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The executive task force is provided for students of 5th courses of medical faculties for helping to study of some topics in the fields of pulmonology diseases incorporated into the discipline «Internal Medicine». There is the information about the most important topics regarding diagnosis of pulmonology diseases.

The textbook is addressed to students of 5th courses of medical university for helping to study of internal medicine in the field of pulmonology diseases.

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CONTENT

List of abbreviations

EIA	exercise-induced asthma
EIB	exercise-induced bronchospasm
FEV_1	forced expiratory volume in one second
ICU	intensive care unit
GERD	gastroesophageal reflux disease
NO	nitric oxide
RAST	radioallergosorbent tests
PEF	peak expiratory flow
GINA	Global Strategy for Asthma Management and Prevention
BMI	body mass index

Part 1. BRONCHIAL ASTHMA

Preface

Asthma is one of the most common chronic diseases worldwide and is the most common cause of hospitalization for children in worldwide. Despite recent advances in understanding of the pathophysiology and treatment of asthma, the condition continues to have significant medical and economic impacts worldwide. In 1991, the National Asthma Education and Prevention Program Expert Panel from the US National Institutes of Health issued its first report on the guidelines for the diagnosis and management of asthma. While the web-based alterations appeared successful, it was felt an appropriate time to consider producing a new paper-based version in which to consolidate the various yearly updates. The 2020 guideline considered literature contains a completely rewritten section on diagnosis for both adults and children; a section on special situations which includes occupational asthma, asthma in pregnancy and the new topic of difficult asthma; updated sections on pharmacological and non-pharmacological management; and amalgamated sections on patient education and compliance, and on organization of care and audit. The 2020 revisions of The Global Initiative on Asthma (GINA) include updates to pharmacological management, the management of acute asthma. Update searches were conducted on inhaler devices but there was insufficient new evidence to change the existing recommendations.

The GINA updates its evidence-based documents annually, based on research published in the previous year. The methodology underpinning the development and annual updates of these documents is described on the GINA website; in summary, all asthma papers published in the previous year are reviewed by the GINA science committee and relevant findings are incorporated in the updates. In the case of new therapies, GINA makes recommendations based on the best available evidence, after approval by at least one major regulatory agency (such as the European Medicines Agency [EMA] and US Food and Drug Administration [FDA]). For existing medications with evidence for new regimens

or populations, GINA may make recommendations not covered by a regulatory indication in any country at the time if satisfied with the evidence for safety and effectiveness.

Definition of bronchial asthma

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

However, the diagnosis of asthma is a clinical one; there is no standardised definition of the type, severity or frequency of symptoms, nor of the findings on investigation. The absence of a gold standard definition means that it is not possible to make clear evidence based recommendations on how to make a diagnosis of asthma. Central to all definitions is the presence of symptoms (more than one of wheeze, breathlessness, chest tightness, cough) and of variable airflow obstruction. More recent descriptions of asthma in children and in adults have included airway hyper-responsiveness and airway inflammation as components of the disease. How these features relate to each other, how they are best measured and how they contribute to the clinical manifestations of asthma remains unclear. Although there are many shared features in the diagnosis of asthma in children and in adults there are also important differences. The differential diagnosis, the natural history of wheezing illnesses, the ability to perform certain investigations and their diagnostic value, are all influenced by age.

Classification Guidelines

The 2007 NAEPP guidelines and the 2009 VA/DoD asthma management guidelines use the severity of asthma classification below, with features of asthma

severity divided into three charts to reflect classification in different age groups (0-4 y, 5-11 y, and 12 y and older). Classification includes (1) intermittent asthma, (2) mild persistent asthma, (3) moderate persistent asthma, (4) and severe persistent asthma.

Intermittent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing less than twice a week
- Flare-ups are brief, but intensity may vary
- Nighttime symptoms less than twice a month
- No symptoms between flare-ups
- Lung function test FEV 1 is 80% or more above normal values
- Peak flow has less than 20% variability am-to-am or am-to-pm, day-to-day

Mild persistent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing 3-6 times a week
- Flare-ups may affect activity level
- Nighttime symptoms 3-4 times a month
- Lung function test FEV 1 is 80% or more above normal values
- Peak flow has less than 20-30% variability

Moderate persistent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing daily
- Flare-ups may affect activity level
- Nighttime symptoms 5 or more times a month
- Lung function test FEV 1 is above 60% but below 80% of normal values
- Peak flow has more than 30% variability

Severe persistent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing that are continual
- Frequent nighttime symptoms

- Lung function test FEV 1 is 60% or less of normal values
- Peak flow has more than 30% variability

In contrast, the 2019 Global Initiative for Asthma (GINA) guidelines categorize asthma severity as mild, moderate, or severe. Severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations, as follows:

- Mild asthma: Well-controlled with as-needed reliever medication alone or with low-intensity controller treatment such as low-dose inhaled corticosteroids (ICSs), leukotriene receptor antagonists, or chromones
- Moderate asthma: Well-controlled with low-dose ICS/long-acting beta2-agonists (LABA)
- Severe asthma: Requires high-dose ICS/LABA to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment

The 2013 joint European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines on evaluation and treatment of severe asthma reserves the definition of severe asthma for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.

The 2019 GINA guidelines stress the importance of distinguishing between severe asthma and uncontrolled asthma, as the latter is a much more common reason for persistent symptoms and exacerbations, and it may be more easily improved. The most common problems that need to be excluded before a diagnosis of severe asthma can be made are the following:

- Poor inhaler technique
- Poor medication adherence
- Incorrect diagnosis of asthma, with symptoms due to alternative conditions such as upper airway dysfunction, cardiac failure, or lack of fitness
- Comorbidities and complicating conditions such as rhinosinusitis, gastroesophageal reflux, obesity, and obstructive sleep apnea

Ongoing exposure to sensitizing or irritant agents in the home or work environment.

Pathophysiology

The pathophysiology of asthma is complex and involves the following components:

- airway inflammation,
- intermittent airflow obstruction,
- bronchial hyperresponsiveness.

The classic pathway of asthma involves the release of thymic stromal lymphopoietin by epithelial cells when an allergen or infectious agent enters the airway. This then activates Th2 cells, which produce various cytokines, including IL-4, IL-5, and IL-13. These cytokines then lead to the IgE formation and eosinophil activation responsible for airway hyper-responsiveness. Activation of mast cells via the attachment of IgE to high-affinity IgE receptors leads to the release of histamine, cysteinyl leukotrienes, and prostaglandins, which are also involved in bronchoconstriction.

The non-eosinophilic pathway of asthma involves activation of airway epithelial cells and macrophages by TLR4 and CD14, which leads to the production of NFκB and IL-8, which further activate neutrophils.

The mechanism of inflammation in asthma may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity. Varying degrees of mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling are present.

Some of the principal cells identified in airway inflammation include mast cells, eosinophils, epithelial cells, macrophages, and activated T lymphocytes. T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines. Other constituent airway cells, such as fibroblasts, endothelial cells, and epithelial cells, contribute to the chronicity of the disease. Other factors, such as adhesion molecules (eg, selectins, integrins), are

critical in directing the inflammatory changes in the airway. Finally, cell-derived mediators influence smooth muscle tone and produce structural changes and remodeling of the airway.

The presence of airway hyperresponsiveness or bronchial hyperreactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli. The mechanisms involved include direct stimulation of airway smooth muscle and indirect stimulation by pharmacologically active substances from mediator-secreting cells such as mast cells or nonmyelinated sensory neurons. The degree of airway hyperresponsiveness generally correlates with the clinical severity of asthma.

Airflow obstruction can be caused by a variety of changes, including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling. Acute bronchoconstriction is the consequence of immunoglobulin E–dependent mediator release upon exposure to aeroallergens and is the primary component of the early asthmatic response. Airway edema occurs 6-24 hours following an allergen challenge and is referred to as the late asthmatic response. Chronic mucous plug formation consists of an exudate of serum proteins and cell debris that may take weeks to resolve. Airway remodeling is associated with structural changes due to long-standing inflammation and may profoundly affect the extent of reversibility of airway obstruction.

The pathogenesis of EIA is controversial. The disease may be mediated by water loss from the airway, heat loss from the airway, or a combination of both. The upper airway is designed to keep inspired air at 100% humidity and body temperature at 37°C (98.6°F). The nose is unable to condition the increased amount of air required for exercise, particularly in athletes who breathe through their mouths. The abnormal heat and water fluxes in the bronchial tree result in bronchoconstriction, occurring within minutes of completing exercise. Results from bronchoalveolar lavage studies have not demonstrated an increase in inflammatory mediators. These patients generally develop a refractory period,

during which a second exercise challenge does not cause a significant degree of bronchoconstriction.

Phenotypes of bronchial asthma

There are many phenotypes and endotypes of asthma, each with a distinct clinical presentation and pathophysiology. Prior large studies have used clinical presentations such as sex, age of onset, allergic status, lung function, and asthma symptoms to categorise asthma patients into clusters. Many different phenotypes have been described but most can be distinguished by early versus late onset, the presence of atopy and significant allergic symptoms, severity of lung function reduction, and response to treatment.

The early-onset, allergic phenotypes include those who present with symptoms early in childhood that last into the adulthood. These patients often have elevations in IgE along with associated allergic and atopic symptoms and respond well to treatments that target Th2 response and IgE downregulation. Patients with the late-onset eosinophilic phenotype, on the other hand, present with more severe, persistent symptoms that are less allergic in origin. These patients often do not respond to corticosteroids as well, and their disease process involves predominantly cysteinyl leukotriene pathway upregulation. Eosinophilic phenotype includes patients who exhibit significant sputum eosinophils (>2%) and have good response to corticosteroids. The exercise-induced asthma phenotype involves mast cell and Th2 cytokine activation, often with mild intermittent symptoms that occur during exercise. Patients with the obesity-related phenotype lack Th2 biomarkers and have a less clear pathway to airway hyper-responsiveness. The neutrophilic phenotype includes patients with persistent asthma who are less responsive to corticosteroids. These patients often have elevated neutrophils with exacerbations and tend to respond better to biologics and alternative treatments, including macrolide therapy. Patients with aspirin sensitivity, exercise-induced asthma, and bronchopulmonary mycosis will need additional treatment targeting each non-allergic cause. Therefore, understanding the different phenotypes and endotypes is important in determining one’s treatment course. As we better understand different

asthma phenotypes and the biomarkers that identify them, we can target medical therapy more precisely and develop new agents that target specific pathological pathways of asthma

Frequency

Asthma affects 5-10% of the population or an estimated 14-15 million persons, including 5 million children. The prevalence rate of EIA is 3-10% of the general population if persons who do not have asthma or allergy are excluded, but the rate increases to 12-15% of the general population if patients with asthma are included. The rate of exercise-induced symptoms in persons with asthma has been reported to vary from 40-90%. Asthma is common in industrialized nations such as Canada, England, Australia, Germany, and New Zealand, where much of the data have been collected. The prevalence rate of severe asthma in industrialized countries ranges from 2-10%. Recent trends suggest an increase in both the prevalence and morbidity of the disease, especially in children younger than 6 years. Factors that have been implicated include urbanization, air pollution, passive smoking, and change in exposure to environmental allergens.

Mortality/Morbidity

The estimate of lost work and school time from asthma is approximately 100 million days of restricted activity. More than 1.8 million emergency department evaluations occur annually. The figures from the 1997 National Institutes of Health report1 indicate an estimated 500,000 hospitalizations and 5000 deaths annually. International asthma mortality is reported as high as 0.86 deaths per 100,000 persons in some countries. Mortality is primarily related to lung function, with an 8-fold increase in patients in the lowest quartile, but has also been linked with management failure, especially in young persons. Other factors that impact mortality include age older than 40 years, cigarette smoking greater than 20-pack years, blood eosinophilia, forced expiratory volume in one second (FEV_1) of 40-69% predicted, and greater reversibility.

EIA has not been reported to cause death. Morbidity is associated with exercise limitation. This is observed most dramatically in elite athletes with high levels of exercise who may be limited by airway hyperreactivity.

Race

Asthma occurs in persons of all races worldwide. In the United States, asthma prevalence, especially morbidity and mortality, are higher in blacks than in whites.

Although genetic factors are of major importance in determining a predisposition to the development of asthma, environmental factors play a greater role than racial factors in the onset of disease. National concern is that some of the increased morbidity is due to differences in treatment afforded certain minority groups.

Sex

Asthma predominantly occurs in boys in childhood, with a male-to-female ratio of 2:1 until puberty, when the male-to-female ratio becomes 1:1. Asthma prevalence is greater in females after puberty, and the majority of adult-onset cases diagnosed in persons older than 40 years occur in females. Boys are more likely than girls to experience a decrease in symptoms by late adolescence.

Age

Asthma prevalence is increased in very young persons and very old persons because of airway responsiveness and lower levels of lung function. Two thirds of all asthma cases are diagnosed before the patient is aged 18 years. Approximately half of all children diagnosed with asthma have a decrease or disappearance of symptoms by early adulthood. The diagnosis of EIA is made more often in children and young adults than in older adults and is related to high levels of physical activity. It can be observed in persons of any age based on the level of underlying airway reactivity and the level of physical exertion.

History

A detailed medical history should address (1) whether symptoms are attributable to asthma, (2) whether findings support the likelihood of asthma (eg,

family history), (3) asthma severity, and (4) the identification of possible precipitating factors.

Symptoms may include the following:

- Cough
- Wheezing
- Shortness of breath
- Chest tightness
- Sputum production
- Decreased exercise tolerance
- Symptom patterns can vary as follows:
- Perennial versus seasonal
- Continual versus episodic
- Duration, severity, and frequency
- Diurnal variations (nocturnal and early-morning awakenings)

Precipitating or aggravating factors, also discussed in Causes, may include the following:

- Allergens
- Occupation
- Medications
- Exercise
- Disease development variables include the following:
- Age at onset

History of injury early in life due to infection or passive smoke exposure

- Progress of disease
- Current response to management
- Comorbid conditions

Family history may reveal the following conditions:

- Asthma
- Allergy

- Sinusitis
- Rhinitis

Social history may reveal the following conditions:

- Home characteristics
- Smoking
- Workplace or school characteristics
- Educational level
- Employment
- Social support

Determine the profile of a typical exacerbation.

The impact on the patient and family may have involved the following:

- Emergency department visits, hospitalizations, intensive care unit (ICU) admissions, intubations
- Missed days from work or school or activity limitation

Assess the patient's disease perception based on the following elements:

- Knowledge of asthma and treatment
- Use of medications
- Coping mechanisms
- Family support
- Economic resources

The clinical history for EIA is typical of asthma, with symptoms such as cough, wheezing, shortness of breath, and chest pain or tightness. Some individuals also may report sore throat or GI upset.

- Symptoms are usually associated with exercise but may be related to exposure to cold air or other triggers, such as seasonal allergens, pollutants (eg, sulfur, nitrous oxide, ozone), or upper respiratory infections.
- Initially, airway dilation is noted during exercise. If exercise extends beyond approximately 10 minutes, bronchoconstriction supervenes, resulting in asthma symptoms. If the exercise period is shorter, symptoms may develop up to 5-10

minutes after completion of exercise. A higher intensity level of exercise results in a more intense attack. Running produces more symptoms than walking.

- Patients may note symptoms are related to seasonal changes or the ambient temperature and humidity in the environment in which a patient exercises. Cold, dry air generally provokes more obstruction than warm, humid air. Consequently, many athletes have good exercise tolerance in sports such as swimming. Athletes who are more physically fit may not notice the typical symptoms and may only report a reduced or more limited level of endurance.
- Several modifiers in the history should prompt an evaluation for causes other than EIA. While patients may report typical obstructive symptoms, a history of a choking sensation with exercise, inspiratory wheezing, or stridor should prompt an evaluation for evidence of vocal cord dysfunction.

Physical

General

- Evidence of respiratory distress manifests as increased respiratory rate, increased heart rate, diaphoresis, and use of accessory muscles of respiration.
- Marked weight loss or severe wasting may indicate severe emphysema.
- Pulsus paradoxus: This is an exaggerated fall in systolic blood pressure during inspiration and may occur during an acute asthma exacerbation.
- Depressed sensorium: This finding suggests a more severe asthma exacerbation with impending respiratory failure.

Chest examination

- End-expiratory wheezing or a prolonged expiratory phase is found most commonly, although inspiratory wheezing can be heard.
- Diminished breath sounds and chest hyperinflation may be observed during acute exacerbations.

- The presence of inspiratory wheezing or stridor may prompt an evaluation for an upper airway obstruction such as vocal cord dysfunction, vocal cord paralysis, thyroid enlargement, or a soft tissue mass (eg, malignant tumor).

Upper airway

Look for evidence of erythematous or boggy turbinates or the presence of polyps from sinusitis, allergic rhinitis, or upper respiratory infection.

Any type of nasal obstruction may result in worsening of asthma or symptoms of EIA.

Skin: Observe for the presence of atopic dermatitis, eczema, or other manifestations of allergic skin conditions.

Causes

Factors that can contribute to asthma or airway hyperreactivity may include any of the following:

- Environmental allergens (House dust mites, animal allergens [especially cat and dog], cockroach allergens, and fungi are most commonly reported.)
- Viral respiratory infections
- Exercise; hyperventilation
- Gastroesophageal reflux disease (GERD)
- Chronic sinusitis or rhinitis
- Aspirin or nonsteroidal anti-inflammatory drug hypersensitivity, sulfite sensitivity
- Use of beta-adrenergic receptor blockers (including ophthalmic preparations)
- Obesity (Based on a prospective cohort study of 86,000 patients, those with an elevated body mass index are more likely to have asthma.)
- Environmental pollutants, tobacco smoke
- Occupational exposure
- Irritants such as household sprays and paint fumes

- A variety of high and low molecular weight compounds are associated with the development of occupational asthma such as insects, plants, latex, gums, isocyanates, anhydrides, wood dust, and fluxes.
- Emotional factors or stress
- Perinatal factors (Prematurity and increased maternal age increase the risk for asthma; breastfeeding has not been definitely shown to be protective. Both maternal smoking and prenatal exposure to tobacco smoke also increase the risk of developing asthma.)
- Factors that contribute to EIA symptoms include the following:
- Exposure to cold or dry air
- Environmental pollutants (eg, sulfur, ozone)
- Level of bronchial hyperreactivity
- Chronicity of asthma and symptomatic control
- Duration and intensity of exercise
- Allergen exposure in atopic individuals
- Coexisting respiratory infection

Diagnosis

The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them. The key is to take a careful clinical history. In many cases this will allow a reasonably certain diagnosis of asthma, or an alternative diagnosis, to be made. If asthma does appear likely, the history should also explore possible causes, particularly occupational. In view of the potential requirement for treatment over many years, it is important even in relatively clear cut cases, to try to obtain objective support for the diagnosis. Whether or not this should happen before starting treatment depends on the certainty of the initial diagnosis and the severity of presenting symptoms. Repeated assessment and measurement may be necessary before confirmatory evidence is acquired. Confirmation hinges on demonstration of airflow obstruction varying over short periods of time. Spirometry, which is

now becoming more widely available, is preferable to measurement of peak expiratory flow because it allows clearer identification of airflow obstruction, and the results are less dependent on effort. It should be the preferred test where available (although some training is required to obtain reliable recordings and to interpret the results). Of note, a normal spirogram (or PEF) obtained when the patient is not symptomatic does not exclude the diagnosis of asthma. Results from spirometry are also useful where the initial history and examination leave genuine uncertainty about the diagnosis. In such cases, the differential diagnosis and approach to investigation is different in patients with and without airflow obstruction. In patients with a normal or near-normal spirogram when symptomatic, potential differential diagnoses are mainly non-pulmonary; these conditions do not respond to inhaled corticosteroids and bronchodilators. In contrast, in patients with an obstructive spirogram the question is less whether they will need inhaled treatment but rather exactly what form and how intensive this should be. Other tests of airflow obstruction, airway responsiveness and airway inflammation can also provide support for the diagnosis of asthma, but to what extent the results of the tests alter the probability of a diagnosis of asthma has not been clearly established, nor is it clear when these tests are best performed. Diagnostic algorithm is referred in Figure 1.

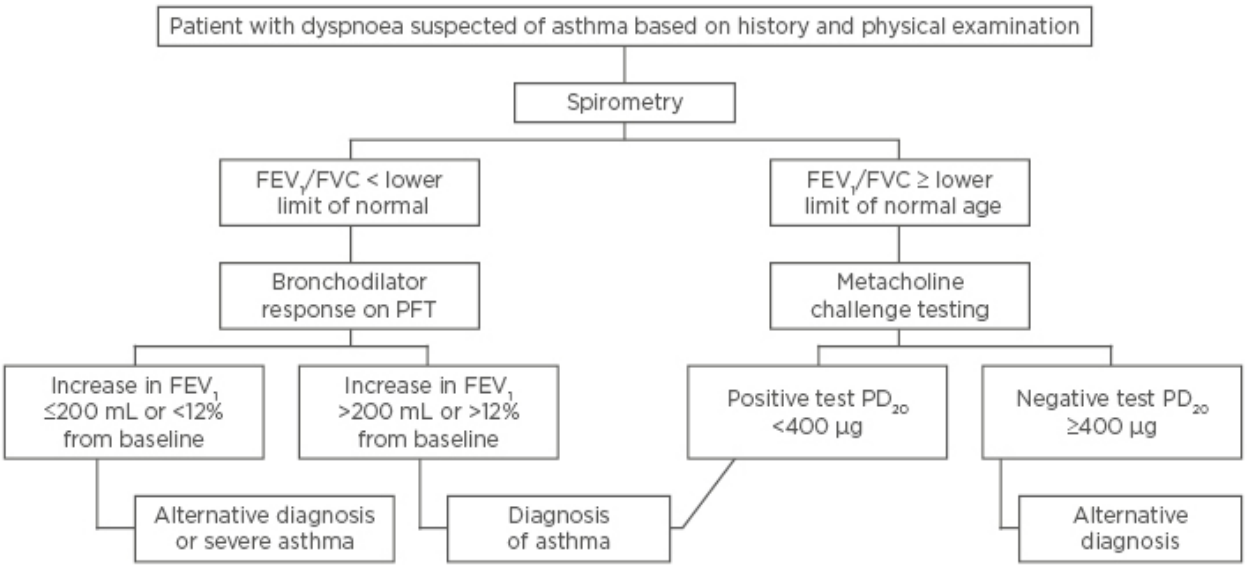


Figure 1: Diagnostic algorithm for identification of bronchial asthma in adults.

Abbreviations: FEV1: forced expiratory volume in 1 second; FVC: functional vital capacity; PC20: provocative concentration causing a 20% decline in FEV1; PD20: provocation dose causing a 20% decline in FEV1; PFT: pulmonary function testing.

Lab Studies

Laboratory studies are not routinely indicated for asthma but may be used to exclude other diagnoses.

- *Blood eosinophilia greater than 4*% or 300-400/μL supports the diagnosis of asthma, but an absence of this finding is not exclusionary. Eosinophil counts greater than 8% may be observed in patients with concomitant atopic dermatitis. This finding should prompt an evaluation for allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, or eosinophilic pneumonia.
- *Test of Eosinophilic Airway Inflammation*. Eosinophilic inflammation in children can be assessed non-invasively using induced sputum differential eosinophil count or exhaled nitric oxide concentrations (FENO). Sputum induction is feasible in school age children. Higher sputum eosinophil counts are associated with more marked airways obstruction and reversibility, greater asthma severity and atopy. In children with newly diagnosed mild asthma, sputum eosinophilia is present and declines with inhaled steroid treatment. Sputum induction is possible in approximately 75% of children tested, but it is technically demanding and time consuming and at present remains a research tool. It is feasible to measure FENO in unsedated children from the age of 3-4 years. A raised FENO is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma. FENO is closely linked with atopic status, age and height. In some studies, FENO correlated better with atopic dermatitis and allergic rhinitis than with asthma. It is not closely linked with underlying lung function. FENO could not differentiate between groups once atopy was taken into account. Home measurements of FENO have a highly variable relationship with other measures of disease activity and vary

widely from day to day. At present, there is insufficient evidence to support a role for markers of eosinophilic inflammation in the diagnosis of asthma in children. They may have a role in assessing severity of disease or response to treatment.

- *Tests of Atopy.* Allergy skin testing is a useful adjunct in individuals with atopy. Results help guide indoor allergen mitigation or help diagnose allergic rhinitis symptoms. The allergens that most commonly cause asthma are aeroallergens such as house dust mites, animal danders, pollens, and mold spores. Two methods are available to test for allergic sensitivity to specific allergens in the environment: allergy skin tests and blood radioallergosorbent tests (RAST). Allergy immunotherapy may be beneficial in controlling allergic rhinitis and asthma symptoms for some patients. Positive skin tests, blood eosinophilia ≥4%, or a raised specific IgE to cat, dog or mite, increase the probability of asthma in a patients with wheeze, particularly in adults and children over five years of age. It is important to recognise that non-atopic wheezing is as frequent as atopic wheezing in school-age children.
- *Total serum immunoglobulin E levels greater* than 100 IU are frequently observed in patients experiencing allergic reactions, but this finding is not specific for asthma and may be observed in patients with other conditions (eg, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome). A normal total serum immunoglobulin E level does not exclude the diagnosis of asthma.
- *In monitoring of asthma control, the British Thoracic Society* recommends using sputum eosinophilia determinations to guide therapy. An improvement in asthma control, a decrease in hospitalizations, and a decrease in exacerbations were noted in those patients in whom sputum-guided therapy was used.
- *Fractional Excretion of Nitric Oxide (NO*) analysis has been shown to predict airway inflammation and asthmatic control. NO is produced by the airway epithelium is an indirect marker of elevated airway inflammation. The level of NO in exhaled breath can easily be measured and has been used for detecting airway inflammation in patients suspected of and with the diagnosis of asthma.

However, fractional excretion of NO (FeNO) is more sensitive to eosinophilic airway inflammation and is not as useful in the diagnosis of non-eosinophilic asthma. The American Thoracic Society (ATS) recommends the use of FeNO measurements <25 ppb in adults to indicate a lower likelihood of eosinophilic inflammation and corticosteroid responsiveness. There have been conflicting data regarding the use of FeNO in monitoring asthma. Studies have shown that an elevated FeNO level correlates closely with severity of asthma and that using FeNO and sputum eosinophil count to monitor asthma can help reduce the total exposure to inhaled corticosteroids (ICS). However, there was no significant reduction in asthma exacerbations or the total amount of ICS use in those monitored using FeNO compared to those not monitored. Despite these findings, the ATS guidelines continue to recommend the use of FeNO measurements in monitoring of disease activity in asthma patients.

