Clinical Diagnosis & Management of SARS

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Diagnosis of SARS

WHO criteria (revised 1 May 2003)

- High fever (>38°C) AND
- Cough or breathing difficulty AND
- One or more of the following exposures during the 10 days prior to onset of symptoms:
  - close contact with a person who is a suspect or probable case of SARS;
  - history of travel to an area with recent local transmission of SARS
  - residing in an area with recent local transmission of SARS

www.who.int/csr/sars/casedefinition/en
A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong

Nelson Lee, M.D., David Hui, M.D., Alan Wu, M.D., Paul Chan, M.D.,
Peter Cameron, M.D., Gavin M. Joynt, M.D., Anil Ahuja, M.D.,
Man Yee Yung, B.Sc., C.B. Leung, M.D., K.F. To, M.D., S.F. Lui, M.D.,
C.C. Szeto, M.D., Sydney Chung, M.D., and Joseph J.Y. Sung, M.D.

138 patients
20 doctors
34 nurses
15 allied health
16 medical students
Common Symptoms of SARS

- Fever
- Chills & Rigor
- Myalgia
- Cough
- Headache
- Dizziness
- Sputum
- Sore throat
- Running nose
- Nausea & Vomiting
- Diarrhea

% of patients
Chest Radiographs
CT Thorax
Diarrhea

Amoy Garden
N=75

Prince of Wales Hospital
N=138

Diarrhea
No Diarrhea

73% 62%

27% 38%
Features of Diarrhea

- Large volume
- Watery
- No blood
- No mucus
Diarrhea is associated with Fever

Peiris et al. Lancet 2003
## Diarrhea affects clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea (%)</th>
<th>No diarrhea (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>28 (52.8)</td>
<td>37 (43.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean age in years ± SD</td>
<td>42.1 ± 16.5</td>
<td>37.8 ± 16.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>11 (20.8)</td>
<td>9 (10.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hospital stay (Day)</td>
<td>24.0 ± 14.6</td>
<td>20.0 ± 11.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Ventilatory support</td>
<td>14 (26.4)</td>
<td>7 (8.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>ICU care</td>
<td>26 (49.0)</td>
<td>10 (11.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>8 (15.1)</td>
<td>7 (8.2)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

PWH cohort
Colon

A. lipofusin-laden macrophage

B. Dilated ER & viral particle at microvilli

C. Vesicles containing viral particles

D. Viral particles on the luminal surface of villi
E. Normal mucosa, sub-mucosa and muscle layer

F. No inflammation

G. Viral particles on villi

H. Cytoplasmic vesicles with viral particles
Lymphopenia

B cell number (cells/ul)

CD4 cell number (cells/ul)

CD8 cell number (cells/ul)

CD4/CD8 ratio

Day of Admission

Day of Admission

Day of Admission

Day of Admission

Significance levels:

- 0.0227
- 0.0024
- 0.0171

* Indicates statistical significance.
Prolonged APTT

Wong et al. BMJ 2003
Thrombocytopenia

Wong et al. BMJ 2003
Lymph node, Spleen & Bone Marrow

Wong et al. BMJ 2003
1. Survival Analysis
   • Subject – 1,700+ SARS cases in e-SARS Registry

2. Retrospective Statistical Analysis
   • Subject – 1,315 SARS discharged cases with information captured into SARS Clinical Data Collection
   • Method – Univariate and Multivariate analyses (such as Logistic Regression, Discriminant Analysis)
Survival Analysis

- **Sex**: 
- **Age**: 
- **Comorbidity**: 
- **Cohort**: 
Figure 2: Thin-section electron micrograph of lung biopsy sample from patient with SARS (A) and of human pneumonia-associated coronavirus infected cells (B).
SARS: a tri-phasic disease

- Viral replicative phase
- Immune hyperactive phase
- Pulmonary-destruction phase

Max. daily body temperature (°C)

Days after onset of disease
Protocol

Fever & Chills
Suspected SARS

IV Cefotaxime
IV Levofloxacin

De-saturation

Oral Ribavirin 3.6g per day
Oral Prednisolone 1mg/kg/day

IV Ribavirin 1.2g per day
IV hydrocortisone 100mg q6h

IV Methyl-prednisolone 0.5 g/day
For 3 consecutive days
Protocol

**IV Methyl-prednisolone 0.5 g/day**
For 2 consecutive days

- **Fever persist**
  - Radiograph show sign of deterioration

  - **3rd or 4th Pulse Steroid**
    - Convalescent serum therapy
      - Plasma exchange

