

Chapter 2:

The relationship between the management and control of asthma in primary health care

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CHAPTER 2

LITERATURE REVIEW

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CHAPTER 2



The horrors of the asthmatic paroxysm far exceed any acute bodily pain; the sense of impending suffocation, the agonizing struggle for the breath of life, are so terrible, that they cannot even be witnessed without sharing in the sufferer's distress. With a face expressive of the intensest anxiety, unable to move, speak, or even make signs, the chest distended and fixed, the head thrown back between elevated shoulders, the muscles of respiration rigid and tightened like cords, and tugging and straining for every breath that is drawn, the surface pallid or livid, cold and sweating – such are the signs by which this dreadful suffering manifests itself.

--- Henry Hyde Salter, *On Asthma: Its Pathology and Treatment*, 1821

The story of asthma: proves to be ancient and uncertain, even when it is seen as a modern disease. Since Hippocrates, Homer's *Iliad* and Henry Hyde Salter (460 B.C -1871), the George Ebers Papyrus in hieroglyphics (1870s), up until today, asthma in principle has remained only a single most useful clinical entity in an individual's management (Marketos & Ballas, 1982:263). The comprehension of the natural history of asthma (even more so in the populations of primary care) is intricate, with disease biological knowledge and clinical management not matching up (WinklerPrins *et al.*, 2004:110).

After all these years of research and development, the natural history of asthma still remains an abstruse mystery of chronic disease or syndrome. Is it merely shortness of breath, a wheeze, atopy or a phantasm?

Defining asthma accurately, continues to be problematic, an unsolved problem on clinical, epidemiological and physiological levels. There is no definite succour for asthma, no gold ensign or single test to define or measure it accurately and no way to comprehend the quota of treatment necessary or the duration of therapy (Keirns, 2004; Ruffin *et al.*, 2005:S38; WinklerPrins *et al.*, 2004:110). Even the fluctuating asthma prevalence leads to uncertainties (Anderson, 2005:1037; Bousquet *et al.*, 2005:549; Furlong, 1999; Woolcock & Peat, 1997:122).

Asthma is a common illness worldwide that made progress in research, with improved condition detection and advances in treatment, but still it remains mainly uncontrolled. It is even complicated more by the level of undiagnosed asthma (WHO, 2009). Furthermore it touches on intertwined relationships of technological medicine, converse relations between diseases and its treatment, and the great social trends in outlining the experience of shortness of breath and wheezing (Keirns, 2004:xiv).

All of this tends to leave substantial space for interdisciplinary arguments, since differences in tools and ideas have frequently translated into different visions of the disease and disputes about treatment indications. Nowadays treatment is aimed at triggers and symptoms, whereas back in history, patients were recommended to visit the Mediterranean coast or the Swiss mountains, later even told to use cocaine or inhale some remedy, but yet there is no direct cause management. Murray (2008:77) summarises the work on inhaled corticosteroids (ICS) by saying that it is only “controlling symptoms” but not altering the cause.

2.1 INTRODUCTION

Chapter one presented with an effigy of the problems faced by health care providers (HCPs) in a primary health care study area, by introducing and outlining the background and significances of asthma control and quality of care provided.

A critical step in the process of research is a literature review which allows researchers to do research within an existing knowledge field, hereby preventing unnecessary duplication of work. The transformations of asthma across time and space and the tremendous amount of problems around these areas were explored.

To try and make out anything about asthma and its vast expanse of consequences, it is always a good idea to start right at the beginning. This would be to start with ABC: airways, breathing and clinical presentation.

*“At first glance, asthma seems easy to treat,
but under the surface, it’s a complex disorder ---
involving environment, the immune system,
family history and the lungs.”*

*--- Mike Tringale, director of communications for the
Allergy and Asthma Foundation of America, 2006.*

Airways, in particular bronchial airway mucosa, need a normal homeostasis for efficient and effective functioning. The functioning is dependent on, the complex harmonious interaction between the autonomic neural control and the microvascular network, which is still unclear. A deep breath of air sets off a chain of reactions starting off with activation of the sensory nerves, inducing certain reflexes and triggering vascular processes (e.g. vasodilatation or exudation)(Giovanna *et al.*, 2009:176). The end of this chain is usually a passive muscleless effort of pressure equalisation. What, then, forms the missing link for asthma?

2.2 BACKGROUND TO THE PROBLEM

Undiagnosed (failure to diagnose (Van Weel, 2002:65)) asthma makes out up to one third of all identified asthma cases (Marklund *et al.*, 1999:112), where the majority tends to be female (69% according to the study done in 1988-9 which followed on the study of 1985-6 (Siersted *et al.*, 1998)). Under-treated asthma can be due to under- or misdiagnosis (Gordon, 2008; Marklund *et al.*, 1999:112; Montnémy *et al.*, 2002:365), and can be enervative and grave (Jackson *et al.*, 1988:914), while correct and early diagnosis might lead to proper management, thereby improving the overall prognosis with morbidity and mortality figures to improve on the long run (Van Schayck *et al.*, 2000:562; Van Schayck & Chavannes, 2003:16s; Van Weel, 2002:65). Even in places like New Zealand, where asthma morbidity and mortality has waned, one in seven children and adults demonstrated uncontrolled asthma with almost all of these undertreated (90% failure to treat with long-acting β -agonists, 40% inadequate dosing of inhaled corticosteroids) (Beasley & Masoli, 2003:1174).

Dr. Jeff Garrett claims that after some nitric oxide level testing, it appears that up to 50% of asthma 'labelled' patients have asthma imitated conditions, such as inimical viral infections, functional breathing disorders (FBD)(dyspnoea without airway obstruction) (Marklund *et al.*, 1999:112), vocal cord dysfunction (VCD), even congestive heart failure and many more (Gordon, 2008). Shawn *et al.* (2008:1121) claim that in Canada and developing countries as many as a third of bogus asthmatics (obese or non-obese) were over- or misdiagnosed. This obviously follows the pathway of lost opportunities: not investigating the cause, therefore not treating the cause; missing medication adverse effects; and an increasing impact on cost, social followings and psychological stigmatisation (labelled with a chronic respiratory disease) (Shawn *et al.*, 2008:1121; Sibbald *et al.*, 1994:127; Weiss *et al.*, 1992:862).

Various respiratory conditions present with similar clinical features (e.g. cough, wheezing and dyspnoea), and although there are some outright disparities it remains one of the reasons for misdiagnosis. Distinguishing between these so-called 'pseudo-asthma' conditions (see more details in section 2.6.3) and asthma itself requires a poignant incisive clinical history taking, with an examination focusing on the specific character of the respiratory sounds and other possible add-on features. Special examinations or investigations such as spirometry, exercise testing and determining blood-gas levels can help to come to a justifiable diagnostic conclusion (Piness, 1921:29; Van Weel *et al.*, 2008:999).

One of these asthma imitating conditions is chronic obstructive pulmonary disease (COPD), where even the differences and similarities become controversial (Lazarus, 2001) (inflammation mediators and obstruction reversibility), but where differentiation is of supreme importance for treatment and adverse effects (Crockett, 2000:548; Marklund *et al.*, 1999:112). James F. Donohue (2004:125S) looked at the disparities from the angle of the inflammatory cascade and found that right from the onset of inflammation the two follow a separate pathway. Asthma has an eosinophil predominance with the presence of leukotrienes (C₄; D₄ and E₄) and cytokines (IL-3; IL-4; IL-5 and IL-13), whereas COPD's characteristics lie within the neutrophil predominance with IL-8; tumour necrosis factor-alpha (TNF α) and leukotriene B₄ (LTB₄) as associating factors. These findings are supposed to help with the split of asthma's sequence of therapy versus the treatment of COPD and other respiratory diseases, but according to a survey done all over the UK (2008), 80% of general practitioners still find the asthma-COPD differentiation defiant (The family GP, 2008), since the subdivision of phenotypes prove to make some inflammatory responses overlap, for example: Eosinophilic inflammation and allergic asthma; neutrophilic inflammation, and

refractory asthma and chronic airflow obstruction (Bioportfolio, 2007;Guerra, 2005:7; Sood & Garrett, 2007:24).

<u>Eosinophilic inflammation dominance:</u>	<u>Neutropilic inflammation dominance:</u>
• Atopic asthma (typical), non-atopic asthma (rare)	• Non-atopic asthma (most common)
• Occupational asthma (allergen-triggered)	• Asthma due to occupational irritants, smoking related
• Wheezing (post viral)	• Functional small airway damage
• Bronchitis (eosinophilic)	• Bronchiectasis

Table 2.1 Inflammation response subtypes

(Source adapted from: Sood & Garett, 2007:24)

In 2001 Al-Shadli *et al.* (2001:121) linked underdiagnosis and undertreatment in the age group 16 – 44 years to patients' education levels and opened a new field for investigations, since the outcome was that the higher educated group was more at risk than the lower level of the education chain. This seems to link up with the reluctance of patients to consult a doctor; the few symptoms revealed to doctors; patients' low symptom perception (Lurie *et al.*, 2007:2150); and the reluctance of people to take up the role of a patient which will be treatment bound (Kolnaar *et al.*, 1994:133). According to Van Weel (2002:65) this 'un-presented' clinical picture of health is not always bad, since it portrays a reflection of self-reliance and autonomy, but contrariwise only 10% of community health problems now feature in the professional medical care surroundings, forming only the tip of the iceberg (morbidity phenomenon). An utmost important concatenation of community and professional medical care is therefore reached by means of primary health care (Van Weel, 2002:65).

As if all reasoning thus far is not enough, it is also said that even if correctly diagnosed and treated, asthma control is for the greater part ineffective or suboptimal. Even in the AIRLA (Asthma Insights and Reality in Latin America) survey only 2.4% were optimally controlled (Barnes, 1987:359; Chapman *et al.*, 2008:324; Green *et al.*, 2007:173; Moyer, 2007; Neffen *et al.*, 2005:191). The Real-World Evaluation of Asthma Control and Treatment (REACT) study presented 'uncontrolled asthma', or so-called 'difficult/therapy resistant' asthma (Ayres, 2001:115; ERS Task Force, 1999:1198) results of 55%, with only 34.9% of these patients ever been offered an asthma action plan for management (Peters *et al.*, 2007:1456; The Sydney Morning Herald, 2007). Suboptimal treatment can be referred to treatment cost

and safety concerns, control achievement uncertainties and right at the top of the list and in bold print: the lack of recognition of the poor quality of control, by both patient and health care provider (HCP) (Bateman, 2006:1; Green *et al.*, 2007:172; Prieto *et al.*, 2007:461). Dr. Pramod Kelkar, MD, an allergist/immunologist quoted: “Patients need to have optimal control for many reasons, including the relationship between poor control and increased costs”. He also stressed the importance of optimal allergy symptom control and that patients must be acquainted with their triggers and the manner to manage their environment, since this will work along to optimise asthma control (Moyer, 2007). Quality health care (including asthma action plans) (The Sydney Morning Herald, 2007) and patient education play crucial roles in this voluminous character of asthma control and management (Moyer, 2007) as a ubiquitous burden, since an increased risk of uncontrolled disease can be seen in younger age groups, male patients, lower income groups, chronic sinusitis, high blood pressure and gastroesophageal reflux disease (GERD) (Boggs, 2007). Recurring symptoms of asthma (several times per day / week) can contribute to insomnia (“sleeplessness”), daytime fatigue, reduction in levels of activity or productivity and frequent days off school or work, which makes asthma an even greater and more costly burden to society (Shohat *et al.*, 2005:275). According to Weiss *et al.* (1992:862) “...efforts to improve the effectiveness of primary care interventions for asthma...may reduce the costs of this common illness”.

2.3 DEFINING ASTHMA

The definition of asthma in 1959 was merely an indication of lung function impact, namely: limitations to airflow, the reversibility thereof, and the hyperresponsiveness of the airway (Nadel & Busse, 1998:S130). During the later years the definition evolved to a more comprehensive and integrated appreciation of the functional consequences of inflammation of the airways, which led to a clinical operational description of asthma (Nadel & Busse, 1998:S130), yet it is still not of any help when it comes to diagnosing asthma (Strunk, 2002:357), due to ambivalent assumptions such as: “...episodes are *usually* associated with...”, “...widespread but *variable* airflow obstruction...”, and “...*often* reversible...” (Ruffin *et al.*, 2005:S38).

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper responsiveness to a variety of stimuli.

--- NHLBI, 2007

Asthma diagnosis can be seen as a name for a succession of symptoms. The way we look at asthma (disease, disorder or condition) directly steers the way we manage and control asthma. It is, therefore, important to take a stand on defining asthma, and as for essential hypertension, maybe side with the comfortless population view of asthma as a disease. This will mean to say that the upper and lower respiratory tract will be seen as one, and that asthma will make out merely one component of a disease / syndrome: "One airway, one disease" or the so-called "United airway disease hypothesis" (Orie *et al.*, 1961:43; Rimmer & Ruhno, 2006:565). It groups all the symptoms and diseases of the respiratory tract together as one systemic disease complex (Voelkel & Spiegel, 2009), since it has a bidirectional influence on each other with an allergic undertone, according to Braunstahl (2006:20). This might be a mere altercation about names and that the outcome is of no importance whether it is the one or the other, but it will surely direct the goal setting and management of each individual. The perennial quandary of the lack of a definitive definition, other than a description of components of asthma, continues (Burney, 1997:111; Hargreave & Parameswaran, 2006:266). According to Chanez & Godard (2006:897) there are two descriptive elements to the definition of asthma: clinical and functional, where clinical further describes the symptom variables such as: chronicity, variability and reversibility.

2.3.1 Epidemiology of asthma (Disease, History and Cause)

Asthma's multiteity, expenditure and high demand for care compel the world to take a serious look at it as a worldwide health problem (De Marco *et al.*, 2005; Peters *et al.*, 2006:1139). Fact sheet N° 307 of the World Health Organization (WHO, May 2008) claims that an estimated 300 million people worldwide (around 7% of Americans) suffer from asthma, with an incidence increment of more than 50% over the last fifteen years (Healthcare South, 2001), irrespective of the country's developmental level, although most cases of fatal asthma occurred in 'low- and lower-middle income countries'. Fatalities are low in comparison to chronic respiratory diseases such as COPD, and demonstrate a wide international diversity (Jackson *et al.*, 1988:914), but still accounted for 255 000 deaths in 2005 (WHO, 2009), with South Africa ranking 4th or 5th highest in the world, depending on surveys (Green *et al.*, 2007:173). Swineford (1962:144) quoted in 1962 that there is no denial of the fact that asthma is prevalent but that no one knows its true incidence, since it appears that asthma diagnosis and asthma awareness are interdependent (Shawn *et al.*, 2008:1121). John Morrison Smith initiated asthma prevalence studies in the 1950s, published in 1976, and by the mid 1990s the proof was there for a definite increase in asthma. The increase called for an explanation. The question was whether this was real or artefactual, and if real, why (Barnes, 1987:359; Downs *et al.*, 2002:ii36)?

