Viruses in Severe Respiratory Infections

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Disclosures

- Grant funding
  - US Centers for Disease Control and Prevention (CDC)
  - Massachusetts Department of Public Health
Outline

- Epidemiology & significance
- Diagnosis
- Treatment
- Prevention
Outline

- Epidemiology & significance
- Diagnosis
- Treatment
- Prevention
Etiology of Community-Acquired Pneumonia

- Prospective evaluation of 2,259 adults admitted to 5 hospitals in Chicago and Nashville with pneumonia
- Extensive evaluation for etiology of pneumonia

Viruses more than twice as common as bacteria!

26% of all pneumonias
60% of pneumonias with an identified pathogen
Etiology of Community-Acquired Pneumonia
2,259 adults admitted to 5 hospitals in Chicago and Nashville

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>8.6%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5.8%</td>
</tr>
<tr>
<td><em>Strep. pneumoniae</em></td>
<td>5.1%</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>3.9%</td>
</tr>
<tr>
<td>RSV</td>
<td>3.0%</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>3.0%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>2.3%</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>1.9%</td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
<td>1.6%</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1.4%</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>1.4%</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1.4%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0.5%</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>0.4%</td>
</tr>
<tr>
<td>Other</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

*From N Engl J Med 2015;373:415-427*
Prevalence of Viruses in CAP

<table>
<thead>
<tr>
<th>First author [ref.]</th>
<th>Proportion (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Templeton [1]</td>
<td>0.56 (0.47–0.65)</td>
<td>2.71</td>
</tr>
<tr>
<td>Angeles Marcos [3]</td>
<td>0.23 (0.18–0.30)</td>
<td>3.25</td>
</tr>
<tr>
<td>Saito [32]</td>
<td>0.16 (0.12–0.22)</td>
<td>3.39</td>
</tr>
<tr>
<td>Holm [22]</td>
<td>0.13 (0.06–0.25)</td>
<td>2.73</td>
</tr>
<tr>
<td>Jennings [8]</td>
<td>0.29 (0.24–0.34)</td>
<td>3.35</td>
</tr>
<tr>
<td>Hochental [21]</td>
<td>0.11 (0.08–0.14)</td>
<td>3.56</td>
</tr>
<tr>
<td>Charles [17]</td>
<td>0.16 (0.13–0.18)</td>
<td>3.62</td>
</tr>
<tr>
<td>Johnstone [27]</td>
<td>0.19 (0.14–0.25)</td>
<td>3.29</td>
</tr>
<tr>
<td>Diederen [20]</td>
<td>0.23 (0.18–0.28)</td>
<td>3.33</td>
</tr>
<tr>
<td>Mermel [11]</td>
<td>0.52 (0.46–0.59)</td>
<td>3.10</td>
</tr>
<tr>
<td>Shiblu [4]</td>
<td>0.14 (0.11–0.17)</td>
<td>2.90</td>
</tr>
<tr>
<td>Jh Anna [28]</td>
<td>0.32 (0.25–0.39)</td>
<td>3.13</td>
</tr>
<tr>
<td>Liebermann [30]</td>
<td>0.09 (0.05–0.16)</td>
<td>3.04</td>
</tr>
<tr>
<td>Harla [6]</td>
<td>0.09 (0.06–0.12)</td>
<td>3.58</td>
</tr>
<tr>
<td>Callonzi [18]</td>
<td>0.41 (0.29–0.53)</td>
<td>3.23</td>
</tr>
<tr>
<td>Choi [2]</td>
<td>0.36 (0.28–0.44)</td>
<td>2.91</td>
</tr>
<tr>
<td>Sangili [33]</td>
<td>0.12 (0.08–0.17)</td>
<td>3.44</td>
</tr>
<tr>
<td>Yin [36]</td>
<td>0.23 (0.18–0.27)</td>
<td>3.12</td>
</tr>
<tr>
<td>Luchsinger [9]</td>
<td>0.39 (0.34–0.44)</td>
<td>3.35</td>
</tr>
<tr>
<td>Takahashi [10]</td>
<td>0.16 (0.11–0.23)</td>
<td>3.29</td>
</tr>
<tr>
<td>Wiemken [11]</td>
<td>0.23 (0.19–0.28)</td>
<td>3.46</td>
</tr>
<tr>
<td>Musker [12]</td>
<td>0.16 (0.12–0.21)</td>
<td>3.42</td>
</tr>
<tr>
<td>Vargas [35]</td>
<td>0.22 (0.19–0.25)</td>
<td>3.58</td>
</tr>
<tr>
<td>Huisakens [24]</td>
<td>0.29 (0.25–0.33)</td>
<td>3.44</td>
</tr>
<tr>
<td>Kim [29]</td>
<td>0.26 (0.19–0.28)</td>
<td>3.41</td>
</tr>
<tr>
<td>Karhu [28]</td>
<td>0.49 (0.36–0.63)</td>
<td>2.06</td>
</tr>
<tr>
<td>Holter [23]</td>
<td>0.34 (0.29–0.40)</td>
<td>3.27</td>
</tr>
<tr>
<td>Qu [31]</td>
<td>0.27 (0.25–0.30)</td>
<td>3.59</td>
</tr>
<tr>
<td>Das [19]</td>
<td>0.30 (0.23–0.39)</td>
<td>2.93</td>
</tr>
<tr>
<td>Jain [25]</td>
<td>0.23 (0.22–0.25)</td>
<td>3.66</td>
</tr>
<tr>
<td>Overall (I²=92.9%, p=0.001)</td>
<td>0.24 (0.21–0.27)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Pooled Prevalence 24%
…and so too in hospital-acquired pneumonia