Imaging Studies

In most patients, chest radiography findings are normal or indicate hyperinflation. Findings may help rule out other pulmonary diseases such as allergic bronchopulmonary aspergillosis or sarcoidosis, which can manifest with symptoms of reactive airway disease.

Sinus CT scan may be useful to help exclude acute or chronic sinusitis as a contributing factor. In patients with chronic sinus symptoms, a CT scan of the sinuses can also help rule out chronic sinus disease.

Other Tests

In patients with asthma and symptoms of GERD, 24-hour pH monitoring can help determine if GERD is a contributing factor.

Procedures

Pulmonary function testing (spirometry)

Perform spirometry measurements before and after inhalation of a short-acting bronchodilator in all patients in whom the diagnosis of asthma is considered. Spirometry measures the forced vital capacity, the maximal amount of

air expired from the point of maximal inhalation, and the FEV_1. A reduced ratio of FEV1 to forced vital capacity, when compared with predicted values, demonstrates the presence of airway obstruction.

Reversibility is demonstrated by an increase of 12% and 200 mL after administration of a short-acting bronchodilator.

The diagnosis of asthma cannot be based on spirometry findings alone because many other diseases are associated with obstructive spirometry indices.

As a preliminary evaluation for EIA, perform spirometry in all patients with exercise symptoms to determine if any baseline abnormalities (ie, the presence of obstructive or restrictive indices) are present.

Methacholine- or histamine-challenge testing

Bronchoprovocation testing with either methacholine or histamine is useful when spirometry findings are normal or near normal, especially in patients with intermittent or exercise-induced symptoms. Bronchoprovocation testing helps determine if hyperreactive airways are present, and a negative test result usually excludes the diagnosis of asthma.

Trained individuals should perform this testing in an appropriate facility and in accordance with the guidelines of the American Thoracic Society published in 1999. Methacholine is administered in incremental doses up to a maximum dose of 16 mg/mL, and a 20% decrease in FEV_1, up to the 4 mg/mL level, is considered a positive test result for the presence of bronchial hyperresponsiveness. The presence of airflow obstruction with an FEV1 less than 65-70% at baseline is generally an indication to not perform the test. The role of tests of airway responsiveness (airway hyper-reactivity) in the diagnosis of bronchial asthma is unclear. For example, a methacholine challenge test has a much lower sensitivity than symptoms in diagnosing asthma in children and only marginally increases the diagnostic accuracy after the symptom history is taken into account. However, a negative methacholine test in patients, which has a high negative predictive value, makes a diagnosis of asthma improbable. Similarly, a negative response to an

exercise challenge test is helpful in excluding asthma in children with exercise related breathlessness

Exercise testing

Exercise spirometry is the standard method for evaluating patients with EIA. Testing involves 6-10 minutes of strenuous exertion at 85-90% of predicted maximal heart rate and measurement of postexercise spirometry for 15-30 minutes. The defined cutoff for a positive test result is a 15% decrease in FEV_1 after exercise.

Exercise testing may be accomplished in 3 different ways, using cycle ergometry, a standard treadmill test, or free running exercise. This method of testing is limited because laboratory conditions may not subject the patient to the usual conditions that trigger EIA symptoms, and results have a lower sensitivity compared with other methods.

Eucapnic hyperventilation

- Eucapnic hyperventilation with either cold or dry air is an alternate method of bronchoprovocation testing.
- It has been used to evaluate patients for EIA and has been shown to produce results similar to those of methacholine-challenge testing.

Peak-flow monitoring

- Peak-flow monitoring is designed for ongoing monitoring of patients with asthma because the test is simple to perform and the results are a quantitative and reproducible measure of airflow obstruction.
- It can be used for short-term monitoring, exacerbation management, and daily long-term monitoring.
- Results can be used to determine the severity of an exacerbation and to help guide therapeutic decisions.

Guidelines for the use of peak-flow meters are as follows:

Advise the patient to use the peak-flow meter upon awakening in the morning before using a bronchodilator.

Instruct the patient on how to establish a personal best peak expiratory flow (PEF) rate.

Inform the patient that a peak flow of less than 80% of the patient's personal best indicates a need for additional medication and a peak flow below 50% indicates severe exacerbation.

Advise the patient to use the same peak-flow meter over time.

Exhaled NO

The use of exhaled NO as a measurement of airway inflammation has been suggested as a nonspecific marker. Elevated levels of NO have been shown in people with asthma compared with people without asthma, but limited data exist on the applicability of exhaled NO in the diagnosis of asthma.

Monitoring of bronchial asthma

In the majority of patients with asthma symptom-based monitoring is adequate. Patients achieving control of symptoms with treatment have a low risk for exacerbations. Table 1 summarizes the methodology, measurement characteristics and interpretation of some of the validated tools used to assess symptoms and other aspects of asthma. Some measures provide information about future risk (ie sputum eosinophil count, airway responsiveness and FENO) rather than immediate clinical control. Risk reduction, eg minimising future adverse outcomes such as exacerbations and accelerated decline in lung function, is also a goal of asthma management. A management strategy that controls eosinophilic airway inflammation or airway hyperresponsiveness results in better control of exacerbations than one which controls immediate clinical manifestations. The benefits of this more intensive approach are greater in patients with severe asthma, when exacerbations can occur frequently and unpredictably. More research is needed to assess the relative roles of the different measures and to address the feasibility and cost of incorporating them into monitoring protocols before they can be recommended more widely.

Monitoring in primary care

Asthma is best monitored in primary care by routine clinical review on at least an annual basis. The factors that should be monitored and recorded include: symptomatic asthma control: best assessed using directive questions such as the RCP ‘3 questions’, or the Asthma Control Questionnaire or Asthma Control Test, since broad non-specific questions may underestimate symptoms, lung function, assessed by spirometry or by PEF. Reduced lung function compared to previously recorded values may indicate current bronchoconstriction or a long term decline in lung function and should prompt detailed assessment exacerbations, oral corticosteroid use and time off work or school since last assessment inhaler technique, compliance which can be assessed by reviewing prescription refill frequency bronchodilator reliance which can be assessed by reviewing prescription refill frequency possession of and use of self management plan/personal action plan.

Table 1.

Summary of tools that can be used to assess asthma.

Measurement	Methodology	Measurement characteristics	Comments
Spirometry	• Widely available. • Enables clear demonstration of airflow obstruction. • FEV1 largely independent of effort and highly repeatable. • Less applicable in acute severe asthma.	• Normal ranges widely available and robust. • Short term (20 minute) 95% range for repeat measure of FEV1 <160 ml; FVC <330 ml, independent of baseline value.	• Good for short and longer term reversibility testing in subjects with pre-existing airflow obstruction. • >400 ml increase in FEV1 highly suggestive of asthma. • Less helpful in

	• Only assesses one aspect of the disease state.		subjects with normal pre-treatment values because of ceiling effect.
Peak expiratory flow (PEF)	• Widely available and simple. • Applicable in a wide variety of circumstances including acute severe asthma. • PEF variability can be determined from home readings in most subjects. • PEF effort dependent and not as • PEFrepeatable as FEV1. • Only assesses one aspect of the disease state.	• Normal ranges of PEF are wide, and currently available normative tables are outdated and do not encompass ethnic diversity. • Change in PEF more meaningful than absolute value. • >60 l/min increase in PEF suggested as best criteria for defining reversibility. • Normal range of PEF variability defined as amplitude % highest <8% or <20% depending	• Useful for short and longer term reversibility testing in subjects with pre-existing airflow obstruction. • Less helpful in subjects with normal pre-treatment values because of ceiling effect. • Little information on the use of PEF variability as an index of treatment response.

		on number of readings and degree of patient coaching.	
Royal College of Physicians (RCP) 3 Questions	Yes/no or graded response to the following three questions: In the last week (or month) 1. Have you had difficulty sleeping because of your asthma symptoms (including cough)? 2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)? 3. Has your asthma interfered with your usual activities (eg housework, work/ school etc)?	No to all questions consistent with controlled asthma.	• Not well validated. • Simplicity is attractive for use in day to day clinical practice.

Asthma Control Questionnaire	• Response to 7 questions, 5 relating to symptoms, 1 rescue treatment use and 1 FEV1. • Response usually assessed over the preceding week. • Shortened, five question symptom only questionnaire is just as valid.	• Well controlled ≤0.75, inadequately controlled ≥1.5. • 95% range for repeat measure +/- 0.36. • Minimal important difference 0.5.	• Well validated composite scoring system with a strong bias to symptoms. • Could be used to assess response to longer term treatment trials. • Shortened five-point questionnaire is probably best for those with normal or near normal FEV1.
Asthma Control Test (ACT)	Response to 5 questions, 3 related to symptoms, 1 medication use and 1 overall control. 5 point response score	• Well controlled >19. • Within subject intraclass correlation coefficient 0.77. • 95% range for repeat measure and minimally clinically important difference not defined.	• Could be used to assess response to longer term treatment trials, particularly in those with normal or nearnormal spirometric values. • 95% range for repeat measure and minimally clinically

			important difference need to be defined.
Airway responsiveness	• Only available in selected secondary care facilities. • Responsive to change (particularly indirect challenges such as inhaled mannitol). • Less of a ceiling effect. • Not applicable in severe asthma or in acute severe asthma	• Normal methacholine PC20 > 8 mg/ml. • 95% range for repeat measure +/- 1.5-2 doubling doses.	• Has not been widely used to monitor disease and assess treatment responses. • Some evidence that using airway responsiveness as an additional measure for monitoring asthma results in a reduction in asthma exacerbations and improved airway pathology.
Exhaled nitric oxide (FENO)	• Not widely available. • Monitors still expensive, although expect the technology to become cheaper and more	• Normal range <25 ppb at exhaled flow of 50 ml/sec. 95% range for repeat measure 4 ppb. • >50 ppb highly predictive of	Raised FENO (>50 ppb) very predictive of a positive response to corticosteroids. Use of FENO to guide corticosteroid

	widespread. • Measurements can be obtained in almost all adults and children over 5 years. Immediate results are available. • Reasonably close relationship between FENO and eosinophilic airway inflammation, which is independent of gender, age, atopy and inhaled corticosteroid use. Relationship is lost in smokers. • Not closely related to other measures of asthma morbidity.	eosinophilic airway inflammation. • <25 ppb highly predictive of its absence.	treatment has been shown to result in a non-significant 25% reduction in exacerbations with 40% less corticosteroid. Low FENO (<25 ppb) may be of particular value in identifying patients who can step down corticosteroid treatment safely. Protocols for diagnosis and monitoring have not been well defined and experience with the technique is limited.
Sputum eosinophil differential count	• Only available in specialist centres although technology is	Normal range <2%; 95% range for repeat measure +/- 2-3 fold.	• Close relationship between raised sputum eosinophil count and

	widely available and inexpensive. • Information available in 80-90% of patients although immediate results are not available. • Sputum eosinophil count not closely related to other measures of asthma morbidity		corticosteroid responsiveness. • Use of sputum eosinophil count to guide corticosteroid therapy has been consistently shown to result in better outcome for the same exposure to corticosteroids. • Benefits are greater in patients with more severe disease.

TREATMENT

Medical Care

The goals for successful management of asthma outlined in the 2016 US National Heart, Lung, and Blood Institute publication "Global Strategy for Asthma Management and Prevention" and 2020 GINA guideline include the following:

- Achieve and maintain control of symptoms.
- Prevent asthma exacerbations.
- Maintain pulmonary function as close to normal levels as possible.
- Maintain normal activity levels, including exercise.
- Avoid adverse effects from asthma medications.

A stepwise approach to pharmacologic treatment is recommended. The initial choice of medication is determined by the aforementioned asthma severity classification by NAEPP (intermittent, mild, moderate, and severe persistent). A step-up or step-down therapy is recommended depending on symptom control based on GINA guidelines. Currently, it is recommended that all patients with asthma have SABA inhalers for rescue therapy. In those with persistent asthma, addition of low-dose ICS in titrating doses is recommended. For those with moderate-to-severe persistent asthma, long-acting beta-2 agonists (LABA) or leukotriene inhibitors are often added to the ICS regimen. Select use of biologic agents can be considered for those patients with more severe, difficult-to-control forms of asthma

Beta-2 Agonists

Beta-2 agonists are bronchodilators that play an important role in asthma control and treatment of acute exacerbations. They bind to the beta-2 adrenergic receptors on the bronchial smooth muscle cells, causing smooth muscle relaxation and bronchodilation. SABA are often used to treat mild intermittent asthma and acute exacerbations but should not be considered a controller medication; increased use of SABA has been associated with worse asthma control and ICS can sometimes be added to the treatment of those with mild intermittent asthma to limit SABA use. SABA are most effective in treating acute bronchoconstriction and have a rapid onset of action of 1–5 minutes, with peak effects at 2 hours and median duration of action of 3 hours. Examples of SABA include albuterol, levalbuterol, terbutaline, metaproterenol, and pirbuterol.

LABA include salmeterol and formoterol and can have bronchodilatory effects lasting >12 hours. However, LABA should only be prescribed in conjunction with ICS in asthma patients. There was found that there were more respiratory and asthma-related deaths and life-threatening experiences in those treated with LABA than those receiving placebo. The safety and benefits of the LABA/ICS combination, however, have been shown in multiple studies. The use

of a LABA–ICS combination inhaler is safe and a potential step-up therapy for asthma patients.

Corticosteroids

Corticosteroids are integral to the management of acute asthma exacerbations and chronic disease control because a significant portion of asthmatic patients have an inflammatory phenotype. ICS are an important part of persistent asthma management, especially for those patients with an eosinophilic phenotype. The drugs decrease airway hyper- responsiveness and inflammatory response to allergens by downregulating eosinophil and mast cell activation. Studies have shown that the use of ICS (budesonide) improved peak flow measurements in asthma patients compared to those on beta-agonist treatment only. ICS have also been shown to reduce the rates of exacerbations and improve lung function.51,52 In patients with moderate-to-severe persistent asthma, the addition of LABA to ICS has been found to be beneficial. It has been shown that a combination of salmeterol and fluticasone resulted in improvements in PEFR, reduced symptom scores, nocturnal symptoms, and albuterol use compared to fluticasone alone. Examples of currently available ICS include beclomethasone, triamcinolone, flunisolide, ciclesonide, budesonide, fluticasone, and mometasone.

Systemic corticosteroids are especially important in the treatment of uncontrolled asthma and acute asthma exacerbations. Short-term use of systemic corticosteroids can be an effective tool in decreasing systemic inflammation and bronchial constriction. However, long-term use of systemic corticosteroids is discouraged due to their association with numerous long-term side effects, including weight gain, gastritis, osteoporosis, hypertension, adrenal suppression, and psychosis. There is no standard recommended duration or dosage of corticosteroids for acute asthma exacerbation treatment. Patients who are unable to be weaned from systemic corticosteroids to maintain disease control should be assessed for treatment with biologic medications and for comorbid conditions and referred to an asthma specialist

Leukotriene Receptor Antagonists and Synthesis Inhibitor

Leukotrienes are lipid mediators involved in bronchoconstriction and airway inflammation. Leukotriene-modifying drugs, including zafirlukast, montelukast, and zileuton, work by inhibiting leukotriene synthesis or as competitive antagonists of the leukotriene receptors. Cysteinyl leukotrienes are released from mast cells and eosinophils and are involved in bronchial smooth muscle contraction and increased mucus secretion. By working as receptor antagonists and inhibiting leukotriene synthesis, these drugs downregulate airway inflammation; they have also been shown to improve asthma symptoms and lung function and serve as an add-on therapy to ICS. Current guidelines recommend the use of leukotriene receptor antagonists only as an alternative treatment to ICS in those with moderate persistent asthma who cannot tolerate ICS and as an add-on therapy to those receiving combined LABA/ICS.

Antimuscarinics

The use of antimuscarinics for alleviating bronchoconstriction and dyspnoea dates back hundreds of years. The parasympathetic system, controlled by acetylcholine and the activation of muscarinic receptors, contributes to airway smooth muscle constriction and mucous secretion. Antimuscarinics are used to disrupt this vagally mediated muscarinic receptor activation, leading to subsequent bronchodilation. Currently available short-acting muscarinic antagonists (SAMA) include ipratropium and long-acting muscarinic antagonists (LAMA) include tiotropium, aclidinium, umeclidinium, and glycopyrronium.

Both SAMA and LAMA can be used to treat severe, poorly controlled asthma exacerbations and as an add-on maintenance therapy to LABA/ICS therapy. The results of numerous studies showed that the addition of tiotropium had greater improvements in PEFR, asthma control days, FEV1, and daily symptoms compared to the doubling of ICS or addition of salmeterol. In addition, there was shown that those who received additional tiotropium had an improved FEV1 and time to first severe exacerbation, and a 21% reduction in exacerbation risk. LAMA remain a potential treatment for those with poorly controlled asthma.

Biologic Therapy

For those with severe asthma, the use of biologic agents should be considered carefully. Targeted use of biologic therapy allows these patients to achieve control while limiting their oral corticosteroid exposure. Omalizumab is the first approved biologic for asthma and works by binding to IgE and downregulating activation of airway inflammation. In clinical trials, omalizumab has been shown to reduce overall asthma exacerbation rates by 25% and severe exacerbations by 50%, as well as improving asthma quality of life in those with uncontrolled moderate-to-severe asthma with perennial aeroallergen sensitivity.

Newer biologic agents targeting IL-5 pathways are also available. IL-5 is a major cytokine responsible for the growth, differentiation, and survival of eosinophils, which play a large role in airway inflammation. Mepolizumab is a humanised monoclonal antibody against IL-5, hence it blocks the IL-5 pathway. Mepolizumab trials have shown a >50% reduction in overall exacerbation rate, >60% reduction in hospitalisation or emergency room visitation rates, improvements in quality of life scores, and a 50% reduction of oral corticosteroid dose for those who are on chronic oral corticosteroids.

Reslizumab is another monoclonal antibody against IL-5 that is approved for use in those with poorly controlled asthma and with IgE levels ≥400 cells/uL. Clinical trials have shown an improved exacerbation rate by >50%, increased asthma quality of life, and improved lung function by 90–160 mL over placebo, especially in those with higher levels of peripheral eosinophils.

Benralizumab is also a monoclonal antibody against IL-5 receptor that causes the body's own natural killer cells to target and eliminate eosinophils. It has been shown to reduce exacerbations by >50%, reduce the dose of chronic oral corticosteroids use by 75%, and improve lung function by 24%.

Other biologics include dupilumab, a monoclonal antibody against IL-4 receptor that blocks IL-4 and IL-13. From Phase III trial data, dupilumab has been shown to reduce exacerbations, improve lung function, and reduce chronic oral corticosteroid use. It is particularly more effective in patients with peripheral eosinophil levels >300 cells/μL and FeNO levels ≥25 ppb.

Tezepelumab is a monoclonal antibody that blocks the action of the cell signalling protein thymic stromal lymphopoietin and downregulates the inflammatory pathway responsible for asthma. This drug is currently undergoing Phase III studies but has shown a significant decrease in asthma exacerbation rates in a Phase II study. As more biologics become available, phenotyping and endotyping of each patient are necessary to provide insights into the most appropriate long-term therapy.

Bronchial Thermoplasty

Bronchial thermoplasty (BT) offers a non-pharmacologic therapy for those with asthma unresponsive to standard treatment with ICS and bronchodilators. BT uses thermal energy to bronchoscopically ablate airway smooth muscles to decrease bronchoconstriction and airway hyperplasia. The effectiveness of this treatment was initially seen in the AIR trial in 2007, which randomised patients with moderate or severe asthma to BT or a control group. Those who received BT had significant improvements in morning PEFR, percentage of symptom-free days, and symptom score reduction. These studies were followed by the AIR2 trial, which again demonstrated significant improvements in asthma symptoms and exacerbations in those randomised to BT. BT may therefore be an effective non-pharmacologic treatment for asthma in those with severe disease resistant to pharmacotherapy; however, there are significant adverse reactions associated with BT, including life-threatening severe exacerbations and death

2020 update of GINA guideline and 2016 National Asthma Education and Prevention Program

In 2020 update of GINA guideline was included the term control of bronchial asthma, because the aim of asthma management is control of the disease. Control of asthma is defined as:

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no exacerbations

- no limitations on activity including exercise
- normal lung function (in practical terms FEV1 and/or PEF>80% predicted or best) with minimal side effects.

In clinical practice patients may have different goals and may wish to balance the aims of asthma management against the potential side effects or inconvenience of taking medication necessary to achieve perfect control.

Prevent the development of irreversible airflow limitation.

Prevent asthma mortality.

The long-term outpatient management of asthma should follow the stepwise therapy model based on the 2020 Global Initiative for Asthma guidelines. These recommendations were updated during the 2016 National Asthma Education and Prevention Program, the results of which were published by the National Institutes of Health.

Management should incorporate 4 treatment components:

(1) objective measures of lung function,

(2) environmental control measures and avoidance of risk factors,

(3) comprehensive pharmacologic therapy, and

(4) patient education.

Two additional management strategies include management of exacerbations and regular follow-up care. Classify the severity of asthma before treatment, based on symptom prevalence and measurement of lung function. Classification of severity and treatment options are shown below.

Step 1 - Intermittent

- Intermittent symptoms occurring less than once a week
- Brief exacerbations
- Nocturnal symptoms occurring less than twice a month
- Asymptomatic with normal lung function between exacerbations
- No daily medication needed

- FEV1 or PEF rate greater than 80%, with less than 20% variability

Step 2 - Mild persistent

- Symptoms occurring more than once a week but less than once a day
- Exacerbations affect activity and sleep
- Nocturnal symptoms occurring more than twice a month
- Inhaled:
    - steroid (low dose),
    - cromolyn (adult: 2-4 puffs tid/qid; child: 1-2 puffs tid/qid),
    - or nedocromil (adult: 2-4 puffs bid/qid; child: 1-2 puffs bid/qid) (Children usually begin with a trial of cromolyn or nedocromil.)
- FEV1 or PEF rate greater than 80% predicted, with variability of 20-30%

Step 3 - Moderate persistent

- Daily symptoms
- Exacerbations affect activity and sleep
- Nocturnal symptoms occurring more than once a week
- Anti-inflammatory, inhaled steroid (medium dose), or inhaled steroid (low-to-medium dose) and long-acting bronchodilator, especially for nighttime symptoms (either long-acting inhaled beta2-agonist [adult: 2 puffs q12h, child: 1-2 puffs q12h], sustained-release theophylline, or long-acting beta2-agonist tablets) (If needed, give inhaled steroids in a medium-to-high dose.)
- FEV1 or PEF rate 60-80% of predicted, with variability greater than 30%

Step 4 - Severe persistent

- Continuous symptoms
- Frequent exacerbations
- Frequent nocturnal asthma symptoms
- Physical activities limited by asthma symptoms
- Anti-inflammatory or inhaled steroid (high dose) and long-acting bronchodilator (either long-acting inhaled beta2-agonist [adult: 2 puffs

q12h, child: 1-2 puffs q12h] and sustained-release theophylline or long-acting beta2-agonist tablets and steroid tablets or syrup long term) (Make repeated attempts to reduce systemic steroid and maintain control with high-dose inhaled steroid.)

- FEV1 or PEF rate less than 60%, with variability greater than 30%

Accordingly new update of GINA (2020) bronchial asthma has been graduated to two ranges: controlled and uncontrolled stages. Respectively mentioned opinion some medications should be use in up-titrated doses until achieve the control stage of asthma. That why step-by-step therapy of bronchial asthma pivots the important role to be try to achieve the control stage.

The pharmacologic treatment of asthma is based on stepwise therapy. Medications should be added or deleted as the frequency and severity of the patient's symptoms change

Step 1. Mild intermittent asthma

1. A controller medication is not needed.
2. The reliever medication is a short-acting beta-agonist as needed for symptoms.
    - The following medicines act as short-acting bronchodilators:
    - inhaled short-acting β2 agonists
    - inhaled ipratropium bromide
    - β2 agonist tablets or syrup
    - theophyllines.
    - Short-acting inhaled work more quickly and/or with fewer side effects than the alternatives. Prescribe an inhaled short-acting β_2-agonist as short term reliever therapy for all patients with symptomatic asthma.

Frequency of dosing of inhaled short-acting β_2- agonists

Using short-acting β_2-agonists as required is at least as good as regular (four times daily) administration. Unless individual patients are shown to benefit from

regular use of inhaled short-acting β_2-agonists then as required use is recommended. Good asthma control is associated with little or no need for short-acting β_2-agonists. Using two or more canisters of β_2-agonists per month or >10-12 puffs per day is a marker of poorly controlled asthma that puts patients at risk of fatal or near-fatal asthma. Patients with a high usage of inhaled short-acting β_2-agonists should have their asthma management reviewed.

Step 2. introduction of regular preventer therapy

- The controller medication is an inhaled corticosteroid (200-500 mcg), cromolyn, nedocromil, or a leukotriene antagonist. If needed, increase the dose of corticosteroid and add a long-acting beta-agonist or sustained-release theophylline, especially for nocturnal symptoms.
- The reliever medication is a short-acting beta-agonist as needed for symptoms.

For steps 2, 3, and 4, treatments have been judged on their ability to improve symptoms, improve lung function, and prevent exacerbations, with an acceptable safety profile. Improvement of quality of life, while important, is the subject of too few studies to be used to make recommendations at present.

Comparison of inhaled steroids

Many studies comparing different inhaled steroids are of inadequate design and have been omitted from further assessment. In view of the clear differences between normal volunteers and asthma patients in the absorption of inhaled steroids, data from normal volunteers have not been taken into account. Only studies in which more than one dose of at least one of the inhaled steroids or both safety and efficacy had been studied together in the same trial were evaluated. Non-blinded studies also had to be considered because of the problems of obtaining competitors' delivery devices. A series of Cochrane reviews comparing different inhaled steroids using a different methodology have come to the same conclusion. BDP and budesonide are approximately equivalent in clinical practice, although there may be variations with different delivery devices. There is limited evidence from two open studies of less than ideal design that budesonide via the

turbohaler is more clinically effective. However, at present a 1:1 ratio should be assumed when changing between BDP and budesonide. Fluticasone provides equal clinical activity to BDP and budesonide at half the dosage. The evidence that it causes fewer side effects at doses with equal clinical effect is limited. Mometasone appears to provide equal clinical activity to BDP and budesonide at half the dosage. The relative safety of mometasone is not fully established.

Ciclesonide is a new inhaled steroid. Evidence from clinical trials suggests that it has less systemic activity and fewer local oropharyngeal side effects than conventional inhaled steroids. The clinical benefit of this is not clear as the exact efficacy to safety ratio compared to other inhaled steroids has not been fully established. Non-CFC beclometasone is available in more than one preparation, and the potency relative to CFC beclometasone is not consistent between these.

