

Editorials

Step 3 of the asthma guidelines

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Asthma may cause anything from trivial symptoms to intractable breathlessness and treatment needs to be tailored accordingly. To provide a rational and easily applicable approach to prescribing for asthma, most clinical guidelines on asthma management rank the drugs available in hierarchical order, simplified in a series of steps.^{1,2} For the British guidelines these range from a β agonist as required (step 1) to the need for oral corticosteroids (step 5).¹ Patients can be started at any step and, indeed, if their asthma is poorly controlled may well be advised to start on oral corticosteroids and reduce treatment when control is achieved. The guidelines do not mean that all patients with asthma of a given severity should be treated in an identical fashion, since patients clearly vary in their response to drugs. What the stepped approach is attempting to do is to suggest a hierarchy in which treatment is most likely to provide the best value for a patient with asthma of a given severity.

Fortunately most patients lie towards the mild end of the asthma spectrum and can be managed with an occasional β agonist or regular prophylactic treatment with low dose inhaled corticosteroid or a cromone. In a recent community survey in Nottinghamshire only 16% of patients were on step 3 or above,³ a relatively small proportion of the asthmatic population but still some three quarters of a million people in the UK. Furthermore, these are the patients with most morbidity and hospital admissions and who consume the most medical time and resources,^{4,5} and the figure quoted may well be an underestimate of the number of patients who should have been on step 3 or above. Determining which options should be available at step 3 has implications for a large number of patients, for the health service, and for the pharmaceutical industry.

In the first British guidelines on asthma management published in 1990, high dose inhaled corticosteroid was the only option at step 3.⁶ Long acting β agonists were added as an alternative in the most recent review of these guidelines¹ and long term studies support this approach.⁷⁻¹⁰ With the introduction of leukotriene modifying drugs there is a further potential contender and some would push the case for theophyllines to be considered. The merits of the different drugs will be debated by the various guidelines committees and it is not our brief to pre-empt the outcome of these discussions. It seems sensible, however, to start to debate the criteria that should be used to decide whether a drug should be introduced at step 3 rather than at step 4.

We would start by suggesting that, in principle, the only criteria for including a drug at step 3 should relate to its efficacy and safety and the balance between the two. To many this will seem self-evident, but the frequent attempts to justify the use of a drug on the grounds of its mechanism of action suggests that this is not universally accepted. Purists would argue that it should be the effectiveness of a drug that should be considered rather than its efficacy, but

effectiveness is more difficult to study and rarely measured in practice.

Simplifying the criteria to efficacy and safety is conceptually simple but the practical assessment is less straightforward. Randomised controlled clinical trials can provide much of the information required to assess the short term effects of a drug, on efficacy in particular, but they are less able to provide information on the effects of long term use over many years and this is often required to assess safety fully. Furthermore, not all controlled trials are relevant to guidelines. We discuss some of the pitfalls in using controlled trials and the difficulties that have to be faced when evidence from controlled trials is not available.

Assessing data from randomised controlled clinical trials

PRIMARY OUTCOME MEASURES SHOULD BE RELEVANT TO EFFICACY AND SAFETY

If efficacy and safety are the criteria that should be used to position a drug, it follows that the only end points from clinical trials that should be considered are those directly relevant to the patient such as symptoms, relief inhaler use, lung function, quality of life, asthma exacerbations, adverse effects, and mortality. Even lung function is a proxy measure though its practical value is widely recognised. Knowing the effect of a drug on a particular cell or mediator is relevant to our understanding of the way that a drug works but not to its value in clinical practice. It is worth remembering that inhaled corticosteroids were recommended for use in patients with asthma in the early 1970s because they improved asthma symptoms and lung function and had few adverse effects¹¹; it was another 20 years before their effects on airway inflammation were confirmed in patients with asthma.¹²

SOME STUDIES ARE MORE RELEVANT TO GUIDELINES THAN OTHERS

New drugs for asthma are often studied in highly selected patients and this may be entirely appropriate for certain purposes. Such studies are not relevant to positioning a drug, however, as the size of response in a selected group of patients may bear little relation to the effect of the drug in the "run of the mill" patient with asthma. Patients in one study of montelukast were clearly atypical, for example, since their increase in forced expiratory volume in one second (FEV₁) in response to salbutamol was more than 40%.¹³ We cannot assume that the response to montelukast would be the same in a more representative asthmatic population where the response to a β agonist is probably closer to 10%. The studies used to inform guidelines should involve patients who are broadly representative of asthmatic patients treated at step 3.

