candidate genes or whole genome sequencing should be used to identify rare gene variations with the potential to identify rarer genetic effects on drug response phenotypes. Some of the genetic variants that determine drug response have lower frequencies but are not rare and should be validated through prospective studies with a genotype-stratified design.

Keywords: Asthma/therapy; Asthma/genetics; Pharmacogenetics.

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The authors declare that they do not have any potential conflict of interest.

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INTRODUCTION

Asthma is a common disease affecting more than 300 million people worldwide (1). It is a disease characterized by variable degrees of airflow obstruction and inflammation of the airways resulting from multiple, complex pathways. Asthma is a chronic and complex disease with marked heterogeneity in disease expression determined by the interaction of genetic and environmental factors (2,3). Individuals with asthma are treated with a combination of different short-term, rescue, and long-term, controller medications which include β_2-adrenergic receptor agonists (beta agonists), leukotriene modifiers, inhaled corticosteroids (ICS), systemic corticosteroids, anticholinergics, and theophylline. In the future, biologic therapies will be used in responder subsets that can be identified using pharmacogenetic and biomarker-based approaches.

Asthma is as heterogeneous in its response to different drug therapies as it is in phenotypic expression. An analysis of responses to common asthma therapies demonstrates that 70-80% of patients with asthma exhibit variable clinical responses to these medications. This large variance in drug response is beyond what would be expected by patient adherence alone and suggests that a heritable or genetic factor is involved in determining drug response among asthma patients (4). Despite large differences in drug response between individuals in the general population, intraindividual variability remains low consistent with the role of a heritable factor to drug responses (5,6). In fact, genetic variation might account for a larger percentage of the observed variability in drug response, whether beneficial or adverse (5).

Pharmacogenetics is the study of the role of genetic variability in determining interindividual responses to pharmacological therapies and represents the analysis of a gene by environment interaction where the environment is exposure to a medication (Figure 1). Pharmacogenetic research attempts to characterize genetic determinants and their effects on drug response in two fundamental ways: the analysis of genetic effects on clinical response to a drug resulting in measurable changes in a clinical phenotype (pharmacodynamics) and genetic effects on drug metabolism resulting in toxic or subtherapeutic levels within a target organ (pharmacokinetics).

The majority of pharmacogenetic studies in asthma have been limited to pharmacodynamic endpoints due to the retrospective study design used in the majority of studies in current literature. In a retrospective pharmacogenetic study design, pharmacodynamic or clinical endpoints such as airflow obstruction—as measured by FEV_1 and PEF rate (PEFR)—and asthma exacerbations are analyzed for genotypic associations using DNA from participants in a clinical trial. A small number of pharmacogenetic trials have employed a prospective trial design in which patients with asthma are allocated to treatment or placebo groups based on genotypes from DNA obtained prior to randomization. Retrospective pharmacogenetic analyses are essential for the identification of genetic variants or candidate genes of interest and can employ unbiased genome-wide approaches, whereas prospective, genotype-stratified approaches are appropriately powered for the analysis of genetic variants that might be somewhat less common by permitting the study of an adequate sample size containing the risk genotype.

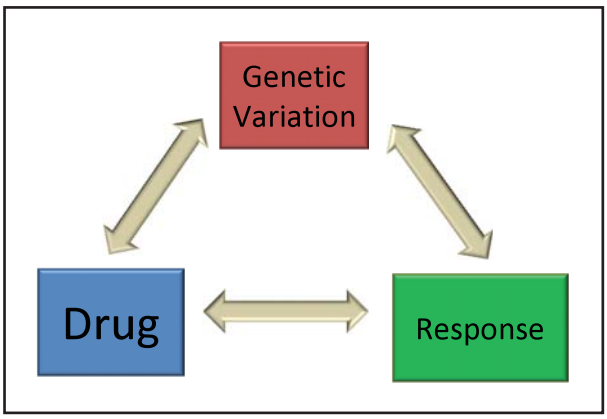

Figure 1 - Pharmacogenetics is the study of the role of genetic variability in determining interindividual responses to pharmacological therapies and represents the analysis of a gene by environmental interaction in which the environment is exposure to a medication.

RELEVANCE OF PHARMACOGENETIC STUDIES IN ASTHMA

Pharmacogenetic research in asthma is driven by two unresolved problems in asthma treatment that would benefit from a personalized approach. The first problem is that a small subset of individuals with asthma (5-10%) experience uncontrolled symptoms and recurrent exacerbations despite treatment with multiple asthma therapies or high doses of ICS (7,9). This subset of severe cases represents a small proportion of the total asthma population; however, this refractory asthma population experiences substantial morbidity and represents a financial burden at least six times greater than that of the population of individuals with milder asthma (9). The second issue is that there are adverse effects related to the use of some asthma therapies, particularly the rare adverse events attributed to medications such as beta agonists (10-12). Overall, the use of pharmacogenetic approaches has the potential of improving personalized therapeutic approaches in which asthma therapies are stratified to optimize therapeutic responses and reduce adverse side effects in an individual.

To date, pharmacogenetic studies of asthma have investigated the role of genetic variability in drug response for three major drug classes including the leukotriene modifiers, corticosteroids, and beta agonists. We will also discuss how pharmacogenetic approaches have recently allowed investigators to identify a subset

of patients that might benefit from these agents. We will then conclude with present and future approaches that have the potential to bring us closer to an era of personalized medicine.

PHARMACOGENETICS OF THE LEUKOTRIENE PATHWAY

The cysteinyl leukotriene pathway plays an important role in the pathogenesis and treatment of asthma in a subset of patients. Cysteinyl leukotrienes mediate a variety of biological processes relevant to asthma, including smooth muscle contraction and allergic airways inflammation through eosinophil migration. Leukotrienes are synthesized by a cascade of enzymes initiated by the conversion of arachidonic acid to leukotriene A_4 by 5-lipoxygenase (5-LO), the rate-limiting step of this pathway encoded by the *ALOX5* gene. Subsequent steps in the leukotriene biosynthetic cascade include enzymes that mediate the conversion of leukotriene A_4 to leukotriene B_4 (leukotriene A_4 hydrolase encoded by *LTA4H*), leukotriene C_4 (leukotriene C_4 synthase encoded by *LTC4S*), or leukotriene D_4. Leukotriene C_4 is transported to the extracellular space by the multi-drug resistance protein 1, a genetic product of *MRP1*. Leukotriene C_4 and leukotriene D_4 signal biologic effects by binding and activating cysteinyl leukotriene receptors, which are G-protein coupled receptors that are a product of the *CYSLTR1* and *CYSLTR2* genes. As depicted in Figure 2, genetic variations in this pathway have been associated with asthma susceptibility but also are genetic determinants of response to medications that target this pathway (13-17).

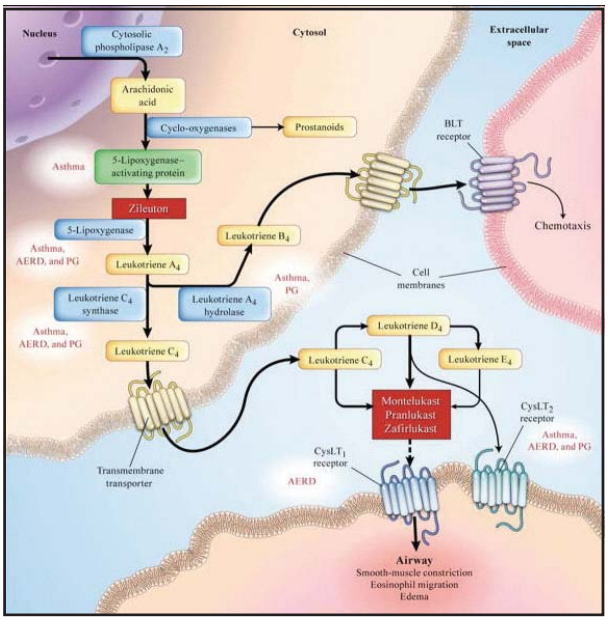

Figure 2 - Overview of the leukotriene pathway. Boxes highlighted in red indicate known genetic associations.

AERD: aspirin exacerbated respiratory disease; PG = pharmacogenetic.
Reproduced from Tantisira and Drazen (17).

There are two major classes of medications that target the cysteinyl leukotriene pathway for the management of asthma: 5-LO inhibitors and cysteinyl leukotriene receptor 1 antagonists (pranlukast, montelukast, and zafirlukast), as well as other leukotriene modifiers under current development. When asthma study populations are analyzed, these agents are associated with beneficial effects on lung function and symptom control (18,19). Despite these effects, a crossover trial randomizing 126 children with asthma to either an ICS (fluticasone) or a leukotriene receptor antagonist (montelukast) demonstrates inter-individual variability in the response to these agents. Treatment with fluticasone or montelukast resulted in improvements in lung function as measured by FEV_1 in asthma (Figure 3); however, 17% had a treatment response (i.e., ≥ 7.5% increase in FEV_1) to both medications, 23% responded to the corticosteroid alone, 5% responded only to montelukast, and 55% did not show a response to either medication; certain subsets also experienced adverse responses to one or both medications (20). This interindividual variability in the response to montelukast and ICS therapy emphasizes the rationale for pharmacogenetic research to identify therapies that are efficacious, ineffective, or even harmful for individual asthma patients.

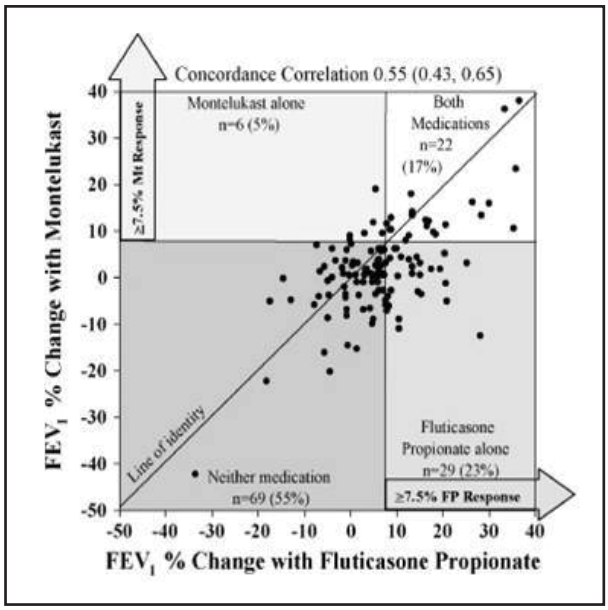

Figure 3 - Variability of response and differential response to fluticasone and montelukast, as measured by change in FEV_1. Four categories of response are displayed, with a favorable response defined as an increase of ≥ 7.5% in FEV_1. The line of identity designates patients favoring montelukast above the line, and those favoring fluticasone below the line.

Reproduced from Szefler et al. (20).

In an early pharmacogenetic analysis in asthma, Drazen et al. performed a retrospective candidate gene analysis of the *ALOX5* gene through a clinical trial consisting of asthma patients treated with a 5-LO inhibitor,

ABT-761 (21). The *ALOX5* gene contains a variable tandem repeat of a transcription factor binding motif that had previously been shown to reduce gene transcription *in vitro*; thereby, potentially diminishing 5-LO activity and reducing downstream cysteinyl leukotriene synthesis. In that clinical trial cohort, 104 homozygotes and heterozygotes for the common allele of the *ALOX5* promoter experienced significant improvements in FEV_1 (18.8-23.3%) with ABT-761, respectively. In contrast, participants who were homozygotes for the variant *ALOX5* promoter region did not respond to the 5-LO inhibitor (−1.2% change in FEV_1). These findings were replicated in a smaller clinical trial of 61 patients treated with montelukast, further demonstrating that asthma patients with the *ALOX5* promoter region variant have a reduced therapeutic response (22).

Pharmacogenetic studies of the leukotriene pathway in patients with asthma have also included retrospective candidate gene analyses of other pathway-related genes. Lima et al. genotyped 28 single-nucleotide polymorphisms (SNPs) in genes throughout the pathway using DNA from 61 non-Hispanic White participants with poorly controlled, mild to moderate persistent asthma randomized to treatment with montelukast. The SNPs in *ALOX5* (rs2115819) and *MRP1* (rs119774) were found to be significantly associated with a change in FEV_1 in response to montelukast (Figure 4). In addition, the variant or minor allele of a promoter SNP in *LTC4S* (rs730012) was associated with a reduced risk of exacerbation while the minor variant of an intronic SNP in *LTA4H* (rs2660845) was associated with an increased risk of exacerbation during montelukast therapy (23).

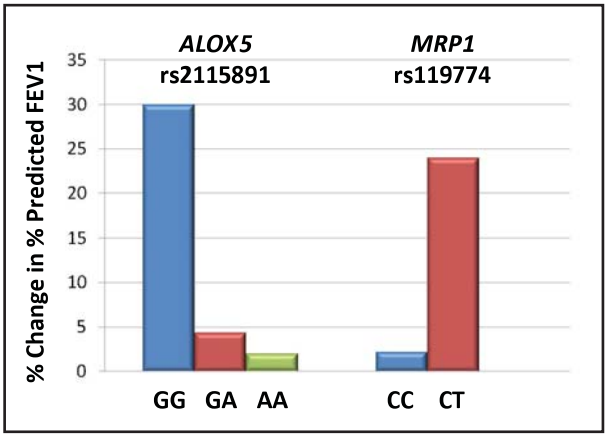

Figure 4 - Influence of genotype on percentage change in % of predicted FEV_1. Percentage increase in FEV_1 (% of predicted) over baseline after 6 months of montelukast treatment in patients with the *MRP1* rs119774 and *ALOX5* rs2115819 genotypes.

Adapted from Lima et al. (23).

These pharmacogenetic studies demonstrate that genetic variation in the leukotriene pathway contributes to the variability in drug response with medications that target this pathway. Larger clinical trials with retrospective candidate gene analyses of the leukotriene pathway or prospective trials should be performed to replicate these findings in order to determine how variation in this pathway can be used in guiding therapy.

PHARMACOGENETICS OF THE CORTICOSTEROID PATHWAY AND PERSONALIZING ASTHMA THERAPY

Corticosteroids or glucocorticoids are the primary anti-inflammatory medication used in the management of asthma. Inhaled glucocorticoids have consistently been shown to have a greater effect on lung function and asthma symptom control when compared with the leukotriene receptor antagonists. Despite this observation, there is a subset of patients who are less responsive to glucocorticoids and might respond to other asthma controller medications (19,20). In asthma subjects who are less responsive to ICS (Figure 3), pharmacogenetic approaches might lead to improved personalized approaches to controller therapy with ICS in asthma (3,8). For example, high-dose ICS might not be preferable in a less responsive asthma patient and the use of an alternative controller therapy may be considered.

The pharmacogenetics of the corticosteroid pathway is based on multiple potential candidate genes encompassing the biosynthesis of glucocorticoids, the cytosolic glucocorticoid receptor heterocomplex, and the chaperone proteins that bind glucocorticoid receptors during the resting state within the cytosol. Glucocorticoids exert their anti-inflammatory effects by activating receptor-chaperone complexes that translocate in the nucleus to repress the transcription factors of pro-inflammatory genes and bind to glucocorticoid response elements in the promoter of anti-inflammatory genes (24,25). Pharmacogenetic studies have investigated the role of candidate genetic variation within the corticosteroid pathway and its impact on the response to corticosteroid therapy.

One of the earliest pharmacogenetic studies investigating glucocorticoid response involved the glucocorticoid receptor gene (*NR3C1*) located in chromosome 5q31, a chromosomal region associated with asthma and related phenotypes in family-based linkage studies (26-28). In a cohort of 216 elderly participants, a nonsynonymous SNP at codon 363 resulted in an asparagine-to-serine substitution. The resulting serine, $Asn^{363}Ser$, was assessed for genotypic effects on glucocorticoid response. Of those 216 participants, 13 (6%) had the variant allele and showed greater sensitivity to glucocorticoids, as determined by cortisol and insulin responses to dexamethasone suppression testing (29).

Genetic variation within the corticosteroid biosynthetic pathway has the potential to determine endogenous glucocorticoid levels and influence the therapeutic response to corticosteroid therapy. A retrospective pharmacogenetic analysis performed by Tantisira et al. investigated SNPs in the corticotropin-releasing

hormone gene (*CRHR1*) in three different clinical trial populations where participants were randomized to ICS therapy: a primary population of 470 adult asthma patients (hereafter, "Adult Study"), 311 childhood asthma patients from the Childhood Asthma Management Program (CAMP), and 336 adult asthma patients from the Asthma Clinical Research Network (ACRN) of the United States National Heart, Lung and Blood Institute. A *CRHR1* SNP, rs242941, was associated with variation in the lung function response to ICS. In the "Adult Study" and CAMP populations (Figure 5), there was a doubling of the FEV_1 response among T homozygotes (TT genotype) when compared with G homozygotes (GG genotype). Another *CRHR1* SNP, rs1876828, was also associated with corticosteroid response in the ACRN population, in which there was a greater FEV1 response among asthma patients with the AA genotype than among those with the GG genotype (30).

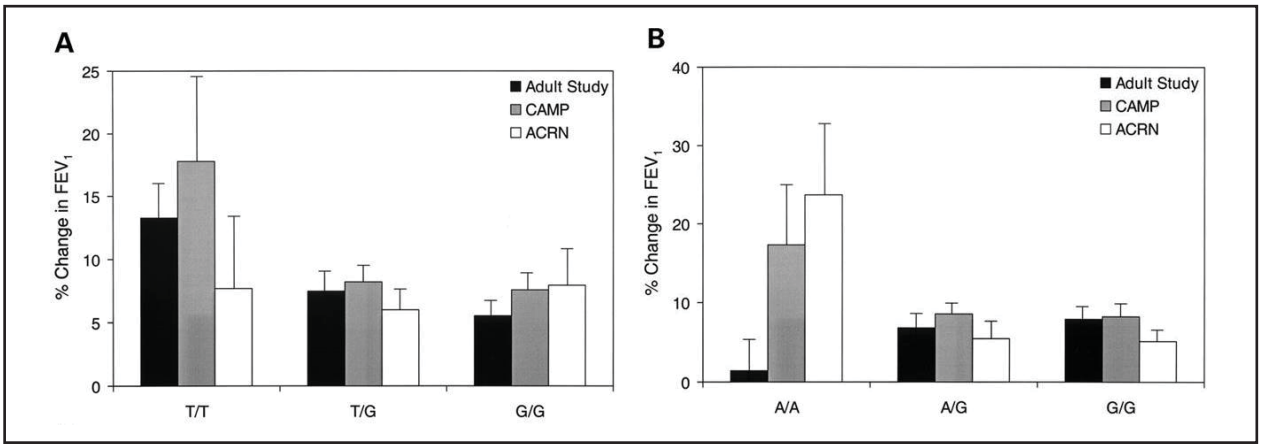

Figure 5 - *CRHR1* genotypes and association with longitudinal response to ICS in asthma patients, adjusted for age, sex, height, and baseline FEV_1. The SNP rs242941 was associated with response over 8 weeks in the "Adult Study" and CAMP populations. The SNP rs1876828 was associated with response over 6 weeks in the ACRN population.

Reproduced from Tantisira et al. (30).

Multiple genes encode for the heterocomplex of chaperones and immunophilins that bind the glucocorticoid receptor and mediate proper assembly and activation of the receptor. Hawkins et al. performed a retrospective genetic analysis of genes encoding for the heterocomplex of chaperones in a clinical trial of 450 asthma patients randomized to treatment with ICS (31). The authors found that genetic variations within the gene encoding for the heat shock organizing protein, *STIP1*, were significantly associated with improvement in FEV_1 response after four weeks of corticosteroid therapy (associated with the SNPs rs6591838 and rs2236647), as well as after eight weeks of the same (associated with the SNPs rs6591838 and rs1011219).

A major challenge in the pharmacogenetic investigation of the corticosteroid pathway lies in its interactions with other genes or pathways that are also regulated by glucocorticoids, such as the β_2-adrenergic receptor pathway (32,33). This challenge is best illustrated in the pharmacogenetics of the *TBX21* gene which encodes for the T-box expressed in the T-cell transcription factor, which influences the development of naïve T lymphocytes. A retrospective candidate gene analysis of *TBX21* in the CAMP clinical trial cohort demonstrated that a nonsynonymous SNP, $His^{33}Glu$, determined improvement in bronchial hyperresponsiveness in response to ICS therapy (34). The pleiotropic effects of glucocorticoids make the study of the corticosteroid pathway crucial to understanding the pharmacogenetics of asthma and call for unbiased, genome-wide approaches be employed.

A recent study was based on a small, family-based, genome-wide association study with replication in additional cohorts. The authors of that study demonstrated a novel pharmacogenetic determinant of ICS response in 118 asthma probands from the CAMP cohort randomized to ICS (budesonide) treatment. The investigators analyzed 13 significantly associated SNPs in four independent replication cohorts totaling 935 asthma patients. The analysis identified a SNP in the promoter region of the glucocorticoid-induced transcript 1 gene (*GLCCI1*), rs37972, which was associated with lung function responses to inhaled glucocorticoids among the CAMP probands and the 935 participants from the replication cohorts (Figure 6). The SNP rs37972 is also in strong linkage equilibrium (i.e., strongly correlated, or "tagged") with another *GLCCI1* promoter SNP, rs37973, which determines gene transcription *in vitro*, demonstrating a functional or molecular-based rationale for the observed genetics effects of variation in this gene on corticosteroid response (35). It will be important to replicate these corticosteroid response gene variants in other, larger populations and determine whether they are independent predictors or have additive effects that regulate corticosteroid responses in asthma.