Inhaled steroids

Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years with asthma. Many non-atopic children with recurrent episodes of viral-induced wheezing in children under five years do not go on to have chronic atopic asthma. The majority do not require treatment with regular inhaled steroids. Inhaled steroids should be considered for adults, children aged 5-12 and children under the age of five with any of the following features: using inhaled β2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, inhaled steroids should be considered in adults and children aged 5-12 who have had an exacerbation of asthma requiring oral corticosteroids in the last two years.

Starting dose of inhaled steroids

In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit Start patients at a dose of inhaled steroids appropriate to the severity of disease. In adults, a reasonable starting dose will usually be 400 mcg BDP per day and in children 200 mcg BDP per day. In

children under five years, higher doses may be required if there are problems in obtaining consistent drug delivery. Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

Frequency of dosing of inhaled steroids

Most current inhaled steroids are slightly more effective when taken twice rather than once daily, but may be used once daily in some patients with milder disease. There is little evidence of benefit for dosage frequency more than twice daily.

Safety of inhaled steroids

The safety of inhaled steroids is of crucial importance and a balance between benefits and risks for each individual needs to be assessed. Account should be taken of other topical steroid therapy when assessing systemic risk. It has been suggested that steroid warning cards should be issued to patients on higher dose inhaled steroids, but the benefits and possible disadvantages, particularly with regard to compliance, of such a policy remain to be defined.

Adults

There is little evidence that doses below 800 mcg BDP per day cause any short term detrimental effects apart from the local side effects of dysphonia and oral candidiasis. However, the possibility of long term effects on bone has been raised. One systematic review reported no effect on bone density at doses up to 1,000 mcg BDP per day. The significance of small biochemical changes in adrenocortical function is unknown.

Other preventer therapies

Inhaled steroids are the first choice preventer drug. Long-acting inhaled β_2-agonists should not be used without inhaled corticosteroids. Alternative, less effective preventer therapies in patients taking short-acting β_2-agonists alone are:

- Chromones
- Sodium cromoglicate is of some benefit in adults and is effective in children aged 5-12 years.
- Nedocromil sodium is also of benefit in adults and children >5 years

- There is no clear evidence of benefit with sodium cromoglicate in children aged
- <5 years
- Leukotriene receptor antagonists have some beneficial clinical effect
- Theophyllines have some beneficial effect
- Antihistamines and ketotifen are ineffective

Step 3. Initial add-on therapy

- The controller medication is an inhaled corticosteroid (800-2000 mcg) and a long-acting bronchodilator (either beta-agonist or sustained-release theophylline) A combination medication of salmeterol/fluticasone (Advair) is a preferred choice to improve compliance. Other agents may include leukotriene modifying agents or omalizumab.
- The reliever medication is a short-acting beta-agonist as needed for symptoms.

A proportion of patients with asthma may not be adequately controlled at step 2. Before initiating a new drug therapy practitioners should recheck compliance, inhaler technique and eliminate trigger factors. The duration of a trial of add-on therapy will depend on the desired outcome. For instance, preventing nocturnal awakening may require a relatively short trial of treatment (days or weeks), whereas preventing exacerbations of asthma or decreasing steroid tablet use may require a longer trial of therapy (weeks or months). If there is no response to treatment the drug should be discontinued.

Criteria for introduction of add-on therapy

No exact dose of inhaled steroid can be deemed the correct dose at which to add another therapy. The addition of other treatment options to inhaled steroids has been investigated at doses from 200-1,000 mcg BDP in adults and up to 400 mcg BDP in children. Many patients will benefit more from add-on therapy than from increasing inhaled steroids above doses as low as 200 mcg BDP/day. At doses of inhaled steroid above 800 mcg BDP/day side effects become more frequent. An

absolute threshold for introduction of add-on therapy in all patients cannot be defined.

Add-on therapy

Options for add-on therapy are summarized in Figure 2.

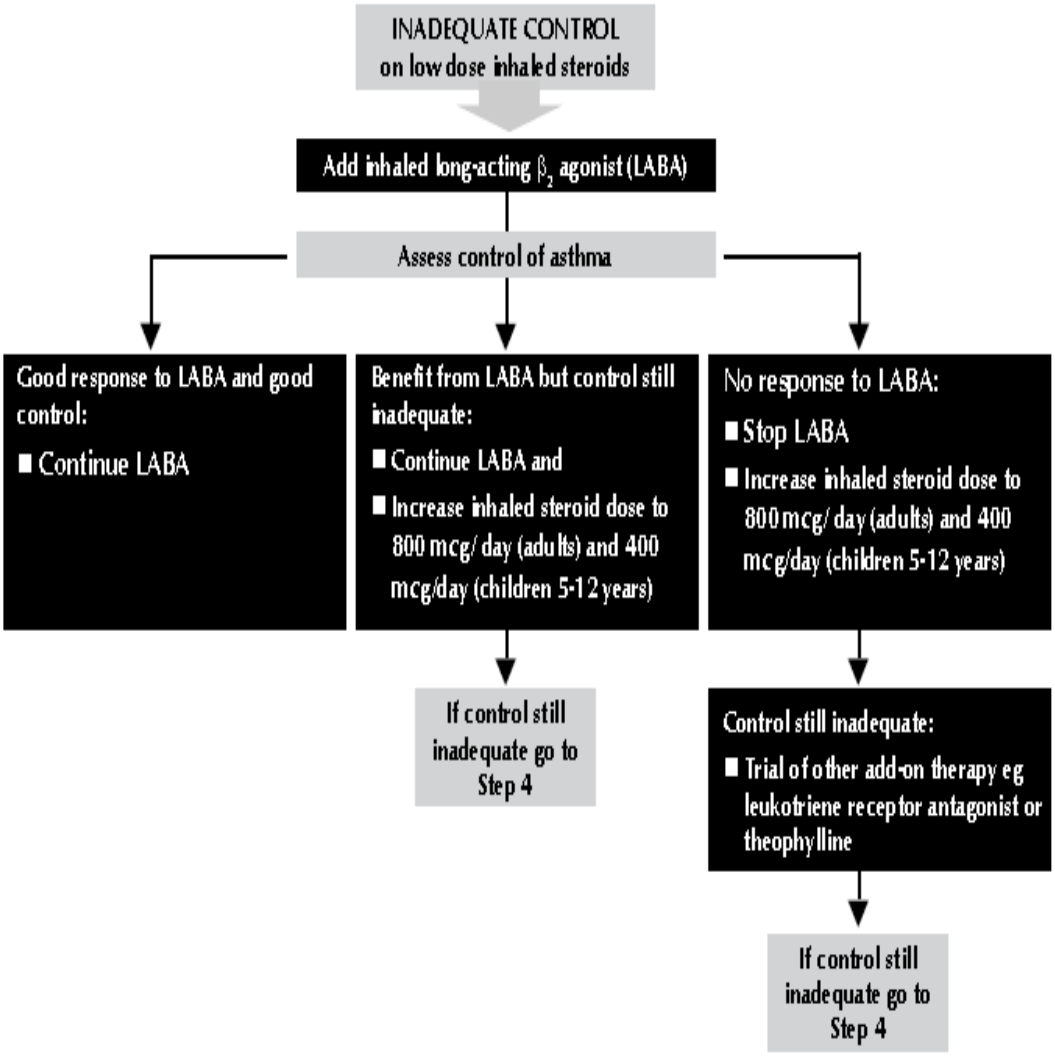


Figure 2: Summary of step 3: Add-on therapy

In adult patients taking inhaled steroids at doses of 200-800 mcg BDP/day and in children taking inhaled steroids at a dose of 400 mcg/day the following interventions are of value: first choice would be the addition of an inhaled long-acting β_2 agonist (LABA), which improves lung function and symptoms, and decreases exacerbations. The first choice as add-on therapy to inhaled steroids in adults and children *(5-12 years*) is an inhaled long-acting β_2 agonist, which should be considered before going above a dose of 400 mcg BDP or equivalent per day and certainly before going above 800 mcg BDP. The first choice as add-on

therapy to inhaled steroids in children under five years old is leukotriene receptor antagonists. If, as occasionally happens, there is no response to inhaled long-acting β_2 agonist, stop the LABA and increase the dose of inhaled steroid to 800 mcg BDP/day *(adults)* or 400 mcg BDP/day *(children)* if not already on this dose. If there is a response to LABA, but control remains suboptimal, continue with the LABA and increase the dose of inhaled steroid to 800 mcg/day (adults) or 400 mcg/day (children 5-12 years). f asthma control remains suboptimal after the addition of an inhaled longacting β_2 agonist then the dose of inhaled steroids should be increased to 800 mcg/day in adults or 400 mcg/day in children *(5-12 years)*, if not already on these doses. Leukotriene receptor antagonists may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms. Theophyllines may improve lung function and symptoms, but side effects occur more commonly. Slow-release β_2 agonist tablets may also improve lung function and symptoms, but side effects occur more commonly. If control remains inadequate after stopping a LABA and increasing the dose of inhaled steroid, consider sequential trials of add-on therapy, ie leukotriene receptor antagonists, theophyllines, slow-release β_2 agonist tablets *(this in adults only).* Addition of short-acting anticholinergics is generally of no value. Addition of nedocromil is of marginal benefit.

In selected adult patients at step 3 who are poorly controlled or in selected adult patients at step 2 (above BDP 400 mcg/day who are poorly controlled), the use of budesonide/formoterol in a single inhaler as rescue medication instead of a short-acting β_2 agonist, in addition to its regular use as controller therapy has been shown to be an effective treatment regimen. When this management option is introduced the total regular dose of daily inhaled corticosteroids should not be decreased. The regular maintenance dose of inhaled steroids may be budesonide 200 mcg twice daily or budesonide 400 mcg twice daily. Patients taking rescue budesonide/formoterol once a day or more should have their treatment reviewed. Careful education of patients about the specific issues around this management strategy is required.

In patients on inhaled steroids whose asthma is stable, no intervention has been consistently shown to decrease inhaled steroid requirement in a clinically significant manner compared to placebo. The Medicines and Healthcare products Regulatory Agency (MHRA) has completed a full review of the balance of risks and benefits associated with long-acting β_2 agonists in the management of asthma and chronic obstructive pulmonary disease. They have concluded that long-acting β_2 agonists can continue to be used in the management of asthma provided they are used with inhaled corticosteroids. This issue has been reviewed by the guideline development group, which came to the same conclusion.

Step. 4. Poor control on moderate dose of inhaled steroid + add-on Therapy: addition of fourth drug

In a small proportion of patients asthma is not adequately controlled on a combination of shortacting β_2 agonist as required, inhaled steroid (800 mcg BDP daily), and an additional drug, usually a long-acting β_2 agonist. There are very few clinical trials in this specific patient group to guide management. The following recommendations are largely based on extrapolation from trials of add-on therapy to inhaled steroids alone.

Step 5. Continuous or frequent use of oral steroids

For the small number of patients not controlled at step 4, use daily steroid tablets in the lowest dose providing adequate control.

Prevention and Treatment of Steroid tablet-induced Side effects

Patients on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) will be at risk of systemic side effects.

- blood pressure should be monitored
- urine or blood sugar and cholesterol should be checked. Diabetes mellitus *and*
- hyperlipidaemia may occur
- bone mineral density should be monitored. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered.

- growth (height and weight) should be monitored in children
- cataracts may be screened for in children through community optometric services

Steroid tablet-sparing medication

The aim of treatment is to control the asthma using the lowest possible dose or, if possible, to stop long term steroid tablets completely. Inhaled steroids are the most effective drug for decreasing requirement for long term steroid tablets. There is limited evidence for the ability of long-acting β2 agonists, theophyllines, or leukotriene receptor antagonists to decrease requirement for steroid tablets, but they may improve symptoms and pulmonary function. In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2,000 mcg/day, if required. In children aged 5-12, consider very carefully before going above an inhaled steroid dose of 800 mcg/day. Immunosuppressants (methotrexate, ciclosporin and oral gold) decrease long term steroid tablet requirements, but all have significant side effects. There is no evidence of persisting beneficial effect after stopping them; and there is marked variability in response.

Immunosuppressants (methotrexate, ciclosporin and oral gold) may be given as a three month trial, once other drug treatments have proved unsuccessful. Their risks and benefits should be discussed with the patient and their treatment effects carefully monitored. Treatment should be in a centre with experience of using these medicines. Colchicine and intravenous immunoglobulin have not been shown to have any beneficial effect in adults. Continuous subcutaneous terbutaline infusion has been reported to be beneficial in severe asthma but efficacy and safety have not been assessed in RCTs. Anti-TNF alpha therapy has been investigated in severe asthma but these studies are too small and too short term to allow recommendation of anti-TNF therapy outside the context of a controlled clinical trial.

Anti-IgE monoclonal antibody

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE, markedly reducing levels of free serum IgE. In adults and children over 12, it is licensed in the UK with the following indication; patients on high-dose inhaled steroids and long-acting β2 agonists who have impaired lung function are symptomatic with frequent exacerbations, and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every two to four weeks depending on dose. The total IgE must be less than 700 iu/litre for it to be effective. In the single study in the licensed group, there was a 19% reduction in exacerbations of asthma requiring oral steroids which was non-significant. When corrected for imbalance in the exacerbation history at baseline, there was a 26% reduction in severe exacerbations. This was associated with a 2.8% increase in FEV_1, a non-significant 0.5 puffs/day decrease in β2 agonist use and 13% more patients having a significant improvement in health related quality of life. At IgE levels below 76 iu/l the beneficial effect is reduced. Local skin reactions may occur. Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as the first dose, but has also occurred after one year. Due to risk of anaphylaxis, omalizumab should only be administered to patients in a healthcare setting under direct medical supervision. Omalizumab treatment should only be initiated in specialist centre's with experience of evaluation and management of patients with severe and difficult asthma.

Steroid formulations

Prednisolone is the most widely used steroid tablet for maintenance therapy in chronic asthma. There is no evidence that other formulations offer any advantage.

Frequency of dosing of steroid tablets

Although popular in paediatric practice, there are no studies to show whether alternate day steroids produce fewer side effects than daily steroids. Contemporary management of bronchial asthma is defined in Figure 3.

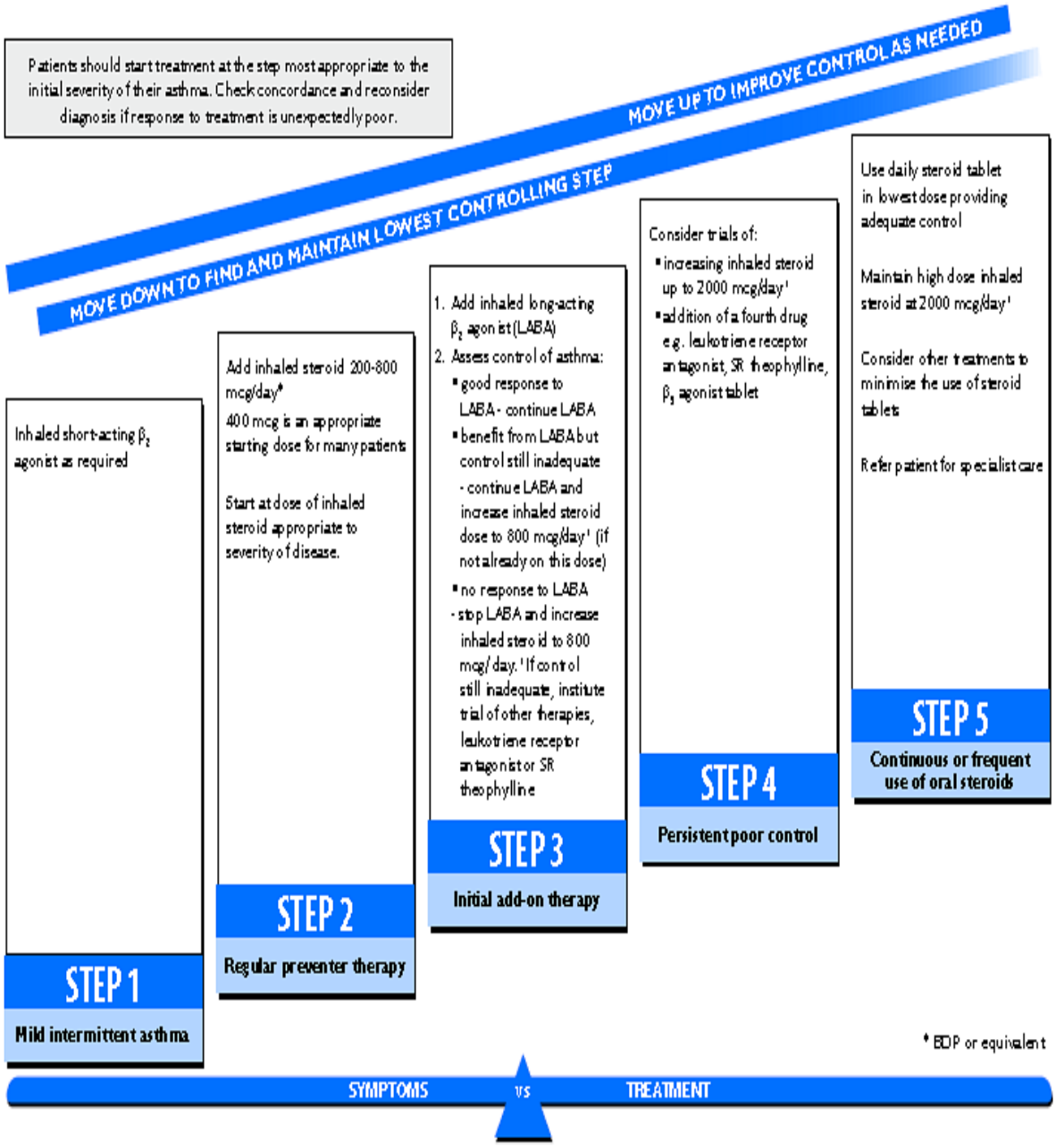


Figure 3: Contemporary management of bronchial asthma

Stepping down

Stepping down therapy once asthma is controlled is recommended, but often not implemented leaving some patients over-treated. There are few studies that have investigated the most appropriate way to step down treatment. A study in adults on at least 900 mcg per day of inhaled steroids has shown that for patients who are stable it is reasonable to attempt to halve the dose of inhaled steroids every

three months. Some children with milder asthma and a clear seasonal pattern to their symptoms may have a more rapid dose reduction during their ‘good’ season.

Regular review of patients as treatment is stepped down is important. When deciding which drug to step down first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient’s preference should all be taken into account. Patients should be maintained at the lowest possible dose of inhaled steroid. Reduction in inhaled steroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25-50% each time.

Consultations

Refer any patient with difficult-to-control asthma to a pulmonologist or allergist to ensure proper stepwise management of asthma, or refer for further evaluation to help rule out other diagnoses such as vocal cord dysfunction.

Refer patients to a pulmonologist for evaluation of symptoms consistent with EIA. These patients should undergo either exercise or bronchoprovocation testing to document evidence of airway hyperreactivity and response to exercise.

Refer patients to an otolaryngologist for treatment of nasal obstruction from polyps, sinusitis, or allergic rhinitis or for the diagnosis of upper airway disorders.

Refer patients to an allergist or immunologist for skin testing to guide indoor allergen mitigation efforts and consideration of immunotherapy to treat seasonal allergic rhinitis. The use of immunotherapy for the treatment of asthma is controversial. Several large, well-conducted studies did not demonstrate any benefit, but a meta-analysis of 54 randomized controlled trials confirmed efficacy in asthma. The National Asthma Education and Prevention Program Expert Panel Report recommend that immunotherapy be considered if the following criteria are fulfilled:

- A relationship is clear between symptoms and exposure to an unavoidable allergen to which the patient is sensitive.
- Symptoms occur all year or during a major portion of the year.

- Symptoms are difficult to control with pharmacologic management because the medication is ineffective, multiple medications are required, or the patient is not accepting of medication.

Diet

New information from prospective cohort studies and population-based studies in the past several years suggests an association between asthma and obesity. Patients with an elevated BMI have an increased risk for developing asthma. A prospective cohort study of 86,000 adults observed for 5 years showed a linear relationship between BMI and the risk of developing asthma.

No special diets are generally indicated. Food allergy as a trigger for asthma is uncommon. Avoidance of foods is recommended after a double-blind food challenge that yields positive results. Sulfites have been implicated in some severe asthma exacerbations and should be avoided in sensitive individuals.

Activity

Activity is generally limited by patients' ability to exercise and their response to medications. No specific limitations are recommended for patients with asthma, although they should avoid exposure to agents that may exacerbate their disease.

A significant number of patients with asthma also have EIA, and baseline control of their disease should be adequate to prevent exertional symptoms. The ability of patients with EIA to exercise is based on the level of exertion, degree of fitness, and environment in which they exercise.

Many patients have fewer problems when exercising indoors or in a warm, humid environment compared with outdoors or in a cold, dry environment.

PECIFIC MANAGEMENT ISSUES

Exacerbations of asthma

Although recommended for both adults and children in previous guidelines and as part of asthma action plans, doubling the dose at the time of an exacerbation is of unproven value. In adult patients on a low dose (200 mcg BDP) of inhaled

steroids, a five-fold increase in dose at the time of exacerbation leads to a decrease in the severity of exacerbations. This study should not be extrapolated to patients already taking higher doses of inhaled steroids and further evidence in this area is required.

There is some limited evidence that leukotriene antagonists may be used intermittently in children with episodic asthma. Treatment is started at the onset of either asthma symptoms or of coryzal symptoms and continued for seven days. The benefits of parent-initiated oral steroids at the start of an exacerbation has not been proven.

Exercise induced asthma

When given chronically the following medicines give protection against exercise induced asthma:

- inhaled steroids
- short-acting β_2-agonists
- long-acting β_2-agonists
- theophyllines
- leukotriene receptor antagonists
- chromones
- β_2 -agonist tablets.

The following medicines do not give protection against exercise induced asthma at normal doses:

- anticholinergics
- ketotifen
- antihistamine.

Long-acting β_2-agonists and leukotriene antagonists provide more prolonged protection than short-acting β_2-agonists, but a degree of tolerance develops with LABA particularly with respect to duration of action. No tolerance has been demonstrated with leukotriene receptor antagonists. For most patients, exercise induced asthma is an expression of poorly controlled asthma and regular treatment

including inhaled steroids should be reviewed. Patients with asthma often have rhinitis. The most effective therapy is intranasal steroids. Treatment of allergic rhinitis with intranasal steroids has not been shown in double blind placebo-controlled trials to improve asthma control.

Allergic Bronchopulmonary Aspergillosis

In adult patients with allergic bronchopulmonary aspergillosis (ABPA), itraconazole may decrease steroid tablet dose and improve asthma control. Careful monitoring for side effects, particularly hepatic, is recommended.

Aspirin-intolerant Asthma

There are theoretical reasons to suggest that leukotriene receptor antagonists might be of particular value in the treatment of aspirin-intolerant asthma. However, there is little evidence to justify managing patients with aspirin-intolerant asthma in a different manner to other patients with asthma, apart from the rigorous avoidance of non-steroidal anti-inflammatory medications.

Gastro-oesophogeal reflux

A Cochrane review of twelve double blind controlled trials found that treatment of gastrooesophageal reflux had no benefit on asthma symptoms or lung function when both conditions were present. Reduction in dry cough was observed although this was probably not due to improved asthma control.

β-blockers

β-blockers, including eye drops, are contraindicated in patients with asthma.

Inhaler devices

Although studies of inhaler devices are more suitable for an evidence based approach than many other aspects of asthma management, a number of methodological issues complicate evidence review in this area. In young (0-5 years) children, little or no evidence is available on which to base recommendations.

Technique and training

Studies of technique and the effects of training have used arbitrary non-standardised scores making comparison difficult. Although technique will have some bearing, it does not necessarily relate to clinical effectiveness. The proportion of patients making no mistakes with an inhaler in one well conducted study was 23-43% for pMDI, 53-59% for dry powder inhaler (DPI) and 55-57% for pMDI + spacer. When technique was assessed as number of steps correct out of the total number of steps, pMDI + spacer was slightly better than DPI. Teaching technique improved the correct usage score from a mean of 60% to 79%. Figures for no mistakes post-teaching were 63% for pMDI, 65% for DPI, and 75% for breath-actuated MDI. Thus, prescribe inhalers only after patients have received training in the use of the device and have demonstrated satisfactory technique**.**

β_2 agonist delivery

Acute asthma

Take into consideration, pMDI + spacer is at least as good as a nebuliser at treating mild and moderate exacerbations of asthma in children and adults. Children and adults with mild and moderate exacerbations of asthma should be treated by pMDI + spacer with doses titrated according to clinical response. There are no data to make recommendations in severe (life threatening) asthma.

Stable asthma

For children aged 0-5, there is no evidence comparing nebuliser and other inhalers and the data are insufficiently extensive or robust to draw conclusions for pMDI vs. DPI. In children aged 5-12 there is no significant difference between pMDI and DPI. In adults there is no significant difference between pMDI + spacer and DPI. The lower pulse rate with pMDI versus Turbohaler is the only difference with regard to side effects. Patients have been shown to prefer Turbohaler to pMDI. Choice of reliever inhaler for stable asthma should be based on patient preference and assessment of correct use. Many patients will not be prepared to carry a spacer.

Inhaled steroids for stable asthma

There are no comparative data on inhaled steroids for stable asthma in children under five years. A single study included 4-5 year olds, but the data were not extractable. For the delivery of inhaled steroids in stable asthma in children aged 5-12 years, pMDI is as effective as Clickhaler, and Pulvinal is as effective as Diskhaler. No significant clinical difference was found between pMDI and Turbohaler at half the dose for the same drug (budesonide). This comparison cannot necessarily be made against other inhaled steroid/device combinations. In adults, there is no clinical difference in effectiveness of pMDI ± spacer v DPI. Breath-actuated MDI is as effective as pMDI. More recent DPIs are as effective as older DPIs. Nebulisers have not been shown to be superior to pMDI + spacer for delivery of inhaled steroids in chronic asthma. A specialised specific nebuliser may provide improved lung function and reduced rescue therapy use, but at high prescribed doses. Higher doses (>2 mg) are generally only licensed for use from a nebulizer. No recommendation can be given for nebulised therapy in children aged 5-12 years and there is no evidence relating to children aged <5 years.

CFC propellant pMDI vs HFA propellant pMDI

HFA pMDI salbutamol is as effective as CFC pMDI salbutamol at standard therapeutic doses. It is important to differentiate Qvar from other HFA beclametasone products. It has been showed Qvar equivalence at half the dose of CFC BDP pMDI, whereas non-Qvar HFA BDP pMDI studies show equivalence at 1:1 dosing. HFA fluticasone is as effective as CFC fluticasone across the standard clinical dose range.

Prescribing devices

There is no evidence to dictate an order in which devices should be tested for those patients who cannot use pMDI. In the absence of evidence, the most important points to consider are patient preference and local cost. The choice of device may be determined by the choice of drug.

