Milestones in asthma management

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Abstract

Background: Asthma is an old and common disorder of respiratory function whose prevalence is increasing everywhere particularly in urban centres. This situation, coupled with the problem of suboptimal management has led to an increase in the morbidity of the disease and enormous economic losses through lost productivity and absenteeism from work and schools. There is therefore a need to review the evolution of the management of this disease with a view to drawing attention to currently recommended management guidelines. This should help to improve the outlook for the asthma patient and hopefully reduce the morbidity and mortality of this rampant disease.

Methods: A review of the literature regarding the history of asthma and the evolution of its management was undertaken with the aid of textbooks, journal publications and the Internet via Google Pubmed. The history of asthma and the evolution of the management of asthma was surveyed with emphasis on major and spectacular developments particularly in respect of chronic asthma.

Results: Asthma management started from the naming of the disorder, a description of its pathogenesis, pathology and attempts at the therapy of the disease with a variety of agents notably adrenaline, noradrenaline and cortisone. This was followed by the invention of various drug delivery systems and the discovery of salbutamol and cromoglycate. The invention of the bronchoscope led to the development of anti-inflammatory drugs like inhaled corticosteroids and leucotriene antagonists while the discovery of the synergy between salmeterol and fluticasone (an inhaled corticosteroid), made possible the development of combination therapy. Guidelines were devised to ensure the optimal management of the disease through the proper classification of the disease according to severity as well as the efficient utilization of available effective therapies.

Conclusion: Although asthma management began in the pre-christian era, the most spectacular and revolutionary developments occurred during the last 55 years and include the discovery of various drug delivery systems, salbutamol, combination therapy and the development of asthma management guidelines.

Key words: Asthma, Management, Developments, Guidelines

Introduction

Asthma is a disorder characterized by variable airflow obstruction; symptoms of wheeze, cough, dyspnoea, and chest tightness; reversibility to bronchodilators and corticosteroids; increased airway responsiveness to a variety of stimuli; and evidence of inflammation in which eosinophils, mast cells and lymphocytes together with a multitude of cytokines have important roles. The prevalence of asthma is increasing everywhere but is generally higher in Europe and North America than in Asia and Africa, in warmer climates than in colder regions like the Scandinavian countries and in certain countries like Australia and New Zealand. There is also evidence that the prevalence is higher in urban than in rural areas and in more westernized countries.

In its latest report, based on a comprehensive survey of the prevalence and impact of asthma
around the world using standardized data collected in epidemiological studies in over 80 countries, the Global Burden of Asthma Report noted that about 300 million people currently have asthma worldwide with sub-Saharan Africa having 50 million and South Africa having the highest prevalence rate of 8% in Africa. It also observed that social and economic factors including limited access to health care are major contributors to rising morbidity and mortality in Africa. Another factor cited by this report, is the lack of adherence to WHO recommended management guidelines for asthma in many African countries.

**Pathogenesis**

The disorder is believed to result from an interaction between a susceptible individual and suitable environmental factors. The most important predisposing factor appears to be atopy while various mineral, animal and vegetable dusts constitute the sensitizers and triggers of the disease. The requisite interaction involves T-lymphocyte-dependent immunological mechanisms and a variety of inflammatory cells like mast cells, eosinophils and lymphocytes which in conjunction with a host of cytokines and inflammatory mediators like histamine, platelet activating factor, leucotrienes and prostaglandins produce airway inflammation, smooth muscle contraction and airway remodelling.

In view of the common problem of suboptimal management and the consequent rising morbidity and mortality from this disease especially in sub-Saharan Africa, there is a need to review the management of this common disease in order to emphasize currently recommended management options and their rationale. This should help to reduce the morbidity and mortality of the disease.

**The history of asthma**

The name “asthma” which means “panting” was coined by the Greeks who also thought the disorder was caused by the blockage of the air passages of the lungs by an excess of phlegm. This was thought to occur as a result of an imbalance between phlegm and bile, the two principal humours of the body. Hippocrates ascribed this imbalance to a combination of constitutional and environmental factors. The Chinese made reference to the combination of constitutional and environmental factors. The Chinese made reference to the treatment of asthma with the plant *Ma huang* which in later times was found to contain adrenaline. But it was the Egyptians who made the first written reference to the disease in 1550BC in ancient Egypt which thus became the cradle of asthma literature as well as the cradle of civilization.