COMPARATIVE DATA ARE REQUIRED IN THE SAME PATIENTS

We can assume that any drug, and certainly new drugs on the market, will have demonstrated efficacy and a reasonable safety profile to satisfy the requirements of the regulatory authorities. The question when positioning a drug therefore is not whether it works but how effective it is in relation to the other drugs available. This can only be determined by a direct comparison of the two drugs in the same patients. Comparing the response of two drugs in different populations is dangerous. The FEV₁ response to a long acting β agonist has ranged from 4%¹⁴ to 13%⁹ in different studies and a similar range can be found for all drugs, depending crucially on the inclusion criteria used for the study. Studies can be designed to ensure that a given drug is more likely to be effective—for example, by only including in studies of long acting β agonists patients who demonstrate good reversibility.

LARGE STUDIES ARE REQUIRED BUT WHO FUNDS THEM?

The need for large studies to provide clear cut answers about the effects of treatment in patients with asthma has been appreciated relatively recently. Such studies are expensive and hence tend to be carried out by large pharmaceutical companies. Although this has resulted in several high quality studies addressing important clinical questions, such dependence on industry limits the scope of the studies that are undertaken and it would undoubtedly be healthier if more independent funding were available. The reasons why almost no published studies instigated by the pharmaceutical industry reflect adversely on their product are multifactorial but selection of the study design and patients who are most likely to benefit from their drug is clearly one factor. If more independent support for large studies was available there would still be the potential problem that many prospective studies require placebo inhalers and their availability is currently dependent on the goodwill of the pharmaceutical industry. Once a drug is on the market it would surely be reasonable for companies to be required to provide placebo inhalers at a reasonable price.

Use of information from sources other than randomised clinical trials

Data from controlled clinical trials should be used to inform guidelines whenever possible, but such trials do not, and sometimes cannot, provide all the information required to make a balanced judgement of the efficacy and safety of competing drugs. This is particularly true for assessing the adverse effects of a drug which may increase with duration of treatment, as with oral corticosteroids. A rare but serious adverse effect such as aplastic anaemia with chloramphenicol also needs to be considered when producing guidelines. But how does a very rare risk of an arrhythmia or Churg-Strauss syndrome compare with a more widespread increase in the risk of osteoporosis 20 or 30 years later? Assessment of the importance of such effects is difficult, as instanced by the range of views on the importance of systemic effects from long term use of inhaled corticosteroids. This does not mean that the questions are unimportant nor that the effects are necessarily trivial. Responsible prescribing attempts to take such long term effects into account, something we do every day when

advising or prescribing to patients. Guidelines need to do the same, presumably by a sensible assessment of the evidence that is available, albeit evidence that is less robust than that obtained from randomised trials. This is much more difficult than summarising the findings of controlled trials and the challenge perhaps is to be able to summarise the way we make these decisions and judgements more explicitly.

Conclusion

Step 3 is likely to remain the most contentious area of the asthma guidelines. Some of the difficulties in determining the positioning of drugs in the guidelines are due to problems that will always be difficult to answer, such as assessing a rare risk and balancing risks and benefit. Others, however, are due to a paucity of appropriate large comparative studies in relevant patients. Well designed studies comparing the different drugs available in appropriate patients will help to determine their efficacy and safety relative to each other. Other approaches such as post-marketing surveillance may be required to determine the longer term effects of the drugs. Treatment for asthma is often taken for decades, if not throughout life, so the long term effects—beneficial and adverse—are important considerations when positioning a drug in the guidelines.

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Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension

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Considerable progress has been made in the diagnosis and management of acute pulmonary thromboembolism (PTE) but there are few data about the true incidence, early mortality, and long term progress of this condition. Recurrent PTE or incomplete resolution of the initial event leading to the development of secondary pulmonary hypertension is even less well understood. In the UK the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) remains infrequently considered and even less frequently confirmed. Many physicians remain unaware that the condition is potentially curable by corrective operation and rely on transplantation or palliative medical management.