**Fail to maintain oxygen saturation: ICU?**
## Response to Rx

<table>
<thead>
<tr>
<th></th>
<th>Board-spectrum Antimicrobial* (%) N=138</th>
<th>Ribavirin + Corticosteroid# (%) N=138</th>
<th>IV Methyl-prednisolone⁺ (%) N=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained response</td>
<td>0 (0)</td>
<td>16 (11.6)</td>
<td>50 (46.7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0 (0)</td>
<td>9 (6.5)</td>
<td>45 (42.1)</td>
</tr>
<tr>
<td>No response</td>
<td>138 (100)</td>
<td>113 (81.9)</td>
<td>12 (11.2)</td>
</tr>
<tr>
<td>Concentration (µg/ml)</td>
<td>Ribavirin</td>
<td>Lopinavir</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>200µg/ml</td>
<td>100µg/ml</td>
<td>10µg/ml</td>
<td></td>
</tr>
<tr>
<td>50µg/ml</td>
<td>25µg/ml</td>
<td>5µg/ml</td>
<td></td>
</tr>
<tr>
<td>25µg/ml</td>
<td>12.5µg/ml</td>
<td>2.5µg/ml</td>
<td></td>
</tr>
<tr>
<td>12.5µg/ml</td>
<td>6.25µg/ml</td>
<td>1.25µg/ml</td>
<td></td>
</tr>
<tr>
<td>6.25µg/ml</td>
<td>3.125ng/ml</td>
<td>625ng/ml</td>
<td></td>
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</tbody>
</table>

Control: 100 PFU, CO₂, 48 h, SARS-associated coronavirus (HKU-39849 isolate) added.
## Study Subjects

- **SARS Patients Admitted before May 2003**

<table>
<thead>
<tr>
<th>Cases*</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K as Initial Rx (n = 34)</td>
<td>K as Early rescue (n = 33)</td>
<td>K as Late rescue (n = 33)</td>
</tr>
<tr>
<td>Timing of treatment</td>
<td>Dx made - ribavirin/steroid</td>
<td>Pulse MP if CXR/SaO2↓</td>
<td>Intubation if pulse MP fails</td>
</tr>
</tbody>
</table>

| Matched cohort (4-D match) | Ribavirin | Ribavirin + Ever Pulse MP | Ribavirin + Ever Pulse MP + Ever Intubation |

* All cases have Ribavirin
<table>
<thead>
<tr>
<th></th>
<th>Case_A (n = 34)</th>
<th>Control_A (n = 690)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate by Day 30</td>
<td>0%</td>
<td>10.4% (standardised)</td>
<td>0.04</td>
</tr>
<tr>
<td>Intubation rate</td>
<td>0%</td>
<td>12.6% (standardised)</td>
<td>0.03</td>
</tr>
<tr>
<td>De-saturation rate (min SaO2&lt;=90%)</td>
<td>27.3%</td>
<td>27.9% (standardised)</td>
<td>1.0 NS</td>
</tr>
<tr>
<td>De-saturation rate (min SaO2&lt;=95%)</td>
<td>63.6%</td>
<td>85.2% (standardised)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Kaletra as early rescue therapy (with pulse MP)

<table>
<thead>
<tr>
<th></th>
<th>Case_B  (n =33)</th>
<th>Control_B (n = 431)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate by D30</td>
<td>3.0%</td>
<td>8.8% (standardised)</td>
<td>0.34 NS</td>
</tr>
<tr>
<td>Intubation rate</td>
<td>0%</td>
<td>19.5% (standardised)</td>
<td>0.002</td>
</tr>
<tr>
<td>De-saturation rate (min SaO2&lt;=90%)</td>
<td>54.5%</td>
<td>35.4% (standardised)</td>
<td>0.04</td>
</tr>
<tr>
<td>De-saturation rate (min SaO2&lt;=95%)</td>
<td>93.9%</td>
<td>89.4% (standardised)</td>
<td>0.56 NS</td>
</tr>
</tbody>
</table>

By D21
Kaletra as late rescue after intubation

<table>
<thead>
<tr>
<th></th>
<th>Case_C (n = 33)</th>
<th>Control_C (n = 77)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death rate by Day 30</td>
<td>21.2%</td>
<td>42.9% (standardised)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Summary

- SARS has both pulmonary & extra-pulmonary manifestations
- Age, gender, comorbidity, LDH, neutrophil & lymphocyte count affects mortality
- SARS is a tri-phasic disease
- Antiviral & immuno-suppressant may be beneficial
- RCT for antiviral therapy is needed