Other noteworthy early developments include the first accurate description of the pathology of asthma by Thomas Willis (1621-1675); the development of the concept of bronchial hyperreactivity by Salter in 1864; the synthesis of isoprenaline in 1940 by Konzette; the first use of cortisone in the therapy of asthma by Carryer in 1948 and the discovery of alpha and beta receptors by Alquist in 1949. These early references and discoveries could be regarded as the first milestone in asthma management as they not only identified the disease as an entity, but also paved the way for later developments and milestones.

**The metered dose inhaler (MDI), Cromoglycate and Salbutamol**

The discovery of the first MDI in 1956 was a major development in asthma management as it enabled measured doses of drugs to be delivered directly and quickly into the airways the seat of asthma. In the course of time other drug delivery systems like the Spinhaler, Rotahaler, Accuhaler, Turbohaler and the Nebuliser were invented. This important development coincided with the discovery in the early 1960's by Altouyan of sodium cromoglycate, a drug that reduced the asthmatic response to inhaled allergens in sensitized individuals. This discovery demonstrated that asthma control was not just about bronchodilators but also about controlling the basis of the broncho-constriction. At about the same time, researchers at Allen and Hanburys, which eventually became part of GlaxoSmithKline (GSK) were searching for that illusive beta agonist which could relax the smooth muscle of the airways without affecting the heart muscle. This search produced inhaled salbutamol (Ventolin) in 1969.
the first drug specifically targeted at the \( \beta_2 \) agonist receptor \(^{31}\). This landmark discovery brought tremendous relief to the wheezing patient by virtue of its ability to produce rapid relaxation of bronchial smooth muscle and bronchodilatation. It however failed to deal with the underlying problem in asthma about which little was known at that time.

**The bronchoscope and beclomethasone dipropionate (BDP)**

The invention of the bronchoscope, an instrument for visualizing the asthmatic airways and observing the underlying inflammatory process at work, provided the pathological basis and rationale for the next milestone in asthma management: the first inhaled corticosteroid (ICS), beclomethasone dipropionate (BDP) in 1972 \(^{33,34}\). This development made it possible to deliver the drug as quickly as possible whenever needed. The local concentration could be high yet systemic absorption minimal and the side-effects of steroid therapy avoided. Earlier attempts to deliver other steroids like hydrocortisone and dexamethasone in aerosol form into the airways resulted in significant systemic absorption and troublesome systemic side-effects \(^{34}\). BDP then became the only steroid to be effectively delivered by aerosol through an MDI to the airways without significant systemic side-effects. In the course of time similar inhaled corticosteroids like fluticasone and budesonide were developed.

**The period of doubt and debate**

Although the discovery of BDP and other inhaled steroids was remarkable, in view of their obvious benefits, many doctors and patients regarded them with considerable concern during the 1960's due to the phenomenon that later came to be known as "cortico-phobia". This was because of the problem of adverse effects such as growth suppression in children \(^{35-37}\). This led to a long period of debate about their usefulness during the 1980's and 1990's against a backdrop of clinical studies. There was also debate about the safety of regular doses of \( \beta_2 \) agonists. Studies in New Zealand, Canada and other countries appeared to suggest a link between their regular use and increased risk of death as well as loss of control of asthma. There was also a suggestion that \( \beta_2 \) agonists may not be directly responsible for these deaths but may just have been a marker for more severe asthma \(^{38-46}\).

In the course of time a number of studies \(^{47-56}\), demonstrated the effect of regular treatment with inhaled steroids in the reduction of the risk of hospital admissions, the prevention of exacerbations, near fatal and fatal episodes of asthma and accelerated loss of lung function. These studies also emphasized the importance of the initiation of therapy with inhaled steroids early in the course of the disease. One of the studies showed that early intervention with inhaled steroids may lead to long term remission of the disease \(^{47}\).

Inhaled corticosteroids have been referred to as the "gold standard" for asthma treatment in a report by an expert panel based on the analyses of findings from 180 studies regarding the benefits and adverse effects of inhaled steroids in asthma. A report whose conclusion is that the benefits far outweigh the risks \(^{56}\). All these studies tend to suggest that the asthma deaths previously thought to have been due to heavy use of \( \beta_2 \) agonists might have been due to a lack of use or under use of steroids.

