Chest Medicine

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This article discusses recent guidelines and management of common respiratory conditions and reviews key papers published over the past five years.

Asthma

The incidence and prevalence of this common chronic condition has risen over the past few decades both in developed and developing countries. Acute asthma is responsible for 1000 deaths a year in the United Kingdom.

ß-agonists and oral or parenteral corticosteroids remain the main drugs used in acute attacks. Guidelines recommend treatment with ipratropium and aminophylline in cases that do not respond to first-line treatment.[1]

Magnesium has been shown to have a bronchodilatory effect in patients with asthma. Trials have revealed variable results and further data will be more helpful to determine its role. Nonetheless, it has been recommended in patients with acute asthma and a severely reduced FEV1 who have not responded to conventional treatment.[1] It may be given as an intravenous infusion of magnesium sulphate at a dose of 1.2-2g over twenty minutes.[2]

The role of newer drugs, such as leukotriene receptor antagonists is being studied. Studies have shown that when intravenous monteleukast in the 7 or 14 mg dose was given with standard treatment, there was a more rapid recovery in FEV1 over a two hour period as compared to placebo. Zafirlukast reduced the risk of relapse over a one month period when given together with standard treatment. It must be noted that ipratropium was not included as part of the standard treatment. Further data are needed before either of these agents can be included in the guidelines.[1]

Inhaled corticosteroids have become standard treatment for the control of chronic asthma. The dose response curve for the effect of inhaled corticosteroids on lung function becomes flat only at moderate doses, thus showing that higher doses worsen the overall therapeutic ratio. This has led to the use of lower doses of inhaled steroids together with inhaled long-acting ß-2 agonists. The addition of the latter has been found to be more effective in the control of mild, moderate and severe asthma rather than increasing the dose of inhaled corticosteroid. This also leads to a decrease in local and systemic side effects associated with steroid treatment.[1]

Leukotriene receptor antagonists have been recommended in the UK asthma guidelines for those patients who despite treatment with both inhaled corticosteroids and long acting ß-2 agonists, remain symptomatic (Step 4).[1]

The role of anti-immunoglobulin E in asthma has also been studied. The effect of a recombinant humanised monoclonal antibody, omalizumab given to 405 patients suffering from both allergic asthma and allergic rhinitis was observed in a double blind study carried out. Patients were randomly given a placebo or parenteral anti-immunoglobulin E over 24 weeks. Subjects chosen had elevated serum IgE levels and at least one positive skin-prick test. Those receiving the anti-immunoglobulin were found to have fewer exacerbations of asthma. In a separate study patients with poorly-controlled moderate to severe allergic asthma were given omalizumab at four weekly intervals for a year. Reduction in exacerbation rates and improvement in symptom scores and ventilatory function were noted in patients receiving the treatment. More studies will be required for this treatment to become standard.[1] It is important to note that this is a very expensive from of therapy costing around US$ 15,000 per patient per year.

Newer treatments may focus on the use of antibodies to interleukin 5 and 12, though as yet trials have not been very promising.[1]

Certain studies have suggested that chronic and recurrent pulmonary inflammation in asthma may lead to remodelling of the airways and irreversible airflow obstruction. In one such study carried out in the Netherlands 136 non-smoking asthma patients were enrolled. All had received long-acting inhaled bronchodilator therapy and inhaled corticosteroids for at least one year. Some were taking pulse steroid therapy and a few were on continuous oral steroid therapy for disease control. The patients were investigated using spirometry, airway responsiveness to histamine and by measuring the eosinophil count in both peripheral blood and expectorated sputum. Of these patients 48.5% were found to have persistent airflow obstruction that is a post-bronchodilator FEV1/FVC ratio less than 75% of the predicted value. Associations between persistent airflow obstruction and older age, longer duration of asthma,

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greater response to histamine and a higher eosinophil count in the sputum were noted. These patients had less exacerbations of asthma in the previous year which may suggest a decrease in disease variability with time.

This opens the debate of whether progression of asthma to irreversible airflow obstruction can be prevented or delayed by more aggressive treatment than is necessary for symptom control. Further studies are necessary to confirm this. [3,8]

Chronic obstructive pulmonary disease (COPD)

Physicians may be failing to recognize mild COPD and in certain cases even considerable lung impairment. This information was derived from the Third National Health and Nutrition Examination Survey of 20,000 US adults.

