Severe Community-Acquired Pneumonia:
We don’t know what we don’t know

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Chicago, IL, USA
Conflicts of Interest

• Achaogen
• Arsanis
• Bayer
• Glaxo/Smith/Kline
• KBP Biosciences
• Meiji-Seiko
• Melinta
• Merck
• Microbiotix
• Nabriva
• Pfizer
• Polyphor
• Roche/Genentech
• Shionogi
• The Medicines Co
• IDBYDNA
• Accelerate Diagnostics
• bioMerieux
• Curetis
• GenMark
Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
Pneumonia is the leading Cause of Infectious Deaths in US

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Deaths</th>
<th>Years of Life Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infectious diseases</td>
<td>113.65 (108.76-117.94)</td>
<td>1865.53 (1820.40-1932.73)</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>89.88 (86.25-93.82)</td>
<td>1221.41 (1178.72-1272.52)</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>8.03 (2.77-8.88)</td>
<td>118.31 (60.32-128.40)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>7.75 (7.66-7.84)</td>
<td>299.13 (296.03-302.53)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1.34 (1.28-1.41)</td>
<td>50.89 (48.72-53.66)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0.97 (0.89-1.07)</td>
<td>27.99 (25.53-30.69)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.85 (0.81-0.89)</td>
<td>17.71 (16.93-18.49)</td>
</tr>
</tbody>
</table>

el Bcheraoui et al, JAMA, 2018
Figure 2. County-Level Mortality From Lower Respiratory Infections

A Age-standardized mortality rate from lower respiratory infections, both sexes, 2014

el Bcheraoui et al, JAMA, 2018
B Percent change in age-standardized mortality rate from lower respiratory infections between 1980 and 2014, both sexes

C Age-standardized mortality rate from lower respiratory infections over time, both sexes

el Bcheraoui et al, JAMA, 2018
Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
  - Probably underestimated by CDC
- CAP is a disease of health disparities and underlying co-morbidities
Incidence: 634/100,000 population
- NO exclusions
- Recent hospitalization and immunocompromised included

Translates into 1.5 million admissions/year in US

Second most common admission diagnosis in both adults and children – HCUP database
Impact of Comorbid Conditions

Ramirez et al, CID, 2017
Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
- CAP is a disease of health disparities and underlying co-morbidities
- Outcome of many critical illnesses, including CAP, is determined by the **timely provision of appropriate antibiotic(s)**
Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case-control study

$p < 0.01$ for all
ARDS Preventive Strategies: Appropriate Antibiotics

### Septic Shock

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed goal-directed resuscitation</td>
<td>3.55</td>
<td>1.52-8.63</td>
<td>.004</td>
</tr>
<tr>
<td>Delayed antibiotics</td>
<td>2.39</td>
<td>1.06-5.59</td>
<td>.039</td>
</tr>
<tr>
<td>Respiratory rate (per sd)</td>
<td>2.03</td>
<td>1.38-3.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6.47</td>
<td>1.99-24.9</td>
<td>.003</td>
</tr>
<tr>
<td>Chronic alcohol use</td>
<td>2.09</td>
<td>.88-5.10</td>
<td>.098</td>
</tr>
<tr>
<td>Transfusion</td>
<td>2.75</td>
<td>1.22-6.37</td>
<td>.016</td>
</tr>
<tr>
<td>Aspiration</td>
<td>3.45</td>
<td>1.22-10.75</td>
<td>.024</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>.44</td>
<td>.17-1.07</td>
<td>.076</td>
</tr>
</tbody>
</table>

### Pneumonia

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate initial antimicrobial treatment</td>
<td>3.1</td>
<td>1.5-7.0</td>
</tr>
<tr>
<td>Any transfusion</td>
<td>3.2</td>
<td>1.3-8.8</td>
</tr>
<tr>
<td>HAP</td>
<td>1.8</td>
<td>0.9-3.8</td>
</tr>
</tbody>
</table>

HAP, hospital-acquired pneumonia; PSI, pneumonia severity index.