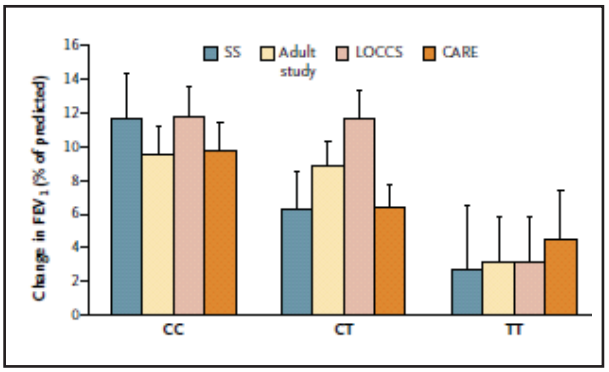

Figure 6 - The association of GLCCI1 rs37972 genotypes (CC, CT, and TT) with change in lung function as a change in FEV_1, expressed as a percentage of the predicted value, after 4 to 8 weeks of therapy with inhaled glucocorticoids in four replication populations: the Salmeterol or Corticosteroids and the Salmeterol with or without Inhaled Corticosteroids trials (SS); the "Adult Study"; the Leukotriene Modifier or Corticosteroid Salmeterol (LOCCS) trial; and the Childhood Asthma Research and Education (CARE) Network trials.

Liptak combined P = 0.0007.

Reproduced from Tantisira et al. (35).

THE B_2-ADRENERGIC RECEPTOR PATHWAY

Inhaled beta agonists are the most commonly prescribed medical therapies for the management of asthma. Inhaled beta agonists exist in two classes: the short-acting beta agonists (SABA: fenoterol, isoproterenol, pirbuterol, levalbuterol, and albuterol) and the long-acting beta agonists (LABA: salmeterol and formoterol). The LABA therapy is administered in combination with an ICS as regular controller therapy, while SABA therapy is used for rescue, as-needed treatment for acute symptom relief or the prevention of exercise-induced symptoms (36). Beta agonists bind to the extracellular β_2-adrenergic receptor, a seven-transmembrane receptor which activates a G-protein coupled receptor pathway through adenylyl cyclase type 9 activation, resulting in airway smooth muscle relaxation (37).

Despite the common use of these agents, this drug class is the center of a controversy related to concerns over adverse events beginning in the 1960s, when high doses of SABAs with less selective β_2 adrenergic receptor activity were associated with serious adverse effects (including death), which resulted in the withdrawal of the SABAs isoproterenol and fenoterol from the market (38-42). Additional data from Sears et al. showed that the regular use of fenoterol results in a loss of asthma symptom control (43). The ACRN Beta Agonist Study (BAGS) demonstrated that regular albuterol was not harmful, albeit no more effective than as-needed therapy for symptom control (44).

Two recent surveillance studies have raised concerns about an increased risk for asthma-related life threatening exacerbation and death among patients with asthma randomized to the addition of LABA to current medical therapy (11,12). These observations and a subsequent meta-analysis based on these findings have resulted in a black-box warning from the United States Food and Drug Administration for all inhalers containing LABAs (10-12). Subsequent randomized, placebo-controlled clinical trials, large meta-analyses, and case-control analyses have not shown an increased risk for life-threatening or fatal adverse events when LABA is administered with an ICS (45-49). In addition, LABA-ICS combination therapy results in improvement in exacerbation rates and symptom control, suggesting that these adverse events are exceedingly rare (45,50-53). The potential for heterogeneity in beta agonist response should be borne in mind, because various pharmacogenetic studies have attempted to identify the small subset of patients with asthma who are susceptible to rare adverse responses to beta agonist therapy.

Initially, pharmacogenetic analyses focused on SABA therapy, LABA therapy, and the encoding of the β_2-adrenergic receptor gene, *ADRβ2* (Figure 7), which is a small intronless gene located in chromosome 5q31, a region linked to asthma and related phenotypes (26-28). The first detailed mutational analysis of *ADRβ2* was performed in 1992 by Reihsaus et al. (54), who characterized nine genetic variants including $Gly^{16}Arg$, $Gln^{27}Glu$, $Val^{34}Met$, and $Thr^{164}Ile$. As can be seen in Figure 7, other investigators have identified 49 polymorphisms spanning the 5' promoter, coding region, and 3' untranslated region of *ADRβ2* (55,56).

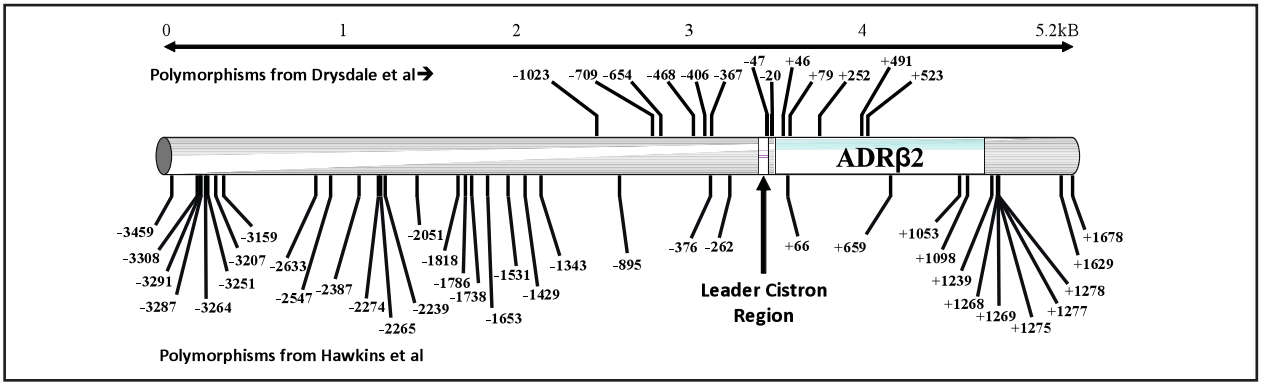

Figure 7 - Diagram of the β_2-adrenergic receptor gene (*ADRβ2*) with polymorphisms denoted by nucleotide position relative to the start codon, in two separate studies.

Adapted from Drysdale et al. and Hawkins et al. (55,56).

In Chinese hamster fibroblasts and human airway smooth muscle cells, Gly^{16}Arg and Gln^{27}Glu have been shown to downregulate the receptor response to beta agonist *in vitro*. The Gly^{16} variant results in enhanced receptor downregulation in response to isoproterenol compared with Arg^{16}, whereas Gln^{27} results in resistance to receptor downregulation compared with Glu^{27} (57,58). These common SNPs have been the focus of multiple candidate gene analyses of *ADRβ2*.

One of the earliest pharmacogenetic studies involving *ADRβ2* was conducted by Martinez et al. (59), who demonstrated that Arg^{16} homozygotes and Gly^{16}Arg heterozygotes were, respectively, 5.3 times and 2.3 times more likely to respond to albuterol than were Gly^{16} homozygotes. This effect was not observed for Gln^{27}Glu (59). Subsequently, Silverman et al. demonstrated that, among the children in the CAMP cohort, the Arg^{16} homozygotes had the highest post-bronchodilator FEV_1 (percentage of predicted) in response to albuterol (60). Other investigators have replicated the genotypic effects of Gly^{16}Arg on the bronchodilator response to a one-time administration of albuterol in smaller populations of asthma patients that have included ethnic groups such as Puerto Ricans (61-64).

Drysdale et al. analyzed estimated *ADRβ2* haplotypes using 13 polymorphisms and reported seemingly contrasting effects of Gly^{16}Arg on bronchodilator responses to a SABA (albuterol). The authors proposed 12 haplotypes, including the Gly^{16}-containing "haplotype 2", which was associated with higher levels of gene transcription and translation when compared with the Arg^{16}-containing "haplotype 4." These *in vitro* findings also corroborated with the *in vivo* finding that haplotype 2 homozygotes experienced the greatest degree of FEV_1 albuterol bronchodilation, while haplotype 4 homozygotes experienced the lowest (55). In a larger resequencing analysis, these haplotype effects were not observed (56).

Pharmacogenetic studies of *ADRβ2* and the response to regular SABA therapy have also focused on variations at Gly^{16}Arg. A retrospective analysis of the ACRN BAGS trial investigated the effects of Gly^{16}Arg and Gln^{27}Glu in 190 participants with mild asthma who were randomized to regular or as-needed albuterol over a 16-week period. The Arg^{16} homozygotes randomized to regular albuterol therapy experienced a decline a PEFR, whereas no such effect was observed among Gly^{16} homozygotes or those randomized to as-needed albuterol therapy, as shown in Figure 8 (65).

Taylor et al. also performed a retrospective candidate gene analysis of a placebo-controlled, cross-over trial consisting of 106 patients with asthma randomized to salmeterol or regularly scheduled albuterol therapy. The Arg^{16} homozygotes experienced a decline in PEFR and a higher frequency of exacerbations during regular albuterol therapy; however, no adverse effects were noted during salmeterol therapy (66). This pharmacogenetic finding has been replicated in retrospective and prospective candidate gene analyses performed by ACRN investigators (65,67). The results of this retrospective genetic analysis and the analysis of the BAGS trial led to the design and implementation of the ACRN Beta Agonist Response by Genotype (BARGE) trial (67).

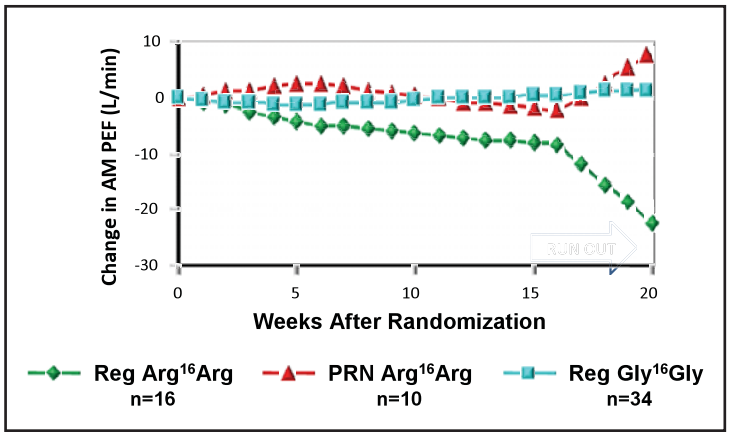

Figure 8 - A retrospective analysis of the BAGS trial investigating the effects of Gly16Arg and Gln27Glu in 190 participants with mild asthma who were randomized to regular or as-needed albuterol over a 16-week period. Arg16 homozygotes randomized to regular albuterol therapy experienced a decline in morning (AM) PEFR, although no such effect was observed among Gly16 homozygotes or those randomized to as-needed albuterol therapy.

Reproduced from Israel et al. (65).

The BARGE trial was one of the first prospective, genotype-stratified, placebo-controlled, cross-over trials where 37 Arg^{16} homozygotes and 41 Gly^{16} homozygotes were randomized to 16-week treatment with regular albuterol or placebo with both groups receiving ipratropium as a rescue inhaler to minimize beta agonist exposure throughout the trial. The Arg^{16} homozygotes experienced no change in PEFR during regular albuterol treatment; however, PEFR improved during intermittent treatment. In contrast, Gly^{16} homozygotes experienced an improvement in PEFR during regular albuterol therapy. The Arg^{16} homozygotes also experienced reduced responses (FEV_1, FVC, asthma symptom scores, and rescue inhaler use) during regular albuterol therapy, whereas Gly^{16} homozygotes experienced improvement in those same endpoints, as can be seen in Figure 9 (67). The contrasting effects of Gly^{16}Arg during acute, one-time exposure versus regular, chronic SABA therapy is thought to be related to variation in receptor kinetics or the pro-inflammatory effects of beta agonists (51,68-70).

Investigators subsequently hypothesized that the observed effects of the Gly^{16}Arg locus on the response to SABA therapy might apply to adverse responses to LABA therapy. Taylor et al.'s The retrospective candidate gene analysis conducted by Taylor et al. did not show genotypic effects at the Gly^{16}Arg locus among

106 asthma patients; however, a small retrospective candidate gene analysis of two ACRN clinical trials demonstrated that, during salmeterol treatment, Arg^{16} homozygotes experienced a significant deterioration in PEFR, asthma symptom scores, and rescue inhaler use when compared with Gly^{16} homozygotes (71). This retrospective pharmacogenetic finding, albeit from two small cohorts, prompted retrospective candidate gene analyses in larger clinical trial populations and two prospective, genotype-stratified trials. Bleecker et al. genotyped five *ADRβ2* SNPs in 183 asthma patients randomized to salmeterol with concomitant ICS therapy or montelukast and demonstrated that all participants experienced sustained and significant improvement in morning PEFR despite the $Gly^{16}Arg$ genotype (72). Subsequently, two cohorts of 2,250 and 405 asthma patients, respectively, randomized to salmeterol or formoterol with concomitant ICS therapy, were genotyped for 11 *ADRβ2* SNPs and did not show significant differences between $Gly^{16}Arg$ genotypes in terms of the time to first exacerbation, PEFR, FEV_1, or rescue inhaler use (73).

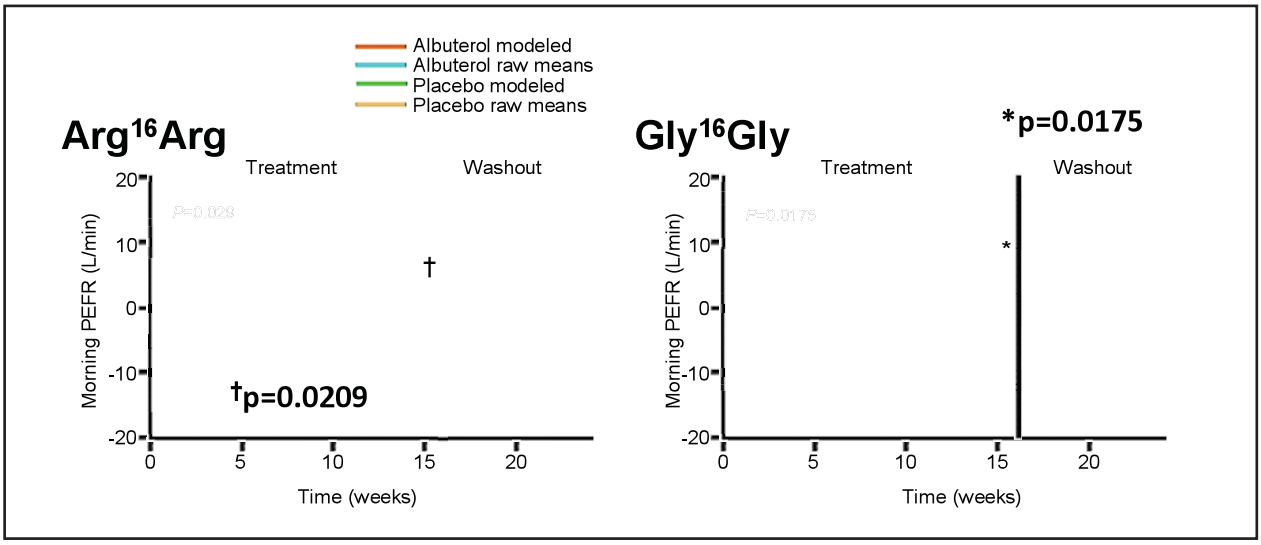

Figure 9 - The BARGE trial was a prospective, genotype-stratified, placebo-controlled, cross-over trial in which 37 Arg16 homozygotes and 41 Gly16 homozygotes were randomized to 16-week treatment with regular albuterol or placebo, both groups receiving ipratropium as a rescue inhaler to minimize beta agonist exposure throughout the trial. Arg16 homozygotes experienced no change in PEFR during albuterol treatment; however, PEFR improved during placebo treatment. Nevertheless, Gly16 homozygotes experienced an improvement in PEFR during regular albuterol therapy.

Reproduced from Israel et al. (67).

One prospective, genotype stratified clinical trial analyzing $Gly^{16}Arg$ genotypes and responses to LABA treatment was performed by ACRN investigators, the Long-Acting Beta Agonist Response by Genotype (LARGE) trial. In the LARGE trial, 42 Arg^{16} homozygotes and 45 Gly^{16} homozygotes were randomized, in a cross-over fashion, to salmeterol or placebo in addition to ICS therapy for 18 weeks with ipratropium rescue inhaler therapy to minimize beta agonist exposure. At the end of the treatment periods both genotype groups experienced similar improvements in lung function; however, Gly^{16} homozygotes experienced a greater increase in bronchial reactivity to methacholine, a "bronchoprotective effect" that was not observed among Arg^{16} homozygotes and requires further investigation (74). A larger prospective, genotype-stratified, pharmacogenetic trial was performed by Bleecker et al., who randomized 179 Arg^{16} homozygotes, 182 $Gly^{16}Arg$ heterozygotes, and 183 Gly^{16} homozygotes to 16 weeks of salmeterol with ICS or salmeterol monotherapy. That trial is important because it showed similarities in lung function response between $Gly^{16}Arg$ genotypes during LABA therapy with or without concomitant ICS. The study showed that the absence of a $Gly^{16}Arg$ genotype effect is unrelated to concomitant ICS therapy, which acts synergistically with LABA during combination therapy, as depicted in Figure 10 (32,33,75).

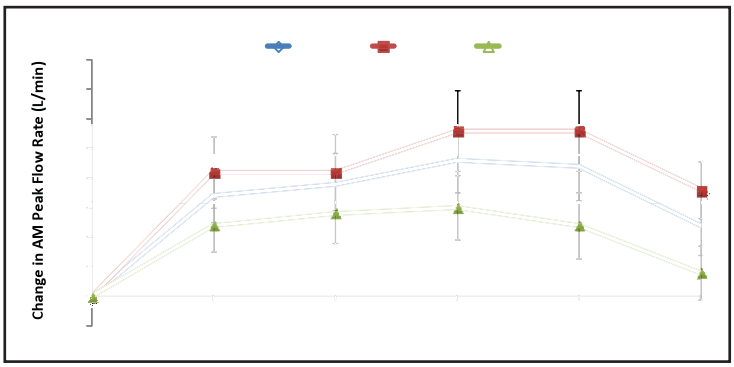

Figure 10 - Morning (AM) PEFR by genotype for subjects randomized to salmeterol monotherapy in a prospective, genotype-stratified trial.

Reproduced from Bleecker et al. (74).

Current evidence consistently suggests that a variation in *ADRβ2* at the Gly[16]Arg locus is a determinant for the response to acute and chronic SABA therapy. Despite these observations, this variant does not determine response to LABA therapy with or without concomitant ICS therapy. The lack of a genotypic effect for a common variant such as Gly[16]Arg suggests that if an effect does exist, it is either on an outcome so rare that studies to date have been underpowered to detect it or an effect that depends on interactions with other variants in *ADRβ2* and pathway-related genes to determine the response to LABA therapy. For example, a common coding variant in a pathway-related gene encoding for adenylyl cyclase type 9 (ADCY9) has also been shown to affect the response to albuterol among children with asthma treated with ICS (37).

It is also possible that rare variants that might have larger effects on phenotypes determine rare responses to LABA therapy, including life-threatening exacerbations. A rare variant identified within *ADRβ2*, Thr[164]Ile, is associated with diminished receptor coupling to the pathway-related Gs protein, as demonstrated by a 50% decrease in adenylyl cyclase activity and results in a 4-fold decrease in receptor binding affinity for isoproterenol and epinephrine. In addition, pharmacogenetic pathway analyses in larger asthma populations utilizing genome-wide approaches and detailed resequencing will be necessary in order to identify common and rare variants along the β_2-adrenergic receptor pathway that determine the risk for rare but serious adverse responses to beta agonists. This might help to identify the small subset of asthma patients that might benefit from alternatives to long-acting bronchodilator therapies, for example, long-acting muscarinic antagonists (76).

FINAL CONSIDERATIONS: ALTERNATIVE PATHWAYS AND THE FUTURE OF PHARMACOGENETICS

Pharmacogenetic approaches have the promise of determining drug responses to therapies that are expansive or have potential side effects, making it necessary to determine the subpopulation that is responsive to a given therapy. Molecular inhibitors and monoclonal antibodies have been designed to target alternative inflammatory pathways for the management of asthma. Pitrakinra is a recombinant IL-4 variant that inhibits binding of IL-13 and IL-4 to the IL-4α receptor subunit to attenuate Th2 lymphocyte-mediated allergic inflammation. In a randomized, placebo-controlled trial of patients with atopic asthma, inhaled pitrakinra treatment was associated with improvements in antigen-induced airway hyperresponsiveness with effects determined by coding variants in the gene encoding for the IL4α receptor subunit (*IL4RA*) (77,78). More recently, in a large phase IIb clinical trial, Slager et al. showed that response to this IL-4α antagonist was determined by specific *IL4RA* genotypes. Approximately one third of severe asthma patients responded in a significant dose-response paradigm to this drug, while the remaining two thirds of the population had no response (79). Thus, the nonresponsive asthma patients should not receive this therapy and *IL4RA* genotypes could serve as a useful therapeutic biomarkers. There are multiple experimental biologic therapies currently under development for the management of severe asthma. Therefore, it will become increasingly important to design pharmacogenetic studies to identify the subset of asthma patients that would benefit from these novel therapies.

