Inaugural Scientific and Clinical Symposium on Pneumonia

December 9, 2016
LEARNING OBJECTIVES
This course will enable participants to:

- Review current state of the art concepts in the pathogenesis of pneumonia
- Discuss current understanding and guidelines for community acquired pneumonia
- Discuss new guidelines for hospital acquired pneumonia
- Discuss new guidelines for ventilator-associated pneumonia
- Determine the utility of new diagnostic tools for determining etiology of the pneumonia
- Discuss how procalcitonin and other biomarkers can be used in pneumonia management
- Review new therapies for respiratory infections
- Highlight new guidelines for antibiotics resistance and stewardship
- Discuss recent influenza and pneumococcal vaccines

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The Yale School of Medicine designates this live activity for a maximum of 7.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Inaugural Scientific and Clinical Symposium on Pneumonia

Schedule

7:00am  Registration and Continental Breakfast

8:00am  Welcome
        *Naftali Kaminski MD*

        Introduction and Overview of Symposium and State of Pneumonia
        *Charles S. Dela Cruz MD, PhD*

8:15am  *Scientific*
        Concept of Disease Resilience in Pneumonia
        *Joseph P. Mizgerd ScD*

8:40am  *Scientific*
        Influenza Pneumonia and Pathogenesis
        *Adolfo Garcia-Sastre PhD*

9:05am  Refreshment Break

9:15am  *Clinical*
        Community Acquired Pneumonia (CAP): Current Guidelines
        *Michael S. Niederman MD, MACP, FCCP, FCCM, FERS*

9:40am  *Clinical*
        Hospital Acquired Pneumonia / Ventilator Associated Pneumonia (HAP/VAP): New Guidelines
        *Mark L. Metersky MD*

10:05am  *Clinical*
        Viral Diagnostic Tools and Strategies for Pneumonia
        *Marie-Louise Landry MD*

10:25am  *Clinical*
        Bacterial Diagnostic Tools and Strategies for Pneumonia
        *David R. Peaper MD, PhD*
10:45am  Panel Discussion

11:15am  Break / Lunch

12:30pm  **Scientific**
Cutting-edge Therapies for Respiratory Infection
*Chad R. Marion DO, PhD*

12:55pm  **Scientific**
The Lung Microbiome: Insights into Precision and Personalized Approach to Pneumonia
*Leopoldo Segal MD*

1:20pm  **Clinical**
Nuts and Bolts on Antimicrobial Treatment for CAP/HAP/VAP and Multidrug Resistant Organisms
*Jeffrey E. Topal MD*

1:45pm  Refreshment Break

1:55pm  **Clinical**
Antibiotic Resistance and Stewardship
*Louise-Marie Dembry MD, FACP, MS, MBA*

2:20pm  **Clinical**
Prevention of Pneumonia
*Manisha Juthani MD*

2:45pm  **Clinical**
Pneumonia Vaccines in 2016
*Albert C. Shaw, MD, PhD*

3:10pm  Panel Discussion

3:50pm  Closing Remarks

4:00pm  Cocktail Reception
Faculty

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Yale School of Medicine

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Inaugural Scientific and Clinical Symposium on Pneumonia

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After review by the Course Director, it has been determined there are no conflicts of interest.
Inaugural Scientific and Clinical Symposium on Pneumonia

This conference is supported by educational grants from:

Cempra, Inc.
Pfizer, Inc.

We are grateful for their support
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Recording of this session by attendees is strictly prohibited
Concept of Disease Resilience in Pneumonia

Joseph P. Mizgerd, Sc.D.
Pulmonary Center, Boston University School of Medicine

Lung infections are important.

[Graph showing the Global Burden of Disease with Acute Lung Infection at the top and other conditions listed below it.]

DALYs lost worldwide are driven by many children dying in less affluent regions

Childhood respiratory infections matter everywhere, even the wealthiest countries.

[Graph showing Childhood hospitalizations in US (number of discharges in 2009) with Pneumonia at the top and other conditions listed below it.]
Children with pneumonia tend to be young. About half have underlying conditions when they develop pneumonia, while half do not. Most survive (in the US) but pneumonia can be severe; a fifth need critical care, of which a third need ventilator support. Survivors have increased prevalence of chronic pulmonary diseases in later years.


Pneumonia is an even greater concern for adults than for children, beginning in middle age. Most survive but pneumonia can be severe; a fifth need critical care, of which a third need ventilator support (21% ICU, 6% MV). Survivors have accelerated decline from respiratory disease, cardiovascular disease, neurological disease, and other co-morbidities.


Pneumonia is less a story about microbes and more a story about how the host responds to microbes.
Parallel host responses during infection prevent/limit disease – resistance and resilience

Immune resistance: Host pathways that diminish the number of living pathogens during infection, by killing or removing them (or by hastening processes of their killing or removal).

Tissue resilience: Pathways by which the host withstands, endures, or tolerates the stress of a given microbial challenge. Rather than altering microbial burdens, these pathways diminish pathophysiology by limiting damage elicited by pathogens or by immune resistance pathways.

Resistance and resilience form twin pillars of lung defense

Changes in resistance and resilience may dictate pneumonia susceptibility and outcome

Immune Resistance

- Innate Immunity
  - Resident (epithelial cells, alveolar macrophages, etc.)
  - Recruited (neutrophils, monocytes, innate lymphocytes, etc.)
  - Systemic (acute phase proteins, natural antibodies, complement, etc.)
The epithelial cells of the lungs have unique and specialized responses to respiratory infection

Kamata et al., Am J Respir Cell Mol Biol 2016.

Rapid neutrophil recruitment is one role of epithelial cells that is essential to immune defense

Yamamoto et al., Am J Respir Cell Mol Biol 2014.

Hepatic responses erect a vascular shield to prevent dissemination of infection from the lungs

Quinton et al., J Clin Invest 2012.

Immune Resistance

- Innate Immunity
  - Resident, recruited, and systemic arms

- Adaptive immunity
  - Multiple arms
    - Primary vs. Secondary/Recall/Memory
    - Homotypic vs. Heterotypic
    - Central/Circulating/Systemic vs. Resident
      - Dominant adaptive immune responses protecting against pneumonia may be driven by the fact that the microbes causing pneumonia are common respiratory pathobionts
Adults have heterotypic (specific yet broad) immune responses to respiratory pathobionts like pneumococcus. Pneumococcus products that do not include capsule (hence not serotype-specific) induce proliferation of BPMCs from healthy Swedish adults.

Malley and colleagues, Vaccine 2012.

Plasma antibodies recognize pneumococcal “whole cell antigen” (WCA, killed acapsular bacteria).

Those with more heterotypic immunity do better (less virus, less symptoms) during respiratory infection.

Malley and colleagues, Vaccine 2012.

The lungs of adult humans contain very many resident memory T (TRM) cells, and these have distinct phenotypes from other memory T cells.

van Lier and colleagues, Nat Immunol 2016.

Lung TRM cells can be generated in mice and provide superior protection against influenza pneumonia.

Farber and colleagues, J Immunol 2011.
"Natural" exposures to microbes remodel circulating and resident immune systems


The naturally acquired immunological memory that protects against pneumonia needs to be better defined, including where it is and what it recognizes and how it responds to infection.

**Tissue Resilience**

- Anti-inflammatory pathways
  - Limit the degree of injurious inflammation
- Pro-resolution pathways
  - End inflammatory process, clean up the mess
    - Efferocytosis
    - Edema fluid resorption
- Structure/function-preserving pathways
  - Diminish cell death and tissue degradation
    - Anti-apoptotic programs, anti-proteases, anti-oxidants, etc.
- Repair and regeneration pathways
  - Restore or replace tissues that were damaged

**Anti-inflammatory pathway: “sessile” alveolar macrophages use gap junctions to communicate to the epithelium and dampen inflammation**

Connexin 43, here targeted using CD11c-Cre, mediates calcium signaling from macrophages to epithelial cells, limiting chemokine expression and neutrophil recruitment elicited by LPS in the lungs.

Pro-resolution pathway:
Lipid mediators produced during pneumonia accelerate efferocytosis and resolution


Structure/function preservation pathway:
STAT3 in epithelial cells prevents lung injury, dependent on LIF


Tissue repair pathway:
Distinct cells can lead to healthy restoration or aberrant scarring; controversial still


Tissue resilience also matters over longer term and outside of lung: sequelae of surviving pneumonia include...

- Severe pneumonia survivors have worse declines and increased subsequent morbidity and mortality from seemingly “unrelated” causes...
  - COPD (*NEJM* 359:2355, 2008)
  - Cardiovascular events (*JAMA* 313:264, 2015)
  - Cognitive decline (*AJRCCM* 185:596, 2013; *NEJM* 369:1306, 2013)
  - Depression (*AJRCCM* 185:517, 2012)
  - Functional disability (*NEJM* 364:1293, 2011)
  - Risk of death over ensuing 1-10 years (*CID* 56:1145, 2013)
- Pneumonia-related vaccines can decrease “unrelated” morbidity and mortality.
  - Influenza vaccination decreases major adverse cardiovascular events (*JAMA* 310:1711, 2013)
  - Pneumococcal vaccination decreases strokes (*BMC Public Health* 12:222, 2012)
The BIG QUESTIONS in pneumonia biology:

1) Which are the components of immune resistance and of tissue resilience that determine pneumonia susceptibility and outcome(s), and are some most important?

2) How are components compromised due to aging or other co-morbidities (like obesity, diabetes, COPD, etc.) and exposures (like smoking, drinking, air pollution, etc.)?

3) Can we generate a biologic metric that differentiates those subjects more susceptible to pneumonia compared to matched but less susceptible peers?

4) Can we boost immune resistance and tissue resilience, particularly in those in whom these processes are flagging, to prevent or cure pneumonia?
Influenza pneumonia and pathogenesis

Adolfo García-Sastre

Disclosures

• I have research agreements with GSK and Merck

• I’m consultant for Avimex, Contrafect and Medivector
HUMAN INFLUENZA VIRUS PANDEMICS

Estimated deaths in the U.S.

1918

H1N1

H2N2

1957

1968

H3N2

1977

NEW H1N1

2009

500,000

70,000

35,000

12,000

Evolution and spread of flu viruses

Human

Ducks

Cats

Pigs

Horses
HUMAN INFLUENZA: SYMPTOMS AND SIGNS

ASYMPTOMATIC
MILD RESPIRATORY SYMPTOMS
TRACHEO-BRONCHIOLITIS
PNEUMONIA (primary, secondary)
ARDS
ENCEPHALITIS

DETERMINANTS OF DISEASE

VIRUS

Pathogenesis
Host tropism

HOST

ENVIRONMENTAL / COINFECTIONS
VIRUS

DETERMINANTS OF DISEASE

H1N1
1918
U.S. Life Expectancy
By age

1918 flu epidemic
Lung tissue samples (1918)

1918 influenza AFIP lung block

Extract RNA, sequence, clone the virus

Signatures of virulence of the 1918 influenza virus

Pathological specimen (circa 1918)

Gene sequencing

Gene reconstruction

Reverse genetics

Phenotypic characterization in:
- Tissue culture
- Animal models
Influenza A/CDC/1918 virus
Extinct around 1920, resurrected 2005

Intranasal inoculation of mice, $10^6$ pfu
Viral titers in lungs, day 4

% survival

Days after infection

1918 $10^6$ pfu
1918 7:HA Tx/91
1918 5:3 Tx/91
10^5 pfu
Tx/91
10^3 pfu
1918 VIRUS

*What do we know now?*

1. The 1918 virus is the only known human influenza virus lethal to mice, ferrets, macaques and embryonated eggs.

2. The glycoprotein (HA and NA) and non-structural (NS1 and PB1-F2 genes) of the virus contribute to enhanced virulence.

3. Viruses containing 1918 genes are sensitive to existing antivirals.

4. H1N1 based vaccines are protective.

---

**Critical Amino Acids for Influenza HA Receptor-Binding Specificity**

- **Hu-H3**: D2-6 NeuAc
- **1918-H1**: D190, D225
- **Av-H5**: E190, G225

Changes receptor specificity

*No effects on virulence*

*Prevents respiratory transmission*
Which host factors are important for virus replication, host tropism and pathogenesis?

*Potential targets for therapeutic intervention*

Cellular pathways

**Fluomics**
Integration of proteomics (interactome), genomics (microarrays, deep sequencing), functional genomics (siRNA and other gene screenings), epigenomics (functional transcriptome), and metabolomics.

**Required factors**
Restriction factors?

**Roles in virulence?**
Tropism?
Transmission?
Antivirals?
Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency

**IRF7**

![Graph showing virus titers over hours post-infection for different conditions.](image)

Immortalized human fibroblasts

Host restriction factor

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Meta- and Orthogonal Integration of Influenza "OMICs" Data Defines a Role for UBR4 in Virus Budding.
Tripathi et al, Cell Host Microbe 18 (2015)

**UBR4**

![Graph showing virus titers and UBR4 expression over time.](image)

Host proviral factor
DETERMINANTS OF DISEASE

Pre-existing immunity
Predisposing factors: age, obesity, pregnancy, etc
Cooperation with other pathogens
Influence of the metagenome

ENVIRONMENTAL / COINFECTIONS

Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation. Rialdi et al, Science 352 (2016)

Life
Death
Survival
Infection Cytokine storm
Top1 Therapy (camptothecin)

Percent of survival

PR8 (5/5)
S. aureus (5/5)
PR8 + S. aureus (0/8)
PR8 + CPT + S. aureus (8/9)

time (days)
INFLUENZA VACCINES

Human influenza strains change frequently by antigenic drift.
Human influenza strains dramatically change every 10-40 years by antigenic shift.
Influenza vaccines need to be frequently updated and annually administered.
Challenges due to vaccine mismatches and vaccine availability during pandemics.

Universal flu vaccines?

UNIVERSAL FLU VACCINES?

Repeated vaccination with influenza virus chimeric HA vaccines induce protective antibodies against multiple subtypes of influenza virus.
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs

- cH4/3 vaccination
- cH5/3 vaccination
- H3 vaccination
- Shanghai (H7N9) challenge
Induction of protective levels of stalk-reactive antibodies using chimeric HA constructs

Titers in mouse lungs, day 3 postinfection
SUMMARY

• Influenza disease is multifactorial, and it can be studied by integrating both systems biology and conventional scientific approaches

• Viral and host functions represent potential targets for therapeutic intervention

• Vaccines that induce antibodies against the conserved viral HA are broadly neutralizing

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Leah Shriver
Ben Tenoever
Terry Tumpey
Steven Wollinsky
Community Acquired Pneumonia 2016: Guidelines and Current Issues

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FINANCIAL DISCLOSURE

- Dr. Niederman is a speaker or consultant for:
  - Bayer, Pfizer, Merck/Cubist, N8 Medical, Cempra, Paratek, Thermo Fisher, Theravance

- He has received research grants from:
  - Bayer, Cubist
  - Research: funding of Procalcitonin assay for clinical trial by bioMerieux

Pneumonia

Sir William Osler: The Principles and Practice of Medicine (1892)

“Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old man escapes those ‘cold gradations of decay’ so distressing to himself and to his friends.”

Topics In 2007 ATS/IDSA Guidelines

- The admission decision
- The value of diagnostic testing (blood cultures, sputum culture, antigen testing)
- Risk factors for specific pathogens
- Recommended empiric antibiotic therapy
- The role of adjunctive and supportive therapies
- Quality improvement and performance measures
- The value of prevention efforts: smoking cessation, vaccination

Modifiers Affecting Bacteriology

- **DRSP**
  - Age > 65 years, β-lactam therapy within 3 months, alcoholism, immune suppression (including steroids), multiple medical co-morbidities, exposure to child in day care
- **Enteric Gram-negatives**
  - Nursing home residence, underlying cardiopulmonary disease, multiple medical co-morbidities, recent antibiotic therapy
- **Pseudomonas aeruginosa**
  - Structural lung disease (bronchiectasis), corticosteroids (> 10 mg prednisone/day), broad-spectrum antibiotics for > 7 days within the past month, malnutrition

**Community-acquired Pneumonia:**
**Empiric Therapy – ATS/IDSA 2007**

**Outpatient**
- **Previously well:** Advanced Macrolide, Doxy
- **CoMorbidity or recent ATB use**:
  - Resp Fluoroquinolone
    - (Levofloxacin 750 mg or Moxifloxacin 400 mg)
  - High dose Beta-lactam** +
    - (macrolide or doxycycline);
  - Ceftriaxone + macrolide or doxycycline

*Base decision on 'prior antimicrobial used'; use alternate
**Amox 1 gm TID; Amoxicillin 2 gm BID preferred; alternatives: cefpodoxime, cefuroxime (500 mg BID)


**Inpatient – general ward**
- Respiratory fluoroquinolone (levofloxacin 750 mg/day, moxifloxacin 400 mg/day) » OR
- β-lactam PLUS macrolide/doxycycline
  - (preferred agents include: cefotaxime, ceftriaxone, ampicillin/sulbactam; consider ertapenem in selected patients)
  - Cefepime, imipenem, meropenem, piperacillin/tazobactam only if pseudomonal risks present

(For carefully selected patients without risk factors for DRSP or GNR, monotherapy with azithromycin can be considered)
Consider ‘Other pathogens’ based on epidemiology


**Therapy of Severe CAP: ATS /IDSA 2007 Regimens**

- **No Pseudomonal Risk Factors**
  - Selected Beta –lactam (cefotaxime, ceftriaxone, ertapenem)
    - PLUS
      - IV Macrolide
      - IV Quinolone

- **Pseudomonal Risk Factors Present**
  - Selected Beta-lactam (ceftazidime, piperacillin/tazobactam, imipenem, meropenem)
    - PLUS
    - Ciprofloxacin or High Dose Levofloxacin (750 mg)
  - Selected Beta-lactam PLUS Aminoglycoside
    - PLUS
    - IV macrolide OR
    - IV anti-pneumococcal quinolone

Pseudomonas aeruginosa risk factors:
- Structural lung disease (bronchiectasis), corticosteroids (> 10 mg prednisone/day), broad-spectrum antibiotics for > 7 days within the past month, malnutrition
- CONSIDER MRSA THERAPY IN SELECTED PATIENTS, ESP POST INFLUENZA
Relevant Issues For New CAP Guidelines

- Cardiac Disease and Monitoring/ Site of Care
- HCAP: What Now??
  - Pseudomonal and MDR risk factors
- Macrolides and their benefits
- New antibiotic therapies
- Therapy of CA-MRSA
- Biomarkers and Duration of Therapy
- Steroids for severe CAP
- Vaccines

Acute Heart Disease in CAP Patients

- 170 patients with pneumococcal pneumonia to look for MI, atrial fib, vent fib, new CHF
- 19.4% with at least one major cardiac event (46 events in 33 patients) and 7.1% with MI. Higher mortality if had cardiac event (p<0.006).
- 500 CAP patients and 5.8% with acute MI.
  - 15% of 86 with severe CAP had MI. 20% of 65 with clinical failure had MI.
  - MI with higher mortality, LOS, clinical failure, time to stability

Cardiac Arrest in CAP

- Retrospective analysis of 55,276 in-hospital cardiac arrest (IHCA) within 72 hours of admission. 4453 with pneumonia prior to IHCA.
  - 52% in ICU, rest on ward. 52% of these on pressors, 56% on ventilator.
  - 7% ABRUPT cardiac arrest in many, without warning.
  - Only 52% on wards with cardiac monitor.
  - 13.4% with pneumonia had cardiac ischemia
Criteria for Severe CAP: 2007 IDSA/ATS Guidelines

• Maybe OTHER MINOR CRITERIA
  • Hyponatremia
    – On admit: 28% of 342 CAP patients with hyponatremia (<136 mEq/L), 4.1% <130 mEq/L.
    – Hyponatremia on admit with increased mortality and increased length of stay
    – 10.5% developed in hospital, unrelated to severity of illness on admit.