- If the patient is unable to use a device satisfactorily an alternative should be found.

- The patient should have their ability to use an inhaler device assessed by a competent healthcare professional.
- The medication needs to be titrated against clinical response to ensure optimum efficacy.
- Reassess inhaler technique as part of structured clinical review

Use and care of spacers

- The spacer should be compatible with the pMDI being used.
- The drug should be administered by repeated single actuations of the metered dose inhaler into the spacer, each followed by inhalation.
- There should be minimal delay between pMDI actuation and inhalation.
- Tidal breathing is as effective as single breaths.
- Spacers should be cleaned monthly rather than weekly as per manufacturer's recommendations or performance is adversely affected. They should be washed in detergent and allowed to dry in air. The mouthpiece should be wiped clean of detergent before use.
- Drug delivery may vary significantly due to static charge. Metal and other antistatic spacers are not affected in this way.
- Plastic spacers should be replaced at least every 12 months but some may need changing at six months.

Management of acute asthma

Lessons from studies of asthma deaths and near-fatal asthma

Confidential enquires into over 200 asthma deaths in the EU conclude there are factors associated with the disease, the medical management and the patient's behaviour or psychosocial status which contribute to death. Most deaths occurred before admission to hospital.

Disease factors

Most patients who died of asthma had chronically severe asthma. In a minority the fatal attack occurred suddenly in a patient with mild or moderately severe background disease.

Medical management

Many of the deaths occurred in patients who had received inadequate treatment with inhaled steroid or steroid tablets and/or inadequate objective monitoring of their asthma. Follow up was inadequate in some and others should have been referred earlier for specialist advice. Asthma deaths are associated with fewer general practice contacts and more home visits.

There was widespread under-use of written management plans. Heavy or increasing use of β_2 agonist therapy was associated with asthma death. Deaths continue to be reported following inappropriate prescription of β-blockers and NSAIDs; all asthma patients should be asked about past reactions to these agents. Patients with acute asthma should not be sedated unless this is to allow anaesthetic or intensive care procedures (Table 2).

Table 2: Patients at risk of developing near-fatal or fatal asthma

A COMBINATION OF SEVERE ASTHMA recognised by one or more of:

- previous near-fatal asthma, eg previous ventilation or respiratory acidosis
- previous admission for asthma especially if in the last year
- requiring three or more classes of asthma medication
- heavy use of β2 agonist
- repeated attendances at ED for asthma care especially if in the last year
- "brittle" asthma.

AND ADVERSE BEHAVIOURAL OR PSYCHOSOCIAL FEATURES recognised by one or more of:

- non-compliance with treatment or monitoring
- failure to attend appointments
- fewer GP contacts
- frequent home visits
- self discharge from hospital
- psychosis, depression, other psychiatric illness or deliberate self harm

- current or recent major tranquilliser use
- denial
- alcohol or drug abuse
- obesity
- learning difficulties
- employment problems
- income problems
- social isolation
- childhood abuse
- severe domestic, marital or legal stress.

Adverse psychosocial and behavioural factors

Behavioural and adverse psychosocial factors were recorded in the majority of patients who died of asthma.

Seasonal factors

In the EU, especially in UK, there is a peak of asthma deaths in people aged up to 44 years in July and August and in December and January in older people.

Prediction and Prevention of a Severe Asthma Attack

Most attacks of asthma severe enough to require hospital admission develop relatively slowly over a period of six hours or more. In one study, over 80% developed over more than 48 hours. There is, therefore, time for effective action to reduce the number of attacks requiring hospitalization. There are many similarities between patients who die from asthma, patients with near-fatal asthma and control patients with asthma who are admitted to hospital.

ACUTE ASTHMA IN ADULTS

Annexes 2-4 contain algorithms summarising the recommended treatment for patients presenting with acute or uncontrolled asthma in primary care, ED and hospital.

Recognition of Acute Asthma

Definitions of increasing levels of severity of acute asthma exacerbations are provided in table 3. Predicted PEF values406 should be used only if the recent best PEF (within two years) is unknown. Patients with asthma, and all patients with severe asthma, should have an agreed written action plan and their own peak flow meter, with regular checks of inhaler technique and compliance. They should know when and how to increase their medication and when to seek medical assistance. Asthma action plans can decrease hospitalisation for and deaths from asthma.

Table 3: Levels of severity of acute asthma exacerbations

<table>
<tr><td>Near-fatal asthma</td><td colspan="2">Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures</td></tr>
<tr><td rowspan="8">Life threatening asthma</td><td colspan="2">Any one of the following in a patient with severe asthma</td></tr>
<tr><td>Clinical signs</td><td>Measurements</td></tr>
<tr><td>Altered conscious level</td><td>PEF <33% best or predicted</td></tr>
<tr><td>Exhaustion</td><td>SpO_2 <92%</td></tr>
<tr><td>Arrhythmia</td><td>PaO_2 <8 kPa</td></tr>
<tr><td>Hypotension</td><td>“normal” $PaCO_2$ (4.6–6.0 kPa)</td></tr>
<tr><td>Cyanosis</td><td rowspan="3"></td></tr>
<tr><td>Silent chest</td></tr>
<tr><td>Poor respiratory effort</td></tr>
<tr><td>Acute severe asthma</td><td colspan="2">Any one of:
- PEF 33-50% best or predicted
- respiratory rate ≥25/min
- heart rate ≥110/min
- inability to complete sentences in one breath</td></tr>
<tr><td>Moderate asthma exacerbation</td><td colspan="2">- Increasing symptoms
- PEF >50-75% best or predicted
- no features of acute severe asthma</td></tr>
<tr><td>Brittle asthma</td><td colspan="2">Type 1: wide PEF variability (>40% diurnal variation for >50% of the time over a period >150 days) despite</td></tr>
</table>

	intense therapy
	Type 2: sudden severe attacks on a background of apparently well controlled asthma

The assessment of acute asthma exacerbations

The initial assessment of acute asthma exacerbations should focus on several key areas. Perform a functional assessment of airway obstruction with a measurement of the FEV1 or PEF initially to assess the patient's response to treatment. Assess the adequacy of arterial oxygen saturation in patients with severe distress. Obtain a brief history to include symptoms, onset of exacerbation, medications, prior emergency department visits, and hospitalizations (including endotracheal intubations). Perform a physical examination to assess the severity of the exacerbation, the overall patient status, the presence of other diseases or complications, and to rule out upper airway obstruction.

Laboratory studies should be considered based on the status of the patient. These and other studies may include arterial blood gas measurement, complete blood cell count, serum theophylline level (if indicated), chest radiograph to assess for complications, and electrocardiograms in patients older than 50 years.

Once the initial assessment is completed, begin treatment based on the severity of the asthma exacerbation. Supplemental oxygen should be used in most patients to maintain oxygen saturations greater than 90%.

Inhaled short-acting beta-agonists are the initial treatment.

Repetitive or continuous administration by nebulizer.

In the emergency department, 3 treatments every 20-30 minutes as initial therapy.

High-dose (6-12 puffs) beta-agonist by MDI or nebulizer therapy (Nebulizer is most effective with more severe exacerbations.)

Consider inhaled ipratropium bromide in patients with severe exacerbations.

Administer systemic corticosteroids early in the course of disease in patients with an incomplete response to beta-agonists. Oral administration is equivalent in

efficacy to intravenous administration. Corticosteroids speed the resolution of airway obstruction and prevent a late-phase response.

Methylxanthines (theophylline) can be considered in patients with severe exacerbations, but their use is controversial.

Antibiotics should be reserved for patients with fever and purulent sputum or other evidence of pneumonia or sinusitis.

Aggressive hydration is not recommended for adults.

Chest physiotherapy, mucolytics, and sedation are not recommended.

Indications for hospitalization are based on findings from the repeat assessment of a patient after the patient receives 3 doses of an inhaled bronchodilator. Determine the decision to admit on

(1) the duration and severity of symptoms,

(2) the severity of airflow obstruction,

(3) the course and severity of prior exacerbations,

(4) medication use and access to medications,

(5) the adequacy of support and home conditions, and

(6) the presence of psychiatric illness.

In certain situations, admit the patient to the ICU for close observation and monitoring.

Rapidly worsening asthma or a lack of response to the initial therapy in the emergency department is an indication for ICU admission.

If patients have confusion, drowsiness, signs of impeding respiratory arrest, or loss of consciousness, they should be admitted to the ICU.

Impending respiratory arrest, as indicated by hypoxemia (PO_2 <60 mm Hg) despite supplemental oxygen and/or hypercarbia with PCO_2 greater than 45 mm Hg, should prompt ICU admission.

If intubation is required because of the continued deterioration of the patient's condition despite optimal treatment, admit the patient to the ICU.

Management of acute severe asthma in adults in general practice is reffered in Figure 4, 5, 6.

Figure 4: Management of acute severe asthma in adults in general practice

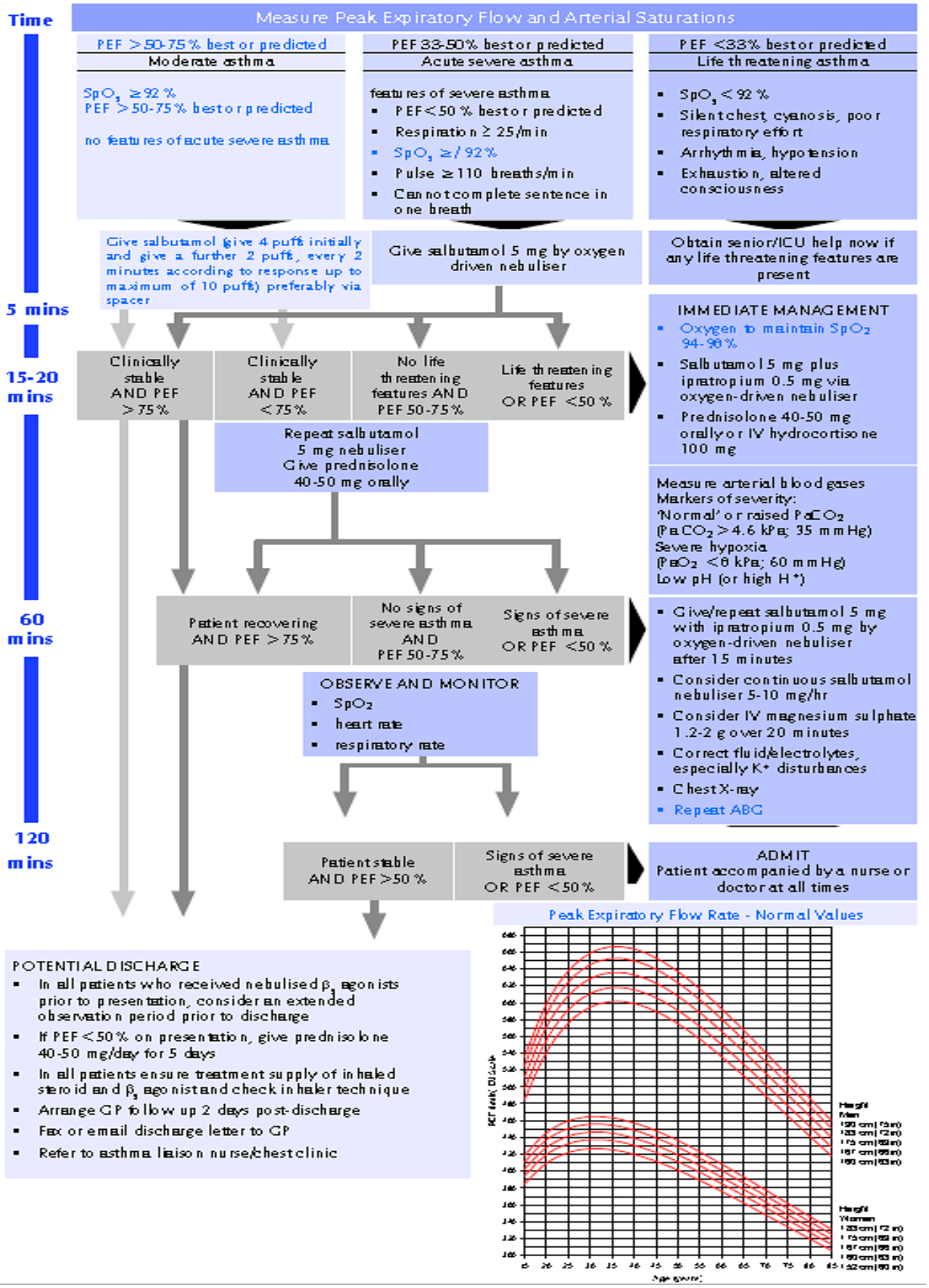


Figure 5: Management of severe acute asthma in adults in Emergency Department

Features of acute severe asthma

- Peak expiratory flow (PEF) 33-50% of best (use % predicted if recent best unknown)
- Can't complete sentences in one breath
- Respirations ≥25 breaths/min
- Pulse ≥110 beats/min

Life threatening features

- PEF <33% of best or predicted
- SpO_2 <92%
- Silent chest, cyanosis, or feeble respiratory effort
- Arrhythmia or hypotension
- Exhaustion, altered consciousness

If a patient has any life threatening feature, measure arterial blood gases. No other investigations are needed for immediate management.

Blood gas markers of a life threatening attack:

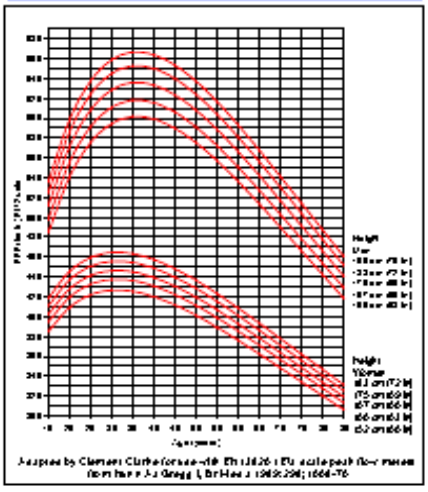
- 'Normal' (4.6-6 kPa, 35-45 mm Hg) $PaCO_2$
- Severe hypoxia: PaO_2 <8 kPa (60 mm Hg) irrespective of treatment with oxygen
- A low pH (or high H^+)

Caution: Patients with severe or life threatening attacks may not be distressed and may not have all these abnormalities. The presence of any should alert the doctor.

Near fatal asthma

- Raised $PaCO_2$
- Requiring mechanical ventilation with raised inflation pressures

Peak Expiratory Flow Rate - Normal Values



IMMEDIATE TREATMENT

- Oxygen to maintain SpO_2 94-98%
- Salbutamol 5 mg or terbutaline 10 mg via an oxygen-driven nebuliser
- Ipratropium bromide 0.5 mg via an oxygen-driven nebuliser
- Prednisolone tablets 40-50 mg or IV hydrocortisone 100 mg
- No sedatives of any kind
- Chest X ray if pneumothorax or consolidation are suspected or patient requires mechanical ventilation

IF LIFE THREATENING FEATURES ARE PRESENT:

- Discuss with senior clinician and ICU team
- Consider IV magnesium sulphate 1.2-2 g infusion over 20 minutes (unless already given)
- Give nebulised β_2 agonist more frequently e.g. salbutamol 5 mg up to every 15-30 minutes or 10 mg per hour via continuous nebulisation (requires special nebuliser)

SUBSEQUENT MANAGEMENT

IF PATIENT IS IMPROVING continue:

- Oxygen to maintain SpO_2 94-98%
- Prednisolone 40-50mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulised β_2 agonist and ipratropium 4-6 hourly

IF PATIENT NOT IMPROVING AFTER 15-30 MINUTES:

- Continue oxygen and steroids
- Use continuous nebulisation of salbutamol at 5-10 mg/hour if an appropriate nebuliser is available. Otherwise give nebulised salbutamol 5 mg every 15-30 minutes
- Continue ipratropium 0.5 mg 4-6 hourly until patient is improving

IF PATIENT IS STILL NOT IMPROVING:

- Discuss patient with senior clinician and ICU team
- Consider IV magnesium sulphate 1.2-2 g over 20 minutes (unless already given)
- Senior clinician may consider use of IV β_2 agonist or IV aminophylline or progression to mechanical ventilation

MONITORING

- Repeat measurement of PEF 15-30 minutes after starting treatment
- Oximetry: maintain SpO_2 >94-98%
- Repeat blood gas measurements within 1 hour of starting treatment if:
  - initial PaO_2 <8 kPa (60 mm Hg) unless subsequent SpO_2 >92%
  - $PaCO_2$ normal or raised
  - patient deteriorates
- Chart PEF before and after giving β_2 agonists and at least 4 times daily throughout hospital stay

Transfer to ICU accompanied by a doctor prepared to intubate if:

- Deteriorating PEF, worsening or persisting hypoxia, or hypercapnea
- Exhaustion, altered consciousness
- Poor respiratory effort or respiratory arrest

DISCHARGE

When discharged from hospital, patients should have:

- Been on discharge medication for 12-24 hours and have had inhaler technique checked and recorded
- PEF >75% of best or predicted and PEF diurnal variability <25% unless discharge is agreed with respiratory physician
- Treatment with oral and inhaled steroids in addition to bronchodilators
- Own PEF meter and written asthma action plan
- GP follow up arranged within 2 working days
- Follow up appointment in respiratory clinic within 4 weeks

Patients with severe asthma (indicated by need for admission) and adverse behavioural or psychosocial features are at risk of further severe or fatal attacks

- Determine reason(s) for exacerbation and admission
- Send details of admission, discharge and potential best PEF to GP

Figure 6: Management of acute severe asthma in adults in hospital

Further Outpatient Care

- For all patients with asthma, monitoring should be performed on a continual basis based on the following parameters, which helps in the overall management of the disease:
- Monitoring signs and symptoms of asthma: Patients should be taught to recognize inadequate asthma control, and providers should assess control at each visit.
- Monitoring pulmonary function: Regularly perform spirometry and peak-flow monitoring.
- Monitoring quality of life and functional status: Inquire about missed work or school days, reduction in activities, sleep disturbances, or change in caregiver activities.
- Monitoring history of asthma exacerbations: Determine if patients are monitoring themselves to detect exacerbations and if these exacerbations are self-treated or treated by health care providers.
- Monitoring pharmacotherapy: Ensure compliance with medications and usage of short-acting beta-agonists.
- Monitoring patient-provider communication and patient satisfaction

Complications

The most common complications of asthma include pneumonia, pneumothorax or pneumomediastinum, and respiratory failure requiring intubation in severe exacerbations.

- Risk factors for death from asthma include the following:
- Past history of sudden severe exacerbations, history of prior intubation, or ICU admission

Two or more hospitalizations or 3 or more emergency department visits in the past year; hospitalization or emergency department visit in the past month

- Use of more than 2 short-acting beta-agonist canisters per month
- Current use of systemic corticosteroids or recent taper

- Comorbidity from cardiovascular disease
- Psychosocial, psychiatric, or illicit drug use problems
- Low socioeconomic status or urban residence
- Complications associated with most medications used for asthma are relatively rare. However, in those patients requiring long-term corticosteroid use, complications may include osteoporosis, immunosuppression, cataracts, myopathy, weight gain, addisonian crisis, thinning of skin, easy bruising, avascular necrosis, diabetes, and psychiatric disorders.

Prognosis

Approximately half the children diagnosed with asthma in childhood outgrow their disease by late adolescence or early adulthood and require no further treatment.

Patients with poorly controlled asthma develop long-term changes over time, ie, with airway remodeling. This can lead to chronic symptoms and a significant irreversible component to their disease.

Many patients who develop asthma at an older age also tend to have chronic symptoms.

Patient Education

The "Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma" emphasizes the need for patient education about asthma and the establishment of a partnership between patient and clinician in the management of the disease. The key points of education include the following:

Integrate patient education into every aspect of asthma care.

All members of the health care team, including nurses, pharmacists, and respiratory therapists, provide education.

Clinicians teach patients asthma self-management based on basic asthma facts, self-monitoring techniques, the role of medications, inhaler use, and environmental control measures.

- Develop treatment goals for the patient and family.

- Develop a written, individualized, daily self-management plan.
- Encourage adherence by the patient.

Medical/Legal Pitfalls

The most important factor in the diagnosis of asthma is to recognize exacerbating factors or other diagnoses that may affect the treatment of the disease.

Sinusitis: Of patients with asthma, 50% have concurrent sinus disease. Sinusitis is the most important exacerbating factor for asthma symptoms. Either acute infectious sinus disease or chronic inflammation may contribute to worsening airway symptoms. Treatment of nasal and sinus inflammation reduces airway reactivity. Treatment of acute sinusitis requires at least 10 days of antibiotics to improve asthma symptoms.

Gastroesophageal reflux disease: Patients with asthma are 3 times more likely to also have GERD. Aggressive antireflux therapy may improve asthma symptoms and pulmonary function in selected patients. Treatment with proton pump inhibitors, antacids, or H2 blockers may improve asthma symptoms or unexplained chronic cough. The treatment of asthma with agents such as theophylline may lower esophageal sphincter tone and induce GERD symptoms.

An important observation is that some people with asthma have significant GE reflux without esophageal symptoms. GE reflux was found to be a definite asthma-causing factor (defined by a favorable asthma response to medical antireflux therapy) in 64% of patients; clinically silent reflux was present in 24% of all patients.

Respiratory infections: Viral respiratory infections have not been shown to cause asthma but can aggravate chronic asthma symptoms or induce symptoms in patients with allergic rhinitis. Rhinoviruses are the principal triggers of wheezing and worsening of asthma in older children and adults, but all viral respiratory infections are associated with increased asthma symptoms.

Aspirin-induced asthma: The triad of asthma, aspirin sensitivity, and nasal polyps affects 5-10% of patients with asthma. Most patients experience symptoms during the third to fourth decade. A single dose can provoke an acute asthma

exacerbation, accompanied by rhinorrhea, conjunctival irritation, and flushing of the head and neck. It can also occur with other nonsteroidal anti-inflammatory drugs and is caused by an increase in eosinophils and cysteinyl leukotrienes after exposure. Primary treatment is avoidance of these medications, but leukotriene antagonists have shown promise in treatment, allowing these patients to take daily aspirin for cardiac or rheumatic disease.

Vocal cord dysfunction: Paradoxical inspiratory closure of the vocal cords may mimic asthma. Patients with symptoms of inspiratory wheezing or those whose asthma is refractory to standard therapy should be evaluated for evidence of vocal cord dysfunction. Usually, the diagnosis can be made by direct laryngoscopy, but only during symptomatic periods or after exercise. The presence of flattening of the inspiratory limb of the flow-volume loops may also suggest vocal cord dysfunction but is only seen in 28% of patients at baseline. Patients with chronic symptoms suggestive of asthma, normal spirometry, poor response to asthma medications, and frequent evaluations should be evaluated for vocal cord dysfunction.

Occupational asthma: Occupational factors are associated with 10% of adult asthma cases. More than 300 specific occupational agents have been associated with asthma. High-risk jobs include farming, painting, janitorial work, and plastics manufacturing. Two types of occupational asthma are recognized. Immune-mediated asthma has a latency of months to years after exposure. Non–immune-mediated asthma or irritant-induced asthma (reactive airway dysfunction syndrome) has no latency period and may occur within 24 hours of an accidental exposure to high concentrations of respiratory irritants. Pay careful attention to the patient's occupational history. Those with a history of asthma who report worsening of symptoms during the week and improvement during the weekends should be evaluated for occupational exposure. Peak-flow monitoring during work for 2 weeks and a similar period away from work is one recommended method to establish the diagnosis.

The Asthma-COPD Overlap Syndrome

Asthma and COPD have traditionally been viewed as distinct clinical entities. Recently, however, much attention has been focused on patients with overlapping features of both asthma and COPD: those with asthma COPD overlap syndrome (ACOS). Although no universal definition criteria exist, recent publications attempted to define patients with ACOS based on differences in clinical features, radiographic findings, and diagnostic tests. Indeed, some individuals share characteristics of asthma and COPD.

Definition: The ACOS has been defined as symptoms of increased variability of airflow in association with an incompletely reversible airflow obstruction.

Prevalence: Around 15-20% of COPD patients may have an ACOS.

Clinical features: Patients with ACOS make up a large percentage of those with obstructive lung disease and have a higher overall health-care burden. Patients with the ACOS have a lower quality of life and suffer from more complications than those affected by either disease alone. Patients with ACOS are characterized by increased reversibility of airflow obstruction, eosinophilic bronchial and systemic inflammation, and increased response to inhaled corticosteroids, compared with the remaining patients with COPD. Patients with ACOS have more frequent exacerbations, more wheezing and dyspnoea, but similar cough and sputum production compared with COPD.

Diagnosis of ACOS is difficult because of the clinical similarities between the two diseases and the various phenotypes that comprise the syndrome. The relevance of the ACOS is to identify patients with COPD who may have underlying eosinophilic inflammation that responds to inhaled corticosteroids. So far, the previous diagnosis of asthma in a patient with COPD is the more reliable criterion for ACOS.

Treatment: Defining treatment strategies for ACOS has been challenging because many clinical trials for asthma therapy have purposefully excluded

patients with features of COPD, and COPD clinical trials have not included patients who might have an asthmatic component to their disease.

Identifying patients with ACOS has significant therapeutic implications particularly with the need for early use of inhaled corticosteroids and the avoidance of use of long-acting bronchodilators alone in such patients. However, unlike asthma and COPD, no evidence-based guidelines for the management of ACOS currently exist. Smoking cessation and appropriate vaccinations are cornerstone therapies, and pharmacologic therapy has focused on bronchodilators and inhaled corticosteroids.

The role of biologics, such as omalizumab and IL-5 antagonists, in ACOS treatment is still being defined. As of now, with the paucity of randomized control trials guiding treatment strategies, the Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease guidelines recommend treating ACOS according to the dominant phenotype.

Special Concerns

Nocturnal asthma

A large percentage of patients with asthma experience nocturnal symptoms once or twice a month. Some patients only experience symptoms at night and have normal pulmonary function in the daytime. This is due, in part, to the exaggerated response to the normal circadian variation in airflow.

Bronchoconstriction is highest between the hours of $4^{:00}$ am and $6^{:00}$ pm (the highest morbidity and mortality from asthma is observed during this time). These patients may have a more significant decrease in cortisol levels or increased vagal tone at night. Studies also show an increase in inflammation compared with controls and with patients with daytime asthma.

Nocturnal asthma is a significant clinical problem that should be addressed aggressively. Peak flow meters should be used to allow objective evaluation of symptoms and interventions. Sleep apnea, symptomatic GE reflux, and sinusitis should be controlled when present.

Medications should be appropriately timed and consideration should be given to the use of a long-acting inhaled or oral beta2-agonist, a leukotriene modifier, and inhaled corticosteroids. A once-daily sustained release theophylline preparation and changing the timing of oral corticosteroids to the mid afternoon can be also be used.