Review of the pharmacogenetics of asthma therapies and their respective pathways, shows that genomics research can contribute to the personalized medicine of the future where genetic determinants could predict clinical responses, whether beneficial or adverse. Our understanding of the pharmacogenetics of the leukotriene, corticosteroid, and β_2-adrenergic receptor pathways have improved our understanding of the genetic determinants of clinical response but are limited by the inherent weaknesses of candidate gene analyses in smaller cohorts. Most of the current analyses are limited to small clinical trial populations with a biased candidate gene approach with SNPs that might "tag" for causative variants, requiring replication in larger trial cohorts. Future clinical trials will need to analyze larger populations using genome-wide association approaches in order to identify new, unbiased pharmacogenetic targets that predict drug response. In addition, resequencing of candidate genes or whole exome sequencing can identify rare variants or other forms of gene variation such as polynucleotide insertions or deletions that have the potential for strong genetic effects on drug response phenotypes. Some of the genetic variants we have discussed have low allele frequencies and are suited for analysis with a prospective, genotype-stratified design ensuring that individuals with less common risk variants are well represented in a clinical trial population. In order for personalized medicine to be translated to clinical medicine, it is important to replicate pharmacogenetic discoveries with analyses of larger clinical trial cohorts and, when appropriate, prospective, genotype-stratified pharmacogenetic studies.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-78.
2. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol 2004;113:101-8.
3. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med

2010;181:315-23.
4. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. Br Med Bull 2000;56:1054-70.
5. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics 1998;8:283-9.
6. Vesell ES. Pharmacogenetic perspectives gained from twin and family studies. Pharmacol Ther 1989;41:535-52.
7. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med 2000;162:2341-51.
8. Chan MT, Leung DY, Szefler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. J Allergy Clin Immunol 1998;101:594-601.
9. Serra-Batlles J, Plaza V, Morejon E, Comella A, Brugues J. Costs of asthma according to the degree of severity. Eur Respir J 1998;12:1322-6.
10. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med 2006;144:904-12.
11. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306:1034-7.
12. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.
13. Holloway JW, Barton SJ, Holgate ST, Rose-Zerilli MJ, Sayers I. The role of LTA4H and ALOX5AP polymorphism in asthma and allergy susceptibility. Allergy 2008;63:1046-53.
14. Kedda MA, Shi J, Duffy D, et al. Characterization of two polymorphisms in the leukotriene C4 synthase gene in an Australian population of subjects with mild, moderate, and severe asthma. J Allergy Clin Immunol 2004;113:889-95.
15. Pillai SG, Cousens DJ, Barnes AA, et al. A coding polymorphism in the CYSLT2 receptor with reduced affinity to LTD4 is associated with asthma. Pharmacogenetics 2004;14:627-33.
16. Thompson MD, Capra V, Takasaki J, et al. A functional G300S variant of the cysteinyl leukotriene 1 receptor is associated with atopy in a Tristan da Cunha isolate. Pharmacogenet Genomics 2007;17:539-49.
17. Tantisira KG, Drazen JM. Genetics and pharmacogenetics of the leukotriene pathway. J Allergy Clin Immunol 2009;124:422-7.
18. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. Arch Intern Med 1998;158:1213-20.
19. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. Ann Intern Med 1999;130:487-95.
20. Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005;115:233-42.
21. Drazen JM, Yandava CN, Dube L, et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. Nat Genet 1999;22:168-70.
22. Telleria JJ, Blanco-Quiros A, Varillas D, et al. ALOX5 promoter genotype and response to montelukast in moderate persistent asthma. Respir Med 2008;102:857-61.
23. Lima JJ, Zhang S, Grant A, et al. Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. Am J Respir Crit Care Med 2006;173:379-85.
24. Pratt WB, Galigniana MD, Harrell JM, DeFranco DB. Role of hsp90 and the hsp90-binding immunophilins in signalling protein movement. Cell Signal 2004;16:857-72.
25. Schoneveld OJ, Gaemers IC, Lamers WH. Mechanisms of glucocorticoid signalling. Biochim Biophys Acta 2004;1680:114-28.
26. Xu J, Meyers DA, Ober C, et al. Genomewide screen and identification of gene-gene interactions for asthma-susceptibility loci in three U.S. populations: collaborative study on the genetics of asthma. Am J Hum Genet 2001;68:1437-46.
27. Meyers DA, Postma DS, Stine OC, et al. Genome screen for asthma and bronchial hyperresponsiveness: interactions with passive smoke exposure. J Allergy Clin Immunol 2005;115:1169-75.
28. Ober C, Cox NJ, Abney M, et al. Genome-wide search for asthma susceptibility loci in a founder population. The Collaborative Study on the Genetics of Asthma. Hum Mol Genet 1998;7:1393-8.
29. Huizenga NA, Koper JW, De Lange P, et al. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab 1998;83:144-51.
30. Tantisira KG, Lake S, Silverman ES, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum Mol Genet 2004;13:1353-9.
31. Hawkins GA, Lazarus R, Smith RS, et al. The glucocorticoid receptor heterocomplex gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. J Allergy Clin Immunol 2009;123:1376-83 e7.
32. Profita M, Gagliardo R, Di Giorgi R, et al. Biochemical interaction between effects of beclomethasone dipropionate and salbutamol or formoterol in sputum cells from mild to moderate asthmatics. Allergy 2005;60:323-9.
33. Usmani OS, Ito K, Maneechotesuwan K, et al. Glucocorticoid receptor nuclear translocation in airway cells after inhaled combination therapy. Am J Respir Crit Care Med 2005;172:704-12.
34. Tantisira KG, Hwang ES, Raby BA, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. Proc Natl Acad Sci U S A 2004;101:18099-104.
35. Tantisira KG, Lasky-Su J, Harada M, et al. Genomewide association between GLCCI1 and response to

glucocorticoid therapy in asthma. N Engl J Med 2011;365:1173-83.
36. Bousquet J. Global initiative for asthma (GINA) and its objectives. Clin Exp Allergy 2000;30 Suppl 1:2-5.
37. Tantisira KG, Small KM, Litonjua AA, Weiss ST, Liggett SB. Molecular properties and pharmacogenetics of a polymorphism of adenylyl cyclase type 9 in asthma: interaction between beta-agonist and corticosteroid pathways. Hum Mol Genet 2005;14:1671-7.
38. Stolley PD. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972;105:883-90.
39. Pearce N, Burgess C, Crane J, Beasley R. Fenoterol, asthma deaths, and asthma severity. Chest 1997;112:1148-50.
40. Pearce N, Grainger J, Atkinson M, et al. Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977-81. Thorax 1990;45:170-5.
41. Grainger J, Woodman K, Pearce N, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-7: a further case-control study. Thorax 1991;46:105-11.
42. Pearce N, Beasley R, Crane J, Burgess C, Jackson R. End of the New Zealand asthma mortality epidemic. Lancet 1995;345:41-4.
43. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990;336:1391-6.
44. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med 1996;335:841-7.
45. Peters SP, Prenner BM, Mezzanotte WS, Martin P, O'Brien CD. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients. Allergy Asthma Proc 2008;29:499-516.
46. Sears MR, Ottosson A, Radner F, Suissa S. Long-acting beta-agonists: a review of formoterol safety data from asthma clinical trials. Eur Respir J 2009;33:21-32.
47. Anderson HR, Ayres JG, Sturdy PM, et al. Bronchodilator treatment and deaths from asthma: case-control study. BMJ 2005;330:117.
48. Ni Chroinin M, Greenstone IR, Danish A, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev 2005:CD005535.
49. Walters EH, Walters J. Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Cochrane Database Syst Rev 2003:CD001285.
50. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171:129-36.
51. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA 2001;285:2583-93.
52. Lemanske RF, Jr., Sorkness CA, Mauger EA, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA 2001;285:2594-603.
53. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164:1392-7.
54. Reihsaus E, Innis M, MacIntyre N, Liggett SB. Mutations in the gene encoding for the beta 2-adrenergic receptor in normal and asthmatic subjects. Am J Respir Cell Mol Biol 1993;8:334-9.
55. Drysdale CM, McGraw DW, Stack CB, et al. Complex promoter and coding region beta 2-adrenergic receptor haplotypes alter receptor expression and predict in vivo responsiveness. Proc Natl Acad Sci U S A 2000;97:10483-8.
56. Hawkins GA, Tantisira K, Meyers DA, et al. Sequence, haplotype, and association analysis of ADRbeta2 in a multiethnic asthma case-control study. Am J Respir Crit Care Med 2006;174:1101-9.
57. Green SA, Turki J, Bejarano P, Hall IP, Liggett SB. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. Am J Respir Cell Mol Biol 1995;13:25-33.
58. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry 1994;33:9414-9.
59. Martinez FD, Graves PE, Baldini M, Solomon S, Erickson R. Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. J Clin Invest 1997;100:3184-8.
60. Silverman EK, Kwiatkowski DJ, Sylvia JS, et al. Family-based association analysis of beta2-adrenergic receptor polymorphisms in the childhood asthma management program. J Allergy Clin Immunol 2003;112:870-6.
61. Lima JJ, Thomason DB, Mohamed MH, Eberle LV, Self TH, Johnson JA. Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. Clin Pharmacol Ther 1999;65:519-25.
62. Cho SH, Oh SY, Bahn JW, et al. Association between bronchodilating response to short-acting beta-agonist and non-synonymous single-nucleotide polymorphisms of beta-adrenoceptor gene. Clin Exp Allergy 2005;35:1162-7.
63. Choudhry S, Ung N, Avila PC, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. Am J Respir Crit Care Med 2005;171:563-70.
64. Kotani Y, Nishimura Y, Maeda H, Yokoyama M. Beta2-adrenergic receptor polymorphisms affect airway responsiveness to salbutamol in asthmatics. J Asthma 1999;36:583-90.
65. Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med 2000;162:75-80.
66. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. Thorax 2000;55:762-7.
67. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 2004;364:1505-12
68. Panina-Bordignon P, Mazzeo D, Lucia PD, et al. Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12. J Clin Invest 1997;100:1513-9.

69. Agarwal SK, Marshall GD, Jr. Beta-adrenergic modulation of human type-1/type-2 cytokine balance. J Allergy Clin Immunol 2000;105:91-8.
70. Liggett SB. Pharmacogenetics of beta-1- and beta-2-adrenergic receptors. Pharmacology 2000;61:167-73.
71. Wechsler ME, Lehman E, Lazarus SC, et al. beta-Adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med 2006;173:519-26.
72. Bleecker ER, Yancey SW, Baitinger LA, et al. Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. J Allergy Clin Immunol 2006;118:809-16.
73. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to longacting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. Lancet 2007;370:2118-25.
74. Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet 2009;374:1754-64
74. Bleecker ER, Nelson HS, Kraft M, et al. Beta2-receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate. Am J Respir Crit Care Med 2010;181:676-87.
75. Green SA, Cole G, Jacinto M, Innis M, Liggett SB. A polymorphism of the human beta 2-adrenergic receptor within the fourth transmembrane domain alters ligand binding and functional properties of the receptor. J Biol Chem 1993;268:23116-21.
76. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010;363:1715-26.
77. Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. Lancet 2007;370:1422-31.
78. Slager RE, Hawkins GA, Ampleford EJ, et al. IL-4 receptor alpha polymorphisms are predictors of a pharmacogenetic response to a novel IL-4/IL-13 antagonist. J Allergy Clin Immunol 2010;126:875-8.
79. Slager RE, Hawkins GA, Yen YP, Peters SP, Wenzel SE, Meyers DA, Bleecker ER. Interleukin 4 receptor polymorphisms predict reduction in asthma exacerbations during 1 response to an anti-interleukin 4 α receptor antagonist. J Allergy Clin Immunol 2012;[in press].

Artigo original

Corticosteroid Therapy for Asthma

Corticoterapia no Tratamento da Asma

Peter J. Barnes[1]

RESUMO

Os corticosteroides são os mais efetivos controladores da asma. Eles suprimem a inflamação, principalmente através da inativação de múltiplos genes inflamatórios ativos através da reversão da acetilação da histona via recrutamento da histona desacetilase 2. Suprimindo a inflamação da via aérea, os corticosteroides inalatórios (CSi) reduzem a hiper-responsividade brônquica e controlam os sintomas da asma.

Atualmente, os CSi representam a primeira linha de tratamento para todos os pacientes com asma persistente, controlando os sintomas e prevenindo as exacerbações. A associação de β_2-agonistas de longa duração aos CSi aumenta o controle da asma e, habitualmente, ambos são administrados em um mesmo dispositivo inalatório, o que aumenta a adesão e o controle da asma com menores doses. A absorção dos CSi dos pulmões para a circulação sistêmica causa efeitos colaterais sistêmicos desprezíveis nas doses que a maioria dos doentes requer. Corticosteroides sistêmicos são usados no tratamento das exacerbações agudas da asma e como tratamento de manutenção em pacientes com asma grave não controlada com a terapia inalatória máxima. Corticosteroides orais têm numerosos efeitos colaterais metabólicos e endócrinos e devem ser usados na menor dose necessária para controlar a doença.

Descritores: Inflamação; Histona desacetilases; Asma/prevenção & controle; Agonistas de receptores adrenérgicos beta 2; Córtex supra-renal/efeitos de drogas.

ABSTRACT

Corticosteroids are by far the most effective controllers of asthma. They suppress inflammation mainly by switching off multiple activated inflammatory genes, which is achieved by reversing histone acetylation via the recruitment of histone deacetylase 2. Through suppression of airway inflammation, inhaled corticosteroids (ICS) reduce airway hyperresponsiveness and control asthma symptoms.

The use of ICS, which is now recommended as the first-line therapy for all patients with persistent asthma, controls asthma symptoms and prevents exacerbations. Inhaled long-acting β_2 agonists added to ICS further improve asthma control and are commonly given as combination inhalers, which improve compliance and control asthma at lower doses. The use of ICS, which are absorbed from the lungs into the systemic circulation, has negligible systemic side effects at the doses most patients require. Systemic corticosteroids are used in the treatment of acute exacerbations of asthma and as maintenance therapy in patients with severe asthma that is not controlled by the maximum dose of ICS. Oral steroids have numerous metabolic and endocrine side effects. Therefore, the lowest dose needed to control the disease should be used.

Keywords: Inflammation; Histone deacetylases; Asthma/prevention & control; Adrenergic beta-2 receptor agonists; Adrenal cortex/drug effects.

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The authors declare that they do not have any potential conflict of interest.

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INTRODUCTION

Corticosteroids (also known as glucocorticosteroids, glucocorticoids, and steroids) are by far the most effective controllers used in the treatment of asthma and the only drugs that can effectively suppress the characteristic inflammation in asthmatic airways. After discussing the mechanism of action and pharmacology of corticosteroids, I will discuss their use in the treatment of asthma.

MECHANISMS OF ACTION

There have been major advances in understanding the molecular mechanisms whereby corticosteroids suppress inflammation, based on recent developments in understanding the fundamental mechanisms of gene transcription (1,2). Corticosteroids activate or suppress many genes relevant to understanding their action in asthma.

Cellular effects

At a cellular level, corticosteroids reduce the numbers of inflammatory cells in the airways, including eosinophils, T lymphocytes, mast cells and dendritic cells (Figure 1). This is achieved by inhibiting the recruitment of inflammatory cells into the airway by suppressing the production of chemotactic mediators and adhesion molecules and by inhibiting the survival in the airways of inflammatory cells, such as eosinophils, T lymphocytes and mast cells. Epithelial cells might be the major cellular target for inhaled corticosteroids (ICS), which are the mainstay of modern asthma management. The ICS suppress many activated inflammatory genes in airway epithelial cells and epithelial integrity is restored by regular ICS therapy. The suppression of mucosal inflammation is relatively rapid with a significant reduction in eosinophils detectable within 6 h and associated with reduced airway hyperresponsiveness (3). Reversal of airway hyperresponsiveness may take several months to reach a plateau, probably reflecting recovery of structural changes in the airway.

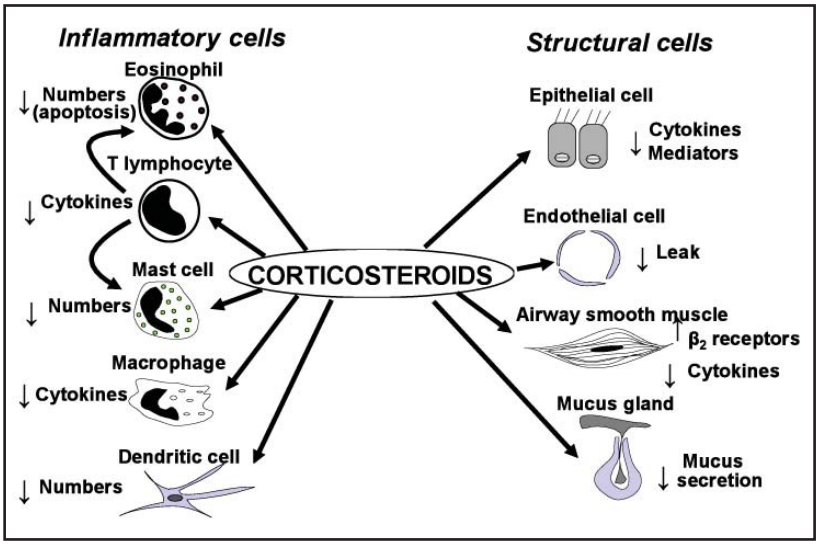

Figure 1 - Cellular effect of corticosteroids.

Glucocorticoid receptors

Corticosteroids diffuse across the cell membrane and bind to glucocorticoid receptors (GRs) in the cytoplasm. There is only one form of GR that binds corticosteroids, termed GRα. An alternatively spliced form of GR that interacts with DNA but not with corticosteroids is GRβ, which could act as a dominant negative inhibitor of corticosteroid action by interfering with the binding of GR to DNA (4). Whether GRβ is involved in steroid resistance in asthma is controversial. Activated GRs rapidly translocate to the nucleus, where they produce their molecular effects. A GR pair (GR dimer) binds to glucocorticoid response elements in the promoter region of steroid-responsive genes and this interaction switches on (and sometimes switches off) gene transcription. Examples of genes that are activated by corticosteroids include genes encoding β_2-adrenergic receptors and the anti-inflammatory proteins secretory leukoprotease inhibitor and mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1) which inhibits MAP kinase pathways. These effects may contribute to the anti-inflammatory actions of corticosteroids. Interaction between GRs and negative glucocorticoid response elements could suppress gene transcription, and this is thought to be important in mediating many of the side effects of corticosteroids. For example, corticosteroids inhibit the expression of osteocalcin, which is involved in bone synthesis (5).

Switching off inflammation

The major action of corticosteroids is to switch off multiple activated inflammatory genes that encode for cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors (2). These genes are switched on in the airways by pro-inflammatory transcription factors, such as nuclear factor kappa B (NF-κB) and activator protein-1, both of which are activated in asthmatic airways and switch on inflammatory genes by interacting with co-activator molecules, such as cAMP response element binding protein-binding protein, that have intrinsic histone acetyltransferase activity, resulting in acetylation of core histones, which opens up the chromatin structure so that gene transcription is facilitated. Corticosteroid-activated GRs also interact with co-activator molecules, and this inhibits the interaction of NF-κB with co-activators, thus reducing histone acetylation (6,7). Reduction of histone acetylation also

occurs through the recruitment of histone deacetylase 2 to the activated inflammatory gene complex by activated GRs, resulting in effective suppression of all activated inflammatory genes within the nucleus (Figure 2). This explains why corticosteroids are so effective in the control of asthmatic inflammation but also why they are safe, because other activated genes are not affected.

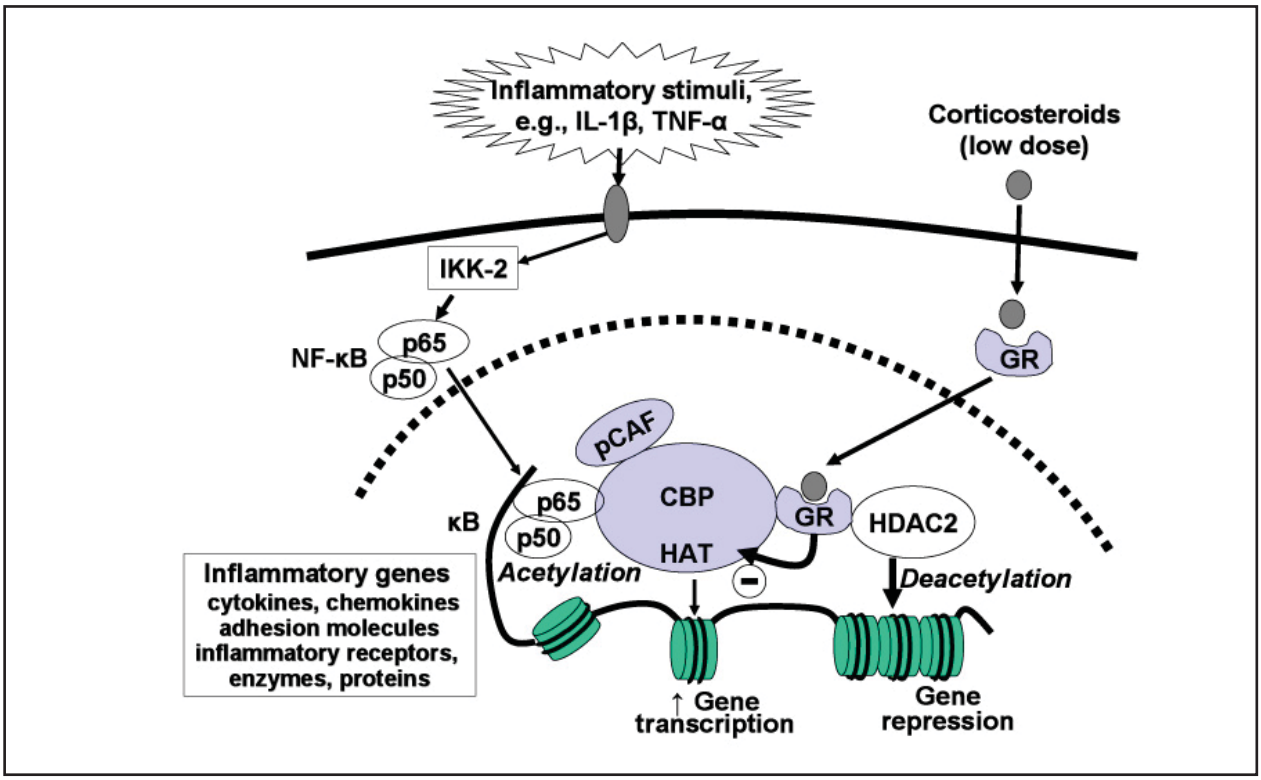

Figure 2 - Corticosteroid suppression of activated inflammatory genes. Inflammatory genes are activated by inflammatory stimuli, such as IL-1β and TNF-α, resulting in activation of the I-κB kinase-2 (IKK-2) inhibitor, which activates the transcription factor NF-κB. A dimer of the p50 and p65 NF-κB proteins translocates to the nucleus and binds to specific κB recognition sites and to co-activators, such as the cAMP response element binding protein-binding protein (CBP) or p300/CBP-activating factor (pCAF), which have intrinsic histone acetyltransferase (HAT) activity. This results in acetylation of core histone H4, resulting in increased expression of genes encoding multiple inflammatory proteins. After activation by corticosteroids, GRs translocate to the nucleus and bind to co-activators to inhibit HAT activity directly and recruiting histone deacetylase-2 (HDAC2), which reverses histone acetylation leading to suppression of these activated inflammatory genes.

