Bronchial Asthma
From
A to Z

Editor in Chief
Prof. M. Samir Khedr

Volume 2
2008
PREFACE
Bronchial Asthma from A to Z

This book provides an illustrative summary of the role of IgE in asthma and allied allergic disorders and the effects of the anti IgE treatment. With little new having been introduced into the armamentarium for asthma therapy in the last five decades other than improvements in 132-agonists, ICS and Montelukast, the introduction of omalizumab is likely to provide a new way of treating allergic asthma with effects which extend beyond a single affected organ and tissue. Its clear efficacy and safety provide a clear statement about the importance of anti IgE across the full spectrum of allergic diseases.

Because allergic asthma is a common and variable disease in its presentation, clinicians need to have a clear understanding of the diagnostic features and to be able to differentiate it from other diseases that present in the same fashion, that is why the chapter of asthma simulators.

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PART (I)
Remodeling in Asthma and Chronic Obstructive Pulmonary Disease

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Airway and lung tissue remodeling and fibrosis play an important role in the development of symptoms associated with lung function loss in asthma and chronic obstructive pulmonary disease (COPD). In the past decades, much attention has been paid to the inflammatory cellular process involved in airway remodeling in these two diseases. However, it is increasingly clear that resident cells contribute to airway and lung tissue remodeling and to associated fibrosis as well. This article deals with some new aspects and discusses the role of vasculature and vascular endothelial growth factor in the development of airway obstruction and airway wall fibrosis in asthma and COPD. Moreover, it addresses the extracellular matrix (ECM) turnover as present in both asthma and COPD. All components of lung ECM (collagen, elastic fibers, proteoglycans) have been shown to be potentially altered in these two diseases. Finally, the interaction between transforming growth factor (TGF), Smad signaling, and TGF in the ECM turnover will be discussed. We propose that ECM damage and repair contribute to airway and lung tissue pathology and that the vasculature may
enhance this process. The localization of this process is dependent on the etiology of the disease (i.e., allergen-driven in asthma and smoke-driven in COPD) and the local environment in which the pathologic process takes place.

Remodeling is an important feature in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD). It may contribute to a large extent to the progressive nature of airflow limitation that occurs in virtually all patients with COPD. Moreover, it may negatively influence the severity of symptoms and progression of asthma as well. It is now well accepted that pathologic processes leading to respiratory symptoms occur in the large airways in asthma. In the last decade research has elucidated that inflammation and remodeling in the small airways is equally important. Conversely, peripheral airway disease long has been acknowledged as the core feature of COPD, whereas the last decade has seen much progress toward understanding of the airway inflammation and remodeling in the larger airways in COPD. Studies have only recently compared both airway compartments and it has become somewhat clearer that the inflammatory and remodeling processes may not always be similar in these compartments. One of the features that is important in this respect is the dissection of the role of inflammatory cells, resident cells (e.g., epithelial cells and fibroblasts), and remodeling with fibrosis of the airways. It is not clear how these cells and the extracellular matrix (ECM) proteins interact, at least not as far as the order of activation and deactivation. Furthermore, the role of the
vasculature and of growth factors for vasculature in remodeling processes in the large and small airways is currently underexposed. This article discusses the current views on peripheral and central airway disease. We will put this in perspective of the contribution of the vasculature and vascular endothelial growth factor (VEGF), as well as the interaction between transforming growth factor (TGF), Smad signaling, and the ECM turnover in asthma and COPD.

**Thickening of The Lamina Reticularis.**

The "true" basement membrane, comprising the lamina rare and lamina dense, separates the airway epithelium from the mesenchyme. Although the lamina rare and lamina densa in airways of subjects with asthma are not reported to differ from nonasthmatic subjects, the lamina reticularis is altered in patients with asthma. This region, which is composed of collagen I, collagen III, collagen V, fibronectin, and tenascin, and is situated just below the basement membrane, has an overall thickness of 3 to 4 µm in nonasthmatic subjects, whereas in asthma this is increased two- to threefold. Functionally, thickening of the lamina reticularis has been linked to reduced airway distensibility and increased airflow limitation in asthma, suggesting that this altered structure has a negative impact on lung function. However, it has been suggested that thickening of the lamina reticularis may actually serve as a protective mechanism by increasing the stiffness of the airways to attenuate the sporadic bronchoconstriction.
Less is known about the basement membrane in COPD, with some reports mentioning increased airway wall thickness and others failing to report it. Whatever the reason behind this (e.g., patient selection, sample bias), it is clear that the constituents of the basement membrane are not similar to those of asthma.

**Increased Vasculature and VEGF Contributing to Airway Obstruction and Fibrosis.**

Vasculature, VEGF, and Asthma Angiogenesis is an important event both in the development of allergic inflammation and in the pathophysiology of tissue remodeling in atopic diseases. In the 1960s, a study by Dunnill demonstrated for the first time that subjects with asthma who die of acute attacks have an enlarged capillary bed in the airway wall. Later, increased vascularity in the airways was recognized not only in patients with severe asthma but also in those with mild disease. These characteristics can account for considerable swelling and stiffening of the airway wall. Recent studies in the airways of patients with asthma have revealed that the ratio between the level of VEGF and endostatin, proangiogenic and antiangiogenic mediators, respectively, is increased in the sputum of subjects with asthma in comparison with that of control subjects. Therefore, it seems that an imbalance in favor of proangiogenic factors leads to the abnormal growth of new blood vessels in asthma. This may then contribute to engorgement of the Vasculature and either thickening or stiffening of the airway wall and hence affect airway obstruction.
VEGF and The Vasculature.

Numerous inducers of angiogenesis have been identified, including members of the fibroblast growth factor (FGF) family, vascular permeability factor/VEGF, angiogenin, TGF-α and TGF-β3, platelet-derived growth factor, tumor necrosis factor α (TNF-α), hepatocyte growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukins, chemokines, and angiopoietin 1 and 2. Among them, VEGF is the most potent directly acting regulator of angiogenesis, and its expression is often excessive in chronic inflammation and fibrosis (Figure 1, Table 1). The submucosa of the airways of subjects with asthma has higher VEGF, FGF-2, and angiogenin immunoreactivity than that of healthy individuals. Importantly, expression of VEGF and its receptors VEGFR-1 and VEGFR2 inversely correlates with the level of airway obstruction.

Furthermore, higher numbers of VEGF-positive cells in the airway wall are associated with basement membrane thickening; involving VEGF in remodeling processes VEGF induces proliferation, migration, and tube formation of endothelial cells. It promotes secretion of interstitial collagenase (matrix metalloproteinase [MMP]-1) and the expression of chemokines, as well as leukocyte adhesion molecules, such as intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin.
VEGF and immune Cells.

Interestingly, VEGF also modulates immune cell functions. For example, it inhibits dendritic cell maturation and increases the production of B cells and immature myeloid cells. It can also inhibit the development of T cells from early hematopoietic progenitor cells. In addition, VEGF stimulates monocyte chemotaxis and contributes to hematopoietic stem cell survival and recruitment of bone marrow-derived endothelial cells in angiogenesis.

Regulation of VEGF and Angiogenesis

Many growth factors and cytokines can regulate VEGF expression. TGF-β was shown to induce VEGF gene expression and secretion in fibroblasts and epithelial cells. Interleukin (IL)-5 and GM-CSF have a similar effect on eosinophils. Many

<p>| Localization of Vascular Endothelial Growth Factor in Asthma and Chronic Obstructive Pulmonary Disease |</p>
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COPD: Chronic Obstructive Pulmonary Disease
inflammatory mediators, such as prostaglandin E1 (PGE1), PGE2, TNF-α, IL-1, IL-6, IL-8, nitric oxide, and platelet-activating factor, have been shown to induce expression of VEGF, angiogenesis, or both. Concerning negative regulation of angiogenesis and VEGF, at least 15 molecules are currently known to be endogenous inhibitors, including endostatin, thrombospondin 1, IFN-α, angiostatin, and tissue inhibitors of metalloproteinases (TIMPs). Macrophages, neutrophils, epithelial cells, fibroblasts, and smooth muscle cells are all important sources of VEGF in inflamed tissue. Different conditions can induce these cells to release VEGF. Several cytokines and growth factors involved in allergic inflammation and in remodeling are responsible for increasing the basal level of VEGF in fibroblasts, smooth muscle cells, and keratinocytes. For example, bradykinin, IL-1, IL-5, IL-13, and TGF-β, are potent inducers of VEGF in airway smooth muscle cells, and TGF-β, together with IL-4 and IL-13, enhances the synthesis of VEGF in bronchial fibroblasts.
VEGF as Chemoattractant.

VEGF is a potent chemoattractant for leukocytes in experimental asthma and induces migration of mononuclear cells across an endothelial cell monolayer in vitro (Figure 1). Recent evidence indicates that eosinophil infiltration could be reduced by administration of antiVEGF receptor antibodies in a murine model of toluene diisocyanate-induced asthma. This is possibly due to the fact that VEGF induces eosinophil migration and eosinophil cationic protein release, mainly through VEGF receptor 1 (VEGFR-1). Together with eosinophils, mast cells can also migrate in vivo and in vitro in response to VEGF, suggesting their recruitment to sites of neovascularization during physiologic or pathologic angiogenesis.
These results indicate that a positive feedback loop can take place in allergic inflammation, with Th2 mediators inducing VEGF release by eosinophils and mast cells and consequent angiogenesis and VEGF enhancing activation of mast cells and eosinophils.

**Vasculature, VEGF, and COPD.**

Vascular abnormalities have been associated with development of COPD. Wright and colleagues reported that there was an increase in wall area of small pulmonary vessels by intimal thickening in patients with mild to moderate COPD and medial thickening in severe cases as well. This thickening was correlated with a decline in FEV1. Hashimoto and colleagues compared asthmatic and COPD small and large airways and found that the number of vessels in the medium and small airways in patients with asthma showed a greater increase than those in patients with COPD and control subjects, and the vascular area in the small airways was increased in patients with COPD versus control subjects, but not in asthma. Furthermore, it was shown recently that muscular pulmonary and bronchiolar arteries have increased adventitial infiltration of CD8 T lymphocytes, cells that are also increased in airway walls in peripheral and central airways.

**VEGF and Angiogenesis.**

Little is known, however, about the molecular mechanisms underlying the loss of alveolar tissue, including the vasculature, in emphysema. VEGF is one of the angiogenic factors that is also
associated with COPD. Kranenburg and colleagues found increased VEGF expression and their receptors (VEGFR-1, also called FLT-1, and VEGFR-2 also called KDR/Flk-1) in 14 exsmoking patients with COPD in comparison with 14 ex-smoking healthy control subjects.

Patients and control subjects had similar pack-years of smoking (on average, 42 and 44 pack-years, respectively). Patients with COPD hadGOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II, and four patients used inhaled steroids. They investigated both central and peripheral airways. VEGF expression was increased in bronchial and bronchiolar and alveolar epithelium, and in bronchiolar macrophages, as well as airway smooth muscle cells and vascular smooth muscle cells in both bronchiolar and alveolar regions. The VEGF receptors were increased in patients with COPD as well. Finally, they found an inverse correlation between VEGF and FEV1 in bronchial mucosal microvessels and airway smooth muscle cells, bronchiolar epithelium, and medial vascular smooth muscle cells of the larger pulmonary arteries associated with the bronchiolar airways.

TGF-β staining in the bronchiolar epithelium also correlated with VEGF in the same patients. They postulated that VEGF and its receptor system may contribute to the maintenance of endothelial and epithelial cell viability in response to injury. In patients with pulmonary fibrosis, fibrotic regions are densely populated by mast cells and macrophages with increased KDR/Flk-1 expression. These
cells are also increased in bronchiolar airway epithelium in COPD and have increased expression of TGF-β. Together, these data suggest that TGF-β-VEGF represents a molecular link between inflammatory cell infiltration at sites of smoking-induced injury contributing to airway remodeling in COPD.

**Fibrosis and Destruction in Asthma and COPD: Role of the Smad Pathway.**

With respect to pathogenesis of COPD, there is a seeming contradiction in the destructive effect of cigarette smoke (CS) exposure in development of emphysema and, at the same time, a fibrotic effect of CS on inner and outer parts of the airway wall of in particular small airways. In asthma, the initial focus was on thickening of the reticular basement membrane, which is an early event; more recently, more attention has been given to ECM changes in other parts of the airway wall, like the outer adventitial part. With respect to remodeling events in the pathogenesis of COPD, the main focus has been on the destructive effects (as a consequence of imbalance between oxidants and antioxidants and between proteases and antiproteases). More recently, more attention has been given to an aberrant repair process, which also may contribute to development or progression of the disease.
**Proteolysis and Fibrosis.**

The MMPs and their inhibitors are a main component in the destructive part of the remodeling events, whereas in the tissue repair/fibrotic changes, basic FGF (bFGF) and TGF-13 play a main role. In particular, with respect to the seeming contradictory events in parenchyma and bronchial wall, interactions between MMPs and TGF-13 have been suggested. The increased presence of MMP-9 (gelatinase/collagenase), which is associated with COPD, could then coincide with increased presence of TGF-ß, which has been found to be up-regulated in bronchial epithelial cells and alveolar type II cells.

This could, depending on relative contribution of each component in a specific compartment, result in either destructive or fibrotic events respectively. Similarly, increased TGF-ß together with possible activation of MMP-12 (elastase) could, similar to the interaction between MMP-9 and TGF-ß, have elastolytic together with fibrotic effects, depending on exact localization in either the airways or parenchyma.

**Sources of Matrix Production.**

The main effector cells implied in tissue remodeling events are the fibroblasts, which themselves are a main component of the interstitium and are also main producers of ECM. Epithelial cells are resident cells, also capable of ECM production, and fibroblasts as well as epithelial cells are capable of producing TGF-ß, MMPs, and
proinflammatory mediators. With respect to the further intercellular interactions determining the outcome of remodeling events, mediators produced by local inflammatory cells play an important role by activation or inhibition of local production of MMPs and ECM.

**Role of the Smad Pathway in Remodeling.**

With respect to tissue remodeling, apart from the intercellular interactions, aberrations in intracellular events may be of relevance in unravelling the aberrant response to CS as observed in patients with COPD. A very important intracellular pathway that may play a role in pathogenesis of COPD as well as asthma is the Smad pathway (Figure 2), activated through the TGF-β receptor.

In the Smad pathway, stimulatory as well as inhibitory pathways can be recognized. The main stimulatory pathway involves association of Smad-2 and Smad-3, which, together with Smad-4, leads to activation of nuclear transcription of some main ECM proteins such as collagens, versican, and biglycan. The inhibitory pathway is mainly mediated by Smad-7 (Figure 3), which inhibits the pathway described above and in this way also inhibits the transcription for collagen, versican, and biglycan. Together with this inhibitory activity, Smad-7 induces a pathway that leads to nuclear transcription of a limited number of other matrix proteins, of which decorin is most prominent. The fact that the balance in this intracellular Smad pathway itself is also important for actual production of matrix
proteins implies that not only changes in TGF-β or TGF-β receptors as such determine whether this would lead to fibrosis or lack of adequate tissue repair. In a previous study on determinants relevant in airway fibrosis and emphysema, we found no differences in collagens in airway walls of small airways in a comparison between patients with mild or severe COPD and normal subjects. In lung tissue of patients with severe COPD as compared with mild COPD and control subjects, we found a significant prominent reduction of decorin, and less significantly, of biglycan, in particular in the outer parts (adventitia) of small airways, whereas in the adventitia from arterioles at the same location, no difference in decorin was present.

**Role of the Smad Pathway in Abnormal Composition of Matrix.**

Proteoglycans such as decorin and biglycan have important functions, not only as a component of integral construction of the ECM but also as a main regulatory molecule by their ability to bind several cytokines and growth factors (30, 40). With respect to the architecture of ECM, decorin has a main function as a cross-linking molecule between collagen fibrils; in this way, the amount of decorin that is present determines how tight or loose collagen fibrils are attached together. Consequently, a strong increase in decorin would imply stiffening of local collagens, whereas loss of decorin would lead to a loosening and perhaps destruction of collagen structure. This implies that even when an aberrant increase or sustained presence of
collagens as seen in small airways would suggest rigidness and fibrosis, this still could be a very loose structure if insufficient decorin were present. Consequently, considering the decrease in decorin we found in the adventitia of small airways in patients with severe COPD with sustained collagen (Figure 4), this implies that although there may still be a thickening of the airway wall, this would be accompanied by loosening of the adventitial collagen and, in due time, loss of elastic recoil. Together with the smoking-related net proteolytic and oxidative effects in COPD, this vulnerability would lead to easy destruction of the peribronchial attachments of the parenchyma to the adventitia of small airways. Moreover, using polymerase chain reaction on tissue derived from small airways in patients with COPD, Springer and colleagues demonstrated that there was a significant decrease of Smad-6 and Smad-7 when compared with normal individuals.

