REVIEW ARTICLE

Severe acute respiratory syndrome (SARS): lessons learnt in Hong Kong

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ABSTRACT

Many healthcare workers were infected while looking after the SARS patients on the medical wards in 2003. The high infectivity of the SARS coronavirus with peak viral load on day 10 of illness when patients were ill, overcrowding of the old medical wards with low air changes/hr (ACH), and aerosol-generating procedures while resuscitating the patients were the major factors. Procedures reported to present an increased risk of SARS transmission include tracheal intubation, non-invasive ventilation, tracheotomy and manual ventilation before intubation whereas oxygen therapy and bed distance <1 m were also implicated. Studies based on laser visualization technique with smoke particles as smokers in the human patient simulator has shown that oxygen therapy via Hudson mask and nasal cannula could disperse exhaled air of patients to 0.4 and 1 m respectively whereas jet nebulizer could disperse exhaled air >0.8 m from the patient. Bigger isolation rooms with 16 ACH are more effective than smaller isolation rooms with 12 ACH in removing exhaled air and preventing room contamination but at the expense of more noise and electricity consumption. Non-invasive ventilation via face masks and single circuit can disperse exhaled air from 0.4 to 1 m. Both higher inspiratory pressures and use of whisper swivel device (to facilitate carbon dioxide removal) could increase the exhaled air leakage and isolation room contamination during on-invasive ventilation. Addition of a viral-bacterial filter during manual ventilation by bagging may reduce the exhaled air leakage forward and yet increase the sideway leakage. N95 mask was more effective than surgical mask in preventing expelled air leakage during patient's coughing but there was still significant sideway leakage to 15 cm. Clinicians should be aware of air leakage from the various face masks and adopt strict infection control measures during resuscitation of patients with severe respiratory infections. Carefully designed clinical trials are required to determine the optimal timing and dosage of any antiviral agents, convalescent plasma, and immuno-modulating agents in the treatment of the possibly immune-mediated lung injury in SARS and newly emerged infection such as the Middle East Respiratory Syndrome.

KEY WORDS

Severe acute respiratory syndrome (SARS); management; lessons; Middle East Respiratory Syndrome (MERS)

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Introduction

The rapid emergence of severe acute respiratory syndrome (SARS) due to SARS-coronavirus (CoV) in 2003 took the world by surprise (1-3). By the end of the epidemic in July 2003, 8,096 cases were reported in 29 countries and regions with a mortality of 774 (9.6%) (4). The viral kinetics of patients hospitalized with SARS-CoV appeared like an inverted v-shaped curve over time, with the nasopharyngeal viral loads peaking on day 10 of illness onset whereas many patients progressed to respiratory failure around the same time of the illness (5,6). About 50% of patients required supplemental oxygen whereas 25% would need intensive care support during the second week of the illness (3,7,8). Except for re-emergence at small scales in late 2003 and early 2004 in South China after resumption of wild animal trading activities in markets (9,10), SARS-CoV has fortunately not returned to the community. However the emergence of the Middle East Respiratory Syndrome (MERS) due to MERS-CoV in the Arabic Peninsula and neighboring countries in the Middle East since 2012 has created concern of another severe respiratory infection with a potential for global outbreak (11-13).

This article reviews the clinical lessons learnt from the clinical management of the SARS outbreak in Hong Kong and the subsequent progress in hospital infection control, in addition to research of the ward environmental airflow and the safety of common respiratory therapies. The clinical lessons and research findings may facilitate our preparedness for managing other emerging severe acute respiratory infections.

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Lessons learnt from SARS and progress

General medical wards with crowding and inadequate ventilation are not suitable for managing highly infectious diseases

Prior to the outbreak of SARS, most of the hospital wards in HK were designed as general wards without proper partition between beds whereas few isolation facilities were available. Beds were separated by mobile curtains and the distance between beds often fell short of 1 m due to heavy clinical load. Such medical ward design was clearly not ideal in managing highly infectious diseases such as SARS. Following admission of the index patient (a visitor of Hotel M), who presented with community acquired pneumonia (CAP) to a general medical ward at the Prince of Wales Hospital (PWH) on 4th March 2003, 138 patients [many of whom being healthcare workers (HCWs)] were hospitalized with SARS within 2 weeks following exposure to the index case (2,3). This super-spreading event was thought to be related to a combination of the use of salbutamol via a jet nebulizer for its muco-ciliary clearance effect to the index case who had non-productive cough and dyspnoea, overcrowding of beds, and poor ventilation in the hospital ward (3,14). During early Apr 2003, exhaust fans were installed on the windows in the corners of every medical ward as a temporary measure in order to improve the ward ventilation.