In the study airflow obstruction was defined as an FEV1/FVC ratio below the lower limit of normal. Values were matched for age. 90% of those with undiagnosed obstructive lung disease had a mild condition with the above ratio just below the lower limit of normal. In 50% of the patients with undiagnosed obstructive lung disease the FEV1 was more severely reduced, at less than 75% of the predicted value.

Undiagnosed obstructive lung disease impairs both health and function in patients. This data should raise awareness among physicians when faced with patients reporting dyspnoea or feelings of ill-health. Screening for COPD with spirometry was recommended for at risk patients, especially smokers. [4,8]

Four randomised, controlled multi-centre trials were carried out to determine the effect of inhaled steroids on disease progression in COPD. Results were similar for all trials. In one such study current or recently abstinent smokers were randomised to receive either a high dose of triamcinolone, six inhalations twice a day, or an inhaled placebo.

Inhaled steroids were not found to decrease disease progression in mild to moderate COPD, in patients who had recently stopped smoking and in smokers. They were found, however, to modestly improve symptoms of dyspnoea and decrease frequency of exacerbations. This was at the expense of steroid-induced side effects, most notably a decrease in bone density and a faster progression to osteoporosis. [5,8]

Recent guidelines from the National Institute for Clinical Excellence recommend that pulmonary rehabilitation is made available to those patients who would benefit. Pulmonary rehabilitation involves a multidisciplinary team consisting of respiratory physiotherapists, nurses, occupational therapists, a dietician, a smoking cessation adviser, a social worker, a pharmacist and a respiratory physician. Until recently the effects of early pulmonary rehabilitation had not been studied. A study carried out in a London hospital involving 42 patients has shown that early pulmonary rehabilitation after admission to hospital for acute exacerbations COPD is safe and improves the clinical outcome of patients at three months. Further studies are needed to define the long term effects of this treatment. [6]

Thromboembolic lung disease

Diagnosis of pulmonary embolism may be difficult, as clinical manifestations are often non-specific. The first methods of diagnosis were designed to confirm the presence of emboli while newer techniques focus on excluding pulmonary embolism. Various methods used to diagnose or exclude embolism include the following:

Pulmonary angiography: In a large study conducted the failure rate of this method was estimated at 0.8%. The failure rate was defined as the number of patients with symptoms of thromboembolic disease who had falsely negative results on diagnostics tests. Patients were followed up for a period of three months from the time of diagnostic testing.

Lung scintigraphy: Studies have revealed a failure rate of 0.9% for this test. Adding compression ultrasonography or impedance plethysmography to scintigraphy did not increase the accuracy of a normal perfusion scan.

D-Dimer alone or combination of D-Dimer and clinical probability: In two studies a normal D-Dimer level on ELISA (enzyme-linked immunosorbent assay) was used to exclude pulmonary embolism and was found to have a sensitivity and negative predictive value of 98% to 100%. Other studies used D-Dimer assays to exclude pulmonary embolism in patients with low or moderate clinical probability of embolism. ELISA and whole-blood agglutination assays had a sensitivity and negative predictive value of nearly 100%.

Spiral Computed Tomography and Compression Ultrasonography: The combined failure rate for these methods was found to be 1.8% in one study. This reveals newer, easier and more cost-effective methods for excluding pulmonary embolism in certain clinical situations. [7]

Pulmonary hypertension

Pulmonary hypertension is characterised by an increase in pulmonary vascular resistance and increased pulmonary arterial pressure leading to decreased exercise tolerance and right-sided heart failure. The disease can be either primary or secondary to other conditions, such as connective tissue diseases, congenital heart disease causing a left to right shunt, drugs and HIV infection. [9]

Pulmonary hypertension may be classified as follows:

- *Stage 1:* There is a raised pulmonary arterial pressure but the patient is asymptomatic (New York Heart Association stage 1).
- *Stage 2:* The patient is dyspnoeic on exertion (New York Heart Association stages 2 and 3).
- *Stage 3:* The patient is dyspnoeic at rest (New York Heart Association stage 4). [9]

The BREATHE-1 study, (Bosentan Randomised Trial of Endothelin Antagonist Therapy) analysed the effects of the endothelin-receptor antagonist bosentan on primary pulmonary hypertension and that secondary to connective tissue disease. Patients classified as stage three were enrolled in the study. These were patients who had been on more traditional treatment such as oxygen therapy, anticoagulants and calcium channel blockers. A double-blind placebo-controlled study was conducted which included 213 patients who received the placebo, 125mg bosentan bd or 250mg bosentan bd for twelve

weeks. 48 of the 213 patients received the placebo or the endothelin antagonist for a total of twenty-four weeks.