This could fit well with our findings that a reduced Smad-7 would be in concordance with a lack of inhibition of fibrotic events in the small airways together with a reduction of presence of decorin production at the same spot. In asthma, similar events are observed in the airways, with reduced decorin in the bronchial mucosa, but in fatal asthma less decorin is also found in the external area of small airways. Similar to the findings in airways in COPD, a reduction of Smad-7 was found in epithelial cells in patients with asthma, with an inverse correlation with basement membrane thickness.
Modulating Factors in the Smad Pathway.

Although TGF-β is the main inductor of the Smad pathway, the inhibition of the Smad pathway as mediated by Smad-7 can be induced by extracellular influences of TNF-α, as produced by the CS-exposed epithelium, and also by CS itself. This would mean that, in a study of the role of tissue repair in development of COPD, not only a locally increased presence of TGF-β is the main determinant of actual production or lack of production of matrix proteins, but also whether and to what extent mediators like TNF-δ, IFN-Y, and CS are present in the same pulmonary compartment. This would mean that the actual state of inflammation in airways and also whether a patient with COPD actually smokes are main components in
determining the outcome of the local capabilities of matrix production. Although smoking is generally associated with COPD, it should be recognized that the percentage of patients with asthma who smoke is about the same as in the general population. This implicates the relevance of the above also for (smoking) patients with asthma. When considering the reduced presence of Smad-7, it is not yet clear whether this is really a structural difference between tissue from the bronchial wall of patients with COPD and normal subjects or whether this is due to long-term exposure to TNF-α or, IFN-Ƴ, CS, or other inhibiting factors. However, because an increase in TGF-13 is mainly found in bronchial epithelial cells, and in type 2 alveolar epithelial cells, mainly present around the peribronchial adventitia, this would mean that effects from TGF-β might be expected primarily in the small airway wall and not as much in the parenchyma.

Speculatively, if Smad-7 were structurally reduced in patients with COPD or asthma, this could lead to profibrotic events mediated by the regular Smad pathway, with lack of inhibition by Smad-7, but with loosening of the collagenic tissue by lack of decorin. Both in asthma and in COPD, this could lead to fibrotic changes in the airway wall with loss elastic recoil of peribronchial attachments, which would contribute to airway obstruction. As can be concluded from the above, understanding of the pathogenesis of COPD and asthma includes knowledge of the development of remodeling changes in small and large airways. In COPD, the latter should be studied in conjunction with destructive events in the parenchyma. Pathogenetic
studies should therefore include abnormal regulation of remodeling events affecting the local ECM, the connective tissue cells, and vascular changes contributing to the final remodeling effect. As discussed in this overview, the contribution of vascular changes to remodeling in asthma and COPD is not limited to simple increase in number of small vessels or changes in blood. Such vascular changes are phenomena that are the result of the complex regulatory abnormalities in which VEGF and its receptors can be considered as key factors.

As described above, VEGF is not only involved in angiogenesis but also plays an important role in regulation of local inflammation and, by its interaction with TGF-β, in regulation of matrix production. The other important issue in this overview is that the scope of studies of ECM remodeling goes beyond MMPs and TGF-β. In particular, changes in regulation and balance of components of the Smad pathway in epithelial cells and (myo-) fibroblasts deserve attention. Further studies involving this smad pathway will shed light on complex changes in amount of ECM in general as well as in the
composition of this matrix. The latter, particularly where proteoglycans are concerned, can be expected to have profound functional effects on structural integrity as well as on regulation of inflammation.

As the authors have illustrated above for some important parameters in remodeling, results of studies regarding pathogenesis of asthma and COPD should be placed in a perspective of the intercellular as well as intracellular main events in the respective specific pulmonary compartments such as large airways, small airways, alveoli, or lung parenchyma. Such an approach would allow one to find clues for pathogenetic events in these particular tissue compartments and to determine the contribution of the changes in these compartments to the development and progression of disease. An important implication of realizing differences in the microenvironment of the different lung compartments is that this will have consequences for future targets for therapy and thus for the way future therapeutic interventions have to be targeted to the selective pulmonary compartments.
Severe Asthma

By

Prof. M. Samir Khedr

The Majority of patients who have asthma have mild to moderate disease that can be controlled with standard treatment including regular use of inhaled corticosteroid and long acting Beta agonists. There is however a subset of asthmatic patients uncontrolled even with high doses of regular treatment fails to control the disease. Sever asthma remains poorly understood and frustrating to treat particularly it's a heterogeneous disease Wenzel.2006 .) Approximately 5 -10% of asthmatics have severe disease Humbert et al 2007 .) It is not one disease but a multifaceted condition that can be subdivided into different phenotypes. Bateman 2006 .)

Severe Asthma Phenotype can be Classified Using a Number of Features of Disease including:

- Symptoms
- Health status
- Asthma control
- Air way obstruction variable or partiality fixed )
- Air way hyperresponsiveness
- Atopy
- Inflammation
There Are Several important Clinical Phenotypes:-

- Brittle asthma
- Frequent exacerbators
- Those with irreversible airway obstruction
- Those with oral corticosteroid dependency or resistance

Additional Phenotypes:

- Date of onset of symptoms
- Aspirin sensitive

When Assessing Airway Inflammation We Could identify:

- Eosinophilic
- Neutrophilic
- Pauci granulocytic Phenotyping severe asthma may help to guide current therapy and aid in understanding pathophysiology (Partridge et al 2007)

Limitations of Severe Asthma

A European Study (Dock fell et al 2007) The European Federation of Allergy and Airways disease (EFA) 2007
Most Patients Reported:

- Limitation to their life style 82%
- Restriction of their physical activities 70%
- Restriction of from having a pet 50%
- No chance for holiday 30%
- Feeling their job prospects were limited 65%

Patients indicated That They Are In Need Of The Following Therapy:

- Fast acting
- Long lasting
- Minimal side effects

They were optimistic for the development of the effective therapies over the next five years. The results of this study provide insights into how patients’ lives are affected by severe asthma.

Burden of Uncontrolled in Severe or Difficult to Treat Asthma (SULLIVAN et al 2007) (TEVAR 2007).

Through Out The Study:

- 83% had uncontrolled Asthma
- 16% inconsistent Control
- 1.3% Controlled

Costs for uncontrolled patients were more than double those of controlled patient throughout the study.
Controlled Patients Experienced:

- Fewer work or school absence
- Less health care resource use than the uncontrolled patients in all the study (2 years), So fewer cases of severe or difficult to treat asthma achieved control over 2-years period and the economic consequence of the uncontrolled disease is substantial.

The most recent strategies based on the use of monoclonal antibodies & soluble receptors aimed at inhibiting mediators believed to play a key role in asthma. Omalizumab, an anti IgE monoclonal antibodies indicated as added therapy for patients with severe persistent allergic asthma whose symptoms persist despite receiving optimized treatment with high does of ICS and LABAs augmented with additional controller medication as necessary (GINA Step 4 Therapy) Bouseqet et al 2005.

Is Asthma Controlled in Real Life?

Surveys in USA, Canada, Central and Western Europe, Asia, Japan (Rabe 2004) have been carried out in around 12000 subjects with clinical diagnosis of asthma and who had symptoms or treatment for asthma during the past year.

These studies have shown that the disease is not well controlled as defined by the national asthma education and prevention program (NAEPP - Ressel 2003), Canadian Baulet 2004), or GINA guide lines 2006).
Why??

- Physicians and patients often under estimate severity and over estimate control?! - Patients are under treated (Inhaled Corticosteroids!!)
- Patients have insufficient education and monitoring it is important to assess the control of asthma.

A review of recent worldwide large population epidemiological surveys and clinical asthma studies of more than 20000 children shows that only a small percentage of children with asthma reach the goals of good asthma control set out by GINA (Gustafsson et al. 2006). Better control over time may reduce the severity of asthma (Joint task force on practice parameters of allergy and immunology Coppehneimmer et al. 2006). Assessment of asthma relies in two concepts; control and severity.

Control and severity are complementary approaches to asthma management with different goals and implications. Both influence asthma related costs from an economical point of view, severity may be used to predict these costs while improving control maybe the most important goal to reduce them. (Godarp 2007)

GARD

Asthma is only one of the major preventable CRDs which include: respiratory allergies, COPD, occupational lung diseases,
sleep apnea syndrome and pulmonary hypertension. This lead to the formation of WHO Global Alliance Against Chronic Respiratory Diseases (GARD) which considers all CRDs together taking into account co-morbidities and risk factors.

**Objective of GARD :**
- To develop standard procedures of obtaining relevant data in CRD and risk factors.
- To encourage countries to implement health promotion and CRC prevention policies.
- To propose recommendations of simple strategies for CRD management.

Although asthma guidelines may not be perfect, they appear to be the best vehicle to assist primary care physicians and patient to receive the best possible care of asthma (Bousquet et al. 2007).

**Profile of Difficult to Treat Asthma**

**Severe Asthma Can include**
- ↑↑ symptoms
- ↑↑ airflow limitation
- ↑↑ morbidity and mortality
- ↓↓ response to therapy
Causes

- greater and more persistent environmental stimulation
- repeated and recurrent insult to airways
- altered immunoregulation response
- altered target organ response to both mental and immunoregulator response

Age → Persistent Wheezes
- Genetic factors
- Immunoregulation
- Environmental factors
- Allergen
- Infections
- Pollution
- Stress

P.M.N → EOS

corticosteroid response is impaired

airway injury

severe asthma

needs other ways of treatment
Eosinophils persist in the distal airways of severe asthmatics despite low numbers in proximal airways. Severe asthmatics will persist distal lung eosinophilia though high level of inhaled corticosteroids.

Alveolar eosinophilia differentiates moderate and severe asthmatics from mild asthma, better than large airways eosinophils-in the absence of eosinophils in large airways, it does persist in alveolar tissues. Alveolar eosinophilia doesn't correlate with F'V1 but correlates with residual volume. 
Exhaled Nitric Oxide as a Predictor of Lung Function Decline in Patients with Sever Asthma.

- Onset and deterioration of disease
- Atopy
- Eosinophils in blood and sputum
- Exhaled nitric oxide
- Airway hyperreactivity

- So increase in nitric oxide decreases decline in FEV₁, so nitric oxide estimation is important for identification of patients at risk for persistent airway inflammation, who are more prone to alteration in lung functions and will have accelerated decline.

SARP (severe asthma research program).

In severe asthma there is more air trapping. BA with air trapping have greater airway limitation and more neutrophils in sputum and BAL.
There are two novel phenotypes in severe asthma which require distinctive treatment. Severe asthma corticosteroids insensitive (they are heterogeneous groups).

Asthmatic bronchial epithelium has a deficient innate immune response to infection with Rhino virus. As there is increasing recognition that asthma is not likely to be simply a Th2 mediated disease.

There is a defect in the innate immunity at the level of the epithelial cells of asthmatic patients which may limit the ability of the asthmatic to clear viral infection (WARKP et al 2005) the ability to reverse this defect with exogenous beta interferon suggests that the manipulation of the innate immune system may provide a new avenue for treatment of asthmatics chronically or during viral exacerbation (Vengas J et al 2005).

The use of biomarker FENO in the management of moderate asthma results do not conclusively support the use of FENO to decrease exacerbations, control on lower dose of ICS.

**Berry M et al 2006.**

Despite the association of asthma with inflammation, the majority of patients treated for asthma are with non specific anti-inflammatory agents i.e. ICS.
Recently anti IgE has shown efficacy in asthma suggesting that targeted anti-inflammatory-immune therapies may have role in therapy.

TNFα is a well described innate cytokine produced by mast cell, macrophage and other cells. Blocking TNFα had quite dramatic effect on numerous chronic diseases as rheumatoid arthritis and Crohn's disease. (HOWARTH 2005)

**ETANERCEPT**

Add on

- Significant improvement in FEV₁
- ↓ BHR (2-5 falls)
- ↑ Asthma quality of life
- Sputum
  - a- Inflammatory cells
  - b- Exhaled NO → not changed
  - c- Significant reduction in sputum histamine level
The Problem of Difficult to Treat Asthma.

Treatment and Control of Asthma.

- The Global initiative for asthma (GINA guidelines classify asthma severity into four steps: intermittent asthma (step 1), mild persistent asthma (step 2), moderate persistent asthma (steps 3) and severe persistent asthma (steps 4).
- Treatment should be tailored to severity, proceeding to the next step if control is not achieved.
- Most step 1, 2 and 3 asthma can be effectively treated with inhaled corticosteroids (CS) and if needed, long-acting β₂-agonists (LABA).
- Step 4 asthma often cannot be adequately controlled with these agents and the aim should be to achieve the best control possible.

The GINA guidelines recognize that in patients with the most severe asthma (steps 4), it is often not possible to achieve complete control using ICS and LABA—the aim should be to achieve the best control possible.
The previous table shows the treatments recommended for each step of asthma severity in the GINA guidelines. Rapid-acting $\beta_2$ agonists are recommended for treatment of intermittent asthma and to relieve exacerbations in patients with persistent asthma. ICS are the mainstay of long-term control in persistent asthma. LABA are recommended as additional medications to improve control of their asthma. Xolair is now included in the GINA guidelines as add-on therapy to high-dose ICS and LABA (GINA step 4 therapy) in patients with severe persistent allergic asthma.
Additional medications are frequently required to improve asthma control in patients with severe persistent asthma who are receiving high-dose ICS and LABA. The GINA guidelines list several options as add-on therapy, including anti-IgE therapy (Xolair).

<table>
<thead>
<tr>
<th>Controller</th>
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<th>Outcome: best possible results</th>
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<td>- High-dose inhaled corticosteroid + long acting inhaled β2-agonist plus if needed</td>
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<td>- Theophylline-SR</td>
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<td>inhaled β2-agonist</td>
<td>- Leukotriene modifier</td>
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<td>modifier,</td>
<td>(theophylline,</td>
<td>- Long-acting oral β2-agonist</td>
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<td>leukotriene modifier,</td>
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<tr>
<td></td>
<td></td>
<td>oral β2-agonist</td>
<td>- Anti-IgE</td>
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The four therapy regimes described in GINA guidelines necessary to optimally treat different degrees of asthma severity.

**Burden of Severe Allergic Asthma.**

- Asthma affects an estimated 300 million people worldwide.
- in Europe, an estimated 20% of asthma patients have severe disease, 20% of whom are inadequately controlled,
- Gaining control of severe asthma is often not possible with ICS and LABA alone.
- Patients with inadequately controlled severe persistent asthma are at high risk of hospitalization and death.
- There is a large unmet need for improved asthma control to reduce the burden of hospitalization morbidity and impairment of quality of life that these patients experience.

**Hospitalization.**

Every year, a large number of patients with asthma are admitted to hospital because of their condition. A survey of almost 8,000 adults and 3,000 children with asthma in Europe, North America and Asia showed that between 7% and 19% were admitted to hospital due to asthma during the past year, 1023% made a hospital emergency department visit, and 25-47% had an unscheduled emergency visit to other healthcare facilities during the previous year. Compared with mild asthma, severe asthma is associated with a four-fold increase in hospitalization.

Patients with servers asthma are four times as likley to be hospitalized due to their condition, compare with patients with mild asthma.

Patients who have been hospitalized due to asthma are highly likely to need to be readmitted and have a high risk asthma-related mortality. The potentially severe consequences of asthma exacerbations (including hospitalization and death) place ahuge burden on patients in survey conducted by Asthma UK in the UK, more than half of the 5.1 million people with asthma in the UK expereinced serious asthma symptoms, including debilitating
breathlessness, speech-limiting attacks, fear of death, and emergency admissions.

**Mortality.**

The World Health Organization estimated that asthma caused 239,000 deaths worldwide in 2002. There is a strong link between increased asthma severity or previous hospitalizations and increased asthma mortality. Patients with moderate to severe asthma are almost twice as likely to die due to any cause during 1 year of follow up, compared with patients with mild asthma. Patients with severe unstable asthma have the greatest risk of fatal asthma attacks, with severe uncontrolled asthma accounting for 80-50% of asthma-related deaths. Patients with moderate to severe asthma are almost twice as likely to die during the next year, compared with patients with mild asthma. Uncontrolled severe asthma accounts for 80-50% of asthma-related deaths.

**Resource Utilization.**

Managing patients with severe persistent asthma utilizes considerable amounts of healthcare resources; in addition, asthma places a substantial cost burden on society through indirect costs. The total cost of asthma in Europe is approximately £17.7 billion per annum, of which more than half (£9.8 billion) is accounted for by
indirect costs such as asthma-related work impairment and productivity losses.