The incidence of acute pulmonary embolism (PE) in the USA has been estimated at between 300 000 and 650 000 symptomatic events per year.¹⁻³ This ranks venous thromboembolism as the third most common cardiovascular disorder after coronary artery disease and stroke.⁴ Reported mortality rates for PE have varied from 2% to 25% with the net result in the USA being between 50 000 and 200 000 deaths per year.⁵⁻⁷ However, this number may be an underestimate of the actual morbidity and mortality resulting from PE. Routine necropsy studies have found grossly identifiable clot in up to 30% of cases and microscopic evidence of recent or old thromboemboli in over 50%.^{8,9} Other studies have shown the diagnosis of acute pulmonary embolism to be unsuspected in 70-80% of patients in whom it was the principal cause of death.^{10,11} How accurately these data reflect the current position is unclear since modern diagnostic algorithms and approaches to treatment will undoubtedly alter these figures.

For many patients who survive acute PE the natural history is one of total or near total resolution of emboli without significant residual occlusion. In a recent study from France, however,¹² 52% of patients with a diagnosed and treated acute central PE were shown to have persisting endovascular abnormalities at 11 months (incomplete resolution of clot in 39% and chronic thromboembolic changes in 13%). Additionally, recurrent PE is estimated to occur in 4-23% of patients.^{5-7,13}

Chronic thromboembolic pulmonary hypertension is the result of incomplete clot lysis with subsequent organisation resulting in its adherence to the vessel wall. Recanalisation may restore some blood flow through the obstructed vessel lumen but this is often insufficient to allow normal flow rates. Progressive pulmonary hypertension, right ventricular failure, and death often ensue. The reason for this sequence of events is unclear. It is possible that the natural clearing mechanisms are overcome by the nature, extent, or location of the embolus. It is thought that less than 10% of this group will demonstrate the presence of a procoagulant factor,¹⁴ and studies have failed to show any consistent abnormality in the fibrinolytic cascade or the pulmonary vascular endothelium. It is estimated that 1-5% of patients who suffer a PTE will develop CTEPH,¹⁵ and it is not expected that current therapeutic advances will appreciably influence this incidence.

Preoperative assessment

Progressive exertional dyspnoea and exercise intolerance are common to all patients and usually prompt the

individuals to seek medical advice. Other symptoms include cough, pre-syncope and palpitations. Haemoptysis is uncommon. Syncope is associated with severe disease, representing either a severely compromised cardiac output and/or dysrhythmias. Physical examination can be unremarkable in the early stages of the disease but with time signs of pulmonary hypertension and right heart failure develop. Early symptoms are frequently attributed to other aetiologies such as coronary artery disease or left ventricular dysfunction and respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD). The diagnosis of CTEPH is not usually considered until the patient has experienced a significant diagnostic delay and, sadly, this delay has not decreased in recent years—a fact that highlights the importance of considering pulmonary vascular disease in any patient with dyspnoea of uncertain aetiology.

Differentiation of CTEPH from other forms of pulmonary hypertension can be difficult and referral to a specialist centre with experience in the diagnosis and management of pulmonary vascular disorders is advisable. Once a diagnosis of pulmonary hypertension has been made it is vital to establish whether thromboemboli are the actual cause, and to this end ventilation/perfusion scanning and spiral CT angiograms may be helpful.¹⁶

Specific evaluation includes right heart catheterisation to document right sided pressures and function, and pulmonary angiography to assess operability. Patients who are symptomatic with unremarkable haemodynamics at rest often show severe increases of pulmonary artery pressures and right heart dysfunction on exercise. In experienced hands, pulmonary angiography is safe with selective power injections of non-ionic contrast media. The existence of concomitant cardiac disease necessitates specific investigation including coronary angiography, but is not in itself a reason to exclude patients from consideration for surgical intervention. Finally, all patients are assessed for the need for the placement of an inferior vena caval filter preoperatively.