The fundamental causal factor for asthma has remained relatively unpredictable and utterly controversial over many years, but it seems that there is a degree of concord that genetic predisposition (for asthma, allergic rhinitis and eczema, otherwise known as atopic dermatitis) and environmental factors interact to set off the asthma pathway (Braunstaal, 2006:20; Comeau, 2006; Demehri *et al.*, 2009; Lilly, 2005:S526; Piness, 1921:29; Postma & Boezen, 2004:S96; Thomsen *et al.*, 2009:428). Environmental factors here include substances inside the house (dust-mites being small insects in bedding, stuffed furniture or carpets, mould, animals and second hand tobacco smoke) as well as outside (pollens, job-related irritants and pollution). Less common factors include: aspirin, non-steroidal anti-inflammatory drugs (NSAID), beta-blockers (treatment for hypertension, heart conditions & migraine), cold air, extreme emotional excitation, exercise and Western lifestyle diet factors. Other risk factors proposed include, *inter alia*, low socio-economic status, ethnic minority groups, former episodes of acute bronchitis and an asthmatic family history. This primarily physiological disease also features with strong psychological elements and may even mimic asthma (Haden & Khan, 2003:72).

According to Burgess *et al.* (2009:429) the environmental- and food factors elicit the production of specific IgE antibodies, which then provoke the so-called progressive atopic march or otherwise known in South Africa as the allergic march. This refers to the following: a natural history of allergic or atopic manifestations and a series of clinical symptoms and conditions being persistent over a number of years, residing in a certain age period (Ker & Hartert, 2009:282; Weinberg, 2005:4). In this chain of events eczema tends to be the first step leading to allergic rhinitis or asthma, where allergic rhinitis in its turn can be a risk factor or preceding factor for asthma (Spergel, 2005:17). Pawankar & Takizawa (2007:77) found that some 40% of patients with allergic rhinitis also present with asthma, while up to 80% of asthmatic patients experience nasal symptoms. Furthermore, Braunstahl (2006:20) states that 30% of the population show an atopic composition, and of these only two thirds will present with a clinical picture.

Upper- and lower airway links were still an uncertainty in 2003 with data pointing towards some systemic link involving the bloodstream and bone marrow (Braunstahl & Hellings, 2003:46). In 2007 the atopic march was in question due to the Early Treatment of the Atopic Child (ETAC) study where asthma was unpreventable by Cetirizine treatment in children with early eczema. In 2009, however, there was a shift towards the direct correlation of inflammation markers (eosinophils and cytokines) of the upper- and lower airways (supportive of the 'united airways' concept) (Boulay & Boulet, 2003:51) and therefore detection of these markers in the first two years of life are coupled to prevention of atopy ('placelessness'). This makes us believe that the rise in asthma prevalence is predominantly due to the change in allergic sensitisation prevalence, (Crane, 2004:263) but then, what about the 'dynamic equilibrium theory' of Manton (1982) (Agree & Freedman, 1998:WP98-05) that suggests that increased life expectancy (through postponed disease onset and disease management) will expand the time spent with chronic diseases (Van de Water, 1997:1819)? This might mean that the age of onset might stay the same, but the prevalence will increase, a scenario that seems to best fit data of places like New Zealand (Graham *et al.*, 2004:665).

In early life boys tend to demonstrate a higher prevalence for asthma and an association with infantile eczema, which then makes a prevalence shift during puberty (Horwood *et al.*, 1985), leaving more women to have asthma than men (Mccallister & Mastronarde, 2008:853). The Behavioral Risk Factor Surveillance System of 2000 highlighted an asthma prevalence of 9.1% in adult females with a lower 5.1% in adult males (CDC, 2001:682). These differences may be due to sexual hormones that again influence the prevalence of asthma during different life cycles (Brenner *et al.*, 2005:806; Fanta, 2009:1002; Lowe *et al.*,

2008:1194; PausJenssen & Cockcroft, 2003:34), but research is still in the speculation phase, since contradictory results cause conflict (Martinez-Moragón, 2004:242).

A consensus around the rise in prevalence of asthma in most Western countries over the last decades of the 20th century and the fact that the rate and severity of asthma are much higher and greater in blacks than in whites was reached (Anderson, 2005:1037; Brugge, 2008:785; Fanta, 2009:1002; Furlong, 1999; Tai *et al.*, 2009:343). Dr. Margaret Chan, the Director-General of the WHO said at the 61st World Health Assembly (19-24 May 2008): “Diabetes and asthma are on the rise everywhere” (AAAAI, 2009; WHO, May 2008; Centers of Disease Control, 1998:SS1). Alsowaidi *et al.* (2009) came to comparable findings in the transitional countries such as the United Arab Emirates (UAE).

2.3.2 Pathogenesis of asthma

Asthma is a common chronic phenotypical heterogenic airway disorder (Holgate, 2008:872; Miranda *et al.*, 2004:101). It is multi-focused and intertwined through asthmatic symptoms, goblet cell metaplasia, airflow obstruction due to excessive mucus secretion and airway muscle contraction (bronchoconstriction), inflammation and bronchial hyperresponsiveness (BHR). The core is the underlying inflammation (Hargreave & Parameswaran, 2006:264; Nadel & Busse, 1998:S130; Nakanishi *et al.*, 2001:5175; Planaguma & Levy, 2008:697) that fluctuates over time. This chain of happenings provokes distinct symptoms of prolonged coughing, shortness of breath, chest pain or tightness, and expiratory wheezing, through oedema of the mucosa, submucosa, and adventiae; cell infiltration (eosinophils, neutrophils, activated helper T lymphocytes and mast cells); increased secretions of the airways; engorged capillaries; smooth muscle hyperplasia; and excessive collagen deposits (Fanta, 2009:1002), thence the term ‘asthma’ from the Greek verb ‘άσθμα’ / aazein, translating to ‘pant’ or ‘exhale with an open mouth’ (Marketos & Ballas, 1982:263). Allergens give cause to two different responses, an early and a late phase response (Pawankar & Takizawa, 2007:77), the first being within 15-30 minute after exposure, and the latter, 4-6 hours after exposure (Elias *et al.*, 2003:291). Several concepts featured as explanation for these responses, but with limited results. Researchers followed the routes of: abnormality of the airway’s smooth muscle (no results) (Leary, 1995:13), syndrome of autonomic dysfunction (no positive or negative results), and degranulation of the IgE-mediated mast cells (more decisive results) (Elias *et al.*, 2003:291).

Genetic predisposition of IgE antibody development towards specific allergens, referring to 'atopy', seems to be the main risk factor for asthma (Liu, 2009). Atopy is defined by the World Allergy Organization as: "a personal and/or familial tendency, usually expressed in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens" (Casale & Martin, 2009:20). Although these allergens show no toxicity themselves, they demonstrate the ability to start up an IgE response when in contact with mucosal surfaces, which become noxious. A chain of reactions results in the degranulation of mast-cells and the inception of bronchoconstriction followed by the ongoing of the inflammatory response. The immunohistopathology of asthma features around inflammatory cells such as: neutrophils (whereas the inflammatory injury contribution is still obscure), eosinophils (the amount inversely related to lung function of asthmatics), lymphocytes, mast cell activation and epithelial cell injury (epithelium as a source of pro-inflammatory mediators also becomes the target of inflammatory mediators) (Heinecke, 2000:1331; Nelson *et al.*, 1999:173). One of the key mediators in the inflammatory response is leukotrienes (LTs), mainly LTB4 and cysteinyl LTs (cysLTs), which are formed by the phospholipids bilayer of cell membranes as soon as there is a crosslink of IgE-receptor on the mast cell surface. Powerful proinflammatory as well as bronchoconstrictive features are displayed by these 5-lipoxygenase (5-LO)-derived lipid mediators (Planaguma & Levy, 2008:698). Diagram 2.1 set out the basics of the inflammatory response.

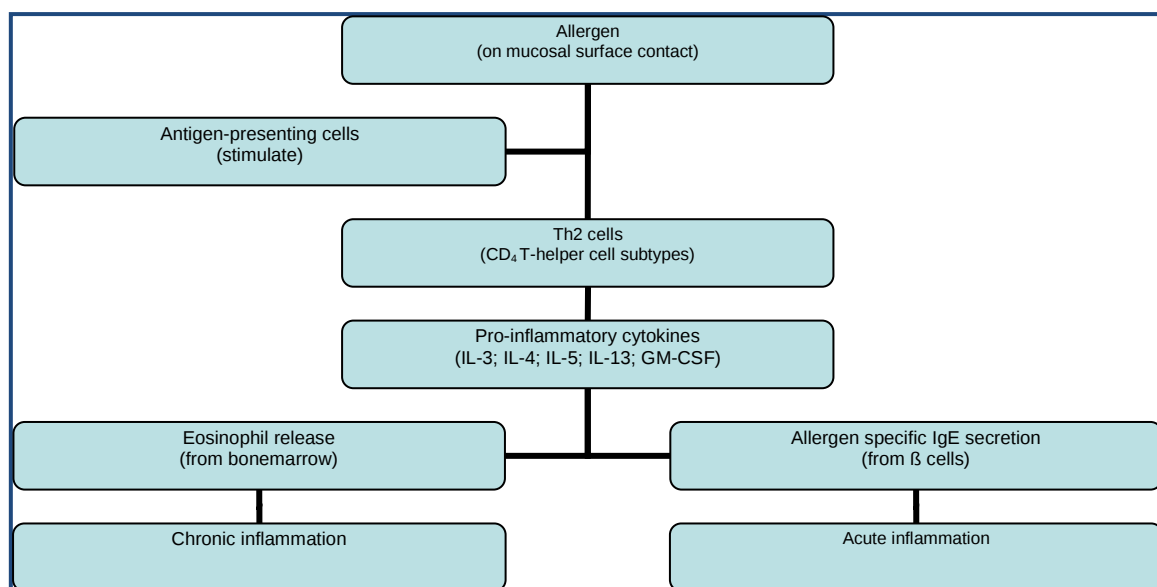


Diagram 2.1The immunological cascade of atopy and asthma

(Source adapted from: Gilliet *et al.*, 2003:1059; Heinecke, 2000:1331; Yoo *et al.*, 2005:541)

Defects in lipoxin (LX) (a chemical arachidonic acid derived protective mediator) formation showed to be present in chronic or uncontrolled airway inflammation, which leads to a provocative LT and a protective LX imbalance, resulting in airway inflammation exacerbations and obstruction of airflow, typical of asthma (Planaguma & Levy, 2008:698). Eosinophils as multifunctional proteinase producing leukocytes, contribute to asthma's pathology by degrading and remodelling tissue matrix, secreting several proinflammatory factors, promoting secretion of mucus, and constricting smooth muscle cells (Cortez-Retamozo *et al.*, 2008:4058). Furthermore, T-helper (Th)-lymphocyte immune regulation defects (e.g. Lyn-deficiency), can lead up to a "severe, persistent asthma-like syndrome", due to T-helper type-2 (Th2)-mediated airway obstruction and inflammation (Beavitt *et al.*, 2005:1874; Demehri *et al.*, 2009).

The natural history of classical asthma is that of reversible obstruction of airflow, but the degree of obstruction differs and can even become totally irreversible, the cause: airway remodelling. Several factors are named as contributors to this persistency of obstruction, although the questions are still manifold. Contributors are listed in Table 2.2 (Sears, 2000).

- Gender being female
- Second hand tobacco smoke exposure (child)
- Personal tobacco smoke (adult & adolescent)
- Age of symptom(s) onset
- Severity of asthma (child)
- Asthma duration
- Lung function abnormality level (child)
- Reversibility using bronchodilators
- Airway hyperresponsiveness (degree)
- Anti-inflammatory use (delay in initiation)

Table 2.2 Contributing factors to irreversible airflow obstruction

(Source adapted from: Sears, 2000)

2.3.2.1 Airway Inflammation

Alex Sevanian, a professor of molecular pharmacology and toxicology at the University of Southern California (USC) School of Pharmacy, says that: “inflammation is considered a form of oxidative stress, and when it occurs in places where it’s not suppose to be for a protracted time, it causes injury”. What is meant by oxidative stress? Well, it seems like the good “stuff” in life, namely: the ubiquitous gas, oxygen, also has a dark side to it, like the changes of the apple in contact with air, or even rust. Oxygen needs two more electrons to become complete / neutral, and will combine with any given atom that is able to donate electrons. Oxygen will destroy to execute its purpose, by using protein molecules, or fats in cell membranes, or even the DNA that forms part of normal cell function. This constant breath-to-breath oxygen ravage is known as oxidative stress (Oliwenstein, 2002**b**). Rahman *et al.* (1996:1055) proved that triggers such as smoking, COPD and asthma inflammation are linked to blood level imbalances of oxidant-antioxidant. This oxidant favourable imbalance is undesired for normal functioning and set-off oxidants, which leads to inflammation and then again to asthmatic symptoms (Bowler, 2004:116; Bowler & Crapo, 2002:349; Swindle *et al.*, 2009:25). The lung protects itself through an antioxidant system that is well developed, although it seems as if in asthmatic patients there is a deficiency of antioxidants, with a marked lowered level during exacerbations (Caramori & Papi, 2004:170). Increased levels of oxidative stress markers have been demonstrated in asthmatic patients’ urine, blood, sputum, broncho-alveolar lavage fluids (BAL) and lung tissue.

Another antioxidant system, peroxynitrite inhibitory activity, shows reduced sputum levels in stable asthma, which might relate to reponsiveness of the airways, sputum eosinophils and forced expiratory volume (FEV₁) (Caramori & Papi, 2004:170). Summarising: enhanced oxidative stress is present in asthma patients and is not lung confined, therefore the non-invasive measurement of oxidative stress markers, which are elevated in these patients, are more and more explored as options for asthma monitoring (Van de Kant *et al.*, 2009).

