



**The Evolution of
Clinical Management Strategy for SARS
– Past, Present and Future**

HA SARS 26/03

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Purpose

This paper provides an account of the process through which treatment of SARS was formulated and evolved during the crisis, and how experience, information and expert opinions were collected, reviewed and disseminated among clinicians.

Background

2) An outbreak of unusually severe atypical pneumonia took place in HK starting from end of February 2003. Very little was known in the beginning. Not until a month had passed before we learnt that a new form of Coronavirus not previously seen in human was causing the disease. This new epidemic posed serious challenge to the healthcare system due to its high infectivity, uncertainties concerning mode of transmission, lack of proven effective treatment and potentially very serious outcomes.

3) Being a new disease it has been managed with an empirical approach. Unfortunately, conventional treatment was rather disappointing with 10 - 20% of hospitalized patients progressing to respiratory failure and possible death. Everyone was longing for and looking for a better treatment protocol in the middle of the crisis, and clinicians tried different options to rescue patients who deteriorated despite given adequate conventional support. Further treatment choices were often influenced by severity of illness and the prevailing understanding of disease pathogenesis, viz. viral aetiology and observation suggesting a tri-phasic course in disease progression: an initial viral replication phase, followed by an immune hyperactive phase and later a pulmonary destruction phase. As a consequence, treatment options evolved around selection of antiviral agents and/or immune modulation therapies.

Use of ribavirin

4) Ribavirin was chosen for its broad range anti-viral effects (on many respiratory, hepatic and haemorrhagic fever viruses) and the need to suppress viral replication during concomitant use of steroid, as it is considered risky to induce immuno-suppression in persons suffering from a severe infection.

5) In March, the HKU research team identified coronavirus as a leading aetiological cause of SARS (formal report on March 27, 2003). Literature review

showed that ribavirin could be effective in treating fulminant hepatitis in mice infected with the mouse hepatitis coronavirus.

6) Despite weak in-vitro inhibition of mouse hepatitis coronavirus, ribavirin decreases the release of pro-inflammatory cytokines from mouse macrophages. This suggested a possible beneficial immune modulating effect.

7) The use of ribavirin was encouraged by favorable anecdotal reports. Less than 5% mortality was cited in the Prince of Wales (PWH) cohort.

8) Ribavirin has been tried empirically in other countries with SARS. It is noteworthy that the dosage used in Hong Kong is less than half of that used in Canada where high incidence of side-effects have been reported.

Use of corticosteroid

9) Use of hydrocortisone (one form of corticosteroid) was based on the theoretical immuno-modulating effect and the experience in selected patients showing good responses in early March 2003. (Dramatic response of an Accident & Emergency Department nurse from Kwong Wah Hospital was presented in early March to other respiratory colleagues)

10) Methylprednisolone (MP) (another form of corticosteroid with stronger potency) (1mg/kg/day) was resorted to in desperate cases because of (i) its specific anti-inflammatory effect; and (ii) Pamela Youde Nethersole Eastern Hospital (PYNEH) experience in its use in status asthmaticus (a severe form of asthma). MP dosage was increased to 3mg/kg/day for a PYNEH health care worker with worsening clinical condition on March 16, 2003. On the same day, at the Hong Kong Thoracic Society Annual Scientific Meeting, experts corroborated with the management approach of severely ill SARS patients using high dose corticosteroid, supplemented with non-invasive ventilatory support.

Evaluation of standard treatment modalities

11) If situation allows, any potentially effective treatment modalities have to go through objective scientific evaluation. Falling short of any randomized control trials, systematic prospective observational studies should still be the target. The Hospital Authority has facilitated the evaluation process by providing necessary venues and opportunities for frontline clinical colleagues to collect, review and disseminate useful information relevant to treatment outcomes.

12) A central database, capturing clinical information (including laboratory data) of the SARS patients managed under HA hospitals, has been set up to facilitate

not only clinical management but also to form the template for research to answer relevant hard pressed clinical questions. (Appendix I)

Investigation of exploratory treatment

13) Based on well-defined principles (including the current stage of research and clinical practice), vetting by the relevant advisory groups was carried out on various exploratory treatment modalities. Research protocols were developed for use when these experimental therapies are tested on patients. The basic philosophy is to do no harm right from the start.

