Viruses in the ICU: Are they prime time?

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Disclosures

• I have no financial interests or other relationship with commercial concerns related directly or indirectly to this presentation.
Learning Objectives

- Identify and evaluate patients at risk for development of a viral infection
- Review the pathogenic viruses seen in the critically ill population
  - Influenza
  - CMV
  - RSV
Influenza
Influenza – 100th anniversary of the 1918 pandemic

• ~500 million people became infected
  • 1/3 of the world’s population
• At least 50 million deaths worldwide
  • ~675,000 in the United States
• Life expectancy fell by about 12 years
  • 36 years for men and 42 years for women
• Disproportionately affected younger adults

2017-2018 Seasonal Flu

Chart: Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2017-2018 and Selected Previous Seasons

2017-2018 Seasonal Flu

- H3N2 predominated

Vaccine Effectiveness

- Overall 36%
  - H3N2 25%
  - H1N1 67%
  - Flu B 42%


Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System
Data through the week ending August 25, 2018, as of September 13, 2018

80,000 deaths
900,000 hospitalizations
Influenza

- Acute respiratory illness, caused by influenza A, B, and C viruses
- Occurs in local outbreaks or seasonal epidemics
- Short incubation period
- Presentation ranges from asymptomatic to fulminant
- Influenza A
  - Host - Birds, swine, humans
  - Evolves rapidly, more virulent
  - Classified into subclasses based on hemagglutinin and neuraminidase antigens
- Influenza B
  - Hosts - Humans
  - Less genetically diverse
Influenza Clinical Presentation

- High fever
- Headache
- Severe malaise
- Dry cough
- Body ache
- Primary or secondary Pneumonia
Diagnosis and Interpretation of Testing

- PCR Based Methods
- Rapid, non-PCR methods false-negatives

Influenza negative result

Cannot rule out infection, especially if not using high sensitivity test or >4 days after illness onset

Use C/S, history, exam and local influenza activity to decide if treatment is indicated
*consider additional influenza testing if indicated and testing for other pathogens
# Antiviral Therapy

<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir (Tamiflu®)</td>
<td>75mg PO BID x5 days</td>
<td>• Initiate as promptly as possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Longer duration and high-dose can be considered in certain patients</td>
</tr>
<tr>
<td></td>
<td>150mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Zanamivir (Relenza®)</td>
<td>10mg INHALED BID x5 days</td>
<td>• Not recommended for severe disease</td>
</tr>
<tr>
<td>Peramivir (Rapivab®)</td>
<td>600mg IV as a single dose</td>
<td>• Uncomplicated</td>
</tr>
<tr>
<td></td>
<td>600mg IV daily x5 days</td>
<td>• Hospitalized patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If clinically unstable on day 4, continue for 10 days total</td>
</tr>
</tbody>
</table>

Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. [https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm](https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm)
High-dose Oseltamivir

- Optimal dose and duration unknown for severe cases
- Doubling the dose of oseltamivir has been suggested
  - Severely ill patients with H5N1 avian influenza
  - Certain severely ill patients (eg, immunocompromised hosts) during the 2009 to 2010 H1N1 influenza pandemic
High-dose Oseltamivir

- Randomized trial of hospitalized patients with severe influenza
  - 165 and 161 patients randomized to double or standard dose oseltamivir

- RT-PCR negativity on day five of treatment was similar
- Mortality was similar
- No differences in median days on supplemental oxygen, intensive care, or mechanical ventilation
- No differences in tolerability
Extended Duration Antivirals

• Optimal duration for severe cases uncertain

• Clinical judgment and virologic testing of lower respiratory tract specimens by RT-PCR should be used to help guide decisions to treat longer for severe and prolonged illness or immunosuppressed patients

• Careful attention to ventilator and fluid management and to the prevention and treatment of secondary bacterial pneumonia
  • *S. pneumoniae*, *S. aureus* (including MRSA), and *S. pyogenes*
Prevention

• 2017-2018 Influenza Vaccine
  • 38.5% of adults vaccinated last season
  • 58% of children vaccinated

• Everyone ≥6 months of age should get a flu vaccine every season

• Vaccines include:
  • Inactivated influenza vaccine
  • Recombinant influenza vaccine
  • Live attenuated influenza vaccine