Scientists have looked into airway inflammation from all possible angles, and yet new fields and possibilities evolve on a regular basis, leaving space for genetics (Van de Kant *et al.*, 2009), phenotyping (Lilly, 2005:S529), and many more. A few of the views are merely mentioned briefly:

- ❖ Asthmatics that smoke demonstrate a different inflammatory pattern. They find themselves with increased levels of neutrophils and IL-8 of the airways, while there is a decline in sputum eosinophils (Hylkema *et al.*, 2007:441). Predisposed genes proved to interact with environmental tobacco smoke (ETS) to reveal unhealthy effects. Some of these genes are present on chromosome 5q, and associations were also found with the CD14 gene, that of the beta receptor gene, glutathione S-transferase (GST) genes, as well as the GSTM1 null genotype gene (Hylkema *et al.*, 2007:440; Swindle *et al.*, 2009:25).
- ❖ A multifunctional gene located on chromosome 20, named, a disintegrin and metalloprotease 33 (ADAM33), as well as dipeptidyl peptidase 10 (DPP10) and PHD finger protein 11 (PHF11), are all associated with asthma. These might affect airway cell growth and influence regulatory receptors and ligands' expression (Lilly, 2005:S530). Munc18-2 alteration leads to suppression of mucus secretion and reduction of obstructive airflow (Evans *et al.*, 2002:91S).
- ❖ A compound named human thymic stromal lymphopoietin (hTSLP) found in cells of damaged skin (skin keratinocytes) and that gets secreted into the blood stream, elicits an acute immune response which when reaching the lungs, triggers the well-known hypersensitivity characteristics of asthma (Ericson, 2009). hTSLP largely functions on myeloid cells which give rise to T cell-attracting chemokine release, enhancing CD_{11c}⁺ dendritic cell maturation and triggering of allogenic naïve CD₄⁺ T cells and CD₈⁺ proallergic T cells to produce IL-4, IL-5 and IL-13, which then leads to allergic and inflammatory responses (Al-shami *et al.*, 2005:837; Gilliet *et al.*, 2003:1062; Reche *et al.*, 2001:336; Zhou *et al.*, 2005:1047). This can now narrow the 'atopic march' down to one molecule or substance, since Demehri *et al.* (2009) indicated a block in the atopic march through removal of the hTSLP gesticulation (Kool *et al.*, 2009:1074; Yoo *et al.*, 2005:541).
- ❖ Vascular endothelial growth factor (VEGF) and sphingosine-1-phosphate (S₁P) are both angiogenesis factors that form part of the inflammatory response of the lungs by increasing the vascularity of the lung. According to Voelkel & Spiegel (2009), a 'bone-marrow lung axis' model can be assumed, where the inflamed lung sends signals of chemotactic nature and thereby triggers the bone marrow to release angiogenesis contributing cells.

- ❖ Airway smooth muscle (ASM) cells play an important role in the inflammation of asthma, by expressing active B7-H2, CD40 and OX40L. An in depth discussion on molecular level is available at: Kajiwara *et al.*, 2009.
- ❖ Leukotriene B4 (LTB4) directly or indirectly stimulates the production of interleukin 6 (IL-6) through the activation of an IL-6 gene. Transcription factors involved in this process are: NF- κ B and NF-IL6. Transcription factor AP-1 did not show any activation (Brach *et al*, 1992:2705).
- ❖ Q576R polymorphism particularly increases IL-4R α (interleukin-4 alpha receptor chain) -dependent signalling and thereby directly contributes to asthma (Tachdjian *et al.*, 2009:2191).
- ❖ Chitin (a substance plentiful in fungi, crustaceans, helminths, cockroaches and dust mites) couples with a chitinase-like protein known as YKL-40 to induce its breakdown. YKL-40 is believed to be an inflammatory response marker (not an asthma cause), and is seen more frequently in asthmatic than in non-asthmatic patients. If chitin is present in the human lung, the body starts defending itself against this acting 'helminth infection' and can start-up a serious response towards harmless dust mites. According to Dr. G. Chupp, an associate professor of medicine at Yale University School of Medicine, YKL-40 levels are easy to establish in the blood (Drugs.com, 2008).

All of the above-mentioned theories of inflammation lead to possible ways and means to determine the severity and control of asthma and to treat the cause of asthma, not only the symptoms (Caramori & Papi, 2004:171).

2.3.2.2 Mucus and airway oedema

Mucus, being a complex protective semi-fluid (slimy, viscous substance) coating of various organs (e.g. nose, throat and lungs) produced by membrane linings and mainly consisting of mucin (a large, high charged nitrogenous substance protecting body surfaces, with MUC5B and MUC5AC being in the main), water, inorganic salts and desquamated epithelial cells, aids in the natural defence against bacteria (Swindle *et al.*, 2009:26). Other soluble agents present in mucus are: complement, immunoglobins, specific proteins such as surfactant and Clara cell proteins, and antimicrobials that upset the normal bacterial outer surface, isolates microbial nutrients or lure microbial attachment. Cytology after an asthma attack showed

mucus plugs with eosinophils, Charcot-Leyden crystals (degranulation of eosinophils form these base to base fitted bipyramidal hexagons), and Curshmann's spirals (mucus derived fuzzy spirals that stain dark to a Papanicolaou stain, with a lighter mucous) (Husain, 2009). Elevated mucin levels are present in patients with asthma, bronchitis and COPD, while asthma and atopy association are viewed with β -defesins' gene 1, but no levels of this were measured in asthmatic airway secretions, thus, leaving an open field for studies (Swindle *et al.*, 2009:25).

Mucus accumulation can be a result of mucus hypersecretion, or due to defects in the ciliary clearing mechanism, that leads to decreased overall clearance of mucus. This can predispose to respiratory infections, and contribute to airflow obstruction. Physical and pharmacological therapy can be of use to alleviate the problem (Kim, 1997:1914). Rogers (2004:241) refers to the pathology of mucus hypersecretion in the airways as the "ugly sister" to bronchoconstriction and eosinophilic inflammation" and highlights the fact that it now plays an important role even in newer asthma guidelines, which can lead to new pharmacotherapeutic advances. According to Rose (2006), mucus can be seen as an entity with numerous functions, all working together to initiate a defence mechanism, thereby serving as protection of the airways. Mucus secretion is triggered by the cholinergic nervous system and mechanisms that can inhibit these secretions are antagonists of the muscarinic M_3 receptor, of the tachykinin NK_1 receptor, as well as, muscarinic M_2 receptors, nitric oxide (NO) and vasoactive intestinal peptides. With no effective, available hypersecretion therapy (Dimov, 2007; Kaliner *et al.*, 1986:612), a potential therapeutic target may be that of the opening of calcium-activated potassium channels as inhibitory mechanism (Rogers, 2002:249).

Mucins MUC5AC and MUC5B significantly influence the characteristics of mucus by setting out the framework of the protection barrier against inhaled particles, and rendering the viscoelastic properties vital to mucus clearance (Rubin, 2007:4). Mucus and serous cells of the submucosal glands, as well as goblet cells, are the main producers of mucins throughout the bronchial tree, but in asthmatic patients there is an abnormal production level of mucins, which can be the cause of 'mucus plugging of the airways' (Swindle *et al.*, 2009:26), which in its turn contributes to limiting airflow and hyperresponsive airways (Morcillo & Cortijo, 2006:1). Some other contributing factors are those of DNA, serum proteins and eosinophilic basic proteins, as well as, oedema of the bronchial mucosa, submucosa & extravasation of plasma due to a bronchial microvascular leakage (Barnes, 1987:359; Fanta, 2009:1002).

The dangerous myth of milk causing mucus, dates back to the 12th century, but according to Dr. Janet Rimmer, director of National Asthma Council Australia, an allergist and respiratory physician, “There have been studies, both in Australia and overseas, that suggest that if you have regular intake of dairy in childhood, you are less likely to develop asthma” (Ward, 2009).

2.3.2.3 Bronchoconstriction

Asthma being mainly a bronchial disease shows signs of bronchial wall membrane thickening (Brown *et al.*, 2006:36), neovascularisation, oedema of the submucosa, as well as hypertrophy of the submucosal glands and the smooth muscle cells, which lead to bronchus narrowing. These changes are commonly known as airway remodelling. Excessive narrowing due to an exaggerated response of airway bronchospasm is referred to as: bronchial hyperresponsiveness (BHR), which is non-specific and fluctuates over time (Swindle *et al.*, 2009:23), but is nevertheless set as purview of inflammation, severity, and management of asthma (Brown *et al.*, 2006:37; Grootendorst & Rabe, 2004:77). Contraction of the smooth muscle of the airways around the bronchial tubes, are directly affected by immune disorders and stimuli from agents such as histamine and metacholine. This is used to measure the reaction of bronchial hyperresponsiveness (Van den Berge *et al.*, 2001:1546) which can be defined as: “a provocative concentration of metacholine producing a 20% fall in $FEV_1 \leq 80\text{mg/ml}$ ” (Grootendorst & Rabe, 2004:77; Wanchai *et al.*, 2006:602). Asthmatic patients’ bronchial hyperresponsiveness level towards histamine and metacholine relates to mast cell, eosinophil and CD_8^+ T cell numbers. Indirect stimuli like adenosine 5'-monophosphate (AMP) have minimal effect on mentioned muscle contraction but trigger the bronchial inflammatory reaction through causation of histamine release and thereby induce bronchoconstriction (Van den Berge *et al.*, 2001:1548). Abnormal contractility of, as well as excessive mass of, the smooth muscle plays a role in this (Fanta, 2009:1002). Since indirect stimuli tests (AMP, hypertonic saline, eucapnic hyperventilation or exercise) are not so well standardised as the histamine and metacholine challenge tests, the latter are most suitable for clinical use (Grootendorst & Rabe, 2004:77). According to Lilly (2005:S526), bronchial hyperresponsiveness is the “physiological hallmark for asthma but also occurs in individuals without asthma and can be found in 10% to 15% of the general population”.

Bronchial hyperresponsiveness demonstrates a noticeable increased level of the *gob-5* gene (Nakanishi *et al.*, 2001:5179), with mast cells and sensory nerves seen as a functional unit, due to its bidirectional crosslink. Smooth muscle cell (SMC) interaction through mast cell infiltration of the smooth muscle layer of the airways leads to airways obstruction. Cell adhesion molecule-1 (CADM₁), a unique mast cell adhesion molecule, serves not only as an adhesive, but also communicates between nerve, as well as smooth muscle, and mast cell (Ito *et al.*, 2008:83).

2.4 CLINICAL PRACTICE GUIDELINES

“Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”.

--- Institute of Medicine, 1990

In 1989 the worsening asthma epidemic steered the National Heart, Lung, and Blood Institute to the release of their first asthma management guidelines, issued in 1991. The so-called ‘Expert Panel Report 2’ (EPR2) was a revised set of guidelines, published in 1997, and updated again in 2002. The latest version is the EPR3, “Guidelines for the diagnosis and management of asthma”, that was distributed in 2007 (Li, 2009:673; NAEPP, 2007; Wechsler, 2009:707)

(See <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf> for EPR3), rendering guidance to the health care provider as to optimal asthma management, ensuring patients a life with limited to no symptoms and/or functional restrictions, as well as a good quality of life (Stoloff, 2007:1021). Furthermore, the Global Initiative for Asthma (GINA) formed in 1993, started distributing information on asthma patient care, based on scientific reviews (Bateman *et al.*, 2008:143; GINA, 2009)

(See <http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=1561> for GINA® guidelines). As for South Africa, The National Asthma Education and Prevention Program (NAEPP) disseminates information regarding asthma and asthma management to the public as well as health care professionals, while the Standard Treatment Guidelines and Essential Drugs List for South Africa (EDL) is the asthma management aid more readily available to health care providers in primary health care clinics (See Annexure A for the EDL’s section on asthma). All of the above mentioned guidelines,

both National and International, make use of a similar therapy pattern (Table 2.3), dependent on availability, cost, and individual patient profile:

Six steps to a “step-up or step-down” asthma therapy approach:

1. Short acting inhaled β_2 -agonists as needed (mild intermittent asthma only)
2. Inhaled β_2 - agonists as needed **and**
Low dose inhaled corticosteroid (ICS) (250-500 ug per day Beclomethasone dipriopionate equivalent)
(START HERE FOR PATIENTS WITH CHRONIC PERSISTENT ASTHMA)
3. Inhaled β_2 -agonists as needed **and**
Low dose inhaled corticosteroid **plus**
Long-acting inhaled β_2 -agonists (**PREFERED**)
OR
Inhaled β_2 -agonists as needed **and**
Low dose inhaled corticosteroid **plus**
Oral leukotriene modifier
OR
Alternatively, Moderate dose of 500-1000 ug per day Beclomethasone dipriopionate equivalent inhaled corticosteroids
4. Inhaled β_2 -agonists as needed **and**
Moderate dose inhaled corticosteroid **plus**
Long-acting inhaled β_2 -agonists (**PREFERED**)
OR
Moderate dose inhaled corticosteroid **plus**
Oral leukotriene modifier
OR
Moderate dose inhaled corticosteroid **plus**
Oral slow-release theophyllines
5. Inhaled β_2 -agonists as needed **and**
High dose inhaled corticosteroid (>1000 ug per day Beclomethasone dipriopionate equivalent) **plus**
Long-acting inhaled β_2 -agonists
AND
Oral leukotriene modifier
OR
Oral slow-release theophyllines
6. Inhaled β_2 -agonists as needed **and**
High dose inhaled corticosteroid **plus**
Long-acting inhaled β_2 -agonists **plus**
Oral leukotriene modifier **plus**
Oral slow-release theophyllines
AND / OR
Long-term oral corticosteroids

Table 2.3 General step-wise asthma therapy

Guidelines aid health care providers and patients in making health care decisions that are appropriate and individualised according to diagnosis, management, prevention, and needs. It is not a set of fixed rules, but rather a range of generally accepted approaches meant to improve quality of care, while still calling for trustworthy judgment by health care providers.

But, patients continue to receive suboptimal care, or otherwise they receive unnecessary care that can cause harm (Grol & Grimshaw, 2003:1225). Steven *et al.* (2004:74) explain that patients seem satisfied with asthma control other than ideal. Given the conditions, time limitations, and circumstances that health care providers in primary care find themselves in, the implementation, documentation and adherence to these guidelines are further challenged (Levy, 2008:231), and have proved to be below satisfactory (Roghmam & Sexton, 1999:381). This shows to have a direct impact on patient care (Liyanage *et al.*, 2006:191).