There could be additional mechanisms that are important in the anti-inflammatory actions of corticosteroids. Corticosteroids have potent inhibitory effects on MAP kinase signalling pathways through the induction of MKP-1, and this could inhibit the expression of multiple inflammatory genes (8). Some inflammatory genes, such as granulocyte-macrophage colony stimulating factor, have an unstable messenger RNA that is rapidly degraded by certain RNases but stabilised when cells are stimulated by inflammatory mediators. Corticosteroids reverse this effect, resulting in rapid degradation of mRNA and reduced inflammatory protein secretion (9).

INTERACTION WITH B_2-ADRENERGIC RECEPTORS

Inhaled β_2 agonists and corticosteroids are frequently used together in the control of asthma. Figure 3 shows the important molecular interactions between these two classes of drugs (10). As discussed above, corticosteroids increase the gene transcription of β_2 receptors, resulting in increased expression of cell surface receptors. This has been demonstrated in human lung *in vitro* and nasal mucosa in vivo (after topical application). Thus, corticosteroids protect against the downregulation of β_2 receptors after long-term administration of β_2 agonists. This could be important for the non-bronchodilator effects of β_2 agonists, such as mast cell stabilization. Corticosteroids might also enhance the coupling of β_2 receptors to G proteins, thus enhancing β_2 agonist effects and reversing the uncoupling of β_2 receptors that can occur in response to inflammatory mediators, such as interleukin-1β through a stimulatory effect on a G protein-coupled receptor kinase.

There is evidence that β_2 agonists affect GR function and thus enhance the anti-inflammatory effects of corticosteroids. In addition, β_2 agonists increase the translocation of GR from cytoplasm to the nucleus after activation by corticosteroids. This effect has now been demonstrated in sputum macrophages of asthma patients after an ICS and inhaled long-acting β_2 agonist (11). This suggests that β_2 agonists and corticosteroids enhance each other's beneficial effects in asthma therapy.

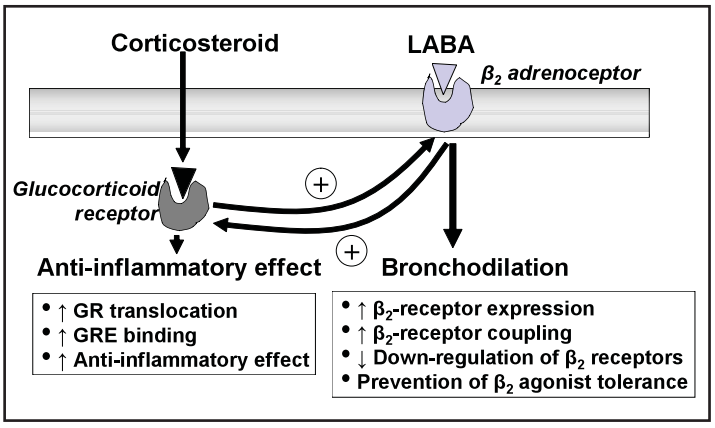

Figure 3 - Molecular interaction between corticosteroids and β_2 agonists

LABA: long-acting β_2 agonist; GRE: glucocorticoid response element.

reduces oropharyngeal deposition, thereby reducing the systemic absorption of corticosteroids, although this effect is minimal in corticosteroids with a high first-pass metabolism. Mouth rinsing has a similar effect, and this procedure should be used with high-dose dry powder inhalers, because spacers cannot be used with these devices.

A recently introduced corticosteroid, ciclesonide, is an inactive prodrug that is activated by esterases in the lung to the active metabolite desisobutyryl-ciclesonide (13). This could reduce oropharyngeal side effects, as esterases appear to be less active at this site than in the lower airways. Ciclesonide is also reported to be effective as a once-daily therapy.

PHARMACOKINETICS

Prednisolone is readily and consistently absorbed after oral administration with little inter-individual variation. Prednisone is converted in the liver to active prednisolone. Drugs such as rifampin, phenobarbitone, and phenytoin, which induce CYP450 enzymes, lower the plasma half-life of prednisolone, which is metabolized in the liver. The plasma half-life of prednisolone is 2-3 h, although its biological half-life is approximately 24 h, making it suitable for daily dosing. Prednisolone is approximately 92% protein-bound, the majority to the specific binding protein transcortin and the remainder to albumin; it is the unbound fraction that is biologically active. Certain patients, typically those with severe asthma, apparently fail to respond to corticosteroids. "Steroid-resistant" asthma is caused not by impaired absorption or metabolism of steroids but rather by reduced anti-inflammatory actions of corticosteroids. Measurement of plasma concentrations of prednisolone are useful in monitoring compliance with oral corticosteroid therapy and in assessing whether a poor therapeutic response to corticosteroids is due to poor absorption or increased metabolism.

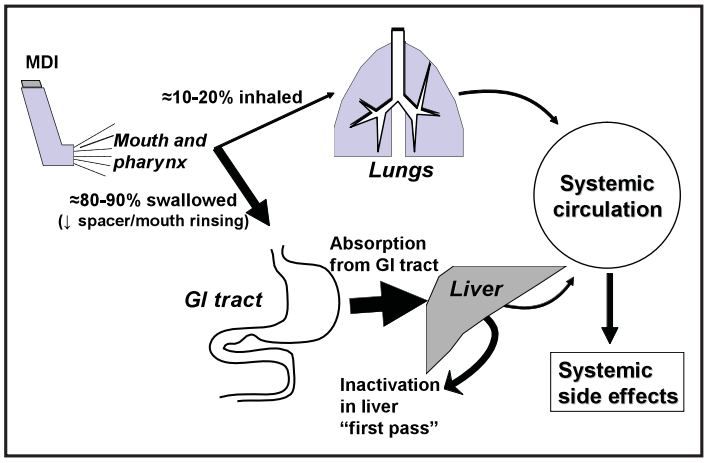

Figure 4 - Pharmacokinetics of inhaled corticosteroids.

GI: gastrointestinal.

Inhaled delivery

The pharmacokinetics of ICS is important in relation to their systemic effects (12). The fraction of steroid which is inhaled into the lungs acts locally on the airway mucosa but can be absorbed from the airway and alveolar surface. That fraction therefore reaches the systemic circulation (Figure 4). The fraction of ICS that is deposited in the oropharynx is swallowed and absorbed from the gut. The absorbed fraction can be metabolized in the liver before reaching the systemic circulation (first-pass metabolism). Budesonide and fluticasone propionate have a greater first-pass metabolism than does beclomethasone dipropionate and are therefore less likely to produce systemic effects at high inhaled doses. The use of a large-volume spacer

SYSTEMIC STEROIDS

There is no apparent advantage in giving very high doses of intravenous steroids (such as methylprednisolone at 1 g), as this only increases the risk of side effects, such as hyperglycaemia and increased susceptibility to infections. Intravenous steroids are indicated in acute asthma if lung function is < 30% of predicted and if there is no significant improvement with a nebulised β_2 agonist. Oral prednisolone (40-60 mg) has an effect similar to that of intravenous hydrocortisone and is easier to administer. High doses of ICS can also substitute for a course of oral steroids in controlling acute exacerbations of asthma. In a family practice setting and in children in an emergency room setting, high-dose fluticasone propionate (2,000 µg daily) was found to be as effective as was a course of oral prednisolone in controlling acute exacerbations of asthma, although this route of delivery is more costly (14). Although doubling the dose of ICS has been recommended for mild exacerbations of asthma, this does not appear to be useful (15). Although there is no proven effect of ICS in the management of severe acute asthma in a hospital setting (16), trials of nebulized steroids, which can be delivered in large doses, are underway.

Maintenance treatment with oral steroids is reserved for patients in whom asthma cannot be controlled with the maximum doses of other drugs, the dose being titrated to the lowest that provides acceptable control of symptoms. For any patient taking regular oral steroids, objective evidence of steroid responsiveness should be obtained before maintenance therapy is instituted. Short courses of oral steroids (30-40 mg of prednisolone daily for 1-2 weeks) are indicated for exacerbations of asthma, and the dose can be tapered over 1 week once the exacerbation is resolved (although the tapering period is not strictly necessary, patients often find it reassuring).

INHALED CORTICOSTEROIDS

There is no doubt that the early use of ICS has revolutionized the management of asthma, with marked reductions in asthma morbidity and improvement in health status. Currently, ICS are recommended as the first-line therapy for all patients with persistent asthma (17) and are highly effective in controlling asthma symptoms in patients of all ages and with any degree of asthma severity. These drugs improve the quality of life of patients with asthma, allowing many patients to lead normal lives, as well as improving lung function, reducing the frequency of exacerbations, and potentially preventing irreversible airway changes.

The use of ICS is as effective in children, including young children, as in adults. Nebulized budesonide has been shown to reduce the need for oral corticosteroids and improve lung function in children under 3 years of age (18). In infants and preschool children, ICS given via a large-volume spacer device improve asthma symptoms and reduce the number of exacerbations.

Some patients with asthma develop an element of irreversible airflow obstruction, which could be the result of chronic airway inflammation and could be prevented by treatment with ICS. A 5-year study of low-dose budesonide in patients with mild asthma showed improved lung function after ICS therapy (19). A delay in starting ICS can result in less overall improvement in lung function, in adults and children (20,21). However, there is no evidence that early use of ICS is curative. Even when ICS therapy is introduced at the time of diagnosis, symptoms and lung function revert to pre-treatment levels when ICS are withdrawn (20).

A retrospective review of the risk of mortality and prescribed anti-asthma medication showed that regular ICS therapy provided significant protection (22). In contrast, asthma mortality appears to increase with increasing usage of short-acting β_2 agonists, reflecting the fact that increased use of rescue medications is a marker of poor asthma control (23).

As previously mentioned, ICS are now recommended as first-line therapy for patients with persistent symptoms. Any patient who needs to use a β_2 agonist inhaler for symptom control more than twice a week should be started on ICS. Once control (defined as normal or best possible lung function and infrequent need to use an inhaled β_2 agonist) has been achieved, the dose of ICS should be reduced in a step-wise manner to the lowest dose needed for optimal control. It might take as long as three months to reach a response plateau, and any subsequent changes in dose should be made at intervals of three months or more. When daily doses of ≥ 800 µg are needed, patients should use a large-volume spacer device (for metered dose inhalers) or mouth rinsing (for dry powder inhalers), in order to reduce local and systemic side effects. Although the dose of ICS should be increased to 2,000 µg daily if necessary, higher doses can have systemic effects. It may be preferable to add a low dose of oral corticosteroid, since higher doses of ICS are costly and have a high incidence of local side effects. Nebulized budesonide has been advocated in order to give an increased dose of ICS and to reduce the requirement for oral corticosteroids (24). However, that treatment is expensive and likely achieves its effects largely via systemic absorption.

Add-on therapy

Previously, it was recommended that the ICS dose be increased if asthma was not controlled. The assumption was that there was residual inflammation of the airways. However the dose-response effect of ICS is relatively flat, so that there is little improvement in lung function after increasing the dose of ICS. An alternative strategy is to add some other class of controller drug. For most patients, that is more effective than is increasing the dose of ICS (25).

Many studies have demonstrated the great efficacy of using an ICS-long-acting β_2 agonist combination, in comparison with using higher doses of a long-acting β_2 agonist or higher doses of an ICS (26). Recent studies have shown that combining formoterol with budesonide (as reliever therapy) provides better asthma control than does the standard regimen of using a short-acting β_2 agonist as a rescue medication with either the same dose of combination inhaler or a high dose of ICS as maintenance treatment (27). The mechanism by which ICS (used as needed) improve asthma control and reduce exacerbations is likely to involve preventing the increase in inflammation that occurs prior to a clinical exacerbation (28).

The addition of low doses of theophylline (achieving plasma concentrations of < 10 mg/L) are more effective than is doubling the dose of inhaled budesonide, regardless of the degree of asthma severity (29-31). However, this is less effective than is using a long-acting inhaled β_2 agonist as add-on therapy (32). Anti-leukotrienes have also been used as an add-on therapy (33,34), although this is also less effective than is the addition of a long-acting β_2 agonist (35).

SIDE EFFECTS

The efficacy of ICS is now established in short- and long-term studies of adults and children. However, there are still concerns about side effects, particularly in children and when high inhaled doses are used. A number of side effects have been recognized (Chart 1).

Chart 1 - Side effects of inhaled corticosteroids

Local side effects

- Dysphonia
- Oropharyngeal candidiasis
- Cough

Systemic side effects

- Adrenal suppression
- Growth suppression
- Bruising
- Osteoporosis
- Cataracts
- Glaucoma
- Metabolic abnormalities (glucose, insulin, triglycerides)
- Psychiatric disturbances

Local side effects

Although side effects due to the local deposition of ICS in the oropharynx might occur, the frequency of complaints depends on the dose and frequency of administration, as well as on the delivery system used. The most common complaint is of hoarseness (dysphonia), which occurs in over 50% of patients using metered dose inhalers. Dysphonia can be caused by myopathy of laryngeal muscles and can reverse when treatment is withdrawn. For most patients, dysphonia is not troublesome, although it can be disabling in singers and lecturers. With concomitant oral corticosteroids and more than twice daily administration, oropharyngeal candidiasis (thrush) can be a problem in some patients, particularly in elderly patients. Large-volume spacer devices protect against this local side effect by reducing the quantity of ICS that deposits in the oropharynx.

Systemic side effects

Systemic side effects of ICS have been extensively investigated. Effects such as cataract formation and osteoporosis have been reported, although often in patients who are also receiving oral corticosteroids. There has been particular concern about growth suppression in children using ICS. However, in most studies, doses of 400 µg or less have not been associated with impaired growth, and there might even be a growth spurt because asthma is better controlled.

Pharmacokinetics are important. The fraction of corticosteroid inhaled into the lungs acts locally on the airway mucosa and can be absorbed from the airway and alveolar surface, thereby reaching the systemic circulation. The fraction of ICS deposited in the oropharynx is swallowed and absorbed from the gut. The absorbed fraction can be metabolized in the liver before it reaches the systemic circulation. Budesonide and fluticasone have a greater first-pass metabolism than does beclomethasone dipropionate and are therefore less likely to produce systemic effects at high inhaled doses. The use of a spacer reduces oropharyngeal deposition, thereby reducing systemic absorption of ICS.

Preliminary data suggest that adrenal suppression occurs only when inhaled doses of > 1,500 µg daily are used. More sensitive measurements of systemic effects include indices of bone metabolism (e.g. serum osteocalcin, urinary pyridinium crosslink excretion) and, in children, short-term growth of the lower leg, which can be increased at inhaled doses as low as 800 µg. The clinical relevance of these measurements is unclear. Nevertheless, it is important to reduce the risk of systemic effects by using the lowest dose of ICS needed to control asthma and by using a large-volume spacer to reduce oropharyngeal deposition.

REFERENCES

1. Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol 2010; 120(2-3):76-85.
2. Barnes PJ. Glucocorticosteroids: current and future directions. Br J Pharmacol 2011; 163:29-43.
3. Ketchell RI, Jensen MW, Lumley P, Wright AM, Allenby MI, O'Connor BJ. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5'-monophosphate in mild asthma. J Allergy Clin Immunol 2002; 110(4):603-606.
4. Lewis-Tuffin LJ, Cidlowski JA. The physiology of human glucocorticoid receptor beta (hGRbeta) and glucocorticoid resistance. Ann N Y Acad Sci 2006; 1069:1-9.:1-9.
5. Dostert A, Heinzel T. Negative glucocorticoid receptor response elements and their role in glucocorticoid action. Curr Pharm Des 2004; 10(23):2807-2816.
6. Ito K, Barnes PJ, Adcock IM. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits IL-1β-induced histone H4 acetylation on lysines 8 and 12. Mol Cell Biol 2000; 20:6891-6903.
7. Barnes PJ. How corticosteroids control inflammation. Br J Pharmacol 2006; 148:245-254.
8. Clark AR. MAP kinase phosphatase 1: a novel mediator of biological effects of glucocorticoids? J Endocrinol 2003; 178(1):5-12.
9. Bergmann MW, Staples KJ, Smith SJ, Barnes PJ, Newton R. Glucocorticoid inhibition of GM-CSF from T cells is independent of control by NF-κB and CLE0. Am J Respir Cell Mol Biol 2004; 30.:555-563.
10. Barnes PJ. Scientific rationale for combination inhalers with a long-acting β2-agonists and corticosteroids. Eur Respir J 2002; 19:182-191.
11. Usmani OS, Ito K, Maneechotesuwan K, Ito M, Johnson M, Barnes PJ et al. Glucocorticoid receptor nuclear translocation in airway cells following inhaled combination therapy. Am J Respir Crit Care Med 2005; 172:704-712.
12. Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. J Clin Pharmacol 2007; 47(6):782-789.
13. Manning P, Gibson PG, Lasserson TJ. Ciclesonide versus other inhaled steroids for chronic asthma in children and adults. Cochrane Database Syst Rev 2008;(2):CD007031.
14. Manjra AI, Price J, Lenney W, Hughes S, Barnacle H. Efficacy of

nebulized fluticasone propionate compared with oral prednisolone in children with an acute exacerbation of asthma. Respir Med 2000; 94(12):1206-1214.
15. FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 2004; 59(7):550-556.
16. Edmonds ML, Camargo CA, Jr., Pollack CV, Jr., Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev 2003;(3):CD002308.
17. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, Fitzgerald M et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008; 31(1):143-178.
18. Berger WE. Budesonide inhalation suspension for the treatment of asthma in infants and children. Drugs 2005; 65(14):1973-1989.
19. O'Byrne PM, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV et al. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. Chest 2006; 129(6):1478-1485.
20. Haahtela T, Järvinsen M, Kava T, Kiviranta K, Koskinen S, Lemtonen K et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. New Engl J Med 1994; 331:700-705.
21. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Resp Med 1994; 5:369-372.
22. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000; 343(5):332-336.
23. Ernst P, Habbick B, Suissa S, Hemmelgarn B, Cockcroft D, Buist AS et al. Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? Am Rev Respir Dis 1993; 148(1):75-79.
24. Otulana BA, Varma N, Bullock A, Higenbottam T. High dose nebulized steroid in the treatment of chronic steroid-dependent asthma. Resp Med 1992; 86:105-108.
25. Kankaanranta H, Lahdensuo A, Moilanen E, Barnes PJ. Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. Respir Res 2004; 5(1):17.
26. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting beta-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. J Allergy Clin Immunol 2007; 119(2):344-350.
27. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest 2006; 129(2):246-256.
28. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. Eur Resp Dis 2007; 29:587-595.
29. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. New Engl J Med 1997; 337:1412-1418.
30. Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H et al. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur Respir J 1997; 10(12):2754-2760.
31. Lim S, Jatakanon A, Gordon D, Macdonald C, Chung KF, Barnes PJ. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. Thorax 2000; 55(10):837-841.
32. Wilson AJ, Gibson PG, Coughlan J. Long acting beta-agonists versus theophylline for maintenance treatment of asthma. Cochrane Database Syst Rev 2000;(2):CD001281.
33. Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Am J Respir Crit Care Med 1999; 160(6):1862-1868.
34. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003; 58(3):211-216.
35. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev 2006;(4):CD003137.

Artigo original

Broncodilatadores

Bronchodilators

Hisbello S. Campos[1], Paulo A. M. Camargos[2]

RESUMO

Broncodilatadores agem através de seu efeito direto relaxante sobre a célula muscular lisa. Eles pertencem a três classes farmacológicas: agonistas dos receptores β_2-adrenérgicos, metilxantinas e antagonistas muscarínicos (ou anticolinérgicos inalatórios). Quando usados pela via inalatória, os beta 2 agonistas e os antagonistas muscarínicos têm ação mais rápida com menos efeitos sistêmicos. Os broncodilatadores de ação rápida são mais usados no tratamento de alívio dos sintomas agudos enquanto os de ação prolongada são melhor usados no tratamento de manutenção. Os β_2-agonistas são os broncodilatadores mais usados no tratamento da asma. Os anticolinérgicos têm início de ação mais lento e menos efeito sobre a função pulmonar, quando comparados aos beta 2 agonistas, sendo mais usados no tratamento de portadores de doença pulmonar obstrutiva crônica (DPOC). O emprego das metilxantinas no tratamento regular é limitado por seus efeitos tóxicos potencialmente perigosos. Os β_2-agonistas de curta e de longa duração, junto com os corticosteroides inalatórios, constituem o pilar terapêutico da asma nos doentes com a asma mal controlada com o uso isolado de corticosteróide inalatório.

Embora esteja havendo grandes esforços para desenvolver novos broncodilatadores, as indústrias farmacêuticas estão aprimorando as classes existentes mais do que descobrindo novas categorias. O principal foco tem sido no desenvolvimento de novos ligantes que interajam com adrenoreceptores beta 2 e/ou receptores muscarínicos, amplificando sua efetividade broncodilatador e duração de ação, bem como sua segurança. Nessa revisão, são apresentados e discutidos os mecanismos de ação, efeitos indesejáveis e indicações clínicas desses broncodilatadores.