• No vaccine preference given

CMV
Cytomegalovirus (CMV) is member of the herpes virus family

- Infects people of all ages – most asymptomatic
  - 1/3 children are already infected by age 5
  - 1/2 infected by the age of 40

- Establishes latent phase mainly within leukocytes

- Past exposure diagnosed with a positive anti-CMV IgG serology

CMV Reaction in ICU Patients

- Reactivation of CMV occurs frequently in critically ill immunocompetent patients
- Cumulative incidence at any level was 33%
- Associated with prolonged hospitalization or death
## CMV Reactivation

### Potential Mechanisms of Injury

<table>
<thead>
<tr>
<th>Direct cytopathic effect</th>
<th>Excessive immune response</th>
<th>Alterations in immune defense</th>
</tr>
</thead>
</table>
Associated Effects of CMV on Outcomes

- Prolonged mechanical ventilation
- Prolonged duration of ICU stay
- Organ system failure
- Nosocomial infections
- Higher mortality rates
Prevention of CMV Reaction

• A Randomized Double-Blind Placebo-Controlled Trial of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (The GRAIL Study)

• 160 non-immunocompromised patients with sepsis or trauma respiratory failure

• Experimental Arm: 5mg/kg IV twice daily for 5 days, then followed by either IV ganciclovir or oral valganciclovir once daily until hospital discharge

• Primary endpoint: IL-6 levels from day 1-14
Cumulative Incidence of Any CMV Reactivation and High-Grade CMV Reactivation

No. of participants

<table>
<thead>
<tr>
<th></th>
<th>Any CMV reactivation</th>
<th>CMV reactivation &gt;1000 IU/mL (high-grade reactivation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>77</td>
<td>83</td>
</tr>
<tr>
<td>Placebo</td>
<td>69</td>
<td>72</td>
</tr>
</tbody>
</table>

Study Day
Effect of Ganciclovir on IL-6 Levels Among CMV + Critically Ill Adults

<table>
<thead>
<tr>
<th>Primary Outcome at Day 14</th>
<th>Intention-to-Treat Group (n = 156)</th>
<th>Sepsis Subgroup (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in plasma IL-6 level, mean, log₁₀ units</td>
<td>Placebo Group (n = 72)</td>
<td>Ganciclovir Group (n = 84)</td>
</tr>
<tr>
<td><strong>Difference in plasma IL-6 level, mean, log₁₀ units</strong></td>
<td>-0.79 (−2.14 to 0.56)</td>
<td>-0.79 (2.06 to 0.48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes at Day 28</th>
<th>Placebo Group (n = 72)</th>
<th>Ganciclovir Group (n = 84)</th>
<th>Absolute Difference (95% CI)</th>
<th>Placebo Group (n = 66)</th>
<th>Ganciclovir Group (n = 71)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence of any plasma CMV reactivation, No. (%)</td>
<td>28 (39)</td>
<td>10 (12)</td>
<td>-27 (−40 to −14)</td>
<td>&lt;.001</td>
<td>26 (39)</td>
<td>10 (14)</td>
<td>-25 (−40 to −11)</td>
</tr>
<tr>
<td>Mechanical ventilation duration, median (IQR), d^a</td>
<td>6 (3 to 12)</td>
<td>5 (3 to 9)</td>
<td>-1 (−3 to −1)^b</td>
<td>.16</td>
<td>6 (3 to 11)</td>
<td>5 (3 to 8)</td>
<td>-1 (−4 to 0)</td>
</tr>
<tr>
<td>Ventilator-free duration, median (IQR), d^a</td>
<td>20 (8 to 24)</td>
<td>23 (16 to 25)</td>
<td>3 (0 to 6)</td>
<td>.05</td>
<td>20 (9 to 24)</td>
<td>23 (16 to 25)</td>
<td>3 (0 to 4)</td>
</tr>
<tr>
<td>ICU length of stay, median (IQR), d^a</td>
<td>8 (5 to 15)</td>
<td>8 (4 to 14)</td>
<td>0 (−4 to 2)</td>
<td>.76</td>
<td>8 (5 to 14)</td>
<td>7 (4 to 12)</td>
<td>-1 (−4 to 1)^b</td>
</tr>
<tr>
<td>Hospital length of stay, median (IQR), d^a</td>
<td>13 (8 to 23)</td>
<td>14 (8 to 22)</td>
<td>1 (−1 to 1)</td>
<td>.92</td>
<td>13 (8 to 22)</td>
<td>13 (8 to 20)</td>
<td>0 (−1 to 1)</td>
</tr>
<tr>
<td>Secondary bacteremia or fungemia, No. (%)</td>
<td>11 (15)</td>
<td>13 (15)</td>
<td>0 (−10 to 10)</td>
<td>.97</td>
<td>9 (14)</td>
<td>10 (14)</td>
<td>0 (−10 to 10)</td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>11 (15)</td>
<td>10 (12)</td>
<td>-3 (−14 to 7)</td>
<td>.54</td>
<td>10 (15)</td>
<td>9 (13)</td>
<td>-2 (−14 to 9)</td>
</tr>
<tr>
<td>Composite end point of mortality and &gt;7 d of mechanical ventilation or &gt;50% increase in IL-6 level, No. (%)</td>
<td>49 (68)</td>
<td>42 (50)</td>
<td>-18 (−33 to −3)</td>
<td>.02</td>
<td>44 (67)</td>
<td>34 (48)</td>
<td>-19 (−35 to −3)</td>
</tr>
</tbody>
</table>
Effect of Ganciclovir on IL-6 Levels Among CMV + Critically Ill Adults