The majority of healthcare costs arise as consequence of inadequate control of asthma. Analysis of direct costs indicate that managing a patient who has an asthma attack is 3.5 times more expensive than managing a patient who has no attacks. Inadequate control of severe persistent asthma often results in hospital admissions, unscheduled physician visits and emergency room visits. Improved control of severe persistent asthma could substantially reduce the non-drug costs of asthma management, as well as reduce indirect costs to society.

Inadequately controlled severe asthma accounts for a disproportionately large amount of the total cost of asthma management - managing a patient who has an asthma attack is 3.5 times more expensive than managing a patient who has no attacks. Many patients with asthma do not meet the goals for asthma control set out in the GINA guidelines - a European survey showed that only 35% had good asthma control (failure to meet ≤ 1 GINA goal).

In many cases, the inadequate control of asthma is due to inadequate use of controller medications. However, studies have also shown that many patients have inadequate asthma control despite GINA Step 4 therapy. For example the Gaining Optimal Asthma Control (GOAL) study investigated whether optimized treatment with
fluticasone propionate or salmeterol/muticasone (Seretide) combination therapy could achieve guideline-base asthma control. In patients with the most severe asthma 38% remained inadequately controlled despite treatment with Seretide. Moreover 31% of patients remained inadequately controlled despite the addition of oral corticosteroids to the treatment regimen upon completion of the 1-year study.

The GOAL study illustrated how difficult it can be to control severe asthma- 38% of patients with the most severe asthma were not well controlled, despite optimized treatment with salmeterol and fluticasone. A trial of oral corticosteroids at the end of the study only resulted in another 7% of patients achieving well-controlled asthma.

The size of the population in greatest need of improved treatment options can be estimated from studies of the prevalence and control of asthma. It has been estimated that severe asthma accounts for 18% of all asthma in Western Europe 1^9°h in the USA and 32% in Central Europe. Of these patients with severe asthma, approximately 20% have uncontrolled disease. Based on these figures, approximately 4% of asthma patients have inadequately controlled severe persistent disease. It has also been estimated that approximately 50% of patients with severe asthma have a positive skinprick test for common aeroallergens, which would suggest that approximately 2% of all asthma patients have uncontrolled severe persistent allergic asthma. Target this relatively small group of
patients might be expected to have a disproportionately large effect on the overall burden of asthma.

Approximately 20% of European asthma patients have severe asthma of which 20% is inadequately controlled. This suggests that approximately 4% of patients have inadequately controlled severe asthma. Half of these patients are likely to have allergic asthma and could be candidates for new treatments that target the allergic inflammation at the heart of their condition.

Patients with inadequately controlled severe persistent asthma suffer a considerable burden of ill health and are at a high risk of severe exacerbations and death. Asthma impairs many aspects of daily life including sleep, work, study, exercise and daily activities, and causes a similar level of disability to diabetes. Impairment of quality of life increase with severity of asthma, with inadequately controlled severe persistent asthma having the greatest impact. In addition, 80-85% of asthma death occur in patients with poorly controlled severe disease and, as we noted earlier, there is a strong association between increased recurrences of hospitalization and asthma severity.

Indequateley controlled severe persistent asthma places a substantial burden on patients. Impairs many aspects of daily life and increases the risk of ill health and death. In order to reduce the burden of severe persistent asthma, there is clearly a need for safe
and effective treatments to improve control when used in combination with high-dose ICS and LABA. In the following pages we will look at how immunoglobulin E (IgE) provides a target for the treatment of severe persistent allergic asthma and investigate how anti-IgE (omalizumab, Xolair®) addresses unmet needs in this difficult-to-treat patient population. Anti-IgE is now included in the GINA guidelines as an add-on therapy to daily high-dose ICS and LABA for patients with severe persistent allergic asthma (treatment step 4).

**Immunoglobulin E (IgE): A Key Trigger and Treatment Target in Allergic Asthma.**

- Allergic asthma begins with exposure to an allergen which initiates the allergic inflammatory cascade and ultimately leads to asthma symptoms. IgE is central to the allergic inflammatory cascade and mediates the interaction between allergens and mast cells that propagates allergic response.
- IgE binds to high-affinity FcsRI receptors on mast cells and forms crosslinks with allergens, stimulating release of mediators that cause inflammation and promoting recruitment of inflammatory cells.
- Xolair acts by binding to the region of the IgE molecule that attaches to the FcsRI receptor thereby removing free IgE from the circulation without affecting IgE that is already bound to the cell surface.
- Removing IgE from the circulation also results in a reduction in the number of FcεRI receptors on the surface of mast cells, further enhancing the effects of Xolair.

**The Allergic-inflammatory Basis of Asthma.**

Allergic asthma begins with exposure to an allergen and then proceeds through three phases: sensitization, early-phase response and late phase response. Sensitization occurs when the patient is exposed to the allergen and the body responds by producing IgE molecules that can recognize specific allergens. Several steps are involved in sensitization (figure 1):

- An antigen-presenting cell ingests and digests the allergen into small peptide fragments
- The peptide fragments are presented in concert with major histocompatibility complex molecules on the surface of the antigen-presenting cells
- Recognition of the fragments by T cells stimulates secretion of cytokines
- The cytokines stimulate production of allergen-specific IgE antibodies by B cells that have recognized the same allergen. Sensitization is the first step in the allergic inflammatory cascade and involves production of IgE antibodies directed at specific allergens. The early-phase response occurs within minutes of exposure to an allergen.
The allergen binds to IgE attached to the mast cell, forming crosslinks between IgE molecules bound to the FcsRI receptors (figure 2). The formation of crosslinks provokes rapid release of a number of inflammatory molecules, including histamine, prostaglandin, leukotrienes and cytokines. These inflammatory mediators cause smooth muscle contraction and stimulate mucus production, leading to airway obstruction and the typical acute symptoms of asthma: coughing, wheezing, chest tightness, shortness of breath, and decreased endurance.

During the early-phase response to allergens, IgE binds to FcsRI receptors and forms crosslinks with allergens. Crosslinking stimulates the mast cell to release inflammatory mediators that cause smooth muscle contraction and stimulate mucus production.
In the late phase inflammatory mediators stimulate outflow of fluid from the blood vessels into the tissues, which leads to localized swelling, adhesion, and infiltration of immune cells such as eosinophils, basophils and Th2 cells. As these cells become activated they release additional inflammatory mediators and propagate the inflammation. The release of cytokines stimulates production of IgE and mast cells, attracting more eosinophils. Eosinophils is a key feature of inflammation in asthma and is strongly associated with asthma severity and risk of exacerbations.

The granules of eosinophils contain proteins (such as major basic protein, peroxidase, collagenase, and neurotoxins) that can damage tissues and cause characteristic latephase responses, such as Congestion in allergic rhinitis and bronchoconstriction in asthma (figure 3).

In the late phase, inflammatory mediators stimulate swelling, adhesion, and infiltration of eosinophils, basophils and Th2 cells. These cells release inflammatory mediators, including cytokines that attract more eosinophils. This process damages tissues and causes bronchoconstriction The sequence of events that occurs during sensitization, early phase
response and late phase response is known as the allergic inflammatory cascade (Figure 4), in patients with asthma the allergic inflammatory cascade ultimately leads to an asthma exacerbation and can be initiated by exposure to a huge variety of different allergens including pet dander, house dust mites, pollen, fungal spores, insects, foods (e.g. peanuts or milk) and additives (e.g. sulphites).

As we have seen, IgE is at the heart of the allergic inflammatory cascade and is frequently present at high levels in patients with asthma. The risk of having asthma is closely correlated with IgE level, the higher the serum IgE level, the greater the likelihood of having asthma (Figure 5). However, there does not appear to be a relationship between total IgE and asthma severity.

**Xolair Acts at an Early Stage in The inflammatory Cascade By Blocking IgE.**

Xolair is the first of a new class of agents specifically designed to target human IgE and interrupt the allergic inflammatory cascade at an early stage.
Xolair works by binding to IgE in the bloodstream and forming complexes that prevent the IgE molecules from attaching to receptors on mast cells. Xolair binds to region of the IgE molecule that interacts with FcsRI receptors (Figure 6), with an affinity similar to that between IgE and the receptor. Since the binding site is hurried within the receptor, Xolair binds only to circulating IgE and not to IgE on the surface of mast cells and basophils. Consequently, Xolair does not cause crosslinking of FcsRI receptors, which means that there is unlikely to be a risk of dangerous anaphylactic reactions in clinical use. In addition to removing IgE from the circulation, Xolair also results in a reduction in the number of FcsRI receptors on the surface of the mast cells.

Xolair blinds to the region of the IgE molecule that interacts with IgE receptors, leading to decrease in circulating IgE levels. Xolair does not affect IgE that is already bound to the surface of cells and is therefore unlikely to cause crosslinking that could lead to anaphylactic reaction. By removing IgE from the bloodstream and reducing the number of IgE receptors on the surface of mast cells, Xolair blocks the allergic inflammatory cascade at an early step and interrupts the sequence of events that leads to asthma exacerbations.
By removing IgE from the bloodstream and reducing the number of IgE receptors. Xolair inhibits the next step of allergic cascade (mast-cell degranulation and inflammatory mediator release) and prevents the development of IgE-mediated inflammation.

By acting at this early step in the allergic inflammatory cascade, Xolair is able to block the sequence of events that would otherwise progress from allergic sensitization to inflammatory mediator release, accumulation of inflammatory cells and ultimately an asthma exacerbation. In patients with allergic asthma the antiinflammatory effects or Xolair include a significant reduction in eosinophilia. The anti-inflammatory effects of Xolair provide proof of concept of the importance of IgE in allergic respiratory disease.

**Clinical Experience with Xolair.**

**Key learning points.**

- The clinical efficacy and safety of Xolair has been investigated in a series of clinical trials of patients with predominantly severe persistent allergic asthma.
- The INNOVATE study provided compelling evidence that Xolair was effective at reducing asthma exacerbations, reducing emergency visits and improving lung function and asthma symptoms scores in patients with inadequately controlled severe persistent allergic asthma.
- A pooled analysis of seven clinical trials provided further evidence of efficacy, with Xolair resulting in reductions in asthma exacerbations and emergency visits in a population of patients with prominently severe allergic asthma.
- As well as reducing exacerbations and emergency visits, Xolair also resulted in significant improvements in quality of life and reduced the need for rescue medication and oral corticosteroids.
- Xolair was generally well tolerated with a frequency and severity profile of adverse events similar to that seen in patients receiving placebo or best available therapy.

The INNOVATE Study.

INNOVATE was a randomized, placebo-controlled, double-blind study that investigated the efficacy, safety and tolerability of Xolair over a 28-week period. The 419 patients included in the efficacy analyses had severe persistent allergic asthma that was inadequately controlled despite treatment with high-dose ICS and LABA + additional controller medication if required (GINA Step 4 therapy). Patients received either Xolair or placebo by subcutaneous injection.
in addition to continued treatment with ICS and LABA. The Xolair clinical use section).

The characteristics of the patients enrolled in INNOVATE show that they had a significant unmet need despite receiving GINA step 4 therapy. The patients had impaired lung function, as illustrated by a mean forced expiratory volume in one second (FEV$_1$) of 61% of predicted, were receiving multiple medications and had experienced an average of 2.1 exacerbations per year requiring oral corticosteroid treatment. In addition, 67% of patients were considered at high risk of asthma-related death.

Asthma was clearly impairing the lives of these patients, who had reduced quality of life and had missed an average of 31 school or work days in the past year due to asthma INNOVATE showed that Xolair had significant benefits for these patients. Adding Xolair to GINA step 4 therapy reduced the rate of clinically significant asthma exacerbations (adjusted post-hoc for an observed imbalance in exacerbation history) by 26% and severe exacerbations by 50% compared with placebo.

The INNOVATE study showed that adding Xolair to GINA step 4 therapy resulted in a 26% reduction in clinically significant asthma exacerbation and 50% reduction in severe exacerbations in patients with inadequately controlled severe persistent asthma.
The INNOVATE study showed that adding Xolair to GINA step 4 therapy resulted in a 44% reduction in emergency visits in patients with inadequately controlled severe persistent allergic asthma.

Xolair also had significant beneficial effects in lung function and asthma symptoms in the patients enrolled in INNOVATE. Several measures of lung function improved in the Xolair-treated patients, including PEF and FEV$_1$ and there were significant improvements in asthma symptom scores and education in rescue medication use.

Xolair was also evaluated more favourably than placebo by both patients and investigators. More than 60% of patients and investigators rated treatment effectiveness with Xolair as excellent or good, compared with 43% for placebo.

**Quality of Life.**

We have already noted the impact that asthma can have on quality of life and daily activities, especially in patients with inadequately controlled severe persistent asthma. By reducing exacerbation and emergency medical visits and improving lung function and asthma symptoms, Xolair would be expected to improve the quality of life of patients with asthma. In INNOVATE, the Asthma Quality of Life Questionnaire (AQLQ) was used to measure scores for four domains: activity, limitations, asthma symptoms, emotional function and environmental exposure. Treatment with Xolair led to
significant improvements in AQLQ scores for each of four domains, as well as for the total score. In addition, patients receiving Xolair were more likely to achieve a clinically meaningful ≥0.5 point improvement in AQLQ score, compared with patients receiving placebo (60.8% vs 47.8% of patients).

The reductions in exacerbations and emergency visits, and improvements in lung function and asthma symptoms in patients receiving Xolair were accompanied by significant improvements in quality of life. In the INNOVATE study, 60.8% of patients receiving Xolair had clinically meaningful 0.5-point improvement in AQLQ score, compared with 47.8% of patients receiving placebo.

**Safety and Tolerability.**

Studies of Xolair have shown that treatment is generally well tolerated with frequency and severity profile of adverse events similar to that seen in patients receiving placebo or best available therapy. More than 7,500 adult and adolescent patients with asthma, rhinitis or related conditions have been studied in clinical tolerability. In addition, more than 45,000 patients have been prescribed Xolair treatment in the USA.

In clinical trials, Xolair was generally well tolerated and had an adverse event profile similar to placebo or best available therapy. The safety of Xolair has been evaluated in more than 7,500 adult and
adolescent patients with asthma, rhinitis or related conditions in clinical trials of Xolair. In addition, more than 45,000 patients have been prescribed Xolair treatment in the USA.

**Who is the Xolair Patients?**

**Key Learning Points**

- Clinical trials have demonstrated that Xolair is effective in patients with severe persistent asthma that is inadequately controlled despite best available therapy.
- Xolair is indicated as add-on therapy for adults and adolescents with severe persistent allergic asthma, a positive skin test or invitro reactivity to a perennial aeroallergen, reduced lung function, frequent daytime symptoms or night-time awakenings, multiple documented severe asthma exacerbations and receiving highdose ICS and a LABA.

As we have already seen, clinical trials have shown that Xolair can reduce the rate of asthma exacerbations, severe exacerbations and emergency visits in patients with severe persistent asthma that is inadequately controlled despite the best available therapy. Xolair is a preventative therapy and is intended for use in patients who do not achieve the goals of asthma management despite receiving the best available therapy. Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and
above) with severe persistent allergic asthma who have the following characteristics:

- a positive skin test or in-vitro reactivity to a perennial aeroallergen
- reduced lung function (FEV$_1$ < 80%)
- frequent daytime symptoms or night-time awakenings
- multiple documented severe asthma exacerbations
- receiving daily high-dose ICS, plus a LABA.

Xolair treatment should only be considered for patients with convincing IgE-mediated asthma. Prescribing physicians should ensure that patients with IgE below 76 IU/mL have unequivocal in-vitro reactivity (RAST) to a perennial allergen before starting therapy. Patients with inadequately controlled severe persistent asthma are difficult to treat if they are already receiving high doses of ICS and LABA. These patients have few effective additional treatment options and could gain significant benefits from treatment with Xolair. This can be illustrated by looking at some typical case studies below.
Patient Case Study 1
Overview and history
- 18-year-old female (b. 1986) with severe allergic asthma and eczema since age 2
- Frequent hospital admissions from 2-5 years of age and again from age 11
- Allergic reaction to dog hair and house dust mite
- Several hospital admissions. Frequent use of nebulizers. From age 11 asthma worsening with numerous courses of oral corticosteroids
- In 2000 asthma difficult to control, high intake of Ventolin, not able to do any exercise without taking Ventolin throughout
- September 2000: Quote from Paediatric Registrar: “Despite the various variations in the drug dosages that she has been given over the last year this made very little impact on the severity of her asthma.”
- Pre-treatment serum IgE: 362 IU/mL; concomitant medications: Seretide and Ventolin
- Started Xolair in 2001
- Concomitant medication: Seretide, Ventolin

According to her parents, her health has improved and they are not worried any more when she is out and about.