After sixteen weeks of treatment with bosentan it was noted that patients improved from stage three to stage two. Improvement lasted twenty weeks and was more marked in patients with primary pulmonary hypertension and in those who received the 250mg bd dosing of bosentan. The drug may be administered orally, contributing to easy administration, but monthly checks of liver enzymes are advised since a dose-related elevation of liver aminotransferase levels was reported. Bosentan is teratogenic and also interacts with cyclosporin. [9,10]

In another study the role of the synthetic salt of prostacyclin epoprostenol was studied. A retrospective cohort study conducted included patients with primary or secondary pulmonary hypertension who either had a 20% decrease in mean arterial pressure on acute vasodilator testing or had not responded to calcium channel blockers.

Epoprostenol was administered as an intravenous infusion to a mean dose of 23ng/kg/min at 12 months. The study included 91 patients and the average follow-up was 2.4 years. Pulmonary arterial pressure decreased by 15%, pulmonary vascular resistance decreased by 38% and cardiac output increased by 25% in the 62 patients who were followed-up. Survival rates were 79%, 70% and 59% at 1, 2 and 3 years respectively. It was also noted that patients with primary hypertension fared best while those with a connective tissue disease, older patients and those in stage 3 had a poorer response to treatment. Drawbacks of the drug include its high price and its short half-life necessitating a continuous infusion to ensure efficacy. [9,11]

Other trials conducted in Europe and the United States have studied the role of other prostacyclin analogues, including trepostinil, a subcutaneous agent, beraprost, which is orally administered, and the drug iloprost which may be given via the inhaled route. In the studies patients from both stages two and three (as classified above) were included. All were associated with clinical improvement. [9,12]

In conclusion, patients with pulmonary hypertension should be anticoagulated. Those with a vasodilatory response on vasoreactivity testing should receive a trial of calcium channel blockers, notably nifedipine or diltiazem. Those who do not respond and are in stage 1 (NYHA) may be regularly monitored. For those who are unresponsive to the older treatment and are in stage 2 (NYHA) trepostinil is indicated though bosentan may also be effective. The latter is preferred for those with class 3 (NYHA) disease except for those who are severely ill. In these patients eprostonol is indicated. The latter is also indicated in those with class 4 disease. [9,12]

Acute respiratory distress syndrome (ARDS)

A study carried out by Angus *et al* on previously healthy survivors of ARDS revealed a poor quality of life during the first year of survival and up to 50% had respiratory symptoms suggesting the presence of irreversible lung damage. The patients also complained of other symptoms, such as unexpected weakness, anxiety, depression, insomnia, cognitive impairment and a reduction in social activity. This revealed the need for counselling and neurorehabilitation in such patients. [8,13]

Treatment of latent tuberculosis

The American Thoracic Society and the Centres for Disease Control and Prevention in the United States recommend reserving tuberculin testing for patients who are at risk for developing tuberculosis and are candidates for treatment of latent infection if they test positive.

It is recommended that skin tests are interpreted at 48 to 72 hours. For high risk patients an area of induration greater than 5 mm in diameter should be considered to be a positive result, thus increasing sensitivity and specificity. High risk patients are those with HIV disease, people with recent contact with patients suffering form tuberculosis, patients with evidence of inactive TB on Chest X-ray and the immunosuppressed.

Patients at intermediate risk include recent immigrants from countries where tuberculosis is endemic, such as the African and Asian continents, intravenous drug abusers, health care workers working in areas such as the inner cities, nursing homes and prisons and patients with chronic disease, such as insulin-dependent diabetes mellitus. For these people an area of induration of 10 mm or more will give the best specificity. The authors do not recommend screening large populations, but if this were to be done an area of induration of 15 mm or more is considered to give the best specificity for low risk people.

The preferred regimen for latent tuberculosis is isoniazid daily or twice weekly for nine months. Monitoring for side effects is recommended. Those receiving the twice weekly regimen should undergo directly observed therapy. The authors allow the course of treatment to be shortened to six months should any financial difficulties or problems with access to healthcare arise.

