Difficult asthma

B D W Harrison

It is hoped that the systematic approach to managing patients with therapy resistant asthma reported in this issue of Thorax will encourage others to study this difficult group of patients and to test hypotheses about improving their management.

Central to any description of difficult asthma is a disconnection between expectations and outcome. Difficult asthma may be defined as being present in a patient with a confirmed diagnosis of asthma whose symptoms and/or lung function abnormalities are poorly controlled with treatment which experience suggests would usually be effective. This immediately begs the questions of who confirmed the diagnosis, how the diagnosis was made, whether the symptoms and lung function abnormalities are due entirely to the diagnosis of asthma, and whose “experience” is being used. It is certainly wise when seeing a patient with difficult asthma to ask the diagnosis. If it is confirmed, are there any co-existing organic respiratory conditions such as COPD or bronchiectasis or psychogenic conditions such as hyperventilation or vocal cord dysfunction with wheeze? If there are co-existing problems, are these the main cause of the uncontrolled symptoms as in pseudo-steroid resistant asthma? It is also wise to be alert when there is discordance between the patient’s symptoms and objective lung function assessment, with the poor perceiver on the one hand and the over reactive on the other. Be aware, too, of the mood enhancing properties of oral steroids and the placebo effect of any new medication in patients at the over reactive end of the spectrum. The combination of supramaximal doses of inhaled steroid and multiple β₂ agonist preparations in patients referred with asthma should always raise alarm bells. Difficult asthma can occur in patients with objectively mild, moderate, or severe disease, but the consequences are most dramatic in patients with severe asthma.

Accepting the above definition of difficult asthma, assuming the diagnosis has been confirmed, and having taken account of co-existing physical diseases, the asthma may be difficult for the patient, for the clinician, or both because of one or more of the following:

• Disease factors—for example, brittle asthma or genuine steroid resistant asthma, both of which are rare.
• Doctor or nurse therapist factors—for example, inexperience or inappropriate therapies, both of which are common.
• Patient factors—for example, poor compliance, other behavioral or personality factors, adverse psychological or social factors, which are also common.

Every chest physician will see patients with difficult asthma in their practice and at least six centres have established special clinics for these patients. In the current issue of Thorax Heaney et al report their experience with therapy resistant asthma (TRA) from such a clinic. Patients were recruited on the basis of having a confirmed diagnosis of asthma, persisting refractory symptoms prompting specialist referral, high dose inhaled steroid therapy coupled with inhaled long acting β₂ agonists, and at least one course of systemic steroids in the preceding 12 months. The protocol included assessment by a respiratory physician, a psychiatrist, and an ENT specialist with appropriate investigations including a high resolution CT scan of the thorax, 24 hour dual probe ambulatory oesophageal pH monitoring, a DEXA scan, and induced sputum evaluation. Patients were then managed according to the BTS guidelines and followed up for a minimum period of 12 months. Seventy three patients were evaluated. At the end of 12 months the 39 whose asthma symptoms were controlled were classified as having non-therapy resistant asthma (non-TRA) and were discharged. Thirty four patients had TRA, which was defined as persisting asthma symptoms despite high dose inhaled steroids plus long acting β₂ agonist therapy with the requirement for either maintenance systemic steroids or at least two rescue courses of steroids during the follow up period of 12 months despite trials of other add-on therapies. Of the 80 subjects initially recruited, two had psychogenic breathlessness or vocal cord dysfunction, another had very poor compliance, one did not have asthma, and three were lost for a variety of other reasons. Twenty five had an additional diagnosis including 14 with chronic airways disease and 10 with psychogenic respiratory problems. Fifty seven of the 60 (95%) who had an ENT examination had one or more abnormalities, and 32 of the 65 (49%) reviewed by a psychiatrist had an ICD10 psychiatric diagnosis which was unrecognised in 27. Oesophageal reflux was found in 31 of the 54 (57%) in whom it was measured. These results emphasise the importance of looking for co-existing diseases in patients with severe or difficult asthma, but no differences were found in any of these areas between the TRA and the non-TRA groups except that the non-TRA group had significantly more additional diagnoses. The high frequency of psychiatric illness corresponds to the high levels of psychosocial adversity found in studies of near fatal asthma and asthma deaths and, indeed, in the control groups of patients admitted to hospital with severe asthma in both of those studies.