Xolair has changed my lifestyle. I do not need as many inhalers any more and less oral steroids. I can exercise.

Patient quote

Patient Case Study 2
Below is an example of severe, persistent allergic asthma patient
Overview and history
- Female social worker, aged 44 years
- Severe asthma symptoms and exacerbations since 1964 (3 years old)
- Frequent exacerbations (4-5 times per year) required emergency treatment or hospitalization
- Exacerbations and symptoms limited her activities of daily living
- Couldn’t do physical education at school
- Worked full-time but had several absence per year due to exacerbations and felt victimized at work
- Could not dance or go to nightclubs due to her shortness of breath which was exacerbated by smoky atmospheres. As a young girl, she felt like an old woman
- Nocturnal symptoms (most night) which severely disturbed her sleep
- Consultant referral in 1991 (30 years old)
- Poor control despite maintenance oral steroids, inhaled steroids, salmeterol cromoglicate and oral theophylline trials. Failed trial of methotrexate
- Partial improvement on avoidance diet

Examination and investigations
- No relevant physical findings
- Skin testing: atopic to house dust mite and cat dander also food positive
- FEV1 1.4 L in 1995, reversing to 2.2 L
- Total serum IgE: 550 IU/mL
- Occasional eosinophilia 0.4-1.0 x 10/L
- No specific complicating factors except possibly weight gain from oral corticosteroids

Diagnosis
- Severe, persistent allergic asthma

Recent management
- Commenced trial of Xolair in 2001. Concomitant medications: prednisolone 15 mg, inhaled Seretide and occasional nebulizer

Outcome
- FEV1 1.9 L in 2003 reversing to 2.6 L (predicted 2.9 L)
- Maintenance prednisolone reduce to 10 mg
- Improved symptoms
- Reduced wheezing, shortness of breath
- Nocturnal symptoms uncommon, Sleeps through the night
- Fewer exacerbations
- Absence from work substantially reduced

Now has a career
- Ability to enjoy social life, including night-life and dancing

I’m in a job I love now, and a career I love now which I couldn’t have done without being on this drug. (Xolair). That’s how it’s changed my life. Asthma doesn’t rule my life anymore. I can get on with life.

Patient quote
Xolair: Clinical Use

Key Learning Points

- The Xolair dose is determined by measuring serum total IgE levels (at initiation treatment) and the patient's bodyweight.
- Treatment is given every 2 or 4 weeks, depending on the dose required.
- Patients receiving Xolair should be assessed by their physician after 16 weeks therapy - the decision to continue treatment should be based on whether a marked improvement or complete control of asthma symptoms is achieved.

Calculating the Xolair Dose.

Xolair doses are determined by serum total IgE levels measured before treatment initiation and the patient's bodyweight. Depending on the dose needed, more than one injection may be required. Dosing tablets are used to calculate the appropriate dose (Table 1).

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Administration every 2 weeks: see Panel B.

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Do not administer data is unavailable for dose recommendation.
Treatment is given every 2 or 4 weeks, depending on the dose required. Once baseline serum IgE levels are obtained, there is no need to re-rest IgE levels during Xolair treatment although dose adjustment, the Xolair dose should be recalculated using the patient's weight changes significantly. If weight change does necessitate a dose adjustment, the Xolair dose should be recalculated using the patient's pre-treatment serum IgE levels new body weight, and the dosing tables.

**Administering the injection.**

1) There is limited experience with the self-administration of Xolair; therefore, treatment is intended to be administered by a healthcare provider.  
2) Prepare the injection site. The injections are given subcutaneously into the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.  
3) Administer Xolair following your centre or facility's standard procedures for subcutaneous injection.  
4) Because the solution is somewhat viscous, the injection may take 5 to 10 seconds to administer.  
5) Any unused product or waste material should be disposed of in accordance with local requirements.
Patients receiving Xolair should be assessed by their physician to determine treatment effectiveness after 16 weeks of therapy. The decision to continue Xolair should be based on whether a marked improvement or complete control of asthma symptoms is achieved.

**Frequently Asked Questions.**

**Who Should Receive Xolair?**

Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients, (12 years of age and above) with severe persistent allergic asthma who have the following characteristics.

- a positive skin test or in-vitro reactivity to a perennial aeroallergen - reduced lung function (FEV$_1$ < 80%) - frequent daytime symptoms or night-time awakenings
- multiple documented severe asthma exacerbations
- receiving daily high-dose ICS- plus a LABA.

Xolair treatment should only be considered for patients with convincing IgE-mediated asthma. Prescribing physicians should ensure that patients with IgE below 76 IU/mL have unequivocal in-vitro reactivity (RAST) to a perennial allergen before starting therapy.
How is Xolair Administered?

Xolair is administered as a subcutaneous injection into the deltoid region of the upper arm either every 2 or 4 weeks, depending on the dose required. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region. The drug is supplied as a sterile, white, preservative-free, lyophilized powder contained in a single-use vial and is reconstituted in sterile water for injection. Once reconstituted, Xolair should be administered within 4 hours if stored at room temperature or 8 hours if stored in a refrigerator.

How is the Xolair Dose Calculated?

Xolair doses are determined by serum total IgE levels measured before treatment initiation and the patient's body weight, using dosing tables. More than one injection may be needed to deliver the whole dose, which is administered every 2 or 4 weeks depending on the dose required. Once baseline serum IgE levels have been obtained, there is no need to re-test IgE levels during Xolair treatment although dose adjustments may be needed if the patient's weight changes significantly.

What Do I Do with an IgE < 100 IU/mL?

An IgE level '100 IU/mL does not necessarily mean that your patient's asthma is not IgE-mediated or that the patient will not benefit from Xolair therapy. Indeed, Xolair is indicated for the treatment of
patients with severe asthma whose IgE levels range from 30 IU/mL to 700 IU/mL. However patients with an IgE level below 78 IU/mL should have unequivocal in-vitro reactivity dBASE for a perennial allergen before Commencing treatment with Xolair.

**What Do f Do with an IgE >700 IU/mL?**

Xolair is indicated for patients with IgE levels between 30 and 700 IU/mL. Studies are planned to investigate the effects of Xolair in patients with IgE levels above 700 IU/mL.

**How Long Should Xolair Be Taken for?**

Xolair is intended for long-term control of asthma as an add-on therapy alongside ICS and LABA. Treatment should be continued as long as the patient continues to benefit. Patients receiving Xolair should be assessed by their physician to determine treatment effectiveness after 16 weeks of therapy. The decision to continue Xolair should be based on whether a marked improvement or complete control of asthma symptoms is achieved.

**Who Should Administer Xolair?**

As there is limited experience with self-administration, Xolair should be administered by a healthcare provider.
What are the Benefits of Xolair?

The benefits of Xolair for patients with inadequately controlled severe persistent asthma have been demonstrated in the INNOVATE study and a pooled analysis of seven clinical trials. INNOVATE showed that Xolair significantly reduced the clinically significant asthma exacerbation rate by 26% after adjustment for baseline exacerbation history. In addition, Xolair halved the severe asthma exacerbation rate, reduced the emergency visit rate by 44%, improved asthma-related quality of life, improved measures of lung function, and was rated as significantly more effective than placebo by investigators and patients. In the pooled efficacy analysis, Xolair reduced the asthma exacerbation rate by 38% and the emergency visit rate by 47%.

Is Xolair Safe?

The safety and tolerability of Xolair has been evaluated in completed clinical studies involving more than 7,500 adult and adolescent patients with asthma, rhinitis or related conditions. These studies showed that Xolair has an excellent safety and tolerability profile. There are some special warnings and special precautions for the use of Xolair, which include allergic reactions, cancer and geohelminth infection. However, there does not appear to be a causal relationship between cancer and Xolair treatment, allergic reactions are rare, and the risk of geohelminth appears to be unaltered (please see the SmPC for full prescribing information). There is no evidence of
an increased risk hypersensitivity reactions, immune complex disease, cancer, or geohelminth infection. Post-launch safety data from the USA (launched June 2003) are consistent with those obtained in the Xolair clinical trial programme.

**Is There a Risk of Anaphylaxis with Xolair?**

As with any protein, local or system allergic reactions, including anaphylaxis, may occur. Therefore medications for the treatment of anaphylactic reactions should be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. Anaphylactic reactions were rare in clinical trials.

**How Does Xolair Work?**

Xolair binds to IgE in the bloodstream, and reduces the number of 19 receptors on the surface of mast cells and basophils. The interaction of IgE with these cells is a key early step in the allergic inflammatory cascade, so by interrupting this process Xolair is able to prevent the subsequent release of inflammatory mediators and accumulation of inflammatory cells that cause the symptoms of asthma.
Abbreviated Prescribing Information.

XOLAIR 75 mg and 150 mg

*Presentation:* Omalizumab, Powder and solvent for solution for injection. One vial XOLAIR® 75 mg contains 75 mg of omalizumab as powder with an ampoule of 2 mL water for injection as solvent for reconstitution. Reconstituted Xolair contains 125 mg/mL of omalizumab (75 mg in 0.6 mL) One vial XOLAIR® 150 mg contains 150 mg of omalizumab as powder with an ampoule of 2 mL water for injection as solvent for reconstitution Reconstituted Xolair contains 125 mg/mL of omalizumab (150 mg in 1.2 mL).

*Indications:* moderate to severe persistent allergic asthma, indicated for adults and adolescents (12 years of age and above).

*Dosage:* 150-375 mg s.c. every two to four weeks according to body Weight and baseline serum total IgE levels

*Contraindications:* Hypersensitivity to omalizumab or to any of the excipients.

*Precautions/Warnings:* Not indicated for the treatment of acute asthma exacerbations, acute bronchospasms or status asthmaticus; caution in use of renal or hepatic impaired patients; patients with diabetes mellitus, the glucose-galactose malabsorption syndrome, fructose intolerance or sucroseisomaltase deficiency should be warned that one 150 mg Xolair dose contains 108 mg of sucrose and 75 mg Xolair dose contains 54 mg of sucrose, respectively;
occurrence of local or systemic allergic reactions, including anaphylaxis; pregnancy; lactation.

**Adverse reactions:** Most common undesirable effects are: injection site pain, swelling, erythema, pruritus and headaches. Rare/serious adverse reactions include: anaphylactic reactions and other allergic conditions, allergic bronchospasm.

**Packs and price:** Country specific

**Note:** Before prescribing consult full prescribing information.

**Important information and Frequently Asked Questions About Xolair.**

**Who is Xolair for?**

Xolair (Omalizumab) is a prescription medicine for people who:
- Are 12 years of age and above
- Have moderate to severe persistent asthma. This means they have 1 or more of the following:

- Asthma symptoms every day
- Daily need for a rescue inhaler
- 2 or more asthma attacks a week
- 1 or more nights a week waking up with asthma symptoms
- A below-normal reading (less than 80%) from a tool called a peak flow meter, which measures how well the lungs work
- Have asthma that is triggered by year-round allergens in the air, which is confirmed by a doctor using a simple skin or blood test. This is known as allergic asthma.
- Continue to have asthma symptoms even though they are taking inhaled steroids.

Adding Xolair injections to treatment with inhaled steroids has been clinically proven to help reduce the number of asthma attacks. Xolair has not been proven to work in other allergic conditions.

**What Can Xolair Mean for You?**

In 2 clinical studies, Xolair helped reduce the number of asthma attacks in patients with moderate to severe persistent allergic asthma who had asthma symptoms even though they were taking inhaled steroids. When the patients' inhaled steroid doses were lowered, those receiving Xolair still had fewer asthma attacks than those receiving placebo (an injection with no active medicine). In a third study, the number of asthma attacks in patients receiving Xolair and in those receiving placebo injections were similar. However, this study was done differently from the other 2 studies. It also included different types of patients. Xolair may not be effective in all patients. Talk to your doctor to see if Xolair is right for you.
How Does Xolair Work?

Xolair is a different kind of medicine called an "IgE blocker". IgE, or immunoglobulin E, is a substance that occurs naturally in the body in small amounts. When people with allergic asthma breathe in a year-round allergen, such as cat or dog dander or dust mites, their bodies make more LIE. This may cause a series of chemical reactions that can lead to asthma attacks and symptoms. Xolair works by helping to block IgE.

How Quickly Does Xolair Work?

You may not see immediate improvement in your asthma after Xolair treatment begins. It takes time for the medicine to work. So if you don't feel a difference right away, it doesn't mean Xolair is not working. It is important to continue your Xolair injections until your doctor tells you otherwise.

Does Xolair Have any Serious Side Effects?

- In clinical studies, cancer was seen in a small number of patients receiving Xolair as well as those receiving placebo injections. The rate was higher in patients treated with Xolair than placebo (0.5% vs 0.2%) Several different types were seen Please discuss this information with your doctor.
- In clinical studies, some patients had a serious allergic reaction called anaphylaxis. This was rare, occurring in less than 0.1% of patients.
- Anaphylaxis quickly causes symptoms such as rash, itching, and swelling of the tongue and throat, which can make it hard to breathe and can be life threatening - if you think you are having an anaphylactic reaction, get medical attention right away.
- Xolair should not be used by people who are allergic to any of its ingredients.

What Other important information Should You Know About?

Xolair is not a rescue medicine and should not be used to treat sudden asthma attacks. It is not a substitute for the medicines you are already taking. Never suddenly stop taking or change the dose of your inhaled steroids or any other asthma medicine you are taking unless your doctor tells you to do so.

Can You Take Xolair with Your Current Medicines?

Xolair is approved for use in patients who are already taking inhaled steroids. As with all medicines be sure to tell your doctor about any medicines you are taking for your asthma or any other condition. This includes prescription and nonprescription medicines, vitamins, and herbal supplements.
**How is Xolair Given?**

Xolair is a subcutaneous injection, which means it is injected just under the skin.

**How Often is Xolair Given?**

You will receive Xolair once every 2 or 4 weeks. Your dose will be determined by your IgE level, which your doctor will measure with a simple blood test, and your body weight. Based on your dose, your doctor will also tell you if you will need 1, 2, or 3 injections per dose. If you need more than 1 injection, each will be given in different place on your body.

**What will Happen if You Stop Taking Xolair?**

If you stop receiving Xolair injections, your symptoms can be expected to return.

**How Can I Get More information on Xolair?**

Talk to your healthcare professional if you have any questions about
PART II

Asthma Simulators
Overview on Asthma Simulators

By
Prof. Mohamed Ehab Atta
Professor of Chest Diseases
Alexandria University

One of the important topics in asthma is its prop diagnosis which represents a great challenge many physicians. This is because the variety diseases that can simulate bronchial asthma both in its clinical picture and in the results of investigations. These "asthma simulators" must be clearly differentiated from actual bronchial asthma a should be considered before categorizing a patient as having severe persistent asthma difficult to treat asthma.

Asthma is a chronic inflammatory disease characterized by intermittent cough, shortness of breath, chest tightness, and wheezing. The onset asthma usually occurs during childhood but it may begin at any age. Mc patients with asthma are atopic; however, some patients, particularly those with adult-onset asthma, have no clear allergic basis for their disease. The cardinal features of asthma are airway obstruction, inflammation, and hyperresponsiveness.

Asthma affects 5% to 10% of the adult population in the United States (U.S.). The worldwide prevalence has increased steadily over the past three decades, predominantly in the industrialized countries;
the reason for to increase is unclear. The prevalence of asthma is higher in black than white Americans.

Although airway obstruction in asthma is typically reversible, longitude studies have shown that, over time, patients with asthma have accelerate loss of lung function compared with unaffected persons. The loss is further enhanced in smokers. Asthma results in significant cost to the U.S. economy and in more than 4000 deaths annually, many of them believed to be preventable with proper therapy and follow-up.

All diseases associated with symptoms of exertions dyspnea, paroxymal cough or noisy breathing can simulate bronchial asthma and add confusion to the proper diagnosis of the disease.

**COPD**

COPD comes at the top of asthma simulators according to the GOLD guidelines, COPD is "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." The ATSIERS definition emphasizes that COPD is a preventable and treatable disease state and adds that the "noxious particles or gases are primarily caused by cigarette smoking."
Chronic inflammation underlies both asthma and COPD, but the nature of the inflammation differs, as does the response to different classes of medications. A 20-year longitudinal study found that physician-diagnosed asthma was associated with an increased risk of chronic bronchitis, emphysema and COPD. Reversibility of airflow obstruction was once thought to be the major distinction between the two disorders, with reversibility being the hallmark of asthma and irreversible obstruction the hallmark of COPD. Partial reversibility is the norm for most patients with COPD, whereas asthmatics have greater reversibility. Asthma differs from COPD by its onset early in life and its more variable symptoms. Which are more prominent at night and early morning. Patients with asthma may have concurrent allergic rhinitis and/or eczema, a strong family history of asthma and reversible airflow limitation.

