Difficult asthma

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 question 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 reactor 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 other 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:

- Doctor or nurse therapist factors—for example, inexperience or inappropriate therapies, both of which are common.
- Patient factors—for example, poor compliance, other behavioural 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 pre-bronchodilator 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 pre-bronchodilator FEV₁ at enrolment was 65% and the best during follow up was 83%. It would be of interest to know the...
number of co-morbidities or adverse factors present in individuals in the TRA and the non-TRA groups and their duration. Our work suggests that patients with large numbers of co-morbidities, including psychosocial adversities which have been present for longer, respond less well to attempts to optimise medical treatment and other supportive measures (S Middellhall, M Noble, personal communication). In these circumstances the secondary gain from attributing all symptoms to asthma can be very powerful. Patients may then not be prepared to accept the psychogenic contribution to their symptoms. When they do, the problems may be so deep seated that even long term psychological therapies, which are rarely available, might be ineffective. A qualitative research study in this group of patients with TRA would be worth exploring.

In view of the paper by Green et al. on the potential value of monitoring induced sputum eosinophilia in the management of asthma, it is unfortunate that sputum eosinophil counts were only available in 31 of the 73 patients (42%) with the remaining subjects failing to expectorate an adequate sample or to tolerate the induction procedure. There is currently a great deal of interest in approaching asthma management through indices of inflammation and in no group is this likely to be greater than in patients with difficult asthma.

**OTHER APPROACHES**

In an earlier study of patients with difficult control asthma Irwin and colleagues concluded that the two most useful interventions were diagnosis and treatment of gastro-oesophageal reflux and treatment with inhaled corticosteroids. A recent Cochrane review of 12 double blind controlled trials found no symptomatic or physiological benefit in asthma following treatment of gastro-oesophageal reflux when both conditions were present. The fact that patients seen by Irwin et al. throughout the 1980s were receiving prednisolone but not inhaled corticosteroids reflects the differences in practice between the USA and northern Europe, Australasia and Canada. What they also concluded was that non-acceptance to treatment was the most likely reason for the asthma continuing to be difficult to control.

We have reported our experience of helping patients with difficult asthma and psychosocial adversity in a clinic run jointly by a psychiatrist and a chest physician. In a recently completed systematic review of psycho-educational interventions for difficult asthma, we have found very few well conducted trials (J Smith, personal communication). Again, more well designed research is needed.

The systematic approach described by Heaney et al. will encourage others to look at this difficult group of patients, many of whom are patients with asthma and co-existing difficulties which will not only increase our awareness of them but also help us to test hypotheses about improving their management.

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**ACE in COPD**

**ACE in COPD: a therapeutic target?**

R Forth, H Montgomery

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 cell (autocrine and organ (paracrine) RAS exist in tissues as diverse as human heart, skeletal muscle, fat, and brain, where they play a variety of roles. Whether in the circulation or the tissues, the presence (insertion, I allele) rather than the absence (deletion, D allele) 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 profibrotic 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 can 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.22 23 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 exertional 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.24 Secondly, respiratory drive may be better sustained in those of II genotype: arterial oxygen saturations in the face of acute hypoxic hypoxia are I allele dependent,25 an effect which may be partly due to increased chemoreceptor drive.26 In congestive heart failure, at least, ACE inhibition also increases respiratory muscle strength27 and exercise tolerance,28 while pulmonary vasoconstriction may be (at least in part) ACE dependent.29 Thirdly, ACE may also influence erythropoiesis and hence (putatively) red cell mass.30 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,31 32 with “less oxygen being burned per unit of work”. The ACE I allele is thus associated with fatigue resistance33 34 and endurance performance in skeletal muscle,35 an effect to which a genotype dependence in muscle fibre type may contribute.36 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,37 with consequent better long term adaptation to hypoxia.38

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 vasculature; (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 search to elucidate further the potential roles for ACE inhibitors and angiotensin II antagonists in the long term treatment of pulmonary disease.

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SARS

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

G W K Wong, D S C Hui

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 apparently started 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 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 light well 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

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Laboratory findings and pathological features</th>
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<tr>
<td><strong>Onset</strong></td>
<td>Fever, chills, myalgia, dry cough and other constitutional symptoms. Approximately 20% of patients have diarrhea</td>
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<td><strong>Week 1</strong></td>
<td>Progressive pneumonia and increasing oxygen dependency</td>
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<tr>
<td><strong>Week 2</strong></td>
<td>Gradual improvement (75%) or recurrence of fever, shifting radiological infiltrates with further deterioration/ARDS (25%) and death (8–15%)</td>
</tr>
<tr>
<td><strong>Week 3 onwards</strong></td>
<td>Gradual recovery of most patients (&gt;80%) or death (8–15%)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>SARS associated coronavirus still detectable from respiratory secretions (47%), stool (67%), and urine (21%) in recovered patients</td>
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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 diziness 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′-coterminal set of subgenomic mRNAs in infected cells. Coronavirus 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. Necropsy 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 methyprednisolone (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 methyprednisolone 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 absolute neutrophil count at presentation.

During follow up of more than 200 adults and children with SARS who have been discharged after 21 days in hospital we have not seen any case of relapse, although side effects of ribavirin (haemolytic anaemia) and steroid (myopathy) have been reported commonly in adults. Many patients who have recovered clinically have expressed concern about the possibility of being infectious to others as their excreta may still contain coronavirus. More research is needed to determine the potential infectivity of these patients.

INFECTION CONTROL

Strict infection control in the hospital setting is essential for the management of SARS. The infection is highly contagious and appears to spread by close contact droplet transmission. Given the right environmental factors, it may also spread by the faecal-oral route as in the outbreak at the Amoy Gardens in Hong Kong. In addition to respiratory secretions, urine and faecal material should be considered and handled as infectious materials. Although it is still not clear how long this new coronavirus can survive in the environment, preliminary studies by the WHO laboratory network have shown that the virus is stable in the urine and faeces for at least 2 days. The virus has been found to be even more stable (up to 4 days) in stools from patients with diarrhoea because of the higher pH of the stools in these patients. It is of paramount importance that healthcare workers are fully trained in infection control, and that patients are managed in wards with proper isolation facilities to avoid cross infection between patients. Ideally, where there is an outbreak in the community, they should be treated in wards designated for SARS patients only. Strict adherence to the steps of infection control is mandatory to avoid an unacceptable rate of infection among healthcare workers. Details of the infection control measures can be obtained from the WHO and related websites. Patients with SARS should be transferred to hospitals with specially trained staff and proper isolation facilities to avoid spread of the infection. Because of the highly infectious nature of this condition, we do not allow visitors into the wards for SARS patients. Furthermore, nebulisers should not be used as they may generate more infective droplets from the patients leading to enhanced transmission to healthcare workers. Similarly, we have reservations about the use of non-invasive positive pressure ventilation (NPPV) for patients with SARS, although some patients can be treated with NPPV to avoid intubation. It is unclear how long patients continue to shed the virus in their respiratory secretions, urine or faeces after recovery; but a preliminary study of 75 patients from Hong Kong suggested that over 50% of patients continued to excrete the virus 3 weeks after the onset of illness. Further studies are needed to define the period of infectivity of these patients. 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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