Descritores: Asma; Broncodilatadores; Progressão da doença.

ABSTRACT

Bronchodilators work through their direct relaxation effect on airway smooth muscle cell. They belong to three different pharmacological classes, as follows: adrenergic receptors β_2 agonists; methylxanthines; and muscarinic antagonists (or inhaled anticholinergic agents). When used through the inhaled route, beta 2 agonists and anticholinergic agents act faster with less systemic effects. Fast-acting agents are best used for rescue of symptoms whereas long-acting agents are best used for maintenance therapy. The β_2 agonists are the most used class of bronchodilators in asthma treatment. Anticholinergic agents have a slower onset of action and inferior effect on lung function, when compared to beta 2 agonists, being preferred for treating patients with chronic obstructive pulmonary disease (COPD). Methylxanthine's use as regular treatment is limited due to potentially dangerous side-effects. The short- and long-acting β_2 agonists, alongside with inhaled steroids, are the mainstay of asthma therapy for patients with asthma poorly controlled with inhaled glucocorticoids alone.

Although there is a great effort trying to develop new bronchodilators, the pharmaceutical industries are improving the existing classes of bronchodilators rather than finding new classes. The main focus is on developing new ligands that interact with beta 2 adrenoreceptors and/or muscarinic receptors enhancing their bronchodilator effectiveness and duration of action and improving their safety profiles. In this review, we discuss and comment on their respective mechanisms of action, side effects, and clinical indications.

Keywords: Asthma; Bronchodilator agents; Disease progression.

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INTRODUÇÃO

Como a dispneia é o sintoma que mais incomoda o asmático, os broncodilatadores constituem o pilar terapêutico do tratamento sintomático da asma. Apesar disso, considerando-se o caráter inflamatório da doença, os broncodilatadores não devem ser usados isoladamente no tratamento regular da asma, devendo ser reservados para o alívio dos sintomas agudos (dispneia e sibilos) ou, em situações particulares, da dispneia e/ou sibilância crônica.

Nos asmáticos frequentemente sintomáticos, os broncodilatadores só devem ser usados regularmente se associados a corticosteroides inalatórios. O uso associado tem efeito poupador de corticosteroide oral e do inalatório. Estudos sugerem que a associação de ambos é mais eficaz que o uso dobrado da dose do corticosteroide inalatório (1).

Há três classes de medicamentos broncodilatadores usados no tratamento do asmático: β_2-agonistas, metilxantinas e anticolinérgicos (Quadro 1). No presente capítulo, serão apresentadas as indicações, os mecanismos de ação e a posição no esquema medicamentoso de cada um desses grupos.

B_2-AGONISTAS

Os agonistas dos receptores β_2 adrenérgicos são os broncodilatadores mais usados no tratamento do asmático. Os β_2-agonistas são divididos em dois grupos: de ação curta e de ação prolongada. Esses últimos são subdivididos em dois subgrupos: os long-acting β_2 agonists (LABA, β_2-agonistas de longa duração), com 12 h de efeito, e os de ultralonga duração, cujo efeito se estende por 24 h.

Os β_2-agonistas são potentes broncodilatadores e podem ser administrados pelas vias inalatória, oral ou intravenosa, sendo a primeira a preferida. Por essa via, os efeitos desejados são mais rápidos e o risco de reações indesejáveis é menor. Os efeitos indesejáveis mais frequentes (tremor de extremidades e taquicardia) resultam, na maior parte das vezes, da absorção da fração oral da dose inalada. Em geral, os β_2-agonistas não trazem risco, apenas desconforto; para evitá-los, deve-se recomendar que o paciente faça higiene oral após cada inalação.

O grupo dos broncodilatadores de ação curta, também chamados de broncodilatadores de resgate, inclui os medicamentos salbutamol, fenoterol e terbutalina. Em média, seu efeito broncodilatador, quando administrados pela via inalatória, tem início em poucos minutos e dura de 4-6 h. São recomendados para o alívio imediato de sintomas agudos e constituem a primeira opção broncodilatadora nas exacerbações. Como a maioria das exacerbações é de intensidade leve a moderada, devem ser administrados, preferencialmente, através de inaladores pressurizados, acoplados ou não a espaçadores. A nebulização está indicada apenas nos casos mais graves, nos quais há a necessidade da administração simultânea de oxigênio.

O grupo dos LABA é composto por formoterol e salmeterol. O efeito broncodilatador de ambos dura aproximadamente 12 h, mas o início de ação do formoterol é mais rápido que o do salmeterol. A monoterapia

Quadro 1 – Broncodilatadores.

Tipos	**Tipos de ação**			**Em desenvolvimento**
	Curta	Prolongada		
	(4-6 h)	(12 h)	(24 h)	
β_2-agonistas	Fenoterol	Formoterol	Indacatero	Carmoterol
	Salbutamol	Salmeterol		Milveterol
	Terbutalina			GSK-642444
				BI-1744-CL
				LAS-100977
				Derivados de adamantil
Metilxantinas	Aminofilina	Teofilina		
	Teofilina	Doxofilina		
Anticolinérgicos	Brometo de ipratrópio	Brometo de tiotrópio		Brometo de aclidinio
				Brometo de glicopirrônio
				GSK-573719
				QAT-370
				CHF 5407
				Brometo de daratrópio
				TD-4208
				Dexpirrônio

com LABA é formalmente contraindicada e, assim, eles nunca devem ser prescritos isoladamente, mas sempre e obrigatoriamente associados à corticoterapia inalatória. A associação LABA-corticosteroide sistêmico está indicada para aqueles pacientes cronicamente sintomáticos, ou seja, sem o necessário controle clínico da enfermidade com o uso isolado de corticosteroide inalatório. Embora haja relatos de ação anti-inflamatória dos LABA, em uma meta-análise recente, concluiu-se que esse efeito não é clinicamente significante (2).

Resumidamente, os LABA estão indicados quando não há resposta adequada ao tratamento com corticosteroides inalatórios (e assegurada adesão e técnica correta de inalação). Deve ser lembrado que mesmo a redução potencial da dose do corticosteroide sistêmico, quando usado em associação ao LABA, não assegura que os efeitos adversos não possam ocorrer, e que crianças são potencialmente mais sujeitas a tais efeitos do que adultos.

Até o momento, há apenas um β_2-agonista de ultralonga duração no mercado, o indacaterol. Seu efeito broncodilatador tem início em poucos minutos e permanece por 24 h. Outros β_2-agonistas de ultralonga duração vêm sendo desenvolvidos (Quadro 1) e, possivelmente, estarão disponíveis em breve (3).

Mecanismo de ação

A ação broncodilatadora dos β_2-agonistas se dá através da ativação do receptor β_2-adrenérgico ($R\beta_2A$) acoplado à proteína G na superfície celular. A ativação desse receptor leva ao aumento da atividade da adenilciclase, enzima que catalisa a conversão do ATP em AMPc. Esse último se liga na unidade regulatória da proteína quinase A, promovendo a liberação de sua unidade catalítica que causa fosforilação de um grande número de proteínas alvo, relaxando o músculo liso peribrônquico. O AMPc inibe a liberação de cálcio dos depósitos intracelulares e reduz o influxo de cálcio através da membrana, auxiliando o relaxamento da musculatura lisa e a broncodilatação (4). A ativação do $R\beta_2A$ também potencializa a atividade anti-inflamatória dos glicocorticosteroides, aumentando a translocação do receptor de glicocorticosteroide do citoplasma para o núcleo da célula (5).

Efeitos adversos

Um pequeno grupo de asmáticos está sujeito a efeitos adversos dos LABA. Ainda não está estabelecido se isso se deve a particularidades genotípicas ou fenotípicas que geram suscetibilidade a um efeito específico desses fármacos. Para minimizá-los e mesmo torná-los praticamente remotos, cabe salientar novamente que eles devem ser administrados juntamente com corticosteroides inalatórios e em um mesmo dispositivo inalatório. As evidências atuais indicam que seria necessário o recrutamento de dezenas ou mesmo de centenas de milhares de pacientes para se determinar com precisão a taxa real de efeitos adversos dos LABA, o que torna praticamente impossível a realização de ensaios clínicos com esse objetivo (6).

Ademais, eles só devem ser prescritos para crianças maiores de quatro (salmeterol) ou seis anos (formoterol). A relação risco benefício será vantajosa quando respeitados esses critérios e pode se traduzir pela menor frequência de hospitalizações por asma.

A variedade nas respostas clínicas aos β_2-agonistas pode ser devida, em parte, a variações genéticas. Até o momento, foram identificados 49 polimorfismos para o gene dos agonistas dos receptores β_2 adrenérgicos. Porém, o real papel dos polimorfismos na patogênese e no tratamento de formas particulares da asma ainda está por ser esclarecido (7).

METILXANTINAS

Historicamente, o emprego das metilxantinas no tratamento da asma remonta ao século XVIII, quando médicos recomendavam que os asmáticos bebessem café forte para o tratamento da dispneia. Em 1860, essa recomendação fazia parte do livro texto de Salter (8). Desde então, o uso clínico das metilxantinas (aminofilina e teofilina) no tratamento da asma passou a ser estudado, e elas já foram os medicamentos mais prescritos para asmáticos em todo o mundo.

Entretanto, com o desenvolvimento de novos fármacos broncodilatadores mais potentes e seguros, particularmente os β_2-agonistas, o emprego das metilxantinas foi reduzido. Seu emprego associado aos β_2-agonistas ou aos anticolinérgicos em doses plenas promove um efeito broncodilatador adicional e pode estar associado a eventos adversos como, por exemplo, náuseas, vômitos, dor abdominal, cefaleia, tremores e arritmias (9,10). Atualmente, as metilxantinas são recomendadas para aqueles asmáticos que não atingem o controle com o emprego regular de corticosteroides e β_2-agonistas inalatórios de ação prolongada ou para aqueles que não têm acesso a esses medicamentos (11).

As metilxantinas são broncodilatadores efetivos, dotadas de propriedades anti-inflamatórias, administradas pela via oral, com velocidade de início de ação e tempo de duração de seus efeitos razoáveis. Durante muitos anos, acreditou-se que o efeito primário das metilxantinas na asma era devido a sua capacidade de relaxar a musculatura lisa dos brônquios. Entretanto, posteriormente, foi demonstrado que a teofilina é capaz de inibir a broncoconstrição induzida por diferentes fatores, como por exercício, indução por metacolina, histamina ou antígenos (12). Como esse efeito é obtido com concentrações baixas, habitualmente inferiores às dos broncodilatadores, é possível que os mecanismos broncodilatadores sejam independentes daqueles broncoprotetores. Estudos sobre esses últimos demonstraram que a teofilina possui efeitos inibitórios sobre as principais células — mastócitos, eosinófilos, neutrófilos, linfócitos e macrófagos — envolvidas no

processo inflamatório das vias aéreas, característico da asma (13-16). Há indícios de que os mecanismos moleculares responsáveis pelos efeitos anti-inflamatórios da teofilina sejam diferentes daqueles dos corticosteroides (17). Diversos mecanismos moleculares foram propostos para explicar as ações broncodilatadora e imunomoduladora das metilxantinas nas vias aéreas de asmáticos. Os mecanismos ligados à broncodilatação incluiriam inibição de fosfodiesterases, antagonismo do receptor de adenosina, estímulo da liberação de catecolamina e elevação do nível intracelular de cálcio. Os mecanismos envolvidos com os efeitos anti-inflamatórios ainda não estão claros; é provável que envolvam, entre outros, a ativação da histona desacetilase no epitélio da via aérea, suprimindo a produção de mediadores inflamatórios tanto pelas células estruturais como pelas células inflamatórias infiltrantes.

Ensaios terapêuticos demonstraram que a teofilina pode reduzir os sintomas crônicos da asma, melhorar a função pulmonar e a tolerância ao exercício, reduzir a necessidade de medicação de resgate e facilitar a retirada de corticosteroides orais (18). O ponto negativo das metilxantinas reside na proximidade entre as doses terapêuticas e as tóxicas, além de a faixa terapêutica ser estreita. Estudos farmacodinâmicos em humanos indicaram que a broncodilatação costuma ocorrer com concentrações séricas de teofilina de 5-20 µg/mL, de modo dose-dependente (19) e que os efeitos tóxicos podem ocorrer nas concentrações mais elevadas da faixa terapêutica. Esses efeitos também podem estar relacionados ao uso concomitante de outros fármacos. Alguns antibióticos (quinolonas, eritromicina e isoniazida), bloqueadores H2, propanolol, bloqueadores de canal de cálcio, anticoncepcionais orais, cafeína e vacina contra influenza reduzem o *clearance* da teofilina ou interferem com seu metabolismo hepático, podendo propiciar toxicidade. Por outro lado, fenobarbital, fenitoína, furosemida, tabagismo e broncodilatadores (salbutamol e isoproterenol) venosos podem aumentar o *clearance* da teofilina, reduzindo seus efeitos. Outros fatores, como dieta rica em carboidratos e pobre em proteínas, presença de alimento no estômago em crianças, febre, infecção viral, cor pulmonale, edema pulmonar, doença hepática e gravidez podem reduzir o *clearance* da teofilina e causar toxicidade. Os efeitos tóxicos não potencialmente letais incluem náusea, vômito, pirose, tremor, cefaleia, ansiedade e insônia. Convulsões e arritmias representam os efeitos tóxicos que podem levar à morte.

Finalizando, principalmente em função de seu baixo custo, a despeito de sua potência broncodilatadora ser inferior ao dos β_2-agonistas e de seu uso agregar riscos potenciais, seu papel imunomodulador e seu sinergismo com os corticosteroides fazem com que ela seja mantida no arsenal medicamentoso da asma, em adultos, tendo valor em situações particulares.

ANTICOLINÉRGICOS

No sistema motor parassimpático regulador do tônus broncomotor, a estimulação dos receptores M1 e M3 media o efeito broncoconstritor, enquanto a estimulação do receptor M2 antagoniza esse efeito, inibindo a liberação de acetilcolina. Assim, um medicamento antimuscarínico ideal para o tratamento da asma deveria inibir os receptores M1 e M3, sem agir sobre o M2 (20).

Os antagonistas muscarínicos, ou anticolinérgicos inalatórios, usados no tratamento do asmático são os brometos de ipratrópio (BI) e de tiotrópio (BT). Têm poucos efeitos colaterais, que incluem boca seca, retenção urinária e cefaleia. O BI tem ação curta (3-6 h após inalação) e o BT tem ação prolongada. Esse último tem como propriedade a afinidade prolongada pelos receptores M1 (14,6 h de inibição) e M3 (34 h de inibição) e por se dissociar rapidamente do receptor M2 (4 h). Assim, ele pode ser considerado um inibidor seletivo M1 e M3 de longa duração (21).

Ao menos teoricamente, a associação do BI ao β_2-agonista tem sinergismo no efeito broncodilatador. Como os mecanismos de ação broncodilatadora de cada uma das duas classes de medicação são diferentes, essa associação está indicada especialmente no tratamento das crises graves de asma (22,23). Nos casos de crise grave em crianças, foi demonstrado em uma meta-análise que o tratamento de cada sete pacientes com a associação BI e β_2-agonista é capaz de evitar a hospitalização de um deles. Uma vez que boa parte dos estudos avaliou o impacto nas taxas de hospitalização, a sua relevância clínica esbarra, sobretudo, na ampla diferença de critérios de hospitalização entre diferentes países e mesmo entre regiões de um mesmo país (23). Portanto, ainda são necessários trabalhos que verifiquem a eficácia do BI em outros desfechos, como a duração da hospitalização, o tempo necessário de uso de oxigênio durante a exacerbação e a taxa de transferência para UTI.

Atualmente, vêm sendo desenvolvidos novos anticolinérgicos de longa duração. Uma qualidade importante nesses novos fármacos, o que permite utilizá-los uma vez ao dia, é que esses anticolinérgicos aliam grande seletividade e dissociação lenta dos receptores muscarínicos M3. Há diversos fármacos em desenvolvimento (3), em diferentes etapas de pesquisa (Quadro 1), e só o futuro dirá quais irão agregar valor ao arsenal terapêutico da asma.

REFERÊNCIAS

1. Gibson PG, Powell H, Ducharme F. Long-acting beta-2 agonist as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. Cochrane Database of Syst Rev. 2005;(4):CD005076.
2. Sindi A, Todd DC, Nair P. Antiinflammatory effects of long-acting beta2-agonists in patients with asthma: a systematic review and metaanalysis. Chest. 2009;136(1):145-54.
3. Cazzola M, Matera MG. Emerging inhaled bronchodilators: an

update. Eur Respir J. 2009;34(3):757-69.
4. Giembycz MA, Newton R. Beyond the dogma: novel beta2-adrenoceptor signalling in the airways. Eur Respir J. 2006;27(6):1286-306.
5. Roth M, Johnson PR, Rüdiger JJ, King GG, Ge Q, Burgess JK, et al. Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. Lancet. 2002;360(9342):1293-9.
6. Rodrigo GJ, Castro-Rodríguez JA. Safety of long-acting β agonists for the treatment of asthma: clearing the air. Thorax. 2012;67(4):342-9.
7. Chung LP, Wateter G, Thompson PJ. Pharmacogenetics of β2 adrenergic receptor gene polymorphisms, long-acting β-agonists and asthma. Clin Exp Allergy. 2011;41(3):312-26.
8. Salter HH. On asthma: its pathology and treatment. London: Churchill Livingstone; 1860.
9. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database Syst Rev. 2000;(4):CD002742.
10. Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane Database Syst Rev. 2005;(2):CD001276.
11. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child. 1998;79(5):405-10.
12. Pauwels R, Van Renterghem D, Van der Straeten M, Johannesson N, Persson CG. The effect of theophylline and enprophylline on allergen-induced bronchoconstriction. J Allergy Clin Immunol. 1985;76(4):583-90.
13. Takeuchi M, Hayakawa A, Takagi K, Hiramatsu K, Shimizu Y, Matsumoto S, et al. Theophylline induces apoptosis of the IL-3 activated eosinophils of patients with bronchial asthma. Apoptosis. 1999;4(6):461-8.
14. Weston MC, Anderson N, Peachell PT. Effects of phosphodiesterase inhibitors on human lung mast cell and basophil function. Br J Pharmacol. 1997;121(2):287-95.
15. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. Lancet. 1994;343(8904):1006-8.
16. Rosenthal LA, Taub DD, Moors MA, Blank KJ. Methylxanthine-induced inhibition of the antigen- and superantingen-specific activation of T and B lymphocytes. Immunopharmacology. 1992;24(3):203-17.
17. Jaffar ZH, Sullivan P, Page C, Costello J. Low-dose theophylline modulates T-lymphocyte activation in allergen-challenged asthmatics. Eur Respir J. 1996;9(3):456-62.
18. Weinberger M, Hendeles L. Theophylline in asthma. N Engl J Med. 1996;334(21):1380-8.
19. Mitenko PA, Ogilvie RI. Pharmacokinetics of intravenous theophylline. Clin Pharmacol Ther. 1973;14(4):509-13.
20. Barnes PJ. Distribution of receptor targets in the lung. Proc Am Thorac Soc. 2004;1(4):345-51.
21. Gross NJ. Tiotropium bromide. Chest. 2004;126(6):1946-53.
22. Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma. An evidence-based evaluation. Chest. 2002;121(6):1977-87.
23. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax. 2005;60(9):740-6.

Artigo original

Medicação anti-inflamatória alternativa aos glicocorticóides para o tratamento da asma: papel dos modificadores de leucotrienos, estabilizadores de mastócitos e outras perspectivas

Anti-inflammatory medication beyond glucocorticoids for asthma therapy: role of leukotriene modifiers, mast cell stabilizers and other perspectives

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RESUMO

A inalação de agentes anti-inflamatórios esteroidais, administrados isoladamente ou combinados a agonistas β_2-adrenérgicos de longa duração, é a melhor opção disponível para o controle farmacológico da asma, embora efeitos adversos e resistência aos glicocorticóides limitem seu benefício. Inibidores da síntese de leucotrienos, antagonistas do receptor CysLT1 e estabilizadores de mastócitos têm sido empregados, como monoterapias alternativas, no tratamento da asma branda e moderada, porém sem a mesma eficácia dos anti-inflamatórios esteroidais. Há evidências de que a combinação do antagonista CysLT1 e glicocorticóide inalado seja eficaz no tratamento de asmáticos graves, com diminuição da dosagem do agente esteroidal. Inibidores da enzima fosfodiesterase 4, bem como lidocaína e análogos não anestésicos da lidocaína, têm igualmente atraído atenção como opções terapêuticas no controle da asma. Esta revisão analisa avanços recentes no campo das alternativas ao uso dos glicocorticóides para regulação anti-inflamatória da asma.

Descritores: Asma; Inflamação alérgica; modificadores de leucotrienos; inibidores de fosfodiesterase; anestésicos locais; estabilizadores de mastócitos.

ABSTRACT

Inhalation of steroidal anti-inflammatory agents, alone or in combination with long-acting β_2-adrenergic agonists is the best asthma therapy available so far, though side effects and steroid-resistance may limit their benefits. Leukotriene synthesis inhibitors, CysLT1 receptor antagonists and mast cell stabilizers have been employed, as monotherapy, for the treatment of mild and moderate asthma, but they are less effective as compared to steroidal anti-inflammatory drugs. Evidence indicates that the combination of CysLT1 receptor antagonists and inhaled glucocorticoid can improve severe asthma control, and enables the steroid dose to be reduced keeping similar efficacy. Phosphodiesterase 4 inhibitors as well as lidocaine and non-anesthetic lidocaine analogs have also attracted interest as putative alternatives for the treatment of asthma. This review addresses recent advances in the anti-inflammatory asthma therapy beyond steroids.