174 Patients with Non-Ventilator HAP  
Barnes-Jewish Hospital, St Louis

- Viruses alone: 22%
- Bacteria alone: 14%
- No pathogen: 63%

99 Patients with HAP Admitted to ICU  
Bichat-Claude Bernard Hospital, Paris

- Viruses alone: 18%
- Viruses & Bacteria: 14%
- Bacteria alone: 63%
- No pathogen: 18% with virus alone
- 14% with virus + bacteria

Respiratory Medicine 2017;122:76-80  
J Clinical Virology 2017;91:52-57
...and so too in severe pneumonias

364 patients with pneumonia (CAP/HAP/VAP) requiring mechanical ventilation, Barnes-Jewish Hospital, St. Louis

Rhinovirus/enterovirus 29%
Influenza 19%
RSV 16%
HMPV 11%
Parainfluenza 10%
Adenovirus 8%
CMV 7%

viruses in 22% of patients

Chest 2018; 154:84-90.
364 patients with pneumonia (CAP/HAP/VAP) requiring mechanical ventilation, Barnes-Jewish Hospital, St. Louis

Mortality Rates High and Similar for Viral and Non-Viral Pneumonias

- Viruses in 22% of patients

...and so too in severe pneumonias
Weekly Pneumonia & Influenza Deaths, USA, 2014-2018

Count of Deaths per Week

Pneumonia

Influenza

US Centers for Disease Control & Prevention
Significance of Viruses

Multiplex PCRs on 747 patients with hematologic malignancies admitted to 17 ICUs in France
60% with acute respiratory failure, 35% on mechanical ventilation

Virus Positive

- Acute Respiratory Failure: 30%
- Non Respiratory Disease: 20%

Virus Types and Prevalence:
- Rhinovirus/enterovirus: 53%
- Coronavirus: 13%
- Influenza: 11%
- RSV: 10%
- Parainfluenza: 7%
- Adenovirus: 3%
- Bocavirus: 1%
- HMPV: 2%
- HMPV: 2%

AJRCCM 2018;ePub (10.1164/rccm.201804-0681OC)
Significance of Viruses

Multiplex PCRs on 747 patients with hematologic malignancies admitted to 17 ICUs in France
60% with acute respiratory failure, 35% on mechanical ventilation

- 14% of patients with positive viral assays did not have any respiratory symptoms
- 27% of patients with positive viral assays and acute respiratory failure had clinically or microbiologically suspected bacterial coinfection
- 10% of patients with positive viral assays were diagnosed with invasive pulmonary aspergillosis (vs 4% of virus negative patients)
- +viral assay associated with adjusted OR for ICU death 2.1 (95% CI 1.2-3.5) in pts w. acute respiratory failure

AJRCCM 2018;ePub (10.1164/rccm.201804-0681OC)
Significance of Viruses 2

1,407 patients requiring mechanical ventilation admitted to 5 Dutch ICUs. Nasopharyngeal swabs and tracheal aspirates sent for respiratory virus PCRs in all patients, regardless of reason for admission.
Significance of Viruses 2

1,407 patients requiring mechanical ventilation admitted to 5 Dutch ICUs. Nasopharyngeal swabs and tracheal aspirates sent for respiratory virus PCRs in all patients, regardless of reason for admission.