2.5 QUALITY OF CARE

“There is no reason why our dysfunctional health system cannot be turned around within five years.”

--- Barbara Hogan, Health Minister (SAHR, 2008)

Evert Reerink (1990:197) stated in an article published in 1990, that: “Finding the definition of quality has haunted mankind since the beginning of time.” In November 2000, at The 128th Annual Meeting of the American Public Health Association (APHA) it was said that: “Quality and related issues of accountability and cost are central to development of health services, yet there is a lack of consensus on the meaning of quality and how quality can be measured in practice” (Macnee & McCabe 2000:2868). Following all of this, Stanley Feld (2007) came up with the statement that the definition used by the Institute of Medicine (IOM) of the National Academy of Science, has become a referring norm: “The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”. This point out the important link between provided care and its health effects (Milchak, 2004:603). Therefore, patients’ views of their illness also need to be identified and addressed (Schneider *et al.*, 2007). Chassin *et al.* (1998:1000) also conclude that the problem lies not with managed care but with the quality thereof. It is of utmost importance to realise that although there are incredible shortfalls in the quality of health care worldwide (Seddon *et al.*, 2001:152), it definitely does not relegate any individual (Chassin *et al.*, 1998:1003), it is of multi-dimensions and therefore it can only improve if everyone and every aspect are integrated and coordinated. The IOM points out that most of the health care quality (HCQ) matters in the United States are related to organisational failures (Casalino *et al.*, 2003:434). To accentuate this issue even further, Cabana *et al.* (2001:1057) and Grol & Grimshaw

(2003:1229) emphasised the fact that certain guideline components ask for customised interventions that can address the obstacles characteristic to local environments. Casalino *et al.* (2003:434) looked at 4 different organised care management processes (CMPs) to help with chronic disease health care quality improvement, by names:

- 1) Physician feedback (where physicians give regular feedback on particular disease management related questions).
- 2) Disease registry (where registers are kept and updated for each chronic disease).
- 3) Clinical practice guidelines (where chronic disease management is outlined).
- 4) Self-management skills (where patients are educated and guided to manage their own disease to a certain extent).

Some studies showed effective individual, and combination application of these CMPs, with improved quality of care (Bodenheimer *et al.*, 2002:1912; Wagner *et al.*, 1996:511), although overall, the use of CMPs varied at large, with relatively scarce use demonstrated.

Quality of care consists of two separate entities with some subdivisions:

- a) Accessibility
- b) Efficacy --- humane & clinical/technical (Campbell *et al.*, 2000:1611; Seddon *et al.*, 2001:153).

This can again be placed in different “ways to-look-at” categories to improve the morbidity, mortality and cost of health care, i.e. including, the effectiveness of care and thereby the management of asthma. Table 2.4 shows the different focus points.

<u>IOM Quality Domains:</u>	<u>Critical components for QOC:</u>	<u>QOC indicators:</u>
• Safety • Effectiveness • Patient-centred • Timely • Efficient • Equitable	• Self-management (Active patient role) • Decision support • Design of health system (Integrated) • Clinical information (Complete) • Health care organisation (Quality improvement) • Community outreach	• Patient recognition (Early childhood asthma detection) • Patient evaluation (Initial & subsequent) • Accurate diagnosis • Initiating therapy • Regular follow-up appointments • Inter-personal care to help with adherence (patient & HCP)

Table 2.4 Quality of Care (QOC) focus points

(Source adapted from: Feld, 2007; Klomp *et al.*, 2008:1013; Macias & Patel, 2009:104)

*“Documentation is like sex: when it is good, it is very, very good;
and when it is bad, it is better than nothing”*
--- Dick Brandon, child actor of the 1920s.

Major stumbling blocks in quality of care seem to be the documentation of clinical patient notes. Since it is time consuming, brief, usually in illegible handwriting, it causes critical detail to go unaccounted for (Kern, 2009).

2.6 DIAGNOSING ASTHMA

The problematic nature of defining and diagnosing asthma stands (Barnes, 1987:359; Hargreave & Parameswaran, 2006:264; Sood & Garrett, 2007:25), with children under the age of 3 years even putting the health care provider’s medicinal art skills further to the test (Zuidegeest *et al.*, 2009:32). Diagnosing asthma requires much more than merely diagnosing: it asks for a multi-faceted approach that would include trust and respect, with generalised broad thinking and ruling out of other possibilities of similar conditions (Strunk, 2002:357). Early and correct diagnoses will help to overrule the problem of under- / over-treatment of patients and will therefore contribute towards improvement of asthma control (Van de Kant *et al.*, 2009). In order to assist health care providers with this task, the use of symptoms and

lung function as determinants for asthma diagnosis falls under national and international guidelines but can be debated (Dejsomritrutai *et al.*, 2006:603; Van Schayck & Chavannes, 2003:19s). According to Dr. Thomas Hudson (2006), named 'scientist of the year 2000', people have different inherited genes for asthma which group them into separate disease sub-types (phenotypes), and can in future help to identify the disease cause and thereby define and pinpoint a specific diagnostic test for each phenotype (Comeau, 2006). Researchers are looking at all the genes in the chromosome 12 (known to be the asthma gene) region to identify the particular mutation evolving around asthma (Comeau, 2006). In order to help reduce asthma-related sickness and deaths, and improve the quality of life, the National Institute of Health started off during March 1989 with the National Asthma Education and Prevention Program (NAEPP) (National Library of Medicine, 2009).

2.6.1 Classification

Every aspect of asthma shows that ambiguous and murky side, where different views lead to different approaches, as for classifying asthma (Graham, 2006:S19). Asthma classification can be according to severity of symptoms, phenotype/underlying cause, triggers, response and dependence to steroids, onset age, exacerbations or asthma control, or even lung function and/or bronchial reactivity (Ayres, 2001:115; Sood & Garrett, 2007:24), each requiring varying approaches of management (Graham, 2006:S19). This would mean that the diagnosis of asthma is interdependent on the amount of information obtained from a patient himself / herself.

Lung inflammation, as asthma was referred to historically, was divided into 2 categories namely: extrinsic (outside), which was treated as the allergic (atopic) type where airborne triggers or collaborative agents played the main roles and accounted for up to 90% of all asthmatics, and intrinsic (inside), the non-allergic (non-atopic) type with the more lengthy episodes of symptoms, more rapid decline in lung function (Miranda *et al.*, 2004:101) and no cause or trigger coupled to it, which is typical to take onset after 40 years of age (Kelley *et al.*, 2005:726; Sood & Garrett, 2007:24), but since the proof of immunopathological differences was little, its use made space for advanced reasoning (Miranda *et al.*, 2004:101). Modern ratiocination leans towards multiple subdivisions of asthma and its provoking factors, still commencing with the 2 main groups: allergic and non-allergic, but then followed with more subdivisions such as: exercise-induced, nocturnal, occupational, and a steroid-resistant group. Some important elements of each of these subdivisions are mentioned in Table 2.5.

<u>Classification Type:</u>	<u>Description:</u>
<u>Allergic Asthma:</u>	❖ Around 90% of all asthma patients ❖ Allergen triggered (wide range)
<u>Non-allergic Asthma:</u>	❖ Typical onset = adults after the age of 40 years ❖ Possible causes: Respiratory irritants, upper respiratory infections and gastroesophageal reflux (GERD) ❖ Less responsive to therapy
<u>Exercise-induced Asthma:</u>	❖ At least 11% of the non-allergic asthmatics ❖ Can have allergies or family history of allergies ❖ Any age ❖ Cough while exercise may be the only symptom ❖ More severe in cold and dry conditions
<u>Nocturnal Asthma:</u>	❖ Around 75% of asthmatics are affected ❖ Sleep-related (any time of day or night) ❖ Worst between midnight and 4 am. ❖ Triggered by: allergens of the bedding or room, decreased room temperature, and GERD
<u>Occupational Asthma:</u>	❖ Estimated 15% of asthmatics ❖ Triggers: Chemical fumes inhalation, wood dust, irritants (long periods of time)
<u>Steroid-resistant Asthma:</u>	❖ Steroid overuse can lead to a severe asthma attack (status asthmaticus) ❖ Stick to health care provider medication dosages

Table 2.5 Asthma Classification: Modern

(Source adapted from: American Academy of Allergy, Asthma and Immunology, 2010; HealthTree, 2010)

Depending then on the notion of the originator, asthma can be classified or sorted into numerous classes. Table 2.6 sets out some of the more frequently used classifications.

<u>Classification type</u>	<u>Classification subdivisions</u>	<u>Components</u>
<u>Severity Classification:</u> (1997)	• Intermittent • Mild Persistent • Moderate Persistent • Severe Persistent	○ Symptoms ○ Night awakenings ○ Short-acting β_2-agonist use ○ Interference with normal activity ○ Lung function
<u>Control Classification:</u> (2007) (GINA [®] , 2007)	• Controlled • Partly Controlled • Uncontrolled	○ Daytime symptoms ○ Activity limitations ○ Night symptoms ○ Use of reliever therapy ○ Lung function (PEF / FEV₁)

Table 2.6 Asthma Classification: More recent

TYPES:	DESCRIPTION:
1. Children:	a. <i>Transient wheezing:</i> - symptoms only during the first 3-5 life years, lung function inhibition, maternal smoking, and day care centre exposure. No family history. b. <i>Non-atopic wheezing:</i> - of the toddler and pre-school-aged child, c. <i>IgE mediated wheezing</i> - (Stein & Martinez, 2004).
2. Epidemiological & clinical characteristics, (children aged 6 to 16 years)	a. <i>Atopic asthma,</i> b. <i>Nonatopic asthma,</i> c. <i>Resolved asthma,</i> d. <i>Respiratory symptoms (frequent), but without an asthma diagnosis,</i> e. <i>A normal group</i> - (Kelley <i>et al.</i>, 2005:726) (See Table 2.6.1(4) for more detail).
3. Physiological & Pathological:	a. <i>Allergic responders,</i> b. <i>Asthmatic symptoms,</i> c. <i>Lung function impediment,</i> d. <i>Inflammatory groupings</i> – (Miranda <i>et al.</i>, 2004:101).
4. Clinical pictures due to the ‘multidimensional nature of the disease’ (different analysing methodologies):	a. <i>Early-onset, atopic asthma,</i> b. <i>Obese, noneosinophilic asthma,</i> c. <i>Early symptom predominance,</i> d. <i>Inflammatory predominance</i> – (Haldar <i>et al.</i>, 2008:222)

Table 2.7 Classifications and phenotyping

(Source adapted from: Haldar *et al.*, 2008:222; Kelley *et al.*, 2005:726; Miranda *et al.*, 2004:101; Stein & Martinez, 2004)

<u>Atopic asthma:</u> (4.8%)	• ↓ mean poverty/income ratio • ↑ mean parental education level • 96.5% reaction to a minimum of 1 allergen
<u>Nonatopic asthma:</u> (1.9%)	• ↑ BMI • ↑ mean parental education level
<u>Resolved asthma:</u> (3.4%)	• ↑ prenatal maternal smoking prevalence • Lower symptom level than atopic / nonatopic asthma, but with the same lung function impairment
<u>Respiratory symptoms:</u> (4.3%)	• ↑ day care attendance prevalence • ↑ mean parental education level • Normal lung function.

Table 2.8 Characteristics of different phenotypes, as compared to the normal child

(Source adapted from: Kelley *et al.*, 2005:726)

Late-onset asthma is usually non-allergic and more than anything else a result of viral and/or bacterial infections. Patients demonstrate lower lung function, with a higher number of lung eosinophils than the early-onset patients, and the group without eosinophils showed no signs of membrane thickening of the subepithelia (Miranda *et al.*, 2004:101). Infections included in the late-onset asthmatics, are difficult to detect bacteria, such as: Mycoplasma, Chlamydia, and Ureaplasma. These patients present with chronic symptoms due to the lack of antibody formation and therefore persistent life-long infection (Markin, 2010).

The asthmatic patient is probably misclassified on a day-to-day basis with this leading again to mismanaged pharmacotherapy (Graham, 2006:S19). The severe end of asthma bears such a heavy burden on the resources of health systems that the use of specific phenotyping, linked to genotypes, could be particularly valuable in the understanding of asthma's pathogenesis and new treatment approaches (Ayres, 2001:115). Genetic susceptibility and living conditions or pollution play a major role in the severity and control of asthma, and go hand-in-hand with the morbidity of this chronic condition.

2.6.2 Clinical diagnosis

Wheezing is not pathognomonic of asthma although asthma is a primarily wheezing disease. Thus, all that wheezes is not asthma, but could very often be. It is therefore important to discern between a coughing and a wheezing child. According to Strunk (2002:357) up to 50% of infants will at least wheeze once in their early childhood and by the age of 6, one third of these patients will have the asthma label linked to them. This means that early treatment would have been possible if it had been diagnosed early and correctly.

Since there is no definite diagnostic test for asthma, the only alternative is to rule out other possible causes that can present with the same or similar symptoms. For the age group under 3 years of age, 3 clinical tests are at use to cost-effectively rule out other conditions and at the same time diagnose asthma. The tests include chest radiography, sweat chloride testing and an allergy skin test (Strunk, 2002:357). Then there are still other useful tests that can include anything from gastrointestinal barium examinations to computed tomography (CT) of the chest or sinus areas. These tests are expensive and therefore their use in primary care is limited.

The thought of an improved asthma understanding leads to an upsurge in specialised second-line test possibilities such as bronchial provocation tests, nitric oxide (NO) measurements, induced sputum analysis, and chest CT scans of high resolution during expiration (HRCT), but all still portraying moderate indistinctness towards diagnosis (Ruffin *et al.*, 2005:S39; Sood & Garrett, 2007:24) and are costly due to expensive equipment on the one hand and training towards interpretation on the other hand. Epstein *et al.* (1970:211) also discussed the possibility of testing bronchial reactivity to intravenous injection of histamine, but came to the conclusion that it is not diagnostic for separating chronic bronchitis from asthmatics.

2.6.3 Diagnostic challenges and differentiating: Asthma and others

One of the main features of all asthma guidelines is the correct diagnosis. Distinguishing between asthma and other asthma-like conditions is of utmost importance since, as previously said: "All that wheezes is not asthma." Table 9 will be helpful to at first differentiate asthma from Chronic Obstructive Pulmonary Disease (COPD).