Keywords: Asthma; Allergic inflammation; leukotriene modifiers; phosphodiesterase inhibitors; local anesthetics; mast cell stabilizers.

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INTRODUÇÃO

A asma é uma inflamação crônica das vias aéreas pulmonares desencadeada por fatores ambientais em indivíduos geneticamente predispostos (1,2). A doença é dirigida por uma resposta imune de perfil T_H2, associada à infiltração da mucosa bronquial por células inflamatórias, com destaque para os eosinófilos, as células T $CD4^+$ e, nos casos mais graves, também para os neutrófilos. A hiperreatividade brônquica inespecífica e episódios recorrentes de falta de ar, sibilo e tosse constituem os principais sintomas da asma, que atinge pessoas de todas as faixas etárias e pode ser fatal (1,3,4). Há 20 milhões de asmáticos no Brasil com cerca de 2160 mortes sendo registradas anualmente. A inflamação das vias aéreas é central na patogênese da asma. O processo é marcado por produção aumentada de IgE, ativação mastocitária e uma polarização da resposta T_H2, com elevação nos níveis das citocinas IL-4, IL-5, IL-13, quimiocinas, além de outros mediadores pró-inflamatórios, incluindo leucotrienos, histamina e neuropeptídeos (1,5). O remodelamento das vias aéreas e a produção exacerbada de muco são alterações que se correlacionam fortemente com a gravidade da doença. O espessamento da parede das vias aéreas pode chegar a 300% causando substancial redução do diâmetro do lúmen e do fluxo aéreo (1,2).

ESTRATÉGIAS TERAPÊUTICAS NA ASMA

A asma é, portanto, uma síndrome complexa e heterogênea, não apenas porque envolve a participação de vários mediadores e células, mas também devido a diferenças de susceptibilidade genética e fatores ambientais que efetivamente contribuem para a manifestação dos múltiplos fenótipos notados nesses pacientes (1,6). Talvez por isso, novas opções terapêuticas direcionadas ao bloqueio específico de um único tipo celular, ou mediador inflamatório, tenham frequentemente apresentado efeitos clínicos pouco satisfatórios (1). A terapia atual essencialmente controla os sintomas da doença, inibindo a inflamação e relaxando a musculatura lisa das vias aéreas. A relevância da inflamação das vias aéreas na asma fica evidente na marcada capacidade antiasmática dos agentes anti-inflamatórios esteroidais. A inalação do glicocorticóide combinado ao agonista β_2-adrenérgico de longa duração é, sem dúvida, o tratamento mais eficaz no controle farmacológico da asma branda, moderada ou grave. A grande maioria dos asmáticos responde bem a essa terapia, embora cerca de 5% deles necessite de tratamentos adicionais e prolongados com glicocorticóides orais, o que aumenta sensivelmente os riscos de efeitos adversos. Ademais, uma parcela desses pacientes é completamente resistente aos glicocorticóides, fazendo urgente a necessidade de se buscar alternativas terapêuticas que possam ser mais eficazes e mais seguras (1,7,8).

MODIFICADORES DE LEUCOTRIENOS

Os leucotrienos (LTs) constituem uma família de mediadores lipídicos pró-inflamatórios que são formados por leucócitos e células estruturais, a partir do ácido araquidônico livre, por ação da enzima 5-lipoxigenase (5-LO) (9,10). Os cisteinil-LTs C4, D4 e E4 induzem broncoconstricção, inflamação, remodelamento, produção de muco e hiperreatividade de vias aéreas. Eles exercem suas ações através da ligação a dois receptores acoplados à proteína G denominados CysLT1 e CysLT2, sendo o primeiro responsável, em grande parte, pelas ações dos cisteinil-LTs observadas na asma. Já o LTB4 tem sido reconhecido por sua potente ação quimiotática e ativadora de neutrófilos, sem significante efeito sobre a função pulmonar quando inalado em asmáticos. O LTB4 também age via ativação de receptores acoplados à proteína G, denominados BLT1 e BLT2, expressos na membrana celular. Os níveis de LTB4 estão aumentados na asma, mas o papel desse mediador parece menos importante, visto que o antagonista BLT1 LY293111 inibiu o acúmulo de neutrófilos nas vias aéreas de pacientes asmáticos, sem modificar os sintomas clínicos da doença.

O receptor CysLT1 medeia a contração das células musculares lisas das vias aéreas, o extravasamento plasmático e a secreção de muco associados ao quadro asmático (11). Os antagonistas do receptor CysLT1 incluindo montelukast, pranlukast e zafirlukast, bem como o inibidor da síntese de leucotrienos, zileuton, são medicamentos eficazes na inibição da broncoconstrição e hiperresponsividade induzidas pelo desafio alergênico (9). A adição dos anti-LTs à terapia com glicocorticóides inalados promove uma melhora dos sintomas dos pacientes asmáticos e reduz a dose de glicocorticóide necessária para controlar a doença (9). Os anti-LTs funcionam por via oral e apresentam poucos efeitos adversos, facilitando a aderência dos pacientes ao tratamento. Apesar do relativo sucesso clínico na asma, os anti-LTs são reconhecidamente menos eficientes e mais caros do que o tratamento com glicocorticóides inalados (12). Além disso, nota-se uma grande variabilidade na resposta dos pacientes aos modificadores de LTs. Há evidências recentes de que esse fato está associado à diversidade genética nas enzimas e proteínas transportadoras, implicadas na síntese dos leucotrienos, abrindo perspectiva para uma abordagem terapêutica mais personalizada no futuro próximo (10).

INIBIDORES DE FOSFODIESTERASE (PDE)

A fosfodiesterase nucleotídica cíclica (PDE) constitui um grupo de enzimas envolvidas na clivagem de ligações fosfodiéster dos mensageiros secundários AMPc e GMPc, levando a degradação desses compostos. O aumento da concentração intracelular de AMPc está relacionado com a redução da ativação de células inflamatórias e células residentes do pulmão. Sendo

assim, o uso de inibidores de PDE pode ser uma alternativa interessante para tratar a inflamação pulmonar (13). Há atualmente 11 famílias de PDE descritas, e aproximadamente 21 isoformas, as quais diferem estruturalmente, na sua distribuição nos tecidos e células, na seletividade do inibidor e na especificidade do substrato (14).

As metilxantinas, como a teofilina, são inibidores fracos e não seletivos de PDE3 e PDE4, que vêm sendo utilizadas há mais de 75 anos no tratamento da asma e de doenças pulmonares obstrutivas crônicas (DPOC). A teofilina é reconhecida por sua potente ação broncodilatadora que resulta do aumento dos níveis de AMPc na célula muscular. Em concentrações terapêuticas, esta substância possui também ações anti-inflamatórias e imunomoduladoras, inibindo a liberação de mediadores pró-inflamatórios por leucócitos e induzindo a apoptose de eosinófilos e neutrófilos (1). A vantagem da teofilina é que sua administração pode ser feita pela via oral, facilitando a aderência do paciente à terapia. Entretanto, a estreita margem terapêutica e a alta frequência de efeitos colaterais, como náuseas, anorexia, vômitos e arritmia cardíaca desestimulam sua aplicação clínica. Recentemente, observou-se que a teofilina, administrada em baixas concentrações, reativa a histona desacetilase 2 (HDAC2), uma enzima nuclear envolvida no desligamento de genes pró-inflamatórias ativados, e que medeia em parte as ações anti-inflamatórias dos glicocorticóides (15). A suplementação com teofilina em baixas doses reverte quadros de resistência a glicocorticóides, contribuindo para aumentar a eficácia desse medicamento em pacientes com asma de difícil tratamento. Esse efeito da teofilina não está relacionado ao bloqueio de enzimas do tipo PDE nem de receptores de adenosina (15).

Em função da sua ampla distribuição em células do sistema imune, a PDE4 é considerada um alvo terapêutico seletivo e importante no controle de doenças inflamatórias pulmonares crônicas. Os inibidores de PDE4 têm efeitos anti-inflamatórios através da inibição de células T, eosinófilos, mastócitos, células musculares lisas das vias aéreas, células epiteliais e nervosas, e funcionam em modelos experimentais de asma (6). O roflumilast, um inibidor de PDE4 administrado por via oral, é capaz de inibir características importantes na asma, como o recrutamento de eosinófilos e a hiperreatividade brônquica. No entanto, suas ações farmacológicas incluem efeitos adversos como náusea, dor de cabeça e diarreia, que limitam sua utilização (6).

ESTABILIZADORES DE MASTÓCITOS

O efeito anti-inflamatório do cromoglicato de sódio está associado com a sua ação direta sobre mastócitos, impedindo a liberação de histamina e de outros mediadores inflamatórios, incluindo eicosanóides. O mecanismo de ação do cromoglicato de sódio e da substância relacionada, nedocromil sódico, ainda é pouco conhecido, mas parece improvável que o efeito antiasmático observado para esta classe de agentes tenha o mastócito como único alvo (16).

O tratamento com cromoglicato de sódio inibe a inflamação e os mecanismos neurogênicos associados à hiperreatividade das vias aéreas na asma, provavelmente devido à depressão de reflexos neuronais (17). Os efeitos colaterais do cromoglicato de sódio são reduzidos, sendo restritos à irritação das vias aéreas superiores. Contudo, sua eficiência é considerada menor do que aquela obtida com baixas doses de glicocorticóides inalados, provavelmente devido ao reduzido tempo de ação dessas substâncias. Devido ao seu curto tempo de ação, as cromonas inaladas devem ser administradas quatro vezes ao dia, um regime inconveniente sobretudo para o tratamento de longo prazo (16).

LIDOCAÍNA

Em um estudo de quantificação de citocinas pró-eosinofílicas no lavado broncoalveolar de asmáticos, Ohnishi e colaboradores (18) descobriram, por acaso, que a lidocaína (utilizada como anestésico local no procedimento de lavagem broncoalveolar) tem a capacidade de inibir a função e sobrevida de eosinófilos. A observação de que a lidocaína, tal qual agentes glicocorticóides, induz a apoptose de eosinófilos estimulou investigações acerca do potencial uso de lidocaína na terapia da asma. Vários estudos confirmaram a capacidade da lidocaína inalada de controlar sintomas e reduzir a necessidade do glicocorticóide oral em pacientes de asma moderada e grave (18-22). A lidocaína mostrou eficácia no tratamento de paciente grávida com asma grave, inteiramente refratária à terapia com medicação convencional, incluindo glicocorticóide intravenoso, agonista β_2-adrenérgico, agente anti-colinérgico, teofilina e antagonista de receptor CysLT1, sugerindo que a inalação combinada de lidocaína e agonista β_2-adrenérgico seja uma opção diferenciada para o controle da asma de difícil tratamento (23). Entretanto, os achados nesse campo são ainda controversos (24). Ademais, há evidências de que a monoterapia com lidocaína induz broncoconstricção inicial em alguns pacientes, o que pode ser de grande risco, especialmente em asmáticos graves. O mecanismo dessa ação é pouco compreendido, mas parece fortemente associado à atividade anestésica local da lidocaína (25).

POTENCIAL ANTIASMÁTICO DE NOVOS ANÁLOGOS NÃO ANESTÉSICOS DE LIDOCAÍNA

Qual seria a importância da ação anestésica no efeito antiasmático da lidocaína? Na pista de estudos anteriores que indicavam a clara dissociação entre a potência anestésica e a propriedade broncodilatadora de agentes anestésicos locais, nosso grupo na FIOCRUZ planejou e sintetizou análogos estruturais da lidocaína, buscando identificar substâncias ativas no controle da asma, mas sem ação anestésica local. Tais

estudos, de fato, resultaram na identificação de uma nova série de análogos marcados por substancial redução da atividade anestésica local, sem prejuízo para as propriedades antiasmáticas, como atestado por ensaios pré-clínicos *in vitro* e *in vivo* (26-29). Os achados demonstraram a clara dissociação entre a ação anestésica e a atividade anti-inflamatória/broncodilatadora da lidocaína, reforçando a perspectiva de que análogos não anestésicos possam ganhar aplicabilidade terapêutica dentro do arsenal antiasmático. O composto mais promissor da série, denominado JMF2-1, previne sinais cardinais da asma, incluindo inflamação eosinofílica e hiperreatividade pulmonar, via inibição da função e sobrevida de células T (28). Vale ressaltar que as propriedades anti-inflamatória e antiespasmódica de JMF2-1 estão associadas ao aumento dos níveis intracelulares de AMPc em células-alvo, como pode ser demonstrado em linfócitos T e células musculares lisas das vias aéreas (29).

CONCLUSÃO

Os glicocorticóides inalados são muito eficazes na asma devido ao seu amplo espectro de atividades anti-inflamatórias, e não tem sido tarefa trivial o desenvolvimento de novas terapias com efetividade comparável àquela dos agentes esteroidais. Entretanto, uma parcela minoritária dos asmáticos permanece refratária a este tratamento, desafiando clínicos e cientistas a buscarem alternativas terapêuticas que possam controlar com segurança todos os fenótipos da doença. Há hoje expectativas positivas quanto a possibilidade de otimizar-se a terapia anti-inflamatória na asma. Uma das apostas é a reversão do estado de resistência ao glicocorticóide, utilizando baixas concentrações de teofilina como tratamento suplementar. Esta ação da teofilina independe do bloqueio de fosfodiesterase ou do receptor de adenosina, e está associada à reativação da enzima HDAC2, fortemente comprometida por estresse oxidativo na resistência a corticóides. Os modificadores de leucotrienos podem apresentar atividade comparável a dos glicocorticóides, a exemplo do que ocorre na asma desencadeada por exercício, com a vantagem dos baixos efeitos adversos e de poderem ser administrados oralmente. Entretanto, há uma substancial heterogeneidade na responsividade clínica dos pacientes, que está relacionada a variações genéticas nas enzimas e proteínas transportadoras, ligadas à síntese dos leucotrienos. Por outro lado, há esperanças também no controle da asma feito com base na inibição mais seletiva da PDE4, embora persista o desafio de superar-se os sérios efeitos adversos que parecem inerentes ao bloqueio dessa enzima. Por último, evidências pré-clínicas indicam que a inalação do derivado JMF2-1 é também uma perspectiva promissora de tratamento, pois através dele é possível atingir os efeitos anti-inflamatório e broncodilatador da lidocaína sem o indesejável efeito anestésico (Figura 1).

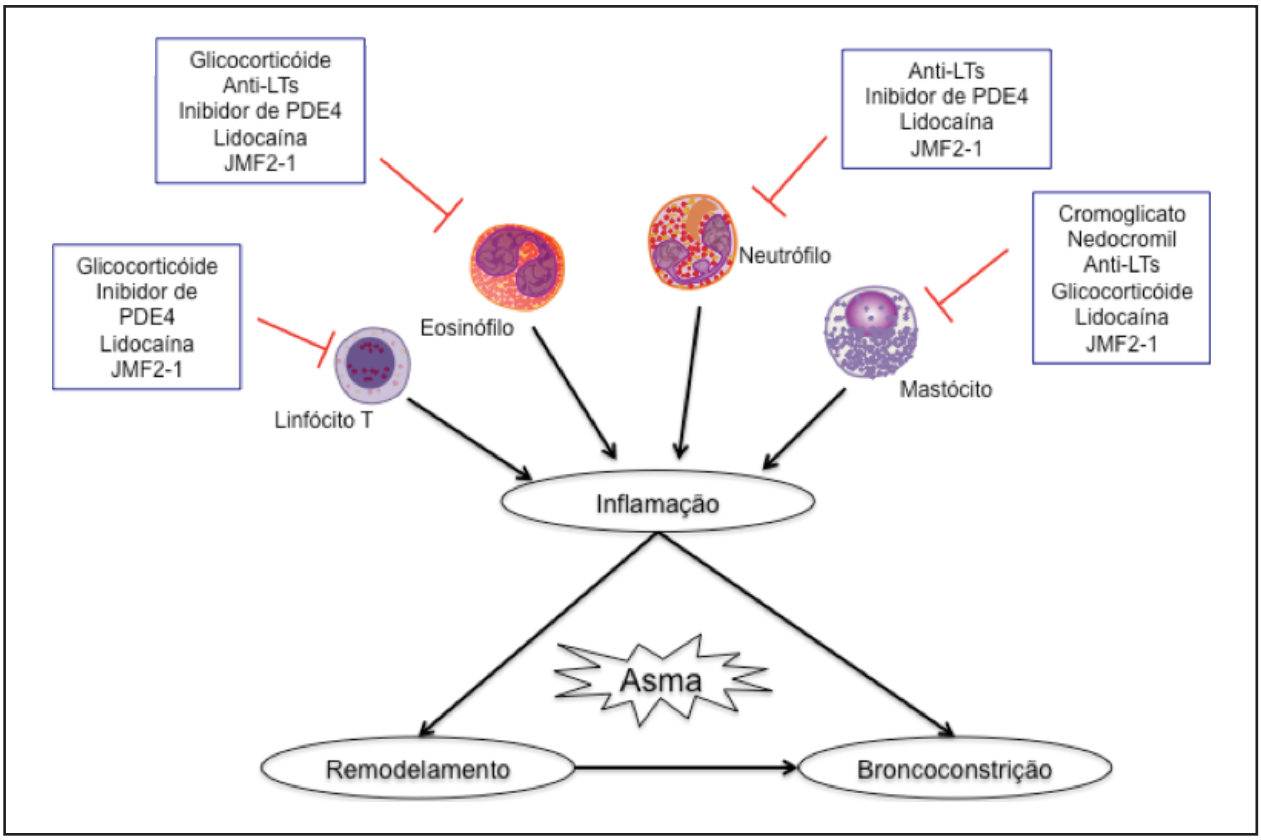

Figura 1: Esquema simplificado dos principais agentes anti-inflamatórios e alvos celulares na asma.

REFERÊNCIAS

1. Barnes PJ: Biochemical basis of asthma therapy. J Biol Chem 2011; 286: 32899-905
2. Lemanske RF, Jr., Busse WW: Asthma: Clinical expression and molecular mechanisms. J Allergy Clin Immunol 2010; 125: S95-102
3. Szefler SJ, Dakhama A: New insights into asthma pathogenesis and treatment. Curr Opin Immunol 2011; 23: 801-7
4. Bosnjak B, Stelzmueller B, Erb KJ, Epstein MM: Treatment of allergic asthma: modulation of Th2 cells and their responses. Respir Res 2011; 12: 114
5. Holgate ST, Arshad HS, Roberts GC, Howarth PH, Thurner P, Davies DE: A new look at the pathogenesis of asthma. Clin Sci (Lond) 2010; 118: 439-50
6. Barnes PJ: New therapies for asthma: Is there any progress? Trends Pharmacol Sci 2010; 31: 335-43
7. Montuschi P, Barnes PJ: New perspectives in pharmacological treatment of mild persistent asthma. Drug Discovery Today 2011; 16: 1084-92
8. Barnes PJ: Glucocorticosteroids: current and future directions. Br J Pharmacol 2011; 163: 29-43
9. Montuschi P, Peters-Golden ML: Leukotriene modifiers for asthma treatment. Clin Exp Allergy 2010; 40: 1732-41
10. Hallstrand TS, Henderson WR, Jr.: An update on the role of leukotrienes in asthma. Curr Opin Allergy Clin Immunol 2010; 10: 60-6
11. Scow DT, Luttermoser GK, Dickerson KS: Leukotriene inhibitors in the treatment of allergy and asthma. Am Fam Physician 2007; 75: 65-70
12. Barnes PJ: New drugs for asthma. Nat Rev Drug Discov 2004; 3: 831-44
13. Spina D: PDE4 inhibitors: current status. Br J Pharmacol 2008; 155: 308-15
14. Houslay MD, Schafer P, Zhang KY: Keynote review: phosphodiesterase-4 as a therapeutic target. Drug Discov Today 2005; 10: 1503-19
15. Spears M, Donnelly I, Jolly L, Brannigan M, Ito K, McSharry C, Lafferty J, Chaudhuri R, Braganza G, Adcock IM, Barnes PJ, Wood S, Thomson NC: Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma: a pilot study. Eur Respir J 2009; 33: 1010-7
16. Yazid S, Solito E, Christian H, McArthur S, Goulding N, Flower R: Cromoglycate drugs suppress eicosanoid generation in U937 cells by promoting the release of Anx-A1. Biochem Pharmacol 2009; 77: 1814-26
17. Storms W, Kaliner MA: Cromolyn sodium: fitting an old friend into current asthma treatment. J Asthma 2005; 42: 79-89
18. Ohnishi T, Kita H, Mayeno AN, Okada S, Sur S, Broide DH, Gleich GJ: Lidocaine in bronchoalveolar lavage fluid (BALF) is an inhibitor of eosinophil-active cytokines. Clin Exp Immunol 1996; 104: 325-31
19. Okada S, Hagan JB, Kato M, Bankers-Fulbright JL, Hunt LW, Gleich GJ, Kita H: Lidocaine and its analogues inhibit IL-5-mediated survival and activation of human eosinophils. J Immunol 1998; 160: 4010-7
20. Decco ML, Neeno TA, Hunt LW, O'Connell EJ, Yunginger JW, Sachs MI: Nebulized lidocaine in the treatment of severe asthma in children: A pilot study. Ann Allergy Asthma Immunol 1999; 82: 29-32
21. Tanaka A, Minoguchi K, Oda N, Yokoe T, Matsuo H, Okada S, Tasaki T, Adachi M: Inhibitory effect of lidocaine on T cells from patients with allergic asthma. J Allergy Clin Immunol 2002; 109: 485-90
22. Hunt LW, Frigas E, Butterfield JH, Kita H, Blomgren J, Dunnette SL, Offord KP, Gleich GJ: Treatment of asthma with nebulized lidocaine: A randomized, placebo-controlled study. J Allergy Clin Immunol 2004; 113: 853-9
23. Saito K, Sato N, Shimono N, Hagiwara K, Kanazawa M, Nagata M: A pregnant woman with severe asthma effectively treated by inhalational lidocaine therapy. Nihon Kokyuki Gakkai Zasshi 2006; 44: 828-32
24. Abuan T, Yeager M, Montgomery AB: Inhaled lidocaine for the treatment of asthma: Lack of efficacy in two double-blind, randomized, placebo-controlled clinical studies. J Aerosol Med Pulm Drug Deliv 2010; 23: 381-8
25. Groeben H, Grosswendt T, Silvanus MT, Pavlakovic G, Peters J: Airway anesthesia alone does not explain attenuation of histamine-induced bronchospasm by local anesthetics: A comparison of lidocaine, ropivacaine, and dyclonine. Anesthesiology 2001; 94: 423-8
26. da Costa JC, Olsen PC, de Azeredo Siqueira R, de Frias Carvalho V, Serra MF, Alves LA, Faria RX, Xisto DG, Rocco PR, Cordeiro RS, Rodrigues ESPM, Martins MA: JMF2-1, a lidocaine derivative acting on airways spasm and lung allergic inflammation in rats. J Allergy Clin Immunol 2007; 119: 219-25
27. Costa JC, Neves JS, de Souza MV, Siqueira RA, Romeiro NC, Boechat N, e Silva PM, Martins MA: Synthesis and antispasmodic activity of lidocaine derivatives endowed with reduced local anesthetic action. Bioorg Med Chem Lett 2008; 18: 1162-6
28. Olsen PC, Ferreira TP, Serra MF, Farias-Filho FA, Fonseca BP, Viola JP, Cordeiro RS, Silva PM, Costa JC, Martins MA: Lidocaine-derivative JMF2-1 prevents ovalbumin-induced airway inflammation by regulating the function and survival of T cells. Clin Exp Allergy 2011; 41: 250-9
29. Olsen PC, Coelho LP, da Costa JC, Cordeiro RS, Silva PM, Martins MA: Two for one: Cyclic AMP mediates the anti-inflammatory and anti-spasmodic properties of the non-anesthetic lidocaine analog JMF2-1. Eur J Pharmacol 2012; 680: 102-107

Artigo original

Asthma Guidelines in Day-to-day Practice

Diretrizes de Asma na Prática Diária

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RESUMO

A morbidade e a mortalidade por asma persistem como problemas no mundo, apesar dos instrumentos efetivos para seu controle. Diretrizes internacionais, tais como as da *Global Initiative for Asthma*, fornecem direções para melhorar o cuidado com a asma. Os elementos dessas diretrizes apresentam: 1) medidas objetivas para dimensionar a asma, como a espirometria, para diagnosticar e monitorar a resposta ao tratamento; 2) conselhos para o controle ambiental efetivo; 3) abordagem por etapas na terapia farmacológica, guiadas pelo controle da doença; 4) desenvolvimento de parcerias com o paciente e, quando apropriado, seu cuidador. Lições dessas recomendações podem ser incorporadas no cuidado diário prestado ao asmático e melhorar os desfechos.