14) During the outbreak, nearly every day, useful suggestions and referrals of alternative treatment options from different sources are sent to HA from Hong Kong and countries around the world via telephone calls, emails and letters through various channels. These correspondences were followed up, vetted for the level of evidence supplied and complemented with appropriate literature search when indicated. At regular intervals, various advisory groups and sub-groups comprising scientists and clinicians with experience and expertise in this field were coordinated to review and discuss diagnostic and treatment approaches with colleagues.

15) There have been seventy-four suggestions submitted to HA for treatment of SARS. Of these suggestions, nine have been selected for research protocol proposals. Out of the nine protocols, three had been implemented, three stopped in the planning stage and the rest are outstanding due to various logistic reasons.

16) Use of convalescence patient plasma, Pentaglobin and Chinese Medicine, widely publicized in the media, intensely demanded by desperate patients and their relatives, was administered under respective research protocols to facilitate evaluation.

Evolution of integrated expertise in treatment protocol formulation

17) In the early phase of the disease when it was still known as Community Acquired Pneumonia (CAP), management of the disease was largely steered by the Infection Control Task Force and the Working Group on Severe Community Acquired Pneumonia (SCAP) was formed. As the situation developed, an Expert Panel was set up to advise on infection control, work on case definition and empirical treatment of the disease.

18) When the disease developed into its peak phase, the virus causing the disease was identified and the Expert Panel concentrated on diagnosis and possible treatment based on available scientific information. During the plateau period, advisory subgroups were formed for specific areas namely infection control, facility and equipment, virology, immunopathology, treatment, Paediatrics, Obstetrics, use of convalescent patient plasma and Chinese Medicine.

19) In early May, the HA SARS Collaborative Committee (HASCOC) was formed to focus on clinical management and information on SARS, with representatives from the various advisory subgroups. It is multi-disciplinary comprising Respiratory Physicians, Accident & Emergency Specialists, Geriatricians, Intensivists, Radiologists, Microbiologists, Rehabilitation Specialists, Paediatricians, Pathologists and Psychiatrists.

20) Meetings are held at regular intervals with different groups of people who can contribute towards the clinical management of SARS:

- a. Daily meetings among Head Office managers, statisticians and professionals in informatics to update, review, realign, plan, coordinate and implement actions on a day-to-day basis;
- b. Weekly meetings are held with the HASCOC to communicate, advise, endorse and monitor ongoing programmes, and plan future projects according to corporate strategies; and
- c. Meetings with the different advisory subgroups to generate knowledge in a timely manner through exchange of expertise, brainstorming of feasible ideas and evidence appraisal, as well as to prioritize available proposed action plans.

Strategies in disseminating management protocols / treatment guidelines

21) Most up-to-date and accurate information on clinical observations, diagnostic and treatment experiences, and scientific evidence was made available quickly, shared and discussed via different channels. SARS information was easily available on HA Internet, Intranet and the e-Knowledge Gateway (eKG). Important knowledge was exchanged via chain emails among concerned parties, eKG's email alerts to clinicians and the SARS Forum. Besides, together with universities, professional colleges and associations, HA clinicians participated in a number of scientific symposia since March 2003.

22) With the participation of HA consultants and university researchers, information on the latest understanding and management of SARS has been shared with overseas colleagues via international peer-reviewed journals. More than 70 such articles have been published so far.

Way Ahead

23) The essentials for outbreak control are to identify, inform and isolate.

Disease outbreak identification and reporting

24) With improved cross-border intelligence, "alert" case definition, laboratory diagnostic accuracy and integrated real-time information sharing among epidemiologists, virologists and clinicians, a team of designated staff will be engaged in investigation of each and every breakthrough infection with enhanced liaison with regional offices of the Department of Health on contact tracing.

25) All HA staff will be required to report fever, flu-like symptoms or diarrhoea to hospital management and receive appropriate treatment. A system for monitoring staff sick leave in all hospitals is being developed to detect unusual patterns.

26) Government funding is being sought to improve and expand the eSARS system into a generic system for clinicians, epidemiologists and virologists to achieve real time surveillance and monitoring of SARS / other infectious disease outbreaks.

Facilities for better treatment

27) Construction of isolation facilities and improvement of ventilation systems are to be carried out in selected HA hospitals to provide enough hospital beds to cater for another SARS epidemic of similar magnitude. Besides, temporary isolation facilities constructed in containers, which can be rapidly fabricated, will be designed in case a future outbreak exceeding the planned isolation facilities in hospitals. Moreover, extra hospital beds in affiliated hospital blocks proposed in three acute hospitals, put to general use in normal times, will be made available for infectious disease use during outbreaks. This proposal helps to make up for the reduced number of hospital beds as a result of reserving space for isolation facilities and spacing out of beds in general wards to minimize nosocomial infections.