<u>COPD:</u>	<u>Asthma:</u>
- Late onset (40 years of age) - Slow progressive symptoms - Smoking history (lengthy) - Exercise dyspnea - Mainly irreversible airflow obstruction	- Early onset (often childhood) - Varying symptoms from day to day - Night or early morning symptoms - Mainly reversible airflow obstruction - Positive family history - Presence of allergy/rhinitis/eczema

Table 2.9 Asthma versus COPD

(Source adapted from: EPR3; Yawn *et al.*, 2005:297)

Table 2.10 to Table 2.12 will summarise other possible conditions (in no set order) that can mimic asthma (Pseudo-asthma conditions).

The main etiological factors for a chronic cough in children are reflux, allergy, and asthma (Koshoo *et al.*, 2003).

<u>Pseudo-asthma conditions:</u>	<u>Specific clinical features:</u>
<i>Gastroesophageal reflux(GER): (also known as gastric reflux)</i>	* Indigestion/heartburn &/or belching, * Sour taste in mouth &/or stomach juices in mouth, * Sore throat (no infection), * Choking &/or night time cough.
<i>Sinusitis or post-nasal drip(PND):</i>	* Nasal congestion &/or headache, * Pain/fullness/pressure over sinus areas &/or radiating pain - to the teeth, * Nausea, * Cough, * PND with/without fever, * Sore throat & bad taste in mouth/bad breath (halitosis).
<i>Pertussis:</i>	* So called 100-day cough, * Dx: Polymerase chain reaction (PCR) - Nasal swab.

<i>Cystic Fibrosis:</i>	* Chronic inflammatory airway disease, * Different mechanism of inflammation, * Same clinical picture, * Some bronchodilator response, * Different physiology of airway responsiveness, * Asthma can coexist, * Dx: Sweat chloride measurement (Quantitative pilocarpine iontophoresis method), * Above-mentioned tests are unreliable due to false results.
<i>Primary Ciliary Dyskinesia:</i>	* From birth, on a daily basis, in association with otitis media, * Associated with otitis media, * Structural and/or functional abnormalities of the airway cilia, * Not responsive to asthma treatment, * Dx: Electron microscope examination of the airway cilia (Several interpretation errors), * Dx: More practical, is the light or phase-contrast microscope examination of the nasal or tracheal epithelia, for coordinated ciliary movement.
<i>Chronic Purulent (Bacterial) Bronchitis:</i>	* No abnormalities identified in the immunity of the child, * No underlying disease, * Positively tested for neutrophilia and lower airway bacteria, * Dx: Bronchoscopy and a bronchoalveolar lavage; cell count and differential demonstrating neutrophilia (>10% of WCC); and a positive fluid culture.
<i>Tracheomalacia:</i>	* Tracheal collapse due to rigidity inadequacy of the tracheal or bronchial cartilage (bronchomalacia), * Secretion presence inhibits normal clearance of the airways, * Dx: Flexible bronchoscopy, conscious sedation & spontaneous respiration, * Sometimes surgical intervention is in need (Aortapexy).

<i>Habit-Cough Syndrome:</i>	* Harsh, barking sound that repeats for hours (several times per minute), * No cough while sleeping, * Also misdiagnosed as tics (Tourette syndrome) - cough is more vocalised, * Easily treated with behavioural techniques.
<i>Other Causes:</i>	* Direct uvula-epiglottis contact, * Uvula impingement by tonsils, * So-called 'upper airway syndrome': Gastroesophageal reflux disease (GERD) or postnasal drip (PND), * Nocturnal asthma (worse at night, with sudden awakening of cough &/or sneezing, and SOB at night).

Table 2.10 Pseudo-asthma conditions associated with coughing

(Source adapted from: Asthma and allergy care, 2008.)

<u>Pseudo-asthma conditions:</u>	<u>Specific clinical features:</u>
<i>Vocal cord dysfunction (VCD):</i> <i>[“abnormal adduction of the vocal cords during the respiratory cycle (especially during the inspiratory phase) that produces airflow obstruction at the level of the larynx.” (Dimov, 2008).]</i>	* Not asthma & not new (in depth studies: 1983), * Mainly females between 20-40 years of age, * Female to male ratio = 2:1 (almost no children), * Features more under HCPs and competitive sport athletes, * Various possible causes, but PND, GERD, & environmental triggers (shouting, singing, smoke, strenuous physical activities) are definite provocative factors, (the relationship between VCD and GERD seem to be like the chicken or the egg, which came first, there seem to be no evidence to support which one came first to cause the other), * Precipitated by psychological stress and therefore often misdiagnosed as panic attacks, * Functional disorder of the vocal cords (abnormal closure of $\frac{2}{3}$ of the cords during breathing), * Paradoxical adduction of the cords lead to an inspiration stridor (high-pitched sound) which mimics wheezing, * 2 Phenotypes, some patients presenting with both (inspiratory or both in- & expiratory types), * Shortness of breath (SOB), intermittent hoarseness &/or wheezing, chronic cough &/or throat clearing, chest &/or throat tightness, and difficulty taking in air, * Normal chest X-ray, * Dx: Spirometry, when symptomatic will allow upper and lower airway obstruction differentiation * $\pm 20\%$ of referred ‘asthma’ patients = VCD.
<i>Partial airway obstruction:</i>	* Differentiate between a foreign body and a mucous plug causing bronchus (airway) obstruction, * Foreign body = continuous one-sided wheezing, * Asthmatic mucous plug = localised intermittent wheezing that changes after coughing.

Table 2.11 Pseudo-asthma conditions associated with wheezing

(Source adapted from: AAFA, 2008; Asthma and allergy care, 2008.)

<u>Pseudo-asthma conditions:</u>	<u>Specific clinical features:</u>
<i>Hyperventilation:</i>	* With/without asthma, * Dx: Spirometry while having an attack, * Dx: Oximetry & blood-gas measurements (low P_{co2} & high pH levels).
<i>Exercise-induced hyperventilation (EIH):</i>	* Chest discomfort experienced as dyspnoea, * Might be due to hypocapnia - due to hyperventilation – no bronchospasm, * Incorrectly known as exercise-induced asthma (EIA), * Symptomatic after 6-8minutes of exercise, and disappear within minutes to an hour.
<i>Anxiety:</i>	* No physiological abnormalities.
<i>Exertional Dyspnoea:</i>	* Asthma/ not asthma related, * Rarely any bronchospasm, * Dyspnoeic perception due to an increased lactic acidosis respiratory drive, * Dx: Treadmill exercise plus cardiopulmonary monitoring.

Table 2.12 Pseudo-asthma conditions associated with dyspnoea

<u>VCD:</u>	<u>EIA:</u>
➤ Symptoms occur ≤5 minutes of exercise starting time, ➤ Sometimes, tightness of the upper chest, ➤ High-pitched inhalation sound, ➤ Repeated episodes, ➤ Inhalers/ICS have no effect, ➤ Throat tightness, ➤ Recovery of < 10 minutes.	➤ > 5-10 minutes of exercise starting time, ➤ Middle/lower chest tightness, ➤ Cough/wheeze with exhaling, ➤ Symptoms do not re-occur for several hours, ➤ Inhalers/ICS do ease symptoms, ➤ Both the naso- and oropharynx play important roles in the cause of EIA.

Table 2.13 Vocal cord dysfunction (VCD) versus Exercise-induced Asthma (EIA)

(Source adapted from: AAFA, 2008; Mangla & Menon, 1981:433.)

2.6.4 Monitoring

“Many patients seem to feel uncomfortable with regular monitoring of the disease and thus need to be repeatedly motivated for self-management.”

---Schneider et al. (2008:186).

Suboptimal patient monitoring leads to suboptimal asthma control (Ko et al., 2009:559). Important is to remember that, a patient might have a normal forced expiratory peak flow at 1second (FEV₁), but still be thwarted with daily activity limitations, therefore asthma management guidelines address the multifactorial approach to reach satisfactory control (alternative measures might be needed to assess control) (Hanania, 2007:483). The Asthma Control Test (ACT) is one way to assess patient control, by means of five easy patient-aimed questions for adults, and seven for children. Ko et al. (2009:565) demonstrated that this method correlated well with treatment decisions, more so than spirometry, PEF/FEV₁ and fractional exhaled nitric oxide (FeNO), since PEF measurements show airflow limitations with severity variation (Quanjer et al., 1997:2S).

2.7 CONTROLLING ASTHMA

“...it takes more work to live with poorly controlled symptoms than it does to control them.”

--- Martha White, Institute for Asthma and Allergy, Wheaton.

2.7.1 Management and Prevention

When asthma has been diagnosed, the severity can be classified for treatment initiation, and the ongoing disease control assessment aimed at improved asthma management can commence (NAEPP, 2007; Wechsler, 2009:709). Managing asthma successfully means integrating patient evaluation, treatment, and adherence, with recommendations (Schmaling et al., 2003:98; Schneider et al., 2008:186). Managing asthma does not only mean surviving it. Management of asthma has taken a shift from morbidity and mortality prevention to continuous control of all clinical features of asthma (Green et al., 2007:172). This would come to say: symptom free, normal activity levels, normal lung function and no need for reliever medication. According to Bateman et al. (2004:842), and the GOAL study (Gaining Optimal Asthma Control) (Bateman et al., 2007:667; Bateman et al., 2008:932; Irusen,

2007:3) this is an achievable goal, therefore, the approach of only managing severity and being satisfied with suboptimal asthma control is not plausible anymore. Control provision should be at hand for the person with the chronic condition. According to Barnes (2004:S4) things are different in the 'real world', and patients fail to understand, and comply with their therapy due to complicated dosing regimens of drugs and incorrect inhaler use. Long-term objectives are only attainable through trigger factor avoidance, therapy reaching for the lowest effective drug dosage, with minimal side-effects (Jain *et al.*, 2006:316), and improvement in inhaled drug delivery (Barnes, 2004:S7).

Patients and health care providers do not always have the same disease care vision, since the typical medical model is focussed on the disease processes and the patient must merely keep up and co-operate. Recognition of the patient as a whole entity (mind, body, emotions and "spiritual force") and not simply as a disease or part of a process thereof, has made space for a new model of 'patient-centred health care' (National Asthma Council Australia, 2009), which, according to the Institute of Medicine, was defined in 2002 as: "Providing the care the patient needs in the manner the patient desires at the time the patient desires". As foreseen, the definition needed some modification to prevent absolute abuse of the health care system, and in 2005 Jo Harkness said: "The healthcare system should be designed around the patient with respect for a person's preferences, values and/or needs and (we need) to formulate tools and targets to achieve this". Doing so would require different service structures and a complete new approach.

*"It is more important to know what sort of person this disease has
than to know what sort of disease this person has."
--- William Osler, Physician (1849-1919)*

Health outcomes are directly and indirectly linked to human behaviour through numerous factors, from health care providers' advice, patients' beliefs, socioeconomics, to ethno-cultural inputs. People want to manage their lives and minimise their disease burden: the way they get to these outcomes may differ throughout their health care journey. The framework for the 'patient-centred health care' model is based on a plan of care (action plan), certain lifestyle changes, informed decision making and developing effective coping skills (National Asthma Council Australia, 2009), to be discussed hereafter.

2.7.1.1 Severity and Control

Current impairments and future risks are the domains of severity and control (Humbert *et al.*, 2007:95). According to the latest guidelines it is important to assess the two separately, although they are concept related, for classification of severity lead to commencement of treatment, and control evaluation help with adjustments or tapering of drugs to exhort health-related life quality (Chen *et al.*, 2007:396). The severity of asthma defines the essential untreated disease, while the control level relates to the disease status (clinically) after intervention (Fuhlbrigge, 2004:1). For any classification to be of use, health care providers must be able to make the accurate and reliable asthma diagnosis, the latter still being characterised by challenges (Graham, 2006:S14).

The assessment of severity is a difficult task, and guidelines need to be fully understood (Doerschug *et al.*, 1999:1735), but the aim of asthma control is constant throughout the scope of asthma severity, independent of therapy (Oppenheimer & Li, 2006:119). Graham (2006:S18) noted that guideline use in terms of classifying asthma severity was very low and showed that only 21% made 60-90% use of guidelines, while 30% hardly ever made use of guidelines (<20% or never). The degree of asthma severity is more of a stable attribute for a specific patient, while the level of control is a variable over time (Stempel *et al.*, 2005:935), influenced by the patient's lifestyle (triggers, precipitating factors and therapy), but there is a link to medical resource utilisation (MRU) for both of them (Van Ganse *et al.*, 2002:260). 'Difficult asthma' as adopted by a European Respiratory Society (ERS) Task Force (1999), and defined as "asthma, poorly controlled in terms of chronic symptoms, with episodic exacerbations, persistent and variable airway obstruction and continued requirement for short-acting β_2 -agonists and a reasonable dose of inhaled corticosteroids" (Chanez & Godard, 2006:897; Chung *et al.*, 1999:1198) are not the only cost-relating factors. According to Cazzoletti *et al.* (2010), moderate-to-severe asthma makes up one third of the asthma population, while severe/refractory asthma accounts for a further 5-10% of all asthmatic patients and is responsible for a sizeable part of health care costs (Haldar *et al.*, 2008:218; Moore *et al.*, 2007:406). Overall, asthma costs and that of asthma severity seem to be comparable (Godard *et al.*, 2002:61; Van Ganse *et al.*, 2002:260).

Without universal definitions for asthma severity and asthma control, Table 2.14 helps to set some guided outlines (Chen *et al.*, 2007:396).

<u>Asthma Severity:</u>	<u>Asthma Control:</u>
• Refers to the pathological state of the disease, • Determined by underlying phenotypes, • Monitored by the intensity of treatment needed to control the asthma.	• Reflection of disease activity, • Determined by objective and subjective factors, • Monitored by symptom changes, daily limitations, and reliever medication use.

Table 2.14 Asthma severity and asthma control

(Source adapted from: Moore *et al.*, 2007; Pedersen, 2009)

Asthma control may be affected by certain concurrent conditions or conditions following the same pathological pathways ('co-morbid conditions'), such as:

- Rhinosinusitis
- GERD (Gastroesophageal reflux disease)
- Psychological disturbances
- Chronic infections
- Obstructive sleep apnoea

The influences of these conditions are inconsistent and most of all open to question. They might influence the phenotype, pathophysiological process, diagnosis, and control, and therefore would need to form part of the clinical assessment of asthma management (Boulet, 2009:897).