Patients intolerant of isoniazid or who have isoniazid-resistant tuberculosis may be given rifampicin and pyrazinamide daily for two months or rifampicin alone in a once daily dose for four months. The combination of rifampicin and pyrazinamide has reportedly caused severe liver injuries and death, with patients suffering from liver disease being particularly at risk. Caution is therefore advised with the above combination.

It is also recommended that patients receiving treatment are visited monthly to reinforce compliance and check for side effects. Current guidelines recommend liver function testing prior to and during treatment in patients at risk for liver disease. Routine liver function testing and serial monitoring in asymptomatic individuals receiving therapy was deemed unnecessary.

Thus the role of the primary care physician and public health officers in the prevention of active tuberculosis is well-established. [8,14]

Sleep apnoea

The relationship between disordered sleep and blood pressure was studied further when Bixler *et al* selected 1741 men and women to undergo a medical history, physical examination,

psychometric testing and overnight polysomnography. In the study, moderate to severe sleep apnoea was defined as an apnoea-hypopnoea index of more than 15 events per hour during overnight polysomnography.

Men with moderate or severe sleep-disordered breathing were found to have a higher incidence of hypertension. The study revealed 59.3% (95% confidence limit, 44% to 73.1%) of the above to have high blood pressure compared with 25.4% (confidence limit, 21.5% to 29.7%) of men with no sleep disorder.[8, 15] It was further noted that patients with the mildest form of sleep-disordered breathing, that is snoring alone were at a higher risk of developing hypertension (odds ratio, 1.56, [confidence limit, 1.09 to 2.20])[8,15]

As sleep-disordered breathing is emerging as an independent risk factor for hypertension, researchers are trying to decipher whether the treatment of sleep apnoea decreases blood pressure. One such study was carried out by Facenda *et al* who randomly assigned 66 normotensive adults with symptomatic sleep apnoea to receive titrated continuous positive airway pressure (CPAP) or an oral placebo. It was noted that those assigned to the group receiving CPAP had a small but significant decrease in 24-hour diastolic pressure compared to the placebo group (mean [± SE]: CPAP group, 77.8 ± 1.0mm Hg; placebo group, 79.2 ±0.9 mm Hg; $P = 0.04$). The differences were greatest between 2:00 a.m. and 10:00 a.m., thus supporting the hypothesis that sleep apnoea leads to intermittent hypoxaemia and subsequent catecholamine release and an increase in blood pressure which is worse in the early hours of the morning. It must be pointed out that the study was criticised for using an oral placebo rather than a mask. The clinical significance of these observations is still unknown but it does shine further light on to the relationship between disordered sleep and blood pressure control.[8,16]

NICE guidelines for diagnosis and treatment of lung cancer

The guidelines issued by the National Institute for Clinical Excellence (NICE) are aimed at improving the survival rates among patients diagnosed with lung cancer. Survival rates in the UK are 5% lower than the European average and 7-10% lower than the United States.

NICE recommends urgent referral for chest radiography for anyone with haemoptysis or unexplained or persistent symptoms, such as cough, chest pain, dyspnoea or weight loss. Patents with lesions on chest x-rays or computed tomograms suggestive of lung cancer should be referred urgently to a chest physician working as part of a multidisciplinary team.

The guidelines emphasize the need for every cancer network to have rapid access to 18F-deoxyglucose positron emission tomography (FDG-PET) for better staging of lung cancer. They also recommend cancer units having specialist nurses trained in lung cancer who will assist the patient both before and after diagnosis.

The use of modern, evidence based treatments was also stressed. Patients with non-small cell lung cancer at stages 1 or 2 who are deemed inoperable should undergo continuous hyperfractionated accelerated radiotherapy (CHART) rather than the standard form. The former is an intensive form of radiotherapy delivered three times a day for a period of just over two weeks. The use of chemotherapy was recommended for non-small cell lung cancer patients at stages 3 and 4 who are relatively well in order to improve survival, disease control and quality of life.[17]

In conclusion there have been several remarkable advances in our understanding of the aetiology, pathology and treatment of a myriad number of diseases of the respiratory system over the last few years, the treatment of which has significantly contributed to decreasing morbidity and mortality for our patients.

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