• Thrombocytosis. Thrombocytosis (>400 K) added to mortality (OR 2.7), but biphasic relationship, with low platelets (<100 K) also a risk.

• Abnormal arterial CO2. Higher mortality with hypocapnia (13.4%) and hypercapnia (20%) vs. normal (5.3%).

Table 4. Criteria for severe community-acquired pneumonia

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<tbody>
<tr>
<td>Respiratory rate &gt;30 breaths/min.</td>
<td>PaO2/FIO2 ratio &lt;200</td>
</tr>
<tr>
<td>Fever &gt;38.5°C</td>
<td>PCT &gt;0.5 µg/L</td>
</tr>
<tr>
<td>Confusing behavior</td>
<td>Hypothermia (temperature &lt;35.5°C)</td>
</tr>
<tr>
<td>Serum (BUN level &gt;20 mg/dL)</td>
<td>Hyponatremia (serum sodium &lt;130 mEq/L)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Hypokalemia (serum potassium &lt;3.5 mEq/L)</td>
</tr>
<tr>
<td>Pneumococcus (pleural 10000 colonies/ml)</td>
<td>Stage II sepsis</td>
</tr>
<tr>
<td>Hypoalbuminemia (serum albumin &lt;3.0 g/dL)</td>
<td>Sepsis shock with the need for vasoressors</td>
</tr>
</tbody>
</table>

Need 1 MAJOR or 3 MINOR


PCT and CAP Outcome


Relevant Issues For New CAP Guidelines

• Cardiac Disease and Monitoring/ Site of Care
• HCAP: What Now??
  – Pseudomonal and MDR risk factors
• Macrolides and their benefits
• New antibiotic therapies
• Therapy of CA-MRSA
• Biomarkers and Duration of Therapy
• Steroids for severe CAP
• Vaccines

The Mistake of HCAP and Why It is Still A Useful Concept

• Not the same as CAP
  – Higher mortality
  – More at risk for MDR pathogens than usual CAP
  – BUT it is a HETEROGENEOUS disease
  – Failure to recognize this, was a MISTAKE in the original HCAP definition
• Some patients can be treated like CAP, but not all
  – Classification of HCAP is fine if avoid overtreatment
  – If we define the HCAP patients who should NOT get CAP therapy, it a useful concept
Using an Algorithm To Avoid Antibiotic Overuse in HCAP

- Prospective Use of Algorithm in 445 pneumonia patients, including 321 with HCAP
- With algorithm, only 53% got broad spectrum rx with 93% appropriate rx
- 27% high risk patients with MDR pathogens
- HCAP mortality related to risk factors and failure of initial therapy, but not to inappropriate therapy (which was uncommon)

Relevant Issues For New CAP Guidelines

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Adjunctive Macrolide Therapy in Non-Severe CAP: CAP-START Study

- Cluster-randomized trial: 4 months each of beta-lactam alone (n=686), BL-M (n=739), quinolone (n=888). Random order among 6 hospitals.
- Shorter duration and earlier oral therapy with FQ.
- Lower mortality (9.0%, 8.8% vs 11.1%) with BL and quinolone vs. BL-M. No regimen sig better, but meet NI criteria for BL vs. BL-M.
  - Atypical pathogens in 2.1%
  - 38.7% in BL group got atypical coverage
  - 25% in all groups with NO radiographic confirmed CAP
  - Lower adherence to BL-M strategy
  - Low severity: median CURB-65 of 1, EXCLUDED ICU patients
  - 131/2299 patients in PSI class V. No mortality diff between groups in PSI V patients.
  - Postma DF et al. NEJM 2015; 372:1312-23

Randomized Trial of BL/M vs. BL Monotherapy in CAP

- Open label, multicenter trial with 580 patients (moderately severe).
- Beta-lactam/macrolide vs. Beta-lactam alone (add macrolide for proven Legionella).
- Primary endpoint: Time to clinical stability (HR, BP, Temp, RR, Oxygenation).
- Non-inferiority of monorx NOT proven for CS (66.4% vs. 58.8%, day 7, CS for combo vs mono).
- Combination best if atypical pathogen or more ill (PSI IV).

Combination Therapy in Severe CAP: Macrolide vs. Quinolone

- Prospective, observational, multicenter study of 218 intubated CAP patients in 27 ICU's
- 75.7% with severe sepsis and septic shock
- 46% got guideline-compliant therapy
- Macrolide, but not quinolone use associated with reduced mortality.

Routine Macrolide Use In Severe CAP?

- Meta-analysis of macrolide use in severe CAP
- 28 studies, nearly 10,000 patients
- Mortality risk of 0.82 with macrolide (21% vs 24% (p=0.02)
- Higher benefit if risk adjusted
- Trend of BL/M being better than BL/F

Conclusions for Adding Macrolide Therapy To a Beta-Lactam in CAP

- In patients with mild CAP or a low likelihood of atypical pathogen infection, macrolide benefits may be small.
- If severe CAP, and severe pneumococcal bacteremia
  - Macrolide addition to a beta-lactam reduces mortality.
- Benefit may be due more to anti-inflammatory effects rather than to anti-microbial effects.
- Multiple anti-inflammatory effects of macrolides.
- Benefit applies even if add to quinolone.
- Benefit applies for macrolide resistant organisms.
- Benefit in VAP due to gram-negatives without eradicating the pathogen.
- Additive benefit to adjunctive corticosteroids.

Relevant Issues For New CAP Guidelines

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New Antibiotics for Pneumonia

- CAP
  - Solithromycin
  - Quinolones: avarofloxacin, nemonoxacin, zabolofloxacin, delafloxacin
  - Omadacycline
  - Eravacycline
  - Lefamulin

Solithromycin For CAP

- Oral solithromycin (n=426) 800 mg day 1, 400 mg daily x 4 vs. moxifloxacin (n=434) 400 mg daily x 7
- Double blinded, PORT II-IV, mostly outpatients
- Both therapies similar in early clinical response (78% at 72 h) and AEs
- 12 total patients with macrolide-resistant pneumococci.

<table>
<thead>
<tr>
<th>Daily Dose (mg)</th>
<th>Solithromycin</th>
<th>Moxifloxacin</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORT</td>
<td>305/213 (79%)</td>
<td>175.7/127 (79%)</td>
<td>29.8 (14.8 to 44.8)</td>
</tr>
<tr>
<td>Age&lt;65 y.o.</td>
<td>285/206 (77%)</td>
<td>160.5/121 (75%)</td>
<td>-24.5 (16.6 to 32.4)</td>
</tr>
<tr>
<td>Age&lt;65 y.o.</td>
<td>70.3/38 (18.7%)</td>
<td>185.5/121 (77%)</td>
<td>-24.5 (16.6 to 32.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>285/206 (77%)</td>
<td>160.5/121 (75%)</td>
<td>-24.5 (16.6 to 32.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>285/206 (77%)</td>
<td>160.5/121 (75%)</td>
<td>-24.5 (16.6 to 32.4)</td>
</tr>
<tr>
<td>Other sites</td>
<td>285/206 (77%)</td>
<td>160.5/121 (75%)</td>
<td>-24.5 (16.6 to 32.4)</td>
</tr>
</tbody>
</table>

Relevant Issues For New CAP Guidelines

- Cardiac Disease and Monitoring/ Site of Care
- HCAP: What Now??
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Differences Between CA-MRSA Pneumonia and MRSA in the HCAP Patient

- Distinguish CA-MRSA in previously healthy patients, from MRSA arising in the community in patients with HCAP risks. CA-MRSA uncommon and often post influenza or viral illness

<table>
<thead>
<tr>
<th>Table 1: Distinguishing characteristics of MRSA strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-Acquired (CA-MRSA)</td>
</tr>
<tr>
<td>Common PFGE pattern</td>
</tr>
<tr>
<td>SCCmec type</td>
</tr>
<tr>
<td>Vancomycin MIC</td>
</tr>
<tr>
<td>Chloramphenicol, TMRLs sensitivity</td>
</tr>
<tr>
<td>PM, toxin production</td>
</tr>
<tr>
<td>Other exotoxin production</td>
</tr>
</tbody>
</table>

Clinical Features of CA-MRSA: Need a High Level of Suspicion

- Often a serious illness, with necrotizing pneumonia, but not always. Usually in previously healthy patient.

<table>
<thead>
<tr>
<th>Table 2: Clinical features to suggest increased risk of CA-MRSA pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary pneumonia</td>
</tr>
<tr>
<td>Lung necrosis in pneumonia infiltrate</td>
</tr>
<tr>
<td>Rapidly increasing pleural effusion</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
</tbody>
</table>
Is Empiric MRSA Therapy Needed in All ICU-Admitted CAP?

- 621 with ICU admitted CAP in CAPO study
  - 57 treated empirically for MRSA (vancomycin or linezolid)
  - MRSA rx group sicker
  - 20 proven MRSA, 35% mortality. 10 treated empirically. Same outcome empiric vs. late rx.
- No difference in-hospital mortality (25%), 28 day mortality, LOS , time to clinical stability with empiric MRSA rx.

PVL Positive S. Aureus Pneumonia: Role of Methicillin Resistance and Proper Therapy

- 133 with PVL positive Staphylococcal CAP
  - 29 MRSA
  - 104 MSSA
  - 39% mortality, Methicillin resistance NOT a mortality predictor.
  - 64% mechran vent. Hemoptysis assoc. with mortality.
  - 33.7% got antitoxin (linezolid, clindamycin or rifampin), with reduced mortality (6.1% vs. 52.3%, p < 0.001)

Toxin Inhibition in the Therapy of CA-MRSA by Linezolid Given Early

- Best therapy is unclear.
  - Vancomycin is slowly bacteridal, and toxin release can continue
  - Linezolid and clindamycin inhibit toxin production
  - Beta-lactams kill rapidly and may eliminate toxin
    - Cetaroline was effective in MRSA pneumonia with bacteremia, unresponsive to vancomycin
  - Rabbit model of USA 300 MRSA necrotizing pneumonia , using direct inoculation into the lung
    - Linezolid w/ 1.5 hours after infection, reduced toxin production (PVL, alpha hemolysin), pro-inflammatory cytokines (IL-8) and mortality vs. vancomycin
    - Diep BA, et al. CID 2013; 28:75-82
Conclusions About CA-MRSA Pneumonia Therapy

- CA-MRSA pneumonia should be distinguished from MRSA in the community arising in HCAP patients
- Often necrotizing, but does not always need ICU care
  - Associated with toxin production (so is MSSA)
- Slow to resolve
- Not all severe CAP patients need empiric MRSA therapy
- Optimal therapy unclear
  - Role of toxin inhibition
  - Therapy of pneumonia with bacteremia: drugs for bacteremia may not penetrate lung well or work on pneumonia: vancomycin and daptomycin

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Pro HOSP Study: Using PCT To Reduce Antibiotic Exposure in RTI’s

- Multicenter trial in 6 Swiss hospitals
- 1359 ED patients with LRTI randomized to PCT (n=671) guidance vs. standard care (n=688)
- 68% in each group with CAP, 17% AECB, 11% acute bronchitis, 4% others
- PCT patients with CAP with shorter duration therapy, fewer antibiotics, fewer antibiotic side effects

Is CRP as Good as PCT to Reduce Antibiotic Use in CAP ?

- CRP can distinguish pneumonia from non-pneumonia, but not as much data that it is useful to limit antibiotic use. Maybe not as good.
- 62 pneumonia patients, showing use of antibiotics without biomarkers, with PCT (0.1 and 0.25 ng/ml) and with CRP (10,30,48 mg/L), using levels measured on admit.
PCT Guidance of Therapy Duration in Dutch ICUs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCT-guided group (n=761)</th>
<th>Standard of care group (n=785)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic consumption (days)</td>
<td>7.6 (4.0-12.0)</td>
<td>9.2 (5.0-16.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time to treatment reduction</td>
<td>5.5 (4.0-8.0)</td>
<td>7.0 (4.0-13.0)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Antibiotic-free days in first 20 days</td>
<td>3.1 (0.0-15.0)</td>
<td>1.5 (0.0-13.0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>14.0 (11.0-15.0)</td>
<td>15.0 (13.0-15.0)</td>
<td>0.0032</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>26.0 (18.0-33.0)</td>
<td>32.0 (25.0-39.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Adverse events</td>
<td>36.0 (25.0-47.0)</td>
<td>70.0 (50.0-89.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Reinfection cases</td>
<td>7.0 (5.0-9.0)</td>
<td>13.0 (7.0-19.0)</td>
<td>0.1722</td>
</tr>
</tbody>
</table>

- Stop if PCT decreases by 80% or <0.5 mcg/L
- PCT guidance led to less antibiotics, shorter duration of therapy, and lower 28-day mortality.
- Higher reinfection with PCT.
- No difference in serial CRP measures.
- No stop by PCT in half, especially if unstable.

* deJong E, et al. Lancet Inf Dis 2016; on line

Getting to Short Duration By Protocol

- Randomized trial of 312 hospitalized CAP patients
- **Guideline (intervention):** minimum 5 days, afebrile for 48 hours, ≤1 clinical instability factor, accurate empiric Rx, no extrapulmonary infection
- Control: dictate duration by clinician
- **Mean of 5 vs. 10 days.** Same outcomes: clinical success and symptom resolution
- If planning short duration, do we need biomarkers?


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Steroids in Severe CAP To Reduce Treatment Failure

- Multicenter randomized trial of 0.5mg/kg methylprednisolone q12h x 5 days (n=61) vs. placebo (n=59). Rx within 36 hours.
- Severe CAP (70-80% in ICU) + elevated CRP > 150 mg/L on admission
- Less treatment failure (esp late and with radiographic progression) in steroid group
- No mortality difference.

* Torres et al. JAMA 2015; 313:677-86.
Meta-Analysis of Steroids for CAP

- Randomized controlled trials of severe and non-severe CAP patients
- Possible reduction in mortality by 3% (in severe CAP), need for MV by 5%, and LOS by 1 day
- More hyperglycemia, not GI bleeding

Relevant Issues For New CAP Guidelines

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High Dose Influenza Vaccine in the Elderly

- Double blind, randomized study of standard vs. high dose influenza vaccine in 31,989 patients > age 65, over 2 years.
- 30 mcg vs. 15mcg of HA per strain
- Less lab confirmed influenza (1.4 vs. 1.9%) and higher antibody titers. 24.2% relative efficacy
- DiazGrandos CA, et al. NEJM 2015; 371:635-45
- Allowed re-vaccination year 2 with either HD or SD, so created 4 groups: SD/SD; SD/HD; HD/SD; HD/HD
- Compared to SD in both years, using HD in year 2 led to better response (disease occurrence and immunogenicity), regardless of initial type of vaccination.

Current ACIP Pneumococcal Vaccine Recommendations

- Immunocompromising conditions: HIV, CRI, nephrotic synd, leukemia, lymphoma, Hodgkin’s, myeloma, malignancy, solid organ transplant, long term steroids, radiation therapy, congenital or acquired immune...
Safety and Efficacy of A Second PCV 13 Vaccination

- 72 Vaccine naïve subjects given PCV 13 twice, 5 year apart
- Antibody titers declined over time but > baseline for 12/13 strains
- 1 month post re-vaccination, titers equal or higher than initial vaccine
- Mild local reaction in < 5%

Relevant Issues For New CAP Guidelines

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Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Mark L. Metersky, MD
University of Connecticut School of Medicine

Guideline Panelists

Andre C. Kalil       IDSA Co-Chair       Ali A. El Solh
Mark L. Metersky     ATS Co-Chair       Santiago Ewig
Michael Klompas      Paul D. Fey
John Muscedere       Thomas M. File, Jr.
Daniel A. Sweeney    Marcos I. Restrepo
Lucy B. Palmer       Jason A. Roberts
Lena M. Napolitano   Grant W. Waterer
Naomi P. O'Grady     Peggy Cruse       (Librarian)
John G. Bartlett     Shandra Knight     (Librarian)
Jordi Carratalà      Jan L. Brozek      (Methodologist)

And special thanks to Jennifer Padberg, IDSA
Disclosures

• Bayer:
  – Consulting to assist with development of educational materials for MSL training
  – Clinical trial support
• Both occurred subsequent to completion of recommendation writing

VAP rates reported by the US Centers for Disease Control and Prevention
A common theme was the tension between avoiding antibiotic overuse vs appropriate initial empiric and ongoing treatment. Based on attempt to balance the relative risks of under-treatment vs risks of overuse, which will have different magnitudes in different situations:
- Eg. presumed lower risk related to under-treatment of VAT than VAP

Difficult to balance risks to individual patient vs. future patients in the same unit and risk to society:
- Generally, we felt it necessary to prioritize the care of the individual patient rather than societal risks, except when there was minimal magnitude of risk/benefit difference between courses of action.
Complexity

• Mostly, we had low to very low quality evidence, further increasing the complexity
• Another tension is between simplicity/usability of the guideline vs. flexibility of the recommendation/ability to tailor recommendation to specific scenarios
  – A one size fits all recommendation is easy to use but may not be optimum

Prevention

• Recently addressed in comprehensive Guidelines from SHEA
• Therefore, not addressed in these guidelines
HCAP

• After extensive literature review and discussion it was decided that this concept should be covered within the CAP guidelines

• Patient characteristics, work flow and specialties of physicians treating these patients more closely aligned with CAP patients

Diagnosis

• The 2005 Guidelines state that lower respiratory tract cultures should be performed
• They point out the potential benefits and potential disadvantages of bronchoscopic sampling with quantitative culture methodologies vs standard semi-quantitative cultures of tracheal aspirates
• They do not recommend one strategy over the other
Diagnosis