2.7.1.2 Triggers and precipitating factors

Despite the importance of genetic risk factors in asthma development, it still is not enough to explain the huge upsurge in asthma prevalence over the last decades (Rumchev *et al.*, 2002:407). A countless number of factors have been offered as an explanation for the increase in asthma, but it would seem as if many factors work together as responsible constituents, namely: air quality, dietary changes, allergens, immunisations, decreased childhood disease exposure, and several lifestyle transformations (Giardino & Schmalting, 2002). Furthermore, several studies as of the 1900s (Sherrington's classic experiments), up until today, have demonstrated that 'Pavlovian conditioning' for example, towards odours, could as well be a role player in asthma symptoms (De Peuter *et al.*, 2005:454; Giardino & Schmalting, 2002; MacQueen *et al.*, 1989:83).

Human life consists of different combustion wonders, one of them being breathing. To breathe, the surrounding environment must be in equilibrium, which implies that for normal human functioning there must be optimal pressurised gaseous air (to keep water from vaporising from body cells and thereby vessels from bursting), fit for the purpose (a sufficient oxygen quantity with constant supply).

“...the reaction between the chemicals in the atmosphere and the sodium contained in the water filling each cell that made up his very being. The moisture was being sucked out of him.”
 --- William Edge, *Breathing without Air*, 2005

Air plays a key role in human functionality, even indirectly by means of thermo-control, sound production and light output, but without enough water sustainable oxygen absorption is impossible, the result being death (NASA, 2007). According to Dan Quayle, vice president to George H.W. Bush, not pollution, but “the impurities in our air and water” are “harming the environment”.

Although several risk factors for asthma were discussed throughout, other exposures to cause temporary airway reactivity are plentiful. Managing allergic respiratory conditions due to these trigger factors implies establishment of the allergen, avoidance thereof, and treating with purposeful immunotherapy (Leung, 1996:309) (See Table 2.15 for a brief summary of common allergens).

<u>Common Allergens:</u>
➤ Pollen: Tiny pollen grains released from trees, weeds, and grasses ➤ Mold: Tiny fungal spores or pieces of fungi ➤ Mites: Dust mites which live in bedding, upholstered furniture and carpets ➤ Indoor insects: Mainly cockroaches ➤ Outdoor insects: Mainly stinging insects, can cause anaphylaxis (life-threatening form of allergic shock) ➤ Animals: Saliva- or urine protein of animals ➤ Chemical: Chemicals such as paints, perfumes, cigarette smoke, plants and plastics (More of an irritant than an allergen) ➤ Trichloroacetic acid (used in the production of sodium salt, again used as an herbicide, etching agent and antiseptic.) (In the environment: found in chlorinated drinking water.)

Table 2.15 Common Allergens

(Source adapted from: GreenFacts, 2009; U.S Department of Health and Human Services, 2003)

Allergies and their reactions are mere exacerbation factors of asthma and not seen as primary cause thereof. Immunochemistry advances lead to intense research in the field of allergy, allergens, sensitivities and IgE antibodies (ab) of the asthmatic patient, and proved a higher IgE ab prevalence in asthmatic patients than in the remaining population, that declined with rigorous avoidance techniques of allergens, while symptom and bronchial hyperreactivity changes were only noticed after 4-12 months of genuine allergen reduction (Chapman *et al.*, 1988:185). Airborne allergens elevate the antibody count of IgE and precipitates acute asthma attacks, but asthmatic patients that are pollen or bacteria sensitive seem to be the only ones where climate plays a role of importance as a pre-disposing factor (Piness, 1921:29). Although there is no resemblance to allergens in the overall intrinsic asthma mechanism of inflammation, the process (Th2 increasing, activation of mast cells and eosinophilic infiltration) and the synthesis of IgE demonstrates many similarities between the 2 major asthma groups (Barnes, 2009). Dowse *et al.* (1985:75) proved that allergen introduction into the environment leads to a drastic asthma prevalence increase. The question now is: "What is the inter-relationship between allergen levels, their particle size and the provocation of asthma attack precipitation?" Fossil fuel combustion, this including elements such as coal, oil and natural gas, increases the concentration of carbon dioxide. These tiny particles (PM2.5) with a diameter less than 2.5 microns, can stay airborne for weeks and on inhalation can react as an irritant to the airways or it can cause direct artery damage (Rosenthal, 2006). An increase in this irritant stimulates abnormal growth of ragweed¹ as well as other plants that in its turn produces up to 60% more pollen than in normal air. This is more frequently found in city air and leads to an increase in childhood asthma. According to recent studies these particles can move across the boundaries of continents and lead to thousands of premature deaths yearly, which again show that asthma becomes a global problem.

There is conclusive evidence that changes of climate do have an effect. This poses many health challenges and also exercises an impact on health outcomes (Brenner & Parker, 2009). Schmier & Ebi (2009:229) investigated the concentration distribution of some airborne allergens and the effect on asthma symptoms. It proved that weed pollen had an enormous effect on asthma exacerbations and hospital visits, although intensive research is still at need for the link between the specific symptoms and the aeroallergens. One to two days after temperature and humidity changes asthma exacerbations are triggered, while

¹ One ragweed plant brings forth ± 1 billion pollen grains on average per season and can do travelling of up to 400 miles (643.7km) depending on the wind conditions (Brown, 2009).

barometric pressure shows no influence (Mireku *et al.*, 2009:220). According to studies done by Hare & Buchdahl (2004) and Tidball (2008), “Every 10% increase in indoor humidity was associated with a 2.7% increase in the prevalence of asthma symptoms”. The number of mites (*Dermatophagoides pteronyssinus* most common in South Africa) in house dust is again dependent on the region’s humidity (Ordman, 1971:739), since the availability of water in the mite habitat, is interdependent with their level of occurrence (Arlian, 1977:484). This might be one of the reasons for the so-called: ‘climate asthma’.

According to the PIAMA study done on children up to the age of 8 years, pets at home seem to sensitise children against inhaled allergens, but this had no positive effect on asthma prevention. In fact, these children demonstrated a higher frequency of asthma symptoms. (From 2 years onwards: wheeze and night time cough – dog related; removal of the dog – asthma symptom development risk increased) (Kerkhof *et al.*, 2009:1202).

Epidemiological and pathophysiological pathways of asthma and allergic rhinitis are similar, and recommendations for a combined guideline might benefit the patients (Gaugris *et al.*, 2006:1). As for asthma management, optimal treatment of allergic rhinitis, and trigger avoidance, proved to have significant effects on asthma symptomology and lung function (Rachelefsky, 1999:296), and can therefore help with reduction of asthma severity, and in this way contribute towards improved or optimal asthma control.

Other triggers and/or precipitating factors for asthma are briefly mentioned below:

A. Smoking shows an increase with regard to the following:

- Asthma frequency and severity
- Chances of infection and/or COPD and/or lung cancer
- Theophylline metabolism (and therefore dose adjustments must follow)
- Links with peptic ulcer disease (PUD), emphysema, strokes, heart disease and chronic bronchitis (Asthma and allergy care, 2008).

“It is estimated that by 2030 smoking will kill one in six people globally, if current trends continue” (SAHR, 2008). Furthermore, smoking interferes with a patient’s response to treatment (Hylkema *et al.*, 2007:438).

- B. Obesity in particular in females, is seen as a risk factor for asthma (Barclay, 2009), but more specifically, abdominal obesity, is known for its influence on systemic inflammation (Von Behren *et al.*, 2009). Von Behren *et al.* (2009) showed a surge in the prevalence of asthma even in females with normal body weights but increased waist sizes². Vahlkvist & Pedersen (2009:1649) also wrote that untreated asthmatic children seem to have lower fitness levels, higher body fat percentages, and are higher up on the obesity ladder.
- C. Formaldehyde (also known as methylene oxide, oxomethane, or methylaldehyde) is derived from human production (a harmless amount), exhaust fumes from vehicles, cigarettes and other tobacco products, some types of fabric, drapes, furniture, glues, adhesives, painting, cleaning products, and insulation materials. It can also be absorbed by porous products such as carpets, to be released on days when there is a rise in temperature and/or moisture in the air. Outdoor air in urban areas seems to have higher concentrates of formaldehyde than that of less populated areas, although our indoor air contains seriously higher amounts. Why are these factors being mentioned? It is known that formaldehyde exposure can induce irritation of the eyes, nose and throat (at low concentration), which in its turn can present, symptom wise, as asthma (Vermont Department of Health). Rumchev *et al.* (2002:406) studied the influence of formaldehyde exposure (levels of $\geq 60 \mu\text{g}\cdot\text{m}^{-3}$ (49 parts per billion)) in children aged 6 months to 3 years. The results showed an asthma increase of 39%.
- D. Air pollution: The American Lung Association President and CEO, Charles D. Connor, said: “We at the American Lung Association believe that the new ozone standard is not yet strong enough to protect human health – an opinion nearly all scientific experts share” (American Lung Association, 2009). “Air pollution worsens asthma...” said Norman H. Edelman, American Lung Association Chief Medical Officer (American Lung Association, 2009).
- E. Infections “trigger and perpetuate asthma” (Mirkin, 2010).

² As for interest: Overweight and obesity are also linked to significantly lower brain volumes in elderly (Cassles, 2009; Raji *et al.*, 2009).

- F. Hypochloride bleach: Zock *et al.* (25/8/09-2) state that: “People who clean their homes with hypochloride bleach are less likely to be atopic but more likely to have respiratory symptoms.”
- G. WORK is another factor. How do you avoid work if it is your work that makes you ill? This is the so-called “occupational asthma”. Now, do not confuse it with “work-aggravated asthma” where the origin is not work-related, but exposure only aggravates the condition (see Table 2.16).

<u>Occupational Asthma:</u>		<u>Work-aggravated Asthma:</u>
<i>‘With latency’:</i>	<i>‘Without latency’:</i>	
- Delayed onset to exposure	- No delay present	- Non-occupational
- Antigenic agent related	- Non-allergic nature	- Non-specific irritant response
- Several exposures		
- Time requisite		

Table 2.16 Occupational and work-aggravated Asthma

It is important to take note that non-occupational work-aggravated asthma can be a cause of work disability due to the fact that this patient cannot measure up to the physical needs of his/her job, but significant tuition and control of asthma and its severity can help in combating work-related asthma (Occupational / Non-occupational).

2.7.1.3 Adherence

Clinical adherence can be divided into two groups: the patient’s adherence to therapy, and the health care provider’s adherence to regimens of management. These groups need to be in sheer harmony to offer near plenary control of asthma (Mangan & Bailey, 2010). The complexity of establishing such harmony reaches far wider than meets the eye. It involves different medication types (inhaled versus oral medications and bronchodilators versus anti-inflammatories), psychobiological factors, and patient behaviour (Kohler *et al.*, 1996:16). According to neuroscientist Richard Davidson (Hatch, 2005) the mind plays an important role in asthma, since asthmatic symptoms have an effect on the patient’s emotional state, which in turn influences the behaviour around medication adherence. Aspects of asthma behavioural change include

- a) trigger removal (Seguin, 2008);
- b) peak flow monitoring;
- c) checking inhaler techniques; and
- d) documenting in the form of an asthma diary (Tousman & Zeitz, 2003:86).

Corsico *et al.* (2007:1363) demonstrated the importance of regular health care provider-patient interaction towards the increased level of adherence, while according to Mangan & Bailey (2010) health care providers need to “adequately inform” patients on regimens and adherence discussions need to figure. In the case of non-adherence, the barriers need to be identified and eliminated as far as possible. Adherence barriers identified by Bender & Bender (2005:107) were the following: cost and drug safety apprehension, patients’ belief or disbelief in the diagnosis and the need for medication, concerns about dependence, long-term drug effectiveness and stigmatisation. Non-adherence factors, according to research, seem to be anything from device or regimen difficulties (Modi & Quittner, 2006:846), side-effects or medication dislikes, travelling costs, health care provider dissatisfaction (be it personal or communication), foible follow-up, under- or overuse of medication and religious beliefs (Babey *et al.*, 2009; Mangan & Bailey, 2010; Mork *et al.*, 2003:815). Van Grunsven *et al.* (1998:1178) hypothesised that patients out of a fear for corticosteroid use refused participation in the “DIMCA” (Detection, early Intervention and Monitoring programme with inhaled corticosteroids in COPD and Asthma) study, but concluded that it was not a significant factor.

It would seem that there is no definite link between asthma knowledge as a single entity and a patient’s adherence to treatment, but more so that attitude and collaboration play a major role towards compliance (De Vries & Petermann, 2008:139; Ho *et al.*, 2003:498; Kohler *et al.*, 1996:16; Scherer & Bruce, 2001:250). Smith *et al.* (2008:765) concluded that suboptimal controlled asthma correlates with factors around ‘low parental expectations for asthma outcomes’ and ‘competing family priorities’. One of the newer strategies followed to link up with the behavioural transformation is that of motivational interviewing (MI) to bridge the gap between the approach of education and self-management, and the resistant patient (Borrelli *et al.*, 2007:1023). According to Ulrik *et al.* (2006:701) non-adherence can be addressed by patient and health care provider education, but on several levels. Also used to help with informed goal settings and adherence are “case-based or video-scenario studies” together with prompt multi-disciplinary feedback and discussion (Clark *et al.*, 1998:831; Yawn *et al.*, 2005:300).

A hard to reach goal is that of long-term adherence. A reported 50% of chronic diseased patients do not adhere to prescribed therapy (Lindberg *et al.*, 2001:375), while health care providers prove not to follow set guidelines. The introduction of National and International guidelines for the management of asthma patients was mainly to improve the quality of care delivered (Lindberg *et al.*, 2001:375), since impaired health and increased health costs are both coupled to a degree of guidelines management failure (Omenaas *et al.*, 2006:S31). In order to improve adherence, more group specific approaches (e.g. African-Americans and Whites) are asked for (Wells *et al.*, 2008:1194), as well as the possibility of local guidelines, that would take regional factors into account, and might influence a patient's behaviour (Price & Thomas, 2006:S6).

Another factor to take into account is that of the asthma disability and stigmatisation.

"Attitudes are the real disabilities"

--- Ms. Trottier, Harvard University's Administrator of Disability Services. (AAFA, 2005)

The Disability Discrimination Act phrases a disability as: "A physical or mental impairment which has a substantial and long-term adverse effect on a person's ability to carry out normal day-to-day activities" (University of Oxford Equal Opportunities), while the wording for a disability by the WHO is: "any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being". In more ways than one these definitions of disability may apply to those who suffer from asthma.

