Emerging infectious disease threats
and the ID physicians in Asia

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Department of Medicine and Therapeutics, &
Stanley Ho Centre for Emerging Infectious Diseases,
The Chinese University of Hong Kong
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.
Lee N et al. NEJM 2003

>138 HCWs, inpatients and students infected

Citation >1900; WHO & CDC/US clinical guidelines
SARS: a Tri-phasic Disease

Viremic phase

Hyperimmune phase

Lung destruction phase

Immune Evasion

Cytokine storm

DAD & ARDS

Radiographic progression, SARS

Pneumonia extent & viral load peak at D10

Nosocomial transmission

Clinical Outcomes and Radiographic Correlations for 138 Patients with SARS

<table>
<thead>
<tr>
<th>Radiographic Feature</th>
<th>Patients Who Required ICU Care and/or Died</th>
<th>Surviving Patients Who Did Not Require ICU Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of consolidation*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>3.30 (1.70–8.78)</td>
<td>1.70 (0–3.30)</td>
</tr>
<tr>
<td>Day 7</td>
<td>15.00 (6.48–28.73)</td>
<td>5.00 (2.50–7.50)</td>
</tr>
<tr>
<td>Number of lung zones involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 (n = 89)</td>
<td>14 (15.7)</td>
<td>75 (84.3)</td>
</tr>
<tr>
<td>&gt;1 (n = 49)</td>
<td>24 (49)</td>
<td>25 (51)</td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 (n = 56)</td>
<td>3 (5.4)</td>
<td>53 (94.6)</td>
</tr>
<tr>
<td>&gt;1 (n = 82)</td>
<td>35 (42.7)</td>
<td>47 (57.3)</td>
</tr>
<tr>
<td>Consolidation at day 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral (n = 67)</td>
<td>13 (19.4)</td>
<td>54 (80.6)</td>
</tr>
<tr>
<td>Bilateral (n = 41)</td>
<td>22 (53.7)</td>
<td>19 (46.3)</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 (n = 97)</td>
<td>17 (17.5)</td>
<td>80 (82.5)</td>
</tr>
<tr>
<td>Non-type 1 (n = 41)</td>
<td>21 (51.2)</td>
<td>20 (48.8)</td>
</tr>
</tbody>
</table>

Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak

J J Y Sung, A Wu, G M Joynt, K Y Yuen, N Lee, P K S Chan, C S Cockram, A T Ahuja, L M Yu, V W Wong, D S C Hui

[PWH managed >320 SARS cases]

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad spectrum antimicrobial* (n = 138)</td>
<td>Ribavirin + corticosteroid† (n = 138)</td>
</tr>
<tr>
<td>Sustained response</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No response</td>
<td>138 (100%)</td>
</tr>
</tbody>
</table>

**Early-Phase Clinical Outcomes:** 37 patients (26.8%) required admission to the intensive care unit and 21 (15.2%) required invasive mechanical ventilation. There were 15 deaths (mortality rate 10.9%), most with significant co-morbidities, whereas 122 (88.4%) had been discharged

Early corticosteroid treatment may increase viral replication:
→ implications on management of avian influenza (H5N1, H7N9) and MERS-CoV
[WHO guidelines]

The controversies of corticosteroids therapy

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| **Clinical & Radiological responses**  
[Sung JJ, Thorax 2004; Chen RC, Chest 2006; Ho JC, AJRCCM 2003] | **Metabolic complications:** hyperglycaemia, hypertension, hypokalemia  
| **Suppression of cytokine**  
[Ho JC, AJRCCM 2003; Poutanen SM, ICHE 2005; Yap F, Clin Inf Dis 2004] |
| | **Avascular osteonecrosis (AVN)**  
(0.6% if CS use < 3 g)  
| | **Reduced viral clearance**  
[Lee N, JCV 2004; WHO 2004] |
| | **Others (e.g. acute psychosis)**  

**WHO guidelines:** low-dose HC for ‘septic shock’, adrenal insufficiency; clinical trial setting?
-- lower doses? e.g. Pred. 150-250 mg/d
-- later time? e.g. when viral load drops

Chen RC, Chest 2006; Lee N, JCV 2004; Sung JY, Thorax 2004
Quantitative Analysis and Prognostic Implication of SARS Coronavirus RNA in the Plasma and Serum of Patients with Severe Acute Respiratory Syndrome

Enders K.O. Ng,1 David S. Hui,3 K.C. Allen Chan,3 Emily C.W. Hung,2 Rossa W.K. Chiu,1 Nelson Lee,3 Alan Wu,3 Stephen S.C. Chim,1 Yu K. Tong,1 Joseph J.Y. Sung,3 John S. Tam,9 and Y.M. Dennis Lo1,9