Surgery: pulmonary thromboendarterectomy

Surgery for CTEPH has evolved considerably over recent years. The first pulmonary thromboendarterectomy was performed in 1957 and to date there have been approximately 1000 procedures performed worldwide. The operation involves a bilateral approach via a median sternotomy utilising cardiopulmonary bypass. Brief periods of circulatory arrest are required to improve operative exposure, thus ensuring adequate removal of the chronic thromboembolic material. An endarterectomy plane is raised centrally in each of the main pulmonary arteries and then followed distally reaching subsegmental levels. A typical operative specimen is shown in fig 1. The right atrium is opened and inspected for evidence of an atrial septal defect, which should be closed if present (25% of patients). During systemic rewarming additional procedures such as valve replacement or coronary artery bypass may be performed if necessary.

The pulmonary artery pressures are commonly reduced immediately after surgery and decrease further over the next 48 hours. The cardiac index usually shows immediate

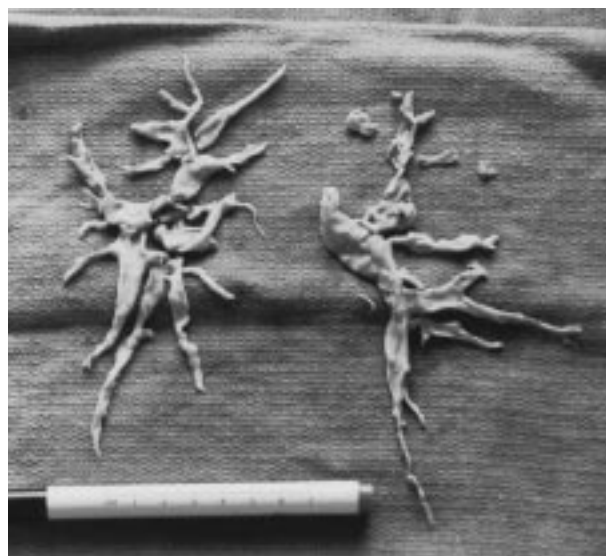


Figure 1 A typical specimen obtained at pulmonary thromboendarterectomy.

improvement compared with the preoperative state. Up to 20% of patients may experience reperfusion pulmonary oedema. This becomes clinically significant in around 10% of patients and causes death in 1–2%. Ventilation/perfusion mismatch occurs when endarterectomised segments experiencing injury on reperfusion become perfused following removal of the obstructing thrombus. Severe abnormalities of gas exchange are managed with continued ventilation, with or without the use of nitric oxide. All patients are anticoagulated for life with warfarin.

Results of surgery

CTEPH is the only form of pulmonary hypertension for which there is a surgical operation other than lung transplantation. With best medical treatment the five year survival for patients with a mean pulmonary artery pressure of >50 mm Hg complicating pulmonary embolism is only 10%.¹⁷ At the University of California, San Diego Medical Centre (UCSD)—the unit with the largest experience of this procedure—the operative mortality for pulmonary thromboendarterectomy is around 7% (personal communication) which compares favourably with lung transplantation. Operative mortality is usually related to an incorrect diagnosis of CTEPH, an incomplete endarterectomy having been performed, or the occurrence of fulminant reperfusion pulmonary oedema.

Long term results of PTE document persistent haemodynamic and functional improvement. Reduction in pulmonary vascular resistance is sustained and right ventricular remodelling is marked with resolution of tricuspid regurgitation and right heart failure. Whereas preoperatively 95% of the patients at UCSD were in NYHA functional class III–IV, postoperatively 95% are in class I–II. The results of transplantation are less predictable, require long term immunosuppression, and are not sustained beyond five years for a significant proportion of patients.

Conclusions

It is clear that chronic thromboembolic disease has a significant incidence and yet the diagnosis of CTEPH is made infrequently. Pulmonary thromboendarterectomy offers a potential surgical cure for CTEPH and is the surgical procedure of choice for patients with this condition. It has a perioperative mortality which compares favourably with lung transplantation and long term benefits which exceed those of both long term medical treatment and transplantation. Life expectancy is improved for patients with pulmonary artery pressures in excess of 50 mm Hg. The full benefit of surgery will only be realised as early diagnosis and intervention become more commonplace. Early recognition of this group of patients is pivotal in improving the outcome from CTEPH. Early referral to a centre specialising in the management of pulmonary hypertension and with the necessary operative experience will allow timely intervention, resulting in improved operative mortality and long term outcome.

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