Descritores: Asma/diagnóstico; Asma/terapia; Educação de pacientes como assunto.

ABSTRACT

Despite effective means of asthma control, asthma morbidity and mortality persist worldwide. International guidelines such as the Global Initiative for Asthma Guidelines have provided a roadmap for improved asthma care. The elements of these guidelines are to 1) use objective measures of asthma, such as spirometry, to diagnose and monitor the response to treatment; 2) provide advice on effective environmental control; 3) use a step-up approach to pharmacologic therapy guided by disease control; and 4) develop a partnership of care with the patient and, when appropriate, the caregiver. Lessons from these guidelines can be incorporated into the day-to-day care of asthma and can improve asthma outcomes.

Keywords: Asthma/diagnosis; Asthma/therapy; Patient education as topic.

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CAUSE FOR OPTIMISM FOR ASTHMA PATIENTS

The end of the 20th century introduced a dramatic new approach to asthma care. No longer was there a reliance on bronchodilator medications alone to control the symptoms of asthma. The disease became recognized as a chronic inflammatory disease of the airways. With the advent of safe anti-inflammatory medications, symptom prevention as well as symptom control became possible. The long-term goal of asthma treatment is directed at reducing and possibly eliminating airway inflammation. Medications referred to as "controller therapies" are used for this purpose. Inhaled corticosteroids have become the mainstay of controller therapy for persistent asthma symptoms. Agents that are capable of inhibiting the synthesis or action of pro-inflammatory mediators called leukotrienes were introduced in the 1990's as controller therapies for asthma.

With new insights into the pathogenesis of asthma, as well as new and safer medications to control the disease, there is reason for optimism in the management of asthma. A global strategy through international asthma guidelines, developed as part of the Global Initiative for Asthma (GINA), has provided a roadmap for asthma care, including the goals of treatment (Chart 1) and evidence-based protocols to lead clinicians to successful outcomes for their patients (1). The GINA has made an effort to raise awareness of the growing importance of asthma worldwide.

Chart 1 - Goals of asthma treatment

1. Limit symptoms of dyspnea, wheeze, chest tightness, and cough, day and night
2. Provide normal daily activity level; no absenteeism from work or school
3. Maintain normal or near-normal lung function
4. Reduce or eliminate asthma exacerbations; avoid emergency visits and hospitalizations
5. Minimize use of rescue medication and use lowest dose and fewest medications possible
6. Avoid side effects of medications

BARRIERS TO IMPROVED CARE

Coupled with the optimism regarding the prospects for improving asthma care are the sobering statistics with which we must contend. There has been a sharp increase in the global prevalence, morbidity, mortality, and economic burden associated with asthma over the last 50 years, particularly in children, in whom it has become the most common chronic disease (2). Although the reasons for this increased prevalence remain largely unknown, the increase has been noted to parallel the increase in that of atopic diseases worldwide. The World Health Organization has estimated that there are approximately 235 million people worldwide who currently suffer from asthma, and it has become increasingly common in the developing countries, probably because of the increased urbanization of communities (3).

Studies indicate that asthma is underdiagnosed and undertreated worldwide, and this has created a substantial burden on individuals and their families (4-8). Poor asthma control can restrict the activities of patients and impair their quality of life for years. Internationally, trends indicate an increasing number of hospital admissions for asthma. This has been most pronounced in young children, and reflects an increase in the number of cases of severe asthma, poor disease management, and poverty. However, most asthma deaths occur in individuals who are 45 years of age or older and are largely preventable. Such deaths are frequently related to inadequate long-term medical care or to delays in obtaining medical treatment during the fatal attack (9). Over 80% of asthma deaths occur in low- and lower-middle-income countries (3).

Although a number of barriers to reducing the burden of asthma, such as poverty, a low national public health priority, poor health care infrastructure, limited patient access to medication, and environmental factors, are out of the hands of ordinary clinicians, other barriers can be addressed. In day-to-day asthma care, stressing avoidance of asthma triggers, such as tobacco smoke and occupational pollutants, and improving patient education about this condition can have a major positive impact on outcomes.

The barriers to reducing the burden of asthma are particularly problematic in developing countries, where many patients have limited access to care and to essential medications. The GINA has outlined a 6-point patient management plan that can improve asthma care, especially that provided by primary care clinicians (10). The plan focuses on patient education and written treatment plans, together with ongoing communication and review by patients and their providers. Adherence to evidence-based principles of asthma treatment can also have a positive impact on patient outcomes.

USING ASTHMA GUIDELINES IN DAY-TO-DAY PRACTICE

The introduction of international guidelines to improve asthma outcomes provided a practical, clinician-friendly approach to this disease. The new definition of asthma reminded us that asthma is an inflammatory airway disease and that inhaled corticosteroids that have anti-inflammatory properties are the foundation of treatment for those with persistent asthma symptoms. Four cornerstones of asthma care were outlined. (Chart 2) Each has relevance in the day-to-day care of asthma patients.

Chart 2 - Essential components of successful asthma care

Monitoring	Use of self-assessment questionnaires, peak flow measures, spirometry
Avoidance	Eliminate asthma "triggers" such as allergen exposure and home/workplace irritants
Treatment	Anti-inflammatory therapy is the foundation of successful treatment for persistent asthma; short-acting bronchodilators for rescue therapy
Patient education	Provide the necessary tools for self-management including an action plan for exacerbation of symptoms

Lung function testing

As the main symptoms of asthma, including shortness of breath, cough and wheeze, are not specific to this disease, objective assessment of lung function is important for diagnosis. In addition, because of the poor correlation between lung function and patient symptoms and clinical outcomes, spirometry has been advocated for measuring disease severity and the response to therapy. In the majority of underdeveloped areas in the world however, spirometry is not readily available, resulting in incorrect assessment and underdiagnosis of asthma.

Environmental control

Control of environmental influences is the second cornerstone of care. Allergens and occupational factors are considered to be the most important triggers of asthma. For successful long-term management of asthma, these triggers must be identified and prevention of exposures should be the first line of defense (11,12). Symptoms and the need for medication correlate with the level of household exposure of known allergens in susceptible individuals (13,14). Improvement of asthma symptoms occurs when allergen exposure is reduced (15-18).

The important allergens for children and adults are those that are inhaled. Food allergens, although an important cause of anaphylaxis, are not a common precipitant of asthma symptoms. Important indoor allergens include a number of domestic factors: house dust mites; cockroach allergen; fungi (Alternaria, Aspergillus, Cladosporium, and Candida); and warm-blooded animals (cats, dogs and rodents). Rodents are problematic as they excrete urine, feces, and saliva, as well as producing dander that can be highly allergenic. Although removal of a pet from the home of a sensitized patient is encouraged, it may require several months before allergen levels decrease (19). House dust has been shown to be composed of several organic and inorganic compounds, including insects and insect feces, mold spores, animal dander, pollen grains, fibers, mites, and mite feces. In poor and inner-city locations, mouse and rat allergen exposure and sensitization are common in children who have asthma (20). Rodent exposure is also common in underdeveloped regions of the world and must be considered in asthma control in these populations.

In high-risk urban children with asthma, multiple-intervention environmental control studies have been conducted with comprehensive allergen reduction methods. Such studies have demonstrated positive outcomes (21-24). Successful interventions include construction remediation aimed at moisture sources within homes of those with a documented mold problem (23) and home visits by community health workers who promote dust mite and cockroach control and stress behavioral changes such as smoking cessation. Multiple visits are required in order to encourage completion of asthma action plans and deliver resources to reduce exposures. These have included allergy control pillow and mattress encasements, low-emission vacuums, commercial-quality door mats, cleaning kits, roach bait, and rodent traps.

Both outdoor and indoor pollutants contribute to worsening asthma symptoms (25-29). The two main outdoor pollutants are industrial smog (sulfur dioxide particulate complex) and photochemical smog (ozone and nitrogen oxides). It is advisable to recommend that asthma patients avoid, to the extent possible, exertion or exercise outside when levels of air pollution are high.

Indoor pollutants include cooking and heating fuel exhausts, as well as insulating products, paints, and varnishes. Clinicians should advise patients to be aware of the potential irritating effects of newly installed furnishings and finishes which can arise from new linoleum flooring, synthetic carpeting, particleboard, wall coverings, furniture, and fresh paint. The use of poorly vented gas stoves and appliances results in increased indoor levels of nitrogen dioxide and has been associated with increased respiratory symptoms (30,31). Installing non-polluting, more effective heating in the homes of children with asthma does not significantly improve lung function but can reduce symptoms of asthma, days off school, healthcare utilization, and visits to a pharmacist (32). In addition, fumes from wood-burning appliances or fireplaces, which may be used for heating or cooking, can precipitate symptoms in persons who have asthma (33). Sprays and strong odors, particularly perfumes, can also irritate the lungs and precipitate asthma symptoms.

In asthma sufferers, active smoking is a cause of worsening symptoms and deterioration of lung function and also reduces the efficacy of inhaled and systemic corticosteroids in treating asthma (34,35). Long-term passive cigarette smoke exposure has been linked to new-onset asthma in children and adults, as well as to the worsening of asthma symptoms, decreased lung function, and greater use of health services in those with pre-existing asthma (36). Children are more likely

to be affected when the mother smokes rather than when others in the household do so (37). In adults with asthma, exposure to tobacco smoke exposure might be more likely to occur in the work environment (38).

Estimates of the prevalence of occupational asthma vary (39,40). It has been reported that 2-15% of all cases of adult-onset asthma arise from workplace exposure. Taking an occupational history can be very rewarding and can lead to primary prevention and avoidance of the offending environment.

Drug therapy

The third cornerstone of asthma care is pharmacologic therapy. Asthma is an episodic disease, the clinical presentation and natural history of which are highly variable from patient to patient and for any individual patient. Some patients have persistent symptoms and exacerbations from time to time. Others show long periods of remission, with sudden worsening upon exposure to asthma triggers. Treatment protocols are based on this variability and use a step-care pharmacologic approach based on the intensity of the asthma over time (1). As symptoms and lung function worsen, step-up or add-on therapy is given. As symptoms improve, therapy can be stepped down.

It has been challenging to clinicians to quantify the degree of asthma for any given patient and to make decisions based on that assessment regarding treatment. Although lung function is often used as the primary endpoint, guidelines have suggested a composite of measures to gauge disease severity, the intrinsic intensity of the disease, and asthma impairment (1). The latter measures daily symptoms, nighttime awakenings, need of quick relief rescue therapy, work/school days missed, interference with normal daily activities, and lung function, as measured by spirometry.

When symptoms appear more than two times per week, nocturnal symptoms appear more than twice per month, or FEV_1 is less than 80% of predicted, regular treatment with anti-inflammatory therapy (preferably low-dose inhaled corticosteroids) is recommended and the patient is considered to have "persistent" asthma. The response to therapy, i.e., how the manifestations of asthma have been reduced or removed, is the degree of asthma control achieved. Asthma control has two components: the level of clinical asthma control (symptoms and quality of life) and the risk of future adverse events (exacerbations of asthma, loss of lung function, side effects of the therapy). At each visit, the patient should be assessed for the level of asthma control, adherence to the recommended treatment, and potential side effects of the drugs used. A simplified scheme has been developed to identify patients with controlled, partly controlled, and poorly controlled asthma (1). Several composite control measures have been developed to help the clinician assess asthma control (41-45). According to the guidelines, step-up therapy is advised for patients with asthma that is not well controlled. There are no hard and fast rules on stepping down asthma care, but it is recommended that a reduction in medication be attempted only after at least three months of stability. The lowest dose of medication to maintain stability is offered. At each step, reliever medication with a short-acting β_2-agonists agonist is used for breakthrough symptoms, but increased use implies poor control and the need for step-up therapy.

Significant reductions in the rate of severe exacerbations and improvements in quality of life can be achieved by aiming at achieving guideline-defined asthma control and by adjusting therapy to achieve it (46).

The patient/clinician partnership

4) The last cornerstone of asthma management is the patient/clinician partnership (1). Patient education that fosters a partnership among the patient, his or her family, and those caring for the patient is essential. Self-management education is essential to provide patients with the skills necessary to control asthma and improve outcomes. The goals of asthma care should be discussed and agreed upon by the patient and all members of the health care team, and sites for self- management education outside the usual office setting should be explored. The actions of the medications should be reviewed and the potential complications should be understood. Action plans should be written down and used as guidelines for daily care. An action plan for the acute exacerbation of asthma is essential, including when to use oral corticosteroids, when to call the physician and when to use emergency services. Often however, professionally provided, medically focused action plans do not "fit" with and incorporate the views on asthma held by the patient or caregiver. If this occurs, management strategies will be underutilized (47). Providers of asthma care need to have a patient-centered, partnership-based approach to the joint development and review of action plans.

In the Asthma Insights and Reality surveys (48), 32-49% of patients experiencing severe symptoms believed that their asthma was completely or well controlled, as did 39-70% of patients with moderate symptoms. For asthma sufferers that have frequent symptoms and exacerbations or for those who have a poor perception of their symptoms, the use of handheld peak flow meters can be useful to monitor daily lung function. An action plan for worsening lung function may be extremely helpful in avoiding emergency room visits and near-fatal attacks.

FINAL CONSIDERATIONS

International guidelines have offered a four-pronged approach to asthma care that will improve outcomes for patients and reduce the burden of this disease on families and society in general. The ap-

proach is practical, patient-centered, and easily adapted to the day-to-day management of asthma by all clinicians. Using tools such as spirometry for diagnosis and follow up, advice on environmental avoidance of respiratory irritants, and step-up pharmacologic care, as well as empowering a patient with self-management skills, will optimize asthma care, thereby reducing morbidity and mortality.

REFERÊNCIAS

1. Global strategy for asthma management and prevention (GINA) updated December 2011. Available at http://www.ginasthma.org/uploads/users/files/GINA_Report_2011.pdf
2. Braman SS The Global Burden of asthma Chest 2006;130;4S-12S
3. WHO asthma fact sheet #307 May 2011 Available at www.who.int/entity/mediacentre/factsheets
4. Fuhrman C, Dubus JC, Marguet C, et al. Hospitalizations for asthma in children are linked to undertreatment and insufficient asthma education J Asthma. 2011;48:565-71.
5. Stupka E, deShazo R Asthma in seniors: Part 1. Evidence for underdiagnosis, undertreatment, and increasing morbidity and mortality. Am J Med. 2009;122:6-11.
6. Backer V, Nolte H, Pedersen L et al. Unawareness and undertreatment of asthma: follow-up in a different geographic area in Denmark. Allergy. 2009; 64:1179-84.
7. de Benedictis D, Bush A. The challenge of asthma in adolescence. Pediatr Pulmonol. 2007;42:683-92.
8. Mattos W, Grohs LB, Roque F, et al. Asthma management in a public referral center in Porto Alegre in comparison with the guidelines established in the III Brazilian Consensus on Asthma Management. J Bras Pneumol. 2006;32:385-90.
9. Braman SS, Hanania NA. Asthma in older adults. Clin Chest Med. 2007 ;28:685-702.
10. Masoli, M, Fabian, D, Holt, S, et al Global Initiative for Asthma (GINA) program: the global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59,469-478
11. Ashrad SH. Primary prevention of asthma and allergy J Allergy Clin Immunol. 2005;116:3-14
12. Gaffin JM, Phipatanakul W. The role of indoor allergens in the development of asthma. Curr Opin Allergy Clin Immunol. 2009;9:128-35
13. Sporik R, Holgate ST, Platts-Mills TA, et al. Exposure to house-dust mite allergen(Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med 1990;323:502–7.
14. Vervloet D, Charpin D, Haddi E, et al. Medication requirements and house dust mite exposure in mite-sensitive asthmatics. Allergy 1991;46:554–8
15. Piacentini GL, Martinati L, Fornari A, et al. Antigen avoidance in a mountain environment: influence on basophil releasability in children with allergic asthma. J Allergy Clin Immunol 1993;92:644–50.
16. Simon HU, Grotzer M, Nikolaizik WH, et al High altitude climate therapy reduces peripheral blood T lymphocyte activation, eosinophilia, and bronchial obstruction in children with house-dust mite allergic asthma. Pediatr Pulmonol 1994;17:304–11.
17. Morgan WJ, Crain EF, Gruchalla RS, et al. Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351:1068–80.
18 Peroni DG, Piacentini GL, Costella S, et al. Mite avoidance can reduce air trapping and airway inflammation in allergic asthmatic children. Clin Exp Allergy 2002;32:850–5.
19 Wood, RA Chapman MD, Adkinson NF, Jr. et al The effect of cat removal on allergen content in household-dust samples J Allergy Clin Immunol. 198;83:730-4
20 Phipatanakul W, Cronin B, Wood RA, et al. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. Ann Allergy Asthma Immunol 2004;92:420–5.
21. Morgan WJ, Crain EF, Gruchalla RS, et al.; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351:1068–80.
22. Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Health Homes Project: a randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. Am J Public Health 2005;95:652–659.
23. Kercsmar CM, Dearborn DG, Schluchter M, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. Environ Health Perspect 2006;114:1574-80.
24. Kattan M, Stearns SC, Crain EF Cost-effectiveness of a home-based environmental intervention for inner-city children with asthma J Allergy Clin Immunol 2005;116:1058-63
25. Abbey DE, Petersen F, Mills PK, Beeson WL. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. Arch Environ Health 1993;48:33–46.
26. Moseholm L, Taudorf E, Frosig A. Pulmonary function changes in asthmatics associated with low-level SO2 and NO2 air pollution, weather, and medicine intake. An 8-month prospective study analyzed by neural networks. Allergy 1993;48:334–44.
27. Garrett MH, Hooper MA, Hooper BM, Rayment PR, Abramson MJ. Increased risk of allergy in children due to formaldehyde exposure in homes. Allergy 1999;54:330–7.
28. Jaakkola JJ, Parise H, Kislitsin V, Lebedeva NI, Spengler JD. Asthma, wheezing, and allergies in Russian schoolchildren in relation to new surface materials in the home. Am J Public Health 2004;94:560–2.
29. Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. Association of domestic exposure to volatile organic compounds with asthma in young children. Thorax 2004;59:746–51.
30. Garrett MH, Hooper MA, Hooper BM, Abramson MJ. Respiratory symptoms in children and indoor exposure to nitrogen dioxide and gas stoves. Am J Respir Crit Care Med 1998;158:891–5.
31. Withers NJ, Low L, Holgate ST, et al. The natural history of respiratory symptoms in a cohort of adolescents. Am J Respir Crit Care Med 1998;158:352–7.
32. Howden-Chapman P, Pierse N, Nicholls S et al. Effects

of improved home heating on asthma in community dwelling children: randomised controlled trial. BMJ. 2008;337:469-476
33. Ostro BD, Lipsett MJ, Mann JK, Wiener MB, Selner J. Indoor air pollution and asthma. Results from a panel study. Am J Respir Crit Care Med 1994;149(6):1400–6.
34. Chaudhuri R, Livingston E, McMahon AD,et al Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med. 2006;174:127-33
35. Chalmers GW, Macleod KJ, Little SA, et al Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax. 2002;57:226-30
36. 40. Sippel JM, Pedula KL, Vollmer WM, et al Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. Chest 1999;115(3):691–6.
37. Ehrlich R, Jordaan E, Du TD, et al Household smoking and bronchial hyperresponsiveness in children with asthma. J Asthma 2001;38:239–51.
38. Radon K, Busching K, Heinrich J, et al. Passive smoking exposure: a risk factor for chronic bronchitis and asthma in adults? Chest 2002;122:1086–90.
39. Malo JL, Lemiere C, Gautrin D, et al. Occupational asthma. Curr Opin Pulm Med 2004; 10:57-61
40. Tarlo SM, Balmes J, Balkissoon R, et al Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement.Chest. 2008;134(3 Suppl):1S-41S.
41. Juniper EF, Guyatt GH, Feeny DH, et al Measuring quality of life in children with asthma. Qual Life Res 1996;5:35–46.
42. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902–7.
43. Bayliss MS, Espindle DM, Buchner D, et al. A new tool for monitoring asthma outcomes: the ITG Asthma Short Form. Qual Life Res 2000;9:451–66.
44. Marks GB, Dunn SM, Woolcock AJ. An evaluation of an asthma quality of life questionnaire as a measure of change in adults with asthma. J Clin Epidemiol 1993;46:1103–11.
45. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the Asthma Control Test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59–65.
46. Pereira ED, Cavalcante AG, Pereira EN, et al Asthma control and quality of life in patients with moderate or severe asthma. J Bras Pneumol. 2011;37:705-711 Asthma control improves quality of life.
47. Ring N, Jepson R, Hoskins G, et al Understanding what helps or hinders asthma action plan use: a systematic review and synthesis of the qualitative literature. Patient Educ Couns. 2011;85:e131-43.
48. Rabe KF, Vermeire PA, Soriano JB, et al. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J 2000; 16:802–807

Artigo original

Education of the Person with Asthma as a Fundamental Part of the Management Strategy

Educação do Indivíduo com Asma como Parte Fundamental da Estratégia de Manejo

Martyn R. Partridge[1]

RESUMO

Os demais capítulos do presente suplemento demonstram os principais avanços na compreensão da patogênese e no manejo ideal da asma nas últimas décadas. Muito desse progresso representa uma compreensão científica amplificada, mas a extrapolação e a implementação dessa compreensão, apesar de levar a melhoras, geralmente reflete a atividade da indústria farmacêutica na produção e na promoção de medicamentos eficazes. Em muitos países, isso levou a uma queda no número de mortes por asma e, em parte deles, à redução no número de hospitalizações causadas por exacerbações. Agora, entretanto, esse declínio se estabilizou, e uma melhoria dos desfechos somente deverá ocorrer se os médicos abraçarem componentes não prescritivos do cuidado ao asmático de forma mais ampla. Tais componentes incluem aumentar a comunicação, dividir o processo decisório, apoiar o automanejo e tornar o acompanhamento mais simples e conveniente. Esta revisão foca um desses componentes — que é vital dentro desse grupo de cuidados — o automanejo.