Pregnancy

Asthma complicates 4–8% of pregnancies. Mild and well-controlled moderate asthma can be associated with excellent maternal and perinatal pregnancy outcomes. Severe and poorly controlled asthma may be associated with increased prematurity and other perinatal complications to include maternal morbidity and mortality. Optimal management of asthma during pregnancy includes objective monitoring of lung function, avoiding or controlling asthma triggers, patient education, and individualized pharmacologic therapy. Inhaled corticosteroids are the preferred medication for all levels of persistent asthma during pregnancy. Pregnant women with asthma are safer to be treated with asthma medications than to have asthma symptoms and exacerbations. The ultimate goal of asthma therapy is maintaining adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother.

With the exception of alpha-adrenergic compounds other than pseudoephedrine and some antihistamines, most drugs used to treat asthma and allergic rhinitis have not been shown to increase any risk to the mother or fetus. The National Institute of Health stated that albuterol, cromolyn, beclomethasone, budesonide, prednisone, and theophylline, when clinically indicated, are considered appropriate for the treatment of asthma in pregnancy.

Poorly controlled asthma can result in low birth weight, increased prematurity, and increased perinatal mortality. The ACOG Guidelines for Management of Asthma During Pregnancy may be a helpful resource.

Surgery

Complications associated with surgery include acute bronchoconstriction resulting from intubation, impaired cough, hypoxemia, hypercapnia, atelectasis, respiratory infection, and exposure to latex.

The likelihood of these complications occurring depends on the severity of the underlying asthma, the type of surgery (thoracic and upper abdominal), and the type of anesthesia.

If evidence of airflow obstruction (<80% of baseline values) is present, a brief course of corticosteroids is recommended. Patients who have received oral corticosteroids for an asthma exacerbation in the past 6 months should receive systemic corticosteroids in the perioperative period.

Part 2. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) remains a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2025 in burden of disease caused worldwide, according to a study published by the World Bank/World Health Organization. Furthermore, although COPD has received increasing attention from the medical community in recent years, it is still relatively unknown or ignored by the public as well as public health and government officials.

The definition of COPD

COPD has had many names in the past including; Chronic Obstructive Airways Disease, (COAD); Chronic Obstructive Lung Disease, (COLD); Chronic Airflow Limitation, (CAL or CAFL) and Chronic Airflow Obstruction. COPD actually comprises two related diseases, chronic bronchitis and emphysema, one rarely occurring without a degree of the other.

The definition of COPD, that is recognised by both the American Thoracic Society and the European Respiratory Society, is a disorder that is characterised by reduced maximal expiratory flow and slow forced emptying of the lungs; features that do not change markedly over several months. COPD is a slowly progressive lung disease involving the airways and/or pulmonary parenchyma, resulting in a gradual loss of lung function.

While the American Thoracic Society (ATS), British Thoracic Society (BTS), and European Respiratory Society (ERS) definitions of COPD emphasize chronic bronchitis and emphysema, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposes a definition of COPD that focuses on the progressive nature of airflow limitation and its association with abnormal inflammatory response of the lungs to various noxious particles or gases. According to the GOLD document, COPD is defined as "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.

PREVALENCE AND EPIDEMIOLOGY

The prevalence of COPD is increasing. In 1994, there were approximately 16.2 million men and women suffering from COPD in the United States and more than 52 million individuals around the world. The worldwide prevalence is likely to be underestimated for several reasons, including the delay in establishing the diagnosis, the variability in defining COPD, and the lack of age-adjusted estimates. Age adjustment is important because the prevalence of COPD in individuals under 45 years old is low, while the prevalence is highest in patients over 65 years old. Because of its chronic and progressive nature, COPD represents a massive and growing burden, both in direct and indirect costs. In developing countries where smoking continues to be extremely prevalent, the health and economic burdens are higher than in developed nations. Because human capital constitutes an essential role in the economy of developing countries, the disability caused by COPD further magnifies the problem. Although it has been difficult to estimate the costs associated with COPD, they include direct costs pertaining to outpatient and inpatient care expenses as well as the indirect costs resulting from the loss of productivity caused by premature death and disability, and the additional cost of disability. In the United States, for instance, hospitalization constitutes the bulk of all COPD-related health costs. In the United States, COPD affects more than 5% of the adult population and is the 4th leading cause of death and the 12th leading cause of morbidity. Mortality from COPD in the UK is higher than from other lung disease.

PATHOGENESIS, PATHOLOGY, AND PATHOPHYSIOLOGY

As indicated in the definition of emphysema, the pathologic hallmark is elastin breakdown with resultant loss of alveolar wall integrity. This process is triggered by the exposure of a susceptible individual to noxious particles and gases. Cigarette smoke remains the main causative agent, involved in over 90% of cases; however, other gases and particles have been shown to play a role in

pathogenesis, which is due to an inflammatory process. In contrast to the eosinophilic inflammation seen in asthma, the predominant inflammatory cell is the neutrophil. Macrophages and CD8+ T lymphocytes are increased in the various parts of the lungs, and several mediators, including leukotriene B4, interleukin 8, and tumor necrosis factor, contribute to the inflammatory process.

Oxidative stress is regarded as another important process in the pathogenesis of COPD, and altered protease/antiprotease balance, at least in individuals with severe deficiency of alpha1-antitrypsin, has been shown to predispose to a panacinar form of emphysema. Individuals with severe deficiency of alpha1-antitrypsin may develop emphysema at an early age (fourth decade), in contrast to the "usual" emphysema, which typically begins in the sixth decade.

This limitation in airflow is only minimally reversible with bronchodilators. Emphysema has a pathological definition, which is a condition where there is permanent destructive enlargement of the airspaces distal to the terminal bronchioles without obvious fibrosis. Chronic bronchitis is defined clinically by the presence of chronic bronchial secretions, enough to cause expectoration, occurring on most days for a minimum of 3 months of the year for 2 consecutive years. The pathological basis of chronic bronchitis is mucus hypersecretion secondary to hypertrophy of the glandular elements of the bronchial mucosa. Patients with COPD have features of both conditions, although one may be more prominent than the other.

The pathologic hallmark of chronic bronchitis is an increase in goblet cell size and number that leads to the excessive mucus secretion. Airflow obstruction and emphysematous change is a frequent but not universal accompaniment. Finally, when COPD is complicated by hypoxemia, intimal and vascular smooth muscle thickening may cause pulmonary hypertension, which is a late and poor prognostic development in COPD.

The causes of COPD and who is at risk?

Smoking and Bronchial Hyperreactivity

Chronic Bronchitis only really became recognised as a distinct disease rather than a set of symptoms in the late 1950's. The great British Smogs of the 1950's precipitated the deaths of many patients from respiratory failure, and on the continent, chronic bronchitis was referred to as the English Disease. There can be little doubt now that the most important risk factor in the development of COPD is cigarette smoking. The effects of cigarette smoke on the lung are manifold. Cigarette smoke has been found to attract inflammatory cells into the lungs and stimulates the release of of the proteolytic enzyme elastase from these cells. Elastase breaks down elastin, a normal structural component of lung tissue, but normally, the lung is protected from the destructive effect of elastase by an inhibitor, alpha-1 antitrypsin (AAT). However, cigarette smoke attracts more cells and stimulates the release of more elastase than can be inhibited by the circulating levels of AAT. In addition, cigarette smoke itself may inactivate AAT therefore swinging the balance in favour of more lung destruction by elastase. The development of COPD , and in particular emphysema, is thought to be due to the imbalance between the destructive elastase and protective AAT.

Not all people who smoke, however, develop COPD; and not all patients with COPD are smokers or have smoked in the past. There seems to be a varying susceptibility to lung damage due to cigarette smoke within the general population. Only a proportion of smokers (maybe only 10-15%) show a rate of decline of lung function over the years that is fast enough to result in the severe impairment that is typical of patients who present with breathlessness due to COPD. Susceptible subjects have an accelerated rate of decline of lung function (50-90ml of FEV1/yr compared with 20-30ml of FEV1/yr after the age of 30 in non-smokers). Subjects with COPD who stop smoking slow down the progression of disease and may return to normal levels of FEV1 decline. Unfortunately, they do not improve after they stop smoking (fig 3). By the time subjects are symptomatic with breathlessness, they will have already have severe impairment of lung function, and stopping smoking at this stage may extend their life expectancy but may not improve their symptoms.

One possibility to account for these differences is that there is a genetically determined predisposition to develop allergy and bronchial hyperresponsiveness, the "Dutch Hypothesis". According to this, asthma, emphysema and chronic bronchitis are different manifestations of a single disease process. Whether an individual develops asthma, bronchitis or emphysema is a result of genetic and environmental factors that are modulated by age and gender. An alternative school of thought is the "Two-type Hypothesis", which includes a Dutch-type limb termed "Chronic Asthmatic Bronchitis" or "Overlap Syndrome", and a more insidious form which leads to "Chronic Obstructive Bronchitis and Emphysema". Both schools of thought, however, emphasise the inter-relationship between bronchial hyperreactivity (atopy), infection and smoking. Focus has recently been placed in trying to identify the population most at risk of developing COPD.

Alpha-1 Antitrypsin Deficiency

Another well established risk factor is deficiency of the protective protease inhibitor, Alpha-1 Antitrypsin (AAT). This is an inherited autosomal recessive (designated PiZZ) disorder which is fairly rare in the general gene pool. The estimated prevalence of the heterozygote phenotype (PiMZ) is about 2-3% of the western population. The incidence of homozygous births is in the region of 1 in 3000 live births. As such, AAT deficiency account for probably less than 5% of all cases of COPD.

Low levels of AAT allow the uninhibited action of elastase on the lung parenchyma giving rise to destruction of the alveoli and the eventual development of emphysema rather than chronic bronchitis. The pattern of emphysema in AAT deficiency differs slightly from that of smoking induced pure emphysema in that AAT deficiency produces panlobular emphysema affecting predominantly the lower lung fields, and smoking induced emphysema is usually centrilobular affecting the upper lung fields initially. Not all people with PiZZ have very low levels of AAT. Only serum levels below 35% normal are at risk of developing emphysema. Subjects who are PiMZ may also have reduced levels but not as low as PiZZ, and are not thought to be at more risk from developing emphysema than

PiMM subjects. Subjects who are PiZZ may not progress to have emphysema, but PiZZ subjects who smoke have a greatly increased risk of developing emphysema, especially at an early age

Air Pollution and Occupational Exposure

The role of outdoor air pollution in the evolution of COPD is still controversial. Respiratory deaths in the UK reached a peak during the great smogs of the 1950's. Following the passing of the Clean Air Acts of 1956 and 1968 which established "smokeless zones" in populated areas and allowing only the use of smokeless fuels, the quality of British air has improved. The people that died during the smogs were people at the greatest risk, i.e. the elderly and infirmed, and those with chronic respiratory and cardiac problems. The question of whether atmospheric pollution itself can cause or contribute to the development of COPD is still uncertain.

Outdoor air pollution is very heterogeneous and is different in different areas. It is mainly comprised of particulates and gases with some background radioactivity. The particulates mainly originate from the incomplete combustion of solid fuels and diesel, ash and fine dusts. The main gaseous components are the various oxides of sulphur, nitrogen and carbon, again from the combustion of fossil fuels; hydrocarbons and ozone. Studies from the UK have shown a relationship between levels of atmospheric pollution and respiratory problems (particularly cough and sputum production) in both adults and children, and similar studies from the USA have confirmed these findings. Some studies have reported lower levels of lung function in adults living in highly polluted areas and this seems to related to pollution by acidic gases and particulates. As with the problem of smoking, there will be individuals who are more susceptible to the effects of atmospheric pollution than others.

Any occupation in which the local environment is polluted with the aforementioned gases and particulates increases the risk of developing of COPD. In addition, there is evidence that cadmium and silica also increase the risk of COPD. This is especially true if the subject smokes. Occupations at risk include

coal miners, construction workers who handle cement, metal workers, grain handlers, cotton workers and workers in paper mills. However, the effect of smoking far outweighs any influences from the work environment.

Passive Smoking

Most of the tobacco smoke in a room it that which is coming form the burning end of the cigarette rather than the smoke exhaled from the smoker's lungs. This smoke (called sidestream smoke) is actually higher in concentration of toxic substances than exhaled smoke (mainstream smoke). However, it has been very difficult to judge how much smoke is passively inhaled and what effects this passively inhaled smoke has on the lungs. Studies on passive smoking are plagued by methodological difficulties. Studies in which questionnaires are used to assess the degree of passive exposure to cigarette smoke are prone to bias. Recently, it has been possible to assess the degree of exposure by measuring levels of the nicotine metabolite, cotinine, either in the blood, saliva or urine. Most of the studies using these techniques have been cross sectional ones on children from smoking or non-smoking families. The evidence suggests that respiratory infections and respiratory symptoms are more common in children in households where one or both parents smoke. Also, there is a small but significant difference in the prevalence of respiratory symptoms and lung function in adults and children who are regularly exposed to passive smoking. Whether these differences are clinically significant is yet to be resolved.

Infections

The role of viral infections of upper and lower respiratory tract in the pathogenesis of COPD remains to be clarified. Viral infections in the lung enhance inflammation and predispose to bronchial hyperreactivity. There is increasing evidence between early childhood infections and increase in respiratory symptoms and lower lung function in adulthood. The viruses that have been implicated are adenovirus and respiratory syncytial virus. Once COPD is established, repeated infective exacerbations of airflow obstruction, either viral or bacterial, may speed up the decline in lung function.

Race, Gender and Socioeconomic status

Chinese and Afro-Caribbean races seem to have a reduced susceptibility to developing COPD. It is frequently stated that COPD is more prevalent in men. However, when smoking and occupational exposure is taken into account, the relative risk of developing COPD is not significantly higher in men than women. With smoking on the increase in women, it is possible that women may catch up with men in terms of absolute numbers. The beneficial effects of stopping smoking on the rate of lung function decline may greater for women than men.

There is a clear social class gradient for COPD with it being more prevalent in the lower socioeconomic strata. This may be related to poorer housing and nutrition and use of fossil fuels for heating without adequate ventilation. Also, there is a higher prevalence of smoking in the lower socioeconomic strata, and they are more likely to be employed in jobs where they may be a risk from occupational exposure. However, this socioeconomic gradient for COPD is now becoming more smoothed out as standards of living improve.

Diagnosis of COPD

History

Most patients will have been smoking cigarettes for many years (probably in excess of 20 pack years). The two main symptoms of COPD are breathlessness and cough which may or may not be productive of purulent sputum. A history of persistent productive cough or recurrent infections especially in the winter months is common. The cough is usually worse in the mornings but bears no relationship to the severity of the disease. Excessive sputum volumes are unusual and may suggest bronchiectasis. Haemoptysis should alert the physician for the presence of a carcinoma of the bronchus as this is a frequent co-morbidity in patients with COPD, but is often just due to infective exacerbations

Breathlessness is a common feature of acute infective exacerbations, but breathlessness during normal every day activity develops insidiously over many years and most patients will have lost more than 50% of their predicted FEV_1 by

the time that breathlessness becomes a problem. Wheeze is often an accompanying feature of breathlessness and may be erroneously attributed to asthma.

Weight loss is common in patients with long standing disease with predominately emphysema (the old fashioned pink puffer), although weight gain may also be a feature suggesting chronic hypoxaemia and the onset of cor pulmonale (the blue bloater). Patients can rarely be classified as pink puffers or blue bloaters, and the two states do not have any pathophysiological correlation. Therefore the usefulness of this classification is questionable and its use is discouraged by both sets of guidelines.

Examination

The symptoms of COPD range from chronic cough, sputum production, and wheezing to more severe symptoms, such as dyspnea, poor exercise tolerance, and signs or symptoms of right-sided heart failure.

There are no specific findings on examination, although signs of hyperinflation of the chest are highly suggestive of emphysema. These include a barrel shaped chest (increased antero-posterior diameter), use of accessory muscles of respiration, reduction of the cricosternal distance, tracheal tug, paradoxical indrawing of the lower ribs on inspiration (Hoover's sign), intercostal recession, hollowing out of the supraclavicular fossae, pursed lip breathing and reduced expansion. In addition the patient may have hyperresonant lung fields, prolongation of expiration, especially forced expiration >5s, and audible wheeze. None of these signs are specific to COPD and do not correlate very well with the severity of the disease which emphasises the need for objective assessment. Their presence, however, should alert the physician to the possible diagnosis of COPD.

As the disease progresses, signs of right ventricular dysfunction may develop (Cor pulmonale) because of the effects chronic hypoxaemia and hypercapnia which include peripheral oedema, raised jugular venous pressure, hepatic congestion, and the presence of metabolic flapping tremor. Despite the widely held belief that these signs are due to right ventricular failure, the pathophysiology cor pulmonale is likely to be due to altered renal function giving

rise to salt and water retention rather than cardiac dysfunction secondary to pulmonary hypertension.

Measurements of Lung Function

Both sets of guidelines emphasise the use of simple spirometric measurements to assess the severity and predict the prognosis of patients with COPD. However, they are less specific on the use of the other measurements of lung function in the diagnosis and management of COPD. It is probably good practice to perform routinely a minimum of spirometry with bronchodilator reversibility, static lung volumes, carbon monoxide gas transfer and pulse oximetry as baseline measurements. The addition of walk distance and a quality of life questionnaire may also be helpful as a baseline for future reference.

1. Spirometry

In the European guidelines, the presence of mild airflow limitation is recognised by a reduction in the ratio of FEV1 to VC or FVC (<1.64 residual standard deviation below predicted FEV1/VC). In both sets of guidelines, severity is based on the measured FEV1 as a percent of predicted FEV1. The European guidelines and The American guidelines define 3 stages of severity (Schema 1).

Schema 1.

Staging of Disease Severity

Disease Severity FEV_1 % Predicted	ATS	ERS	BTS	GOLD
Stage 0: at risk	—	—	—	Normal
Stage 1: mild	≥ 50	≥ 70	≥ 60	> 80 but FEV_1/FVC < 70
Stage 2: moderate	35-49	50-69	40-59	30-79
Stage 3: severe	< 35	< 50	< 40	< 30

ATS = American Thoracic Society
ERS=European Respiratory Society
BTS= Thoracic Society
GOLD=Global Initiative for Chronic Obstructive Lung Disease
FEV_1=Forced expiratory volume in 1 second
FVC=Forced vital capacity

Therefore a subject in the European Severe category may only be the equivalent of American stage II, and there is no European equivalent for the American stage III. This may lead to problems in the future when trying to compare trials in the managment of COPD patients. There is likely to be few patients recognised in the mild to moderate European stages since many of these patients will not be very symptomatic and will remain undiagnosed unless specifically screened for.

Most modern electronic spirometers will be able to produce an expiratory flow-volume curve or loop. The appearance of the flow volume curve is highly characteristic is airflow obstruction, especially when there is dynamic airways compression as in patients with predominately emphysema (fig 4). The flow volume loop in severe airflow obstruction is a good graphical representation of the severe impairment of airflow at low lung volumes due to dynamic airways compression. This information can also be obtained as absolute values from the spirometer. Neither set of guidelines emphasises the utility of flow volume loops as an aid to diagnosis although the appearances in severe disease are fairly specific. Severely obstructed flow volume loops may also be seen in obliterated bonchiolitis although there should be little difficulty in differentiating between the two on history alone.

The absolute value of the FEV1 and the yearly rate of decline of the FEV1 may also provide information on the prognosis. The FEV1 at diagnosis can be a predictor of long term survival. The yearly loss of FEV1 is about 20-30ml/yr after the age of 30 in normal non-smoking individuals. In smokers susceptible to developing COPD, the rate may increase to 50-90ml/yr and thus this susceptible population can be identified and efforts increased to stop them smoking before developing disabling disease. The use of peak expiratory flow rate (PEFR) for diagnosis is not recommended but may be useful for domiciliary monitoring or to document diurnal variation to differentiate from asthma. However, in severe COPD, the PEFR will tend to seriously underestimate the severity of airflow obstruction.

2. Response to bronchodilators and corticosteroids

Most patients with COPD will show an increase in FEV1 in response to a bronchodilator, and some by more than 15% of the baseline value (which is often used as a diagnostic test for asthma), but never back to normal levels of lung function. In COPD expressing reversibility as a percentage of baseline values is of limited value because of its dependence on the pretreatment level. Expression of reversibility as an absolute value or as a percentage of predicted values is more reproducible and independent of baseline FEV1. Improvement of the peak flow in response to bronchodilator is not recommended as a guide to reversibility. Many patients report subjective symptomatic improvement without any objective change in their spirometry. The absence of measurable spirometric reversibility therefore is not a reason to withhold bronchodilator treatment.

Some patients with stable COPD may show an increase in FEV1 following a prolonged trial of oral corticosteroids (e.g. Prednisolone 40mg od for 2 weeks). In Europe, this is often seen as an indication for continuing these drugs long term via the inhaled route. However, routine spirometry may not identify all responders to oral corticosteroids, since the improvement may be due to a reduction in FRC and an increase in FVC rather than FEV1. Therefore, there is case for measuring full lung function at the beginning and end of a trial of oral corticosteroids.

3. Static lung volumes and lung compliance

Total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC) are all characteristically increased in COPD and are related to the degree of hyperinflation of the lungs, especially when there is predominately emphysema. Although these measurements are useful and can help differentiate COPD from asthma, neither set of guidelines suggests that the use of these tests is essential in the diagnosis and managment of COPD. Similarly, although lung compliance is increased and lung recoil pressure is reduced and there are characteristic changes in the pressure-volume curve, these measurements are mainly research tools and not necessary in routine clinical practice.

4. Gas Transfer

Carbon monoxide gas transfer capacity (DLco)and coefficient (Kco) are both reduced in symptomatic patients with COPD. The transfer coefficient is a good indicator of the presence and severity of emphysema and thus reduction in the Kco is helpful in distinguishing patients with emphysema from those with asthma. There are also studies which relate the likelihood of hypoxaemia at rest and on exertion to the level of the Kco.

5. Pulse Oximetry and Arterial Blood Gases

The relationship between symptoms, FEV1 and hypoxaemia is weak. The combination of FEV1 and gas transfer strengthens the prediction of resting hypoxaemia. Regular assessment of hypoxaemia is recommended in all patients with moderate to severe COPD (hypoxaemia is more likely when FEV1<1.0l). Rather than regular arterial blood gases analysis, it would be more sensible to use pulse oximetry as a screening test since this is a simple, cheap, painless and non-invasive technique which is fairly accurate. A reasonable strategy would be to perform pulse oximetry on all patients and perform arterial blood gas analysis only on patients with an arterial saturation of less than 93% (since this equates to PaO2 of about 8kPa or 60mmHg on the haemoglobin-oxygen saturation curve). Arterial blood gases should always be measured in patients with suspected CO2 retention. although this will rarely be present in the absence of arterial hypoxaemia and desaturation.

Imaging

1. Chest X-ray

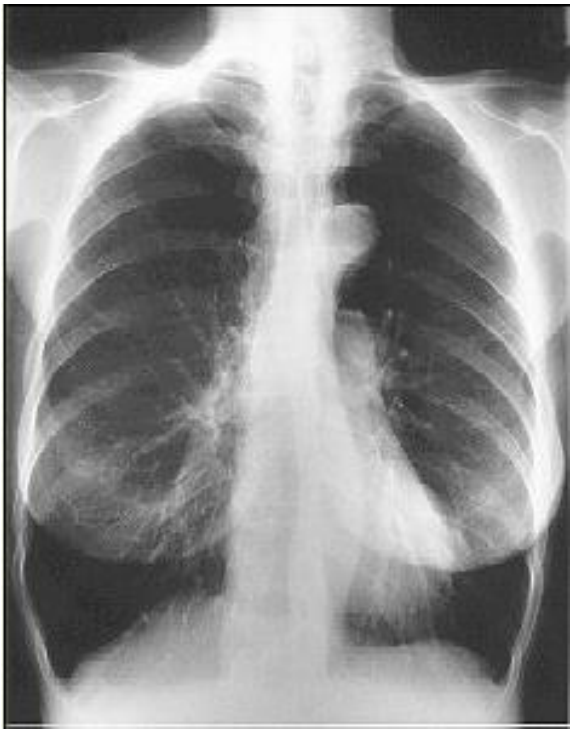
The presence emphysema can be suspected on routine chest radiography but this is not a sensitive technique for diagnosis. Large volume lungs with a narrow mediastinum and flat diaphragms are the typical appearances of emphysema.

In addition, the presence of bullae and irregular distribution of the lung vasculature may be present. In more advanced disease, the presence of pulmonary hypertension may be suspected by the prominence of hilar vasculature. The chest X-ray is not a very good indicator of the severity of disease and will not be able to identify patients with COPD without significant emphysema. However, the chest

X-ray is useful to look for complications during acute exacerbations and to exclude other pathology such as lung cancer (figura 7).

Figura 7.

Emphysema sings on chest X-ray



2. CT scan

Computerised tomography of the chest, especially with an high resolution algorithm (HRCT) has much greater sensitivity and specificity than plain chest radiography in diagnosing and assessing the severity of emphysema. CT can identify areas of bullous disease that may be amenable to surgery that is not evident on plain chest radiography and is useful in predicting the outcome of surgery. HRCT is also capable of differentiating between the various pathological types of emphysema. However, the use of CT scanning in the routine clinical assessment of patients with COPD is not recommended by either set of guidelines, and is reserved for patients in which the diagnosis is in doubt, to look for co-existent pathologies and to assess the suitability of surgical intervention.

Other tests

1. Exercise testing

The routine assessment of functional capacity is not recommended in either set of guidelines. This is rather surprising since often the main presenting symptom is limitation of walking and other activities of daily life by breathlessness. Since FEV1 and other measurements of lung function are poorly correlated to function capacity and subjective sensations of breathlessness, an objective measurement of the main presenting problem should be useful in helping to determine therapies that are actually beneficial. There may be little point in prescribing a treatment that may improve airflow obstruction, but the patients gain any improvement in functionality. Currently, the physician relies heavily on the subjective sensations of the COPD patient to help determine the efficacy of therapy. Thus, there may be a case for the routine assessment of of functional capacity with simple tests such as six minute walk distance or shuttle walk distance in the management of patients with moderate to severe COPD. The European guidelines states that the reproducibility of these tests is poor, yet they are frequently used as research tools in the development of new treatments for COPD. The use of more sophisticated tests of exercise performance such as VO2max should be limited to research or when the diagnosis is in doubt (i.e. when breathlessness is out of proportion to the degree of impairment of lung function).

