Severe acute respiratory syndrome (SARS): a review

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ABSTRACT – Severe acute respiratory syndrome (SARS) is a newly emerged disease that rapidly spread around the world. The disease originated in southern China and a novel coronavirus (SARS CoV) has been implicated as the causative organism. The path this virus took to set up human infection remains a mystery, though preliminary data point to origins in an animal reservoir. Nosocomial transmission of SARS CoV has been a striking feature in this epidemic. The clinical illness is similar to many acute respiratory infections, although a large proportion of patients show a rapid deterioration with respiratory distress towards the end of the second week of illness. The management principles are broadly similar to treating any community acquired pneumonia but the infection control measures take a pivotal role. There is no proven antiviral agent against SARS CoV. The most remarkable feature about the SARS epidemic was the speed with which the global community acted in a coordinated way to control it.

KEY WORDS: community acquired pneumonia, coronavirus, epidemic, SARS, SARS CoV, severe acute respiratory syndrome

Severe acute respiratory syndrome (SARS) is a recently emerged human disease associated with pneumonia. This disease was first recognised in Guangdong Province, China, in November 2002.[1] Subsequent to its introduction to Hong Kong in mid-February 2003, the virus spread to more than 30 countries causing disease in over 8,000 patients across five continents. Through a massive worldwide response coordinated by the World Health Organization (WHO), SARS was successfully contained in less than four months.[2] Much has been learned about this syndrome since March 2003, including its causation by a new coronavirus (SARS CoV), but our knowledge about SARS coronavirus infection remains limited. The WHO warns that resurgence of SARS remains a distinct possibility and does not allow for complacency.

History

Plagues are as certain as death and taxes.[3] Over the last century several important human microbes causing severe acute respiratory disease have emerged (Table 1). SARS CoV is not the first, and nor will it be the last of its kind. All these infections, with the exception of Legionnaires' disease, have one thing in common: the origin of the infective agent is in animals, either domestic or wild. *Chlamydia pneumoniae* and human metapneumovirus are examples of other new pathogens causing severe acute respiratory illness in which humans have always been the likely host. The source of SARS CoV remains to be determined.

When reports of a mysterious respiratory illness began to emerge from southern China in late 2002, no one knew what caused it. Would history be repeated with a strain as deadly as the 1918 pandemic strain which killed up to 40 million people? Was this caused by a supervirulent strain of flu, as seemed to be suggested by the coincidence of two deaths due to H5N1 influenza? Even in mid-March, when outbreaks elsewhere in Asia caused the WHO to release its first ever global alert that shot SARS on to the world's news agenda, the pathogen remained unknown.[1] The infectiousness of the disease, its mode of transmission and death rate were also unclear. Health officials were not sure whether they were dealing with a troubling, but ultimately limited, threat or a global mass killer.[4]

The earliest cases are now known to have occurred in mid-November 2002 in Guangdong Province, China. SARS was carried out into the world at large on 21 February 2003 when an infected medical doctor from Guangdong checked into a ninth floor room of a Hong Kong hotel. That single hotel floor

Key Points

SARS is a 'new' human respiratory disease, first encountered in 2002, and is caused by a newly identified coronavirus

The origin of the infection is probably in animals, but the infection is transmissible between humans, which led to rapid spread to over 8,000 people

A significant proportion of those affected were healthcare personnel

Treatment is supportive, as no effecive antiviral treatment has yet been identified

The epidemic was halted by infection control procedures, but it may re-emerge in the future

Table 1. History of epidemics over the last century.

Year	Outbreak
1918	Great flu pandemic, worldwide
1976	Legionnaires' disease, Philadelphia, USA
1993	Hanta virus pulmonary syndrome, USA
1994	Hendra virus infection, Australia
1997	H5N1 influenza infection, Hong Kong
1999	Nipah virus encephalitis/pneumonitis, Malaysia

became the setting, in ways that remain incompletely understood, for the international spread of SARS.[5] At least 14 hotel guests and visitors carried the virus with them to the hospital systems of Hong Kong, Toronto, Vietnam and Singapore and triggered severe outbreaks. Hospital staff responding to the earliest cases failed to protect themselves from infection as the risks of transmission were unknown. As a result, the disease rapidly spread within hospitals, infecting staff, other patients and visitors, and then spilled out into the larger community as family members and their close contacts became infected.