A nosocomial outbreak of seasonal influenza A (H3N2) occurred in the same old medical ward setting in 2008 at PWH when a patient hospitalized with acute exacerbation of chronic obstructive pulmonary disease (COPD) was given non-invasive positive pressure ventilation (NPPV) for treatment of hypercapnic respiratory failure despite implementation of droplet and contact precaution (15). Several patients located in the same bay of the COPD patient and some in the distant bays of the same medical ward were infected with the same strain of H3N2 influenza virus in the following week. The nosocomial outbreak was related to imbalanced airflow in the ward due to different HEPA filter fan rates, allowing exhaled air from the patient who was receiving NPPV to be blown towards other bays of the same ward. Following infection outbreak investigation including examination of ward airflow and computer fluid dynamics analysis, this case was an example of how seasonal influenza could possibly be converted from droplet into airborne transmission through NPPV and imbalanced environmental airflow (15).

After the outbreak of SARS, the HKSAR Government injected substantial funding to improve the medical ward environment and upgrade facilities in the public hospitals in preparation for emerging infectious diseases including influenza pandemic. Nowadays there are more than 1,400 isolation beds with double-door and negative pressure in the public hospitals in HK. Bigger isolation rooms with 16 air changes per hour (ACH) at the Princess Margaret Hospital are more effective than smaller isolation rooms with 12 ACH at PWH in removing exhaled air and preventing room contamination but at the expense of relatively more noise and electricity consumption (16). In addition, there is adequate supply of personal protective equipment such as N95 masks, eye shields, gowns, *etc.* on the isolation wards. The improvement in hospital ward environment and infection control measures has facilitated management of infectious diseases in HK.

Risk factors for super-spreading events within hospitals

Super-spreading events of SARS occurred in hospitals in HK (3), the mainland of China (1), Canada, and other countries (17,18). Globally 1,706 healthcare workers were infected while providing care to the SARS patients at close distance in 2003 (4). A case control study involving 124 medical wards in 26 hospitals in Guangzhou and HK has identified 6 independent risk factors of super-spreading nosocomial outbreaks of SARS: minimum distance between beds <1 m, performance of resuscitation, staff working while experience symptoms, SARS patients requiring oxygen therapy or NPPV whereas availability of washing or changing facilities for staff was a protective factor (19). Procedures reported to present an increased risk of SARS transmission include tracheal intubation, non-invasive ventilation, tracheotomy and manual ventilation before intubation (20). Following the outbreak of SARS, hospital beds on the general wards in HK have been separated at least 1 m apart. HCWs have also developed very good infection control habits (e.g., wearing surgical masks before entering any general ward on duty and maintaining good infection control measures such as hand hygiene, droplet and contact precautions when managing patients with influenza or pneumonia, and upgrading to airborne precaution as appropriate for aerosol-generating procedures).

Exhaled air dispersion distances/directions of common respiratory therapies

To improve our understanding of the risks of various respiratory therapies when managing patients with respiratory due to infectious diseases, we have examined the exhaled air dispersion during application of various respiratory therapies on a high fidelity human patient simulator using the laser visualization technique and smoke particles as markers (20,21).

Oxygen therapy via Hudson mask (22,23) and nasal cannula (16) can disperse exhaled air of patients to 0.4 m lateral to the center of the mask and 1 m towards the end of the bed respectively whereas a jet nebulizer, driven by air or oxygen at 6 L/min, can disperse exhaled air >0.8 m laterally from the patient (24).

NPPV via different brands of face masks and single circuit can disperse exhaled air between 0.4 and 1 m (21,25). Both higher inspiratory pressures and use of a whisper swivel device

(to facilitate carbon dioxide removal) can increase the exhaled air leakage and isolation room contamination during NPPV (25). During resuscitation, addition of a viral-bacterial filter during manual ventilation by bagging may reduce the exhaled air leakage forward but it increases the sideway leakage (26).

Patients hospitalized with influenza or pneumonia are often required to wear protective masks to prevent nosocomial infection. Normal cough produces a turbulent jet about 0.7 m towards the end of the bed from the recumbent subject. N95 mask is more effective than surgical mask in reducing expelled air leakage forward during patient's coughing but there is still significant sideway leakage to 15 cm (27). Thus for practical purpose and taking into account patient's comfort and compliance, we would recommend putting patients on the surgical masks for infection control purpose.

Use of antiviral therapy, convalescent plasma, and immunomodulating agents

Ribavirin

Ribavirin, a nucleoside analogue, was widely used for treating SARS patients (2,3,5,6,8,17,18). However, it was later known that ribavirin had no significant *in vitro* activity against SARS-CoV (28,29), and it caused significant haemolysis in many patients (3,17,18,30).