Stigmatisation or pessimism can lead to a vicious circle of discrimination, marginalisation and devaluation, but according to Snadden & Belle Brown (1991:329) it is not featuring high in the 'illness experience' of asthmatic patients, where on the other hand, the prevalence of asthma disabilities and their radical effects (especially on children) continue to escalate at a larger level than in other chronic diseases. Newacheck & Halfon (2000:292) demonstrated in their research that the "prevalence of disability due to asthma has increased more than 3-fold over the past quarter century". Detection and management of co-morbid conditions (e.g. psychological distress) along with asthma would play a very important role in the control of disabilities, since it has been proved that asthmatic patients with adjacent psychological distress have a higher prevalence with regard to functional disabilities (Schmitz *et al.*, 2009:42).

2.7.1.4 Goal setting, Self-management and Primary care Targets

Optimising accurate asthma diagnosis, giving effective treatment with minimal adverse effects and attaining proper asthma control will help to combat this mostly invisible chronic illness (Koshak, 2007:45). The aim of all national and international guidelines is to reach the point of managing a complete asymptomatic patient with nullified target organ damage (Irusen, 2007:3), but factors ranging from the health care provider (e.g. overestimation of the disease control level) to the patient (e.g. toleration of substantial symptoms) and everything in between lead to suboptimal control of asthma (Irusen, 2007:3; Wechsler, 2009:707). With this in mind, management goals would include the following:

1. Minimum of the following:
 - Chronic symptoms
 - Exacerbations
 - Need for reliever β -agonists
 - Medication adverse effects
2. None of the following:
 - Emergency visits
 - Daily activity limitations
3. Presence of the following:
 - Normal to near-normal PEF
 - Circadian PEF variation of < 20% (GINA, 2009; Yawn *et al.*, 2005:295)

According to Willems *et al.* (2006:436) self-management can lead to cost savings if guidelines are followed. This calls for clear succinctly written, but also discussed and provided, action plans as set by both national and international guidelines for asthma management. However, these seem to be non-existing in most cases (Modi & Quittner, 2006:847; Scheck, 2006). These action plans reduce work absences, emergency visits and hospital admissions, as well as the use of reliever medication. Furthermore, there is improvement of lung function (National Asthma Council Australia, 2009). The content of such plans need to include the following:

- The dose and frequency of the control and/or reliever medication
- Treatment adjustments in the case of exacerbations and/or severity changes
- Seeking medical help: signs to be on the lookout for (National Asthma Council Australia, 2009)

The focus is now set on asthma control, and the health care provider needs to assess the level of control for each patient, then to adjust the treatment to achieve and maintain optimal control.

Analysing a patient's treatment response can be very useful, it can help to get to the root of the problem, and in this way establish the accuracy of the diagnosis (Taniguchi *et al.*, 2009). According to To *et al.* (2009), health care providers believe that asthma care programmes, based on national/local guidelines, offer approaches that are well-accepted and deliver improved asthma care and management in the primary health care system.

2.7.2 Treatment



Photo: courtesy of inhalatorium.com

Asthma treatment in the 19th century evolved around allergen free environments by means of high altitude or dry climate centres with clean water, clean air, and sunshine as medication. Between the 19th and 20th century medicinal substances (such as tobacco and stramonium) were introduced through cigarette and pipe smoking, and later tablets, powders, inhaled remedies of various herbs and substances, and morphine in combination with cocaine injections were acceptable in addition to the smoking. By the end of the 20th century new and more effective treatment was established. As of the 1900s adrenaline injections (epinephrine) continued to be the therapy mainstay, but altered, gave “birth” to isoproterenol. Theophylline introduction only came around the 1930s with anti-inflammatory medication (corticosteroids, cromolyn sodium, and anti-leukotriene) looming in the 1960s after the proof of an inflammatory component to asthma, as a physical condition (Asthma & Allergy Foundation of America, 2009; Rutkowski, 2003:doi 10.1016). The rapid progress in asthma comprehension consequently expanded the “as-needed” bronchodilator use for asthma management to action plans and maintenance therapy (Szeffler, 2000:S139).

2.7.2.1 Pharmacotherapy in asthma

Effective and optimal management of a patient with asthma requires diagnosis verification, evaluation, and trigger factor or co-morbid condition management, together with individual adjustment of the pharmacotherapy, in order to attain and maintain long-term symptom control, inhibit exacerbation, achieve the maximum lung function and daily activities, as well as minimise the adverse effects of therapy (Lima *et al.*, 2009; Tai & Ranganathan, 2007:520). According to a workshop group (American Thoracic Society Workshop Report, 2000), pharmacotherapy needs to be in harmony with the guidelines as set out in the Expert Panel Report 3 (EPR3), of the National Asthma and Education Prevention Program (NAEPP), highlighting the high dose/high-potency inhaled corticosteroids (ICS), oral corticosteroids (CS) at low dosage due to adverse effects or side effects, and controller agents varying from one to three. Clinic visits on a regular basis, daily PEF recordings and an appropriate patient-directed action plan are required.

Asthma treatment can be divided into 2 main categories:

- A. *Quick-reliever medication*, that brings about relaxation of the smooth muscles of the airways to reverse acute bronchoconstriction
- B. *Long-term controller medication*, which exerts anti-inflammatory effects (Schmaling *et al.*, 2003:98)

Several types of drugs are available for the treatment of asthma, whether they are meant to relieve or to control the symptoms, on long- or short-term. These would be the determining factors for drug choice (or so was the belief).

- A. Quick-relievers: - These drugs render short-term relief by easing the symptoms of asthma episodes, therefore they are used only as required ('rescue therapy'). If use of this therapy is required more than twice a month for night awakenings, or more than two days per week, the need for controller therapy exists (Fanta, 2009:1003).
 - i. Bronchodilators: Relax muscle in and around the airways, (reversing obstruction of airflow) within ≤ 5 minutes, while lasting 4-6 hours, and include the following:



Short-acting β_2 -selective adrenergic agonists (SABAs):

- Rescue medication for virtually all asthmatics
- Reversibility varies to a great extent
- Also reduce exercise-induced asthma
- Regular use (4 plus times per day) leads to shortened duration of action, although the potency stays the same
- The need for use before inhaled corticosteroid use, as an improved delivery mechanism, has fallen out of place (Mackay & Dyson, 1981:75)
- Spacing of inhaled puffs (10-15 minutes apart), has luckily enough also proved to be unnecessary (Lawford & McKenzie, 1983:77)
- Pressurised aerosol (inhaler β_2 -agonist) use was at question from the 1950s, but was set aside after the sequencing of β_2 -adrenergic receptor gene (ADRB2) (Lima *et al.*, 2009)
- Fenoterol proved to worsen asthma control, although albuterol showed no detrimental effects, the reasoning of different genotypes (variants in ADRB2) being the cause (Lima *et al.*, 2009) seems not to be a reliable prediction
- Side-effects at the level of two puffs per administration dose are most unlikely, although at higher dose levels, symptoms can be of the following: tremors, anxiety, tachycardia, palpitations, and decreased levels of potassium and magnesium (Fanta, 2009:1003)
- No contraindications for patients on β -blocker therapy (Salpeter *et al.*, 2002:137)
- Oral use by means of liquid or tablet form, relates to regular side-effects, are less potent, and have a longer onset of action (Nathan, 1992:49)
- Tradenames (South African use): Albuterol (also known as salbutamol) and branded as: Ventolin™.
- Tradenames for international use: Brethaire™; Bronkosol™; Isoetharine™; Medihaler-Iso™; Metaprel™; Tornalate™; albuterol (also known as salbutamol), branded as: Ventolin™ / ProAir™ / Proventil™; levalbuterol (purified albuterol isomer), branded as: Xopenex™; pirbuterol ('breath-actuated metered-dose inhaler'), branded as:

Maxair™; and recently withdrawn, metaproterenol, branded as: Alupent™.



Long-acting β_2 -agonists (LABAs):

- As the name indicate, long-acting β_2 -agonists are more of controller therapy, but their quick onset of action give them a place as a reliever and therefore need to be mentioned here as well.
- These preparations have a quick onset of action (5 minutes) (as rescue therapy use), and last at least 12 hours (maintenance). Therefore the combined use with inhaled corticosteroids helps to prevent night symptoms and see to a prolonged control time (Mayo Clinic, 2006).
- Formoterol, branded as: Foradil™.

In order to personalise SABA and LABA therapy, major research in pheno- and genotyping are still called for.

ii. Anticholinergics:

- Use as a quick-reliever is only indicated in β -agonist intolerance or β -blocker induced asthma.
- The onset time of action is 20-30 minutes, with a less than optimal bronchodilation effect (Fanta, 2009:1005).
- Not registered by the Food and Drug Administration (FDA) for quick relief therapy in asthma.
- Ipratropium, branded as: Atrovent™.

B. Long-term controllers:

- Used on a regular basis for chronic symptom control as well as for long-term prevention of asthma attacks.



Inhaled corticosteroids (ICS):

- Anti-inflammatory drugs that reduce, and prevent, airway swelling and mucus production
- It is the most commonly used chronic therapy, and prove to be the most effective drug
- It proves to have an up- and down-regulatory transcription effect on several genes, thereby altering the typical asthma abnormalities (Barnes, 2006:148)
- Furthermore, it results in a decrease of the bronchial hyperresponsiveness (factor 2-4) (Haahtela *et al.*, 1991:325)
- Thus, it controls, but does not cure inflammation.
- Keep in mind, differing benefit levels, and the fact that it may have dangerous adverse effects
- Some tradenames: Aerobid™; Azmacort™; Beclovent™; fluticasone branded as: Flovent™; budesonide (for South African use) branded as: Pulmicort™. (Fanta, 2009:1006)

Personalising inhaled corticosteroid treatment would mean more pharmacogenetic studies to identify sites of responsible heterogeneity. Adverse effects include hoarseness or loss of voice, coughing, sore throat, oral yeast infections, the risks of thinning of the skin, bruising, osteoporosis, increased intraocular pressure and cataracts, as well as mouth and/or throat irritations. With growth retardation in children on higher doses of inhaled corticosteroids (as high as 1000 µg per day) (Fanta, 2009:1007). Studies have shown that low-dose inhaled corticosteroids (budesonide 200-400 µg per day, and up to 500 µg into adulthood) do not stunt children's growth over an overall treatment period of up to 6 years (Agertoft & Pedersen, 2000:1066; Priftis *et al.*, 2006:317; The childhood Asthma Management Program Research Group, 2000:1060;).



Oral corticosteroids (CS):

- Short- /long-term use.
- Some tradenames: (SA) Celestone™, Decadron™, Medrol™, Prednisone™
(Other) Aristocort™, Sterapre™
- Some tradenames for paediatric use: Pediapred™, Prelone™ (SA).

For oral and intravenous corticosteroids, as used in acute asthma attacks and very severe asthma, to be fully functional, it takes a few hours up to a few days, and can present with serious adverse effects such as cataracts, osteoporosis, muscle weakness, decreased levels of infection resistance, elevated blood pressure, and can even be life-threatening (Mayo Clinic, 2006).



Long-acting β -agonist bronchodilators (LABAs):

- Onset of action: 15-20 minutes
- Used for relief of day or night symptoms as well as exercise-induced asthma.
- Another hot debate on safety: Salmeterol (Serevent Diskus) use (with/without inhaled corticosteroids) demonstrated notably worse asthma control to placebo users. (For current study: see <http://www.acrn.org>)
- Salmeterol branded as: Serevent™; formoterol branded as: Foradil™.



Leukotriene modifiers:

- Prevent inflammation and swelling of the airways, reduce mucus and open airways by means of leukotrienes' action inhibition.
- Optimal bronchodilation within a few days, but it already starts within hours of the first dose.
- Added benefit is that of an eosinophil level decrease in circulating blood, but no proof yet of airway eosinophil changes (Pizzichini *et al.*, 1999:12).
- Safe and effective with a unique mechanism of action and a convenient oral dosing (LTRAs – once daily), although some advantages are detracted by heterogeneity (Lima *et al.*, 2009).
- Zileuton asks for liver function testing, since 2-4% of patients develop a reversible chemical hepatitis, whereas LTRAs and the Churg-Strauss syndrome have been linked lately (Wechsler *et al.*, 2000:708), but are still debatable.
- Two classes available namely 5-lipoxygenase (5-LO) inhibitors (zileuton), and leukotriene receptor antagonists

(LTRAs) (montelukast branded as Singulair™; zafirlukast branded as Accolate™, pranlukast) (Lima *et al.*, 2009).



Daily inhaled nonsteroids:

- Such as cromolyn sodium (Intal) or nedocromil sodium (Tilade)
- Prevent airway swelling after allergen contact, and can be useful in prevention of exercise-induced asthma.



Daily oral use of theophylline:

- May be useful for relieving persistent or night symptoms
- Important is the optimal and constant level of drug needed for therapy to be at its best. High levels can be dangerous, therefore regulation of symptoms both in normal situations, as well as under stress, is essential (Mayo Clinic, 2006).
- Some tradenames: Aerolate™, Elixophyllin™, Theolair™, Theo-24™, Theo-Dur™ (SA), Theo-X™, Uni-Dur™, Uniphyll™, Resbid™, Slo-bid™, Quibron-T™.



Combined therapy:

- Contains both control and relief medication (Bronchodilator and corticosteroid).



Injected Anti-IgE therapy:

- Monoclonal antibodies
- Helps to stop allergy by biologically immunoregulating (treating the cause instead of the symptom)
- Intravenous therapy decreases IgE levels by 95% (Milgrom *et al.*, 1999:1966), but subcutaneous administration is the method of choice
- Adverse effects are minimal, but can include anaphylaxis, hives at the injection site, and systemic reactions counteracted by 'prefilled epinephrine-containing auto-injectors' for self-management (Cox *et al.*, 2007:1373)
- A major drawback of this therapy is the cost that is currently set at \$10,000 to \$30,000 per year (Fanta, 2009:1011)
- Omalizumab (Xolair™).