Aetiology

Although SARS currently has no absolutely confirmed cause, a first approximation of Koch's postulates has been satisfied for a newly discovered virus within the family Coronaviridae:[6]

- Oropharyngeal specimens from patients with SARS induced a cytopathic effect on Vero E6 tissue culture cells.
- Electron microscopic examination of cultures revealed ultrastructural features characteristic of coronaviruses.
- Immunohistochemical and immunofluorescence staining revealed reactivity with group I coronavirus polyclonal antibodies.
- Consensus coronavirus primers designed to amplify a fragment of the polymerase gene by reverse transcriptase-polymerase chain reaction (RT-PCR) were used to obtain a sequence that identified the isolate as a unique coronavirus only distantly related to previously sequenced coronaviruses.
- PCR methods detected the SARS virus in clinical samples from affected patients in diverse geographical locations.
- Serological evidence has shown the presence of antibodies specific to the new coronavirus in the serum of patients with SARS.[6–11]
- In experimental animal studies, infection of cynomolgus macaques (*Macaca fascicularis*) with SARS CoV resulted in pneumonia and necropsy proven pulmonary damage similar to that seen in human beings with SARS.[12]

Collectively, these data strongly implicate this newly identified coronavirus SARS CoV as the cause of SARS.

Coronaviruses are large enveloped viruses with a positive stranded RNA genome ranging in size from 27 to 30 kb, the largest of any of the RNA viruses. In humans, coronaviruses are usually associated with the common cold but in animals they can lead to highly virulent respiratory, enteric and neurological diseases as well as hepatitis.

Analysis of the complete genome sequence of SARS CoV published in May 2003 suggests that it is not closely related to any of the three previously identified coronavirus subfamilies, nor does it seem to have arisen through a chance genetic recombination between known coronaviruses.[13] Its unique sequence suggests that it has evolved independently from other members of the family, probably in an animal host.[14,15]

Epidemiology

The SARS coronavirus is believed to have jumped from an animal host to people in the animal markets in towns in the Guangdong province of southern China. The path the virus took to set up human infection – essential information for assessing the likelihood of recurrence – remains a mystery.

Knowledge of the chains of animals involved in transmitting the SARS virus to humans would help in the design of preventive measures. For example, when the Nipah virus epidemic began causing fatal encephalitis in livestock and people in Malaysia in 1998, about one million pigs were slaughtered. Later, when the natural reservoir of the virus was found to be fruit bats, farmers could take measures to isolate their livestock from bats; this eventually led to the control of that epidemic.[16]

The early cases of SARS in Guangdong province reportedly occurred in restaurant workers handling wild animals as exotic food,[17] so attention was focused on wild animals recently captured and marketed for culinary purposes. Researchers from the University of Hong Kong examined 25 animals belonging to seven wild and one domestic animal species in a live animal market in southern China that supplies restaurants in Guangdong province.[18] Six of the animals tested were masked palm civets (*Paguma larvata*) (which look like long-nosed cats); four of these, which came from several different owners and appeared healthy, tested positive for SARS-like virus. One raccoon dog (a member of the dog family native to eastern Asia) was tested and found to have the virus in faeces. Sera from three animal species, the palm civets, raccoon dog and a Chinese ferret badger, had neutralising antibody to the animal coronavirus. Sera from up to 40% of the humans working in the market were also positive for the antibody. The serum from animals inhibited growth of the human SARS virus in the laboratory. Similarly, serum from people who recovered from SARS hindered growth of virus from the civets. This cross-reaction is a strong indication that these viruses are similar. Importantly, the full-length genome sequence of this animal coronavirus (S CoV) had 99.8% homology to the human SARS CoV, indicating that they are closely related. The only difference is a 29-nucleotide sequence which is not found in most human isolates.[18]