Detects viraemia within 3.6 days (WHO endorsed)

Serum Proteomic Fingerprints of Adult Patients with Severe Acute Respiratory Syndrome

Ronald T.K. Pang,1,2 Terence C.W. Poon,1,2,5 K.C. Allen Chan,1,2 Nelson L.S. Lee,2 Rossa W.K. Chiu,1,3 Yu-Kwan Tong,1,3 Ronald M.Y. Wong,2 Stephen S.C. Chim,4 Sai M. Ngai,4 Joseph J.Y. Sung,1,2 and Y.M. Dennis Lo1,3

Pathogenesis (e.g. complement activation), diagnosis, prognostication

Clin Chem 2003

Laboratory Diagnosis of SARS


Combination of Upper/Lower respiratory, stool, and blood samples to optimize diagnosis

"LRT > URT"

Clin Chem 2006
Disease transmission

Hotel ‘Metropole’

Estate ‘Amoy Garden’
Amoy Gardens SARS Outbreak
Block E

Cumulative Cases per Apartment By Day of Disease Onset

21st Mar, 2003

Index case/apartment
Amoy Gardens SARS Outbreak
Block E

Cumulative Cases per Apartment By Day of Disease Onset

28th Mar, 2003

Index case/apartment

0 cases
1 case
2 cases
3 cases
4 cases
5 cases
Re-entrant of infectious aerosols
‘Super-spreading events’

Evidence of Airborne Transmission of the Severe Acute Respiratory Syndrome Virus


NEJM 2004

Temporal-Spatial Analysis of Severe Acute Respiratory Syndrome among Hospital Inpatients

Ignatius T. S. Yu, Tze Wai Wong, Yuk Lan Chan, Nelson Lee, and Yuguo Li

Clin Inf Dis 2005
‘Super-spreading events’

Airborne transmission of influenza

Possible Role of Aerosol Transmission in a Hospital Outbreak of Influenza


Computational fluid dynamics modeling

“International Young Investigator Award”
Infectious Diseases Society of America (IDSA) conference, 2010

Temporal-Spatial Analysis of Severe Acute Respiratory Syndrome among Hospital Inpatients

Ignatius T. S. Yu, Tze Wai Wong, Yuk Lan Chan, Nelson Lee, and Yeguo Li

Clin Inf Dis 2005

[Diagram showing concentration gradient and spread of airborne virus]
Emerging Infectious Diseases

- 2003 SARS-CoV
- 2009 H1N1pdm
- 2012 MERS-CoV
- 2013 H7N9
- 2020 H5N1
MERS-CoV: the new SARS?

**SARS-CoV**

- Origin: bats virus
- Intermediate host: civet cat?
- >30 countries affected
- total no. of cases 8096
- $R_0$ 2.2-3.7
  - nosocomial outbreaks ✓
  - super-spreading events
- pneumonia, ARDS
- no. of deaths 774 (9.6%)
  - range 6-16%
- ICU admission 15-25%

**MERS-CoV**

- Origin: bat virus
- Intermediate host: camels?
- >10 middle-east countries
- total no. of cases >700
- $R_0$ ?
  - nosocomial outbreaks ✓
  - super-spreading events?
- pneumonia, ARDS, renal failure
- no. of deaths >200 (~30-50%)
- ‘majority have comorbid illnesses and critically ill’

WHO 2004, 2013
Lee N. *Crit Care Clinics* 2013
Infectious Disease Units, Hong Kong

2004-2014: we managed & studied >4000 influenza cases


We reported:
• clinical manifestations
• complications, outcomes
• antiviral effectiveness
• pathogenesis, virokinetics in adults hospitalized for severe influenza
• annual seasonal flu
• 2009/2010 H1N1 pandemic
• 2013/2014 H7N9 epidemic

[IDSA 2010; CDC 2011-13; WHO/NEJM 2010; UpToDate 2011-13]
Infectious Disease Units, Hong Kong

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• 2013/2014 H7N9 epidemic

[IDSA 2010; CDC 2011-13; WHO/NEJM 2010; UpToDate 2011-13]
**Viral Loads and Duration of Viral Shedding in Adult Patients Hospitalized with Influenza**

Nelson Lee,1,3 Paul K. S. Chan,2,3 David S. C. Hui,1,3 Timothy H. Rainer,4 Eric Wong,5 Kin-Wing Choi,4 Grace C. Y. Lui,1 Bonnie C. K. Wong,1 Rita Y. K. Wong,1 Wai-Yip Lam,1 Ida M. T. Chu,2 Raymond W. M. Lai,2 Clive S. Cockram,1 and Joseph J. Y. Sung1,3