**Suggestive Features of COPD**

- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history
- Dyspnea during exercise
- Largely irreversible airflow limitation

**Suggestive Features of Asthma**

- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning - Allergy, rhinitis, and/or eczema
  also present - Family history of asthma
- Largely reversible airflow limitation

  Although bronchial asthma is associated with bronchial
  hyperresponsiveness i.e. bronchial hyperreactivity (BHR), yet BHR -
  as detected by bronchoprovocation test - is also present in COPD
  patients and smokers.

  Also some degree of reversibility of airway obstruction - as
detected by bronchodilator reversibility test with improvement in FEV$_1$
  between 10-20% - can also be observed in COPD.

  Moreover, chronic & uncontrolled asthma may be associated
with airway remodeling and structural changes in the airways leading
to a lesser degree of reversibility of airway obstruction with
administration of bronchodilators. All these add more difficulty is
differentiating bronchial asthma from COPD.

**Interstitial Pulmonary Fibrosis**

  Interstitial lung diseases (ILD) in general and idiopathic
pulmonary fibrosis (IPE) in particular are considered as ¡Asthma
simulatorsî. They are manifested by exertional dyspnea, sometimes
with dry cough-simulating cough variant asthma-and occasionally
with wheezing. The latter occurs if interstitial fibrosis is associated
with respiratory tract infection or in the late stage of the disease. In this late stage pulmonary function tests reveal combined restrictive and obstructive pulmonary dysfunction. Presence of persistent symptoms, progression course finger clubbing, central cyanosis Velcro crepitations (with leathery character) by auscultation direct the attention to diagnosis of interstitial fibrosis.

Moreover, abnormalities in chest X-ray, high resolution CT scan of chest ~ pulmonary function tests can clearly differentiate bronchial asthma from this asthma simulator.

**Bronchiectasis**

Bronchiectasis is a chronic suppurative lung disease characterized by permanent dilatation of the bronchi and is associated with expectation of large volume of purulent sputum associated with infection, clubbing and cripitations. The disease is also characterized by remission on receiving treatment and relapse on stopping it. The copious sputum in the airways leads to frequent coughing, airway narrowing with occasional wheezing thus simulating bronchial asthma. Pulmonary function tests reveal combined obstructive and restrictive pulmonary dysfunction.

Plain chest radiography and high resolution CT scan of chest shows dilated airways, honeycomb appearance and bronchial wall thickening in bronchiectasis in short features of bronchiectasis which differentiate it from asthma are:
- Large volumes of purulent sputum Common association with bacterial infection
- Coarse crackles/clubbing on auscultation
- Bronchial dilation bronchial wall thickening on chest radiograph/CT scan

Bronchiectasis may be acquired e.g. following recurrent infections or prolonged bronchial obstruction e.g. by foreign bodies. It may also be congenital e.g. is cystic fibrosis (CF) which is seen in the childhood period and even in adults (adult CF). Certain types of infections e.g. infection caused by fungi of the Aspergillus species can cause central bronchiectasis (bronchocentric bronchiectasis) and bronchial asthma. This type is known as allergic bronchopulmonary aspergillosis.

(ABPA). A subset of patients with asthma who do not respond to therapy have underlying allergic bronchopulmonary aspergillosis (ABPA). These patients develop humoral and cell-mediated immune responses to Aspergillus fumigatus in their airways, leading to persistent inflammation, airway damage with development of central bronchiectasis, and eventually pulmonary fibrosis. Clinically ABPA manifests as persistent severe asthma with central bronchiectasis expectoration of brown sputum that contains Aspergillus organisms, pulmonary infiltrates, and fibrosis. Affected patients typically have significant elevation in total serum IgE (>1000 ng/mL), positive skin test to Aspergillus, increased blood eosinophil counts, elevated serum specific IgE or IgG to A. fumigatus, and pulmonary infiltrate most often seen in the upper lobes. The five-
stage natural history of ABPA includes an acute phase (stage 1), remission (stage 2), exacerbation (stage 3) where the symptoms are similar to those seen in stage 1, corticosteroid-dependent asthma (stage 4), and pulmonary fibrosis stage 5). The treatment of ABPA is similar to that of asthma, although these patients require oral corticosteroids for several weeks until remission is achieved. Their response is monitored by measuring total serum IgE level, pulmonary function tests, and chest radiography.

**Tuberculosis (TB)**

Tuberculosis is also included in the differential diagnosis of asthma, but patients with tuberculosis have night sweats and low-grade fever and can be diagnosed by chest radiograph with microbiological confirmation. Endobronchial TB may also cause bronchial obstruction and wheezing. TB mediastinal lymphadenopathy can cause extrinsic compression of bronchial tree and leads to wheezing and features simulating bronchial asthma especially in children.

**Bronchial Pathology**

Pathological lesions of the bronchial tree can cause airway narrowing, cough, wheezing and dyspnea, features simulating bronchial asthma. Endobronchial neoplasm whether benign (e.g. hamartoma) or malignant tumors (e.g. bronchial carcinoma or bronchial secondaries) may cause dyspnea and wheezing which is
usually localized to the affected lobe or segment. However, bronchial carcinoid tumors can release histamine and thus can cause generalized wheezes and dyspnea (carcinoid syndrome).

Other endobronchial pathology that can simulate asthma are foreign body inhalation (aspiration), endobronchial tuberculosis, extrinsic compression of the bronchi by enlarged mediastinal lymph nodes i.e. mediastinal lymphadenopathy caused by TB, lymphoma or sarcoidosis. Other mediastinal lesions compressing tracheobronchial tree may also be considered. Endoscopic examination of the bronchial tree by fiberoptic bronchoscopy (FOB), chest X-ray, and CT scan are usually sufficient for proper diagnosis of these asthma simulators.

Congenital as well as acquired causes of endobronchial compression should also be in mind when considering asthma simulators in children and infants. These include endobronchial pathology as congenital web or foreign body aspiration and extrabronchial compression e.g. by TB lymphadenopathy or congenital vascular anomalies as right sided aortic arch and vascular ring.

Cardiac Asthma

It is another asthma simulator. It occurs in cases associated with pulmonary versus congestion secondary to left heart failure or congestive heart failure (CHF) or in mitral valve disease. Here, there
is dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), cough and wheezing. All these features can be also present in bronchial asthma. However, the presence of cardiovascular lesion or history of cardiac disease generalized or lower limb edema, fine crepitations by auscultation and more manifest orthopnea and PND directs the attention for diagnosis of cardiac asthma rather than bronchial asthma. Moreover, chest X-ray reveals pulmonary venous congestion associated with cardiomegaly and the ECG and echocardiography reveal the underlying cardiovascular disease.

It should be noted that both cardiac and bronchial asthma may be associated with bronchial hyperreactivity. To summarize the main features of cardiac asthma which differentiates it from bronchial asthma are:
- Presence of congestive heart failure - Fine basilar crackles on auscultation
- Dilated heart, pulmonary edema on chest radiograph
- Volume restriction with slight airflow limitation on pulmonary function tests

**Pulmonary Embolism**

Pulmonary embolization (PE) may be associated with dyspnea and occasionally with wheezing, thus simulating bronchial asthma and considered one of the asthma simulators. Presence of deep vein thrombosis or other possible source for embolization, presence of risk
factor, blood examination for D-dimer and multislice CT pulmonary angiography are considered for diagnosis of PE.

**ENT- Asthma Simulators**

Ear-nose-throat (ENT) problems which may be associated with cough, noisy breathing and occasional dyspnea may be considered as asthma simulators. These include rhinitis sinusitis, post nasal drip syndrome, vocal cord dysfunction (abduction of vocal cords during inspiration) & recurrent upper respiratory tract infections (whether viral or bacterial infections). Upper airway obstruction (whether caused by extrathoracic or intrathoracic causes) should also be considered.

**Causes of wheezing based on anatomic site of obstruction**

A- Extrathoracic upper airway obstruction:

1) Hypertrophied tonsils
2) Laryngostenosis
3) Postextubation granuloma
4) Retropharyngeal abscess
5) Benign airway tumors
6) Malignant airway tumors
7) Obesity (obstructive sleep apnea)
8) Mobile supraglottic soft tissue
9) Laryngocele
10) Vocal cord hematoma
11) Wegenerís granulomatosis
B- Intrathoracic upper airway obstruction:
1) Tracheal stenosis / web
2) Foreign body aspiration
3) Benign airway tumors
4) Malignancies
5) Intrathoracic goiter
6) Mediastinal cysts
7) Tracheobronchomalacia
8) Right sided aortic arch
9) Congestive vascular ring

**Miscellaneous Asthma Simulators**
Lastly, there is a group of miscellaneous disorders that can be considered as asthma simulators, these include:
- Gastro-oesophageal reflex disease (GERD) with recurrent aspiration
- Oesophageal dysfunction
- Pharyngeal pouch
- Deglutition abnormality secondary to central nervous system (CNS) disease
- Eosinophilic bronchitis
- Bronchiolitis
- Recurrent lower respiratory tract infection (viral or bacterial)
- Recurrent aspiration
- Some systemic (autoimmune) disease
It should be noted that some systemic diseases and autoimmune or collagenic diseases may be manifested as pulmonary vasculitis and bronchial asthma. These include: polyarteritis nodosa (which causes systemic hypertension and bronchial asthma) and Chung Strauss syndrome which is allergic angitis and granulomatosis. Churg-Strauss disease is a small vessel necrotizing vasculitis that presents as eosinophilic pneumonia in patients with corticosteroid dependent asthma. It has features as polyarteritis nodosa but with extravascular granulomas.

**Psychogenic Dyspnea**

Finally, psychic dyspnea may be considered after excluding all features of bronchial asthma and asthma simulators. Psychic dyspnea is usually characterized by frequent sighing and clear relation to anxiety and emotional troubles.

All these asthma simulators should be kept excluded before diagnosing any case as bronchial asthma or considering it as severe or uncontrolled asthma or a case of difficult to treat asthma and also before planning its lines of management.

It goes without saying that all these asthma simulators which represent differential diagnosis for asthma should always be considered because they require different diagnosis approaches and different therapeutic modalities than that of bronchial asthma.
How to Differentiate Dyspnea of Bronchial Asthma From That of Interstitial Lung Disease?

By
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Chest Department,
Cairo University

Dyspnea is a commonly reported symptom in the practice of medicine. It is frequently developed as a result of respiratory or non-respiratory disease. Dyspnea due to primary respiratory illness could originate from one of the following basic anatomical regions: airways, lung parenchyma (pulmonary), interstitium and pleura. Furthermore, dyspnea classification includes extra pulmonary but intrathoracic causes such as mediastinal and cardiac causes. Moreover, several non-respiratory causes could be the primary cause of dyspnea and these include general and central causes.

Apparently, the list of causes of dyspnea is an extensive one. Accordingly, there are several approaches developed to address the origin of dyspnea and its contribution to the patient's complaint.

In view of the increasing incidence of interstitial lung diseases it is highly important to differentiate dyspnea due to bronchial asthma from that of an interstitial lung disease. Concerning bronchial asthma, the salient feature of airway disease is dyspnea associated with
wheezes. Accordingly, bronchial asthma is typically associated with wheezes. Which is usually lacking in interstitial pulmonary fibrosis.

Prior to clinical examination, it is of utmost importance to specify whether dyspnea is due to airway disease or interstitial lung disease. Such important information is obtained early during history taking and could direct our attention to particular points of clinical examination.

In Support of diagnosis of bronchial asthma is positive family history. Which may point at similar cases of asthma or other forms of allergy such as allergic rhinitis or skin allergy. Likewise past history may point may draw our attention to a similar condition that was previously diagnosed as asthma.

**Onset and Course**

Commonly bronchial asthma has an intermittent onset followed by progressive, regressive or stationary course. Such a variable course could be met with throughout the duration of the disease. In other words, the patient may pass into ups and downs several times during his illness. Which is not typical for a patient with interstitial lung disease. Progressive dyspnea is the dominant feature of interstitial lung disease while the onset is usually insidious.
Bronchial asthma is a chronic disease but less commonly the onset of first attack of acute asthma is positively linked to a particular cause. Which is not the case for interstitial lung disease.

Aiming at provisional diagnosis, symptoms associated with dyspnea might be conclusive for an interstitial lung disease. In particular, dry cough that usually precedes dyspnea of interstitial lung disease might be the clue for diagnosis. However, cough variant asthma should be kept in mind as an unusual presentation of acute or chronic intermittent bronchial asthma.

Nevertheless, it may worth mentioning that recurrent respiratory infections could be manifested during the course of both diseases due to several reasons. For this reason, cough with variable sputum production may be apparent in most of the patients from time to time and we should not be mislead be its association. Likewise, non-specific irritants (smoking, air pollution, psychological status) are well known to aggravate the symptoms of the patients and further contribute to the subject sense of dyspnea.

**Exposure**

Once interstitial lung disease is suspected it is essential to enquire about current and previous exposure to several factors. Remote exposure is as important as recent exposure. It is a must to enquire about detailed occupational and environmental exposures as
well as drug or substance intake, however minimal. Additionally, hobbies and history of residency and travel are equally important. Trivial exposure is sometimes the key for correct diagnosis.

Extrapulmonary manifestations (e.g. joint symptoms among other general manifestations) are sometimes remarkable enough to point at an interstitial lung disease rather than an airway disease. It should be remembered that manifestations of collagen-vascular disease may infrequently include airway symptoms.

**Clinical Examination**

Clinical examination is important for demonstration of expiratory rhonchia in case of bronchial asthma or late inspiratory capitation if it is a case of interstitial lung disease. Typically, sibilant rhonchi are present in acute asthma while sonorous rhonchi are shown in chronic asthma. The distribution of both additional respiratory sounds (rhonchi or crepitations) is typically bilateral. Unilateral finding should draw our attention towards complication or associated morbidity like lower respiratory tract infection.

General examination is much more important in proving sequale and complication. On top of these, one must Look for pulmonary hypertension and cor pulmonale which must be excluded from the initial assessment.
Finger clubbing is an advanced sign of progressive hypoxemia and it is usually common in late presentation of the patient. Central cyanosis at rest indicates advanced diseases. For early detection of cyanosis, it is exercise-induced that could be demonstrated clinically or proven with pulse oximeter.

What is really important is to exclude another local disease of allergic nature which is HP (hypersensitivity pneumonitis). It is usually indistinguishable from an interstitial lung disease. However, traditional symptoms of HP typically include dry cough and non-wheezy dyspnea that develop after few and up to several hours of acute exposure in the workplace. For the purpose of proper diagnosis, a patient with HP should demonstrate two positive factors; namely; definite history of exposure to an inflicting factor and positive laboratory tests showing IgG in serum (i.e antibodies against the specified allergen) together with lack of IgE yet, unrecognized causes of HP remain to be revealed.
Asthma Simulator: Endobronchial Obstruction

By

Prof. Emad Eldin Mustafa Hassan Ibrahim, MD, FCCP, ERSF

Pulmonary Medicine,

Asthma is a common disease that affects any age, race, gender, and social strata. Although, asthma may develop at any age, the majority of people with asthma are diagnosed in childhood. The clinical history in an adult should include questions about the presence of symptoms earlier in life.

Other historic clues that are highly suggestive of asthma include episodic symptoms, the presence of typical triggers (especially exercise, cold air, or allergen exposure), and personal or family history of allergic disease. Physical examination may be normal. The presence of abnormal findings such as wheezing) is suggestive of asthma, although not specific. Asthmatic wheezing is typically composed of multiple high-pitched sounds audible during expiration. Nasal examination should be included to check for the pale, swollen mucosa of associated allergic rhinitis, or nasal polyps suggesting aspirin-sensitive asthma.
Other Conditions Causing Similar Symptoms

Alternative diagnoses that may cause cough, wheeze, or shortness of breath include the following:
In adolescents and young to middle-aged adults, the principal considerations include recurrent bouts of bronchitis, bronchiolitis, bronchiectasis, vocal Cord dysfunction, pulmonary embolism, gastroesophageal reflux disease (GERD), panic disorder, and sarcoidosis. In older-aged patients, especially Cigarette smokers, considerations include COPD and left-ventricular heart failure.