2. Quality of Life

There are several established questionnaires on quality of life (QoL) in chronic respiratory disease available (e.g. St.George's Hospital Respiratory Questionnaire, Chronic Respiratory Questionnaire) and other general health questionnaires with a respiratory component (e.g. SF-36, Nottingham Health Profile). Also, there are questionnaires on anxiety and depression which can contribute significantly to symptoms in COPD (Hospital Anxiety and Depression Score). These tools are frequently used in studies on the efficacy of new treatments in COPD but none have been accepted for use in everyday practice and have not been recommended for routine use. However, quality of life considerations are becoming increasingly important, and soon measures of QoL will soon be essential.

3. Sleep Studies

Many patients with COPD may have worsening hypoxaemia and hypercapnia during rapid eye movement (REM) sleep, and if this is combined with obstructive sleep apnoea it is called the Overlap syndrome. The role of nocturnal desaturation in the evolution of pulmonary hypertension is uncertain. Those who are most likely to desaturate at night are those who are already hypoxaemic during the day. Detailed sleep studies are currently only recommended in those with additional suspected obstructive sleep apnoea or those with cor pulmonale or polycythaemia with only mild or moderate COPD.

Determine the risk of exacerbations of COPD

Determine the risk of exacerbations of the disease, its impact on the patient's health status and the risk of future events (for example exacerbations) to guide therapy. Consider the following aspects of the disease separately:

- current level of patient's symptoms
- severity of the spirometric abnormality
- frequency of exacerbations
- presence of comorbidities.

To assess risk of exacerbations use history of exacerbations and spirometry:
Two or more exacerbations within the last year or an FEV1 < 50 % of predicted value are indicators of high risk.

Assessment of symptoms

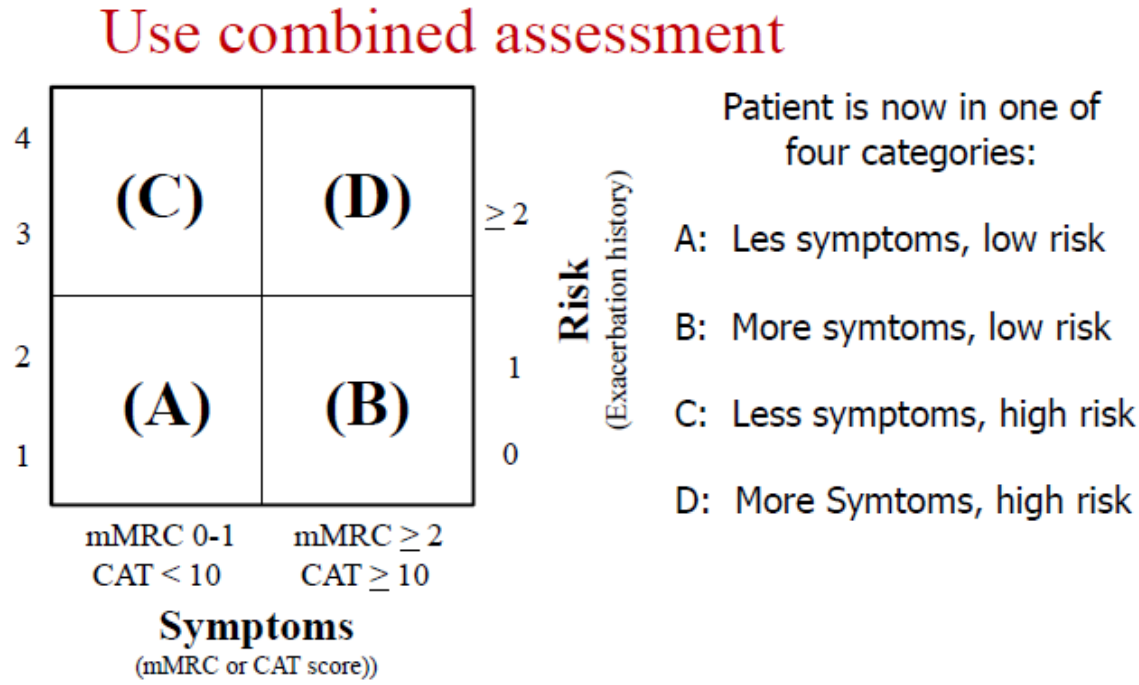
There are at least two questionaries' to determine severity of symptoms of the disease: *COPD Assessment Test (CAT) and Breathlessness Measurement using the Modified British Medical Research Council (mMRC)*

*CAT is a*n 8-item measure of health status impairment in COPD (http://catestonline.org).

Breathlessness Measurement using the Modified British Medical Research Council Questionnaire: relates well to other measures of health status and predicts future mortality risk.

The principles of completed assessement of symptoms severity in COPD is reported Algorithm 1 and Principal scheme 1.

Algorithm 1: Use questionnaires for assessment of severity of symptoms in COPD



Principal scheme 1: Interrelation between risk of exacerbations and patients' characteristics in COPD

Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

Treatment of Stable COPD

Once the diagnosis is established and the stage of the disease is determined, attention turns to patient education and risk factor modification as well as

pharmacologic and nonpharmacologic modalities needed to ameliorate the signs and symptoms of COPD and to optimize patients' longevity and functional status.

Patient education is an essential component because it facilitates reduction of risk factors and improves the individual patient's ability to cope with the disease. Education requires a team approach that includes, in addition to the physician and the patient, home health nurses, social workers, physical therapists, occupational therapists, and others. In addition to risk-factor reduction, education should provide a basic, simple-to-understand overview of COPD, its pathophysiology, therapeutic modalities and their proper use, and instructions on when to seek help. Discussing end-of-life issues and establishing advance directives are facilitated by the educational process, especially when applied in the setting of pulmonary rehabilitation.

Smoking cessation is a cornerstone of patient education and confers many benefits, including slowing the accelerated rate of FEV1 decline among smokers, improvements in symptoms, and lessening the risk of lung cancer. For example, data from the Lung Health Study (LHS) show that in the sustained non-smokers over the 11-year study, the rate of FEV1 decline slowed to 30 ml/year in men and 22 ml/year in women compared to the 66 ml/year and 54 ml/year decline in continuing male and female smokers, respectively. The result was that 38% of continuing smokers had an FEV1< 60% of predicted normal at 11 years compared to only 10% of sustained quitters. Aggressive smoking cessation intervention with counseling and nicotine patch allowed 22% of LHS participants to achieve sustained smoking cessation over 5 years, and 93% of these individuals were still abstinent at 11 years.

Available strategies for smoking cessation including nicotine replacement, available as gum, patch, or nasal spray; bupropion (an antidepressant), smoking-cessation programs, counseling; and combinations of these. Randomized, controlled trials suggest that the combination of nicotine replacement and bupropion confers greater likelihood of achieving smoke-free status than either alone.

Beyond education and smoking cessation, the goals of pharmacologic and non-pharmacologic treatment are to enhance survival, quality of life, and functional status, and to lessen mortality. Available treatments include bronchodilators, corticosteroids, immunizations, antibiotics, mucokinetics, and others.

Bronchodilators

Bronchodilators are a mainstay of COPD treatment, and include ß-adrenergic agonists, anticholinergics, and methylxanthines. Beta-adrenergic agonists are effective in alleviating symptoms and improving exercise capacity, and can produce significant increases in FEV1. Oral theophylline has been shown to lessen dyspnea despite lack of significant rises in FEV1. In the early stages of COPD, a short-acting ß-adrenergic agonist (albuterol, terbutaline, etc) or anticholinergic is used on an as-needed basis. As the disease progresses (stages 2 and 3), regular use of one or more bronchodilators is frequently recommended. Some data suggest that a combination of albuterol and ipratropium bromide provides better bronchodilation than either agent alone. Recently, the FDA approved a new anticholinergic agent, tiotropium, for the long-term, once daily, maintenance treatment of bronchospasm associated with stable COPD, including chronic bronchitis and emphysema. Although this is the same indication granted to ipratropium, tiotropium has shown significant advantages over ipratropium, both pharmacologically and clinically. Specifically, tiotropium blocks the M1-M5 muscarinic receptors with a 6-20 fold greater affinity than ipratropium and for a more prolonged period of time; and dissociates more rapidly from the M2 receptor associated with acetylcholine release, thereby conferring theoretical advantages over ipratropium. These advantages were shown in clinical trials comparing the two agents. Specifically, tiotropium demonstrated significantly greater bronchodilation than ipratropium and users experienced less dyspnea, fewer acute exacerbations, reduced albuterol use, and improved nocturnal oxygen saturation. Furthermore, when compared with long-acting ß2-agonists, tiotropium provided greater bronchodilation and reduced dyspnea than salmeterol.

Theophylline

Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable. There is evidence for a modest bronchodilator effect and some symptomatic benefit compared with placebo in stable COPD. Addition of theophylline to salmeterol produces a greater increase in FEV_1 and breathlessness than salmeterol alone. Low dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function

Corticosteroids

Though widely used, oral and inhaled corticosteroids have a very limited role in managing patients with stable COPD. Several groups suggest brief trials of oral corticosteroids for patients with stable COPD. For example, the BTS suggests a course of oral prednisone (eg, 30 mg daily) taken for 2 weeks, or a course of inhaled steroid (eg, beclomethasone 500 mcg twice daily or equivalent) taken for 6 weeks.6 Similarly, the ERS suggests a trial of corticosteroids (eg, 0.4 to 0.6 mg/kg/day) taken for 2 to 4 weeks. Patients with significant FEV1 responses are considered candidates for long-term inhaled corticosteroids.5 At the same time, 4 randomized, placebo-controlled trials of inhaled corticosteroids in patients with COPD have shown no effect on the rate of FEV1 decline, although one study suggested that steroid recipients experienced fewer COPD exacerbations than non-recipients.

Immunizations

Prophylactic immunization with the influenza vaccine yearly and with the 23-polyvalent pneumococcal vaccine every 5-10 years is recommended. *Influenza vaccines* can reduce serious illness. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an $FEV_1 < 40\%$ predicted.

The use of *antibiotics,* other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated

Roflumilast

In patients with severe and very severe COPD (GOLD 3 and 4) and a history of exacerbations and chronic bronchitis, the phospodiesterase-4 inhibitor (*PDE-4*), roflumilast, reduces exacerbations treated with oral glucocorticosteroids.

Antibiotics

Prophylactic antibiotics have not shown benefit in the management of stable COPD and are not recommended.

Mucokinetics

Mucokinetic drugs (eg, ambroxol, erdosteine, carbocysteine, iodinated glycerol, etc) are not beneficial and are not recommended.

Other drugs

Antitussives containing narcotics and other therapies, such as inhaled nitric oxide, may be harmful. Their use is contraindicated.

In the specific case of alpha 1-antitrypsin deficiency, intravenous augmentation therapy with pooled human plasma antiprotease can raise serum levels of alpha 1-antitrypsin above a protective threshold value (of 11 micromolar). Available evidence suggests that augmentation therapy can slow the rate of FEV1 decline in individuals with severe deficiency of alpha 1-antitrypsin (eg, PI*ZZ phenotypes) and established airflow obstruction of moderate severity (eg, FEV_1 30-65% predicted). Currently available alpha 1 proteinase inhibitors in the United States include Prolastin, Aralast, and Zemaira.

Non-pharmacologic treatments include pulmonary rehabilitation, long-term oxygen therapy (LTOT), ventilatory support, and lung volume reduction surgery (LVRS). Pulmonary rehabilitation is recommended at all stages by all available guidelines. Aerobic lower extremity training can improve exercise endurance, dyspnea, health care utilization, and overall quality of life, whereas the role of upper extremity exercise and respiratory muscle training remains unclear. Long-term oxygen therapy for patients with hypoxemia has been shown to improve survival in eligible patients with COPD.

Criteria for prescribing long-term oxygen therapy include a PaO2 < 55 mm Hg or SaO_2 < 88% with or without increased $PaCO_2$, or PaO_2 between 55 and 59

mm Hg or SaO_2 < 89%, with right-sided failure reflected by evidence of pulmonary hypertension or polycythemia (eg, hematocrit > 55%).

Nocturnal non-invasive ventilatory support still has an unproven role in managing patients with stable COPD. LVRS involves the resection of 20% to 35% of the emphysematous lung in order to allow improved lung mechanics. The procedure was first proposed by Brantigan and Mueller in the late 1940s, but was abandoned then because of unacceptably high mortality. More recently, as surgical mortality rates have decreased to 3% to 5%, the role of LVRS is being actively investigated. Available randomized, controlled trials to date show that LVRS is contraindicated in individuals with severely impaired lung function (eg, FEV1 < 20% predicted, homogeneous emphysema, and/or lung diffusing capacity for carbon monoxide < 20% predicted), but that LVRS recipients with moderate degrees of airflow obstruction may experience an improved FEV1, walking distance, and quality of life. In the recently published results of the National Emphysema Treatment Trial, a randomized controlled trial of LVRS vs. medical therapy (including rehabilitation) in which 1218 individuals with moderate COPD (FEV1 < 45% predicted) were enrolled, the LVRS group overall experienced improved disease-specific quality of life and exercise capacity compared to the medically managed group. On the other hand, the LVRS group had similar rates of survival as the medically managed group. In subsets defined by pre-specified exploration, a survival advantage was observed in the subgroup of patients with both predominantly upper lobe emphysema and low baseline (ie, post-rehabilitation) exercise capacity (defined as a maximal workload at <25 W for women and 40 W for men).

Finally, lung transplantation is an option for patients with severe airflow obstruction and functional impairment. Five-year actuarial survival rates for patients undergoing single-lung transplantation for COPD are 43.2%.43 Selection criteria include an FEV1 < 25% predicted and/or a PaCO2 > 55 mm Hg and/or cor pulmonale.

Treatment of Acute Exacerbations of COPD:

Acute exacerbation of COPD (AECOPD) represents an acute worsening of the baseline COPD, generally characterized by worsened dyspnea and increased volume and purulence of sputum. Depending on the severity of baseline COPD, additional derangements may become manifest such as hypoxemia, worsening hypercapnia, cor pulmonale with worsening lower extremity edema, or altered mental status. The main goals of treating AECOPD are to restore the individual patient to his or her previous stable baseline and to take measures that prevent or reduce the likelihood of recurrence. This requires identification of the precipitating factor or condition and its reversal or amelioration, while optimizing gas exchange and improving the individual patient's symptoms. Treatment modalities similar to the ones used in stable COPD are utilized in managing acute exacerbations. They include oxygen therapy, bronchodilators, antibiotics, corticosteroids, and mechanical ventilation, and others.

Oxygen Therapy

The role of oxygen therapy is to correct the hypoxemia that usually accompanies the AECOPD. The end-point is to maintain oxygen tension around 60 to 65 mm Hg, thereby assuring near-maximal hemoglobin saturation while minimizing the potential for deleterious hypercapnia. Hypercapnia complicating supplemental oxygen is best ascribed to ventilation-perfusion mismatch rather than to depression of the respiratory drive or the Haldane effect.

Bronchodilators

Bronchodilators are widely used in AECOPD, and ß-adrenergic agonists and anticholinergics are first-line therapy. As in stable COPD, both can improve airflow in AECOPD, and although recommendations vary, combined therapy is often recommended. Beta-adrenergic agonists have a quicker onset of action whereas anticholinergics have a more favorable side-effect profile. Because of their potential side effects as well as their limited benefit, methylxanthines are used mostly as second-line therapy. The use of sustained-release preparations seems to lessen the potential for side effects.

Antibiotics

Antibiotics play a favorable role in treating AECOPD, especially in the setting of increased volume and purulence of phlegm. A narrow-spectrum antibiotic (eg, amoxicillin, trimethoprim-sulfamethoxazole, doxycycline, etc.) is the recommended first-line therapy by all available guidelines. The optimal duration of treatment is still unclear, although most guidelines recommend treating for between 7 and 14 days.

Corticosteroids

Randomized clinical trials generally support the use of systemic corticosteroids to enhance airflow and to lessen treatment failure in AECOPD. Prolonged therapy beyond 2 weeks confers no additional benefits, with 5 to 10 days as the likeliest optimal duration.

Noninvasive Positive Pressure Ventilation and Mechanical Ventilation

Noninvasive positive pressure ventilation (NIPPV) is emerging as a preferred method of ventilation in adequately selected patients with acute respiratory acidemia. This mode is currently used in the treatment of acute respiratory failure of many causes, including COPD. Appropriate patient selection is critical to assure the success of nninvasive positive pressure ventilation. Poor candidates are those with acute respiratory arrest, altered mental status with agitation or lack of cooperation, distorted facial anatomy preventing adequate mask application, cardiovascular instability, and/or excessive secretions. Nonvasive positive pressure ventilation IPPV improves symptomatic and physiologic variables, reduces the need for intubation, hospital stay, and mortality, and does not use additional resources.

For patients who do not qualify for NIPPV and/or show evidence of worsening respiratory failure and life-threatening acidemia despite NIPPV, intubation and mechanical ventilation is indicated. This method of ventilation carries numerous risks and complications, including ventilator-acquired pneumonia and barotrauma. Adequate ventilator management is necessary, and every effort should be deployed to minimize the duration of mechanical ventilation.

Other drugs

Mucolytics, expectorants, and chest physiotherapy have not been shown to improve the outcome and are not recommended.

Clinical Examination for Prediction of Airflow Obstruction

The National Health and Nutrition Examination Survey III and a systematic review of 19 studies examining the accuracy of clinical examination to predict airway obstruction were used to estimate the prevalence of COPD and airway obstruction and clinical diagnostic accuracy. Cigarette smoking is the most common cause of COPD. A 70–pack-year history of smoking was the best predictor of AO, with a positive likelihood ratio of 8.0 but a sensitivity of only 40%. The literature showed that findings from physical examination also had high specificity (>90%) but poor sensitivity. In addition, sputum production or wheezing was also associated with an increased likelihood of airway obstruction. Evidence to assess the utility of combining items that were included in a clinical examination to predict airway obstruction showed that combinations of findings were more helpful for diagnosing the presence of airway obstruction. The best combination to exclude COPD included never having smoked, no reported wheezing, and no wheezing on examination. A patient with any combination of 2 findings (70–pack-year history of smoking, history of COPD, or decreased breath sounds) can be considered likely to have AO (defined as FEV1 less than 60% *predicted or FEV1–FVC ratio less than 0.60)*

Incremental Value of Spirometry

Spirometry may be useful to identify patients who may benefit from initiating therapy. The evidence supports inhaled treatment in patients who have symptoms and FEV1 less than 60% predicted. The literature also showed that respiratory symptom status is not a reliable indicator of the presence of airway obstruction. However, as spirometric values worsened, individuals reported more respiratory symptoms, such as cough, sputum, wheezing, or dyspnea. But 33% of individuals with normal spirometric values reported respiratory symptoms. In addition, 21% of individuals who had severe to very severe airway obstruction by spirometry reported no symptoms. Nearly 80% of persons reporting any

respiratory symptom had normal airflow, and only 3% to 4% had severe to very severe airway obstruction. Evidence is insufficient to support widespread use of spirometry for testing adults with no respiratory symptoms, including those with current and past exposure to COPD risk factors. Spirometry may be beneficial in symptomatic adults who have an FEV1 greater than 60% predicted for determining when to initiate therapy. The evidence does not support periodic spirometry after initiation of therapy to monitor ongoing disease status or to modify therapy. Furthermore, no high-quality evidence supports the use of obtaining and providing spirometry results to improve smoking cessation, identify and treat asymptomatic individuals to prevent future respiratory symptoms, or reduce spirometric decline in lung function.

Pulmonary Rehabilitation Programs

The main components of most pulmonary rehabilitation programs included endurance or exercise training, education, behavioral modification, and outcome assessment. Three studies found clinically significant improvement in dyspnea and fatigue. Pulmonary rehabilitation did not result in reduction in deaths, but the studies had small sample sizes and short durations. A review of 6 small RCTs in patients with baseline FEV1 less than 40% predicted showed a reduction in hospitalizations and clinically significant improvement in health status and exercise capacity.

Disease Management and Patient Education

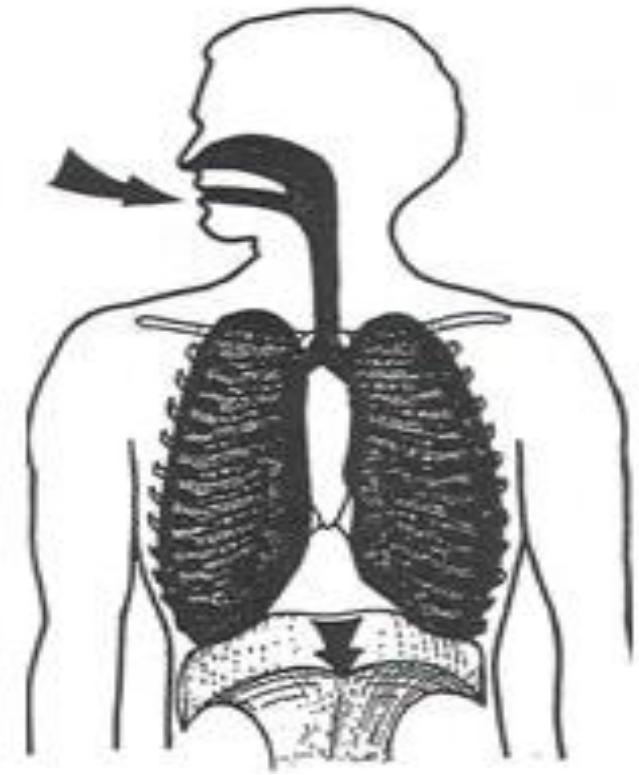
The evidence did not show any effect of disease management programs or patient education on deaths, COPD exacerbations, reduction in all-cause readmissions, hospital length of stay, visits to primary care physicians, clinically meaningful improvement in the St. George Respiratory Questionnaire health status score, patient satisfaction, self-management skills, or adherence to treatment.

Breathing Techniques

Diaphragmatic Breathing

The diaphragm 1 is a major muscle used in breathing and is located beneath the lowest two ribs. At rest, the diaphragm muscle is bell shaped. During inspiration, it lowers and flattens out.

Diagram 1: Diaphragmatic Breathing



Optimizing the use of the diaphragm is beneficial because it pulls air into the lower lobes of the lungs where more gas exchange takes place. Not only is the diaphragm the most efficient of all respiratory muscles, but using it tends to be very relaxing and calming.

Along with our diaphragm, we use intercostal and abdominal muscles in the work of breathing. The intercostals (muscles between the ribs) pull to lift the rib cage up and out. This causes the lungs to open in all directions and air can be pulled down the airways. To exhale, the muscles that have been pulling relax and air is forced out.

The Resistance Created by Breathing Out Through Pursed Lips:

- Slows down the breathing rate.
- Creates a back pressure that helps keep the airways open.

- Exercise Suggestions:
- Use a comfortable chair.
- Relax your back.
- Your feet should touch the floor or be supported comfortably.
- Inhale through your nose, exhale with pursed lips.
- Make exhaling slower and longer than inhaling.

Practice inhaling and exhaling a few times to get used to the slower exhalation.

Inhale

- Spread fingers out.
- Place both hands on stomach.
- Concentrate on expanding belly as you inhale through your nose.
- Exhale
- Slowly exhale through pursed lips.
- The exhale should be longer and slower than the inhale.

Supplemental Long-Term Oxygen Therapy and Death

Two trials showed that supplemental oxygen used 15 or more hours daily to maintain a Pao2 greater than 60 mm Hg reduced deaths in individuals who have very severe AO (FEV1 <30% predicted) and resting hypoxemia (mean resting Pao2 55 mm Hg). Two other studies showed no effect on relative risk for death with use of supplemental oxygen (9 to 13 hours daily) during the day or at night in patients with similar severity of AO but with daytime Pao2 greater than 60 mm Hg. In addition, studies showed no effect of ambulatory oxygen on respiratory health status measures.

COR PULMONALE

Background

Cor pulmonale is defined as an alteration in the structure and function of the right ventricle caused by a primary disorder of the respiratory system. Pulmonary hypertension is the common link between lung dysfunction and the heart in cor

pulmonale. Right-sided ventricular disease caused by a primary abnormality of the left side of the heart or congenital heart disease is not considered cor pulmonale, but cor pulmonale can develop secondary to a wide variety of cardiopulmonary disease processes. Although cor pulmonale commonly has a chronic and slowly progressive course, acute onset or worsening cor pulmonale with life-threatening complications can occur.

Pathophysiology

Several different pathophysiologic mechanisms can lead to pulmonary hypertension and, subsequently, to cor pulmonale. These pathogenetic mechanisms include pulmonary vasoconstriction due to alveolar hypoxia or blood acidemia, anatomic compromise of the pulmonary vascular bed secondary to lung disorders (eg, emphysema, pulmonary thromboembolism, interstitial lung disease), increased blood viscosity secondary to blood disorders (eg, polycythemia vera, sickle cell disease, macroglobulinemia), and idiopathic primary pulmonary hypertension. The result is increased pulmonary arterial pressure.

The right ventricle (RV) is a thin-walled chamber that is more a volume pump than a pressure pump. It adapts better to changing preloads than afterloads. With an increase in afterload, the RV increases systolic pressure to keep the gradient. At a point, a further increase in the degree of pulmonary arterial pressure produces significant RV dilation, an increase in RV end-diastolic pressure, and RV circulatory collapse. A decrease in RV output with a decrease in diastolic left ventricle (LV) volume results in decreased LV output. Since the right coronary artery, which supplies the RV free wall, originates from the aorta, decreased LV output diminishes blood pressure in the aorta and decreases right coronary blood flow. What ensues is a vicious cycle between decreases in LV and RV output. Genetic investigations have confirmed that morphogenesis of the right and left ventricle originated from different sets of progenitor cells and sites. This polymorphism could explain the differing rates of hypertrophy of the right and left ventricles.

Right ventricular overload is associated with septal displacement toward the left ventricle. Septal displacement, which is seen on echocardiography, can be another factor that decreases LV volume and output in the setting of Cor pulmonale and right ventricular enlargement. Several pulmonary diseases cause Cor pulmonale, which may involve interstitial and alveolar tissues with a secondary effect on pulmonary vasculature or may primarily involve pulmonary vasculature. Chronic obstructive pulmonary disease (COPD) is the most common cause of Cor pulmonale in worldwide.

Cor pulmonale usually presents chronically, but 2 main conditions can cause acute cor pulmonale: massive pulmonary embolism (more common) and acute respiratory distress syndrome (ARDS). The underlying pathophysiology in massive pulmonary embolism causing cor pulmonale is the sudden increase in pulmonary resistance. In ARDS, 2 factors cause RV overload: the pathologic features of the syndrome itself and mechanical ventilation. Mechanical ventilation, especially higher tidal volume, requires a higher transpulmonary pressure. In chronic cor pulmonale, right ventricular hypertrophy (RVH) generally predominates. In acute cor pulmonale, right ventricular dilatation mainly occurs.