**References**

- Iscimen et al, Crit Care Med 2008;36:1518-1522
- Kojicic et al, Crit Care 2012;16:R46
- Levitt JE and Matthay MA. Critical Care 2012;1:223
What is (are) the correct antibiotic(s), specifically for Severe CAP?
A 44 yo without prior medical history presents with cough, hemoptysis, shortness of breath and fever. He has marked increase work of breathing and is intubated. CXR demonstrates bilateral infiltrates. Preliminary laboratories demonstrate a neutrophil count of 550/uL. **Your initial antibiotic therapy would be:**

1. Vancomycin and piperacillin/tazobactam
2. Ceftriaxone and azithromycin
3. Vancomycin, cefipime, and doxycycline
4. Moxifloxacin
5. Ceftriaxone, azithromycin, and linezolid
Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

Inpatient ICU treatment

20. A β-lactam (cefotaxime, ceftiraxone, or ampicillin-sulbactam) plus either azithromycin (level II evidence) or a fluoroquinolone (level evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

21. For Pseudomonas infection, use an antipseudomonal β-lactam (piperacillin-tazobactam, ceftazidime, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose)

22. For community-acquired methicillin-resistant Staphylococcus aureus infection, add vancomycin or linezolid

(Moderate recommendation; level III evidence)
What is the most likely reason for treatment “failure” in severe CAP?

1. Antibiotic resistance
2. Unusual pathogen
3. Exaggerated host response
4. Bacterial virulence factors
5. Genetic immunodeficiency
- Prospective observational cohort from 14 Portuguese ICUs over 1 year
- All infections at admission to the ICU
Etiology in SCAP

Pereira et al, J Crit Care, 2018

- Etiology in 35%
- Secondary bacteremia in 11%
- 40% “immunosuppressed”

**Etiology of SCAP (n = 502 episodes).**

<table>
<thead>
<tr>
<th>Microrganisms</th>
<th>n = (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive</strong></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>79 (15.7)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>50 (10)</td>
</tr>
<tr>
<td>Other <em>Streptococcus spp.</em></td>
<td>28 (5.6)</td>
</tr>
<tr>
<td></td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Gram negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em></td>
<td>78 (15.5)</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>16 (3.2)</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>15 (3.2)</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
<td>12 (2.4)</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>12 (2.4)</td>
</tr>
<tr>
<td><em>Proteus spp.</em></td>
<td>7 (1.4)</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>4 (0.8)</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>3 (0.6)</td>
</tr>
<tr>
<td><em>Serratia spp.</em></td>
<td>3 (0.6)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Other Gram negative</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Other virus</td>
<td>37 (7.4)</td>
</tr>
<tr>
<td>Other virus</td>
<td>36 (7.2)</td>
</tr>
<tr>
<td>Other microorganisms</td>
<td>8 (1.6)</td>
</tr>
</tbody>
</table>
Host–pathogen interactions and prognosis of critically ill immunocompetent patients with pneumococcal pneumonia: the nationwide prospective observational STREPTOGENE study

614 Caucasian patients from 51 French ICUs
18.9% hospital mortality
NO strain was resistant to β-lactam

ESM 5. Hospital mortality according to antibiotic regimen

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>N patients (column %)</th>
<th>N deaths (row %)</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted OR(^a) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactam+macrolide</td>
<td>223 (36.3)</td>
<td>45 (20.2)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>β-lactam+quinolone</td>
<td>210 (34.2)</td>
<td>32 (15.2)</td>
<td>0.71 (0.43 to 1.17)</td>
<td>0.73 (0.41 to 1.31)</td>
</tr>
<tr>
<td>β-lactam only</td>
<td>139 (22.6)</td>
<td>26 (18.7)</td>
<td>0.91 (0.55 to 1.56)</td>
<td>1.25 (0.65 to 2.40)</td>
</tr>
<tr>
<td>Other</td>
<td>42 (6.8)</td>
<td>13 (31.0)</td>
<td>1.77 (0.85 to 3.68)</td>
<td>1.60 (0.62 to 4.12)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for the multivariable score predicting hospital death