Category included:
- Sepsis (19% with viruses)
- Cardiac arrest (16% with viruses)
- Congestive heart failure (28% with viruses)
- Cardiogenic shock (25% with viruses)
- Rhythm disturbance (11% with viruses)
- COPD exacerbation (64% with viruses)
Flu Increases Risk of MI 6-fold!

Self-controlled case series in 364 adults with MI and lab-confirmed flu within 1 year of each other. Assessed MI risk in the week following flu vs weekly risk in the preceding and following year.

Count of MIs in the **week following** lab-confirmed flu: 20

Weekly count of MIs in the **year before and after** confirmed flu: 3.3

**Odds Ratio**

for MI with Flu Infection 6.1

(95% CI 3.9-9.5)

Odds Ratio 3.5 for RSV, 2.8 for other respiratory viruses
Outline

- Epidemiology & significance

- Diagnosis

- Treatment

- Prevention
Randomized Controlled Trial

- 720 patients with acute respiratory illness, fever >37.5°C, or both presenting to an emergency department in England in the winter
- Randomized to rapid respiratory virus PCR panel vs usual care
- Outcomes
  - antibiotic starts
  - antibiotic days
  - length-of-stay

*Lancet Respir Med 2017;5:401-11*
Rapid Viral PCR Panels
720 patients randomized to rapid viral PCR panels vs usual care

- No difference in antibiotic starts
- No difference in mean duration of antibiotics

But…

- More patients in the viral PCR group received very brief (<48h) courses of antibiotics (17% vs 9%)
- Length-of-stay shorter in the PCR group (mean 5.7 vs 6.8 days)
- Appropriate antiviral treatment for flu was more common in the PCR group (91% vs 65%)
Procalcitonin and Pneumonia Etiology
1,735 adults admitted to 5 U.S. hospitals with pneumonia

Procalcitonin Level:

- <0.1
- 0.1-0.24
- 0.25-0.49
- ≥0.5

Pathogen Isolated:
- No pathogen isolated
- Virus
- Bacteria

Clin Infect Dis 2017;65:183-90
1,407 patients requiring mechanical ventilation admitted to 5 Dutch ICUs. Nasopharyngeal swabs and tracheal aspirates sent for respiratory virus PCRs in all patients, regardless of reason for admission.

- 20% of viruses isolated exclusively from nasopharyngeal swab
- 51% of viruses found in both NP swab and tracheal aspirate
- 29% of viruses isolated from tracheal aspirates alone
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- Epidemiology & significance
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Oseltamivir in Outpatients

**Time to Resolution of Symptoms**

- Symptom resolution about 25 hours sooner with oseltamivir.

**Hospital Admissions**

- Hospital admissions ~60% less common with oseltamivir.
Oseltamivir in Hospitalized Patients

Randomized trial of usual care vs oseltamivir in 74 patients with confirmed influenza. Median 5 days of symptoms before admission to hospital.

**Clinical Failure**

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Failure*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>30%</td>
<td>P=.41</td>
</tr>
</tbody>
</table>

“Trend” towards less clinical failure with oseltamivir but study grossly underpowered (n=74)!

*No improvement by day 7, transfer to ICU, death or rehospitalization within 30 days.

Clin Infect Dis 2018;67:736-42
Oseltamivir in ICU Patients

Propensity matched analysis of 40 ICU patients treated for influenza with oseltamivir within 48 hours of admission vs 40 patients treated with oseltamivir >48 hours after admission

Lower mortality rate with early oseltamivir but possible residual confounding

Peramivir IV vs Oseltamivir PO

Peramivir 600mg IV x 1 vs oseltamivir 75mg PO bid x 5d

<table>
<thead>
<tr>
<th>Time to Resolution of Symptoms in Outpatients Randomized Trial, N=727</th>
<th>28-day Mortality In ICU Patients Retrospective Cohort Study, N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 vs 82 hours</td>
<td>35% vs 35%</td>
</tr>
</tbody>
</table>


J Medical Virology 2015;87:1649–1655
Outline

- Epidemiology & significance
- Diagnosis
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- Prevention
Preventing Nosocomial Respiratory Virus Infections

- If 20-30% of pneumonias are due to viruses what more could we be doing to prevent transmission?
  - Active patient screening on admission
  - Active visitor screening & exclusion
  - Daily patient screening for flu-like symptoms
  - Broader and more active viral testing of symptomatic patients
  - Contact + Droplet precautions for all patients with suspected or confirmed viral infections
  - Vaccinate all healthcare workers against flu
  - Eye protection for healthcare workers?