These findings suggest that the markets provided a venue for the animal SARS CoV-like virus to amplify and transmit to new hosts, including humans. It is not, however, clear whether any one (or more) of these animals is the natural reservoir in the

wild. It is conceivable that civets, raccoon dogs and ferret badgers were all infected from another, as yet unknown, animal source (possibly a smaller mammal easily consumed by all three), which is possibly the true reservoir in nature. Further extensive surveillance as proposed by the WHO[19] would help to understand the animal reservoir and the interspecies transmission events that led to the outbreak of SARS.

Evolution, propagation and persistence of infectious diseases in the twenty-first century is thought to be facilitated both by the ease of mobility in contemporary society, for example through air travel, and by the growth in the world population, primarily the rise in the number of densely populated urban areas, especially in Asia. The key epidemiological determinants of the magnitude and timescale of an epidemic are:

- the interval between infection and onset of symptoms
- the interval between onset and hospital admission
- the degree and duration of infectiousness of the agent
- the extent of contact and mixing between infectious and susceptible people enabling transmission of the virus
- impact of public health interventions.[20]

For epidemiologists, the key parameter reflecting the above is known as Ro, a measure of a disease's infectiousness. Ro corresponds to the number of people infected by each patient in the absence of public health measures. A model of the spread of SARS gave a Ro of between two and four,[21,22] indicating that public health measures (eg patient isolation) would be sufficient to bring the epidemic under control. This contrasts with flu which has a Ro of about 10; in this case, quarantining those who show symptoms is not enough to bring the average number of new infections caused by each case below one, the level necessary for an epidemic to be contained.

Nosocomial transmission of SARS CoV has been a striking feature of the SARS outbreak, with as many as one in five of all cases being in healthcare workers. Most cases are adults, with children rarely identified. The mean incubation period is five days with a range of 2–10 days, although there are isolated reports of longer incubation periods. There have been no reports of transmission occurring before the onset of symptoms. The mean time from the onset of clinical symptoms to admission to hospital was 3–5 days, with longer times earlier in the epidemic.[20] The dynamics of transmission of SARS fits with the idea that it is spread by close contact, requiring its victims to breathe in droplets of virus laden mucus – explaining why most transmission occurred in confined settings like hospitals.

A recent case control study in five Hong Kong hospitals looked at the effectiveness of precautions against the spread of SARS. It concluded that the practice of droplet and contact precaution is adequate in significantly reducing the risk of infection after exposure to SARS.[23] Transmission by the faecal–oral route has also been reported in some instances.[5]

Pathogenesis

The histological changes of uncomplicated viral pneumonias are rarely described. Reports tend to be derived from post-mortem examination of patients who succumb to the pneumonia, and thus may not be representative of the majority of pneumonia patients who survive. The same is also true of SARS. Several distinct features of fatal coronaviral pneumonia have been identified:[24]

- epithelial cell proliferation
- diffuse alveolar damage
- macrophage infiltration of the lungs
- haemophagocytosis (a feature attributed to cytokine dysregulation).

These pathological features of SARS CoV pneumonia are similar to H5N1 influenza pneumonia.[25] Experimental studies in

Table 2. Clinical symptoms (%) at presentation of patients with severe acute respiratory syndrome.

Study	Peiris et al[29] (Hong Kong)	Lee et al[32] (Hong Kong)	Booth et al[33] (Canada)	Donnelly et al (Hong Kong)
Patient numbers	50	138	144	1,425
Age (mean)	43	39.3	–	–
Fever	100	100	85	94
Chills or rigor	74	73	–	65
Myalgia	54	61	49	51
Malaise	50	–	–	64
Anorexia	20	–	–	55
Cough	62	57	69	50
Breathlessness	20	–	42	31
Diarrhoea	10	20	–	27
Runny nose	24	22	–	25
Sore throat	20	23	–	23
Headache	20	56	–	50
Dizziness	12	42	–	31