Protease inhibitors

Lopinavir and ritonavir in combination is a boosted protease inhibitor regimen widely used in the treatment of human immunodeficiency virus (HIV) infection. *In vitro* activity against SARS-CoV was demonstrated for lopinavir and ribavirin at 4 and 50 μg/mL, respectively whereas inhibition of *in vitro* cytopathic effects was achieved down to a concentration of 1 μg/mL of lopinavir combined with 6.25 μg/mL of ribavirin (31). A retrospective review has shown that the addition of lopinavir 400 mg/ritonavir 100 mg (LPV/r) as initial therapy was associated with lower overall death rate (2.3% *vs.* 15.6%) and intubation rate (0% *vs.* 11%) than a matched historical cohort that received ribavirin alone as the initial anti-viral therapy (32). Other reported beneficial effects include a reduction in corticosteroid use, fewer nosocomial infections, a decreasing viral load and rising peripheral lymphocyte count. However, the outcome of a subgroup that had received LPV/r as rescue therapy after receiving pulsed methylprednisolone treatment for worsening respiratory symptoms was not better than the matched cohort (32).

Interferons (IFNs)

Type I IFNs are produced early as part of the innate immune response to virus infections. There are *in vitro* and limited animal and observational data that IFN, particularly early use, has efficacy against SARS (33-37). In experimentally infected cynomolgus macaques, prophylactic treatment with pegylated IFN-α significantly reduced viral replication and excretion, viral antigen expression by type 1 pneumocytes and pulmonary damage, compared with untreated macaques, whereas post-exposure treatment with pegylated IFN-α yielded intermediate results (38). Use of IFN-α 1 plus corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographic lung opacities and lower levels of CPK in SARS patients in Canada (39). These findings support clinical testing of approved IFNs for the treatment of SARS.

Systemic corticosteroids

During the second week of SARS illness when patients progressed to more severe pneumonia and hypoxemia, there was evidence of bronchiolitis obliterans organizing pneumonia radiologically (3,8,40) and histopathologically (41) in some cases and the progression of the pulmonary disease was mediated by the host inflammatory response (5). Intravenous administration of rescue pulsed methylprednisolone (MP) appeared to suppress cytokine-induced lung injury (3,8,30). Systemic corticosteroids significantly reduced interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and IFN-γ inducible protein-10 (IP-10) concentrations from 5 to 8 days after treatment in 20 adult SARS patients at PWH (42). Induction of IP-10 is thought to be a critical event in the initiation of immune-mediated lung injury and lymphocyte apoptosis (43).

The use of rescue pulsed MP during clinical progression was associated with favorable clinical improvement in some patients with resolution of fever and lung opacities within 2 weeks (3,8,30). However, a retrospective analysis showed that the use of pulsed MP was associated with an increased risk of 30-day mortality (adjusted OR 26.0, 95% CI: 4.4 to 154.8) (44). In addition, complications such as disseminated fungal disease (45) and avascular necrosis of bone occurred following prolonged corticosteroid therapy (46). With the rescue pulsed MP approach, avascular necrosis of bone was found in 12 (4.7%) patients after screening 254 patients using magnetic resonance imaging at PWH. The risk of avascular necrosis was 0.6% for patients receiving <3 g, and was 13% for those receiving >3 g prednisolone-equivalent dose (47).

A randomized placebo-controlled study conducted at PWH showed that plasma SARS-CoV RNA concentrations in the second and third weeks of illness were higher in patients given initial hydrocortisone (n=10) than those given normal saline (n=7) during early clinical course of illness (48). Despite the small sample size, our data suggest that pulsed MP given in the earlier phase might prolong viraemia and thus it should only be given during later phase for rescue purpose.

Convalescent plasma

Convalescent plasma, donated by patients including HCWs at

PWH who had recovered from SARS, contained high levels of neutralizing antibody and appeared clinically useful for treating other SARS patients (49,50). Among 80 non-randomised patients with SARS who were given convalescent plasma at PWH, the discharge rate at day 22 was 58.3% for patients (n=48) treated within 14 days of illness onset compared to 15.6% for those (n=32) treated beyond 14 days (50). Convalescent plasma with high antibody titre of >1:160 was given to 20 critically ill patients with infection due to H1N1pdm09 in HK, and treatment was associated with reduced mortality (crude mortality 20% *vs.* 55% in controls) and more rapid virus clearance than other critically ill patients given oseltamivir alone (51).

In summary, the major outbreak of SARS in 2003 has taught us many invaluable lessons and led to subsequent improvement of the medical ward environment, better infection control facilities and measures, in addition to advances in knowledge and experience such as use of antiviral agents and immuno-modulating agents in handling emerging severe acute respiratory infections. Clinicians should be aware of air leakage from the various respiratory therapies and adopt strict infection control measures during resuscitation of patients with severe acute respiratory infections in order to prevent nosocomial outbreaks. Carefully designed clinical trials are required to determine the optimal timing and dosage of any antiviral agents, convalescent plasma, and immuno-modulating agents (52) in the treatment of the possibly immune-mediated lung injury in SARS and newly emerged infection such as MERS.

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