Descritores: Asma/terapia; Autocuidado; Tomada de decisões; Educação de pacientes como assunto.

ABSTRACT

As the other chapters in this asthma supplement have demonstrated, there have been major advances in the understanding of the pathogenesis and the optimal management of asthma over the last few decades. Much of that progress represents enhanced scientific understanding, but extrapolation and implementation of that understanding, whilst leading to improvements, often reflects the activity of the pharmaceutical industry in producing and promoting efficacious medications. In many countries, this has led to a decrease in the number of those dying from asthma and in the number of those being admitted to hospital with exacerbations. That decline may now have plateaued, and further improvement in outcomes is only likely to occur if doctors embrace the wider non-prescription elements of care. Such elements include everything from enhanced communication, shared decision-making, self-management support, and easier, more convenient follow up. This review concerns one vital element of that wider package of care, namely self-management support.

Keywords: Asthma/therapy; Self care; Decision making; Patient education as topic.

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It is possible to find several definitions of self-management within the published literature. Some suffix the term as self-management *education*, whereas others would regard this as being pejorative, as it implies inadvertently that our clients are "uneducated". We should instead think of this subject as being self-management support and it is important from the outset to stress that any such intervention is of limited value unless it is associated with a resulting sustained behavioural change by the patient.

One recent study of patients with asthma surveyed 1,022 patients with asthma in five European countries (1). The survey was concerned with patient expectations of their interaction with health care professionals. As one part of that study, those with asthma were asked to recount how often they went to see their general practitioner for review of their asthma and their recalled duration of the consultation: 83% of those with asthma surveyed in the five European countries reported that they had been to their general practitioner for review of their asthma. However, the frequency of attending was a median of every 13.4 months and patient recall of the average duration of each consultation was 12 minutes. If we recalculate these data, we can see that for 364 days, 23 hours and 49 minutes of each year, the person with asthma looks after their own condition themselves. This is thus the reality as to why self-management support is so important, because patients are self-managing their condition for the vast majority of the time. As international guidelines so clearly stress, it is thus our responsibility as health professionals to provide those with asthma with the tools, skills, and knowledge which they need to enable them to look after themselves appropriately for all but the 12 or 13 minutes a year when they are sitting alongside us in our consulting rooms.

In the same study, those with asthma regarded the most important aspects of their relationship with their doctor as having doctors who did the following:

• listened carefully when I talked about my symptoms and problems

• understood what I was trying to express

• explained clearly what my condition is and the problems it can cause

• devoted an appropriate amount of time to the visit

• explained clearly how to use the inhaler

• explained clearly the possible side effects of medication

• understood clearly what concerns me

• offered me support to help me manage my own condition

• consulted me regarding the choice of inhaler

The concept of self-management support is not new. In the Guidelines for Management of Asthma in Adults (section 1: Chronic Persistent Asthma), published in the British Medical Journal in 1990 (2), it is clearly stated that "as far as possible patients should be trained to manage their own treatment rather than be required to consult their doctor before making changes". However, if we fast forward a decade or two, from 1990 to 2007, we can find studies (3) that look at whether practices comply with key recommendations of the British Asthma Guidelines and find that the major recommendations such as those concerning self-management are still not being implemented. If receipt of a written action plan is used as a marker of whether the patient received self-management support, only 23% of patients surveyed had had this recommendation applied to their care.

When health professionals were questioned as to what the barriers to offering self-management support were, they reported the following:

• doubt about whether the evidence applied to them in primary care

• that they lacked the knowledge and skills to implement this recommendation

• misconceptions about what it involved

• perceived lack of time

• non-availability of resources, such as templates upon which advice is written

• poor teamwork (a doctor thinking that a nurse had offered such support and the nurse in question thinking the opposite)

We therefore need to think about ways in which we can help busy health professionals give advice. That is an issue that was addressed in studies by Roberts et al. (4,5), who devised a simple computer programme that permitted the doctor and patient sitting together to construct a pictorial asthma action plan (Figure 1), which permitted the patient to receive advice about their usual therapy, when they should increase their therapy, when they should start a course of steroid tablets for asthma (or antibiotics or steroids, or both, for COPD: Figure 2) and when they should seek urgent medical attention. These simple programmes can be downloaded for free (http://www1.imperial.ac.uk/medicine/people/m.partridge/) and address the barriers outlined in the earlier survey, in that they provide an easily available template upon which advice can be given and they prompt the health professional as to the correct information to give the patient.

These plans include pictorial representations of a patient's usual medication and pictorial depictions of features suggesting deteriorating asthma and the action one should take. Such pictorial representations help to overcome the problems associated with impaired health literacy. Those with limited literacy skills present with the following (6):

• poorer overall health

• a lower likelihood to make use of screening

• later stages of disease

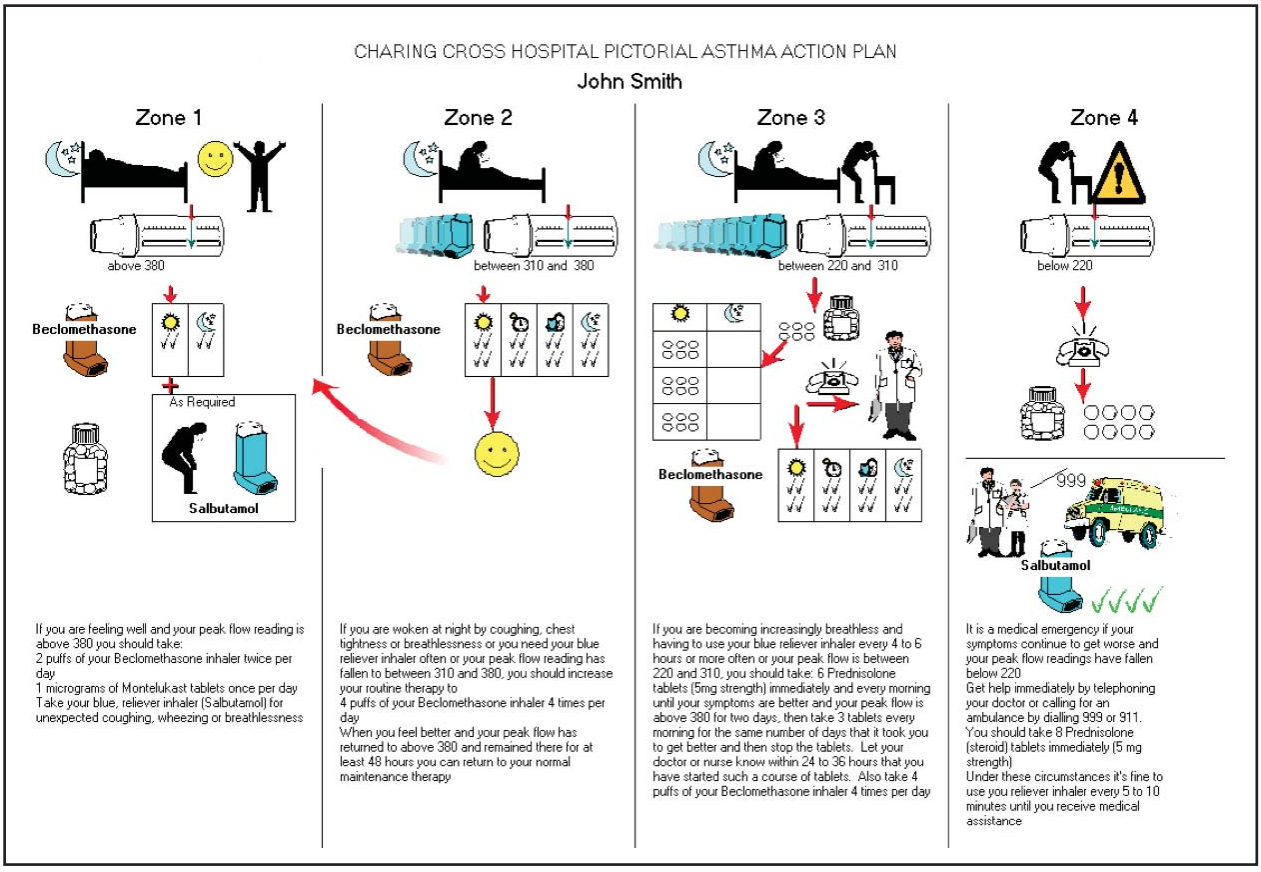

Figure 1 - The Electronic Asthma Action Plan.
Source: http://www1.imperial.ac.uk/medicine/people/m.partridge/

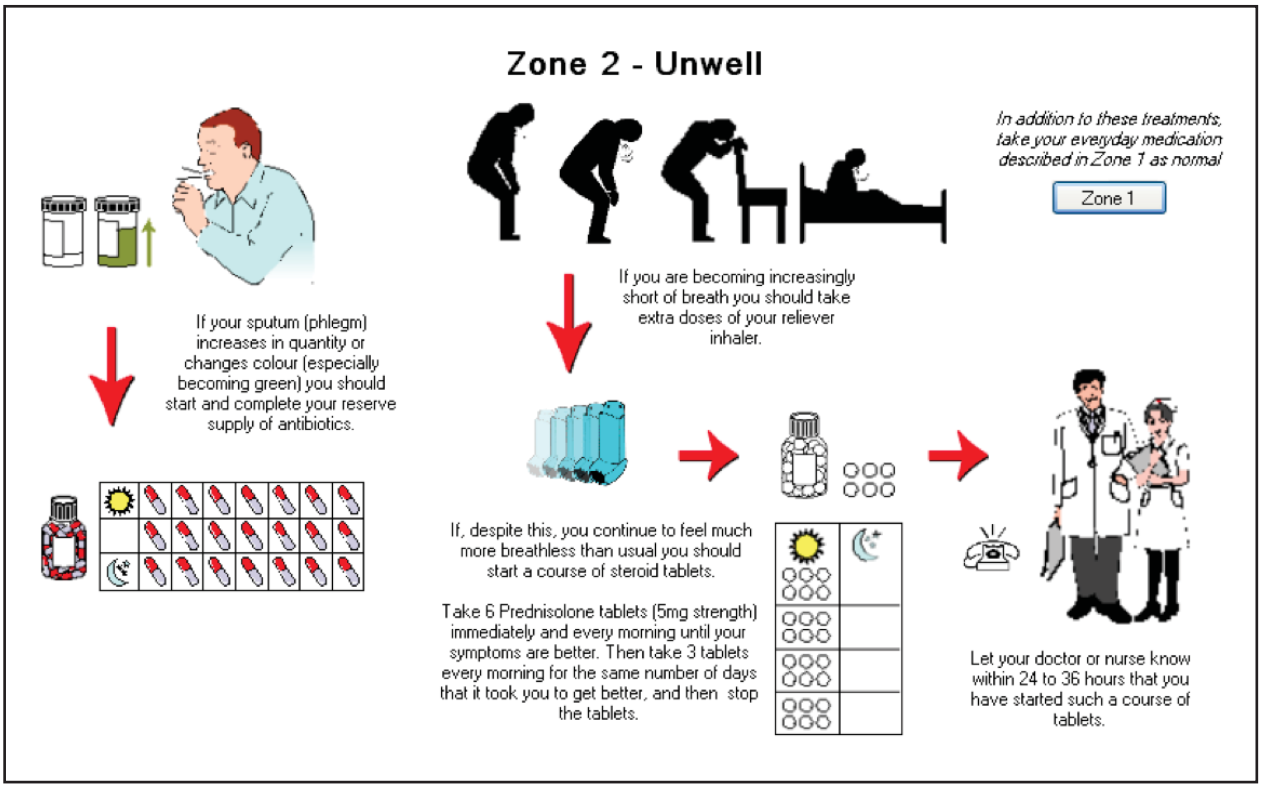

Figure 2 - Part of the Electronic COPD Action Plan.
Source: http://www1.imperial.ac.uk/medicine/people/m.partridge/

- a greater likelihood of being hospitalised
- a poor understanding of treatment
- lower adherence to medical regimens

Others have also described quite detailed pictorial prescription charts for those with limited literacy, including examples where pictorial advice is given not only about when to take the medication but also about what each pill is for (7). More recently, Ghiassi et al. published a pictorial Epworth Sleepiness Scale, which gets round the problems encountered in sleep clinics when patients cannot satisfactorily complete the more traditional written Epworth Sleepiness Scale (8). This use of pictorial representations to give advice to patients for both self-management and other reasons has been shown conclusively to improve patient comprehension and compliance (9).

Is all of this effort appropriate for those with impaired literacy and does it improve their self-management skills? That is a question that was tackled in a large study conducted by Paasche-Orlow et al. (10), who found that 22% of patients hospitalised for severe asthma exacerbations had limited health literacy. They offered those patients advice in a more easily assimilated manner and found that the results were equally as good as those achieved in the fully literate. Health professionals thus have a responsibility to ensure that they offer, to all patients, information about self-management in a useful manner.

Are other sources of information used? In the European study cited earlier (1), the patients were also asked from whom they sought certain information about asthma. Of the asthma patients evaluated, 58% reported that their first source of information was the doctor who was treating their lung condition, although 65% reported that they sought information from the Internet. However, less than 5% of the patients reported having had any website recommended to them by a doctor or a nurse. We should therefore consider recommending respected websites as a source of confirmatory information for our patients.

Are there other interventions we should be promoting in addition to self-management support? Self-management support for those with asthma carries Grade A evidence in all international guidelines, and we have so far considered ways in which we might enhance its implementation. However in addition to self-management support, the evidence is now increasingly strong that *shared decision-making* is important. In one large study, patient desire to be involved in choosing the inhaler they used was prominent (1). Wilson et al. (11) looked in great detail at whether such shared treatment decision-making improves adherence and outcomes in poorly controlled asthma. In a study of 612 patients with poorly controlled asthma, the patients were randomised to usual care or shared decision-making. The latter involved the doctor very carefully eliciting patient goals for treatment and their relative priorities regarding symptom control. They discussed with the patient their desires regarding how convenient the therapeutic regimen should be and the amount of concern they had about the costs of any medications. The health professional then showed the patient a list of all available treatments, both devices and dosing, and, using a work sheet, the clinician and patient together worked out the pros and cons of each treatment regimen before a decision was made. The main outcome measure of that study was adherence to treatment. The results were better for all classes of medication, the need for unscheduled healthcare was less, and quality of life was improved. In addition, this had a long-lasting effect on patient behaviour, because, at two years out, short-acting beta agonist use was still significantly less in the intervention group than in the control group.

If self-management support is to be effective, it is not a delegation of responsibilities to the patient, and health professionals need to make themselves easily available for further advice by the patient when needed. However, we do need to make that convenient for patients. Nevertheless, studies of the reason why patients with lung disease do not return for follow up, such as that conducted by Van Baar et al. (12), show that patients do not return to follow up, sometimes because they forget, sometimes because they did not see the same doctor each time, but note the one further important cause why patients did not come for specialist review was that they were "kept waiting last time". We therefore need to make follow up convenient and remind ourselves that many of these patients have had asthma for ten, twenty, forty or more years, and keeping them waiting and seeing them at inconvenient times is not conducive to patients wanting to come back for review of their condition.

There is very good evidence now that telephone consultations can be equally effective and satisfactory for patients, as well as being much more convenient (13). We need to offer that form of follow up much more often to our patients with these common lung disorders.

The evidence is now of such strength that all respiratory physicians need to move on from the making of a diagnosis and the writing of a prescription alone to accepting the wider responsibilities for these issues such as the way in which we organise care, the methods by which we offer patients specialists review, and, of greatest importance, the way in which we address and implement shared decision-making and meaningful self-management support.

REFERÊNCIAS

1. Partridge MR, Dal Negro RW, Olivieri D. Understanding patients with asthma and COPD: insights from a European study. Prim exploratory qualitative study. Prim Care Respir J 2011; 20:315-23.
2. Guidelines for management of asthma in adults: 1-Chronic persistent asthma. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, Ki n g s Fu n d Cen t r e , Na t i o n a l Asthma Campaign. BMJ 1990; 301:651-3.
3. Wiener-Ogilvie S, Pinnock H, Huby G, Sheikh A, Partridge MR, Gillies J. Do practices comply with key recommendations of the British asthma guideline? If not, why not? Prim Care Respir J 2007:16:369-77.
4. Roberts NJ, Evans G, Blenkhorn P, Partridge MR. Development of an electronic pictorial asthma action plan and its use in primary care. Patient Educ Couns 2010; 80:141-6.
5. Roberts NJ, Mohamed Z, Wong PS, Johnson M, Loh LC, Partridge MR. The development a n d comp r e h en s i b i l i t y o f a p i c t o r i a l asthma action plan. Patient Educ Couns 2009; 74:12-8.
6. Centre for Health Care Strategies. Health literacy fact sheets [Online]. 2002 [cited on October 10, 2011]. Available from URL: http://www.chcs.org/resource/hl.html
7. Kripalani S, Robertson R, Love-Ghaffari MH, Henderson LE, Praska J, Strawder A, et al. Development of an illustrated medication schedule as a low-literacy patient education tool. Patient Educ Couns 2007; 66:368-77.
8. Ghiassi R, Murphy K, Cummin AR, Partridge MR. Developing a Pictorial Epworth Sleepiness Scale. Thorax 2010; 66:97-100.
9. Dows e R, Ehl e r s M. Medicine labels incorporating pictograms: do they influence understanding and adherence? Patient Educ Couns 2005; 58:63-70.
10. Paasche-Orlow MK, Riekert KA, Bilderback A, Chanmugam A, Hill P, Rand CS, et al.Tailored education may reduce health literacy disparities in asthma self-management. Am J Respir Crit Care 2005; 172:980-6.
11. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision-making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care 2010; 181:566-77.
12. Van Baar JD, Joosten H, Car J, Freeman GK, Partridge MR, van Weel C, et al. Understanding reasons for asthma outpatient (non) attendance and exploring the role of telephone and e-consulting in facilitating access to care: exploratory qualitative study. Qual Saf Health Care 2006; 15: 191-5
13. Roberts N, Partridge MR. Telephone consultations in secondary care. Respir Med 2007; 101: 1665-9.

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Resumos

2. Saddy F, Oliveira G, Rzezinski AF, Ornellas DS, Garcia CSN, Nardelli L, et al. Partial Ventilatory Support improves oxygenation and reduces the expression of inflammatory mediators in a model of acute lung injury. Am J Respir Crit Care Med. 2008; 177:A766.

Capítulos de Livros

3. Barbas CS, Rocco PR. Monitorização Da Mecânica Respiratória em Indivíduos respirando espontaneamente e ventilados mecanicamente. In: Rocco PR; Zin WA, editores. Fisiologia Respiratória Aplicada. 1 Edição. Rio de Janeiro: Guanabara Koogan; 2009, p. 193-206.

Publicações Oficiais

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Homepages/Endereços Eletrônicos

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: **http://www.cancer-pain.org/**

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