• The current rules for guideline methodology do not allow us to point out advantages and disadvantages and let the clinician decide

• Rather, we needed to weigh the evidence and give specific guidance, being very clear about the limitations of the evidence and the strength of the recommendation (how confident we were in the recommendation)

Accuracy of different sampling and culturing strategies to diagnose ventilator-associated pneumonia relative to histologically-confirmed disease

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
<th>Diagnostic Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotracheal aspirates* (Any Growth)</td>
<td>75% (58-88%)</td>
<td>47% (29-65%)</td>
<td>61% (45-76%)</td>
<td>1.4 (0.74-2.49)</td>
<td>0.56 (0.17-1.83)</td>
<td>2.5 (0.42-15)</td>
</tr>
<tr>
<td>Endotracheal aspirates* (≥10^5 CFU/ml)</td>
<td>57% (45-69%)</td>
<td>83% (70-92%)</td>
<td>81% (67-91%)</td>
<td>3.3 (0.88-11)</td>
<td>0.53 (0.35-0.81)</td>
<td>6.7 (1.4-31)</td>
</tr>
<tr>
<td>Conventional BAL (≥10^4 CFU/ml)</td>
<td>57% (47-66%)</td>
<td>80% (71-88%)</td>
<td>77% (66-85%)</td>
<td>2.4 (0.99-5.6)</td>
<td>0.56 (0.33-0.96)</td>
<td>5.7 (1.3-25)</td>
</tr>
<tr>
<td>Protected specimen brush (≥10^3 CFU/ml)</td>
<td>48% (38-57%)</td>
<td>72% (63-80%)</td>
<td>60% (49-71%)</td>
<td>1.9 (0.98-3.6)</td>
<td>0.72 (0.51-1.0)</td>
<td>3.5 (1.1-12)</td>
</tr>
</tbody>
</table>
**Diagnosis**

- We suggest non-invasive sampling with semi-quantitative cultures to diagnose VAP, rather than invasive sampling with quantitative cultures and rather than non-invasive sampling with quantitative cultures.
Diagnosis-Biomarkers

- Not recommended for use in determining the initial need for antibiotics
  - PCT
  - sTREM
  - CRP
  - CPIS
- All have limited evidence of predictive value, or safety when used to not start antibiotics

Treatment

- The panel believed that there are geographic variations in the prevalence of MDR organisms that could be useful in tailoring initial empiric antibiotics
- The panel also believed that local resistance patterns were important
- For example, if a hospital had high MDR rates, but GNR sensitivity to carbapenems remained 95%, then it would be appropriate to use a carbapenem alone for initial empiric GN therapy
Other factors potentially altering pre-test likelihood of MDR pathogens

• Caused more discussions than any other issues
  – Patient-related factors (classic MDR risks)
  – Gram stains
  – MRSA screening

Antibiograms

• We recommend that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is specific to their intensive care population(s) if possible.
• We recommend that empiric treatment regimens be informed by the local distribution of pathogens associated with VAP and their antimicrobial susceptibilities.
How often do we need to be right? How often CAN we be right?

- The panel attempted to create guidelines for initial empiric regimens that would be appropriate in ~95% or more of patients
- There is a ceiling effect
- Even with triple antibiotic coverage for everybody, you will not reach 100%

### Distribution of pathogens and antimicrobial resistance patterns associated with 8,474 cases of ventilator-associated pneumonia reported to the U.S. Centers for Disease Control and Prevention, 2009-2010

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Frequency</th>
<th>Antimicrobial Resistance Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>24.1%</td>
<td>Methicillin / oxacillin resistant – 48%</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>16.6%</td>
<td>Ciprofloxacin / levofloxacin resistant – 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem / meropenem resistant – 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidine / ceftazidime resistant – 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piperacillin-tazobactam resistant – 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aminoglycoside resistant – 11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistant to ≥3 of the above classes – 18%</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>10.1%</td>
<td>Cefepime / ceftazidine / cefotaxime resistant – 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem / meropenem resistant – 11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistant to ≥3 classes – 13%</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>8.6%</td>
<td>Cefepime / ceftazidime / ceftriaxone resistant – 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem / meropenem resistant – 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistant to ≥3 classes – 1%</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>6.6%</td>
<td>Imipenem / meropenem resistant – 61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistant to ≥3 classes – 63%</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5.9%</td>
<td>Ciprofloxacin / levofloxacin resistant – 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefepime / ceftazidime / ceftriaxone resistant – 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem / meropenem resistant – 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistant to ≥3 classes – 3%</td>
</tr>
</tbody>
</table>
### SUMMARY OF META-ANALYSES COMPARING DIFFERENT CLASSES OF GRAM-NEGATIVE AGENTS FOR EMPIRIC TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mortality Risk Ratio (95% CI)</th>
<th>Clinical Response Risk Ratio (95% CI)</th>
<th>Acquired Resistance Risk Ratio (95% CI)</th>
<th>Adverse Events Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination versus monotherapy</td>
<td>1.11 (0.90, 1.38)</td>
<td>0.89 (0.75, 1.07)</td>
<td>1.13 (0.42, 3.00)</td>
<td>0.90 (0.69, 1.18)</td>
</tr>
<tr>
<td>Cephalosporin versus non-cephalosporin regimens</td>
<td>0.97 (0.74, 1.27)</td>
<td>0.92 (0.78, 1.09)</td>
<td>2.36 (0.63, 8.86)</td>
<td>1.01 (0.82, 1.25)</td>
</tr>
<tr>
<td>Quinolone versus non-quinolone regimens</td>
<td>1.13 (0.92, 1.39)</td>
<td>1.05 (0.91, 1.20)</td>
<td>0.77 (0.59, 1.01)</td>
<td>0.88 (0.78, 0.99)</td>
</tr>
<tr>
<td>Anti-Pseudomonal penicillin versus non-anti-Pseudomonal penicillin regimens</td>
<td>1.12 (0.76, 1.66)</td>
<td>1.10 (0.80, 1.52)</td>
<td>Not Reported</td>
<td>0.96 (0.77, 1.20)</td>
</tr>
<tr>
<td>Aminoglycoside versus non-aminoglycoside regimens</td>
<td>1.15 (0.88, 1.50)</td>
<td>0.82 (0.71, 0.95)</td>
<td>Not Reported</td>
<td>0.96 (0.70, 1.33)</td>
</tr>
<tr>
<td>Carbapenem versus non-carbapenem regimens</td>
<td>0.78 (0.65, 0.94)</td>
<td>1.02 (0.93, 1.12)</td>
<td>1.16 (0.53, 2.55)</td>
<td>1.08 (0.90, 1.28)</td>
</tr>
</tbody>
</table>

**VAP-Initial Empiric Antibiotics Gram Positive**

We suggest including an agent active against MRSA for the empiric treatment of suspected VAP only in patients with risk factors for antimicrobial resistance, patients being treated in units where >10-20% of *S. aureus* isolates are methicillin-resistant, and patients in units where the prevalence of MRSA is not known.
VAP-Initial Empiric Antibiotics
Gram Negative

We suggest prescribing TWO anti-Pseudomonal antibiotics from different classes for the empiric treatment of suspected VAP only in patients with risk factors for antimicrobial resistance, patients in units where >10% of Gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available.

Early Onset VAP

• Unlike the 2005 GLs, we are recommending coverage for MDR pathogens in many cases of early onset VAP (≤5 days since hospital admission)
• Since 2005, several studies have demonstrated that a substantial percentage of patients with early onset VAP have MDR organisms isolated
  Montravers, Crit Care Med, 2002
  – Variable definitions of “early VAP”
  – Many early onset patients have other risk factors for resistance
  – So...maybe it would be safe to not recommend MDR coverage for early onset VAP in patients without other risks for MDR pathogen
• Nonetheless, the panel did not believe that the evidence was strong enough to recommend against coverage for MDR pathogens in the absence of known low resistance rates in the ICU in question
Hospital-acquired pneumonia

- Very few RCTs on which to base recommendations
- Reviewed the prevalence of specific organisms to guide recommendations
- Wide variation, as expected
- Results probably biased towards increased numbers of MDR pathogens, as sicker patients more likely to be cultures (unlike VAP, for which cultures are routinely obtained)
HAP

- Single gram negative coverage for many patients.
- Similar guidance regarding withholding MRSA coverage in settings where MRSA is unlikely.
Additional Guidance

- Finally, the panel strongly encourages clinicians to consider all relevant, available data about both their individual patient and their practice environment to tailor empiric choices for each patient.
- Some factors could support a decision to omit MRSA coverage within a unit with relatively high rates of antibiotic resistance (for example, if the clinical suspicion for pneumonia is relatively low, the patient is not severely ill, has no risk factors for drug resistant pathogens, and a good quality Gram stain of pulmonary secretions shows Gram negative bacilli alone.

<table>
<thead>
<tr>
<th>A. Gram-Positive Antibiotics with MRSA Activity</th>
<th>A. Gram-Negative Antibiotics with Anti-Pseudomonal Activity: Beta-lactam Based Agents</th>
<th>A. Gram-Negative Antibiotics with Anti-Pseudomonal Activity: Non Beta-lactam Based Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopeptidesa</td>
<td>Anti-Pseudomonal Penicillinsb</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Vancomycin 15mg/kg IV q12h (consider a loading dose of 25-30mg/kg x 1 for severe illness)</td>
<td>Piperacillin-tazobactam 4.5g IV q6h</td>
<td>Ciprofloxacin 400mg IV q8h</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
<td>Levofloxacin 750mg IV q24h</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Cefalosporins</td>
<td>OR</td>
</tr>
<tr>
<td>Linezolid 600mg IV q12h</td>
<td>Cefepime 2g IV q8 - 12h</td>
<td>Aminoglycosidesa,c</td>
</tr>
<tr>
<td></td>
<td>Cefazidime 2g IV q8h</td>
<td>Amikacin 15-20mg/kg IV q24h</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>Gentamicin 5-7mg/kg IV q24h</td>
</tr>
<tr>
<td></td>
<td>Carabapenemsb</td>
<td>Tobramycin 5-7mg/kg IV q24h</td>
</tr>
<tr>
<td></td>
<td>Imipenem 500mg IV q6hb</td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Meropenem 1 - 2g IV q8h</td>
<td>Polymyxinsa,e</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>Colistin 5mg/kg IV x 1 (loading dose) followed by 2.5mg x (1.5 x CrCL + 30) IV q12h</td>
</tr>
<tr>
<td></td>
<td>Monobactamsf</td>
<td>(maintenance dose)³</td>
</tr>
<tr>
<td></td>
<td>Aztreonam 2g IV q8h</td>
<td>Polymyxin B 2.5-3.0 mg/kg/day divided in 2 daily IV doses</td>
</tr>
</tbody>
</table>

Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.
### Recommended initial empiric antibiotic therapy for HAP (non-VAP)

<table>
<thead>
<tr>
<th>Not at high risk of mortality¹ and no factors increasing the likelihood of MRSA²,³</th>
<th>Not at high risk of mortality but with factors increasing the likelihood of MRSA²,³</th>
<th>High risk of mortality or receipt of intravenous antibiotics during the prior 90 days¹,³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 of the following: piperacillin-tazobactam [4.5 gm Q 6 h] or levofloxacin (750 mg daily)</td>
<td>1 of the following: piperacillin-tazobactam [4.5 gm Q 6 h] or levofloxacin or cefepime or ceftazidime [2 gm Q 8 h]</td>
<td>Two of the following, avoid β-lactams: piperacillin-tazobactam [4.5 gm Q 6 h] or levofloxacin or cefepime or ceftazidime [2 gm Q 8 h]</td>
</tr>
<tr>
<td>Cefepime [2 gm Q 8 h] or levofloxacin (750 mg daily) or ciprofloxacin or ceftriaxone or meropenem [1 gm Q 8 h]</td>
<td>Imipenem [1 gm Q 8 h] or amikacin [15-20 mg/kg Q 8-12 h]</td>
<td>Imipenem [1 gm Q 8 h] or meropenem [1 gm Q 8 h]</td>
</tr>
<tr>
<td>Aztreonam [2 gm Q 6-8 h]</td>
<td></td>
<td>Aztreonam [2 gm Q 6-8 h]</td>
</tr>
</tbody>
</table>

**Plus:**
- Vancomycin [15 mg/kg Q 8-12 h] with goal to target 15 to 20 mg/ml trough level (consider a loading dose of 25-30 mg/kg × 1 for severe illness)
- Linezolid [600 mg Q 12 h]

*If MRSA coverage is not going to be used, include coverage for MSSA. Options include: piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the definitive treatment of MSSA, but would ordinarily not be used in an empiric regimen for HAP.*

---

### VAT

- **We suggest against** diagnosis and treatment of VAT
- **We state that in someone with purulent secretions, worsening respiratory mechanics, systemic signs of infection, it is likely VAP even if CXR negative, and treatment should likely be given**
- **In some patients, VAT may prolong mechanical ventilation in due to plugging and/or atelectasis and in such patients, treatment may be appropriate**
- **Otherwise:**
  - Limited evidence for improved outcomes, although the limited evidence does suggest decrease in ventilator days associated with VAT treatment
  - Very concerned about over-diagnosis in actual practice (treatment of anyone with secretions)
Aerosolized Antibiotics

Mortality: Adjunctive inhaled antibiotic vs IV antibiotic alone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adjunctive Inhaled Antibiotic</th>
<th>IV Antibiotic alone</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1990</td>
<td>13</td>
<td>45</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Doshi 2013</td>
<td>17</td>
<td>44</td>
<td>40</td>
<td>51</td>
</tr>
<tr>
<td>Hallaj 2007</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kulberis 2010</td>
<td>10</td>
<td>43</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>Korbiu 2009</td>
<td>31</td>
<td>78</td>
<td>19</td>
<td>43</td>
</tr>
<tr>
<td>LeCerte 2000</td>
<td>2</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Nam et al. 2005</td>
<td>4</td>
<td>11</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Rannaparija 2010</td>
<td>22</td>
<td>33</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>Tumbarello 2013</td>
<td>48</td>
<td>194</td>
<td>48</td>
<td>141</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>465</td>
<td>371</td>
<td>100.0%</td>
<td>0.84 [0.63, 1.12]</td>
</tr>
</tbody>
</table>

Total events 167
150
Heterogeneity: Tau^2 = 0.08, Chi^2 = 14.77, df = 7 (P = 0.04); I^2 = 52%
Test for overall effect: Z = 1.22 (P = 0.23)
Clinical Cure:
Adjunctive inhaled antibiotic vs IV antibiotic alone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adjunctive Inhaled Antibiotics</th>
<th>IV Antibiotics alone</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>400</td>
<td>359</td>
<td>1.29 [1.13, 1.47]</td>
</tr>
</tbody>
</table>

- **Evidence is generally positive, albeit limited**
- **Other limitations include:**
  - Lack of understanding about device specifics
  - Expense
- **Therefore, despite positive evidence, panel felt evidence did not allow a recommendation for universal addition of inhaled to IV Abx**
- **Instead, we recommend adjunctive inhaled Abx in patients for whom the only available IV antibiotics have the least evidence of efficacy**
- **Adjunctive inhaled antibiotics are recommended for patients with VAP due to Gram negatives susceptible to only aminoglycosides or polymyxins**
Length of Antibiotic Therapy

- Meta-analyses showed no difference between 7-8 days vs longer for:
  - Mortality
  - Clinical cure
  - Recurrent VAP
- Analyzed both for all VAP or VAP due to only non-fermenting GNRs

- 7 day course of antibiotics recommended unless patient is slow to respond, including for non-fermenters
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
  - *Stenotrophomonas maltophilia*
- Even with these bacteria, no differences in clinically important outcomes (ventilator days, ICU stay, mortality)
- Higher recurrence rate in one RCT but subject to time bias
  

- Given no difference in outcome, true recurrence vs persistent colonization?

Procalcitonin

PCT- Forest plots

<table>
<thead>
<tr>
<th>Antibiotic Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Bouadma</td>
</tr>
<tr>
<td>Pontot</td>
</tr>
<tr>
<td>Stolt</td>
</tr>
<tr>
<td>Total (95% CI)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.27, Chi² = 2.54, df = 2 (P = 0.29), I² = 21%
Test for overall effect: Z = 5.02 (P < 0.00001)
Length of Antibiotic Therapy

- Yes
  - **PCT**
    - Only likely to be of benefit in units where the standard course of treatment is greater than 7 days
  - **De-escalation**
    - Acknowledging that there is limited evidence that doing so decreases resistance rates
- No
  - **CPIS**

Summary

- Significant changes to recommendations, although “core” antibiotic recommendations remain similar
- Attempt to balance the risk of inappropriate therapy vs risks of antibiotic overuse
- Potentially the biggest impact in terms of numbers of patients is the recommendation for single GN coverage for most HAP patients
Viral Diagnostic Tools and Strategies for Pneumonia

Marie Louise Landry, MD
Director, Clinical Virology Laboratory
Yale New Haven Hospital

Disclosure

None
(Note empty wallet)

I have no financial relationship or any real or apparent conflict(s) of interest that may have a direct bearing on my presentation.
Traditional Methods: Culture
Still done at YNHH on BAL and lung biopsies

**Requires Infectious virus**

**Conventional cell culture**
- *Incubate up to 21 days*
- Examine for cytopathic effects
- Requires extensive training
- Can detect the unexpected

**Rapid shell vial culture**
- Incubate for 1-2 days
- Stain with monoclonal antibody
- Detects the “expected” more quickly (especially CMV)

Traditional Methods: Antigen
Increasingly replaced by rapid molecular tests

**Perform best in young children**

**Direct immunofluorescence**
- Requires respiratory epithelial cells
- Detects 7-8 respiratory viruses
- Sensitivity approaches culture (not PCR)
- Only test to assess sample quality
- Results in 2 hrs
- Requires substantial expertise, manual

**Rapid Flu (RIDT) and RSV tests**
- Lateral flow immunochromatography
- Simply add sample
- Results in 10-20 minutes
- Auto-readers improve sensitivity
- Can be done at point of care
- Detects only high titer positives
- False negatives in season, and false positives outnumber true when virus prevalence is low
At YNHH: **Lab-developed** real-time PCR

- **Respiratory virus real-time PCR panel**
  - Influenza A, B, RSV A, B, parainfluenza 1, 2, 3, adenovirus, rhinovirus, human metapneumovirus
  - 4 coronaviruses to be added in Spring

- Assays and format used in public health labs
- More sensitive and cheaper than kits
- 4-5 hr to complete
- 3 runs/day in winter (batched)
- Ct value* gives viral load estimate

* Ct value is the cycle of amplification the sample crosses the threshold to positive