Many single center, before-after studies have described success aborting outbreaks or reducing respiratory virus infection rates using some or all of these options.
Impact of Active Surveillance for Influenza in Hospitalized Patients

Descriptive study of active influenza screening of all patients on admission and daily thereafter during flu season, North York General Hospital, 2012-2015

10% of hospitalized patients tested for flu
(661 lab-confirmed cases)

85% detected on admission

15% detected after admission

• Many with vague symptoms
• Consider viruses in patients with exacerbations of chronic cardiac & pulmonary disease

55% community-onset with delayed detection
86 roommates exposed
21 tested
0 secondary cases

45% nosocomial onset
57 roommates exposed
16 tested
2 secondary cases

• 7% of flu cases nosocomial!
• Higher secondary attack rate (patients are most infectious early in the course of illness)

ICHE 2017;38:387-392
Impact of Vaccinating Health Care Workers on **Patient Outcomes**

### Influenza-like Illness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Intervention Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI Year</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potter 1997</td>
<td>-0.4972</td>
<td>0.4432</td>
<td>490</td>
<td>569</td>
<td>6.6%</td>
<td>0.61 [26, 145] 1997</td>
<td>0.58 [0.46, 0.73]</td>
</tr>
<tr>
<td>Hayward 2006</td>
<td>-0.6904</td>
<td>0.1424</td>
<td>1249</td>
<td>1232</td>
<td>51.2%</td>
<td>0.50 [38, 0.66] 2006</td>
<td>0.60 [0.51, 0.95]</td>
</tr>
<tr>
<td>Lemaitre 2009</td>
<td>-0.366</td>
<td>0.1606</td>
<td>1722</td>
<td>1678</td>
<td>42.2%</td>
<td>0.60 [51, 0.95] 2009</td>
<td>0.58 [0.46, 0.73]</td>
</tr>
</tbody>
</table>

*Total (95% CI): 3461 3570 100.0%*

Heterogeneity: \( \chi^2 = 0.01; \chi^2 = 2.30, df = 2 (P = .32); I^2 = 13\%

Test for overall effect: \( Z = 4.08 (P < .00001) \)

#### 40% decrease!

### All cause mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Intervention Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI Year</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potter 1997</td>
<td>-0.5235</td>
<td>0.2815</td>
<td>490</td>
<td>569</td>
<td>11.6%</td>
<td>0.59 [34, 1.03] 1997</td>
<td>0.71 [0.59, 0.85]</td>
</tr>
<tr>
<td>Carman 2000</td>
<td>-0.4969</td>
<td>0.1874</td>
<td>749</td>
<td>668</td>
<td>26.2%</td>
<td>0.61 [42, 0.88] 2000</td>
<td>0.71 [0.59, 0.85]</td>
</tr>
<tr>
<td>Hayward 2006</td>
<td>-0.314</td>
<td>0.1554</td>
<td>1249</td>
<td>1232</td>
<td>38.1%</td>
<td>0.73 [54, 0.99] 2006</td>
<td>0.71 [0.59, 0.85]</td>
</tr>
<tr>
<td>Lemaitre 2009</td>
<td>-0.1424</td>
<td>0.1952</td>
<td>1722</td>
<td>1678</td>
<td>24.1%</td>
<td>0.87 [59, 1.27] 2009</td>
<td>0.71 [0.59, 0.85]</td>
</tr>
</tbody>
</table>

*Total (95% CI): 4210 4258 100.0%*

Heterogeneity: \( \chi^2 = 0.00; \chi^2 = 2.18, df = 3 (P = .54); I^2 = 0\%

Test for overall effect: \( Z = 3.60 (P = .0003) \)

#### 30% decrease!

*Clin Infect Dis 2014;58:50-57*
Summary

- Viruses are common in CAP and HAP, including severe cases requiring ICU admission
  - Often also present in patients without overt respiratory disease
- Prognosis for viral pneumonia similar to bacterial pneumonia
- Test for viruses. Think beyond flu alone.
  - Positive results can inform prognosis and treatment (oseltamivir), trigger infection control measures, and allay diagnostic uncertainty
- Bacterial coinfection is common so keep an open mind
- Negative procalcitonin suggestive but not definitive
- Protect the critically ill from viral infections in the hospital
Thank You!

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