**Long-acting \( \beta_2 \) -agonists (LABA)**

The introduction of Salmeterol in 1991 and relevant clinical studies \(^{57-65}\) showed that the molecule was effective in reducing exacerbations and asthma deaths. This development was another milestone in asthma management.

**Combination therapy and synergy**

A landmark paper by Nelson et al \(^{66}\) drew attention to the synergism of a steroid molecule, Fluticasone propionate (FP) and Salmeterol, a long-acting \( \beta_2 \) agonist in asthma control. The mechanisms involved include the attachment of inhaled FP to the genes controlling \( \beta_2 \) receptor production and causing a marked increase in the synthesis of new \( \beta_2 \) receptors thereby increasing the potential for
greater bronchodilatation. Salmeterol on its part facilitates and increases the inflow of activated steroid-receptor complexes into the nuclei of inflammatory cells thereby attenuating their proliferation and subsequent production of inflammatory mediators. This results in consistently enhanced anti-inflammatory action.

Combination therapy with an inhaled corticosteroid (ICS) and a long acting beta, agonist (LABA) became the next major milestone in asthma management. Landmark studies like the Gaining Optimal Asthma Control Study (GOAL) and others have demonstrated a better control of symptoms, greater reduction in exacerbation rates and improved lung function as well as quality of life with combination therapy compared with either drug used separately. Such studies also showed that such better control could be achieved with a smaller dose of steroids with combination therapy.

The need for guidance

With more treatments available and with the development of more efficient and effective drug delivery systems, there was a need for guidelines regarding the optimal use of these inventions. Guidelines are aimed at providing guidance for the non-specialist, improving national and international asthma management and aiding the specialist with reviewed evidence. Their ultimate objective is to achieve optimal disease control as evidenced by the following:

1. Minimal chronic symptoms including nocturnal symptoms
2. Minimal episodes of exacerbations (attacks)
3. No emergency visits
4. Minimal need for rescue (β₂ agonist) medication
5. No limitations on activities including exercise
6. Peak Expiratory Flow (PEF) variability less than 20%
7. Near normal or normal PEF and
8. Minimal or no adverse drug effects

Guidelines should be tailored to the particular or peculiar circumstances of individual patients or

Table 1. Classification and treatment of asthma based on GINA guidelines

<table>
<thead>
<tr>
<th>Level of severity</th>
<th>Clinical features</th>
<th>Lung function</th>
<th>Lung function Variability</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent Asthma</td>
<td>Days with symptoms &lt; 1/week. Nights with symptoms ≤ 2/month</td>
<td>FEV, OR PEF or (Predicted) ≥ 80%</td>
<td>&lt; 20%</td>
<td>Inhaled SABA as needed or Inhaled Anticholinergic Or short Acting Oral beta₂ agonist as needed Or short Acting Theophylline as needed.</td>
</tr>
<tr>
<td>Mild Persistent Asthma</td>
<td>Days with symptoms ≥ 1/week. Nights with symptoms &gt; 1/day</td>
<td>FEV, OR PEF or (Predicted) ≤ 80%</td>
<td>20 - 30</td>
<td>Daily I.C.S. e.g BDP 200 500µg Or equivalent or Cromone Plus SABA as Needed Or short acting Oral beta₂ agonist OR short Acting Theophylline as needed.</td>
</tr>
<tr>
<td>Moderate Persistent Asthma</td>
<td>Days with symptoms &gt; 1/week. Days with symptoms &gt; 1/week.</td>
<td>FEV, or PEF or (Predicted) 60 - 80%</td>
<td>&gt; 30%</td>
<td>Daily I.C.S. e.g BDP 500 1000µg Or equivalent plus inhaled LABA OR LTRA plus Reliever medication as in mild Persistent Asthma</td>
</tr>
<tr>
<td>Severe Persistent Asthma</td>
<td>Daily symptoms. Frequent exacerbations. Frequent Night symptoms</td>
<td>FEV, OR PEF or (Predicted) ≤ 60%</td>
<td>&gt; 30%</td>
<td>Daily I.C.S. &gt; 1000µg BDP or equivalent plus inhaled LABA plus (if needed) SR Theophylline OR LTRA or oral steroid plus Reliever Therapy as in mild Persistent Asthma</td>
</tr>
</tbody>
</table>