which macrophages are infected *in vitro* suggest that the H5N1 influenza viruses are hyperinducers of pro-inflammatory cytokines.[26] Human coronavirus can replicate in human macrophages *in vitro*.[27,28] Taken together, it has been suggested that in SARS CoV pneumonia, pro-inflammatory cytokines released by stimulated macrophages in the alveoli have a prominent role in the pathogenesis of SARS leading to cytokine dysregulation. This idea has implications for the management of coronaviral pneumonia, as interventions with steroids might modulate this cytokine response and prevent fatal outcome.[28]

Clinical features

The clinical illness is like many other acute respiratory infections. Table 2 illustrates the common clinical features in different settings.[29–34] The clinical progression of SARS is mostly uniform, with a biphasic pattern of illness characterised by a wave of deterioration towards the end of the second week (Table 3).

Week 1 of illness

Patients initially develop influenza-like prodromal symptoms. Presenting symptoms include fever, malaise, headache, and rigors. No individual symptom or cluster of symptoms has proven specific. Although history of fever is the most frequently reported symptom, it may be absent on initial measurement.[19]

Week 2 of illness

Cough, dyspnoea and diarrhoea may be present in the first week but are more commonly reported in the second week of illness. At this stage up to 70% of the patients develop diarrhoea, which has been described as large volume and watery without blood or mucus.[35] Towards the end of the second week severe cases deteriorate, developing rapidly progressing respiratory distress with about 20% requiring intensive care.[36]

Laboratory findings include lymphopenia (70%), thrombocytopenia (45%), elevated lactate dehydrogenase (LDH) (70%), raised creatine kinase and alanine aminotransferase (AAT) (30%).[37]

Radiological findings in SARS are well characterised on both chest radiograph and computed tomography (CT) scan.[38–43] On chest radiograph, there is predominant lower zone (65%) and peripheral lung (75%) involvement (Figs 1(a) and 1(b)). These changes are confirmed by high resolution CT scanning and may be seen even when the chest radiograph is normal. Lack of cavitation, lymphadenopathy and pleural effusion are typical of SARS. Other common findings include mainly ground glass opacification and sometimes consolidation, interlobular septal and intralobular interstitial thickening. The pattern of peripheral ground glass opacification is different from the

Table 3. Clinical progression of treated severe acute respiratory syndrome.

Clinical feature	Frequency (%)	Mean time (days)
Recurrent fever	85	9
Watery diarrhoea	73	8
Radiological worsening	80	7
Worsening respiratory symptoms	45	9
New radiological lesions	45	–
Acute respiratory distress syndrome	20	Week 3