Other obstructive lung diseases, including COPD, diffuse bronchiectasis and constrictive bronchiolitis, might also manifest variable airflow obstruction over time and airflow obstruction that improves significantly after bronchodilator administration. Also, the presence of endobrochial lesions and tumors may simulate asthma. However, the variability in airflow obstruction is small in these diseases, and return to normal baseline lung function would not be expected. The differential diagnosis of wheezing includes a variety of congenital and acquired conditions. Clinical history, physical examination, laboratory investigations, and response to treatment all play a role in establishing the underlying etiology of wheezing [1]. An overview of the causes of non-asthmatic wheezing in children are presented here.
Definition and Physiology of Wheezing

A wheeze is a continuous musical sound heard during chest auscultation that lasts longer than 250 msec \[^2\]. It is produced by the oscillation of opposing walls of an airway narrowed almost to the point of closure \[^3\]. Wheezing caused by a large or central airway obstruction has a constant acoustical character throughout the lung, but varies in loudness depending upon the distance from the site of obstruction. It is referred to as monophonic (or homophonous) wheezing. In the setting of small airway obstruction, the degree of narrowing varies from place to place within the lung. As a result, the sounds generated also vary in quality and acoustical character and are described as polyphonic (or heterophonous) wheezes \[^4\].

Some experts distinguish between wheezes and rhonchi based upon the dominant frequency of the sound. Wheezes have a dominant frequency greater than 400 Hz. whereas rhonchi are of lower frequency \[^5,6\]. However, the clinical significance of this distinction, if any, is not well defined \[^6\].

Stridor refers to a monophonic wheeze that is loudest over the central airways. Stridor can be heard during inspiration, expiration, or throughout the respiratory cycle, depending on the location of obstruction. In general, inspiratory strider is prominent in the setting of extrathoracic obstruction, whereas expiratory stridor suggests intrathoracic obstruction. Foreign body aspiration, croup, epiglottitis,
and vocal cord dysfunction are common causes of stridor in children. When a patient presents with stridor, urgent airway evaluation may be required and should be performed by clinicians with substantial experience in airway management. Inhalation of helium-oxygen mixtures may be a useful temporizing measure.

**Diagnosis of Wheezing Illnesses Other Than Asthma In Adults.**

**Etiology.**

Different conditions, which involve a variety of anatomic airway locations, can produce obstruction and expiratory or inspiratory wheezing. Asthma is not the most common cause of wheezing [7]. Postnasal drip syndrome was the most common cause of wheeze in patients referred to a pulmonary outpatient clinic. The expiratory wheeze associated with the postnasal drip syndrome originates from the extrathoracic airway, most likely at the level of the vocal cords [8, 9].

**Causes of Wheezing Based on Anatomic Site of Obstruction**

**A-Extrathoracic Upper Airway Obstruction:**

1) Hypertrophied tonsils
2) Laryngostenosis
3) Postextubation granuloma
4) Retropharyngeal abscess
5) Benign airway tumors
6) Malignant airway tumors
7) Obesity
8) Mobile supraglottic soft tissue
9) Laryngocele
10) Vocal cord hematoma
11) Wegener's granulomatosis

**B-Intrathoracic upper airway obstruction:**

1) Tracheal stenosis
2) Foreign body aspiration
3) Benign airway tumors
4) Malignancies
5) Intrathoracic goiter
6) Right sided aortic arch

**C-Lower airway obstruction:**

1) Aspiration
2) Cystic fibrosis
3) Carcinoid syndrome
4) Lymphangitic carcinomatosis
5) Benign airway tumors
6) Malignancies
**History and Physical Examination**

In evaluating patients with wheezing, it is important to be aware that "All that wheezes is not asthma; all that wheezes is obstructions. Furthermore, there is no characteristic of the wheeze of asthma that reliably distinguishes it from other conditions. In comparison, the presence of the classic triad of wheeze, cough, and chronic dyspnea is highly suggestive of asthma; however, patients often present with only one element of the triad, and asthma is not the most common cause of any one of these symptoms.

Improvement after bronchodilators is not always indicative of asthma. A reversible restrictive lung disease has rarely been described that is clinically indistinguishable from asthma [6]. The diagnosis of wheezing conditions other than asthma should be considered when the initial evaluation suggests their presence or when wheezing does not respond to conventional asthma medications [10].

**Timbre**

- The timbre of the wheeze may provide a clue to its location [3].
- A polyphonic wheeze, consisting of multiple musical notes, is typically produced
- by dynamic compression of the large, more central airways.
- Monophonic wheezes, consisting of single musical notes, typically reflect disease
- in small airways and are suggestive of asthma, especially if multiple wheezes are
- heard. However, monophonic wheezes can also be produced by disorders
- involving the extrathoracic large airways.

**Expiratory Wheezing**

Expiratory wheezing, appreciated either by history or physical examination, is neither sensitive nor specific for asthma. As an example, symptomatic asthma can present without wheeze, while wheezing associated with other conditions can mimic asthma. A prospective study evaluated patients referred to a pulmonary clinic because of wheezing: a history of wheeze was predictive of asthma 35 percent of the time; and the physical finding of expiratory monophonic wheezing was predictive 43 percent of the time [3].

**Inspiratory Wheezing**

Inspiratory wheezing on physical examination is neither a sensitive nor a specific sign of extrathoracic upper airway disease or obstruction. Inspiratory wheezing frequently accompanies expiratory wheezing during acute asthma; in some cases of asthma, however, wheezing may only be heard during inspiration [7]. Patients with upper airway obstruction < 8 mm in diameter develop dyspnea on exertion;
when the diameter is <5 mm, strider is evident [hi 421. Thus, when a patient presents with strider, urgent airway evaluation is indicated, and should be performed by clinicians with substantial experience in airway management. Inhalation of helium-oxygen mixtures may be a useful temporizing measure.

**Diagnosis**

An approach to evaluating wheeze is to localize the site of the obstruction to large or small intrathoracic airways or to the extrathoracic airway.

Pulmonary function testing can be quite helpful in confirming a diagnosis once the diagnostic possibilities have been narrowed by history and physical examination.

**Pulmonary function testing**

Obstruction in the three anatomic areas of the airway can be physiologically differentiated, because each area has different physiologic characteristics. The three areas include:

- The extrathoracic upper airway, which includes the nose, mouth, pharynx, larynx, and extrathoracic trachea.
- The intrathoracic upper airway, ie, from the intrathoracic trachea to airways at least 2mm in diameter.
- The intrathoracic small airways, ie, airways less than 2 mm in diameter [13].

From a physiological standpoint, the distinguishing characteristics of these three anatomic areas are as follows:

The extrathoracic and intrathoracic portions of the upper airway undergo different and opposite transmural pressure changes during the respiratory cycle. Because of these changes, flow-volume loops can be diagnostically useful in pinpointing the level of the airway at which the obstruction is located. Air flow is predominantly turbulent through large airways and mostly laminar through small airways [14].

Obstruction above the level of the carina tie, upper airway obstructions impedes all the air in a uniform manner, while obstruction in small airways is typically in multiple, scattered sites! thus impeding airflow in a non-uniform manner.

Spirometry and flow-volume loops during helium and air breathing can be used to localize airway obstruction, because they are influenced by these phenomena. In addition, spirometry repeated after treatment with a bronchodilator or systemic corticosteroids may demonstrate the presence of a substantial component of reversible airways disease consistent with asthma. On the other hand, branchoprovocation challenge testing may be helpful in patients with normal or nearly normal baseline spirometry, showing clinically
significant bronchial hyperresponsiveness consistent with asthma.
Upper airway obstructing lesions are best identified by flow-volume
loops. Airflow is likely to remain constant during the middle portion of
a maximum respiratory effort when there is only one site of
obstruction, as usually occurs in the trachea.

An upper airway obstruction cannot be localized physiologically
to an extrathoracic or intrathoracic location if it is fixed, because fixed
lesions do not allow the airway to respond to normal transmural
pressure changes. Nevertheless, the flow-volume loop will have a
characteristic box shape that suggests the obstruction is in large
rather than small airways. Airflow is uniformly impeded during
inspiration and expiration, causing flattening of the maximum
inspiratory and expiratory curves because there is no difference
between the amount of narrowing in inspiration and expiration [15].
Because expiratory as well as inspiratory flow rates are decreased in
a fixed upper airway obstruction, spirometry will reflect the expiratory
flow limitation. It is possible to distinguish

Extrathoracic and intrathoracic upper airway lesions if the
obstruction is variable (ie, if it allows the airway to respond to the
normal transmural pressure changes). A variable extrathoracic
obstruction is typically apparent only during maximal inspiratory effort.
The maximal expiratory flow-volume curve and spirometry are usually
normal in this setting, because the extrathoracic airway will dilate
during expiration. In contrast, a variable intrathoracic obstruction is
apparent only during maximal expiratory effort, and spirometry reveals values consistent with expiratory airflow obstruction. Spirometry alone cannot distinguish large from small intrathoracic airway diseases, since FEV₁ peak expiratory flow rate, and FEV₁/FVC are reduced in both situations.

The ratio of Aspiratory to expiratory flow rates may distinguish variable extrathoracic from intrathoracic upper airway lesions [6]. Inspiratory flow rates are normally greater than expiratory flow rates when compared at lung volumes in the lower two-thirds of the vital capacity. Inspiratory flow rates are lower than expiratory (eg, FIF50 percent is less than 1) when a variable extrathoracic lesion is present.

It may also be possible to detect coexisting large and small airway intrathoracic obstructions by comparing maximal expiratory flow-volume curves while patients first breathe room air and then a 20 percent oxygen-80 percent helium mixture [14]. Expiratory flow will substantially increase with the helium mixture when an obstruction occurs in large airways, because the flow that occurs in this region improves when patients inhale the less dense helium mixture [17].
Diagnosis of Wheezing illnesses Other Than Asthma in Children.

Introduction

Wheezing is a common presenting symptom of respiratory disease in children. Epidemiologic studies conducted worldwide have shown that 10 to 15 percent of infants wheeze during the first year of life, and as many as 25 percent of children younger than 5 years of age present to their clinicians with wheezing respiratory illnesses\cite{18-20}.

Most children with recurrent wheezing are very likely to have asthma, regardless of the age of onset, evidence of atopic disease, precipitating causes, or frequency of wheezing \cite{18}. However, other diseases can present with wheezing in childhood, and patients with asthma may not wheeze. Therefore, the initial evaluation of a wheezing child should be directed toward the exclusion of alternative diagnoses followed by a therapeutic trial of bronchodilators if asthma is suspected.

The differential diagnosis of wheezing includes a variety of congenital and acquired condition. Clinical history physical
examination, laboratory investigations, and response to treatment all play a role in establishing the underlying etiology of wheezing \(^\text{[18]}\).

**Causes of Wheezing in Children Simulating Asthma Based on Course**

**A-Acute Course**

1) Foreign body aspiration  
2) Esophageal foreign body

**B-Chronic or Recurrent Course**

I. **Structural abnormalities:**

1) Tracheo-bronchomalacia  
2) Vascular compression/ rings  
3) Tracheal stenosislwebs  
4) Cystic lesions/masses  
5) Tumors/lymphadenopathy  
6) Cardiomegaly

II. **Functional abnormalities**

1) Primary ciliary dyskinesia  
2) Bronchopulmonary dysplasia  
3) Cystic fibrosis  
4) Recurrent aspiration  
5) Retained foreign body  
6) Bronchiolitis obliterans
Clinical History.

When a patient presents with a history of wheezing, it is crucial to ask the patient or the parents to describe what they actually are experiencing or hearing. On many occasions, the word "wheezing" is used as a general term to describe noisy breathing, including snoring, congestion, gurgling noises, or stridor [21]. Two important aspects of the medical history include the patient's age at the onset of wheezing and the course of onset (acute versus gradual). In addition, it is helpful to distinguish between intermittent and persistent wheezing.

Persistent wheezing presenting very early in life suggests a congenital or structural abnormality especially if unilateral; in contrast, paroxysmal or intermittent wheezing is a characteristic finding in patients with asthma. Persistent wheezing with sudden onset is consistent with foreign body aspiration, whereas the slowly progressive onset of wheezing may be a sign of extraluminal bronchial compression by a growing mass or lymph node. In addition, patients with interstitial lung disease can present with persistent wheezing.

Clinical features that suggest a diagnosis other than asthma include the following:

1) A history of neonatal or perinatal respiratory problems and wheezing since birth suggests a congenital abnormality.
2) Association of wheezing with feeding or vomiting can be a result of gastroesophageal reflux or impaired swallowing complicated by aspiration.

3) Symptoms that vary with changes in position may be caused by tracheomalacia, bronchomalacia, or vascular rings.

4) Poor weight gain and recurrent ear or sinus infections suggest cystic fibrosis, immunodeficiency, or ciliary dyskinesia.

5) Wheezing with little cough suggests a purely mechanical cause of obstruction, and raises suspicion for foreign body aspiration. In general, cough is a prominent component of asthma in children \[21\],

6) Poor response to asthma medications.

7) History of progressive dyspnea, tachypnea, exercise intolerance and failure to thrive may suggest interstitial lung disease. Features in the history that favor the diagnosis of asthma include:

8) Intermittent episodes of wheezing that usually are the result of a common trigger (ie, upper respiratory infections, weather changes, exercise, or allergens)

9) Seasonal variation

10) Family history of asthma and/or atopy

11) Good response to asthma medications

**Physical Examination**

General examination of a wheezy child should include measurement of weight and height, vital signs including oxygen saturation, and digital inspection for the presence of cyanosis or
clubbing. The latter findings suggest the presence of a Wheezing illness other than asthma. Chest examination should focus on the following features:

1) Inspection for the presence of respiratory distress, tachypnea, retractions, or structural abnormalities. Pertinent findings include an increased A-P diameter associated with chronic hyperinflation, pectus excavatum caused by chronic airway obstruction and exaggerated swings in intrathoracic pressure, or scoliosis complicated by airway compression.

2) Palpation to detect supratracheal lymphadenopathy or tracheal deviation.

3) Percussion can define the position of the diaphragm and detect differences in resonance among lung regions and is the most underutilized part of the examination.

4) Auscultation allows identification of the characteristics and location of wheezing, as well as variations in air entry among different lung regions. A prolonged expiratory phase suggests airway narrowing, whereas the presence of crackles or other adventitious sounds suggests parenchymal lung disease, interstitial lung disease, or pulmonary edema. Decreased wheezing after bronchodilator therapy is very suggestive of asthma.

**Radiography**

Anteroposterior (AP) and lateral chest radiographs should be obtained in every child presenting with wheezing. In most cases, a
plain chest radiograph provides a good image of the large airways, including the tracheal air column and mainstem bronchi. Plain films also can detect parenchymal lung disease, atelectasis, generalized hyperinflation, and, in some cases, areas of bronchiectasis.

In addition, chest radiographs may reveal cardiomegaly, enlarged pulmonary vessels, pulmonary edema, or other signs of cardiac failure. Plain radiographs also are helpful in detecting mediastinal masses or enlarged lymph nodes, and may suggest the presence of vascular rings (eg right aortic arch). Other radiologic studies may be helpful in selected cases. Chest computed tomography can provide detailed anatomy of the mediastinum, large airways, and lung parenchyma. Magnetic resonance imaging (MRI) should be considered when a vascular problem is suspected. Barium swallow may help in identifying vascular rings, swallowing dysfunction, aspiration syndromes including gastroesophageal reflux, and some cases of tracheoesophageal fistula; however, this study is indicated only when these conditions are suspected.

**Pulmonary Function Tests**

Pulmonary function tests (PFTs) are an important component of to diagnostic evaluation of a wheezy child. Pulmonary function testing infants can detect flow limitation FRC. Moreover, this test CE be used to quantify the response bronchodilators and bronchoconstrictor stimuli \([1, 23, 24]\). Airway resistance and function residual capacity also can t measured using gas dilution or box plethysmography in very
your children and can help quantify airway obstruction and the response bronchodilators \[^{1}\].

In older children who are cooperative pulmonary function testing with inspiratory and expiratory flog volume loops is very helpful in determining the presence, degree and location of airway obstruction as well as the response bronchodilators.

Methacholine challenge testing and exercise testing can confirm airway hyperreactivity in patients for who the diagnosis of asthma still is question.

**Endoscopy**

Endoscopy should be considered patients with suspected foreign box aspiration, persistent symptoms, or inadequate response to therapy. Flexible bronchoscopy performed under conscious sedation can be used to evaluate the airways during spontaneous breathing and to exclude tracheomalacia. Nasopharyngoscopy, which allows visualization of the vocal cords and larynx without lower airway endoscopy, can be considered as a less invasive alternative in infants and children with evidence of extrathoracic obstruction. This approach provided a diagnosis in 75 of 82 cases (91 percent) in one series, without evidence of lower airway disease during a mean follow-up interval of six years \[^{25}\]. Bronchoscopy with bronchoalveolar
lavage should be obtained if infection, aspiration, or Interstitial lung disease are suspected.