---

**Commercial Molecular Tests***

Previously most hospitals had only rapid antigen tests

Now any hospital can provide a rapid molecular diagnosis

*FDA approved for NP swabs, washes and aspirates, not BAL or tissue
Respiratory Virus Molecular Tests

- **Sensitive**: amplify nucleic acid over a million-fold
- Much faster than culture
- Detect viruses that do not grow well in culture
  - e.g. rhinovirus, coronavirus, HMPV, bocavirus, para 4
- Most initial drawbacks have been overcome
  - Cross contamination has been reduced
  - Many kits require minimal expertise or hands-on time
  - Assay time 20 min to 4-8 hrs
  - Respiratory virus tests are now multiplexed
  - Real-time methods allow estimate of viral load

Respiratory Virus PCR Kits

**Detects Flu A/B, +/- RSV:**
- Prodesse Proflu+
- Qiagen Artus
- Quidel Lyra
- Focus Simplexa
- Verigene RV+
- Cepheid Xpert
- Alere
- Liat

**Detects 12-19 viruses***
- xTag
- GenMark eSensor
- ResPlex II
- SeePlex
- BioFire Filmarray RVP
- Verigene Resp Pathogens Flex

*Not real-time PCR.
Results are qualitative only

*May include Flu A & B, Flu A subtypes, RSV A & B, Paraflu 1-4, HMPV, Adenovirus, Rhinovirus or Picornavirus, Coronavirus OC43, 229E, NL63, HKU1, bocavirus
Also may include bacterial targets, e.g. mycoplasma, chlamydia, bordetella

Note: Tests approved for nasopharyngeal samples only
Workflow and Assay Time

<table>
<thead>
<tr>
<th>Test</th>
<th>Extraction</th>
<th>Amplification</th>
<th>Detection</th>
<th>Assay time</th>
</tr>
</thead>
<tbody>
<tr>
<td>xTag, eSensor, SeePlex, RespLex</td>
<td>Separate Extraction</td>
<td>End point PCR</td>
<td>Detection</td>
<td>6-8 hrs</td>
</tr>
<tr>
<td>ProFlu+, Quidel, Focus, and Lab-developed</td>
<td>Separate Extraction</td>
<td>Real-time PCR</td>
<td></td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Verigene RV+</td>
<td>Extraction</td>
<td>End Point PCR</td>
<td>Nanoparticle array</td>
<td>3-4 hrs</td>
</tr>
<tr>
<td>ONE STEP TESTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liat, Xpert</td>
<td>Extraction</td>
<td>Real-time PCR</td>
<td></td>
<td>20 min-1 hr</td>
</tr>
<tr>
<td>Focus Direct</td>
<td>Real-time PCR</td>
<td></td>
<td></td>
<td>1.25 hr</td>
</tr>
<tr>
<td>FilmArray</td>
<td>Extraction</td>
<td>Stage 1 PCR</td>
<td>Real-time PCR</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

Adapted from Peaper and Landry, Clin Lab Med 34:365-385, 2014

GeneXpert: Flu A/B/RSV

- On demand
- ~ 1 hr to result
- Individual modules
- Most expensive
- Flu A, B, pdm H1 or Flu A, B, RSV
- Also used for bacterial tests
Focus Simplexa Direct: Flu A/B/ RSV

- “Direct” version uses no extraction step
- Can test 1 to 8 samples per run
- 75 min to result

LIAT (Lab in a tube)

- On demand
- 20 min assay time
- Can be used at point of care
- One sample at a time
- Flu A, B or Flu A, B & RSV
- Also used for Strep
Verigene- mini and full panel

- Individual cartridges
- On demand
- 3-4 hours to result
- RV+ = Influenza A plus subtypes, Influenza B, and RSV
- Flex=full virus panel
- Qualitative

GenMark eSensor: 14 targets

- Extraction step
- Uses conventional PCR
- Individual modules for detection (24 shown)
- Higher throughput
- 6-7 hrs to result
- Most sensitive kit in some studies
FilmArray/Biofire: 17 viral targets*

- On demand
- 1 hr to result
- One sample at a time
- Low throughput
- Now GI and CSF panels

*Plus 3 bacterial targets: B. pertussis, Mycoplasma and Chlamydia

How to choose?

- **Clinical needs:**
  - Viruses, sensitivity and TAT requirements
  - Infection Control/ Bed management
  - Other actions triggered by results
- **Laboratory issues:**
  - Turnaround time requirements
  - Anticipated test volume; throughput of test system
  - Test menu on system
  - Reagent cost, instrument cost and space constraints
  - Staff expertise
- **Hospital concerns:**
  - Reimbursement issues (inpatient vs outpatient)
  - Value- Does testing improve outcomes to justify costs?
Test Strategy?

Rapid molecular test for influenza +/- RSV for new admissions, with result in < 2 hrs

Full PCR panel for symptomatic or high risk inpatients negative on the mini-panel

Theoretical Benefits from a Rapid and Accurate Respiratory Virus Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid antibiotics or stop at 48 hrs if bacterial cultures negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Reduce unnecessary testing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Shorten hospital stay&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Give antiviral therapy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Institute infection control measures</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cohort patients and staff</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup> More likely in pediatrics, patients without comorbidities, or without pneumonia
<sup>b</sup> Generally available only for influenza
How to maximize value?

- Specify guidelines for testing
  - Inpatient, outpatient
  - Influenza/RSV test only
  - Full 10-19 virus panel
- Clarify which results affect care and how
- How does time to result impact care
- Monitor costs and outcomes; adjust strategy
- May vary with setting and patient population

YNHH RESPIRATORY VIRUSES – INPATIENTS
October 1, 2015 - April 15, 2016

<table>
<thead>
<tr>
<th>Respiratory Virus</th>
<th>Total Cases*</th>
<th>Adult %</th>
<th>Pediatric %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>94</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>hMPV</td>
<td>183</td>
<td>79%</td>
<td>21%</td>
</tr>
<tr>
<td>Influenza A</td>
<td>663</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>Influenza B</td>
<td>234</td>
<td>66%</td>
<td>34%</td>
</tr>
<tr>
<td>Parainfluenza 1-3</td>
<td>72</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>667</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>RSV A, B</td>
<td>506</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>2419</strong></td>
<td><strong>1762</strong></td>
<td><strong>657</strong></td>
</tr>
</tbody>
</table>

Influenza 897/2419 = 37% of positives; RSV 506/2419 = 21% of positives
Influenza and RSV together 58% of positives
Molecular Test Limitations

• Kits vary in sensitivity, especially for
  – adenovirus, influenza B, RSV
• Kits may not be as sensitive as
  the best Lab-developed tests
• Genetic sequence variants can be missed
• Highly multiplexed PCRs give qualitative results
• Respiratory virus panels do not target
  herpesviruses (CMV, VZV, HSV)
• Interpretation can be difficult

Significance of a positive result

• Virus detected is causing the disease
• Virus detected is not causing the disease
  – Latent virus reactivated by the true pathogen
  – Asymptomatic infection, i.e. bystander
  – Residual viral nucleic acid from a past infection
• Virus in NP swab is not causing the disease in the lower tract
• Two viruses are detected- which is the main pathogen?
• Virus detected, but bacteria causing pneumonia*

*Gadsby et al, Clin Infect Dis 2016
Challenges

• Establish guidelines on how positive and negative results should impact care in different settings

• Determine real-world impact on outcomes and cost of care (i.e. value of testing)

• Develop alternate strategies to rule in viruses and rule out bacteria
  – Test for host response (viral and bacterial) instead of individual pathogens?
Bacterial Diagnostic Tools and Strategies for Pneumonia

David R. Peaper, MD, PhD, D(ABMM)
Assistant Professor of Laboratory Medicine
Director of Clinical Microbiology Laboratory, YNHH

Disclosures

- Tangen Biosciences
  - Scientific Advisory Board; Equity
Overview

- Review guidelines for pneumonia diagnosis
- Discuss the current approach to the microbial diagnosis of pneumonia
- Understand the complementary role of different test methods for the identification of some microbes
- Identify deficiencies to current approaches
- Discuss the future of microbial testing for pneumonia

Diagnostic & Clinical Challenges

- The respiratory tract is complex and infections of different anatomic locations have overlapping presentations
- Different microbes, some requiring specialized testing, can affect different locations in the respiratory tract
- Viruses and atypical bacterial pathogens causing potentially severe respiratory tract infections require specific testing
### Methods of diagnosis: Pneumonia

<table>
<thead>
<tr>
<th>Method/Assay Time</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Stains (hrs to days) | • Can be rapid  
• Provide insight into organism                                  | • Routine microscopy not useful for viruses  
• Less sensitive than other methods |
| Antigen testing (hrs to days) | • Rapid and simple; some can be done at point of care                | • Less sensitive than culture or Nucleic Acid Amplified Test (NAAT)              |
| NAAT (hrs to days) | • Very sensitive  
• Excellent for known pathogens  
• Can be rapid                                      | • More expensive  
• Requires special equipment  
• Not comprehensive |
| Serology (days) | • Simple blood draw  
• Less affected by Antibiotics                                         | • Not appropriate for most pathogens  
• Requires acute and convalescent sera for most utility |
| Culture (days to wks) | • Historic gold standard (sensitive)  
• Get isolate for identification and antimicrobial susceptibility testing (AST) | • Some pathogens, e.g. mycobacteria and viruses can take several wks to grow |

### IDSA / ATS Pneumonia Guidelines (2007)

- Microbiological data is not required for the diagnosis of pneumonia
- Routine diagnostic tests to identify an etiologic agent are optional for outpatients
- Patients with CAP should undergo testing when management will be affected
- Testing recommendations → Next Slide
Lab Testing for Hospitalized Patients/Severe CAP

Why Expand Testing?

- Empiric therapy is focused on S. pneumoniae, H. influenza, Atypical bacterial pathogens
- Severe CAP / Hospitalized patients at higher risk for:
  - MRSA
  - P. aeruginosa  
    May Not Respond to Empiric Therapy
  - ESBL/MDR GNR
- Expanded testing is focused on obtaining an isolate for further susceptibility testing
IDSA/ASM Lab Testing Guidelines

A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)

• Published in July 2013 → Methods more up-to-date
• Committee with strong clinical microbiology representation
• Syndrome → Bugs → Methods → Sources

IDSA/ASM Guidelines → Snapshot

Table: Laboratory Diagnosis of Community-acquired Pneumonia

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Diagnostic Procedures</th>
<th>Optimum Specimens</th>
<th>Transport Issues: Optimal Transport Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td>Gram stain</td>
<td>Sputum, bronchoalveolar lavage</td>
<td>Sterile container, RT, 2 h, 0-4°C, 4°C</td>
</tr>
<tr>
<td><em>B. henselae</em></td>
<td>Culture</td>
<td>Urine</td>
<td>Sterile container, RT, 2 h, 0-4°C, 4°C</td>
</tr>
<tr>
<td><em>R. rickettsii</em></td>
<td>Culture</td>
<td>Urine</td>
<td>Sterile container, RT, 2 h, 0-4°C, 4°C</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Culture</td>
<td>Urine</td>
<td>Sterile container, RT, 2 h, 0-4°C, 4°C</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>NAA*</td>
<td>Throat swab, bronchoalveolar lavage</td>
<td>Transport in saline at 4°C or up to 48 h, 4°C, at 2°C-8°C</td>
</tr>
<tr>
<td><em>Chlamydial pneumoniae</em></td>
<td>NAA*</td>
<td>NP swab, throat swab, bronchoalveolar lavage</td>
<td>Transport in saline at 4°C or up to 48 h, 4°C, at 2°C-8°C</td>
</tr>
<tr>
<td><em>Enterococci</em></td>
<td>Culture</td>
<td>Blood/CSF, stool</td>
<td>Sterile container, RT, 2 h, 0-4°C, 4°C</td>
</tr>
</tbody>
</table>

* *NAA* means nucleic acid amplification test; RT indicates real-time.
Topics and Approaches Discussed by Baron et al.

- Bronchitis and Bronchiolitis
- Community Acquired Pneumonia
- Healthcare Associated, Hospital Acquired, and Ventilator Associated Pneumonia
- Infections of the Pleural Space
- Pneumonia in the Immunocompromised Host

Most useful for identifying:
- Optimal testing strategies
- Gaps in current testing approach

Microbiology Culture Workflow

Specimens
- Sputum/BAL
- Pleural Fluid
- Biopsy

Microscopic Examination

Attempt to grow pathogenic bacteria from specimen:
- R/O Pathogens
- Consider normal flora

Species Identification
(1 – 18 hours)

Susceptibility Testing
(8 – 24 hours)
Assessment of the Current System

<table>
<thead>
<tr>
<th>Benefits of current system</th>
<th>Limitations of current system</th>
</tr>
</thead>
<tbody>
<tr>
<td>It works well for most cases</td>
<td>Polymicrobial infections</td>
</tr>
<tr>
<td>Obtains isolates for susceptibility testing</td>
<td>Infections caused by anaerobic bacteria</td>
</tr>
<tr>
<td>Gram stain allows assessment of specimen quality</td>
<td>It takes time to culture (18 hrs +)</td>
</tr>
<tr>
<td></td>
<td>Pre-culture Abx → No Growth</td>
</tr>
</tbody>
</table>

Approach to Testing: “Typical” Pathogens

- Typical Bacterial Pathogens
  - S. pneumoniae, H. influenzae, S. aureus, M. cattharalis, Enterobacteriaceae, P. aeruginosa
  - Sputum/BAL/ET Asp: Culture and gram stain
    - Sputum: Too many epithelial cells → Rejected
    - BAL → Quantitative Plating (cfu/mL)
    - Sputum / ET Asp: Semi-Quantitative plating (1+ → 4+)
  - Selective and differential plates incubated aerobically for 18h for first read; held for 3 days
- All pathogens listed above will grow well w/in 18h
- Look for: S. aureus, β-strep, P. aeruginosa AND any organism in predominance above normal flora
Gaps in Typical Respiratory Culture

- Atypical pathogens
  - Specific serology or PCR for Mycoplasma & Chlamydiophila
  - Urine antigen or special culture for Legionella
- Mycobacteria
  - Specific AFB culture +/- M. tb PCR
  - Special processing and extended incubation
- Fungi
  - Specific fungal culture; some urine antigens
  - Special processing and extended incubation
- Actinomycyes and Nocardia
  - Special processing and extended incubation
- Cystic Fibrosis Patients
  - Specific plates and protocols to look for specific pathogens and reduce overgrowth of microbiota
- Some of these MAY be found in routine culture, but not specifically assessed

CXRES at YNHH 2015

- 9619 specimens from 4845 patients (1 to 55 Cx/patient)
- ~500 Cystic Fibrosis specimens
- ~1000 rejected due to poor quality

<table>
<thead>
<tr>
<th>Age at Testing</th>
<th>ED Only</th>
<th>Outpatient</th>
<th>ED Admit</th>
<th>Inpatient</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 yo</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>1 to 5 yo</td>
<td>2</td>
<td>19</td>
<td>10</td>
<td>110</td>
<td>141</td>
</tr>
<tr>
<td>6 to 17 yo</td>
<td>5</td>
<td>12</td>
<td>6</td>
<td>82</td>
<td>105</td>
</tr>
<tr>
<td>18 to 49 yo</td>
<td>1</td>
<td>123</td>
<td>13</td>
<td>1473</td>
<td>1610</td>
</tr>
<tr>
<td>50 to 64 yo</td>
<td>6</td>
<td>197</td>
<td>13</td>
<td>2563</td>
<td>2779</td>
</tr>
<tr>
<td>65 to 79 yo</td>
<td>0</td>
<td>225</td>
<td>36</td>
<td>2623</td>
<td>2884</td>
</tr>
<tr>
<td>&gt;/= 80 yo</td>
<td>1</td>
<td>53</td>
<td>26</td>
<td>1454</td>
<td>1534</td>
</tr>
<tr>
<td>Grand Total</td>
<td>15</td>
<td>632</td>
<td>106</td>
<td>8360</td>
<td>9113</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRONC</td>
<td>960</td>
</tr>
<tr>
<td>SPUTM</td>
<td>6132</td>
</tr>
<tr>
<td>ENDOT/TA</td>
<td>2021</td>
</tr>
<tr>
<td>Grand Total</td>
<td>9113</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Since Admission</th>
<th>No Pathogen</th>
<th>Pathogen</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=48 hr</td>
<td>2788</td>
<td>1201</td>
<td>3989</td>
</tr>
<tr>
<td>48 to 96 hr</td>
<td>789</td>
<td>287</td>
<td>1076</td>
</tr>
<tr>
<td>&gt;96 hr</td>
<td>2113</td>
<td>1288</td>
<td>3401</td>
</tr>
<tr>
<td>Outpatient</td>
<td>392</td>
<td>255</td>
<td>647</td>
</tr>
<tr>
<td>Grand Total</td>
<td>6082</td>
<td>3031</td>
<td>9113</td>
</tr>
</tbody>
</table>
**CXRES at YNHH 2015: Isolates**

<table>
<thead>
<tr>
<th></th>
<th>&lt;=48 hr</th>
<th>48 to 96 hr</th>
<th>&gt;96 hr</th>
<th>Outpatient</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NF GNR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>244</td>
<td>55</td>
<td>318</td>
<td>87</td>
<td>704</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>13</td>
<td>4</td>
<td>97</td>
<td>11</td>
<td>125</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>7</td>
<td>2</td>
<td>40</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>Other NF GNR</td>
<td>13</td>
<td>6</td>
<td>30</td>
<td>5</td>
<td>54</td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>21</td>
<td>5</td>
<td>101</td>
<td>9</td>
<td>136</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>30</td>
<td>12</td>
<td>74</td>
<td>4</td>
<td>120</td>
</tr>
<tr>
<td>Enterobacter cloacae complex</td>
<td>9</td>
<td>12</td>
<td>89</td>
<td>2</td>
<td>112</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>29</td>
<td>12</td>
<td>66</td>
<td>3</td>
<td>110</td>
</tr>
<tr>
<td>Other Enterobacteriaceae</td>
<td>27</td>
<td>10</td>
<td>107</td>
<td>4</td>
<td>148</td>
</tr>
<tr>
<td><strong>Fastidious GNR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>106</td>
<td>21</td>
<td>23</td>
<td>30</td>
<td>180</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>59</td>
<td>5</td>
<td>9</td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>Other Fastidious GNR</td>
<td>66</td>
<td>13</td>
<td>17</td>
<td>29</td>
<td>125</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>679</td>
<td>162</td>
<td>673</td>
<td>81</td>
<td>1595</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>47</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>74</td>
</tr>
<tr>
<td>Beta Strep</td>
<td>104</td>
<td>16</td>
<td>19</td>
<td>19</td>
<td>158</td>
</tr>
<tr>
<td>Mold</td>
<td>25</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>44</td>
</tr>
</tbody>
</table>