Key

BDP = Beclomethasone Dipropionate
LABA = Long Acting Beta₂ Agonist
SR = Slow Release
SABA = Short Acting Beta₂ Agonist
ICS = Inhaled Corticosteroid
PEFR = Peak Expiratory Flow Rate
LTRA = Leucotriene Receptor Antagonist
FEV = Force Expiratory Volume in one second
Countries according to the availability of financial resources and medical services and resources \(^{73,74}\). Although there have been numerous national guidelines like the British, Canadian, Australian and Swedish guidelines, the Global Initiative for Asthma (GINA) guidelines, first published in 1995 and revised in 2003 has proved to be the most popular and widely acceptable \(^{73,74}\). They provided a guide for asthma management based on disease severity a step wise approach to treatment. The recommendation was to initiate treatment at the level of therapy needed to achieve control and then to step down once this has been achieved or step up if there is failure of control. GINA also identified control of the disease in all respects including symptoms, physiology and pathology which together constitute total or optimal control. It also emphasized patient education and the control of environmental factors. Table 1 shows the GINA classification of asthma according to disease severity and the recommended treatment for each level of severity.

**Future problems and prospects**

Since asthma results from the interaction between a susceptible individual and a suitable environment it is logical and reasonable to expect that the prevention or optimal control of this common health problem will depend on the optimal manipulation of the two arms of the asthma equation the asthmatic and his environment or the interaction of the two. In this regard some goals may be possible and achievable while others may be possible but difficult or very difficult to attain.

The interaction aspect of the equation, namely the therapy of the disease appears to be the most amenable to further manipulation and improvement. This may take the form of better drug delivery systems; longer acting and more potent beta, agonists and anti inflammatory drugs requiring a once daily dose regimen in order to encourage better compliance \(^{55}\); government driven subsidization of asthma treatments to enable all asthmatics especially in the poorer countries of Africa to avail themselves of these effective drugs and more intensive and frequent continuing medical education for health care providers to acquaint them with currently recommended asthma management guidelines in order to improve adherence to these guidelines. It is also hoped and expected that various tiers of governments will ensure a more even distribution of wealth, health services and trained personnel in order to improve and facilitate access to health care facilities which has been cited as a major contributor to rising morbidity and mortality from asthma particularly in sub-Saharan Africa \(^{28}\).

The manipulation of the asthmatic individual may be possible, though difficult to achieve. Research on asthma specific genes and biomarkers of inflammation are on-going and may provide a basis in the future for the manipulation of the asthmatic individual \(^{75,76}\). Several studies \(^{77,81}\), have suggested a possible link between exposure to certain viral infections parasitic infections and BCG vaccination in early childhood and the later protection, from asthma the so-called “hygiene hypothesis”. This has been cited as a possible explanation for the urban/rural gradient in asthma prevalence. It may therefore be possible to develop some vaccinations that may prevent the development of asthma through the alteration of the underlying T-lymphocyte dependent immunological mechanisms.

Because asthma is more prevalent in more westernized, more affluent communities \(^{11,17-27}\) compared to rural, more traditional ones, life-style and dietary modifications is another option that may yield positive results in the future. Allergen avoidance and environmental control can help in the reduction of exacerbations but is practically difficult as it will literally entail enclosing the asthmatic individual in a “mobile cage” of pure, clean, dust-free atmosphere. Ingested allergens are however easier to avoid.

The construction of an all encompassing definition of asthma and the development of widely acceptable and standardized criteria for the diagnosis of asthma for epidemiological purposes is showing promising results in the form of the International Study on Allergies and Asthma in childhood (ISAAC) and the European Community Respiratory Health Study (ECRHS) asthma protocols \(^{13,15,82}\). This will help a great deal to permit meaningful comparisons of asthma prevalence data.
from various regions.

A daunting problem in the management of the asthmatic patient is the satisfactory treatment of the severe persistent asthmatic—a problem that is likely to remain as persistent as its name suggests in view of the airway remodelling that has occurred in this group of patients and the poor reversibility that is achievable with currently available anti inflammatory drugs. The early diagnosis of asthma and the early institution of appropriate treatment including ICS can prevent this difficult problem.

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