- **Hospitalized patients > outpatients**
  ~1.5 log_{10} copies/mL; P<0.01

- **Correlation with symptom scores and complications:**
  Spearman’s ρ, +0.22; P=0.01

- **Slow clearance in compromised host**
  β +0.77, P=0.032

- **Poorer response in influenza B**
  30% vs 67%; P=0.01

**Antiviral treatment improves viral clearance**

**Corticosteroids ×**

<table>
<thead>
<tr>
<th>Variable affecting viral concentration</th>
<th>β (95% CI)</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day from symptom onset (continuous)</td>
<td>-0.457 (-0.668 to -0.246)</td>
<td>0.107</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Comorbidity, major (yes vs no)</td>
<td>+0.765 (+0.065 to +1.465)</td>
<td>0.354</td>
<td>0.032</td>
</tr>
<tr>
<td>Antiviral initiated (yes vs no)</td>
<td>-0.899 (-1.592 to -0.206)</td>
<td>0.351</td>
<td>0.011</td>
</tr>
</tbody>
</table>

**Patients with viral RNA detected at symptom day 7, %**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with virus isolated on symptom day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir initiation time</td>
<td></td>
</tr>
<tr>
<td>Day 1-2</td>
<td>14.3 (.004) 2.3 &lt;0.001</td>
</tr>
<tr>
<td>Day 3-4</td>
<td>35.3 18.2</td>
</tr>
<tr>
<td>Not received</td>
<td>57.1 38.5</td>
</tr>
</tbody>
</table>
Antiviral treatment improves patient survival
Evidence of effectiveness with later treatment >48 h

Outcomes of adults hospitalised with severe influenza

Complications and Outcomes of Pandemic 2009 Influenza A (H1N1) Virus Infection in Hospitalized Adults: How Do They Differ From Those in Seasonal Influenza?


The Journal of Infectious Diseases 2011;203:1739–47

Seasonal Influenza, H3N2 (n=754)

H1N1pdm09 influenza (n=382)

Antiviral within 4 days: ~73% ↓ in mortality risk (~20% ↑ in risk per day delay); shorten O₂ therapy and hospital LOS (~30%); bacterial superinfection x2 mortality risk
A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

(n=155)

No advantage of double-dose (150mg bid) oseltamivir over conventional dosage (75mg bid) in influenza A (H3N2, pH1N1)

Improves viral clearance in influenza B
No advantage of double-dose (150mg bid) oseltamivir over conventional dosage (75mg bid) in influenza A (H3N2, pH1N1)

Improves viral clearance in influenza B

~40% PCR+ at treatment end; therapy >5 days may be necessary in severe cases
pH1N1 influenza pneumonia

Viral replication continues beyond 5 days of treatment

Lee N et al. Antiv Ther 2011

Longer duration in the lower respiratory tract and lung

- Antiviral treatment >10 days
- False-ve URT sample

Cited by WHO. NEJM 2010
Determinants of Antiviral Effectiveness in Influenza Virus A Subtype H5N1

Paul K. S. Chan,1 Nelson Lee,1 Mukhtiar Zaman,3 Wiku Adisasmito,4 Richard Coker,5 Wanna Hanshaoworakul,7 Viktor Gasimov,9 Ahmet Faik Oner,9 Nazim Dogan,10 Owen Tsang,2 Bounlay Phommasack,11 Sok Touch,12 Ebun Bangboye,13 Anna Swenson,14 Stephen Toovey,6 and Nancy A. Dreyer14

Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

Wiku Adisasmito,1 Paul K. S Chan,4 Nelson Lee,9 Ahmet Faik Oner,9 Viktor Gasimov,9 Faik Aghayev,4 Mukhtiar Zaman,7 Ebun Bangboye,9 Nazim Dogan,4 Richard Coker,10 Kathryn Starzyk,9 Nancy A. Dreyer,9 and Stephen Toovey14

H5N1 Avian Influenza in Children

Ahmet Faik Oner,1 Nazim Dogan,2 Viktor Gasimov,3 Wiku Adisasmite,4 Richard Coker,5 Paul K. S. Chan,7 Nelson Lee,7 Owen Tsang,2 Wanna Hanshaoworakul,3 Mukhtiar Zaman,10 Ebun Bangboye,11 Anna Swenson,12 Stephen Toovey,6 and Nancy A. Dreyer12

1 J Infect Dis 2012
2 J Infect Dis 2010
3 Clin Infect Dis 2012

H5N1 disease

(1) Limited human-to-human transmission
(2) children 0-5 yrs have lowest death risk
(3) antiviral effectiveness shown within 6-8 days from onset;
(4) unless complicated by ARDS (‘cytokine storm’)
Dexamethasone in community-acquired pneumonia