Bedos et al, Intens Care Med, 2018
Healthcare-Associated Pneumonia (HCAP)
Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults


July 14, 2015
CDC-EPIC Etiology of CAP: Etiology Results

Percent of patients

<table>
<thead>
<tr>
<th></th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>77</td>
<td>64</td>
</tr>
<tr>
<td>Bacterial</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>None</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>
EPIC – Pathogen Detections

115/2320 (5%) *S. pneumoniae*

7/2320 (0.3%) *Pseudomonas*

38/2320 (1.6%) *S. aureus*
## Independent Risk Factors for Pneumonia Secondary to: CAP-DRP MRSA

<table>
<thead>
<tr>
<th>CAP-DRP</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization $\geq$ 2 days in previous 90 days</td>
<td>Hospitalization $\geq$ 2 days in previous 90 days</td>
</tr>
<tr>
<td>Use of antibiotics in previous 90 days</td>
<td>Use of antibiotics in previous 90 days</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Chronic hemodialysis in previous 30 days*</td>
</tr>
<tr>
<td>Non-ambulatory status</td>
<td>Prior MRSA colonization*</td>
</tr>
<tr>
<td>Tube feedings</td>
<td>Congestive heart failure*</td>
</tr>
<tr>
<td>Gastric acid suppression</td>
<td>Gastric acid suppression</td>
</tr>
</tbody>
</table>

* MRSA- specific risk factors

**Shindo, Am J Respir Crit Care Med, 2013**
Risk for CAP-Drug Resistant Pathogens

![Bar chart showing the risk for CAP-Drug Resistant Pathogens]

Shindo, Am J Respir Crit Care Med, 2013
Treatment Response for Patients with \( \leq 1 \) Risk for CAP-DRPs

<table>
<thead>
<tr>
<th>Empirical Treatment</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>2.1</td>
</tr>
<tr>
<td>Mono β-lactam</td>
<td>10.2</td>
</tr>
<tr>
<td>Broad Spec</td>
<td>13.2</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>9.7</td>
</tr>
</tbody>
</table>

\( p = 0.00001 \)

Shindo, Am J Respir Crit Care Med, 2013
Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

Douwe F. Postma, M.D., Cornelis H. van Werkhoven, M.D.,
Leontine J.R. van Elden, M.D., Ph.D., Steven F.T. Thijsen, M.D., Ph.D.,
Andy I.M. Hoepelman, M.D., Ph.D., Jan A.J.W. Kluytmans, M.D., Ph.D.,
Wim G. Boersma, M.D., Ph.D., Clara J. Compaijen, M.D., Eva van der Wall, M.D.,
Jan M. Prins, M.D., Ph.D., Jan J. Oosterheert, M.D., Ph.D., and
Marc J.M. Bonten, M.D., Ph.D., for the CAP-START Study Group*
CAP-START Endpoints

Postma et al, NEJM, 2015
β-Lactam Monotherapy vs β-Lactam-Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia
A Randomized Noninferiority Trial

TCS difference at 7 days – 7.6% (95% CI: -0.8 to 16, p = .07)

HR PSI IV = 0.81 (0.59-1.10)
HR CURB65 >2 = 0.80 (0.61-1.06)

ICU transfer: 3 (Legionella) vs. 0
Death 2 (Mycoplasma) vs. 0
Significantly more readmissions
Paradigm Change:
Should have good reasons to not treat with traditional CAP drugs, even for SCAP
Paradigm Change

Viruses are a **common cause** of adult CAP
- up to 50% in SCAP

Karhu et al, CID, 2014
EPIC – Pathogen Detections

HRV | Flu | S. pn. | HMPV | RSV | PIV | G. ng.* | CoV | M. pn. | S. au. | AdV | Leg. | Strep | spOther†
NP/OP vs. Sputum PCR

Bacteria detected by TaqMan Array PCR in otherwise negative samples

What is the most likely reason for treatment “failure” in severe CAP?