Fig 1. A 45-year-old Hong Kong resident with severe acute respiratory syndrome (SARS): **(a)** showing bilateral peripheral shadows; **(b)** after pulsed methyl prednisolone showing resolution of chest X-ray (CXR) shadowing (CXRs provided courtesy of Dr KW Tsang).
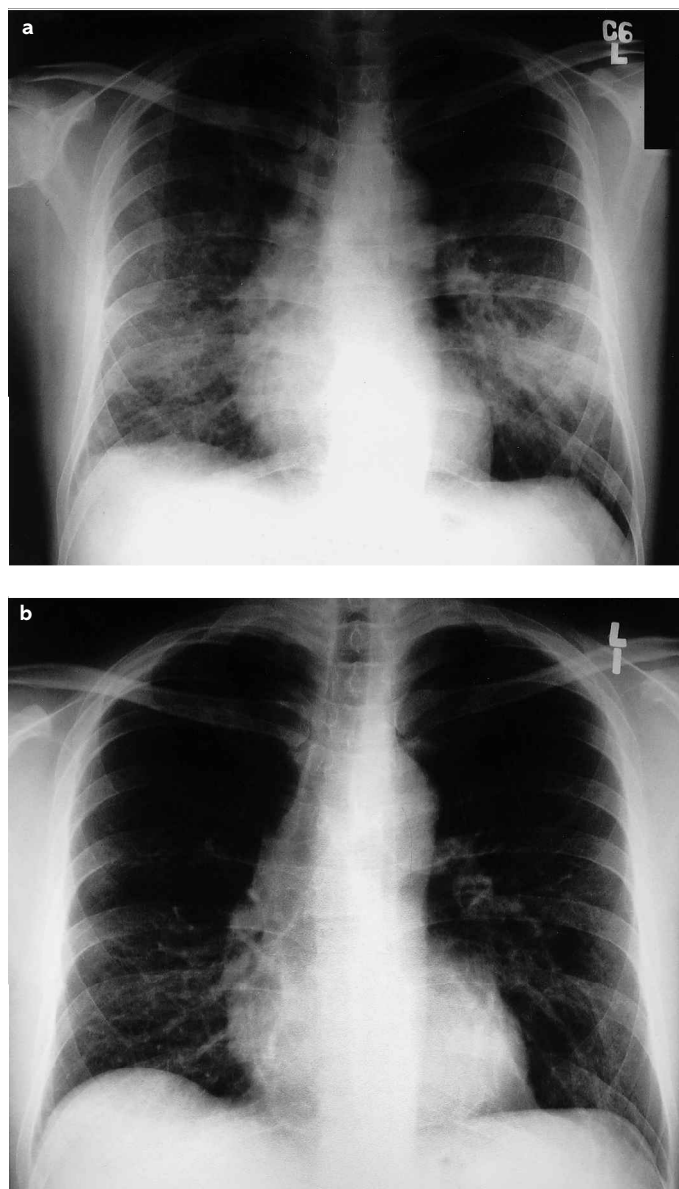
central pattern seen in atypical pneumonias caused by Mycoplasma, Chlamydia and influenza species.[44]

The clinical symptoms of SARS may not allow ready distinction from other common wintertime respiratory viral infections (Table 2). Certain characteristics of SARS are noteworthy: the constellation of absence of upper respiratory symptoms, the presence of dry cough and minimal auscultatory findings with consolidation on chest radiograph may alert the clinician to the possible diagnosis of SARS. However, detailed comparative studies of pneumonia with other causes are yet to be published.

Independent predictors of an adverse outcome or severe disease varied in different trials.[45–47] They included:

- older age
- severe lymphopenia
- impaired AAT
- delayed starting of ribavarin and steroid
- high peak LDH
- high neutrophil count at presentation
- presence of comorbid conditions
- chronic hepatitis B virus infection.

Increasing age is a universal risk factor in all studies; this is reflected in the case fatality rate which is much lower in patients below 60 years (13.2%) than in those over 60 years (43%).[20]

Diagnosis

There was a lack of reliable laboratory tests[48] at the start of the epidemic, so on the basis of early findings in hospitals the WHO produced case definitions for suspected and probable cases of SARS to be used for screening patients before admission to hospital and in non-clinical contexts such as airports. Subsequent prospective validation of the WHO criteria for identifying patients only with SARS out of hospital, in a screening clinic in Hong Kong, showed a sensitivity of only 26% and specificity of 96%.[49] This highlights the limitations of the current WHO guidelines. The authors suggest that daily follow-up, evaluation of non-respiratory systemic symptoms and chest radiography may be better screening tools. The latest WHO case definitions are summarised in Table 4.

Finally, it is important to identify other common microbial causes of community-acquired pneumonia (CAP) by appropriate tests. Co-infection with SARS and conventional respiratory pathogens does occur, so the finding of another microbial cause does not exclude SARS.

Management

Guidelines for the management of SARS have been produced. The principles of its management are listed in Table 5.[50] Broadly

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Table 4. World Health Organization case definitions of severe acute respiratory syndrome (SARS) patients (adapted from Refs 19 and 49).