*Nelson Lee, David S C Hui

*The Lancet 2011

Evidence suggests that use of corticosteroids in influenza virus pneumonia:

1. cannot control excessive inflammation, but

2. compromises the immune response, leading to longer viral shedding, secondary bacterial and fungal infections, and

3. increased mortality

“Alternative immunomodulatory agent is needed”

Hui DS & Lee N. Antiv Res 2013; IORV 2013
Hypercytokinemia and Hyperactivation of Phospho-p38 Mitogen-Activated Protein Kinase in Severe Human Influenza A Virus Infection


<table>
<thead>
<tr>
<th>Cytokine or chemokine</th>
<th>Acute-phase samples</th>
<th>Convalescent-phase samples</th>
<th>Reference range, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>10.6 (4.2–18.4)</td>
<td>2.9 (1.6–7.0)</td>
<td>&lt;3.1</td>
</tr>
<tr>
<td>IL-8</td>
<td>5.4 (2.5–8.7)</td>
<td>2.1 (0.2–3.5)</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>IP-10</td>
<td>7043.0 (4025.1–12381.1)</td>
<td>1423.6 (931.8–1634.8)</td>
<td>202–1480</td>
</tr>
<tr>
<td>MIG</td>
<td>992.1 (499.1–1992.3)</td>
<td>431.7 (198.4–792.9)</td>
<td>48–482</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>16.0 (13.5–18.6)</td>
<td>15.7 (10.1–16.7)</td>
<td>&lt;15.6</td>
</tr>
<tr>
<td>IL-12</td>
<td>1.8 (1.3–1.9)</td>
<td>1.8 (1.7–1.9)</td>
<td>&lt;7.8</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.7 (1.6–1.8)</td>
<td>1.7 (1.6–1.8)</td>
<td>&lt;10.0</td>
</tr>
<tr>
<td>IL-10</td>
<td>4.5 (2.5–6.5)</td>
<td>2.2 (1.9–2.8)</td>
<td>&lt;7.8</td>
</tr>
<tr>
<td>IL-1β</td>
<td>1.4 (1.4–1.9)</td>
<td>1.4 (1.4–1.7)</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>RANTES</td>
<td>1851.8 (687.4–4774.3)</td>
<td>4742.8 (2767.5–5169.7)</td>
<td>4382–18783</td>
</tr>
<tr>
<td>MCP-1</td>
<td>76.5 (49.5–97.0)</td>
<td>56.6 (41.2–84.8)</td>
<td>10–57</td>
</tr>
</tbody>
</table>

Clinical Infectious Diseases 2007; 45:723–31

Uncontrolled viral load and cytokine storm

Sustained proinflammatory cytokine responses correlate with extent of pneumonia, H1N1pdm09

Hui DS, Lee H, Chest 2010
Lee N, Antiviral Therapy 2011
Uncontrolled viral load and cytokine storm

(1) relationship between uncontrolled viral replication and ‘cytokine storm’ (e.g. IL-6, IL-8, MCP-1, TNF-α)

(2) their clinical significance and correlations with disease severity

(3) suppressed adaptive immunity (e.g. Th1, Th17) in severe influenza

(4) role of innate immunity (e.g. TLR)

Cytokine Response Patterns in Severe Pandemic 2009 H1N1 and Seasonal Influenza among Hospitalized Adults

Nelson Lee\(^1,2\star^9\), Chun Kwok Wong\(^3,9\), Paul K. S. Chan\(^2,4\), Martin C. W. Chan\(^1\), Rity Y. K. Wong\(^1\), Samantha W. M. Lun\(^3\), Karry L. K. Ngai\(^4\), Grace C. Y. Lui\(^1\), Bonnie C. K. Wong\(^1\), Sharon K. W. Lee\(^1,3\), Kin Wing Choi\(^1\), David S. C. Hui\(^1,2\)

![Graphs showing cytokine response patterns](image-url)
Negative correlations between expressions of TLRs and influenza viral load in the respiratory tract  [Lee N, et al. IORV 2013]
On-going works

• **Newer antiviral treatment** (e.g. IV peramivir, IV zanamivir, laninamivir, favipiravir, DAS 181, combination therapy; monoclonal antibodies)
  – Lee N and Ison MG. *Clin Infect Dis* 2012; *Antiv Ther* 2012

• **Immunomodulatory therapy**
  – Hui DS, Chan PK, Lee N. *Antiv Res* 2013; *IORV* 2013

• **Rapid diagnosis, primary and secondary antiviral resistance**

• **Vaccine prevention**

• **Other respiratory viruses causing influenza-like illness and pneumonia in adults (e.g. RSV)**
Thank you