28) With the help from the Government, vacant flats in public housing have been reserved for staff accommodation and quarantine of community residents in case of future outbreaks.

Early detection and diagnosis

29) The Visiting Medical Officer scheme for old age homes will be taken forward to train general practitioners to detect and manage early symptoms in the home residents in collaboration of the Community Geriatric Assessment Service under HA. This arrangement would reduce the relatively high utilization of hospital services by the elderly, who stand a greater risk of contracting SARS in hospital settings, compounded by the atypical or cryptic presentation among a significant proportion (14% of them). Elderly are more likely to succumb due to the disease (63% of the fatality).

30) Certain of the General Outpatient Clinic facilities taken over from the Department of Health will be designated as Fever Clinics in the event of an outbreak. These Clinics, with electronic patient record systems and trained professional staff in early detection and treatment of infectious diseases, will screen and follow up patients with fever. This will help alleviate the heavy workload of hospitals in treating non-SARS

fever cases, and decrease the possibility of these patients contracting nosocomial infections.

31) The early diagnostic test developed by the CU will be put to the test with enhancement of laboratory facilities to prepare for the sudden surge of requests after the alert is triggered. Guidelines for the indications, timing, type and number of specimen are being prepared

Interdisciplinary cooperation in clinical management

32) With the establishment of a Central Committee on Communicable Diseases, the subcommittees on infectious diseases, pediatric infectious disease, respiratory infection, critical care medicine, microbiology and infection control shall consist of expertise from infection control, respiratory and intensive care medicine will review the last epidemic and prepare for the next one through training, setting up surveillance mechanism, discussion and performing drills on the outbreak response plan.

33) The professional groups will be responsible for:-

- Real time communication among all units
- Coordination of response and outbreak investigation
- Evidence-based revision of treatment protocols
- Coordinate ethically appraised randomized controlled trials (Appendix II)
- Supervise clinical management
- Review treatment outcome to ensure quality care

34) Within individual Cluster, hospital-based teams shall be formed to determine, train or mobilize necessary number of staff with relevant expertise to identify and isolate patients with SARS / other infections, and inform relevant parties within an acceptable shortest possible timeframe. Members shall man SARS / infection wards, patrol hospital infection control practice, or look out for "cryptic" SARS patients in non-cohort hospital areas.

Intensive care service

35) Additional intensive care unit (ICU) beds in each hospital have to be mobilized during an outbreak as 20% SARS patients may progress to a stage requiring ICU care. Considerations should also be given to increase the workforce of intensivists and ICU nurses by a percentage equivalent to the proportion of ICU beds occupied by SARS patients at the peak of the crisis, to ensure minimal disruption to routine non-SARS services. Actively adding new posts and enhancing promotion opportunities serve to attract well-qualified professionals. A rotational training/placement scheme for doctors and nurses is being designed to increase the

pool of experienced staff to cater for the surge capacity and prevent fatigue and burn-out.

Ensuring staff safety

36) Over-protection may be harmful, while high vigilance and effective audits, are more important to ensure staff safety. Currently enhanced infection control measures and protective equipments need an evidence-based evaluation to rationalize ineffective and non-sustainable practice.

37) Ward staffing, operation and nursing routines would need to be reassessed. Through operation research and computer modeling, a more cost-effective approach to minimize cross-infection among patients in different ward settings, with different high risk procedures could be developed.

Appendix I

To understand the impact of the disease, retrospective analysis of information available from the central clinical database is being conducted in the following areas:

- Case-matched study of Kaletra+Ribavirin
 - Review of treatment with steroid
 - Review of the use of non-invasive ventilation
 - Case-matched study of Chinese Medicine
 - Review of treatment with pentaglobin, convalescent plasma
 - Study of spectrum of disease in relation to fever pattern and virology results
 - Diagnostic index for SARS at Accident & Emergency Department
 - Atypical presentations of SARS patients
 - Scoring system for radiological findings
 - Intensive Care Unit common database
 - Study on SARS patients with residual lung damage
 - Pulmonary and psychological rehabilitation programme
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Appendix II

To better prepare for possible future outbreak, treatment protocols are being developed on selected areas:

- Post-exposure prophylaxis using hyperimmune globulin
- Trial of anti-viral agents
- Trial of immuno-modulating agents
- Common data set collection for post-mortems
- Prevention and treatment of pulmonary fibrosis