Frequency

Cor pulmonale is estimated to account for 6-7% of all types of adult heart disease, with chronic obstructive pulmonary disease (COPD) due to chronic bronchitis or emphysema the causative factor in more than 50% of cases. The incidence of cor pulmonale varies among different countries depending on the prevalence of cigarette smoking, air pollution, and other risk factors for various lung diseases.

Mortality/Morbidity

Development of cor pulmonale as a result of a primary pulmonary disease usually heralds a poorer prognosis. For example, patients with COPD who develop cor pulmonale have a 30% chance of surviving 5 years. However, whether cor pulmonale carries an independent prognostic value or it is simply reflecting the severity of underlying COPD or other pulmonary disease is not clear. Prognosis in

the acute setting due to massive pulmonary embolism or ARDS has not been shown to be dependent on the presence or absence of cor pulmonale.

History

Clinical manifestations of cor pulmonale generally are nonspecific. The symptoms may be subtle, especially in early stages of the disease, and mistakenly may be attributed to the underlying pulmonary pathology.

The patient may complain of fatigue, tachypnea, exertional dyspnea, and cough.

Anginal chest pain also can occur and may be due to right ventricular ischemia (it usually does not respond to nitrates) or pulmonary artery stretching.

Hemoptysis may occur because of rupture of a dilated or atherosclerotic pulmonary artery. Other conditions, such as tumors, bronchiectasis, and pulmonary infarction, should be excluded before attributing hemoptysis to pulmonary hypertension. Rarely, the patient may complain of hoarseness due to compression of the left recurrent laryngeal nerve by a dilated pulmonary artery.

A variety of neurologic symptoms may be seen due to decreased cardiac output and hypoxemia. In advanced stages, passive hepatic congestion secondary to severe right ventricular failure may lead to anorexia, right upper quadrant abdominal discomfort, and jaundice. Syncope with exertion, which may be seen in severe disease, reflects a relative inability to increase cardiac output during exercise with a subsequent drop in the systemic arterial pressure. Elevated pulmonary artery pressure can lead to elevated right atrial pressure, peripheral venous pressure, and then capillary pressure and by increasing the hydrostatic gradient, it leads to transudation of fluid, which appears as peripheral edema. Although this is the simplest explanation for peripheral edema in cor pulmonale, other hypotheses explain this symptom, especially in a fraction of patients with COPD who do not show increase in right atrial pressure. A decrease in glomerular filtration rate (GFR) and filtration of sodium and stimulation of arginine vasopressin (which decreases free water excretion) due to hypoxemia play important pathophysiologic roles in this setting and may even have a role for

peripheral edema in patients with cor pulmonale who have elevated right atrial pressure.

Physical

Physical findings may reflect the underlying lung disease or pulmonary hypertension, RVH, and RV failure. On inspection, an increase in chest diameter, labored respiratory efforts with retractions of the chest wall, distended neck veins with prominent A or V waves, and cyanosis may be seen. On auscultation of the lungs, wheezes and crackles may be heard as signs of underlying lung disease. Turbulent flow through recanalized vessels in chronic thromboembolic pulmonary hypertension3 may be heard as systolic bruits in the lungs. Splitting of the second heart sound with accentuation of the pulmonic component can be heard in early stages. A systolic ejection murmur with sharp ejection click over the region of the pulmonary artery may be heard in advanced disease, along with a diastolic pulmonary regurgitation murmur. Other findings upon auscultation of the cardiovascular system may be third and fourth sounds of the heart and systolic murmur of tricuspid regurgitation. RVH is characterized by a left parasternal or subxiphoid heave. Hepatojugular reflux and pulsatile liver are signs of RV failure with systemic venous congestion. On percussion, hyperresonance of the lungs may be a sign of underlying COPD; ascites can be seen in severe disease. Examination of the lower extremities reveals evidence of pitting edema. Edema in cor pulmonale is strongly associated with hypercapnia.

Causes

A general approach to diagnose cor pulmonale and to investigate its etiology starts with routine laboratory tests, chest radiography, and electrocardiography. Echocardiography gives valuable information about the disease and its etiology. Pulmonary function tests may become necessary to confirm the underlying lung disease. Ventilation/perfusion (V/Q) scan or chest CT scan may be performed if history and physical examination suggest pulmonary thromboembolism as the cause or if other diagnostic tests do not suggest other etiologies. Right heart catheterization is the most accurate but invasive test to confirm the diagnosis of cor

pulmonale and gives important information regarding the underlying diseases. Any abnormal result in each of these tests may need further diagnostic evaluation in that specific direction.

Laboratory investigations are directed toward defining the potential underlying etiologies as well as evaluating complications of cor pulmonale. In specific instances, appropriate lab studies may include the following: hematocrit for polycythemia (which can be a consequence of underlying lung disease but can also increase pulmonary arterial pressure by increasing viscosity), serum alpha1-antitrypsin if deficiency is suspected, and antinuclear antibody level for collagen vascular disease such as scleroderma. Hypercoagulability states can be evaluated by serum levels of proteins S and C, antithrombin III, factor V Leyden, anticardiolipin antibodies, and homocysteine.

Arterial blood gas tests may provide important information about the level of oxygenation and type of acid-base disorder.

Elevated brain natriuretic peptide (BNP) level alone is not adequate to establish presence of cor pulmonale, but it helps to diagnose cor pulmonale in conjunction with other noninvasive tests and in appropriate clinical settings. An elevated BNP level may actually be a natural mechanism to compensate for elevated pulmonary hypertension and right heart failure by promoting diuresis and natriuresis, vasodilation of systemic and pulmonary vessels, and reduction of circulating levels of endothelin and aldosterone.

Imaging Studies

Imaging studies may show evidence of underlying cardiopulmonary diseases, pulmonary hypertension, or its consequence, right ventricular enlargement.

Chest roentgenography: In patients with chronic cor pulmonale, the chest radiograph may show enlargement of the central pulmonary arteries with oligemic peripheral lung fields. Pulmonary hypertension should be suspected when the right descending pulmonary artery is larger than 16 mm in diameter and the left pulmonary artery is larger than 18 mm in diameter. Right ventricular enlargement

leads to an increase of the transverse diameter of the heart shadow to the right on the posteroanterior view and filling of the retrosternal air space on the lateral view. These findings have reduced sensitivity in the presence of kyphoscoliosis or hyperinflated lungs.

Echocardiography: Two-dimensional echocardiography usually demonstrates signs of chronic RV pressure overload. As this overload progresses, increased thickness of the RV wall with paradoxical motion of the interventricular septum during systole occurs. At an advanced stage, RV dilatation occurs and the septum shows abnormal diastolic flattening. In extreme cases, the septum may actually bulge into the left ventricular cavity during diastole resulting in decreased diastolic volume of LV and reduction of LV output.

Doppler echocardiography is now used to estimate pulmonary arterial pressure, taking advantage of the functional tricuspid insufficiency that is usually present in pulmonary hypertension. Doppler echocardiography is considered the most reliable noninvasive technique to estimate pulmonary artery pressure. The efficacy of Doppler echocardiography may be limited by the ability to identify an adequate tricuspid regurgitant jet, which may be further enhanced by using saline contrast.

Ventilation/perfusion (V/Q) lung scanning, pulmonary angiography, and chest CT scanning may be indicated to diagnose pulmonary thromboembolism as the underlying etiology of cor pulmonale. These tests may be performed early in the diagnostic workup if any evidence of pulmonary embolism appears in history and physical examination. The test may also be considered later in the workup if other tests are not suggestive of any other etiology. Pulmonary thromboembolism has a wide range of clinical presentations from massive embolism with acute and severe hemodynamic instability to multiple chronic peripheral embolisms that may present with cor pulmonale.

Ultrafast, ECG-gated CT scanning has been evaluated to study RV function. In addition to estimating right ventricular ejection fraction (RVEF), it can estimate

RV wall mass. Its use is still experimental, but with further improvement, it may be used to evaluate the progression of cor pulmonale in the near future.

Magnetic resonance imaging (MRI) of the heart is another modality that can provide valuable information about RV mass, septal flattening, and ventricular function.

Radionuclide ventriculography can determine RVEF noninvasively. Myocardial perfusion may also show a permanent increase in brightness of the right ventricle.

Other Tests

Electrocardiography (ECG) abnormalities in cor pulmonale reflect the presence of RVH, RV strain, or underlying pulmonary disease. These electrocardiographic changes may include the following:

- Right axis deviation
- R/S amplitude ratio in V1 greater than I (increase in anteriorly directed forces may be a sign of posterior infarct)
- R/S amplitude ratio in V6 less than I
- P-pulmonale pattern (an increase in P wave amplitude in leads 2, 3, and aVF)
- S1Q3T3 pattern and incomplete (or complete) right bundle branch block, especially if pulmonary embolism is the underlying etiology
- Low-voltage QRS because of underlying COPD with hyperinflation
- Increased AP diameter of the chest

Severe RVH may reflect as Q waves in the precordial leads that may be interpreted as anterior myocardial infarction by mistake (on the other hand, since electrical activity of the RV is significantly less than the LV, small changes in RV forces may be lost in ECG).

Additionally, many rhythm disturbances may be present in chronic cor pulmonale; these range from isolated premature atrial depolarizations to various

supraventricular tachycardias, including paroxysmal atrial tachycardia, multifocal atrial tachycardia, atrial fibrillation, atrial flutter, and junctional tachycardia. These dysrhythmias may be triggered by processes secondary to the underlying disease, (eg, anxiety, hypoxemia, acid-base imbalance, electrolyte disturbances, excessive use of bronchodilators, heightened sympathetic activity). Life-threatening ventricular tachyarrhythmias are less common.

In selected cases, pulmonary function testing may be indicated to determine underlying obstructive or interstitial lung disease.

Procedures

Cardiac catheterization: Right-heart catheterization is considered the most precise method for diagnosis and quantification of pulmonary hypertension. It is indicated when echocardiography cannot assess the severity of a tricuspid regurgitant jet, thus excluding an assessment of pulmonary hypertension. Right-heart catheterization is occasionally important for differentiating cor pulmonale from occult left ventricular dysfunction, especially when the presentation is confusing. Another indication may be for evaluation of the potential reversibility of pulmonary arterial hypertension with vasodilator therapy or when a left heart catheterization is indicated. Lung biopsy may occasionally be indicated to determine underlying etiology.

Medical Care

Medical therapy for chronic cor pulmonale is generally focused on treatment of the underlying pulmonary disease and improving oxygenation and RV function by increasing RV contractility and decreasing pulmonary vasoconstriction. However, the approach might be different to some degree in an acute setting with priority given to stabilizing the patient.

Cardiopulmonary support for patients experiencing acute cor pulmonale with resultant acute RV failure includes fluid loading and vasoconstrictor (eg, epinephrin) administration to maintain adequate blood pressure. Of course, the primary problem should be corrected, if possible. For example, for massive pulmonary embolism, consider administration of anticoagulation, thrombolytic

agents or surgical embolectomy, especially if circulatory collapse is impending; consider bronchodilation and infection treatment in patients with COPD; and consider steroid and immunosuppressive agents in infiltrative and fibrotic lung diseases.

Oxygen therapy, diuretics, vasodilators, digitalis, theophylline, and anticoagulation therapy are all different modalities used in the long-term management of chronic cor pulmonale.

Oxygen therapy

Oxygen therapy is of great importance in patients with underlying COPD, particularly when administered on a continuous basis. With cor pulmonale, the partial pressure of oxygen (PO2) is likely to be below 55 mm Hg and decreases further with exercise and during sleep.

Oxygen therapy relieves hypoxemic pulmonary vasoconstriction, which then improves cardiac output, lessens sympathetic vasoconstriction, alleviates tissue hypoxemia, and improves renal perfusion. The Nocturnal Oxygen Therapy Trial (NOTT), a multicenter randomized trial, showed that continuous low-flow oxygen therapy for patients with severe COPD resulted in significant reduction in the mortality rate.8 In general, in patients with COPD, long-term oxygen therapy is recommended when PaO2 is less than 55 mm Hg or O2 saturation is less than 88%. However, in the presence of cor pulmonale or impaired mental or cognitive function, long-term oxygen therapy can be considered even if PaO2 is greater than 55 mm Hg or O2 saturation is greater than 88%.

Although whether oxygen therapy has a mortality rate benefit in patients with cor pulmonale due to pulmonary disorders other than COPD is not clear, it may provide some degree of symptomatic relief and improvement in functional status. Therefore, oxygen therapy plays an important role in both the immediate setting and long-term management, especially in patients who are hypoxic and have COPD.

Diuretics

Diuretics are used in the management of chronic cor pulmonale, particularly when the right ventricular filling volume is markedly elevated and in the management of associated peripheral edema. Diuretics may result in improvement of the function of both the right and left ventricles; however, diuretics may produce hemodynamic adverse effects if they are not used cautiously. Excessive volume depletion can lead to a decline in cardiac output. Another potential complication of diuresis is the production of a hypokalemic metabolic alkalosis, which diminishes the effectiveness of carbon dioxide stimulation on the respiratory centers and lessens ventilatory drive. The adverse electrolyte and acid-base effect of diuretic use can also lead to cardiac arrhythmia, which can diminish cardiac output. Therefore, diuresis, while recommended in the management of chronic cor pulmonale, needs to be used with great caution.

Vasodilator drugs

Vasodilator drugs have been advocated in the long-term management of chronic cor pulmonale with modest results. Calcium channel blockers, particularly oral sustained-release nifedipine and diltiazem, can lower pulmonary pressures, although they appear more effective in primary rather than secondary pulmonary hypertension. Other classes of vasodilators, such as beta agonists, nitrates, and angiotensin-converting enzyme (ACE) inhibitors have been tried but, in general, vasodilators have failed to show sustained benefit in patients with COPD and they are not routinely used. A trial of vasodilator therapy may be considered only in patients with COPD with disproportionately high pulmonary blood pressure.

Beta-selective agonists

Beta-selective agonists have an additional advantage of bronchodilator and mucociliary clearance effect. Right heart catheterization has been recommended during initial administration of vasodilators to objectively assess the efficacy and detect the possible adverse hemodynamic consequences of vasodilators.

The Food and Drug Administration (FDA) has approved epoprostenol, treprostinil, bosentan, and iloprost for treatment of primary pulmonary hypertension. Epoprostenol, treprostinil, and iloprost are prostacyclin (PGI2)

analogues and have potent vasodilatory properties. Epoprostenol and treprostinil are administered intravenously and iloprost is an inhaler. Bosentan is a mixed endothelin-A and endothelin-B receptor antagonist indicated for pulmonary arterial hypertension (PAH), including primary pulmonary hypertension (PPH). In clinical trials, it improved exercise capacity, decreased rate of clinical deterioration, and improved hemodynamics.

The PDE5 inhibitor sildenafil has also been intensively studied and approved by the FDA for treatment of pulmonary hypertension based on a large randomized study. Sildenafil promotes selective smooth muscle relaxation in lung vasculature.

Not enough data are available regarding the efficacy of these drugs in patients with secondary pulmonary hypertension such as in patients with COPD.

Cardiac glycosides

The use of cardiac glycosides, such as digitalis, in patients with cor pulmonale has been controversial, and the beneficial effect of these drugs is not as obvious as in the setting of left heart failure. Nevertheless, studies have confirmed a modest effect of digitalis on the failing right ventricle in patients with chronic cor pulmonale. It must be used cautiously, however, and should not be used during the acute phases of respiratory insufficiency when large fluctuations in levels of hypoxia and acidosis may occur. Patients with hypoxemia or acidosis are at increased risk of developing arrhythmias due to digitalis through different mechanisms including sympathoadrenal stimulation.

Theophylline

In addition to bronchodilatory effect, theophylline has been reported to reduce pulmonary vascular resistance and pulmonary arterial pressures acutely in patients with chronic cor pulmonale secondary to COPD. Theophylline has a weak inotropic effect and thus may improve right and left ventricular ejection. As a result, considering the use of theophylline as adjunctive therapy in the management of chronic or decompensated cor pulmonale is reasonable in patients with underlying COPD.

Warfarin

Anticoagulation with warfarin is recommended in patients at high risk for thromboembolism. The beneficial role of anticoagulation in improving the symptoms and mortality in patients with primary pulmonary arterial hypertension clearly was demonstrated in a variety of clinical trials. The evidence of benefit, however, has not been established in patients with secondary pulmonary arterial hypertension. Therefore, anticoagulation therapy may be used in patients with cor pulmonale secondary to thromboembolic phenomena and with underlying primary pulmonary arterial hypertension.

Surgical Care

Phlebotomy is indicated in patients with chronic cor pulmonale and chronic hypoxia causing severe polycythemia, defined as hematocrit of 65 or more. Phlebotomy results in a decrease in mean pulmonary artery pressure, a decrease in mean pulmonary vascular resistance, and an improvement in exercise performance in such patients. However, no evidence suggests improvement in survival. Generally, phlebotomy should be reserved as an adjunctive therapy for patients with acute decompensation of cor pulmonale and patients who remain significantly polycythemic despite appropriate long-term oxygen therapy. Replacement of the acute volume loss with a saline infusion may be necessary to avoid important decreases in systemic blood pressure.

No surgical treatment exists for most diseases that cause chronic cor pulmonale. Pulmonary embolectomy is efficacious for unresolved pulmonary emboli, which contribute to pulmonary hypertension. Uvulopalatopharyngoplasty in selected patients with sleep apnea and hypoventilation may relieve cor pulmonale. Single-lung, double-lung, and heart-lung transplantation are all used to salvage the terminal phases of several diseases (eg, primary pulmonary hypertension, emphysema, idiopathic pulmonary fibrosis, cystic fibrosis) complicated by cor pulmonale. Apparently, lung transplantation will lead to a reversal of right ventricular dysfunction from the chronic stress of pulmonary

hypertension. However, strict selection criteria for lung transplant recipients must be met because of the limited availability of organ donors.

Diuretics are used to decrease the elevated right ventricular filling volume in patients with chronic cor pulmonale. Calcium channel blockers are pulmonary artery vasodilators that have proven efficacy in the long-term management of chronic cor pulmonale secondary to primary pulmonary arterial hypertension. New FDA-approved prostacyclin analogues and endothelin-receptor antagonists are available for treatment of PPH. The beneficial role of cardiac glycosides, namely digitalis, on the failing right ventricle are somewhat controversial; they can improve right ventricular function but must be used with caution and should be avoided during acute episodes of hypoxia.

In the management of cor pulmonale, the main indication for oral anticoagulants is in the setting of an underlying thromboembolic event or primary pulmonary arterial hypertension. Methylxanthines, like theophylline, can be used as an adjunctive treatment for chronic cor pulmonale secondary to COPD. Besides the moderate bronchodilatory effect of methylxanthine, it improves myocardial contractility, causes mild pulmonary vasodilatory effect, and enhances the diaphragmatic contractility.

Further Inpatient Care

Appropriate treatment is directed both at the underlying etiology and at correction of hypoxia when present.

Further Outpatient Care

Patients with cor pulmonale generally require close attention in the outpatient setting.

Regular assessment of oxygen needs and pulmonary function are appropriate.

Many patients benefit from a formal program of pulmonary rehabilitation.

Complications

Complications of cor pulmonale include syncope, hypoxia, pedal edema, passive hepatic congestion, and death.

Prognosis

The prognosis of cor pulmonale is variable depending upon underlying pathology. Patients with cor pulmonale due to COPD have a high 2-year mortality.

Patient Education

Patient education regarding the importance of adherence to medical therapy is vital because appropriate treatment of both hypoxia and underlying medical illness can improve mortality and morbidity.

Part 3. Pneumonias

The environment of healthcare has become increasingly competitive over the past several years. Cost containment and cost justification have become essential components in the delivery of healthcare. Formulary management has also changed. Business models are now used to determine the cost-effectiveness of treatments for specific disease states, often in lieu of a simple drug class review. Healthcare providers have the responsibility of providing appropriate treatments while managing the financial impact of those treatments. Achieving this balance can be difficult.

Anti-infective agents are often targets of formulary review because they represent a significant portion of the pharmacy budget. In recent years, many new anti-infective agents have been released on the market. These new agents have increased the antimicrobial armamentarium. However, the economic impact of many of these new agents has been astronomical. Management of an anti-infective formulary that is responsive not only to individual agent costs but also to frequency of use and resistance issues requires a thorough understanding of the available agents and their individual safety and efficacy profiles.

Infectious diseases contribute to significant patient morbidity and mortality. Pneumonia is the sixth leading cause of death in the United States. In hospitalized patients, death rates as high as 25% have been reported. In the long-term care setting, infection of the respiratory tract is the leading cause of hospitalization and mortality. More than half of patients hospitalized with a diagnosis of pneumonia

are elderly. These elderly patients are at high risk of mortality related to pneumonia for several years following an initial episode of pneumonia.

Diagnosis and Treatment of Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) is defined as pneumonia not acquired in a hospital or a long-term care facility. Despite the availability of potent new antimicrobials and effective vaccines, an estimated 5.6 million cases of CAP occur annually in the United States. The estimated total annual cost of health care for CAP in the United States is $8.4 billion.

Epidemiology

The epidemiology of CAP is unclear because few population-based statistics on the condition alone are available. The Centers for Disease Control and Prevention (CDC) combines pneumonia with influenza when collecting data on morbidity and mortality, although they do not combine them when collecting hospital discharge data. In 2018, influenza and pneumonia combined were the seventh leading causes of death in the United States, down from sixth in previous years, and represented an age-adjusted death rate of 21.8 per 100,000 patients. Death rates from CAP increase with the presence of comorbidity and increased age; the condition affects persons of any race or sex equally. The decrease in death rates from pneumonia and influenza are largely attributed to vaccines for vulnerable populations (e.g., older and immunocompromised persons). Nowadays, COVID-19 is the most important etiology factor contributing moderate-to-severe pneumonia worldwide.

Severity of Illness

Fine and associates published criteria in 1997 that can be used to classify the risk levels of patients with CAP. The criteria include an evaluation of patient demographics, comorbidities, physical examination findings, and laboratory findings. The criteria help identify CAP patients at low risk for death and other adverse outcomes. Use of these criteria can help physicians determine which patients should be admitted to the hospital for the management of their illness. With this prediction rule, a point scoring system is used to determine a patient's

risk classification. The scoring system uses 20 different factors in the scoring Pneumonia causes significant morbidity and mortality at the extremes of the age spectrum. The very old and the very young are the patient subgroups most likely to experience complications related to CAP. Criteria of severity accordingly PORT system is presented at schema 2.

Clinical Presentation

Pneumonia is an inflammation or infection of the lungs that causes them to function abnormally. Pneumonia can be classified as typical or atypical, although the clinical presentations are often similar. Several symptoms commonly present in patients with pneumonia.

Pathogens

Types of cap

Typical pneumonia usually is caused by bacteria such as Streptococcus pneumoniae. Atypical pneumonia usually is caused by the influenza virus, mycoplasma, chlamydia, legionella, adenovirus, or other unidentified microorganism. The patient's age is the main differentiating factor between typical and atypical pneumonia; young adults are more prone to atypical causes, and very young and older persons are more predisposed to typical causes.

Schema 2.