1. Antibiotic resistance
2. Unusual pathogen - ?
3. Exaggerated host response
4. Bacterial virulence factors
5. Genetic immunodeficiency
# FilmArray® Pneumonia Panel (Investigational Use Only)

## Bacteria
- Semi - Quantitative
  - Acinetobacter calcoaceticus-baumannii complex
  - Serratia marcescens
  - Proteus spp.
  - Klebsiella pneumoniae group
  - Enterobacter aerogenes
  - Enterobacter cloacae
  - Escherichia coli
  - Haemophilus influenzae
  - Moraxella catarrhalis
  - Pseudomonas aeruginosa
  - Staphylococcus aureus
  - Streptococcus pneumoniae
  - Klebsiella oxytoca
  - Streptococcus pyogenes
  - Streptococcus agalactiae

## Atypical Bacteria
- Qualitative
  - Legionella pneumophila
  - Mycoplasma pneumoniae
  - Chlamydia pneumoniae

## Viruses
- Influenza A
- Influenza B
- Adenovirus
- Coronavirus
- Parainfluenza virus
- Respiratory Syncytial virus
- Human Rhinovirus/Enterovirus
- Human Metapneumovirus
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

## Resistance Markers
- mecA/mecC and MREJ
- KPC
- NDM
- Oxa48-like
- CTX-M
- VIM
- IMP

## Sample Types:
- Sputum
  - Induced
  - Aspirated
  - Expectorated
- Bronchoalveolar Lavage
  - BAL
  - Mini - BAL
If not HCAP pathogens, what are resistance issues in CABP?

- Methicillin-resistant *S. aureus* (MRSA)
- Macrolide-resistant *Mycoplasma pneumoniae*
- Cephalosporin-resistant Streptococci or other “normal flora”
  - *S. pneumoniae* - ? Macrolide>beta-lactam>quinolone
  - ESBL Enterobacteriaceae
Empiric therapy directed against MRSA in patients admitted to the intensive care unit does not improve outcomes in community-acquired pneumonia

- No difference in hospital mortality (25% vs. 24%) or 28-day mortality (38% vs. 43%)
- No difference in LOS
- No difference in TCS
MRSA Treatment based on Risk Factor