Heaney et al identify a number of significant differences between the TRA and non-TRA groups of patients. Those with TRA had a longer period of instability before referral and during follow up, a higher dose of inhaled steroid at referral, more rescue courses of prednisolone in the 12 months before referral and during follow up, more frequently required maintenance systemic steroids, were more likely to have attended a previous specialist, had lower FEV₁ % predicted on referral and during follow up and a lower FEV₁/FVC ratio, had fewer additional diagnoses as noted above, had a greater incidence of osteoporosis, and recorded a lower asthma quality of life score during follow up. The authors derived a probability of having TRA from the following: inhaled steroids >2000 μg beclometasone or equivalent at referral, previous specialist attendance, and a prebronchodilator FEV₁ % predicted of <70%. Patients with all three of these had a probability of 0.93 of having TRA. The authors are now exploring the value of using this approach to detect patients with TRA.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Some patients with difficult asthma can be helped by optimising asthma treatment by addressing co-existing morbidities and by accepting which symptoms are due to asthma and which are not. Other patients, most of whom might be identified by the presence of the three factors noted above, have limited benefit from this approach. However, even in this group there was objective evidence of some benefit in that the prebronchodilator FEV₁ at referral was 65% and the best during follow up was 83%. It would be of interest to know the

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ACE in COPD

ACE in COPD: a therapeutic target?
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Chronic lowering of ACE activity may have profound benefits in the long term treatment of patients with chronic lung disease such as COPD.

As a component of the circulating (or endocrine) renin-angiotensin system (RAS), angiotensin converting-enzyme (ACE) plays an important role in circulatory homeostasis. ACE cleaves angiotensin I to yield the potent vasopressor octapeptide angiotensin II while simultaneously cleaving vasodilator kinins, and angiotensin II drives renal salt/water retention through release of adrenal aldosterone. In this way, ACE exerts tonic influence on water balance and blood pressure. However, local cellular (autocrine and organ (paracrine) RAS exist in tissues as diverse as the brain, fat, skeletal muscle, and heart, where they play a variety of roles. Whether in the circulation or the tissues, the presence (insertion, insertion, deletion, deletion) rather than the absence (deletion, deletion) of a 287 base pair fragment in the human ACE gene is associated with increased ACE activity. Increasing RAS activity certainly exerts powerful proinflammatory effects in many systems, while angiotensin II has direct probiotic actions. Local RAS has additional roles in the direct regulation of tissue metabolism. Postoperatively, bradykinin increases forearm glucose uptake and reduces both endogenous hepatic glucose production and protein catabolism. Angiotensin II has glycogenolytic actions and shifts lactate uptake to release. Such actions may be complemented by the potential indirect metabolic effects of altered steroid hormone metabolism. Increasing RAS activity may also detrimentally impact on endothelial function and exert vasoconstrictor and prothrombotic actions.

What, then, of the lung? Given such diverse actions, could pulmonary ACE expression play an important role in the pathogenesis and progression of pulmonary disease, and of COPD in particular? A report in this issue of Thorax would support such a contention. ACE genotype was determined in 36 patients with COPD who underwent right heart catheterisation while exercising for 5 minutes at 60% of peak symptom limited bicycle ergometric work rate. Testing was repeated in a...
randomised double blind crossover trial of the ACE inhibitor captopril in a dose of 25 mg. Analyses are presented by ACE genotype and treatment, and this may be confusing. The authors also recognise that their results are preliminary. However, the data presented seem to confirm earlier related reports from the same group.21,22 Whether the patients in these earlier studies (n = 19 and 39, respectively) represent the same patient cohort as those reported here is not clear. Nonetheless, the message seems interesting—lower ACE activity (whether defined by genotype or pharmacotherapy) is associated with lower pulmonary artery pressure, lower pulmonary vascular resistance, higher mixed venous oxygen saturations, and lower blood lactate levels. Caution must be extended to the interpretation of these data: we do not know precise measures of pulmonary function and true oxygen delivery in these patients, nor do we know that workload/oxygen delivery ratios were indeed the same across genotypes. However, the results would be consistent with known data suggesting benefits to low ACE activity in COPD. Firstly, the extent of lung damage in COPD may be higher among those of DD genotype: acute lung injury responses are certainly genotype dependent in this way.20,21 Secondly, respiratory drive may be better sustained in those of II genotype: arterial oxygen saturations in the face of acute hypobaric hypoxia are I allele dependent,22 an effect which may be partly due to increased chemoreceptor drive.23 In congestive heart failure, at least, ACE inhibition also increases respiratory muscle strength20 and exercise tolerance,21 while pulmonary vasoconstriction may be (at least in part) ACE dependent.22 Thirdly, ACE may also influence erythropoiesis and hence (putatively) red cell mass.24 Exertional minute ventilation may thus be better sustained in the presence of lower ACE activity and oxygen carriage increased. Once delivered, the oxygen may also be more efficiently used: it is known that the mechanical efficiency of lower limb muscle improves with training more in those of II genotype,25 with “less oxygen being burned per unit of work”. The ACE I allele is thus associated with increased exercise capacity26 and endurance performance in skeletal muscle,27 an effect to which a genotype dependence in muscle fibre type may contribute.28 Whether due to better maintained oxygen delivery (pulmonary function, respiratory drive, and red cell mass) or more efficient oxygen use, II genotype may thus be associated with better performance in hypoxic environments,29 with consequent better long term adaptation to hypoxia.30