**Summary of the Current Approach**

- For bacteria, still predominantly culture based
- PCR commercially available and accepted for respiratory viruses, Mycoplasma and Chlamydophila, and M. tuberculosis
- In many cases, specific testing (i.e. other than sputum culture) may have to be ordered for comprehensive evaluation
  - **How well does this system work?**
Jain et al. NEJM 2015

- Community Acquired Pneumonia Requiring Hospitalization Among US Adults
- ~2300 patients in TN and IL
- All Patients
  - Standard Bacterial Culture: blood, pleural fluid, sputum, ET aspirates, BAL
  - PCR for legionella (sputum), Multiple bacteria (pleural fluid), respiratory viruses + Mycoplasma & Chlamyphila (NP or OP swabs)
  - Urine antigens for Legionella or S. pneumoniae
  - Serology (acute and convalescent)
- Fungal and mycobacterial cultures when clinical indicated

Comprehensive evaluation but no sputum PCR

Low Rates of Pathogen Detection

Similar findings from Musher et al. J. Inf. 2013
Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia

- 323 adults in UK
- 18 mos encompassing 2 flu seasons
- Sputum or ET Aspirate subjected to culture and 26-plex respiratory pathogen PCR
- Looked antibiotic de-escalation

Table 1: Characteristics of Included Patients with CAP (n=323)
## Gadsby et al. Pathogens Detected

### Table 2: Pathogen Detection in Patients with CAP Using Molecular Methods (n=323)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N (%)</th>
<th>Culture Only</th>
<th>Culture + PCR</th>
<th>PCR Only</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2 (1.4)</td>
<td>2</td>
<td>51</td>
<td>79</td>
<td>191</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>155 (48.1)</td>
<td>135</td>
<td>20</td>
<td>40</td>
<td>208</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>44 (13.7)</td>
<td>37</td>
<td>7</td>
<td>27</td>
<td>286</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>37 (11.5)</td>
<td>33</td>
<td>4</td>
<td>2</td>
<td>320</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>33 (10.2)</td>
<td>31</td>
<td>2</td>
<td>0</td>
<td>314</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>13 (4.0)</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>5 (1.5)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>3 (0.9)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><em>Non-pneumococcal Legionella spp.</em></td>
<td>3 (0.9)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>2 (0.6)</td>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>Virus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any virus</td>
<td>99 (30.8)</td>
<td>95</td>
<td>4</td>
<td>94</td>
<td>208</td>
</tr>
<tr>
<td>Influenza</td>
<td>2 (7.1)</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>16 (5.0)</td>
<td>14</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>7 (2.2)</td>
<td>6</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>Parainfluenza virus</em></td>
<td>11 (3.4)</td>
<td>10</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>Parvovirus B19</em></td>
<td>9 (2.8)</td>
<td>8</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>Picornavirus</em></td>
<td>6 (1.9)</td>
<td>5</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>Coronavirus</em></td>
<td>2 (0.6)</td>
<td>2</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><em>HCoV-NL63</em></td>
<td>4 (1.2)</td>
<td>3</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>HCoV-229E</em></td>
<td>20 (6.2)</td>
<td>18</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><em>HCoV-HKU1</em></td>
<td>3 (1.0)</td>
<td>3</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><em>Adenovirus</em></td>
<td>7 (2.2)</td>
<td>6</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>Respiratory syncytial virus</em></td>
<td>4 (1.2)</td>
<td>4</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><em>Human metapneumovirus</em></td>
<td>3 (0.9)</td>
<td>3</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><em>Any pathogen</em></td>
<td>280 (86.8)</td>
<td>263</td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>With ≥10^6 CFU/mL, cutoff for bacteria when quantified</td>
<td>263 (81.1)</td>
<td>256</td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

### Additional Bacteria Detected by PCR

- Receipt of antibiotics before specimen collection → More likely PCR Only
- PCR allowed for de-escalation in 77% of patients; escalation in 5.9%
- Majority of de-escalation events were switching amox-clav to amox or doxy OR removal of clarithro for no atypicals
Take Homes from Studies

- Conventional microbiological evaluation + viral PCR fails to identify a causative agent in many cases
- This is UNLIKELY to be due to atypical bacterial pathogens → Not frequently found even when testing performed
- Comprehensive PCR increases rate of bacterial detection, but. . .

Challenges and Pitfalls of PCR

- No commercially available assays (yet)
- PCR asks “YES” or “NO” questions
  - “It depends” or “I don’t know”
  - Quant. PCR much more complex for lab to implement
- Overlap between microbiota and pathogens → Context (and quantity) matters
- PCR does not yield an isolate → NO AST
- Multiplex PCR is EITHER very complex for labs to implement OR very expensive
Future of Pneumonia Diagnostics

- Increasing role for molecular testing to identify potential pathogens
- Likely targeted PCR > Metagenomics or NGS
- Molecular panels have a “real estate” issue → targeted testing for less common pathogens still likely needed
- Cost benefit analyses will have to be performed
- Culture still required for susceptibility

Summary

- YNHH does a high volume of testing on predominantly inpatients
- Microbiologic diagnosis of pneumonia remains based on culture
- Molecular methods are available for some pathogens, and some may be available soon
- Context matters in respiratory tract cultures and molecular methods need to address this
- A multi-faceted approach to testing will still likely be required for some patients in the future
Cutting-Edge Therapies for Pneumonia
Where should we go from here?

Chad Marion DO, PhD
Yale University School of Medicine
Section on Pulmonary and Critical Care

Disclosures

- No disclosures
Objective

- Discuss the limitations of antimicrobial therapies in pneumonia
- Consider non-antimicrobial therapies that target host tissues responses to infection

Outline

- The current paradigm of the survival of pneumonia
  - Bacterial resistance and disease tolerance/tissue resilience
- Antimicrobial therapy, the emerging problem
  - Drug resistance
- Review some therapeutic targets beyond antibiotics
  - Pre-clinical studies
  - Clinical trials
- Microbiota and lung health
  - Pre-clinical studies
Clinical case 1

- 69 y/o Female
- PMH: HTN, bikes and swims
- Med: HCTZ
- 3-4 days of progressive SOB, fevers, chills, cough with productive sputum
- VS: Hypotensive, hypothermic, hypoxemic
- Leukocytosis, AKI, elevated lactate
- Intubated, vasopressors
- Culture: Streptococcus

Clinical care 2

- 69 y/o Female
- PMH: HTN, bikes and swims
- Med: HCTZ
- 3-4 days of progressive SOB, fevers, chills, cough with productive sputum
- VS: tachycardia
- Leukocytosis
- Culture: Streptococcus
Outcomes of Pneumonia

- Bacterial clearance, inflammation resolution
- Bacterial clearance, chronic inflammation
- Chronic infection, inflammation resolution
- Chronic infection, chronic inflammation
- Progressive infection, progressive inflammation

Antimicrobials: The mainstay of treating pneumonia

Antimicrobial Resistance for Selective Pathogens over Time

- Staphylococcus aureus resistant to methicillin
- Enterococcal resistant to vancomycin
- Pseudomonas aeruginosa resistant to imipenem
- Acinetobacter spp resistant to imipenem

https://www.toddcaldecott.com/antibiotic-resistance-1/
The 30-year Void

Where to go from here? Focus on the bacteria or host?

- Void of novel antibiotic therapeutic targets
- Increasing resistance of microbes to current antibiotic regimens
- Difficultly to identify infectious source

- Transition of therapeutic targets to host mediated response to infection
- Efficient killing of microbes and repairing or preventing damage to host tissues
Balancing Microbial Killing and Prevention of Host Tissue Damages Leads to Survival

Tolerance of Infection
Immunomodulation with Corticosteroids for CAP

- Controversy of corticosteroids
- First studies 1952
- Numerous and conflicting
- Heterogeneous doses, single centered

- Placebo controlled RCT at 3 Spanish medical centers
  - 61 treated with 0.5mg of methylprednisolone for 5 days vs placebo
  - Composite end-point early clinical deterioration and late treatment failure
  - Significant reduction on treatment failure in treatment group
  - Correlated with more rapidly improving CXR

Torres et. al. JAMA, 2015
More on Corticosteroids

- Multicenter, Double-blind, Placebo controlled, RTC, Switzerland
- 2009 to 2014
- Included 802 patients with CAP
- Treated with prednisone vs placebo
- Treatment with prednisone:
  - Shortened time to clinical stability by 1.4 days, as defined by guidelines
  - Shortened time to discharge by 1 day

- Meta-analysis through May 2015, included RTC with systemic corticosteroids in patients with CAP
- May reduce all-cause mortality (OR 0.67, CI 0.45 to 1.01)
- Decreased need for mechanical ventilation (OR .045, CI 0.26 to 0.79) and ARDS (OR 0.24, CI 0.10 to 0.56)

Blum et. al. Lancet, 2015

Corticosteroids are Safe and Beneficial for Severe CAP

Bi et. al. PLoS One, 2015
Immunomodulatory Effects of Macrolides Antibiotics

- Enhance phagocytosis
- iNOS → NO release
- Macrolides
- ROS
- ICAM → Neutrophil recruitment
- NF-κB activation
- Inflammatory cytokines

Immunomodulatory Effects of Macrolide Antibiotics

- Frequently used for treatment of CAP, along with β-lactam
- Known to alter both host and microbial response

  - Host: dampens NF-κB-mediated inflammation via modulation of mitogen-activated protein kinases
  - Microbes: alter virulence factor production in pneumococcal pneumolysin and interfere with quorum sensing

  - Non-inferiority RTC with β-lactam monotherapy vs β-lactam and macrolide therapy
  - Patients with CAP, patients categorized by CURB-65 and PSI
  - End-point: 90-day mortality
  - Monotherapy with β-lactam inferior to dual therapy in more severe CAP (CURB-65 > 2, PSI IV)

Garin et al. JAMA Intern Med, 2014
Role of Lung Barrier

Targeting Barrier Function

- Lung barrier consists of:
  - Epithelial cells
  - Endothelial cells
  - Other interstitial cells (DC, ILC, macrophages, etc.)
- Improving barrier integrity would limit bacterial translocation and release of inflammatory cytokines systemically

- Pre-clinical therapies include:
  - Adrenomedullin
  - Angiopoietin/Tie2 system
Modulation of Barrier Function with Adrenomedullin and Angiopoietin/Tie2 System

- **Adrenomedullin:**
  - Expressed in sepsis and acute lung injury models
  - Exaggerated inflammatory response in mice heterozygous for adrenomedullin with LPS stimulation
  - Treatment with exogenous protects against ventilator-induced lung injury in *Staphylococcus aureus* infection
  - Mechanisms: reducing cell contraction and strengthening adherence junctions

- **Angiopoietin/Tie2 System**
  - Regulates angiogenesis, inflammation and vascular permeability
  - Ang2 +/-, reduced levels were protected against lung injury
  - Transgenic expression of Ang1 in lung
    - Reduced cytokine
    - Reduced PMN infiltration
    - Reduced vascular leak

Regulation of Lung Immunity by Microbiota

- Individual’s microbiota begins at birth
- Alterations lead to dysbiosis and less beneficial bacterial species
- Microbiota is essential for immune system development

- GI and pulmonary system have a reciprocal relationship
  - Fluids, particles and microorganisms deposited in the nasal cavity are measured in GI tract
  - GI organisms can be aspirated into lungs
Dysbiosis Alters the Lung-Gut Axis

Effects of Intestinal Microbiota on Lung Health

- Allergies and Asthma
  - Antibiotic-depleted intestinal flora
  - Significantly more CD4+ T-cell-mediated inflammation in response to allergens
  - Altered intestinal flora

- Infectious Disease
  - Antibiotic-depleted intestinal flora
  - Impaired levels of virus-specific CD4 and CD8 T-cell subsets
  - Treatment with TLR agonists (lung or intestine) rescued the immune impairment
  - The normal gut microbiota is required for expression of pro-IL-1β and pro-IL-18
  - Germ-free mice
  - Increased susceptibility to pulmonary infection with bacterial pathogens
  - Increased levels of IL-10 during infection
  - Suppressed neutrophil recruitment
  - Increased pathogen growth and dissemination
  - Treatment with TLR agonist followed restored normal immune responses to bacterial infection
  - Conventionalized germ-free mice exhibit normal immune responses to bacterial infection
  - The "gut lymph" theory
  - Macrophages and other immune cells in the intestine kill the majority of translocating bacteria
  - Bacterial, cell wall fragments, or protein components may reach the lungs
  - Increased activation of alveolar macrophages leading to acute lung injury
  - The "intestinal crosstalk" theory
  - A three-way partnership among the intestinal epithelium, immune tissues, and microflora of the gut
  - Each factor modifies the others through crosstalk
  - Normal homoeostasis at all these components interact normally
  - Critically ill patients exhibit a loss of the balance between these systems
Intestinal Microbiota and Lung Infections

- Intestinal microbiota regulates immune responses to both viruses and bacteria
- Mice infected with influenza and neomycin vs influenza alone: antibiotic exposure has worse outcomes
  - Suggests neomycin-sensitive intestinal population is protective
- Infection of germ-free mice with *Klebsiella pneumonia* have enhanced susceptibility due to bacterial overgrowth
- Germ free mice have more robust IL-10 production
  - Germ free mice have more robust IL-10 production
- Introduction of normal intestinal flora to infected germ free mice
  - Had less *Klebsiella pneumonia* in lungs
  - Less bacteremia
  - Conventionalization restored PMN influx and normalized IL-10 production

Ichinohe et. al. PNAS, 2010
Fagundes et. al. J Immuno, 2012

Who is High-risk for Complications: Bedside Diagnosis

- Major limitation of clinical investigation:
  - need tools for early identification of poor outcomes
- Possible means for early identification
  - Serum
  - Omics profiling
  - Volatile organic profiling
- Much work need to be performed!!
Summary

- Recognition that therapies targeting both microbes and host are needed
- Lack of antimicrobial drugs in the pipeline
- Paradigm of treatment strategies for infection is shifting to include disease tolerance
- Host targeted therapies include
  - Immunomodulatory
  - Barrier function
- Emerging role that GI microbiota play in GI-lung axis
- Need for early prediction tools

Thank you!

Please visit Yale's Center for Pulmonary Infection Research and Treatment

http://cpirt.yale.edu
The Lung Microbiome: Insights into Precision and Personalized Approach to Pneumonia

Leopoldo N. Segal, MD, MS

Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
NYU School of Medicine

Inaugural Scientific and Clinical Symposium on Pneumonia
December 9th, 2016

NYU School of Medicine
NYU Langone Medical Center

Faculty Disclosure

Leopoldo N. Segal, MD

Relevant financial relationships with a commercial interest:
No relevant commercial interests.
38 yo man active smoker, cocaine user, admitted with cough for 3 months, fever, weight loss and malaise
New HIV diagnosis (CD4 count = 7, Viral Load > 100,000 copies/mL)

**Cultures initially negatives**
TST & IGRA negatives
*Mycobacterium avium complex* grew in sputum and blood sample.

**Two cases of Haemophilus influenza pneumonia**

**PNA-07**
- Culture: *H. influenza*
- TST (+)
- IGRA (-)

**PNA-09**
- Culture: *H. influenza*
- TST (-)
- IGRA (+)
Background

HIV is associated with increased risk for bacterial pneumonia

In an antimicrobial-treated pneumonia cohort, decline in airway microbiome diversity and domination of the community by a distinct respiratory pathogen e.g. Streptococcus pneumonia or Pseudomonas aeruginosa is associated with increased 28-day mortality.
In HIV PNA treated decreased diversity is associated with inflammatory cytokines

Compositionally distinct lower airway microbial states
Immune gene expression

Metabolome (serum)
Microbial community states are associated with mortality outcomes

Oral microbes are commonly found in the lower airways

Shenoy et al. AJRCCM Articles in Press

Charfson et al. Am J Respir Crit Care Med. 2011
Bassis et al. MBio. 2015
Beck et al. AJRCCM 2015
Molineaux et al. AJRCCM. 2013
Two distinct lung microbiomes

Segal et al. Nature Microbiology 2016
Host–microbial cross-talk promotes inflammation and could underlie the chronicity of inflammatory lung diseases

Huang et al. J ALLERGY CLIN IMMUNOL 2015

Yadava et al. Am J Respir Crit Care Med 2016
Host-Microbiota Interaction in the Lung

**Butyrate** is present in the lungs of HIV-infected individuals on ART and impairs cellular immunity to tuberculosis

- **Unstimulated PPD**
- **Stimulated PPD**
- **Bytyrate**
- **Propionate**
- **IL-8**
- **PMN Transmigration**
- **FoxP3+ % CD4+ CD25+ BAL Lymphocytes**
- **IfN-γ**, **IL-17A**

**Graphical Data**:
- **Log10 SCFA μM Epithelial Lining Fluid**
- **FoxP3+ % CD4+ CD25+ BAL Lymphocytes**
- **IFN-γ**, **IL-17A**
Lung microbiome of propionate-positive individuals is enriched with anaerobes

**Pathogen Control**
- IFN-γ production
- IL-17A production

**Pathogen Susceptibility**
- IFN-γ inhibition
- IL-17A inhibition

**Increasing Anaerobes/SCFA**

**Taxa Enriched in Propionate-Detectable**

**Taxa Enriched in Propionate-Undetectable**

**Shannon Diversity**

**Relative Abundance**
Many thanks

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FISABIO:
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Alejandro Artacho, Ph.D.