VAMC Community-onset Pneumonia

- MRSA Coverage
- No MRSA Coverage

Teshome et al, BMC Infect Dis, 2015
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MRSA CAP, n (%)</th>
<th>Methicillin-Susceptible Staphylococcus aureus CAP, n (%)</th>
<th>Pneumococcal CAP, n (%)</th>
<th>P Value* (MRSA vs Pneumococcal)</th>
<th>All-Cause non-Staphylococcus aureus CAP, n (%)</th>
<th>P Value* (MRSA vs All-Cause non-Staphylococcus aureus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis use</td>
<td>3 (20.0)</td>
<td>2 (9.1)</td>
<td>3 (2.6)</td>
<td>0.02</td>
<td>82 (3.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>1 (6.7)</td>
<td>1 (4.6)</td>
<td>4 (3.5)</td>
<td>0.46</td>
<td>85 (3.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (46.7)</td>
<td>8 (36.4)</td>
<td>23 (20.0)</td>
<td>0.04</td>
<td>569 (25.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Recurrent soft tissue infections</td>
<td>1 (6.7)</td>
<td>4 (18.2)</td>
<td>9 (7.8)</td>
<td>1.00</td>
<td>145 (6.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2 (13.3)</td>
<td>3 (13.6)</td>
<td>13 (11.3)</td>
<td>0.68</td>
<td>192 (8.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Daily alcohol use</td>
<td>1 (6.7)</td>
<td>3 (13.6)</td>
<td>11 (9.6)</td>
<td>1.00</td>
<td>156 (7.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multilobar or cavitary infiltrates</td>
<td>5 (33.3)</td>
<td>7 (31.8)</td>
<td>39 (33.9)</td>
<td>1.00</td>
<td>667 (30.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>4 (26.7)</td>
<td>5 (22.7)</td>
<td>41 (35.7)</td>
<td>0.58</td>
<td>687 (30.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Concurrent influenza infection</td>
<td>1 (6.7)</td>
<td>2 (9.1)</td>
<td>4 (3.5)</td>
<td>0.46</td>
<td>129 (5.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Current proton pump inhibitor use</td>
<td>5 (33.3)</td>
<td>5 (22.7)</td>
<td>18 (15.6)</td>
<td>0.14</td>
<td>505 (22.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Outpatient antibiotic use prior to admission</td>
<td>2 (13.3)</td>
<td>0</td>
<td>15 (13.0)</td>
<td>1.00</td>
<td>440 (19.8)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Clinical Features Suggesting Community-Acquired MRSA Pneumonia.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary infiltrate or necrosis</td>
</tr>
<tr>
<td>Rapidly increasing pleural effusion</td>
</tr>
<tr>
<td>Gross hemoptysis (not just blood-streaked)</td>
</tr>
<tr>
<td>Concurrent influenza</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Erythematous rash</td>
</tr>
<tr>
<td>Skin pustules</td>
</tr>
<tr>
<td>Young, previously healthy patient</td>
</tr>
<tr>
<td>Severe pneumonia during summer months</td>
</tr>
</tbody>
</table>

Gross Findings: The Lung
Validation of BAL MRSA Rapid Diagnostic Test
MRSA/SA SSTI Assay for Cepheid Xpert® platform

<table>
<thead>
<tr>
<th>MRSA</th>
<th>Growth in Culture</th>
<th>MSSA</th>
<th>Growth in Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>A-PCR Positive</td>
<td>Yes</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1*</td>
<td>220</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>224</td>
<td>247</td>
</tr>
</tbody>
</table>

* Growth 100 cfu/ml in culture, clinically thought negative and no treatment

**MRSA Negative Predictive Value – 99.6%, Negative LR – 0.04**
What is the most likely reason for treatment “failure” in severe CAP?

1. Antibiotic resistance
2. Unusual pathogen - ?
3. Exaggerated host response
4. Bacterial virulence factors
5. Genetic immunodeficiency
**TABLE 2.** Cox regression analysis of factors associated with 30 days mortality in community-acquired, Panton–Valentine leukocidin-positive *Staphylococcus aureus* necrotizing pneumoniaa

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>Multivariate adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway haemorrhage</td>
<td>0.004</td>
<td>2.96 (1.41–6.25)</td>
</tr>
<tr>
<td>Leucocyte count (10⁹/L)b</td>
<td>0.001</td>
<td>0.32 (0.17–0.61)</td>
</tr>
<tr>
<td>Antitoxinic treatment</td>
<td>0.002</td>
<td>0.11 (0.03–0.49)</td>
</tr>
</tbody>
</table>

aThe model was adjusted on severity and presence of the mecA gene.
bIn this model, natural logarithms of leucocyte counts were used.

*Sicot et al, Clin Microbiol Inf, 2012*
Macrolide Combination Therapy

Brown, Chest, 2003

Monotherapy vs. Macrolide Combination Therapy

- Ceftriaxone: 6.31% vs. 2.76% (p < 0.0001)
- Other Ceph: 5.11% vs. 2.16% (p < 0.0001)
- Penicillin: 8.15% vs. 2.46% (p < 0.05)
- Quinolone: 4.94% vs. 2.91% (p < 0.05)

Mortality (%)
A 44 yo without prior medical history presents with cough, hemoptysis, shortness of breath and fever. He has marked increase work of breathing and is intubated. CXR demonstrates bilateral infiltrates. Preliminary laboratories demonstrate a neutrophil count of 550/uL. Your initial antibiotic therapy would be:

1. Vancomycin and piperacillin/tazobactam
2. Ceftriaxone and azithromycin
3. Vancomycin, cefipime, and doxycycline
4. Moxifloxacin
5. Ceftriaxone, azithromycin, and linezolid
A 44 yo male presents with cough and fever. CXR demonstrates bilateral alveolar infiltrates. A urinary antigen is positive for pneumococcus and a nasal swab is positive for influenza A – he has been started on ceftriaxone and azithromycin.