A chronic lowering of ACE activity may therefore have profound benefits in the long term treatment of patients with chronic lung disease such as COPD through (1) potential effects on pulmonary inflammation, architecture and vascularisation; (2) effects on respiratory drive and respiratory muscle function; (3) effects on the efficiency of peripheral use of oxygen; and (4) improvements in skeletal muscle functional capacity in the face of reduced oxygen delivery. It is sad that such data should be accumulating just at the time when ACE inhibitors are losing their patent protection and commercial funding of appropriate trials will be harder to obtain. It falls to committed clinician-scientists to remain dedicated to the cause and further the potential roles for ACE inhibitors and angiotensin II antagonists in the long term treatment of pulmonary disease.

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Severe acute respiratory syndrome (SARS): epidemiology, diagnosis and management

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SARS is a serious respiratory illness that frequently runs a rapidly progressive downhill course. In just 6 weeks it has spread to all continents of the globe. At the time of writing more than 7000 cases have been reported worldwide and over 500 have died. The primary mode of transmission appears to be by droplets. Good supportive care and the judicious use of ribavirin and steroids result in recovery in over 90% of patients, but randomised controlled trials are needed to define the roles of these treatments. Success in controlling the disease relies on early identification of suspect cases, proper isolation, and meticulous infection control measures. Development of sensitive and specific rapid diagnostic tests is underway.

Since February 2003 the world has been hit by a highly contagious respiratory infection which frequently results in rapidly progressive respiratory failure. In late 2002 and early 2003 there were reports of outbreaks of atypical pneumonia of unknown aetiology in Southern China. Initially the condition primarily affected close contacts of the patients and healthcare workers who looked after them. With increasing recognition of this unusual infection, the US Centers for Disease Control and Prevention termed the condition “severe acute respiratory syndrome” (SARS). Over the past few months the global medical community has worked together to achieve an unprecedented speed of progress in our understanding of SARS. Here we review the current knowledge of the epidemiology, clinical presentation, and treatment of this devastating condition.

EPIDEMIOLOGY AND CASE DEFINITION

The outbreak in Hong Kong began when an infected doctor from Southern China checked into a hotel on 21 February 2003. His symptoms of a respiratory tract infection had appeared almost 1 week before his arrival in Hong Kong. He passed on the infection to eight key persons who had either stayed at the hotel as guests or who had visited friends at the hotel. These infected persons subsequently brought the infection back to their home countries and started the outbreaks in Canada, Singapore and Vietnam. A 26 year old man who had visited a friend in the hotel developed a febrile illness and was admitted to the Prince of Wales Hospital on 4 March 2003. Initially, he was found to have right upper lobe pneumonia which subsequently progressed to bilateral consolidation. In addition to intravenous antibiotics, he was also treated with nebulised salbutamol to improve his mucociliary clearance. He subsequently recovered without the use of any antiviral or steroid treatment. Six days after his admission 18 healthcare workers from the same ward reported having an acute febrile illness. Infection control investigations subsequently revealed that a total of 156 subjects were infected and they were admitted to hospital between 11 and 25 March with SARS. Included among them were 69 healthcare workers and 16 medical students who had examined the index case or the patients around him. The others were individuals who had visited other patients in the index ward. The sequence of events was much the same in Vietnam, Singapore, and Toronto. Unprotected healthcare workers are at the highest risk of infection; only about 5% of close family contacts of the initial cohort of patients developed SARS. This may be because healthcare workers were screened and admitted to hospital quickly once symptoms developed, and the infected individuals were probably not infectious during the incubation period.