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Nuts and Bolts of Antimicrobial Therapy for MDR Organisms in Pneumonia

Jeffrey E. Topal, MD
Associate Professor of Medicine
Infectious Diseases Section
Yale School of Medicine

Chair, Antimicrobial Drug Utilization SubCommittee
Yale-New Haven Hospital

Disclosures

- No conflict of interest to disclose
- Will discuss off label use of FDA approved antimicrobials
There is no

- *Enterococcus faecium* (VRE)
- *Staphylococcus aureus* (MRSA)
- *Klebsiella* spp. (ESBL, CRE)
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter species*

From Antimicrobial Resistance

Potential MDR Pathogens in Pneumonia

- With the exception of VRE, all of the ESKAPE organisms are potential pathogens in pneumonia
  - MRSA
  - *Pseudomonas aeruginosa*
  - ESBL *E. coli/Klebsiella* spp.
  - *Enterobacter* spp.
  - *Acinetobacter baumannii*
Objectives

- Review treatment options for MRSA pneumonia
  - vancomycin
  - telavancin
  - ceftaroline
- Review treatment options for MDR *Pseudomonas aeruginosa* pneumonia
- Review potential treatment options for CRE organisms causing pneumonia

Treatment of MRSA Pneumonia
Vancomycin

- Complex soluble glycopeptide
- Very large molecule
  - 1450 Da
- Originally called “Mississippi Mud” due to impurities
  - Current formulation is highly purified

Vancomycin

Mechanism of Action

- Inhibits synthesis and assembly of the second stage of the cell wall peptidoglycan precursor
  - Fits into a pocket in the vancomycin molecule
  - Peptidoglycan cannot undergo transglycosalation or transpeptidation
**Vancomycin’s Inferiority Complex**

- MSSA pneumonia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Treated (%</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin</td>
<td>17 (41.5)</td>
<td>8 (47)*</td>
</tr>
<tr>
<td>cloxacillin</td>
<td>10 (24.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

(Gonzalez et al. CID 1999;29:1171-77)  
*p < 0.01

**Vancomycin MIC Distribution**

*S. aureus 2001-05 (N= 622)*

Vancomycin MIC Distribution
*S. aureus* 2000-04 (N= 6003)
UCLA

(Wang et al. *J Clin Mico* 2006;44:3883-6)

MRSA Bacteremia
Significance of Vancomycin MIC

(Soriano et al. *CID* 2008;46:193-200)
MRSA Bacteremia
Significance of Vancomycin MIC

Table 5. Factors independently associated with mortality in a logistic regression model of patients with episodes of methicillin-resistant Staphylococcus aureus bacteremia.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.02 (1.00–1.04)</td>
<td>.013</td>
</tr>
<tr>
<td>Receipt of corticosteroids</td>
<td>1.85 (1.04–3.29)</td>
<td>.034</td>
</tr>
<tr>
<td>Prognosis of underlying disease</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>1.81 (1.06–3.10)</td>
<td>.029</td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>10.2 (2.66–36.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Source of bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.18 (1.17–4.04)</td>
<td>.014</td>
</tr>
<tr>
<td>High risk</td>
<td>3.60 (1.89–6.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMIC1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VMIC1.S</td>
<td>2.86 (0.87–9.35)</td>
<td>.08</td>
</tr>
<tr>
<td>VMIC2</td>
<td>6.39 (1.68–24.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NA</td>
<td>3.62 (1.20–10.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shock</td>
<td>7.38 (4.11–13.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE. NA, receipt of inappropriate empirical therapy; VMIC1, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 μg/mL; VMIC1.S, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 μg/mL; VMIC2, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL.

(Soriano et al. CID 2008;46:193-200)

Do Increasing vancomycin MIC’s in MRSA correlate with increased mortality?

(Kalil AC et al. JAMA 2014; 312: 1552-64)
Finally, Problem of Determining Vancomycin MIC’s

If vancomycin MIC’s are creeping upward, does this mean that one needs obtain higher vancomycin levels for efficacy?
Origin of Recommending Increased Troughs

- Vancomycin killing activity
  - Pneumonia, *S. aureus* isolates
  - Improved clinical outcomes with:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin AUC/MIC value ≥350</td>
<td>7.19</td>
<td>1.91, 27.3</td>
<td>0.0036</td>
</tr>
<tr>
<td>MSSA as pathogen</td>
<td>3.88</td>
<td>1.10, 14.8</td>
<td>0.0359</td>
</tr>
<tr>
<td>Single lobe involvement</td>
<td>6.32</td>
<td>1.56, 25.6</td>
<td>0.0099</td>
</tr>
<tr>
<td>Baseline serum albumin (per 1 g/dL)</td>
<td>3.73</td>
<td>1.09, 12.8</td>
<td>0.0364</td>
</tr>
<tr>
<td>Baseline CLCR (per 1 mL/min)</td>
<td>1.04</td>
<td>1.01, 1.07</td>
<td>0.0154</td>
</tr>
</tbody>
</table>


Origin of Increased Goal Troughs: AUC/MIC > 350

- Limitations:
  - Confounding of clinical factors
    - Grouped MSSA and MRSA
    - AUC/MIC conclusions made using data from 34 patients
  - More than 1 active agent was allowed
  - No nephrotoxicity evaluation
Achieving the Golden Ratio of AUC/MIC > 350

Origin of Increasing Vancomycin Goal Troughs

- How do we achieve AUC/MIC > 350 or 400?
  - Thought is that achieving higher troughs will give us this AUC/MIC
Origin of Increasing Vancomycin Goal Troughs

- Need to maximize Cmax at this affects the AUC as well as the maintaining the time above the MIC
- Step one for optimization of AUC/MIC, is using weight-based vancomycin dosing in adults
- Need to adjust the interval between doses based on an increased number CrCl stratato ensure the trough levels are appropriate

YNHH Vancomycin Dosing

- Weight based dosing (15mg/kg/dose)
  - < 50 kg  500mg
  - 50-64.9 kg  750mg
  - 65-84.9kg  1000mg
  - 85-99.9  1250mg
  - 100-130kg  1500mg
  - >130kg  2000mg
- The vancomycin order set in EPIC automatically chooses the dose for inpatients based on their weight
YNHH Vancomycin Dosing

- Interval Based on CrCl:
  - > 100 mL/min Q 8 hours
  - 65-99 mL/min Q 12 hours
  - 50-64 mL/min Q 24 hours
  - 30-49 mL/min Q 36 hours
  - 10-29 mL/min Q 48 hours
  - <10 mL/min X 1 dose
- Use serum trough levels to guide dosing

Vancomycin Trough Goal 15-20 Where’s The Beef?

- IDSA & ASHP Guidelines for MRSA, 2011

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (B-II).
However…

Efficacy  Toxicity

How Do Trough Levels of 15-20 as a Goal Hold Up In Real Life?

- Vancomycin Exposure in MRSA Outcomes
  - Evaluated retrospective cohort of 320 patients with MRSA infections
  - Assessed goal troughs and nephrotoxicity

(Kullar et al. CID 2011; 52: 975-981)
Vancomycin Failure by Trough

Table 2. Vancomycin Trough Concentrations and Poor Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 308$^a$</th>
<th>Vancomycin failure n (%)</th>
<th>P (vs reference category)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough &lt;10 mg/L (n=70)</td>
<td>46 (65.7%)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Trough 10-14.9 mg/L (n=90)</td>
<td>52 (57.8%)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Trough 15-20 mg/L (n=86)</td>
<td><strong>34 (39.5%)</strong></td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Trough &gt;20 mg/L (n=62)</td>
<td>31 (50.0%)</td>
<td>0.206</td>
<td></td>
</tr>
</tbody>
</table>

- Lowest rate of failure in 15-20 group
  - However, 40% still had failure!
- > 20 trough did not improve outcomes!
- Note small population size in each group

(Kullar et al. CID 2011; 52: 975-981)

Vancomycin Trough and Nephrotoxicity

- Group with >20 had higher incidence of nephrotoxicity

(Kullar et al. CID 2011; 52: 975-981)
How Does 15-20 Goal Hold Up In Real Life?

- Lodise et al. 2008
  - Retrospective cohort, single study of 92 pts
  - MRSA bloodstream infections
  - Goal: examine MRSA MICs vs clinical outcomes with vancomycin

(Lodise et al. *Antimicrob Agents Chemo* 2008; 52: 3315-3320)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vancomycin Success (n=64)</th>
<th>Vancomycin Failure (n=28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt &gt; 112 kg</td>
<td>9%</td>
<td>29%</td>
<td>0.02</td>
</tr>
<tr>
<td>Dialysis</td>
<td>17%</td>
<td>43%</td>
<td>0.09</td>
</tr>
<tr>
<td>CrCl &lt; 33ml/min</td>
<td>25%</td>
<td>54%</td>
<td>0.008</td>
</tr>
<tr>
<td>APACHE II &gt; 20</td>
<td>6%</td>
<td>39%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>5%</td>
<td>21%</td>
<td>0.02</td>
</tr>
<tr>
<td>Median (IQR) vancomycin trough at steady state</td>
<td>14.3</td>
<td>15.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

No difference in success in < 15 vs > 15 mg/L groups (77% vs 78%)

(Lodise et al. *Antimicrob Agents Chemo* 2008; 52: 3315-3320)
Is 15-20 Safe?

  - 86 pts, elderly, MRSA (all types of infection)
  - Predictors of nephrotoxicity:
    - Concomitant nephrotoxic agents (AMGs, ampho) [p<0.001]
    - High vancomycin troughs [p=0.03]
    - Duration of therapy correlates with high troughs
      - 6% at < 7 days
      - 21% at 8-14 days
      - 30% at > 14 days

Vancomycin Trough > 15
Risk of Nephrotoxicity

(Van Hal SJ et al. AAC 2013;57: 734-744)
Literature Summary

- Although both ASHP and IDSA recommend vancomycin goal troughs 15-20 in serious MRSA infections, the data is lacking
  - Trials are small, mixed infection types
- ? Goal 15-20 → no mortality benefit, efficacy unclear
- Troughs > 15 → increased nephrotoxicity

MRSA Pneumonia
Alternative Therapies

- telavancin
- ? ceftaroline
Telavancin

- Vancomycin derivative
  - Lipoglycopeptide
- Dual mechanism of action
  - Interrupts cell wall cross-linking
  - Triggers rapid dissipation of the cell membrane potential by pore formation

Localization of cellular binding with fluorescent conjugates of telavancin vs vancomycin

- Fluorescence intensity was observed across the entire cell surface, representing binding to d-Ala-d-Ala residues, but telavancin (A) had increased binding to the septum versus cell wall, demonstrating preferential binding to the site of active cell wall biosynthesis. Vancomycin (B) binding was distributed more evenly between the cell wall and the division septum

(Lunde CS et al. AAC 2010;54:2198-2200)
Telavancin Spectrum of Activity

Table 1. Comparative in vivo Minimum Inhibitory Concentrations (MICs) of Telavancin, Vancomycin, Linezolid, and Daptomycin for Gram-Positive Organisms

<table>
<thead>
<tr>
<th>Organism (no of isolates tested)</th>
<th>MICSpan (µg/mL)</th>
<th>Telavancin</th>
<th>Vancomycin</th>
<th>Linezolid</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>MSSA (1217)</td>
<td></td>
<td>0.25</td>
<td>1</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>VISA (23)</td>
<td></td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>DN USA (7)</td>
<td></td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin susceptible (1155)</td>
<td></td>
<td>0.6</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Methicillin resistant (273)</td>
<td></td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecalis vancomycin susceptible (99)</td>
<td>0.25</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis vancomycin susceptible (92)</td>
<td>0.25</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Van A (222)</td>
<td></td>
<td>8</td>
<td>512</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Van B (113)</td>
<td></td>
<td>2</td>
<td>512</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus pyogenes (98)</td>
<td></td>
<td>0.06</td>
<td>0.5</td>
<td>1</td>
<td>0.00</td>
</tr>
<tr>
<td>Streptococcus agalactiae (63)</td>
<td></td>
<td>0.06</td>
<td>0.5</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (204)</td>
<td></td>
<td>0.03</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Actinomyces naeslundii (113)</td>
<td></td>
<td>0.25</td>
<td>1</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Clostridium difficile (18)</td>
<td></td>
<td>0.25</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Clostridium perfringens (12)</td>
<td></td>
<td>0.125</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium ramosum (16)</td>
<td></td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Peptococcus asacchara (16)</td>
<td></td>
<td>0.25</td>
<td>0.5</td>
<td>8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

NOTE: DN USA, daptomycin-sensitive S. aureus; MSSA, methicillin-resistant S. aureus; VISA, vancomycin-intermediate S. aureus; S. aureus; VISA, vancomycin-intermediate S. aureus; S. aureus; VISA, vancomycin-intermediate S. aureus; S. aureus; VISA, vancomycin-intermediate S. aureus; S. aureus; VISA, vancomycin-intermediate S. aureus; S. aureus; VISA, vancomycin-intermediate S. aureus; S. aureus;

(Saravolatz LD et al. CID 2009;49:1908-14)

Telavancin Pharmacokinetics

- **Dose**
  - 10mg/kg IV daily
  - Long half life of 7.5 hours
  - Allows for once daily dosing
  - Requires renal dose adjustment for reduced CrCl
- **Excretion** is primarily renal
  - 65-72% recovered unchanged in the urine
Telavancin

- Hospital Acquired Pneumonia (ATTAIN 1 & 2)
  - Telavancin + aztreonam vs. vancomycin + aztreonam
  - Non-inferior to vancomycin for primary endpoint of clinical cure
  - Mono-microbial S. aureus pneumonia, telavancin was superior to vancomycin

(Rubenstein E. et al. CID 2011;52(1):31–40)

Telavancin

- Teratogenic at clinically relevant doses
  - Must check urine pregnancy before administering in females of child bearing age
- Spurious laboratory elevation of PT/INR and PTT
  - Effect of telavancin on the lipid reagent for these tests
  - Obtain specimen for PT/PTT at telavancin trough
- Nephrotoxicity
- Expensive
Ceftaroline

- How can a cephalosporin have activity against MRSA?
  - Binds 128 fold more tightly to PBP2a, the altered penicillin binding protein coded by the mecA gene than oxacillin or ceftriaxone


Ceftaroline

- oxime group, β-lactamase resistance
- phosphono group, increases solubility; present in prodrug, not present in active form
- 1,3-thiazole ring, anti-MRSA activity
- pyridine ring zwitterion (positive charge)
- 1,2,4-thiadiazole ring, Gram-negative penetration & transpeptidase activity
- carboxyl group zwitterion (negative charge)

Ceftaroline


Ceftaroline

- Half life
  - 1.6-2.7 hours
- Usual dose
  - 600mg IV q 12h
- Route of excretion
  - Renal
    - 65% of drug is excreted unchanged in urine
Ceftaroline--Role in Therapy

- CAP (FOCUS 1 & 2) [n=1153]
  - Why studied for this indication?
  - Non-inferior to ceftriaxone
- MRSA pneumonia
  - No data as patients with known h/o MRSA were excluded from the trials
  - Only 2 patients in the FOCUS trials had MRSA in their sputum (both were in the CTX arm)

(File TM et al. CID 2010; 51:1395–1405)

Ceftaroline MRSA Pneumonia

- Multicenter, retrospective review of patients treated for MRSA infections with ceftaroline
  - Pneumonia: 17% of patients (92/527)

(Casapao AM et al. AAC 2014;58:2541–2546)
Ceftaroline Adverse Reactions

(Blumenthal KB et al. J Allergy Clin Imm Pract 2016, in press)

Development of MRSA Resistance to Ceftaroline

One amino acid substitution in PBP2A (Y446N) resulted in high level ceftaroline resistance

(Long SW et al. AAC 2014;58:6668-74)
Treatment of MDR *Pseudomonas aeruginosa* Pneumonia

**Ceftolozane/Tazobactam**

- 3rd generation cephalosporin combined with a beta-lactamase inhibitor (2:1)
  - Novel MOA
    - inhibits multiple PBPs of *P. aeruginosa* (PBP1b, PBP1c, PBP3)
Ceftolozane/Tazobactam

- Gram negative spectrum of activity
  - Excellent activity against Enterobactericeae
    - But, increased MIC’s for ESBL’s
    - Active against AmpC *in vitro*

<table>
<thead>
<tr>
<th>Organism (no. tested)</th>
<th>MIC₅₀  (mg/L)</th>
<th>MIC₉₀  (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli (368)</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>ESBL phenotype E. coli (76)</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>ESBL phenotype K. pneumonia (132)</td>
<td>4</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Klebsiella oxytoca (74)</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Proteus mirabilis (82)</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Indole positive Proteae (62)</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter spp. (286)</td>
<td>0.25</td>
<td>8</td>
</tr>
<tr>
<td>Serratia spp. (94)</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Citrobacter spp. (70)</td>
<td>0.25</td>
<td>2</td>
</tr>
</tbody>
</table>

(Sader HS et al. *J Antimicrobials* 2014; 43: 533–539)

Ceftolozane/Tazobactam

- Gram Negative Activity
  - Excellent against *Pseudomonas aeruginosa*
  - More active than ceftazidime or Zosyn *in vitro*
    - Including MDR strains

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC₅₀/ MIC₉₀ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1/4</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>2/32</td>
</tr>
<tr>
<td>Cefepime</td>
<td>4/16</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.5/8</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>B&gt;64</td>
</tr>
</tbody>
</table>

(Sader HS et al. 52nd ICAAC, Washington DC, ASM; 2012)
## Ceftolozane/Tazobactam

### Activity against MDR *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Organism (no. tested)/resistance phenotype</th>
<th>No. of isolates (cumulative)</th>
<th>inhibited at ceftolozane/tazobactam MIC in mg/mL of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.5</td>
<td>1</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> (1019)</td>
<td>510 (50.0)</td>
<td>256 (75.2)</td>
</tr>
<tr>
<td>CAZ-nons (269)</td>
<td>2 (0.7)</td>
<td>42 (16.4)</td>
</tr>
<tr>
<td>FEP-nons (239)</td>
<td>3 (1.3)</td>
<td>29 (13.0)</td>
</tr>
<tr>
<td>MEM-nons (268)</td>
<td>49 (18.3)</td>
<td>63 (41.8)</td>
</tr>
<tr>
<td>P/T-nons (144)</td>
<td>18 (1.2)</td>
<td>66 (45.9)</td>
</tr>
<tr>
<td>CAZ &amp; MEM &amp; P/T-nons (159)</td>
<td>-</td>
<td>18 (11.6)</td>
</tr>
<tr>
<td>LVX-nons (217)</td>
<td>57 (26.6)</td>
<td>87 (46.9)</td>
</tr>
<tr>
<td>GEN-nons (127)</td>
<td>24 (18.2)</td>
<td>47 (36.0)</td>
</tr>
<tr>
<td>MDR (156)</td>
<td>9 (6.2)</td>
<td>52 (33.8)</td>
</tr>
<tr>
<td>XDR (134)</td>
<td>2 (1.5)</td>
<td>24 (14.8)</td>
</tr>
</tbody>
</table>

(Sader HS et al. *J Antimicrobials* 2014; 43: 533–539)

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## Ceftolozane/Tazobactam

### YNHH MDR *P. aeruginosa*

- **Purpose:** To test YNHH meropenem resistant *Pseudomonas aeruginosa* against ceftolozane/tazobactam
- **Tested 28** meropenem resistant *Pseudomonas aeruginosa* via E-strip
  - doripenem
  - meropenem
  - piperacillin / tazobactam
  - ceftolozane / tazobactam
Ceftolozane/Tazobactam
YNHH MDR *P. aeruginosa*

- Meropenem-R & Zosyn-R *P. aeurginosa* (n=28)
  - 93% (26/28) susceptible to ceftolozane/tazobactam

Ceftolozane/Tazobactam

- Poor activity against:
  - *Acinetobacter baumannii*
  - *Stenotrophomonas maltophilia*

<table>
<thead>
<tr>
<th></th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>Acinetobacter spp. (233)</td>
<td>32</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia (136)</td>
<td>16</td>
</tr>
</tbody>
</table>