Clinical case definition of SARS	A person with a history of: Fever (>38°C) *and* One or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath) *and* Radiological evidence of lung infiltrates consistent with pneumonia *or* RDS *or* autopsy findings consistent with the pathology of pneumonia *or* RDS without an identifiable cause *and* No alternative diagnosis can fully explain the illness
Laboratory case definition of SARS	A person with symptoms and signs that are clinically suggestive of SARS *and* with positive laboratory findings for SARS CoV based on one or more of the following diagnostic criteria: (a) PCR positive for SARS CoV PCR positive using a validated method from: • At least two different clinical specimens (eg nasopharyngeal and stool) *or* • The same clinical specimen collected on two or more occasions during the course of the illness (eg sequential nasopharyngeal aspirates) *or* • Two different assays or repeat PCR using a new RNA extract from the original clinical sample on each occasion of testing (b) Seroconversion by ELISA or IFA • Negative antibody test on acute serum followed by positive antibody test on convalescent phase serum tested in parallel *or* • Fourfold or greater rise in antibody titre between acute and convalescent phase sera tested in parallel (c) Virus isolation • Isolation in cell culture of SARS CoV from any specimen *and* PCR confirmation using a validated method

ELISA = enzyme-linked immunosorbent assay; IFA = immunofluorescence assay; PCR = polymerase chain reaction; RDS = respiratory distress syndrome; SARS CoV = severe acute respiratory syndrome coronavirus.

speaking, at presentation SARS is like CAP. Hence the management steps should consist of:

- prompt diagnostic procedures
- severity assessment
- use of broad spectrum antimicrobials, as with any CAP, until the infective agent is identified
- infection control measures (a pivotal role in management).

Further issues that may arise and need to be considered while patients are in hospital are discussed below.

Respiratory support and procedures

Procedures and practices that promote aerolisation should be avoided wherever possible to reduce the risk of infection to healthcare workers. These procedures include use of high-flow oxygen, nebulisers, continuous positive airway pressure, non-invasive ventilation, chest physiotherapy, bronchoscopy, tracheal intubation, suctioning and humidification. If essential, these procedures should be planned and controlled.[51]

Table 5. Management of severe acute respiratory syndrome (SARS) (adapted from the BTS/BIS SARS guidelines[50]).

	Suspected SARS		Probable SARS	
	Non-severe	Severe	Non-severe	Severe
Case definition	A person presenting after 1 Feb 2003 with all 3: 1 High fever >38°C 2 Cough or breathing difficulty 3 – H/o travel, to an area with local transmission *and/or* – Close contact with a person with probable SARS		A suspect case with: 1 CXR pneumonia and no response to usual Rx *and/or* 2 RDS	
Infection control issues	• N95 mask for patient to wear • Consult in identified area away from others • HCW to adhere to local infection control measures (gown, gloves, mask, hand washing) • Inform hospital infection control and CCDC		• Admit to negative pressure isolation room • Transfer to regional centre • Inform regional designated SARS ID unit	
Clinical issues	• Confirm travel/contact history + obtain history of close contact/household contacts • Consider other causes of community acquired pneumonia • Note comorbidity (severity risk) • Assess severity (BTS guidelines)			
Investigative issues	• Laboratory testing for SARS (PHLS website): sputum, urine, stool, EDTA blood, acute serology • CXR • Pulse oximetry and blood gases if SpO_2 <92% on air • FBC, U&E, LFT, LDH, CK, CRP • Other microbiological samples (eg blood cultures)			
Treatment	• Consider home management • Patient to record temperature bd • Daily medical review (phone) • Paracetamol for fever • Fluids and bed rest	• Admit to negative pressure room/side room or transfer • Antibiotics as for severe CAP (β-lactam + macrolide) • Careful review • Avoid CT scan	• As for hospital treated non-severe CAP • Oral amoxycillin + macrolide • Fluids and oxygen as appropriate • Observe closely for change in clinical status	• Manage as for severe CAP • iv Co-amoxiclav or cefuroxime + macrolide • Oxygen flow rate >6 l/min not recommended • Avoid procedures that generate aerosols • Critical care • Steroids • Ribavarin not recommended
Discharge	• Afebrile for 48 hours + resolving cough + lab tests returning to normal + CXR improved • Record temperature bd; if >37.9°C × 2 report to healthcare facility • Stay at home with minimum contacts for 7 days • Follow-up at minimum of one week (? at home) • Convalescent serology at 3 weeks			