The disaster that led to a major community outbreak in Hong Kong was caused by a 33 year old man with chronic renal disease on haemodialysis. He had also been admitted to the same index ward at the Prince of Wales Hospital during the same time period. Initially, his main symptom was diarrhoea. He had visited relatives at the Amoy Gardens Apartment complex a few times in late March where over 300 residents were infected. From the preliminary investigations the most likely route of spread in this outbreak was via leaky sewage pipes allowing an aerosol of infectious faecal material to escape into the narrow lightwell between the buildings and to spread in rising air currents. Furthermore, the floor drains of the bathrooms and kitchens are also connected to the sewage pipes, so backflow of contaminated aerosol into other apartments via these routes could also have played a role in the outbreak.

Although the primary mode of transmission is by close contact with contaminated droplets, preliminary studies suggest that the responsible viral agent can also be found in large quantities in urine and faeces from infected individuals. In the absence of a reliable and rapid laboratory test in many hospitals, the diagnosis of SARS is still based on clinical features. The case definition provided by the World Health Organization is updated periodically; the latest update was on 1 May 2003 when SARS was categorised into “suspect” and “probable” cases.
| Table 1 Clinical course, progression, and laboratory features of SARS |
|----------------------|------------------|-------------------------------------------------|
| **Clinical features** | **Laboratory findings and pathological features** |
| **Onset** | Fever, chills, myalgia, dry cough and other constitutional symptoms. Approximately 20% of patients have diarrhoea | Lympohopenia, increased level of LDH. Chest radiographs may be normal |
| **Week 1** | Progressive pneumonia and increasing oxygen dependency | Active viral replication phase: respiratory secretion, stool and urine positive for SARS associated coronavirus. Chest radiographs and CT scan of thorax show progressive air space consolidations |
| **Week 2** | Gradual improvement (75%) or recurrence of fever, shifting radiological infiltrates with further deterioration/ARDS (25%) and death (8–15%) | Immune response phase: severe lung damage possibly related to immunopathological dysregulation. Necropsy of fatal cases showed diffuse alveolar damage, hyaline membrane formation, and desquamation of pneumocytes |
| **Week 3 onwards** | Gradual recovery of most patients (>80%) or death (8–15%) | SARS associated coronavirus still detectable from respiratory secretions (47%), stool (67%), and urine (21%) in recovered patients |

CLINICAL PRESENTATION AND LABORATORY FEATURES

Most patients present with an acute febrile illness after an incubation period of 5–8 days. The commonest symptoms at presentation are fever, myalgia, dry cough, headache and dizziness. The dizziness can be so severe that patients are unable to walk even a few steps. Productive cough and coryza are uncommon. Diarrhoea was found to be a more common symptom (over 50%) in patients from the Amoy Gardens. In a group of 20 patients with SARS from Singapore, dry cough has been reported to be very common (75%) while chills and rigours are relatively rare (15%).

Some patients, especially the elderly, may not present with high fever and other cardinal symptoms. In many patients physical examination reveals a high swinging fever. Auscultation of the chest shows inspiratory crackles predominating in the lung base. For patients presenting with pneumonia who either live in a SARS affected area or have travelled to such an area, physicians should consider the possibility of SARS. A detailed contact history should be taken of any person with a severe respiratory infection. Patients with SARS should be treated under proper isolation and infection control measures to prevent a major outbreak in the hospital ward.

At the onset of fever about 20% of subjects will have normal chest radiographs, so a normal chest radiograph at presentation does not rule out the diagnosis. Careful follow up is necessary. Unilateral and bilateral or multifocal air space consolidations are frequently seen. These findings are similar to other types of bronchopneumonia. Pleural effusions and hilar lymphadenopathy are not usually present. In patients with normal chest radiographs, thoracic computed tomographic (CT) scans frequently show ill defined ground glass opacification, especially in the periphery of the lungs. Some of the CT findings are similar to those seen in patients with bronchiolitis obliterans organising pneumonia (BOOP). Although the laboratory findings of leukopenia (34%), lymphopenia (70%), and mild thrombocytopenia (45%) are non-specific, they provide clues to the possible diagnosis of SARS. Increased D-dimers and mild prolongation of activated partial thromboplastin time (45%) are found in about half the patients, in keeping with a mild picture of disseminated intravascular coagulation. Other biochemical abnormalities include increased levels of lactate dehydrogenase (LDH) and creatinine kinase of skeletal muscle origin.