After 6 hours in the ICU, he is on FiO₂ 0.90, PEEP 20 cmH₂O, assist control mode with 6 cc/kg tidal volume, RR 35 with minimal auto-PEEP. Norepinephrine had to be added when PEEP was increased from 16 to 20 cmH₂O.

**What would you do at this point?**

1. Start high dose steroids
2. Prone positioning
3. Switch antibiotic to vancomycin and piperacillin/tazobactam
4. VV-ECMO
5. Inhaled nitric oxide
Bacterial pneumonia (usually) doesn’t respond to recruitment maneuvers
Pneumonia as Cause of ARDS

- Mortality rate second only to aspiration
- May be less likely to respond to recruitment maneuvers, inhaled pulmonary vasodilators, and/or proning

![Bar chart showing mortality rates and response to treatments](attachment:chart.png)
### Table 2. End Points. ECMO for Severe ARDS (EOLIA) — Combes et al, NEJM, 2018

<table>
<thead>
<tr>
<th>End Point</th>
<th>ECMO Group (N = 124)</th>
<th>Control Group (N = 125)</th>
<th>Relative Risk or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: mortality at 60 days — no. (%)</td>
<td>44 (35)</td>
<td>57 (46)</td>
<td>0.76 (0.55 to 1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Key secondary end point: treatment failure at 60 days — no. (%)‡</td>
<td>44 (35)</td>
<td>72 (58)</td>
<td>0.62 (0.47 to 0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 90 days — no. (%)</td>
<td>46 (37)</td>
<td>59 (47)</td>
<td>-10 (-22 to 2)</td>
<td></td>
</tr>
<tr>
<td>Median length of stay (interquartile range) — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the ICU</td>
<td>23 (13–34)</td>
<td>18 (8–33)</td>
<td>5 (-1 to 10)</td>
<td></td>
</tr>
<tr>
<td>In the hospital</td>
<td>36 (19–48)</td>
<td>18 (5–43)</td>
<td>18 (6 to 25)</td>
<td></td>
</tr>
<tr>
<td>Median days free from mechanical ventilation (interquartile range)§</td>
<td>23 (0–40)</td>
<td>3 (0–36)</td>
<td>20 (-5 to 32)</td>
<td></td>
</tr>
<tr>
<td>Median days free from vasopressor use (interquartile range)§</td>
<td>49 (0–56)</td>
<td>40 (0–53)</td>
<td>9 (0 to 51)</td>
<td></td>
</tr>
<tr>
<td>Median days free from renal-replacement therapy (interquartile range)§</td>
<td>50 (0–60)</td>
<td>32 (0–57)</td>
<td>18 (0 to 51)</td>
<td></td>
</tr>
<tr>
<td>Prone position — no. (%)¶</td>
<td>82 (66)</td>
<td>113 (90)</td>
<td>-24 (-34 to -14)</td>
<td></td>
</tr>
<tr>
<td>Recruitment maneuvers — no. (%)¶</td>
<td>27 (22)</td>
<td>54 (43)</td>
<td>-21 (-32 to -10)</td>
<td></td>
</tr>
<tr>
<td>Inhaled nitric oxide or prostacyclin — no. (%)¶</td>
<td>75 (60)</td>
<td>104 (83)</td>
<td>-23 (-33 to -12)</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids — no. (%)¶</td>
<td>80 (65)</td>
<td>82 (66)</td>
<td>-1 (-13 to 11)</td>
<td></td>
</tr>
</tbody>
</table>
What is the most likely reason for treatment “failure” in severe CAP?