Pneumonia Severity Index

Patient Characteristics	*Points*
Demographics	
Male	Age (years)
Female	Age (years) – 10
Nursing home resident	+ 10
Comorbid illness	
Neoplastic disease	+ 30
Liver disease	+ 20
Congestive heart failure	+ 10
Cerebrovascular disease	+ 10
Renal disease	+ 10
Physical examination findings	
Altered mental status	+ 20
Respiratory rate > 30 breaths per minute	+ 20
Systolic blood pressure < 90 mm Hg	+ 20
Temperature < 35°C (95°F) or > 40°C (104°F)	+ 15
Pulse rate > 125 beats per minute	+ 10
Laboratory and radiographic findings	
Arterial pH < 7.35	+ 30
Blood urea nitrogen > 64 mg per dL (22.85 mmol per L)	+ 20
Sodium < 130 mEq per L (130 mmol per L)	+ 20
Glucose > 250 mg per dL (13.87 mmol per L)	+ 10
Hematocrit < 30 percent	+ 10
Partial pressure of arterial oxygen < 60 mm Hg or oxygen percent saturation < 90 percent	+ 10
Pleural effusion	+ 10

Pathogenesis of pneumonia

Pathogenesis of pneumonia is presented at Schema 3. Bacteria can invade the lower respiratory tract by aspiration of oropharyngeal organisms, inhalation of aerosols containing bacteria, or, less frequently, by hematogenous spread from a distant body site. In addition, bacterial translocation from the gastrointestinal tract has been hypothesized recently as a mechanism for infection. Of these routes, aspiration is believed to be the most important for both nosocomial and community-acquired pneumonia. In radioisotope-tracer studies, 45% of healthy adults were found to aspirate during sleep. Persons who swallow abnormally (e.g., those who have depressed consciousness, respiratory tract instrumentation and/or mechanically assisted ventilation, or gastrointestinal tract instrumentation or diseases) or who have just undergone surgery are particularly likely to aspirate. The high incidence of gram-negative bacillary pneumonia in hospitalized patients might result from factors that promote colonization of the pharynx by gram-

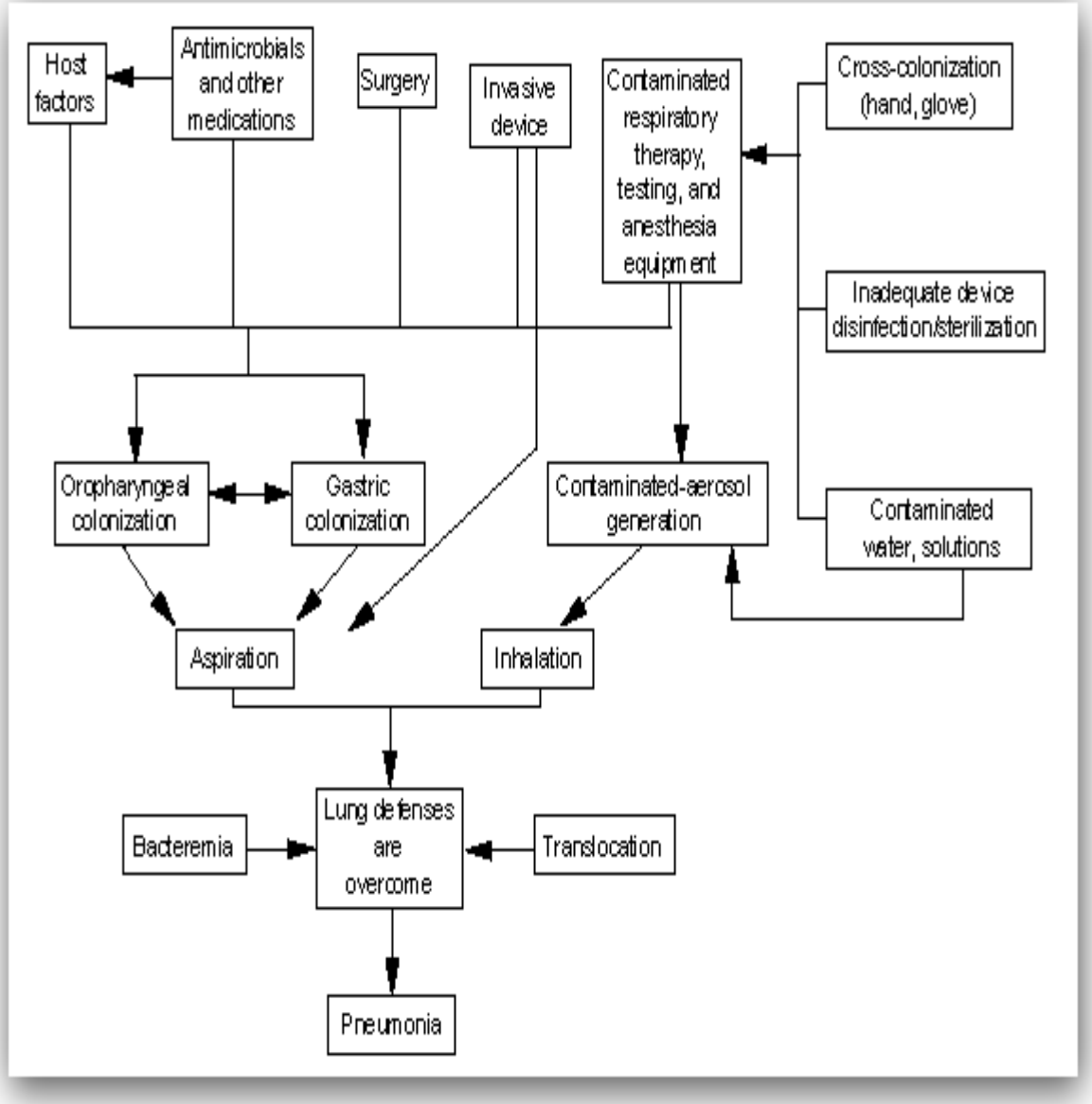
negative bacilli and the subsequent entry of these organisms into the lower respiratory tract. Although aerobic gram-negative bacilli are recovered infrequently or are found in low numbers in pharyngeal cultures of healthy persons, the likelihood of colonization substantially increases in comatose patients, in patients treated with antimicrobial agents, and in patients who have hypotension, acidosis, azotemia, alcoholism, diabetes mellitus, leukocytosis, leukopenia, pulmonary disease, or nasogastric or endotracheal tubes in place. Oropharyngeal or tracheobronchial colonization by gram-negative bacilli begins with the adherence of the microorganisms to the host's epithelial cells. Adherence may be affected by multiple factors associated with the bacteria (e.g., presence of pili, cilia, capsule, or production of elastase or mucinase), host cell (e.g., surface proteins and polysaccharides), and environment (e.g., pH and presence of mucin in respiratory secretions). Although the exact interactions between these factors have not been fully elucidated, studies indicate that certain substances (e.g., fibronectin) can inhibit the adherence of gram-negative bacilli to host cells. Conversely, certain conditions (e.g., malnutrition, severe illness, or postoperative state) can increase adherence of gram-negative bacteria. The stomach also might be an important reservoir of organisms that cause nosocomial pneumonia. The role of the stomach as such a reservoir might differ depending on the patient's underlying conditions and on prophylactic or therapeutic interventions. In healthy persons, few bacteria entering the stomach survive in the presence of hydrochloric acid at pH less than 2. However, when gastric pH increases from the normal levels to greater than or equal to 4, microorganisms are able to multiply to high concentrations in the stomach. This can occur in elderly patients; in patients who have achlorhydria, ileus, or upper gastrointestinal disease; and in patients receiving enteral feeding, antacids, or histamine-2 {H-2} antagonists. Other factors (e.g., duodeno-gastric reflux and the presence of bile) may contribute to gastric colonization in patients who have impaired intestinal motility; these other factors need further investigation. Bacteria also can enter the lower respiratory tract of hospitalized patients through inhalation of aerosols generated primarily by contaminated

respiratory-therapy or anesthesia-breathing equipment. Outbreaks related to the use of respiratory-therapy equipment have been associated with contaminated nebulizers, which are humidification devices that produce large amounts of aerosol droplets less than 4 um via ultrasound, spinning disk, or the Venturi mechanism. When the fluid in the reservoir of a nebulizer becomes contaminated with bacteria, the aerosol produced may contain high concentrations of bacteria that can be deposited deep in the patient's lower respiratory tract. Contaminated aerosol inhalation is particularly hazardous for intubated patients because endotracheal and tracheal tubes provide direct access to the lower respiratory tract. In contrast to nebulizers, bubble-through or wick humidifiers primarily increase the water-vapor (or molecular-water) content of inspired gases. Although heated bubble-through humidifiers generate aerosol droplets, they do so in quantities that may not be clinically important; wick humidifiers do not generate aerosols.

Bacterial pneumonia has resulted, in rare instances, from hematogenous spread of infection to the lung from another infection site (e.g., pneumonia resulting from purulent phlebitis or right-sided endocarditis). Another mechanism, translocation of viable bacteria from the lumen of the gastrointestinal tract through epithelial mucosa to the mesenteric lymph nodes and to the lung, has been demonstrated in animal models. Translocation is postulated to occur in patients with immunosuppression, cancer, or burns; however, data are insufficient to describe this mechanism in humans.

Schema 3

Pathogenesis of pneumonia



Symptoms

Common clinical symptoms of CAP include cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain. Depending on the pathogen, a patient's cough may be persistent and dry, or it may produce sputum. Other presentations may include headache and myalgia. Certain etiologies, such as legionella, also may produce gastrointestinal symptoms.

Diagnosis

Physical examination

Physical examination may reveal dullness to percussion of the chest, crackles or rales on auscultation, bronchial breath sounds, tactile fremitus, and

egophony ("E" to "A" changes). The patient also may be tachypneic. A prospective study showed that patients with typical pneumonia were more likely than not to present with dyspnea and bronchial breath sounds on auscultation.

Radiography

Chest radiography (posteroanterior and lateral views) has been shown to be a critical component in diagnosing pneumonia. According to the latest American Thoracic Society (ATS) guidelines for the diagnosis and treatment of adults with CAP, "all patients with suspected CAP should have a chest radiograph to establish the diagnosis and identify complications (pleural effusion, multilobar disease)." Chest radiography may reveal a lobar consolidation, which is common in typical pneumonia; or it could show bilateral, more diffuse infiltrates than those commonly seen in atypical pneumonia. However, chest radiography performed early in the course of the disease could be negative.

Laboratory tests

Historically, common laboratory tests for pneumonia have included leukocyte count, sputum Gram stain, two sets of blood cultures, and urine antigens. However, the validity of these tests has recently been questioned after low positive culture rates were found (e.g., culture isolates of S. pneumoniae were present in only 40 to 50 percent of cases). Such low positive culture rates are likely due to problems with retrieving samples from the lower respiratory tract, previous administration of antibiotics, contamination from the upper airways, faulty separation of sputum from saliva when streaking slides or plates, or viral etiology. Furthermore, sputum samples are adequate in only 52.3 percent of patients with CAP, and only 44 percent of those samples contain pathogens. Nonetheless, initial therapy often is guided by the assumption that the presenting disease is caused by a common bacterial pathogen.

Findings also cast doubt on the clinical utility of obtaining blood cultures from patients with suspected CAP. In a study of CAP cases in Canadian hospitals over a six-month period, positive blood cultures were obtained in only 5.2 to 6.2 percent of patients, including those with the most severe disease. Based on these

findings, other researchers concluded that a positive blood culture had no correlation with the severity of the illness or outcome. Another prospective study showed that blood cultures were positive in only 10.5 percent of patients with pneumonia. Despite these and other research findings, current ATS guidelines recommend that patients hospitalized for suspected CAP receive two sets of blood cultures. Blood cultures, however, are not necessary for outpatient diagnosis.

Legionella antigens were found in the urine of 48 percent of patients with suspected Legionella pneumophila serogroup 1 infection.

Treatment

Initial treatment of CAP is based on physical examination findings, laboratory results, and patient characteristics (e.g., age, chronic illnesses, history of smoking, history of the illness). Physicians should begin their treatment decisions by assessing the need for hospitalization using a prediction tool for increased mortality, such as the Pneumonia Severity Index, combined with clinical judgment

Outpatient vs. inpatient treatment

Choosing between outpatient and inpatient treatment is a crucial decision because of the possible risk of death. This decision not only influences diagnostic testing and medication choices, it can have a psychological impact on patients and their families. On average, the estimated cost for inpatient care of patients with CAP is $7,500. Outpatient care can cost as little as $150 to $350. Hospitalization of a patient should depend on patient age, comorbidities, and the severity of the presenting disease.

Physicians tend to overestimate a patient's risk of death; therefore, many low-risk patients who could be safely treated as outpatients are admitted for more costly inpatient care. The Pneumonia Severity Index was developed to assist physicians in identifying patients at a higher risk of complications and who are more likely to benefit from hospitalization. Investigators developed a risk model based on a prospective cohort study of 2,287 patients with CAP in Pittsburgh, Boston, and Halifax, Nova Scotia. By using the model, the authors found that 26 to 31 percent of the hospitalized patients were good outpatient candidates, and an

additional 13 to 19 percent only needed brief hospital observation. They validated this model using data from more than 50,000 patients with CAP in 275 U.S. and Canadian hospitals. Although the Pneumonia Severity Index can serve as a general guideline for management, clinical judgment should always supersede the prognostic score.

Pharmacotherapy

The primary goals of pharmacotherapy for patients with CAP include eradicating the causative pathogens, resolving the clinical signs and symptoms, minimizing hospitalization, and preventing reinfection. Physicians should choose a medication based on the pharmacokinetic profile, adverse reactions, drug interactions, and cost-effectiveness. Further, patient evaluation should focus on severity of illness, patient age, comorbidities, clinical presentation, epidemiologic setting, and previous exposure. The majority of patients with CAP are treated empirically based on the most common pathogen(s) associated with the condition.

Consensus guidelines from ATS, Infectious Diseases Society of America, and Canadian Guidelines for the Initial Management of Community-Acquired Pneumonia recommend initial empiric therapy with macrolides, fluoroquinolones, or doxycycline (Vibramycin). A fourth guideline developed by the Therapeutic Working Group of the CDC, however, recommends using fluoroquinolones sparingly because of resistance concerns.

Although data are limited on duration of CAP therapy, current research30 recommends seven to 10 days of therapy for S. pneumoniae and 10 to 14 days of therapy for Mycoplasma pneumoniae and Chlamydia pneumoniae. After a hospitalized patient is clinically stable (i.e., temperature less than 37.8° C [100.0° F], pulse under 100 beats per minute, respiratory rate below 24 breaths per minute, systolic blood pressure above 90 mm Hg, and blood oxygen saturation over 90 percent) and able to tolerate oral intake, the patient may be treated with oral antibiotics for the remainder of the therapy course. This can save money and allow for earlier hospital discharge, which minimizes a patient's risk of hospital-acquired infection.

Pneumococcal Resistance

S. pneumoniae, which accounts for 60 to 70 percent of all bacterial CAP cases, can affect all patient groups and can cause a fatal form of CAP. The alarming rate of resistance to many commonly used antibiotics raises great concern. Penicillin-resistant S. pneumoniae was uncommon in the early 1990s but has since become increasingly prevalent.

Resistant strains are classified as having intermediate or high-level resistance. Surveillance data in the United States30 revealed that, overall, pneumococcal strains had a 28 percent immediate resistance rate and a 16 percent high-level resistance rate. Decreased susceptibility to other commonly used antibiotics has also been observed. The clinical importance of these data is questionable because recruiting patients infected with resistant pathogens for clinical trials is difficult. Furthermore, available outcomes on the treatment of pneumonia caused by resistant pneumococcal strains are conflicting.

The CDC and others recommend outpatient oral empirical antibiotics with a macrolide, doxycycline, or an oral beta-lactam (amoxicillin, cefuroxime [Ceftin], or amoxicillin/clavulanate [Augmentin]) or inpatient treatment with an intravenous beta-lactam (cefuroxime, ceftriaxone [Rocephin], cefotaxime [Claforan]) or a combination of ampicillin/sulbactam (Unasyn) with a macrolide. Conservative use of new fluoroquinolones (levofloxacin [Levaquin], gatifloxacin [Tequin], moxifloxacin [Avelox]) also is recommended to minimize resistance patterns. The new fluoroquinolones (minimum inhibitory concentration: 4 mcg per mL or greater) should be used only when patients have failed recommended first-line regimens, are allergic to alternative agents, or have a documented infection with highly drug-resistant pneumococci such as those resistant to penicillin.

Cost of Antimicrobial Therapy

Economic pressures have accentuated the focus on reducing health care costs and utilizing resources while maintaining or improving quality of care. These pressures are exacerbated by the growing resistance of S. pneumoniae to penicillin.

This pattern of resistance increases the cost of treatment because of prolonged hospitalization, relapses, and the use of more expensive antibacterial agents.

Reducing costs

Numerous methods for reducing costs when treating patients with bacterial infections can be applied to CAP. Choosing monotherapy instead of combination therapy reduces costs associated with administering an antibacterial. Using agents with longer half-lives allows for once-daily administration, which in turn leads to improved compliance and outcomes and decreased costs. In addition, transitioning patients to oral therapy as soon as they are clinically stable can significantly reduce the length of hospitalization-the major contributing factor to health care costs.

Cost-effective care

When choosing a treatment, it is essential to compare costs and outcomes of all recommended drug therapies. Table 66 includes the costs of and common adverse reactions to antimicrobial therapies for CAP.

The goal of a formal pharmacoeconomic assessment is to enhance overall patient care using available resources. The evaluation should lead to a decision that will maximize the value of health care services, not simply reduce the costs of drug therapy. For instance, a particular drug may be more expensive, but it may also be more effective, thus lowering overall costs. Another drug may have a higher rate of treatment failures, creating added costs associated with managing the failures. The overall cost of each therapy should be obtained by comparing the end cost with the probability of achieving a positive outcome. Depending on the relative costs associated with treatment failures compared with the costs of cures, the decision to choose one agent over another may change.

The best way to apply cost-saving approaches to the treatment of patients with CAP is by using a clinical pathway. This is a method of facilitating multidisciplinary patient care by moving processes of care sequentially through various stages, within specified time frames, toward a desired outcome. These pathways should be specific to each institution, taking into account resistance rates

in the community and encouraging the use of the most active, cost-effective agents to produce rapid, positive clinical outcomes.

Ventilator-associated pneumonia

Ventilator-associated pneumonia has a high mortality rate (up to 40%) and has serious complications, such as Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI). In patients on mechanical ventilation the cumulative risk of pneumonia increases with the duration of ventilation.

Risk factors for ventilator-associated pneumonias include pre-existing sinusitis and the administration of paralytic agents but the presence of an endotracheal tube is potentially a contributor. Macro- or micro-aspiration of the oropharyngeal or gastric contents into the lower respiratory tract can occur via the outside of the endotracheal tube; another possible route of infection could be by inhalation of infective particles dislodged from the inside of the endotracheal tube.

Many species, including Pseudomonas aeruginosa and Staphylococcus aureus, produce biofilms, which surround the organisms when attached to endotracheal tubes, and make them relatively resistant to the actions of antibiotics and host defences. The surviving organisms may play a role in relapses by shedding infective particles from the endotracheal tube into the lower respiratory tract.

Aetiology of ventilator-associated pneumonia

- Several factors affect the aetiology of ventilator-associated pneumonia:
- Time of onset after hospitalisation
- Stress-induced flora change
- Antibiotic-induced flora changes
- Exposure to contamination with nosocomial pathogens

Patient interventions.

Certain patient characteristics indicate possible pathogens: Haemophilus influenzae is more common in patients with chronic lung disease, and

Staphylococcus aureus is seen more often in the elderly, diabetics and patients with renal failure as well as following head injury, neurosurgery or recent influenza.

Acute lung injury can be complicated by or can result from ventilator-acquired pneumonia.

Diagnosis of ventilator-associated pneumonia

Clinical

Pneumonia is difficult to diagnose in mechanically ventilated patients, because many of the diagnostic criteria for pneumonia in non-ventilated patients are not specific to infection in mechanically ventilated patients and may be associated with non-infective disorders such as acute lung injury. Factors complicating diagnosis include:

Lack of respiratory symptoms in sedated patients on mechanical ventilation

The isolation of potential pathogens from endotracheal secretions does not necessarily reflect the flora of the lower respiratory tract. A number of attempts have been made to develop diagnostic techniques to improve the specificity of the diagnosis, including invasive bronchoscopic techniques, but this has not yet been reliably achieved. Therefore, the diagnosis of ventilator-associated pneumonia is still based on a combination of radiological and clinical criteria.

Management of ventilator-associated pneumonia

- Early recognition and appropriate management of ventilator-associated pneumonia reduces the incidence of complications such as acute lung injury, multiple organ dysfunction and respiratory decompensation.
- Empirical therapy should be started as a matter of urgency if infection is identified.
- Unnecessary delay in antibiotic therapy leads to adverse outcomes, particularly if the patient is septic.

However, antibiotic therapy for non-infective syndromes is also detrimental. It is important to balance the risks and benefits of treatment and this is a matter for individual clinical judgement. Consult your microbiologist and ITU consultant.

Antibiotic rationale

Empirical therapy will usually take into account:

- Time of onset of illness (<5 vs. ³5 days after admission) and therefore probable pathogens.
- Previous antibiotic administration (rates of Pseudomonas aeruginosa or Acinetobacter spp. infection increase significantly in patients treated with antibiotics within 10 days before the onset of pneumonia).

Severity and speed of progression of the illness

Local pathogens and resistance patterns

Other patient-related factors such as renal or hepatic impairment.

Therapy should be broad-spectrum, and have high activity against the probable pathogens. In patients previously untreated with antibiotics the predominant pathogens are Gram-positive cocci in 'early' infections and aerobic Gram-negative bacilli in 'late' infections. There are some data to suggest that monotherapy may be as effective as combination therapy in severe ventilator-associated pneumonia. However, there is considerable debate about the merits of monotherapy in these patients largely because of some limitations in the data, particularly the range of infections included in the trials, the sample sizes and the use of sub-optimal doses of aminoglycosides. Combination therapy has the advantage of giving cover against a broader-spectrum of organisms and some combinations have a synergistic mechanism of action which reduces the potential for resistance developing during treatment, eg. an aminoglycoside with a beta-lactam. Pseudomonas aeruginosa has been associated with resistance developing during the course of treatment and therefore if pseudomonal involvement is suspected, vigorous anti-pseudomonal therapy is indicated.

Empirical therapy

Given that there is minimal margin for error in seriously ill patients, it would be prudent to use empirical combination therapy. Factors to be considered include:
Previous antibiotic therapy
Known prevalence and resistance patterns

Patient condition.

As many second and third-line antimicrobials are associated with side-effects, a careful risk–benefit analysis must be made. Because the process for choosing appropriate antibiotics is multifactorial, consult local guidelines and the local microbiologist.

Consult expert opinion in these infections.

If a satisfactory clinical response is observed with combination therapy after 3–4 days, monotherapy can be considered and the aminoglycoside withdrawn.

The optimal treatment duration has not been established in ventilator-associated pneumonia. Most studies report treatment durations of 7–10 days, although shorter courses may be effective.If aspiration pneumonia is suspected, the regimen should be active against anaerobes.

Antibiotic prophylaxis for ventilator-associated pneumonia

The use of antibiotics to prevent respiratory tract infections in ventilated patients has been reviewed and is controversial. If considered, this ought to be discussed between the ITU Consultant and the Medical Microbiologist on an individual patient basis.

Nosocomial Pneumonia

Pathogenesis of Nosocomial Pneumonia

It is assumed that most episodes of nosocomial and ventilator-associated pneumonia are caused by micro-aspiration of oral and pharyngeal content. The oral

cavity is increasingly recognized as a reservoir of potentially pathogenic MDR organisms. In patients with poor oral hygiene, a microbial cause of VAP could be traced back to dental plaque harbouring pathogens such as S. aureus, Gram-negative enteric bacilli and P. aeruginosa. Applying gingival and dental plaque antiseptic decontamination decreased oropharyngeal colonization in ventilated patients, although this did not reduce the incidence of pneumonia nor eradicate highly resistant organisms. Apart from endogenous reservoirs, exogenous transmission can serve as a route for acquisition of MDR pathogens, as shown by the simultaneous isolation of the same P. aeruginosa pulsotypes in stomach cultures and tap water in a Spanish study. A third route of acquisition of bacterial pathogens at the ICU is patient-to-patient transmission, which is probably rather limited when standard hand hygiene precautions are applied

Diagnosis of Nosocomial Pneumonia

Approaches to diagnosis of nosocomial pneumonia are variable, which is mainly due to the lack of a uniformly accepted gold standard and, consequently, to differences in medical culture or belief between ICUs and countries. To illustrate this, invasive microbiological sampling, more precisely the use of quantitative culturing of BAL fluid in clinically suspected VAP was performed in only half of 29 inquired ICUs in Germany. A similar but larger survey in 395 French ICUs found a 90% use of quantitative culture techniques, and a 60% use of bronchoscopical sampling.] A wide divergence in practice of bronchoscopy in pneumonia in ICU patients (including both community-acquired and nosocomial pneumonia) was also observed in Australian and New Zealand ICUs, which did not translate in outcome differences.

Although a clinical diagnosis of VAP is unreliable and suffers from a lack of specificity, with unnecessary antibiotic treatment as a potential hazardous consequence, a clinical estimation of the probability of pneumonia remains essential in the interpretation of microbiological results. In a small prospective study in patients with prolonged mechanical ventilation but otherwise being stable

without antibiotic therapy, bacterial growth in respiratory samples often exceeded the commonly accepted threshold of 104 CFU/ml for diagnosing VAP.] On the other hand, quantitative cultures probably have a lower sensitivity for diagnosis of VAP as compared with qualitative cultures, and a study in trauma patients suggests that the quantitative culturing threshold for diagnosing VAP should depend on severity of injury and the type of pathogen recovered. Invasive and quantitative microbiological investigation is probably also prone to sampling variability, as the return in instilled BAL saline and hence dilution of the sample may influence bacterial counts of BAL fluid culture, and as bilateral blind or bronchoscopically guided sampling may yield different results compared with unilateral blind sampling.

This continuing pro-con debate over whether, and which, invasive techniques should be used for diagnosing VAP was partially concluded by the recent meta-analysis of four randomized controlled trials which could not identify a survival benefit associated with the use of invasive techniques. In the updated ATS-IDSA guidelines, both invasive (i.e. bronchoscopical) and non-invasive sampling, and both quantitative and semiquantitative culturing techniques were considered acceptable to establish a microbiological diagnosis. In conclusion, both clinical and microbiological data should be integrated in a holistic diagnostic approach to nosocomial pneumonia. New and promising biomarkers of pneumonia, such as soluble TREM-1, will undoubtedly increase the discriminative power of diagnostic strategies in VAP but should again preferably be used within this clinical-microbiological framework, and not as a single test

Treatment

Treatment of nosocomial pneumonia is complicated by the frequent involvement of potentially multi-drug resistant (MDR) organisms. Antibiotic exposure and a hospital stay of more than a week are well established risk factors for infection with these organisms. Interestingly, a similarly dichotomized risk pattern for the cause of multi-drug resistance was found in a study of nursing-home acquired pneumonia (which is now firmly included in the spectrum of nosocomial

pneumonia): risk factors for MDR organisms were prior antibiotic exposure and the Activity of Daily Living score as a marker of dependency. In early nosocomial pneumonia, community-acquired organisms such as Streptococcus pneumoniae, Mycoplasma pneumoniae and Chlamydia pneumoniae are prevalent. On the other hand, depending on locally prevailing microbial ecology, MDR organisms, such as methicillin-resistant Staphylococcus aureus and resistant Pseudomonas aeruginosa, may be involved in early VAP. Patients admitted from long-term care facilities should be suspected of harbouring potentially MDR organisms, especially when previously exposed to antibiotics. Legionella spp. is a significant cause of nosocomial pneumonia in acute care hospitals and probably also in long-term care facilities. The role of viruses is difficult to ascertain in nosocomial pneumonia but is probably limited. Herpes simplex virus (HSV) was found in lower respiratory tract specimens of a high proportion of ventilated patients: this occurred mostly in the patients with severe illness and probably represented reactivation due to immune suppression. Although the patients with HSV infection fared worse, it is unclear whether HSV contributed to this deterioration. Similarly, cytomegalic virus reactivation with antigenemia was found in 17% of critically ill patients with persisting fever and negative bacteriological cultures. Finally, a recent study identified presence of adenovirus in bronchoalveolar lavage (BAL) fluid of 50 patients without clinical viral illness; again viral load was higher in immunosuppressed patients. To a certain extent, viral replication or reactivation may be a marker of immunosuppression rather than a true pathogen of pneumonia. Fungal infections are generally omitted from studies dealing with nosocomial pneumonia. Yet, invasive aspergillosis is increasingly recognized in ICU patients without apparent immune deficiency and often manifests itself as pulmonary disease. Candida spp. on the other hand is frequently found in respiratory samples of ICU patients but is probably very rarely the cause of pneumonia; hence, isolation of Candida in airway samples represents colonization in most cases. Highly variable practice regarding Candida management in general ICU patients reflects the uncertainty about its clinical significance in airway specimens.

Interestingly, in a recent autopsy series of bone marrow transplant patients, a population at the highest risk of invasive fungal disease, Candida bronchopneumonia was diagnosed in only one patient.

The diagnosis of nosocomial pneumonia remains challenging and should be made by a careful clinical assessment combined with a critical evaluation of microbiological results; the integration of clinical probability and microbiological data is more important than the choice of technique for obtaining and respectively culturing respiratory samples, as each of these techniques has intrinsic limitations. A high suspicion of nosocomial pneumonia should lead to immediate antibiotic therapy likely to cover the offending pathogen. When clinical risk factors for multi-drug resistance cause are present or when MDR pathogens are endemic, the spectrum of the empirical antibiotic therapy should be broadened to include these likely pathogens. Microbiological data should be integrated to guide this initial therapy, firstly by adapting empirical therapy to local ecology and resistance patterns, and secondly by tailoring this therapy to the individual colonization status in selected patients at high risk for MDR organism infection. Downgrading initial antibiotic therapy to the narrowest spectrum possible once the microbial cause is identified should be aimed at as much as possible. In patients failing to improve after several days of antibiotic therapy, efforts should be made to try to discriminate between clinical failure due to inappropriately chosen or inadequately dosed antibiotics, persistent ARDS or an alternative diagnosis.

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