While some patients may have a mild course of pneumonia, many develop progressive dyspnoea and increasing oxygen dependency 6–8 days after the onset of the illness (table 1). In the initial stage many patients may appear to respond to oral steroids with resolution of the fever. However, in week 2 (second stage of the illness) the disease will frequently flare up again and they may respond to high dose pulse steroid therapy. It is thought that this deterioration (immune response phase) is caused by immunopathological dysregulation and uncontrolled activation of the cytokine system resulting in the observed lung damage. A proportion of patients will continue to deteriorate and develop acute respiratory distress syndrome (ARDS, third stage of the illness) requiring mechanical ventilatory support. Patients should therefore be carefully followed for 2–3 weeks before being discharged from hospital. About 25% of adult patients require intensive care, and 15% need mechanical ventilation. Our experience with younger children with SARS suggests that they are less severely affected, while adolescent patients behave very similarly to adults. At the time of writing there have not been any fatalities among approximately 80 paediatric cases in Hong Kong, and only one adolescent patient has required mechanical ventilation.

AETIOLOGY OF SARS

With the establishment of the WHO laboratory network around the world and subsequent rapid progress in the isolation of the possible agent, it is thought most likely that SARS is caused by a novel strain of coronavirus. Coronaviruses are classified as members of the order Nidovirales, a group of enveloped positive sense RNA viruses which synthesise a 3′-terminal co-terminal set of subgenomic mRNAs in infected cells. Coronaviruses are known to cause common respiratory and enteric diseases of humans and domestic animals.

Although there has been significant progress in the development of a rapid diagnostic test, the current rapid reverse transcription (RT) polymerase chain reaction (PCR) test for detection of this new coronavirus is not yet widely available for early diagnosis. The other diagnostic tests currently being used include viral isolation and serum antibody tests. However, these are only useful for epidemiological surveys or retrospective confirmation of the diagnosis and cannot be used to confirm the diagnosis early in the course of the illness. The early management of patients with suspected SARS is therefore still based on the clinical presentation and possible contact with known SARS patients. Among the initial cohort of patients admitted to the Prince of Wales Hospital with SARS, over 90% were subsequently confirmed to have evidence of infection with the SARS associated coronavirus either by serum antibody or RT-PCR testing.

TREATMENT PROTOCOL OF SARS

The medical treatment of SARS remains controversial. None of the currently used medications has been tested in randomised controlled trials. Ribavirin, a broad spectrum antiviral agent, has been widely used. Necroscopic examination of fatal cases has revealed diffuse alveolar damage, hyaline membrane formation, desquamation of pneumocytes in alveolar spaces, and scanty interstitial inflammatory cell infiltrates in the lungs. Furthermore, a proportion of patients may have radiological features similar to those of BOOP, which is sensitive to steroid therapy. We have therefore used a combination of ribavirin and a steroid in treating the cases in Hong Kong, and...
most patients have stabilised and improved with such treatment.

The treatment regime used in Hong Kong is oral ribavirin (loading dose of 2.4 g followed by 1.2 g three times a day) and a “low dose” corticosteroid (prednisolone 0.5–1 mg/kg/day). Those with progressive dyspnoea and hypoxia are treated with intravenous ribavirin (400 mg every 8 hours) combined with hydrocortisone (100 mg every 6 hours). Pulses of high dose methylprednisolone (0.5 g daily for 3 days) are given to patients who continue to have fever and progressive clinical and radiological deterioration. As a last resort, those who continue to deteriorate despite the use of pulsed methylprednisolone have been treated with convalescent serum obtained from patients who have recovered from SARS. Convalescent serum is obtained by apheresis using a cell separator (Baxter CS 300) operating on plasma exchange mode. Only a small number of patients have been treated with convalescent serum and it is too early to judge the effectiveness of this treatment. Other centres might not be as liberal in the use of steroid and ribavirin as we have been in Hong Kong, but they have achieved similar outcomes. Randomised controlled trials are needed to determine the effectiveness of steroid and convalescent serum in the management of SARS. The reported mortality worldwide is about 8–15%. The three independent predictive factors for a poor outcome (ICU admission or death) are advanced age, a high peak level of LDH, and a high LDH (ICU admission or death) are advanced predictive factors for a poor outcome.

In Hong Kong, but they have achieved similar outcomes. Randomised controlled trials are needed to determine the effectiveness of steroid and convalescent serum in the management of SARS. The reported mortality worldwide is about 8–15%. The three independent predictive factors for a poor outcome (ICU admission or death) are advanced age, a high peak level of LDH, and a high LDH (ICU admission or death) are advanced predictive factors for a poor outcome.

Infectious to others as their excreta may still contain coronavirus. Finally, public health and quarantine measures are extremely important in controlling the spread of the infection in the community.

DEDICATION
This paper is dedicated to all those frontline healthcare workers who risked their lives to care for patients with SARS all over the world.

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