(Sader HS et al. *J Antimicrobials* 2014; 43: 533–539)
Ceftolozane/Tazobactam

- **Gram positive activity (in-vitro):**
  - Group A, B streptococci
  - *S. milleri* group
  - *S. pneumoniae*

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ceftolozane/tazobactam

- **Anaerobic activity**

(Snydman DR et al. AAC 2014; 58;1218-23)
ceftolozane/tazobactam
Pharmacokinetics

- Half life
  - 3.12 hours (ceftolozane)
  - 1.03 hours (tazobactam)
- Usual dose
  - 1.5g IV q 8h for non-pneumonia
  - 3g IV q 8h for pneumonia (proposed dose)
- Route of excretion
  - Renal
    - 95% of drug is excreted unchanged in urine

Ceftolozane/Tazobactam

- Place in therapy:
  - FDA approved for treatment of cIAI’s & cUTI’s
  - However, given its cost and antimicrobial spectrum, current use would be reserved for MDR *Pseudomonas aeruginosa* infections
  - ? How well it will hold up over time against MDR *Pseudomonas aeruginosa* remains to be determined
  - Has worked for MDR-Pseudomonas pneumonia at YNHH but resistance has developed after prolonged use
Pneumonia due to CRE

- Carbapenem Resistant Enterobacteriaceae
  - Etiology
    - Production of KPC’s (Bla\textsubscript{KPC})—carbapenemases
    - Metallobetalactamases
      - VIM, IMP, NDM-1
    - Down regulation of outer membrane porins
      - Enterobacter cloacae
  - Accounts for 42% of CRE infections
  - High mortality rate—61%
    (Maio-Carrhilo C et al. BMC Inf Dis 2016;16:629)

Not Many Treatment Options for Pneumonia Due to CRE

- tigecycline
- ceftazidime-avibactam

(Castaheina M et al. AAC 2014;58:833-838)
Tigecycline

- glycylcycline
- Novel 9-t-butyrglycylamido derivative of minocycline
  - Overcomes tetracycline resistance
    - Altered ribosomal binding site
    - Large substituent at position 9 results in steric hindrance
    - Efflux pumps
    - Can up-regulate in KPC producing organisms

Tigecycline Pharmacokinetics

- Intravenous formulation only
- T½ of 36 hours
- Protein binding 68%
- Extremely large Vd > 10L/kg
  - Problem of low serum levels
  - ? Can be used to treat bacteremia
- Elimination: <15% excreted unchanged in the urine
Ceftazidime/Avibactam

- Ceftazidime with a non-beta-lactam, beta-lactamase inhibitor—avibactam in a 4:1 ratio
  - 2g ceftazidime and 0.5g avibactam

What does avibactam add to ceftazidime

- Has activity against class A, C, and D beta-lactamases including ESBL’s
- Has activity against specific KPC’s
- Not active against metallo-beta-lactamases

(Castenheira M et al. AAC 2015; 59:3509-17)
Ceftazidime/Avibactam

- **MDR Pseudomonas aeruginosa**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/mL)</th>
<th>Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime-avibactam</td>
<td>4–16</td>
<td>0.25 to &gt;32</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>32</td>
<td>1 to &gt;32</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>16</td>
<td>1 to &gt;16</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;64</td>
<td>1 to &gt;64</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>≤0.06 to &gt;8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>≤0.01 to &gt;4</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;4</td>
<td>≤0.12 to &gt;4</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>≤1 to &gt;8</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32</td>
<td>≤0.25 to &gt;32</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>≤0.25 to &gt;8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.7±6.36</td>
<td>0.5 to &gt;32</td>
</tr>
<tr>
<td>18.1±1.72</td>
<td>1 to &gt;32</td>
</tr>
<tr>
<td>11.0±3.55</td>
<td>4 to &gt;16</td>
</tr>
<tr>
<td>2.7±0.30</td>
<td>8 to &gt;16</td>
</tr>
<tr>
<td>7.2±0.14</td>
<td>0.12 to &gt;8</td>
</tr>
<tr>
<td>7.2±0.55</td>
<td>0.25 to &gt;4</td>
</tr>
<tr>
<td>3.6±0.12</td>
<td>1 to &gt;8</td>
</tr>
<tr>
<td>37.9±1.0</td>
<td>≤0.25 to &gt;32</td>
</tr>
<tr>
<td>56.0±1.0</td>
<td>≤0.25 to &gt;8</td>
</tr>
</tbody>
</table>

(Sader HS et al. AAC 2015; 59: 3556-9)

Ceftazidime/Avibactam

**YNHH MDR P. aeruginosa**

- **Meropenem-R & Zosyn-R P. aeruginosa** (n=28)
  - 50% (14/28) susceptible to ceftazidime/avibactam
Ceftazidime/Avibactam

- Half life
  - 3.3 hours
- Usual dose
  - 2.5g IV q 8h
  - Requires dose adjustment for renal insufficiency
- Route of excretion
  - Renal
  - 80-90% of drug is excreted unchanged in urine

Ceftazidime/Avibactam

- Place in therapy
  - Treatment of CRE which have KPC activity
  - Extremely expensive at $805/day with standard dosing of 2.5g IV q 8h
  - National shortage due to manufacturer issues
Questions

"Don't forget to take a handful of our complimentary antibiotics on your way out."
Antibiotic Resistance and Antibiotic Stewardship

Inaugural Scientific and Clinical Symposium on Pneumonia

Louise M. Dembry, MD, MS, MBA
December 9, 2016

Disclosures

ReadyDock (not relevant to this presentation)

- US: estimated 2 million infected -> 26,000 deaths/year
- AR costs $55 billion annually
- Pan resistant infections becoming more common
- Global variation in resistance patterns
- Slow pace of discovery of novel antibiotics
- Antibiotic use continues to rise
  - Global consumption increased 40% between 2000 and 2010
- All microbes have the potential to mutate
- Speed and volume of intercontinental travel creates new opportunities to spread resistance

The Review on Antimicrobial Resistance, Chaired by Jim O’Neill
CARB Goals

- Slow the development of resistant bacteria and prevent the spread of resistant infections
- Strengthen national one-health surveillance efforts to combat resistance
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines
- Improve international collaboration and capacities for antibiotic research and development
CDC’s Antibiotic-Resistant Threats (2013)

- **Urgent Threat level pathogens**
  - *C. difficile*
  - Carbapenem-Resistant Enterobacteriaceae (CRE)
  - *Neisseria gonorrhoeae*

- **Serious threat level pathogens**
  - Multidrug-Resistant Acinetobacter
  - Drug-Resistant Campylobacter
  - Fluconazole-Resistant Candida
  - Extended Spectrum B-lactamase (ESBL)-Producing Enterobacteriaceae
  - Vancomycin-Resistant Enterococcus (VRE)
  - Multidrug-Resistant *Pseudomonas aeruginosa*
  - Drug-Resistant Salmonella and Shigella
  - Methicillin-Resistant *Staphylococcus aureus* (MRSA)
  - Drug-Resistant *Streptococcus pneumoniae*
  - Drug-Resistant Tuberculosis

---

Which came first, the antibiotic or resistance?

- Resistance is an inevitable evolutionary outcome
- Gene exchange is a universal property of bacteria throughout eons of microbial evolution
- All organisms develop genetic mutations to avoid lethal selection pressure
- More than 70% pathogenic bacteria resistant to >1 antibiotic
Environmental reservoirs of resistance

FIG. 4. Dissemination of antibiotics and antibiotic resistance within agriculture, community, hospital, wastewater treatment, and associated environments. (Adapted from reference 49 and reference 154 with permission of the publishers.)

Microbiology and Molecular Biology Reviews 2010;74:417-433
What is clear

- All antibiotic use causes selective pressure
- Appropriate use applies the same selective pressure as inappropriate use
- Misuse of antibiotics affects the rate of spread of resistance
- We should stop inappropriate use as it offers no benefit
- Benefit of appropriate use to patients and society outweighs the collective harm (i.e., development of resistance)

Spellberg B; Medscape 10/20/16

BMJ

Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

Côe Costelloe, research associate; Chris Metcalfe, senior lecturer in medical statistics; Andrew Lowning, consultant clinical scientist; David Mant, professor of general practice; Vastar D Hay, consultant senior lecturer in primary health care

WHAT IS ALREADY KNOWN ON THIS TOPIC

Worldwide, primary care is responsible for the majority of antibiotic use by human beings
Although many countries have reduced prescribing rates, substantial variations remain between countries
Many clinicians and patients do not see antibiotic resistance as a reason to refrain from antibiotic use

BMJ 2010;340:c2096
• Observational and experimental studies
• Bacteria sampled from any body site
• Relationship between primary care prescribed antibiotics and antimicrobial resistance at the individual level
• 24 studies
  • 5 RCT, 19 observational studies
  • 15,505 adults; 12,103 children
  • 22 studies sampled bacteria from symptomatic patients
  • 2 studies sampled from asymptomatic adult volunteers

Resistance in urinary bacteria

• Odds of resistance greater in patients exposed to antibiotics than in unexposed
• Strongest association at 0-1 months
• Small, but residual, association within 12 months
Resistance in respiratory bacteria

- Some association between antibiotic use and resistance between 0-1 month, 0-2 months and 0-12 months
- Intervening periods showed less association

- 2 prospective studies
  - Giving ampicillin to a child more than tripled the MIC for ampicillin and doubled risk of isolating *Haemophilus* isolates with ICEHin1056 resistance element
  - RCT examined resistance (azithromycin, clarithromycin) at specific time points
    - Decreasing association with resistance to macrolides at all time points up to 6 months with strong evidence of a time trend
Evidence of an association at individual patient level between prescribing of antibiotics in primary care and antimicrobial resistance in bacteria at different sites
- Effects strongest in the month directly after prescription, detectable for up to 12 months
- Residual effect likely to be important driver for endemic levels of antibiotic resistance in the community
- Greater the number or duration of antibiotic courses prescribed in previous 12 months, greater likelihood resistant bacteria isolated from that patient

BMJ 2010;340:c2096

Antibiotic Stewardship Programs
- Preserve the integrity and effectiveness of antibiotics
- Coordinated approach to ensure optimal prescribing
  - Drug, dose, de-escalation, duration
- Benefits
  - Patient level
    - Decrease adverse events including CDI
    - Mortality
  - Societal level
    - Impact antibiotic resistance rates to select antibiotics
      - ‘Squeezing the balloon’
      - Research to show causal association
        - Most studies are observational
  - Costs
28 recommendations ‘graded’
• Interventions
• Optimization
• Microbiology and Laboratory Diagnostics
• Measurement
• Special Populations

Endorsed 5 antibiotic stewardship interventions
• Pre-authorization and/or prospective feedback
• Implementation of interventions designed to reduce the use of antibiotics with a high risk for \textit{C. difficile} infection
• Interventions to reduce antibiotic therapy to the shortest effective duration
• Implementation of pharmacokinetic monitoring with dose adjustment for aminoglycosides
• Promotion of switching from intravenous to oral administration when clinically feasible
Does the use of preauthorization and/or prospective audit and feedback interventions by ASPs improve antibiotic utilization and patient outcomes?

**Strong recommendation, moderate-quality evidence**
- Pre-authorization (restrictive)
  - Skill of individuals involved
  - ID attending and clinical pharmacist
  - Accuracy of communication
- Prospective audit/feedback (persuasive)
  - Infrastructure
  - Labor intensive
  - Limited PAF

| Table 1. Comparison of Preauthorization and Prospective Audit and Feedback Strategies for Antibiotic Stewardship |
|--------------------------------------------------|--------------------------------------------------|
| Preauthorization | Prospective Audit and Feedback |
| Reduce initiation of inappropriate antibiotic use | Can increase visibility of antibiotic stewardship program and enable ongoing evaluation of various strategies used to optimize antibiotic use |
| Minimize unnecessary antibiotic use | Identify opportunities for stewardship intervention to improve antibiotic use |
| Increase antibiotic utilization | Monitor antibiotic use over time to identify trends and opportunities for improvement |
| Improve antibiotic prescribing | Enable proactive identification of potential prescribing errors and facilitate timely interventions |
| Ensure accurate communication | Facilitate ongoing collaboration between clinicians and pharmacists |

Should ASPs implement interventions designed to reduce the use of antibiotics associated with a high risk of CDI?

**Strong recommendation, moderate-quality evidence**
- ASPs have been shown to reduce hospital onset CDI
  - High risk antibiotics: clindamycin, broad spectrum agents (e.g., cephalosporins, fluoroquinolones)
  - Statistically significant sudden or linear-trend decreases in hospital acquired CDI rates
    - Sustained for up to 7 years
  - Antibiotic restriction can further reduce CDI rates when added to previous infection prevention measures
In hospitalized patients IV intravenous antibiotics, does a dedicated PK monitoring and adjustment program lead to improved clinical outcomes and reduced costs?

- **Strong recommendation, moderate-quality evidence**
- Aminoglycoside dosing
- Vancomycin: lower incidence nephrotoxicity
- Antibiotic dosing, integration of dosing support into EMR ordering system, improves adherence to dosing guidelines and fewer adverse effects

Should ASPs implement interventions to increase use of oral antibiotics as a strategy to improve outcomes or decrease costs?

- **Strong recommendation, moderate-quality evidence**
- Associated with reduced drug costs and length of hospital stay without compromising efficacy or safety
- More advanced assistance when converting from IV antibiotic without an equivalent oral formulation
- Reduction in need for outpatient parenteral antibiotic therapy (OPAT)
Reduce antibiotic therapy to the shortest effective duration (strong recommendation, moderate-quality evidence)

- Written guidelines as part of preauthorization or PAF process
- Specify duration at time of antibiotic ordering
- 'Shorter is better'

Measurement

- Days of therapy (patient level antibiotic use data) vs defined daily doses
- Antibiotic costs: prescriptions or administrations, not purchasing data
- Consider the goals and size of the syndrome specific intervention
CDC: Core Elements of Hospital Antibiotic Stewardship Programs

- Leadership commitment: resources
- Accountability: leader responsible for outcomes
- Drug expertise: pharmacist leader
- Action: implement ≥ 1 recommended action
- Tracking: prescribing and resistance patterns
- Reporting: regular, relevant staff
- Education: resistance, optimal prescribing

Optimize the treatment of infections and reduce adverse events associated with antibiotic use

Utilize specific interventions (cont.)

- Pharmacy driven
  - Automatic iv to oral change
  - Dose adjustments and optimization
  - Automatic alerts for duplicative therapy
  - Time sensitive automatic stop orders
  - Detect and prevent drug-drug interactions

- Infection and syndrome specific
  - CAP, UTI, SSTI, CDI
  - Empiric coverage of MRSA infections
  - Treatment of culture proven invasive infections
Emerging Developments in Antibiotic Stewardship

- Integration of IT into clinical data presentation and decision making
- Diagnostic laboratory testing, rapid diagnostic tests
- Better characterization of impact of stewardship interventions on resistance
- Evaluate which interventions or antibiotic targets yield the greatest benefit in combating resistance
- CDC/NHSN Antimicrobial Resistance (AR) option, use standardized approach
November 14-20, 2016

The one-week observance raises awareness of the threat of antibiotic resistance and the importance of appropriate antibiotic prescribing and use. CARB goal: reduce outpatient antibiotic use by 50% by 2020, reduce inappropriate inpatient antibiotic use by 20% by 2020.
Preventing Pneumonia: Is there hope for anything other than vaccines?

Manisha Juthani-Mehta, MD
Associate Professor of Medicine
Section of Infectious Diseases

*Yale Pneumonia Symposium*
*December 9th 2016*

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**Etiology and types of pneumonia**

- Types of pneumonia
  - Community-acquired pneumonia
  - Healthcare-associated pneumonia
    - Nursing home-acquired pneumonia
    - Hospital-acquired pneumonia
    - Ventilator-associated pneumonia
- Common themes
  - Pathogen specific \(\rightarrow\) vaccines (influenza, pneumococcus) – Dr. Shaw
  - Aspiration
    - Oral hygiene
    - Swallowing difficulty
      - Dietary interventions (i.e., puree vs mechanical soft)
      - Cough reflex preservation (i.e., ACE inhibitors)
      - Enteral feeding tubes (e.g., NGT, PEG, jejunal feeds)
      - Bed position (i.e., semi-recumbent vs supine)
Oral hygiene

- Aspiration of oral flora into lower airway → respiratory pathogens can colonize dental plaque and oral mucosa
- Difficulties performing oral hygiene due to illness, old age, dementia, or functional disabilities
- Prevention strategies:
  - chemical oral disinfection
    - topical application of chlorhexidine
  - broad-spectrum antibiotics
  - mechanical cleaning

Community-acquired pneumonia

Modifiable Risk Factors for Pneumonia Requiring Hospitalization of Community-Dwelling Older Adults: The Health, Aging, and Body Composition Study

Maitha Jatho-Melita, MD,* Nathalie De Rekeneire, MD, MS,* Heather Allore, PhD,* Shi Chen, MS,* John R. O’Leary, MA,* Douglas C. Bauer, MD,† Tamara B. Harris, MD, MS,* Anne B. Neuman, MD, MPH,* Sachin Yende, MD, MS,* Robert J. Weyant, DMD, DrPH,** Stephen Krischensky, PhD,† and Vincent Quagliaello, MD* for the Health ABC Study

- Two modifiable risk factors:
  - incident mobility limitation
  - dental plaque score
- Most important outpatient intervention (other than vaccines) → twice yearly dental cleanings
Oral care interventions for HCAP and NHAP

Prevention of Healthcare-Associated Pneumonia with Oral Care in Individuals Without Mechanical Ventilation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Asako Kameoka, MSc1 Jessica M. Piaseca, MSc2 Kari V. Mikora, MSc3 Mel Lo, MSc3 Hiroki Saiki, MD, MPH3 Luis F. Raubitschek, PhD1 Michael P. LaValley, PhD1 Susan E. Longmire, PhD3

OBJECTIVE. Evidence is lacking on the preventive effect of oral care on healthcare-associated pneumonia in hospitalized patients and nursing home residents who are not mechanically ventilated. The primary aim of this review was to assess the effectiveness of oral care on the incidence of pneumonia in nonventilated patients.

METHODS. We searched 8 databases (EMBASE, Embase, CENTRAL, CINAHL, Web of Science, LILACS, ECUMED, and CINAHL) in addition to trial registries and a manual search. Eligible studies were published and unpublished randomized controlled trials examining the effect of any method of oral care on reported incidence of pneumonia and/or fatal pneumonia. Relative risks (RR) and 95% confidence intervals were calculated. Risk of bias was assessed for eligible studies.