Inhaled corticosteroids has been shown to preserve the lung function (Van Grunsven *et al.*, 1998:1178) with the bronchial hyperresponsiveness to histamine or methacholine improving within weeks of the initiation of inhaled corticosteroid treatment (Colice, 2002:4; Grootendorst & Rabe, 2004:82), while β_2 - adrenoceptor agonists and phosphodiesterase (PDE) inhibitors demonstrated no effects of epithelial repair, and glucocorticoid effects seemed to be controversial (Swindle *et al.*, 2009:30; Wadsworth *et al.*, 2006:376). According to Obase *et al.* (2010:247), corticosteroids (inhaled budesonide), increased the levels of tissue inhibitors of metalloproteinases (TIMP-1) in the tissues of the airways, while it normalised the expression ratio of matrix metalloproteinases-8 (MMP-8) and TIMP-1 by airway macrophages, making this the next possible biomarker to assess the process of remodelling of the airway. On the other hand, undertreatment of asthma, by means of no inhaled corticosteroid treatment, too low dosage of inhaled corticosteroid treatment, or the use of a lower dose as prescribed treatment by own will, can be problematic, so can be the treatment for asthma control. Serious controller treatment side-effects can be incapacitating or life-threatening to these patients (Yawn *et al.*, 2005:295).

The usefulness of inhalation therapy is in the small amounts of drugs it is able to deliver to specific target sites. The problem linked to this method, is the hasty clearing of drugs (lungs to the systemic circulation), which again can be linked to increased dose frequencies and as result, the likelihood of side-effects. Saari *et al.* (1998:1573) wrote about the liposome encapsulation of drugs before administration, using ^{99m}Tc -labeled Beclomethasone-DLPC liposomes for the use of prolonging the lower airway stay of inhaled drugs and thereby limiting the redistribution rate. Furthermore, it is proved that leukotriene receptor antagonists (LTRAs) added to antihistamine treatment for allergic rhinitis demonstrated a quicker relief of sneezing, and less nasal congestion than in mono-therapy (Li *et al.*, 2009:1091).

C. Other:

- ❖ Single inhaler for maintenance and relief therapy (SMART) (inhaled steroid budesonide and long-acting β_2 -agonist formoterol, with a rapid onset, in a fixed combination) (Green *et al.*, 2007:172).

- ❖ Prostaglandin D2 is a proinflammatory mediator, but laropiprant, the prostaglandin D2 receptor type 1 (DP1) gene antagonist, proved not to have an effect on asthma or allergic rhinitis (Philip *et al.*, 2009).
- ❖ Isotonic saline solution (same salt level as the body) used as nasal drops/spray, flushes allergens, decreases the level of inflammation and help with reactivation of airway cilia (Rosenthal, 2008).
- ❖ An inhibitor of the proinflammatory cytokine, tumor necrosis factor-alpha (TNF- α), has been used over a decade already for conditions such as rheumatoid arthritis (RA) and other autoimmune diseases. It is now next in line for possible asthma use, but close monitoring of adverse effects and infections will have to be performed (Kavanaugh, 2009).
- ❖ T-cell epitope mapping might be the breakthrough to future peptide therapy for allergy and asthma, since it helps with the understanding of the immune response (Malherbe, 2009:79), by suppressing responses to other epitopes and inducing IL-10⁺ T cells (Campbell *et al.*, 2009:1546).
- ❖ Clinical and economic burdens as a result of uncontrolled asthma could be lifted somewhat with IgE blockers, such as omalizumab, by reducing exacerbation frequency, minimising symptoms, and improving lung function (Bootman *et al.*, 2004:31).
- ❖ According to Heaney & Robinson (2009:974), severe asthma asks for an increased dose of inhaled corticosteroids in combination with LABA, or anti-IgE therapy.

D. Special clinical circumstances:

Further complication of asthma and its treatment are diseases such as renal and cardiac diseases and the factor of multiple-sensitisation. For younger non-responsive individuals it is important to keep an underlying endocrine dysfunction in mind (Piness, 1921:29).

- Pregnancy and post-partum:

Perry *et al.* (2009:342) demonstrated that total IgE levels seem to increase post partum, although the IgE levels specific to certain allergens decreased.

- Cigarette smoking:

Patients with mild persistent asthma, who smoke, demonstrate impaired therapeutic levels of inhaled corticosteroid (ICS) (Chalmers *et al.*, 2002:226), but this features mainly in low dose therapy (e.g. beclomethasone < 400 µg daily) (Tomlinson *et al.*, 2005:285). It is therefore important to make sure that the treatment asthmatic, smokers receive are optimal.

E. Research developments:

- Professor Konstantin Buteyko points out the single cause for asthma as chronic hidden hyperventilation (CHH) (Buteyko Kent, 2009).
- Easily measured elevated blood levels of chitinase-like protein (YKL-40) (a substance not manufactured by the human body, but plentiful in fungi, crustaceans, helminths, cockroaches and dust mites) were found in severe asthma (Drugs.com, 2008). These proteins trigger the human defence against a believed infection, but a decrease in certain types of tissue inflammation were seen with elimination thereof. According to Dr. Burton Dickey, these findings could have new diagnostic and therapeutic benefits for asthmatics (Drugs.com, 2008). The same goes for tracking down 3-bromotyrosine (formed by eosinophil peroxidase-dependent reactions) which is a trade of the inflammatory response of allergy and asthma. Future studies can lead to development of possible eosinophil peroxidase inhibitors to help manage and control asthma (Heinecke, 2000:1331). Blocking IL-5 with specific antibodies brought about significant eosinophilic changes in patients with mild asthma, but interestingly enough, the changes expected in bronchial hyperresponsiveness were not present. This brings about a new question, and maybe dimension, to the role of eosinophils in bronchial hyperresponsiveness (Grootendorst & Rabe, 2004:83).

- Hitomi *et al.* (2009) reported that the latest findings regarding *NLRP3* SNPs (NLR family, pyrin domain containing 3, single nucleotide polymorphisms) could lead to diagnostic and therapeutic gain for aspirin-induced asthma and food-induced anaphylaxis, since *NLRP3* indirectly controls inflammatory activity, through caspase-1, inflammasomes, procytokines IL-1 β and IL-18.
- Together with decreased LX, the overall capacity to generate 15-LO-derived lipid mediators, as counter-regulatory mechanisms need to be investigated further in terms of aspects such as inter-relationships, sites of action, and signalling mechanisms (Planaguma & Levy, 2008:703).
- Airsonett Airshower (AA) used in patients with perennial allergic asthma proved to result in a better quality of life. This allows laminar airflow to reach the patient's breathing zone while this non-pharmaceutical treatment is still to be looked into (Brodtkorb *et al.*, 2009).

2.7.2.2 Medication adverse effects/side-effects

The WHO Policy Perspectives on Medicines (WHO, 2004) point out the importance of adverse drug reactions (ADRs) by saying that in some countries it grades to the top ten leading causes of death. Furthermore it emphasises the fact that considerable skill is called for to make the correct patient-specific drug choice. In order to do so, pharmacovigilance are at the day. This is a general term for the monitoring process of ADRs, defined by the WHO as: "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (WHO, 2004).

These effects were discussed in section 2.7.2.1 'Pharmacotherapy in asthma', under each therapy, but just a few important areas are highlighted here again:

- ✓ Inhaled corticosteroids (ICS): Relatively safe. High doses can cause systemic ↓ s-cortisol levels.
- ✓ The phospholipid lining of the area between the mucosa of the respiratory tract and the mucus, according to Girod *et al.* (1991:2262), features as a protective barrier which facilitates mucus transport. The study looked at treatment possibilities by altering the adhesion of the mucus, and then testing the overall cough clearance of the mucus.

- ✓ According to Metzger (2008:881), for patients on SABA and/or LABA therapy, that demonstrate poor asthma control despite good clinical adherence, factors such as race and *Arg/Arg* polymorphism must be kept in mind.
- ✓ Steroid side-effects can also include Cushing's syndrome. Alternative medicine for uncontrolled asthma with steroid intolerance is Omalizumab (Xolair™), an anti-immunoglobulin E (anti-IgE) antibody (Ceresnak & Lee-Wong, 2008).
- ✓ High dose glycocorticoid treatment side-effects include cataracts, diabetes, osteoporosis, skin atrophy, emotional lability, cushingoid habitus, increased appetite and weight gain.
- ✓ Dr. Jacob Churg and Dr. Lotte Strauss first described 'Allergic granulomatosis', 'Churg-strauss angiitis (CSA)', or 'Churg-strauss syndrome (CSS)' in 1951, as a syndrome featuring "asthma, eosinophilia [an excessive number of eosinophils in the blood], fever, and accompanying vasculitis of various organ systems". This is typically seen in middle aged (equally male/female distribution) individuals with a new onset of asthma, or else, asthma that has worsened lately. The presence of nasal polyps or allergic rhinitis might be early features, and the cause, although unknown, might be multi-factorial (genetics and environmental factors). For more detailed information on diagnosis and management, The College of Rheumatology (ACR) has set out specific criteria, and it is also discussed in Sinico & Bottero (2009:355) (Johns Hopkins Vasculitis Center).
- ✓ Despite the concern, there is still no definite proof that salmeterol in combination with inhaled corticosteroids lend to more, or more serious adverse events than when used as monotherapy (Cates *et al.*, 2009).
- ✓ Price *et al.* (2002:1191) studied the literature and found several studies on inhaled corticosteroid use and the possible limitations it has on child growth. Out of this it appears that if it is used according to the recommended dosages, none of the inhaled corticosteroids portrays significant final height effects, although fluticasone propionate, if any, might have a minimal effect.

- ✓ The benefits of zafirlukast, branded as Accolate are only of short duration ($\pm$ 5 weeks), with original symptom patterns present within 7 weeks. This drug also worsens symptoms upon drug withdrawal, and has side-effects ranging from diarrhea to liver damage (Reid *et al.*, 2008; Sardi, 2008).
- ✓ Over a short period, β -adrenergic receptors drugs such as Albuterol, ventolin and salbutamol cause airway relaxation, but over longer periods they make airways more sensitive to triggers and airway constriction, and become less effective, with associated exacerbations (McGraw *et al.*, 2003:619; Sardi, 2008).

2.7.2.3 Herbal remedies and other

130-201 BC, Galen, a Greco-Roman doctor, treated asthma with owl's blood in wine. Egyptians believed in crocodile and camel droppings, while exotic animal parts were at the order of the day in Chinese and Eastern countries (The Asthma Foundation of NSW, 2009). Luckily enough times have changed and made space for integrative medicine (also known as: 'integrated medicine'). Other than the known conventional medicine, complementary medicine, and alternative medicine, integrative medicine integrates medical therapies with complementary – and alternative medicine (CAM). One of the outstanding points of the integrative medicine definition as set out by the National Center for Complementary and Alternative Medicine at the National Institutes of Health is: "...for which there is some high-quality scientific evidence of safety and effectiveness" (Lemley, 2010). Therefore, by looking at a patient's diet it can be useful to limit fats that are pro-inflammatory (producing pro-inflammatory prostaglandins), and rather stick to anti-inflammatory fats to reduce inflammation of the airways. These fats include:

- Olive- and hemp oil
- Flaxseed and walnuts, alternatively: their oils
- Actual fish (high in fish oils): salmon and sardines (Anaruk, 2008).

Hydration, low sodium, omega-6 fatty acid and transfatty acid intake, as well as a high omega-3 fatty acid, fruit, onion and vegetable consumption may be beneficial to asthma patients according to Jaber, (2002:231). Swindle *et al.* (2009:25) find Vitamin C and E low in asthmatic patients, so theoretically vitamin C supplementation is at the order of the day, but hazy evidence asks for more long-term research (Jaber, 2002:231). Schaubert & Gallo (2008:782), points out that vitamin D deficiency plays an important role in inflammation, but cannot be distinct about the link between vitamin D and asthma.

Other options for the management of asthma include yoga, hypnosis, breathing exercises, massages and biofeedback –assisted relaxation as addition to controlling asthma, but acupuncture and chiropractic therapy are not recommended (Jaber, 2002:231).

2.8 SUMMARY

*“Asthma is often represented as a new epidemic disease
rooted in modern social conditions”
--- Keirns, C.C. (2004:xiii).*

Asthma tells an ancient story of uncertainty, even in a modern society. It brings together disease knowledge and management, and it asks the question of shortness of breath, wheezing, or fantasy. The unsolved problem of defining asthma pulls through to the level of testing, diagnosing, classifying, and controlling asthma, with under-diagnosed and under-controlled asthmatics wandering the streets. Different visions and fundamental disputes lead to even more chaos, and therefore the demand for some asthma guidelines emerged. The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3) guidelines and the Global Initiative for Asthma (GINA®) guidelines arouse and set out a number of management goals, meant to improve quality of care within the framework of reliable health care provider logic (Hanania, 2009:1). In the case of under-controlled asthmatics, guided confirmation steps are followed to reassess the diagnosis, triggers and co-morbidities, adherence, and therapy, and still there is no management of the cause. The key question then remains: “What are we doing wrong?”

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Essential Medicines
WHO Model List

16th edition (March 2009)

25. MEDICINES ACTING ON THE RESPIRATORY TRACT	
25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease	
☐ beclometasone	Inhalation (aerosol): 50 micrograms (dipropionate) per dose; 100 micrograms (dipropionate) per dose (as CFC free forms).
☐ budesonide [c]	Inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
ipratropium bromide	Inhalation (aerosol): 20 micrograms/metered dose.
☐ salbutamol*	Inhalation (aerosol): 100 micrograms (as sulfate) per dose. Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule. Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose. Oral liquid: 2 mg/5 ml. Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml. Tablet: 2 mg; 4 mg (as sulfate). * Oral salbutamol treatment should only be considered when inhaled asthma therapy is not feasible.
26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	Powder for solution.
26.2 Parenteral	
glucose	Injectable solution: 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	Injectable solution: 4% glucose, 0.18% sodium chloride (equivalent to Na⁺ 30 mmol/L, Cl⁻ 30 mmol/L). Injectable solution: 5% glucose, 0.9% sodium chloride (equivalent to 150 mmol/L Na⁺ and 150 mmol/L Cl⁻); 5% glucose, 0.45% sodium chloride (equivalent to 75 mmol/L Na⁺ and 75 mmol/L Cl⁻) [c].
potassium chloride	Solution: 11.2% in 20-ml ampoule (equivalent to K⁺ 1.5 mmol/ml, Cl⁻ 1.5 mmol/ml). Solution for dilution: 7.5% (equivalent to K 1 mmol/ml and Cl 1 mmol/ml) [c]; 15% (equivalent to K 2 mmol/ml and Cl 2 mmol/ml) [c].
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na ⁺ 154 mmol/L, Cl ⁻ 154 mmol/L).