**Response to treatment**

For patients suspected of having asthma, a trial of inhaled bronchodilators can be used to confirm the diagnosis prior to initiating a more extensive workup. In patients with chronic or persistent symptoms, the combination of inhaled steroids and bronchodilators may result in significant improvement in symptoms. Further workup would be indicated if the response to this therapy is inadequate.

**Summary.**

Wheezing is a common clinical problem in children. It may be either a benign, self-limited process or the presenting symptom of a significant respiratory disease. Clinical history and physical examination often allow accurate diagnosis.

However, radiographic examination pulmonary function testing, bronchoscopy, sweat chloride concentration, and selective laboratory studies can be very helpful tools if used appropriately. The role of the treating clinician is to try to reach the most likely diagnosis as quickly and efficiently as possible so that therapy, if necessary, can be instituted and the parental concerns can be addressed.
References


Cardiac Asthma

By

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Definition

Cardiac asthma may be defined as the clinical syndrome induced by acute passive congestion and edema of the lungs. It occurs when the left side of the heart suffers from a sudden disproportion between workload and work capacity.

Etiology

Cardiac asthma may result therefore from:

1) Disorders which cause rapid impairment of the myocardium, the load being constant for example myocardial infarction and myocarditis.

2) Disorders which suddenly increase the resistance or pressure load such as paroxysmal or poorly controlled hypertension

3) Disorders which markedly elevate the inflow or venous load without impairing the myocardium such as strenuous exertion or supraventricular tachycardia in a person with mitral stenosis.

4) Or from a combination of these factors. The most common cause is increased venous return in a recumbent subject with left ventricular strain consequent to hypertension. Of the numerous
conditions which may produce increased venous return, nocturnal reabsorption of extracellular fluid from dependent parts is probably the most common

**Prevalence**

The prevalence of cardiac asthma has not been specifically reported in studies of heart failure. Nevertheless, recent studies found the rate of wheezing to be 10-15% in non-elderly patients with HF. In elderly patients, a high rate of cardiac asthma, up to 35%, has been reported.

**Pathophysiology**

Patients with chronic CHF and orthopnea have a considerable increase in airflow resistance upon adopting the supine posture associated with supine expiratory flow limitation. Pulmonary function studies have demonstrated increase in airflow resistance upon adopting the supine posture associated with supine expiratory flow limitation. Pulmonary function studies have demonstrated increased airway resistance or decreased forced expiratory flows in CHF. The existence of dysfunction in small airways in CHF is suggested by an increased closing volume. Moreover, some patients with HF, when challenged with methacholine, exhibit nonspecific bronchial hyper responsiveness. Obstructive changes tend to be mild and appear to be more prevalent during periods of acute decompensation of CHF.
They tend to improve with diuresis presumably due to a reduction in extra vascular lung water, and a general reduction in pulmonary and bronchial blood volumes.

**Diagnosis**

Medical history plays a very important role in differentiating cardiac asthma from other respiratory causes of dyspnea. Cardiovascular risk factors such as hypertension and dyslipidemia; history of valvular heart disease, previous myocardial infarction, previous cardiac dyslipidemia; history of valvular heart disease, previous myocardial infarction, previous cardiac surgery or coronary angioplasty and noncompliance to antihypertensive medications all point to a cardiac cause of dyspnea.

On the other hand, chronic cough and sputum production point to a respiratory cause of dyspnea. Patients with chronic obstructive lung disease may also waken at night with dyspnea, but as pointed out above, this is usually associated with sputum production; the dyspnea is relieved after these patients rid themselves of secretions. Physical examination may reveal third and fourth heart sounds and/or there may be evidence of left ventricular enlargement, jugular neck vein distention, and/or peripheral edema. The difficulty in the distinction between cardiac and pulmonary dyspnea may be compounded by the coexistence of diseases involving both organ
systems. Here the role of further investigations cannot be overemphasized.

Chest X-ray or CT scan may reveal features of thoracic distension as defined by the presence of one of the following radiological signs: enlargement of intercostals spaces, horizontalization of the ribs, or flat diaphragm in patients with COPD. Patients with cardiac asthma usually have cardiac enlargement on chest X-ray and sings of pulmonary venous hypertension.

The 12 lead electrocardiogram is very helpful in this clinical setting as it may reveal signs of left ventricular hypertrophy and strain and/or Q waves of previous myocardial infarction.

B-type natriuretic peptide (BNP) and its N-terminal fraction (NT-pro BNP): Plasma BNP is released from the cardiac ventricles in response to increased wall stretch and volume overload and has been used to exclude and/or identify congestive heart failure (CHF) in patients admitted, for dyspnea, to the emergency department. BNP has a good negative predictive value to exclude heart failure. Various clinical conditions may affect the BNP concentration including renal failure and septicaemia. If elevated concentrations are present, further diagnostic tests are required. If AHF is confirmed, increased levels of plasma BNP and NT-pro BNP carry important prognostic information. Transthoracic Doppler-echocardiography is an essential tool in the diagnosis of cardiac
abnormalities. Echocardiography may reveal left ventricular hypertrophy or dilatation, cardiac wall motion abnormalities and/or depressed left ventricular systolic function. Diastolic function can be assessed using different Doppler modalities.

Septal E/Ea ratio is used as a simple and reliable noninvasive surrogate for pulmonary capillary pressure. Pulmonary function tests: the following indices are usually measured: FVC (L), FVC (percentage of predicted), forced expiratory volume in one second (FEV₁) (L), FEV₁ (percentage of predicted), FEV₁ /FVC ratio (%), and forced midexpiratory flow rate (FEF₂₅₋₇₅%) (percentage of predicted). Pulmonary function studies have demonstrated increased airway resistance or decreased forced expiratory flows in CHF. The existence of dysfunction in small airways in CHF is suggested by an increased closing volume. In patients in whom the etiology of dyspnea is not clear, it is desirable to carry out pulmonary function testing, for these tests may be helpful in determining whether dyspnea is produced by heart disease, abnormalities of the chest wall, or anxiety.

These also may be an enhanced degree of airway reactivity that diminishes with diuresis. Small improvements in expiratory flows are observed with anticholinergic and β2-agonist drugs in patients with chronic heart failure. Patients with cardiac asthma tend to have higher hypercapnic acidemia which is thought to be associated with worse prognosis.
Introduction.

The second half of the last century of the past 7 years of the new millennium had witnessed worldwide increase in the incidences of BA

COPD. Industrialization, pollution, immigration, more availability of medical services and heightened awareness to both conditions are among the most influencive contributors to the increases. Despite great advances in management severity of clinical morbidity and mortality are also disproportionately unexpectedly increasing. The problem is further complicated by the reality of chronicity and incurability of either conditions making good control as the best attainable target. Still more disturbing are the costs, direct and indirect, imposed by these ailments on patients, families and the community. It is of prime importance to physicians and especially pulmonologists to be able to recognize, differentiate and properly manage BA and COPD.


**Clinical Picture**

The classic presentation of a case of BA is unmistakable, a young patient with recurrent episodes of wheezing chest at day and night with history of other allergies in the nose, skin or eyes. The episodes are usually satisfactorily responding to bronchodilator inhalation and a family history of allergy and or a specific recognizable allergen may be identified.

On the other hand the classic clinical picture of a COPD patient is presented by an old life long smoking patient complaining of progressive exertional dyspnoea and tightness in the chest, his condition worsens with colds and flues with increased bonts of expectoration and unsatisfactory responses to medications.

The necessary points of good history taking and meticulous examinations need to be substantiated by simple aiding diagnostic tests some of which can be performed at the doctor's office e.g. the FEV\textsubscript{1} or PEFR response to a bronchodilator inhalation with> 15% improvement in asthmatics and a minimal response from COPS patients. Although both conditions might overlap when an acute infection brings the patient to attention, yet a CBC and X-ray can help to discriminate the hyperoesinophilic with almost normal or slightly over inflated X-ray from the COPD patient with leukocytosis and gross hyperinflation may be with emphysematous bullae as well.
Pathophysiology

Both conditions are headed under the title of destructive lung diseases or obstructive airway disease. However asthma is characterized by full as enormous reversibility after bronchodilator inhalation exceeding me 15 % threshold level while COPD patients hardly attain reversibility.

It should be added that asthmatic have two other features
1) Small airway dysfunction Parameters even in between the attacks.
2) Remodeling of asthmatic air ways tend to shift them to a state of fixed airway destruction with decreased reversibility.

Also in COPD patients, if full physiologic assessment can be obtained they will show
1) Progressive increase in their R.V. of T.L.C.
2) Dynamic hyperinflation wit reduction in inspiratory capacity.

Pathogenesis

A basic Th1 / Th2 imbalance with exaggerated outpouring of Th2 inflammatory cells and mediators in the airways play the crucial role in the initiation and perpetuation of the BA syndrome. In COPD patients a protease/antiprotease in balance and oxidant/antioxidant similar defect leased on smoking ingredients provoking leukocytes and other inflammatory cells constitute the pathogenic impetur of COPD patient. Allergy plays a major role in asthma, though mast cell
degranulation can be induced by a variety of non-allergenic stimuli like viruses, exercise, hormonal changes e.g. associating pregnancy and menstruation.

On the other hand industrial exposures and pollutions can induce and definitely accelerate the COPD process. Genetic factors are very clear in COPD patients suffering from α1 antitrypsin deficiency and the rare cases associating Ehlers-Davlos and Cutis Laxa syndromes

In BA genetic factors has harboring the trait for Th2 dominance with hyperesinophilia and excessive IgE are the back bone for the asthma syndrome. It is not yet clear, in both BA and COPD whether there is (are) defect(s) in specific natural anti-inflammatory mechanisms which protect most individuals from developing either BA when exposed to asthma offending antigens and protect smokers from COPD.

**Radiology of COPD and BA**

Although routine X-ray of both cases might appear in either condition as well, yet routine X-ray is mandatory in both conditions for:

1) A bare line and reference evaluation procedure.
2) To elaborate other pathologies like pneumonia atalechtais, pneumothorax which can be undetected by routine clinical examination and can well be life threatening.

Signs of hyperinflation common to both conditions include: wide intercortical spaces, transverse ribs, low flat diaphragm, vertical sleoulder heart, hyperlucencey with decreased vascular markings. Expiratory hyperillumination on fluouroscopy or hyperlucencey on exp. Jilms denotes air trapping. Emphysemetous bullae and cysts can be, sometimes, severe on routine X-rays in COPD patients but C.T.'s are more helpfule in their illusterations. C.T.'s are not indicated in routine check up but are extremely helpful to identify suspicious lesions and shadows in either condition.

**Management of BA and COPD**

A primary step before imitation of pharmacotherapy is patient education, proper staging and evaluation of his clinical morbidity according to international guidelines and sharing the family, guardians, in the management plan.

In both diseases it is extremely important to quit smoking and abandon smoking at the patient's home. It is also mandatory to avoid dusty places and proper job adjustments can very well improve patientís reipoure to treatment and avoid chronicity.
Home insecticides, wood firing, grilling, frying, wool carpets and curtains, detergents perfumes, domestic pets and birds can all deleteriously affect the patient condition and should be strictly avoided.

For asthmatics specific allergen avoidance when identified is a prime target in management and heavy meals and post prandical recumbaucey can precipitate dyspnoea and tightness in both diseases and asthmatic attacks. CERD should be looked for and its comanagement is very helpful. In BA avoidance of specific food allergens is extremely important and refrainement of foods containing preservatives, dyes, colouring and flavouring additives should be strongly and repeatedly emphasized to the family ad the patients of BA. Dietary attention is an essential part of the rehabilitation program of COPG patients as well as there ICU.

Sports and exercise are not prohibited but should be optimized and monitored and premedicated with bronchodilators for asthmatics while for COPD patient a specific individualized program is tailored by the rehabilitation team.

Exercise is contraindicated during acute exacerbations in both diseases and its resumption should be under medical guidance and with full patient, family, school and sport trainers awareness of the patient condition.
Pharmacotherapy of both conditions is very well tabulated in international and national guidelines. Physician caring for switch patients should be very well informed with them. Patient and family information and partnership is extremely required for the success of the management plan. The details of such guidelines are beyond the scope of this review and specific details are available in the literature.

**The important Messages include**

**A- In bronchial asthma**

1) Combination of bronchodilators and the anti inflammatory corticosteroids by the inhalational route are the prime pillars of therapy.
2) Short acting $\beta_2$-agonists are P.R.N. basis quite assist patient's management.
3) The addition of theophylline, autidrolinergics and escalativy LABA and ICS should be the physicians and not the patient's decision.

**B- in COPD Patients**

1) Inhalational combinations of LABA and anticholinergics are the most effective weapons.
2) Corticosteroid use is restricted to needing responders who are identified by the physician judgment according to guidelines.
3) $O_2$ therapy in home and hospital is subjected to scientific rules of any drug usage.
C- In Both Conditions

1) Patient doctor cooperation is essential.

2) Before pharmaceutical escalation resort to clinical re-evaluation and try to find and eliminate a precipitating factor like smoking, infection, GERD ...etc.

3) Anti flu vaccination annually is recommended for BA and COPD patients.

4) Make sure of patients compliance and proper use of their inhalers at each visit.

Conclusions

The tremendous increase in the numbers of BA and COPD cares over the past decades had resulted in more and more presentations of classic cares of either conditions that the G.P. can easily identify and hardly miss. However, an equal number of confusing cares with overlap clinical and radiological manifestations need the attention of the chest physician who, by now, should be very well aware of the discriminating features that enable him to specify and categorise the severity of either condition.
Pulmonary Embolism (PE) as an Asthma Simulator

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PE can be considered as one of the asthma simulants as both are associated with dyspnoea and occasional wheezing. However, presence of chest pain, haemoptysis, dup vein thrombosis (DVT) or other risk factors (operation - pregnancy - occupation as) directs the attention to diagnosis of PE. On clinical examination, the presence of tachypnea, tachycandia, atrial fibrillation, manifestations of hypoxia, pulmonary hypertension or pleural effusion also directs the attention for diagnosis of PE.

It Should be Noted that:

- PE may account for up to 15% of all post-operative deaths.
- 75% of thrombi are generated in the deep venous system of the lower limbs and pelvis.
- 20% of leg thrombi embolize, with a higher incidence in above knee clots than below knee clots.
- Thrombi can also develop in the right heart following myocardial infarction.
- Septic emboli are found in endocarditis.
- As the PAP rises, right ventricular afterload increases, with resulting increase in right ventricular end diastolic pressure.
- The right ventricle will start to fail acutely as the PAP reaches over 40 mmHg.
- Hypoxia results from reduced cardiac output, low mixed venous \( \text{PaO}_2 \) and higher perfusion to the remaining alveoli leading to ventilation/perfusion mismatching in the unaffected lung.
- A patient with a PAP of > 40 mmHg cannot have acute PE as this pressure cannot be achieved acutely. In this setting, the raised PAP raises the possibility of chronic thromboembolic, pulmonary hypertension, or another cause of raised PAP.
# Risk Factors for Venous Thromboembolism (VTE)

**Major risk factors (relative risk x 5-20)**

| Surgery                     | Major abdominal/pelvic surgery  
|                            | Orthopaedic surgery (especially lower limb)  
|                            | Post-operative intensive care    |
| Obstetrics                  | Late pregnancy  
|                            | (higher incidence with multiple births)  
|                            | Caesarean section  
|                            | Pre-eclampsia  |
| Malignancy                  | Pelvic/abdominal  
|                            | Metastatic/advanced |
| Lower limb problems         | Fracture, varicose veins  
| Reduced mobility            | Hospitalization  
|                            | Institutional care  
| Previous proven VTE         |  

**Minor risk factors (relative risk x 2-4)**

| Cardiovascular              | Congenital heart disease  
|                            | Congestive cardiac failure  
|                            | Hypertension  
|                            | Central venous access  
|                            | Superficial venous thrombosis  
| Ostrogens                   | Oral contraceptive pill  
|                            | (especially third-generation higher  
|                            | oestrogen containing)  
|                            | Hormone replacement therapy |
| Miscellaneous               | Occult malignancy  
|                            | Neurological disorders  
|                            | Obesity  
|                            | Inflammatory bowel disease  
|                            | Nephrotic syndrome  
|                            | Dialysis  
|                            | Myeloproliferative disorders  
|                            | Behçet's disease |
Risk of Malignancy.

Occult cancer will be present in 7-12% of patients presenting with idiopathic venous thromboembolism (VTE). 25-50% of patients with VTE have an identifiable inherited thrombophilia, e.g. antiphospholipid syndrome, deficiency of antithrombin III, a prothrombin gene defect, protein C or protein S deficiency.

Clinical Features.