1. Antibiotic resistance
2. Unusual pathogen - ?
3. Exaggerated host response
   ✓ Bacterial virulence factors
5. Genetic immunodeficiency
Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
- CAP is a disease of health disparities and underlying co-morbidities
- Outcome CAP determined by the timely provision of appropriate antibiotic(s)
  - Need to address toxin production for most common pathogens
  - Viral SCAP is underappreciated
- An important minority die of hypoxemic death
- Immune modulation is needed to improve overall outcome
- Required CRP > 150 mg/L for enrollment
- 7.5 years to recruit 112 patients from 3 hospitals = 5 pts/yr
- No mortality difference
- Mostly late failure (> 72 hours) by radiographic criteria
Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia
A Systematic Review and Meta-analysis

Figure 1. Effect of corticosteroids on all-cause mortality in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.
Corticosteroids for CAP

💖 For non-ICU patients:
- Dutch and Swiss studies – β-lactam monotherapy is the standard, lower 95% CI of LOS in placebo is 6 days
- Some increased risk of hyperglycemia and readmission
- Would NOT use but give macrolide instead

💖 For ICU patients, works in some
- Defining patient groups is difficult
- Worse outcome in influenza/viral pneumonia
Genetic Influences on Premature Death

Parent Death < 50

- Infection: 5.81
- Vascular: 4.52
- Cancer: 1.19

Parent Death < 70

- Infection: 0.73
- Vascular: 0.87
- Cancer: 1.92

*p < 0.001
Genetic Risk of Severe Influenza

- Mechanical ventilation
- ECMO

Interferon-induced transmembrane protein-3 (IFITM-3) rs34481144 SNP
EK Allen et al, Nature Medicine, 2017
A 65 yo Type 2 diabetic male with urinary antigen-positive pneumococcal pneumonia had atrial fibrillation for approximately 12 hours and a minor troponin elevation while on noninvasive ventilation in the ICU. In anticipation of discharge 5 days later, you should:

a. Place on aspirin and initiate a statin  
b. Check an echocardiogram  
c. Discontinue amiodarone  
d. Perform a left heart catheterization  
e. Perform noninvasive coronary evaluation
Association between Pneumococcal Pneumonia and Inpatient Acute Cardiac Events

33/170 (19.4%) had at least one major cardiac event

Musher et al, Clin Infect Dis, 2007
Myocardial Infarct and CAP

AMI diagnoses in 5.8% (29/500)
- 15% (13/86) of ICU admissions
- ST changes in 25%, NSTEMI 75%

50% (10/20) of transfers to ICU in first 24 hours had MI

More likely if have clinical failure (51.7% vs. 11%)

Increased mortality
- 27.6% vs. 6.8% in hospital
- 31% vs. 9.6% at 30 days

Retrospective review: 500 cases at Louisville VAMC
- Biomarkers of myocardial injury and either EKG changes or intervention
- Severe sepsis excluded since can elevate troponins

Ramirez, Clin Infect Dis, 2008
Coagulation Abnormalities in Severe CAP

D-dimer

Thrombocytopenia


Brogly et al, J Infection, 2007
Subsequent Mortality in Previously Well-functioning Elderly Admitted for CAP

Mortality from CAP - Louisville

All cause mortality

- Includes recent hospitalized and immunocompromised
- Death certificates of hospitalized don’t necessarily indicate pneumonia
- Emerging data of increased risk of cardiovascular deaths after CAP admission – not infectious

Estimated Annual US Pneumonia Mortality – 484,000
Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
- CAP is a disease of health disparities and underlying co-morbidities
- Outcome determined by the timely provision of appropriate antibiotic(s)
  - Need to address toxin production for common bacterial pathogens
  - Viral SCAP is underappreciated
- An important minority die of hypoxemic death
- Immune modulation is needed to improve overall outcome
- CAP is not just an acute disease