bd = twice daily; BTS = British Thoracic Society; CAP = community acquired pneumonia; CCDC = consultant in communicable disease control; CK = creatine kinase; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; EDTA = ethylene diamine tetraacetic acid; FBC = full blood count; HCW = healthcare worker; H/o = history of; ID = infectious disease; iv = intravenous; LFT = liver function tests; LDH = lactate dehydrogenase; PHLS = Public Health Laboratory Service; RDS= respiratory distress syndrome; Rx = treatment; SpO_2 = functional oxygen saturation (pulse oximetry); U&E = urea & electrolytes.

Critical care

Early intubation of patients with impending respiratory failure is preferred.[52]

Steroids

The biphasic nature of the illness and evidence from pathological studies suggest that steroids could prevent or ameliorate the rapidly progressive respiratory distress by modulating the cytokine dysregulation seen in the later stages of SARS.[29] There is no evidence of any effect on mortality, but use of high-dose steroids has been reported to contribute to decrease in fever and the need for oxygen supplementation.[53] These findings are not based on controlled data and there remains concern regarding the use of high-dose steroids, particularly risk of infection.[54] A recent study has shown the superiority of pulsed steroids over daily treatment.[55] The current recommendation is to consider moderate doses of steroids in severely ill patients with SARS with increasing oxygen requirements, with PaO_2 below 10 kPa or oxygen saturation below 90% on air.

Ribavarin

The evidence for the efficacy of ribavarin is lacking when used blindly in the early stages of the epidemic. In laboratory studies, no *in vitro* activity against SARS CoV has been demonstrated. Use of ribavarin is associated with a significant toxicity, including haemolysis (in about 76% of patients) and decrease in haemoglobin of 2 g/dl (in about 49%).[56] Routine use of ribavarin in patients with SARS is therefore not currently recommended.

Other treatments

A variety of experimental treatments have been administered to patients with severe illness. The risk and benefits of each are currently not documented. They include:

- proteinase inhibitors
- intravenous immunoglobulins
- convalescent serum
- tumour necrosis factor alpha-blockers
- interferons[57]
- traditional Chinese medicines.

Future

New drugs

Are new drugs for SARS on the horizon? A Frankfurt team has shown that glycyrrhizin (derived from liquorice roots) can kill SARS virus cultured in monkey kidney cells.[58] Another German group has recently identified the structure of a key SARS enzyme proteinase which plays a key role in viral replication.[59] Using a computer model of this structure, they have begun to predict which drugs might inhibit the activity of the enzyme.

Vaccination

Will we have a vaccine to combat SARS? Vaccines already exist for animal coronaviruses; vaccine biologists are applying this expertise to SARS.[60,61] Various techniques for vaccine development are being tried. One is targeted genetic modification of SARS virus whereby genes not needed for virus survival but required for it to cause disease are selectively deleted. Another approach uses genetically engineered harmless viruses which contain only those genetic sequences from the SARS virus that are necessary to stimulate the human immune system. This approach has been used to develop a prototype vaccine against a coronavirus that causes bronchitis in chickens.[62]

Conclusions

The sudden appearance of a pestilence like SARS is not without precedent, but what is remarkable is the speed with which the world's health community was ready to act in a coordinated way to develop specific diagnostic tests to identify and institute control measures which led to the control of the epidemic.[63,64]

This epidemic serves to confirm the continued threat of infectious diseases, of new infections to evolve and, above all, their global nature in the twenty-first century. It is to be hoped that the lessons learnt from this epidemic will provide a useful template with which to approach future epidemics of acute respiratory infections when they come along, as they surely will. Whether SARS will re-emerge as an epidemic infection is currently unknown.

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