- Among CMV-seropositive adults with critical illness due to sepsis or trauma, ganciclovir did not reduce IL-6 levels
- Published literature and the current study do not support routine clinical use of ganciclovir as a prophylactic agent in patients with sepsis
RSV
RSV

- Respiratory syncytial virus (RSV) is known to be an important cause of lower respiratory tract infections in infants and young children
- Impact in adults, often underappreciated
  - Infects 3%-10% of adults annually
  - 5%-15% of community-acquired pneumonia
  - 9%-10% of hospital admissions for acute cardiorespiratory diseases
- Little is known about the clinical manifestations, complications, and outcomes of severe RSV infections in adults
  - Exception of severely immunocompromised patients
RSV

- Enveloped, non-segmented, single-stranded RNA virus
- Attachment (G) and fusion (F) proteins account for viral binding and penetration
- Classified as either A or B subgroups based on G protein
- F and G proteins are common targets for antivirals and vaccines
RSV

• Very common respiratory virus in children <2-3 years of age
• Second most common viral pathogen in adults >65 years after influenza
• Most infection cause mild symptoms, but can be a common cause of CAP and COPD exacerbations in older adults
• High-risk groups
  • Elderly
  • Chronic cardiopulmonary diseases
  • Immunosuppressed
• Use highly sensitive rRT-PCR assays for detection
Epidemiology

177,000 hospitalizations among adults older than 65 years

14,000 deaths among adults older than 65 years

Infections occur primarily during fall, winter, and spring with peaks preceding Influenza
Treatment

- Treatment in adults is limited to supportive care
  - Bronchodilators
  - Corticosteroids
  - Supplemental oxygen
- HCT patients may benefit from antiviral and immunotherapy
- Overall research in this area has been underappreciated
  - Insensitive point-of-care diagnostics
  - Lack of a distinct clinical syndrome
  - Broad epidemic curve overlapping influenza
Baseline Characteristics, Presenting Symptoms, Complications, and Outcomes of 607 Adults Hospitalized With RSV Infection, 2009–2011

