Respiratory Viral Infections in Immunocompromised Hosts

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Background

**Viral Factors**
- RNA viruses
  - Diversity & virologic escape
- Improved diagnostics

**Host factors**
- Hematologic malignancies, chemotherapeutics
  - Tacrolimus, mycophenolate, steroids
- Hematopoietic stem cell transplants, solid organ transplants (particularly lung)
  - Lymphocyte-depleting antibodies (eg. thymoglobulin and alemtuzumab)
Incidence in HSCT Recipients

(Single center, Singapore, multiplex PCR)

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Cumulative incidence of respiratory viral infections in HCST patients approaches 40-50%.

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Incidence in HSCT Recipients

Diverse pathogens - most common coronavirus and rhinovirus

Lung Transplants

Of 98 patients, 51 (52%) developed viral RTI
Of 111 detected, 38 (34%) were lower RTI

Nasopharyngeal swabs for PCR

Viral Persistence

No drastic intrahost evolution seen in 5 immunocompromised patients with persistent infection.

Progression to lower respiratory tract infections in 33-58% of patients with hematologic malignancies or HSCTs\textsuperscript{1,2}

- Assoc. with severe lymphopenia (52%) vs. >200 cells/μL (31%)\textsuperscript{3}

Progression to LRTI may be underestimated.

Viral Pneumonia

Progress to lower respiratory tract infections in 33-58% of patients with hematologic malignancies or HSCTs\(^1,2\)
  - Assoc. with severe lymphopenia (52%) vs. >200 cells/μL (31%)\(^3\)

Mortality estimates\(^1,4\)*

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Viral Pneumonia

Progress to lower respiratory tract infections in 33-58% of patients with hematologic malignancies or HSCTs¹,²

- Assoc. with severe lymphopenia (52%) vs. >200 cells/μL (31%)³

Mortality estimates¹,⁴*

- Influenza – 6 to 25%
- RSV – 29 to 88%
- hMPV – 0 to 43%⁶
- PIV – 17 to 35%
- Rhinovirus– 38-83%
- CoV – 0 to 11%⁵

Progression to LRTI may be underestimated.

5. Eichenberger EM, et al. Bone Marrow Transplant. 2018
Therapeutic Targets

- IVIG, Flu-IVIG – (off label) RSV, influenza
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- **Receptor binding**
  - HA monoclonals - Influenza
  - HN inhibitors - BCX 2798 & BCX 2855 - PIV

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- Fusion:
  - DAS181 – PIV, hMPV
  - Presatovir/GS-5806 – RSV
  - AK0529 – RSV
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- **Fusion**:  
  - DAS181 – PIV, hMPV  
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- **Release**:  
  - Neuraminidase (Oseltamivir, Peramivir, Zanamivir) – Influenza
  - M2 (amantadine) – Influenza A

Nucleoside analog:

- Ribavirin – (off label: RSV, MPV, PIV)
- Favipiravir/T-705 – RNA viruses, Influenza
- Lumicitabine/ALS-8176 – RSV, PIV, hMPV
- Remdesivir/GS-5734 - CoV
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mRNA replication
siRNA
- Asvasiran/ALN-RSV01 – RSV

Cap-dependent endonuclease inhibitor
- Baloxavir – Influenza

Therapeutic Targets

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- **mRNA replication**
  - siRNA
    - Asvasirnan/ALN-RSV01 – RSV
  - Cap-dependent endonuclease inhibitor
    - Baloxavir – Influenza

- **Capsid inhibitors:**
  - Pleconaril – RSV
  - BTA798/Vapendavir – RSV

Only influenza has approved therapeutics

Neuraminidase inhibitors for hospitalized influenza

Early administration of neuraminidase inhibitors in adult patients hospitalized for influenza does not benefit survival

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 506)</th>
<th>With early NAI therapy (n = 233)</th>
<th>Without early NAI therapy (n = 273)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>143 (28.3)</td>
<td>46 (19.7)</td>
<td>97 (35.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission</td>
<td>38 (7.5)</td>
<td>10 (4.3)</td>
<td>28 (10.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>22 (4.3)</td>
<td>6 (2.6)</td>
<td>16 (5.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Length of hospital stay, mean days (SD)</td>
<td>6.5 (7.6)</td>
<td>5.3 (4.5)</td>
<td>7.5 (2.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Influenza-related mortality</td>
<td>10 (2.0)</td>
<td>5 (2.1)</td>
<td>5 (1.8)</td>
<td>1.00</td>
</tr>
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Early NAI associated with reduced risk of in-hospital mortality

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Early NAI</td>
<td>0.16 (0.05-0.57)</td>
<td>0.004</td>
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<tr>
<td></td>
<td>0.20 (0.05-0.83)</td>
<td>0.026</td>
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Therapeutic Limitations

Neuraminidase inhibitors for influenza:

- Difficulty of placebo control in hospitalized

“Terminated due to futility… the increased usage of NAI as SOC in the hospital setting created severe challenges to adequate patient enrollment in the non-NAI SOC group.”

Potent Antivirals In Development

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Limitation of rate of symptom resolution in healthy controls?

→ efficacy in immunocompromised hosts not yet assessed, nor in critically ill and hospitalized patients.
Limitations to Potent Antivirals?

- Limitation of rate of symptom resolution in healthy controls?
  - efficacy in immunocompromised hosts not yet assessed, nor in critically ill and hospitalized

Summary

- Immunocompromised hosts have significant risk for complicated respiratory viral infections
  - Incidence of 40-50% in this population
  - Leukopenia associated with progression to lower respiratory tract infection in 30-50%, with associated morbidity/mortality
  - Diagnostics have improved, therapeutics lag behind
  - Ideal population for study

- Anticipated pitfalls
  - Limitation in therapeutic efficacy after infection established
    - Need for immunomodulatory therapeutics?
  - Selection of resistance
    - Need for combination therapies?
Acknowledgements

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Lung Transplants

A  Nasopharyngeal specimens, n = 884
   Positive, n=159 (18%)

   62% 6% 1% 1% 13% 4% 3%

   BAL specimens, n = 276
   Positive, n=34 (12%)

   59% 14% 3% 6% 3% 9% 6%

B  Emergency visits (n=209)
   Positive, n=72 (34.5%)

   44.1% 6.8% 10.2% 3.4% 1.7% 11.9%

Pre-scheduled visits (n=570)
   Positive, n=83 (14.6%)

   72.0% 1.2% 12.2% 6.1% 3.7% 1.2%

Regular visits (n=124)
   Positive, n=19 (15.3%)

   77.8% 22.2%

Overall proportion of positive or negative (RT)-PCR:
- Adenovirus
- Bocavirus
- Coronavirus
- Influenza
- Metapneumovirus
- Parainfluenza
- Picomavirus
- RSV