Acute PE typically presents in four main ways:
- Circulatory collapse in a previously well patient
- Hypotension ± loss of consciousness in 1%
- Pulmonary infarction and haemoptysis (in 60%)
- Isolated dyspnoea (in 25%)
- Collapse, poor reserve (in 10%)

Chronic Thrombolic Disease.

This typically presents with more increasing load of recurrent small volume clot. Dyspnoea and tachypnoea (defined as a respiratory rate > 20) are the commonest presenting features and are absent in only 10% of patients.

Consider PE in the Differential Diagnosis of .

- Unexplained shortness of breath Collapse
- New onset atrial fibrillation
- Signs consistent with right heart failure
- Pleural effusion

**Examination of Patient with PE.**

- May be normal
- Tachycardia and tachypnoea are common
- Artial fibrillation
- Reduced chest movement (due to pain)
- Pleural rub
- Classically loud P2 and splitting of the second heart sound, with a gallop rhythm (acute right heart strain)
- Hypoxia (with hypocapnia due to hyperventilation, and an increased alveolar-arterial gradient) But PaO₂ may be in the normal range in young, healthy individuals
- Low grade fever
- Signs of DVT (common, in around 25%)
- Right heart failure low cardiac output and cardiac output and raised JVP with reduce BP and perfusion pressure

**Diagnosis of Acute PE.**

**Pre-test clinical probability scoring systems**

One example is the BTS protest clinical probability scoring system, shown in the box below.

A standard assessment of pre-test clinical probability might include:
- Patient has clinical features compatible with PE:
  - Raised respiratory rate
• ± Haemoptysis
• ± Pleuritic chest pain

**Plus 2 other factors:**

1) Absence of another reasonable clinical explanation
2) Presence of a major risk factor
   • plus 1 and 2: HIGH pre-test clinical probability
   • plus 1 or 2: INTERMEDIATE pretest clinical probability
   • alone: LOW pre-test clinical probability.

**D-dimer testing** has an important role in diagnosis and excluding PE, and should only be used with a pretest clinical probability assessment. D-dimers are sensitive for thromboembolism, but not specific.
- The sensitivity ranges from 87 to 99% depending on the assay used (ELISA (Vidas) or red cell agglutination (SimpliRED)). Specificity is poorer, around 60-70% (so a large number of false positives)
- D-dimer testing for PE has been validated as an out-patient test, but not in-patient groups
- EGG Non-specific
- CXR No specific features are characteristic in PE, but it may reveal another pathology. Small effusions are present in 40 % (80% are exudates, 20% transudates). Focal infiltrates, segmental collapse, and raised diaphragm can also occur
- Arterial blood gas
- D-dimer
- CTPA is the gold standard investigation
- Isotope lung scanning (ventilation/perfusion or WQ scan) mostly now superseded by CTPA

**Other imaging Techniques**

- Leg ultrasound
- Conventional pulmonary angiogram
- CT venography
- Echocardiogram is diagnostic only in massive PE
- Cardiac troponin A rise indicates acute right heart strain. For prognostic information only; has no role in decision making

**Treatment**

The dyspnoea as well as all other manifestations of PE can improve with thrombolytic therapy or anticoagulant therapy (heparin followed by oral anticoagulant).
E.N.T. Asthma Simulators

By
Prof. Hisham Abd El Faffah

There are conditions which can simulate asthma and mislead the physician into an incorrect diagnosis; these include:

1) Obstructive sleep apnea syndrome
2) Postnasal syndrome
3) Nasal obstruction
4) Millar's asthma (laryngeal asthma)
5) Vocal cord dysfunction
6) Subglottic lesions
7) Tracheal lesion

OBSAS

Definition of Sleep Apnea
- Apnea/Hypopnea index = Number apneas/hypopneas per hour sleep
- AHI = Respiratory Disturbance index (RDI)
- AHI (RDI) ≥ 5 / hour >> Sleep apnea

Types
- Central
- Obstructive: This can simulate asthma
- Mixed
Risk Factors

1) Age
2) Weight (2/3 are 20% over wt)
3) Smoking
4) Alcohol

History

- Sleepiness or fatigue
- Loud long lasting snoring
- Nocturnal arousals, choking or gasping attacks
- Risk factors
- History of multiple car or job accidents
- Bed partner description
Golden Standard for Diagnosis

I. Nasopharyngolaryngoscopy
II. Polysomnography EEG, ECG, EOG, PsO₂, Air flow, chest movement, abdominal movement, leg movement.

- Normal → ≤ 5 apneic events per hour (Al)
- Pediatric age → 1 episode / hour may be abnormal
- Elderly → is not always associated with Significant physiological changes

Methods of Treatment

- Behavioral
  - Medical
  - Surgical

- Wt Loss
  - Alcohol & Sedatives Avoidance
  - Smoking Cessation
  - Regular & Adequate sleep
  - Sleep position training

Pharmacologic
- Supplement O₂
- Oral Appliance

Palatal surgeries
- Nasal surgeries
- Oropharyngeal Surgery
  - Tongue base surgery

Surgical Treatment.
- Laryngeal Surgery
- Mandibular Advancement
- Tracheostomy

**Miller's Asthma.**

- FAUO (Functional Upper Airway Obstruction) (Patterson, Schutz, Horton, 1974)
- Mendelson's Syndrome (Campbell & Perce 1994)

**Characteristics of Miller's Asthma:**

1) Non-responsive breathlessness to beta agonist & steroids en>>>>
   Inspiratory Stridor
2) Flat inspiratory flow volume loop
3) Nasolaryngoscopy shows>>>>
   inspiratory bil cord abduction

**PND Syndrome.**

This commonly associated with chronic rhinopathy particularly allergic rhinosinusitis. It is accompanied with sneezing, rhinorrhea, itching in the nose throat and ears and nasal obstruction. The latter usually leads to a nasopulmonary reflex inducing bronchospasm which is relieved by the relieve of the nasal symptoms
**Subglottic Lesions.**

The frequently miss diagnosed as asthma. These include:
1) Congenital Subglottic haemangioma
2) F. B.
3) Scleroma
4) Carcinoma

This is associated with biphasic stridor. The noise during respiration is long expiratory and short inspiratory, unequal in length.

**Tracheal Lesions.**

This can be secondary to external compression by thyroid gland enlargement in the neck or Mediastinal mass in the chest or endotracheal lesion. The latter include:

1) F. B.
2) Scleroma
3) Carcinoma

This is associated with biphasic strider. The noise during respiration are both in the expiratory and inspiratory phases of respiration of equal length.
Psychogenic Dyspnea

By
Prof. Mostafa El Shazly

Psychogenic dyspnea represents a relatively common presentation that most clinicians readily recognize. As classically defined psychogenic dyspnea (Hyperventilation syndrome) is a condition in which minute ventilation exceeds metabolic demands, resulting in hemodynamic and chemical changes that produce characteristic dysphoric symptoms, which can be reproduced in these patients by including a drop in arterial p CO₂ through voluntary hyperventilation.

Pathophysiology

Psychogenic dyspnea occurs in acute and chronic forms. Acute psychogenic dyspnea accounts for only 1% of cases but is diagnosed more easily. Chronic psychogenic dyspnea can present with a myriad of respiratory, cardiac, neurologic, or GI symptoms without any clinically apparent over breathing by the patient. Hypocapnia can be maintained without any change in the absolute minute volume if the patient exhibits frequent sighs interspersed with normal respirations. The underlying mechanism by which some patients develop hyperventilation is unknown, but theories abound. A population clearly exists in whom certain stressors provoke an exaggerated
respiratory response. Several such stressors have been identified, including emotional distress, sodium lactate and caffeine.

Part of the explanation for psychogenic dyspnea lies in the mechanics of breathing. Normal tidal volumes range from 35-45% of vital capacity at rest. Hyperinflation of the lungs beyond that level is resisted by the elastic recoil of the chest wall, and inspiratory volumes beyond this level are perceived as effort or dyspnea.

Patients with psychogenic dyspnea tend to breathe by using the upper thorax rather than the diaphragm, resulting in chronically over inflated lungs. When stress induces a need to take a deep breath, the deep breathing is perceived as dyspnea. The sensation of dyspnea creates anxiety, which encourages more deep breathing, and a vicious cycle is created.

**Frequency.**

- As many as 10% of patients in a general internal medicine practice are reported to have psychogenic dyspnea as their primary diagnosis,
- Overall up to 6% of the general population may have this condition to a variable degree.

**Mortality / Morbidity.**

- Death attributable to the syndrome is extremely rare. A leftward shift in the HbO₂ dissociation curve and vasospasm related to low
PCO$_2$ may cause myocardial ischemia in patients with coronary artery disease and HVS.

- Certain patients are disabled psychologically by their symptoms, and many patients carry false diagnoses.
- Clearly psychogenic dyspnea not only produces severe and genuine discomfort for the patient, it also accounts for considerable medical expense in excluding more serious pathology.

- **Sex**: female-to-male ratio may be as high as 7:1
- **Age**: The peak age of incidence is from 15-55 years, but cases have been reported in all age groups except infancy.

**History.**

- Patients with acute psychogenic dyspnea may present with great agitation and anxiety.
- Most commonly, the history is of sudden onset of chest pain, dyspnea, or necrologic symptoms (eg, dizziness, weakness, paresthesias, near syncope) following a stressful event.
- Patients with chronic HVS present with similar symptoms of recurrent chest pain, dyspnea, or necrologic deficits but usually have had numerous similar presentations in the past.
- **Acute psychogenic dyspnea**

  - Patients often present dramatically with agitation, hyperpnea and tachypnea, chest pain, dyspnea. wheezing, dizziness, palpitations, tetanic cramps (carpopedal spasm), paresthesias, Perioral numbness is very common, generalized weakness, and syncope.
- The patient often complains of a sense of suffocation. An emotionally stressful precipitating event often can be identified.
- Bloating, belching, flatus, epigastric pressure may result from aerophagia.
- Dry mouth occurs with mouth breathing and anxiety.
- Chronic psychogenic dyspnea

- The diagnosis of chronic psychogenic dyspnea is much more difficult than that of acute psychogenic dyspnea because the hyperventilation usually is not clinically apparent.
- Often, these patient have had extensive medical investigations and have been assigned several misleading diagnoses.

- Two thirds of patients with chronic psychogenic dyspnea have a persistently slightly low PCO$_2$ with compensatory renal excretion of HCO$_3^-$, resulting in a near-normal pH level.
- These patients tend to have more prominent CNS symptoms than patients who maintain normal PCO$_2$ during attacks. These patients usually present due to dyspnea and chest pain.
- The respiratory alkalosis can be maintained with occasional deep sighing respirations, which are observed often in patients with chronic psychogenic dyspnea.
- When faced with an additional stress that provokes hyperventilation, the physiologic acid-base reserve is less, and these patients become symptomatic more readily than patients without HVS.
- Many of these patients suffer from obsessive-compulsive disorders, experience sexual and marital difficulties, and have poor adaptations to stress.
- Patients with chronic psychogenic dyspnea may have symptoms that mimic virtually any serious organic disorder, but usually they have atypical features of these diseases.

**Physical.**

- Acute psychogenic dyspnea
  - Obvious tachypnea and hyperpnea are present.
  - Carpopedal spasm occurs Chvostek or Trousseau signs may be positive because of hypocalcemia.
- Wheezing may be heard because of bronchospasm frame hypocarbia.
- Tremor, mydriasis, pallor, tachycardia, and other manifestations of anxiety can occur.
- Evidence of depersonalization or hallucination may be noted.
- Chronic psychogenic dyspnea
- Hyperventilation usually not readily apparent
- Frequent sighing respirations, 2-3 per minute; frequent yawning
- Chest wall tenderness, numbness, tingling
  - Characteristically, multiple complaints without much supporting physical evidence of disease
Causes.

- The cause of psychogenic dyspnea is unknown, but some persons who are affected appear to have an abnormal respiratory response to stress, sodium, lactate, and other chemical and emotional triggers, thereby resulting in excess minute ventilation and hypocarbia.

- In most patients, the mechanics of breathing are disordered in a characteristic way. When stresses, these patients rely on thoracic breathing rather than diaphragmatic breathing, resulting in a hyperexpanded chest and high residual lung volume. Because of the high residual volume, they are then unable to take a normal tidal volume with the next breath and consequently experience dyspnea.

- The incidence of psychogenic dyspnea in first-degree relatives is higher than in the general population, but no clear genetic factors have been identified.

Treatment

- Stress reduction therapy, betablockers, tricyclic antidepressants, and breathing retraining all have proven effective in reducing the intensity and the frequency of episodes of hyperventilation. If the diagnosis of HVS has been established, the patient should be referred to an appropriate therapist to implement these techniques over the long term.
Closing Remarks on Common Asthma Simulators

By
Prof. Hatem El Mallwany
Professor & Head of Chest Department
Alexandria Faculty of Medicine

From the previous reports more than fifty asthma simulators can be counted taking into consideration their frequency and the salient features that distinguish them from actual bronchial asthma, the following table is considered a good summary for this topic.

Differential Diagnosis of Asthma in Adults

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Common</td>
<td>Variable cough, wheeze, dyspnea Onset usually in childhood Worsе at night and with exercise Pulmonary function tests-reversible airway obstruction Often associated with other atopic diseases Symptoms relieved by β-agonist administration</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Common</td>
<td>Progressive small airway obstruction Poor response to bronchodilator History of tobacco smoking</td>
</tr>
<tr>
<td>Cardiac asthma</td>
<td>Common</td>
<td>Physical signs of cardiac dysfunction Chest radiograph-cardiomegaly Abnormal echocardiogram</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Asthma in Adults (Continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux with recurrent aspiration</td>
<td>Common</td>
<td>Nocturnal symptoms common Vomiting or heartburn Barium swallow</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Common</td>
<td>Triggered by anxiety or exercise Normal pulmonary function tests, no hypoxia Tingling or numbness of extremities Rapid resolution of symptoms with calming</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Common</td>
<td>Hoarseness, stridor Pulmonary function tests-limited inspiratory flow Poor response to asthma therapy</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Common</td>
<td>Tachypnea, tachycardia Hypoxia Chest pain Pulmonary function tests-restricted lung volume Abnormal ventilation/perfusion scan</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Uncommon</td>
<td>Occupational or recreational exposure to molds, organic dusts, or chemical solvents Antigen-specific, precipitating antibodies in serum Pulmonary function tests-restricted lung volumes</td>
</tr>
<tr>
<td>Drug-induced cough</td>
<td>Uncommon</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
</tbody>
</table>
Lastly, it should be emphasized that all Asthma simulators should be first excluded before diagnosing any case with persistent symptoms—despite treatment—as uncontrolled or difficult to treat asthma.
## Asthma Simulators in Children

*By Prof. Mahmoud El Zalabany, Professor of Allergy and Paediatrics, Alexandria University*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Common</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>Common</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>Common</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Common</td>
</tr>
<tr>
<td>Laryngotraechomalacia</td>
<td>Common</td>
</tr>
<tr>
<td>Foreign body aspiration</td>
<td>Common</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Common</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophageal reflux with recurrent aspiration</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Congenital anatomic airway abnormality</td>
<td>Rare</td>
</tr>
<tr>
<td>Vascular ring</td>
<td></td>
</tr>
<tr>
<td>Laryngeal web</td>
<td></td>
</tr>
</tbody>
</table>
### Distinguishing Features

Variable cough, wheeze, dyspnea Worse at night and after exercise
Pulmonary function tests - reversible airway obstruction Often associated with other atopic diseases Symptoms relieved by β-agonist administration

Age < 2 years Associated with respiratory syncytial virus or parainfluenza infection

Chronic cough and nasal congestion
Abnormal sinus radiographs but normal pulmonary function

Triggered by anxiety or exercise - Normal pulmonary function tests, no hypoxia - Tingling or numbness of extremities - Rapid resolution of symptoms with calming

Stridor - Early onset of symptoms - No response to bronchodilator

Sudden onset of symptoms - Coughing or choking while eating - Abnormal expiratory chest radiograph (air trapping) - Bronchoscopy is the definitive study

Pulmonary function tests-decreased inspiratory flow - Hoarseness, stridor Symptoms do not respond to asthma therapy

Chronic airway disease with exacerbations History of premature delivery and respiratory support

Nocturnal symptoms common - Vomiting or cough when recumbent
Barium swallow abnormal

Abnormal sweat test and abnormal chest radiograph - Poor growth, fat malabsorption

Migratory infiltrates on chest radiograph - Positive skin test for Aspergillus (often with serum precipitins) - Elevated total IgE

Early onset of stridor, no response to bronchodilator
Airway compromised on chest radiograph or with barium swallow Bronchoscopy
With Compliments of

NOVARTIS