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSV (N = 607)</th>
<th>Influenza (N = 547)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>75.1 (16.4)</td>
<td>74.7 (16.6)</td>
<td>.650</td>
</tr>
<tr>
<td>Male sex</td>
<td>48.6</td>
<td>49.5</td>
<td>.749</td>
</tr>
<tr>
<td>Resident of long-term care facility</td>
<td>32.9</td>
<td>30.5</td>
<td>.378</td>
</tr>
<tr>
<td>Comorbidity, major systemic (except chronic lung diseases)</td>
<td>74.0</td>
<td>66.8</td>
<td>.003</td>
</tr>
<tr>
<td>Chronic lung diseases</td>
<td>36.6</td>
<td>24.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptom onset to admission, d, mean (SD)</td>
<td>2.6 (2.2)</td>
<td>2.0 (1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fever &gt;37.5°C</td>
<td>75.0</td>
<td>94.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cough</td>
<td>87.5</td>
<td>86.7</td>
<td>.513</td>
</tr>
<tr>
<td>Sputum production</td>
<td>81.2</td>
<td>72.5</td>
<td>.010</td>
</tr>
<tr>
<td>Wheezy breathing and dyspnea</td>
<td>68.9</td>
<td>53.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sore throat</td>
<td>11.8</td>
<td>14.3</td>
<td>.364</td>
</tr>
<tr>
<td>Runny nose</td>
<td>25.6</td>
<td>30.2</td>
<td>.214</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>42.3</td>
<td>36.7</td>
<td>.006</td>
</tr>
<tr>
<td>Lower respiratory complications</td>
<td>71.9</td>
<td>55.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>14.3</td>
<td>13.3</td>
<td>.653</td>
</tr>
<tr>
<td>Complications, any</td>
<td>80.4</td>
<td>72.8</td>
<td>.002</td>
</tr>
<tr>
<td>Bacterial infection, overall</td>
<td>14.8</td>
<td>14.3</td>
<td>.790</td>
</tr>
<tr>
<td>Bacterial infection, at presentation</td>
<td>12.5</td>
<td>9.1</td>
<td>.066</td>
</tr>
<tr>
<td>Supplemental oxygen therapy</td>
<td>87.9</td>
<td>59.0</td>
<td>.002</td>
</tr>
<tr>
<td>Ventilation, noninvasive or invasive</td>
<td>11.1</td>
<td>6.2</td>
<td>.003</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>9.1</td>
<td>8.0</td>
<td>.538</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>11.9</td>
<td>8.8</td>
<td>.086</td>
</tr>
<tr>
<td>Time to death, d, median (IQR)</td>
<td>13 (7–29)</td>
<td>7 (3–13)</td>
<td>.001</td>
</tr>
<tr>
<td>Extended care in subacute hospitals</td>
<td>26.2</td>
<td>19.7</td>
<td>.027</td>
</tr>
<tr>
<td>Duration of hospitalization for survivors, d, median (IQR)</td>
<td>7 (5–14)</td>
<td>6 (5–11)</td>
<td>.238</td>
</tr>
</tbody>
</table>
Variables Associated With Death in Hospitalized RSV Patients

- Advanced age (>75 years)
- Pneumonia
- Requirement of ventilator support
- Bacterial superinfection
- Serum urea concentrations
- Total WBC count
Systemic corticosteroids were given to 38.9% of patients to treat acute airway diseases.

<table>
<thead>
<tr>
<th>Variables Associated With Duration of Hospitalization</th>
<th>Adjusted Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age (&gt;75 y)</td>
<td>0.74 (.62–.89)</td>
<td>.001</td>
</tr>
<tr>
<td>Comorbidity, major systemic</td>
<td>0.77 (.64–.94)</td>
<td>.010</td>
</tr>
<tr>
<td>Requirement of ventilatory support</td>
<td>0.39 (.28–.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use of systemic corticosteroids</td>
<td>0.76 (.63–.91)</td>
<td>.002</td>
</tr>
</tbody>
</table>
RSV Takeaways and Future Direction

• RSV can cause severe lower respiratory complications in older adults
  • Respiratory failure
  • Prolonged hospitalization
  • High mortality similar to influenza
• Corticosteroids did not seem to improve clinical outcomes
• The unmet need for effective antiviral therapy and vaccination against RSV
Influenza vaccine should be offered to patients ≥6 months of age every season.
High-dose oseltamivir may not provide additional benefit.
Early administration of oseltamivir has shown to shorten duration of hospitalization.
Optimal duration is uncertain for severe or complicated influenza.
CMV reactivation is associated with worse outcomes.
Routine use of ganciclovir for CMV prophylaxis in patients with sepsis is not recommended.
RSV can cause severe lower respiratory complications in older adults.
Corticosteroids did not seem to improve clinical outcomes.
Unmet need for effective antiviral therapy and vaccination against RSV.
Influenza virus infection can lead to bacterial superinfection and pneumonia secondary to which of the following organisms.

A. *Streptococcus pneumoniae*

B. *Streptococcus pyogenes*

C. *Staphylococcus aureus*

D. All of the above
Learning Assessment Question #2

CMV infection that occurs in immunocompetent adults with critical illness most commonly occurs due to primary infection.

A. True

B. False