RESULTS. We identified 15 studies consisting of 6,090 subjects that met the inclusion criteria. Of those, 2 trials assessed the effect of chlorhexidine in hospitalized patients; 3 studies examined mechanical oral cleaning in nursing home residents. A meta-analysis could only be done on 4 trials: this analysis showed a significant risk reduction in pneumonia through oral care interventions (RR (95% CI): 0.61 (0.45-0.80); P = 0.02). The effects of mechanical oral care done were significant when pooled across studies. (RR (95% CI): 0.61 (0.45-0.80); P = 0.02). Risk reduction for fatal pneumonia from mechanical oral cleaning was also significant (RR (95% CI): 0.23 (0.11-0.50); P = 0.02). Most studies had a high risk of bias.

CONCLUSIONS. This analysis suggests a preventive effect of oral care on pneumonia in nonventilated individuals. This effect, however, should be interpreted with caution due to risk of bias in the included trials.


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Oral care interventions in non-VAP trials

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Participant (n, mean age)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Pneumonia Diagnosis</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adachi (2002)25</td>
<td>Nursing home residents (181, 84.0)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not defined</td>
<td>Routine care: assisted cleaning after each meal by staff or caregivers</td>
<td>Swallowing with a suppository and denture cleaning after each meal by residents</td>
</tr>
<tr>
<td>Yenopoulo (2002)27</td>
<td>Nursing home residents (41, 82.0)</td>
<td>Stable physical and cognitive function</td>
<td>Not specified</td>
<td>Chest x-ray, temperature &lt;37.5°C, cough or subjective dyspnea</td>
<td>Routine care: toothbrushing after each meal by nurses and caregivers; placebo tablets (1.0%) as necessary</td>
<td>Tooth brushing once a day or irregularly by residents</td>
</tr>
<tr>
<td>Ohana (2003)26</td>
<td>Nursing home residents (85, 83.8)</td>
<td>Stable physical and cognitive function</td>
<td>Not specified</td>
<td>Chest x-ray, temperature &lt;37.5°C, cough or subjective dyspnea</td>
<td>Routine care: toothbrushing after each meal by nurses and caregivers; placebo tablets (1.0%) as necessary</td>
<td>Tooth brushing after each meal by residents and caregivers</td>
</tr>
<tr>
<td>Panditpalna (2009)29</td>
<td>Neuro-intensive care unit (50, 66.0)</td>
<td>All patients admitted to a neuroscare unit</td>
<td>Pregnancy, patients with pneumonia on hospital admission</td>
<td>Chest x-ray, temperature &lt;37.5°C, cough or subjective dyspnea</td>
<td>Routine care: mechanical ventilation 2-3 days/week by nurse or dental hygienist; rinsing and gargling with CHX (0.2%, 10 mL) twice daily</td>
<td>Rinsing and gargling with percutaneous nutrition solution (0.0%, 10 mL) twice daily</td>
</tr>
<tr>
<td>Lam (2013)23</td>
<td>Rehabilitation unit of a teaching hospital (100, 65.7)</td>
<td>Age &gt;50, Barthel Index &gt;70</td>
<td>Satisfactory communication, physical examination, oral hygiene instruction</td>
<td>Not defined</td>
<td>Group 1: CHX by a dentist + CHX (0.2%, 10 mL) mouthwash twice daily by nursing care aids Group 2: CHX (0.2%, 10 mL) twice daily, and assisted tooth brushing by nursing care aids</td>
<td>ORL, electric tooth brushing</td>
</tr>
</tbody>
</table>

Notes: CHX, chlorhexidine; ORL, oropharyngeal rinse; CHS, chlorhexidine mouthwash; CHS, chlorhexidine oral rinse; CHS, chlorhexidine oral rinse
Modifiable risk factors for NHAP

Modifiable Risk Factors for Nursing Home–Acquired Pneumonia

Vincent Kangariello, Sandra Duer, Ling He, Peter Van Ness, Heather Allen, and Mary Tivetti
Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

(See the editorial commentary by Teposo on pages 7-8)

Background. This study sought to identify modifiable risk factors for pneumonia in elderly nursing home residents.

Methods. A cohort of 613 elderly residents (age, >65 years) of 5 nursing homes in the New Haven, Connecticut, area was followed up prospectively from February 2001 through March 2003. The primary outcome was radiographically documented pneumonia within a 12-month surveillance period. Baseline modifiable risk factors were evaluated for their independent association with pneumonia.

Results. Of 613 elderly nursing home residents, 131 (21%) died, and an additional 112 (18%) developed a radiographically documented case of pneumonia during the 12-month surveillance period. Among the 9 candidate modifiable risk factors that were evaluated individually in Cox proportional hazards models, adjusting for covariates (i.e., nursing home facility, age, race, clinical condition, and mobility), inadequate oral care (hazard ratio [HR] 1.40; 95% confidence interval [CI] 1.06–1.87; P = .014) and swallowing difficulty (HR 1.65; 95% CI 1.04–2.63; P = .030) were associated with pneumonia. When modifiable risk factors were evaluated simultaneously in the same Cox proportional hazards model, inadequate oral care (HR 1.55; 95% CI 1.04–2.30; P = .030) and swallowing difficulty (HR 1.64; 95% CI 1.02–2.65; P = .04) remained independently associated with pneumonia, adjusting for the same covariates. Calculation of population-based attributable fractions showed that 21% of all cases of pneumonia in our cohort could have been avoided if inadequate oral care and swallowing difficulty were not prevalent.

Conclusions. Two biologically plausible and modifiable risk factors increased the risk of pneumonia in elderly nursing home residents. These results provide a framework for the development and testing of a targeted pneumonia prevention strategy.

Oral Care for Nursing Home-Acquired Pneumonia

A Cluster-Randomized Controlled Trial of a Multicomponent Intervention Protocol for Pneumonia Prevention Among Nursing Home Elders

Marciha Juthani-Mehta,1 Peter H. Van Ness,2 Jessica McGillivray,1 Stephanie Aragon,1 Chee Chen,1 Peter Charpentier,3 Lauren Miller,1 Kathleen Williams,2 Diane Well,2 Dorothy Baker,2 Mary Tivetti,2 Peter Peduzzi,2 and Vincent J. Gangiello1
Sections of Infectious Diseases, and 1Geriatrics, Department of Internal Medicine, Yale University School of Medicine, and 2Yale Center for Analytical Sciences, Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut

Background. Pneumonia remains an important public health problem among elderly nursing home residents. This clinical trial sought to determine if a multicomponent intervention protocol, including manual tooth/gum brushing plus 0.12% chlorhexidine oral rinse, twice per day, plus upright positioning during feeding, could reduce the incidence of radiographically documented pneumonia among nursing home residents, compared with usual care.

Table 2. Frequency, Person-year Ratios, and Cox Model Results for Outcomes and Death

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (N = 834)</th>
<th>Intervention (n = 434)</th>
<th>Control (n = 400)</th>
<th>Adjusted Cox Modela</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Rate (95% CI)</td>
<td>No. (%)</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>First Pneumonia</td>
<td>213 (25.5)</td>
<td>0.27 (22–33)</td>
<td>119 (27.4)</td>
<td>0.28 (22–37)</td>
</tr>
<tr>
<td>First LRTI</td>
<td>225 (27.0)</td>
<td>0.29 (23–34)</td>
<td>125 (28.8)</td>
<td>0.29 (23–37)</td>
</tr>
<tr>
<td>Death</td>
<td>210 (25.2)</td>
<td>0.22 (19–26)</td>
<td>122 (28.1)</td>
<td>0.24 (20–26)</td>
</tr>
</tbody>
</table>

Yale School of Medicine

Clinical Outcomes

Time to first pneumonia

Time to first lower respiratory tract infection

HAP Prevention

Pneumonia Prevention to Decrease Mortality in Intensive Care Unit: A Systematic Review and Meta-analysis

Antonio Ng'ang'a1, Emmanuel Mureni3, Edward Akobeng3, and Kevin Archibong1,2
1Division of Nephrology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA; 2University of North Carolina School of Medicine, Chapel Hill, NC, USA; 3Department of Anesthesiology and Critical Care, University of North Carolina, Chapel Hill, NC, USA

Background. To determine the strategies of prevention of hospital-acquired pneumonia that reduce mortality in intensive care units (ICUs).

Methods. We performed a systematic review and meta-analysis of studies. The primary outcome was the occurrence of hospital-acquired pneumonia. The primary outcome was mortality in the ICU.

Results. We identified 157 randomized trials in a meta-analysis. The primary outcome was mortality in the ICU. The risk of hospital-acquired pneumonia in the ICU was 0.05 (95% CI 0.04-0.06, P < 0.02). The risk ratio (RR) for hospital-acquired pneumonia was 0.05 (95% CI 0.04-0.06, P = 0.02). The RR for hospital-acquired pneumonia was 0.06 (95% CI 0.05-0.07, P = 0.01). The RR for hospital-acquired pneumonia was 0.06 (95% CI 0.05-0.07, P = 0.01). The RR for hospital-acquired pneumonia was 0.06 (95% CI 0.05-0.07, P = 0.01). The RR for hospital-acquired pneumonia was 0.06 (95% CI 0.05-0.07, P = 0.01). The RR for hospital-acquired pneumonia was 0.06 (95% CI 0.05-0.07, P = 0.01).

Conclusions. Selective digestive decontamination with systemic antimicrobial therapy reduced mortality and should be considered in critically ill patients at high risk for death.
### Figure 2

Hospital mortality rates in critically ill patients receiving a strategy for reducing hospital-acquired pneumonia. All pooled estimates used the random effects model. Boldface P-values indicate significant differences (P < 0.05). Abbreviations: CI, confidence interval; ET, endotracheal tube; NA, not applicable; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial; SD, standard deviation; SDQ, selective decontamination of the digestive tract. SLIDE 11

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of Patients (N)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir oral feeding</td>
<td>1,129; NA</td>
<td>2.97 (90-4.49)</td>
<td>.09</td>
</tr>
<tr>
<td>Tracheal cuff monitoring</td>
<td>2,266; 0</td>
<td>1.12 (09-2.11)</td>
<td>.49</td>
</tr>
<tr>
<td>PEEP</td>
<td>1,127; NA</td>
<td>2.97 (16-2.60)</td>
<td>.89</td>
</tr>
<tr>
<td>Silver-coated ET</td>
<td>1,199; NA</td>
<td>1.14 (99-1.34)</td>
<td>.61</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>2,306; 81</td>
<td>1.14 (26-4.59)</td>
<td>.88</td>
</tr>
<tr>
<td>Patient position</td>
<td>5,785; 0</td>
<td>1.06 (82-1.38)</td>
<td>.65</td>
</tr>
<tr>
<td>Decreased gastric content</td>
<td>9,819; 0</td>
<td>1.06 (83-1.35)</td>
<td>.71</td>
</tr>
<tr>
<td>Tracheal suction instillation</td>
<td>1,126; NA</td>
<td>1.05 (82-1.33)</td>
<td>.97</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>16,363; 0</td>
<td>1.01 (88-1.13)</td>
<td>.89</td>
</tr>
<tr>
<td>SOD</td>
<td>23,366; 0</td>
<td>0.99 (92-1.08)</td>
<td>.85</td>
</tr>
<tr>
<td>Subglottic secretion drainage</td>
<td>7,224; 0</td>
<td>0.98 (84-1.15)</td>
<td>.78</td>
</tr>
<tr>
<td>Heat moisture exchanger</td>
<td>12,262; 0</td>
<td>0.99 (86-1.12)</td>
<td>.88</td>
</tr>
<tr>
<td>Chest percussion systolic</td>
<td>5,990; 0</td>
<td>0.68 (3.1-1.7)</td>
<td>.85</td>
</tr>
<tr>
<td>Acetylcholinesterase</td>
<td>9,482; 23</td>
<td>0.65 (6-1.30)</td>
<td>.64</td>
</tr>
<tr>
<td>Late pharyngeal feeding</td>
<td>5,682; 0</td>
<td>0.59 (57-1.28)</td>
<td>.64</td>
</tr>
<tr>
<td>Prophylactic/sympathetic</td>
<td>15,156; 23</td>
<td>0.59 (16-1.18)</td>
<td>.24</td>
</tr>
<tr>
<td>Early tracheotomy</td>
<td>9,370; 45</td>
<td>0.62 (14-1.22)</td>
<td>.90</td>
</tr>
<tr>
<td>SOD</td>
<td>1,125; 16</td>
<td>0.64 (76-1.92)</td>
<td>.003</td>
</tr>
<tr>
<td>Sutural prophylaxis</td>
<td>1,39C; NA</td>
<td>0.10 (63-1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Early enteral feeding</td>
<td>1,156; NA</td>
<td>0.75 (42-1.35)</td>
<td>.34</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>1,36; NA</td>
<td>0.67 (33-3.55)</td>
<td>.02</td>
</tr>
<tr>
<td>Overall</td>
<td>148, N=37,856; 40</td>
<td>0.85 (62-99)</td>
<td>.02</td>
</tr>
</tbody>
</table>

---

**Figure A**

Hospital-acquired pneumonia in critically ill patients receiving a strategy for preventing hospital-acquired pneumonia. All pooled estimates used the random effects model. Boldface P-values indicate significant differences (P < 0.05). Abbreviations: CI, confidence interval; ET, endotracheal tube; NA, not applicable; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial; SD, standard deviation; SDQ, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination. SLIDE 11

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of Patients (N)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper prophylaxis</td>
<td>16,343; 44</td>
<td>1.05 (84-1.30)</td>
<td>.40</td>
</tr>
<tr>
<td>Tracheal cuff monitoring</td>
<td>1,129; NA</td>
<td>1.14 (47-1.29)</td>
<td>.92</td>
</tr>
<tr>
<td>Decreased gastric content</td>
<td>2,192; 89</td>
<td>0.99 (76-4.38)</td>
<td>.91</td>
</tr>
<tr>
<td>Early enteral feeding</td>
<td>2,192; 89</td>
<td>0.99 (31-2.83)</td>
<td>.25</td>
</tr>
<tr>
<td>Heat moisture exchanger</td>
<td>12,288; 26</td>
<td>0.99 (71-1.33)</td>
<td>.36</td>
</tr>
<tr>
<td>Late tracheotomy</td>
<td>1,186; 72</td>
<td>0.99 (68-4.35)</td>
<td>.25</td>
</tr>
<tr>
<td>Clouded suction system</td>
<td>9,182; 31</td>
<td>0.99 (62-2.49)</td>
<td>.20</td>
</tr>
<tr>
<td>Prophylactic/sympathetic</td>
<td>15,156; 23</td>
<td>0.78 (16-1.03)</td>
<td>.001</td>
</tr>
<tr>
<td>Sutural prophylaxis</td>
<td>1,156; NA</td>
<td>0.73 (56-1.06)</td>
<td>.06</td>
</tr>
<tr>
<td>Late pharyngeal feeding</td>
<td>1,39C; NA</td>
<td>0.73 (55-96)</td>
<td>.001</td>
</tr>
<tr>
<td>SOD</td>
<td>1,156; 16</td>
<td>0.60 (44-83)</td>
<td>.28</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>1,36; NA</td>
<td>0.58 (46-73)</td>
<td>.28</td>
</tr>
<tr>
<td>Subglottic secretion drainage</td>
<td>12,343; 49</td>
<td>0.76 (3.49-1.0)</td>
<td>.09</td>
</tr>
<tr>
<td>Heat moisture exchanger</td>
<td>12,288; 26</td>
<td>0.76 (3.49-1.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>1,186; 72</td>
<td>0.66 (14-1.55)</td>
<td>.20</td>
</tr>
<tr>
<td>Early tracheotomy</td>
<td>1,186; 72</td>
<td>0.64 (22-37)</td>
<td>.001</td>
</tr>
<tr>
<td>Early enteral feeding</td>
<td>1,156; NA</td>
<td>0.46 (15-4.46)</td>
<td>.02</td>
</tr>
<tr>
<td>PEEP</td>
<td>1,156; NA</td>
<td>0.47 (15-88)</td>
<td>.02</td>
</tr>
<tr>
<td>Overall</td>
<td>148, N=37,856; 63</td>
<td>0.99 (63-75)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

---

**Figure A**

Hospital-acquired pneumonia in critically ill patients receiving a strategy for preventing hospital-acquired pneumonia. All pooled estimates used the random effects model. Boldface P-values indicate significant differences (P < 0.05). Abbreviations: CI, confidence interval; ET, endotracheal tube; NA, not applicable; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial; SD, standard deviation; SDQ, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination. SLIDE 11
VAP Prevention

- Ventilator bundles:
  - elevation of the head of the bed
  - routine oral care with chlorhexidine
  - daily sedative interruptions
  - daily assessment of readiness to extubate
  - deep venous thrombosis prophylaxis
  - stress ulcer prophylaxis

- Good evidence for pneumonia prevention:
  - daily sedative interruptions (Kress et al, NEJM 2000;342:1471-7)
  - daily assessment of readiness to extubate (Ely et al, NEJM, 1996;335:1864-9)

- No decrease and may increase risk of VAP:
  - routine oral care with chlorhexidine → only reduced rate of pneumonia in cardiac surgery patients (Klompas, JAMA Intern Med, 2014;174(5):751-61)

Take Home Points

- Routine dental care can prevent CAP, HCAP and possibly NHAP

- Topical oral chlorhexidine has been shown to reduce VAP in cardiac surgery patients
  - most likely not effective long term in NHAP
  - inconclusive evidence for VAP prevention in non-cardiac surgery
  - time to reevaluate ventilator bundles

- Time to reconsider selective digestive decontamination (SDD)
  - PTA (polymixins B and E [colistin], tobramycin, amphotericin) applied as a paste to the oropharynx and in suspension via NG tube plus cefotaxime parenterally (IV) for 4 days
THANK YOU
Overview of Influenza and Pneumococcal Vaccinations

Albert Shaw MD, PhD
Associate Professor of Medicine
Yale School of Medicine

Age Dependence of Invasive Pneumococcal Disease

Active Bacterial Core Surveillance (ABCs) Report, CDC, 2010
Individuals over age 65 who currently comprise about 12% of the US population account for over 35% of visits to general internists, 34% of prescription drug use, 50% of hospital stays, and 90% of nursing home residents (CDC, 2005).

Aging of the Baby Boom Generation (1946-1965)

US Census Bureau, “65+ in the United States”, 2005
Age-Associated Alterations in Innate Immunity

Changes due to aging

- Impaired chemotaxis, phagocytosis and NET formation
- ↓ signal transduction e.g. to TLR-1, GM-CSF
- ↑ PI-3 kinase signal transduction

- ↓ TLR2/2-dependent IL-6 and TNF-α production
- Impaired expression of co-stimulatory proteins
- ↑ TLR-5 induced cytokine production
- ↑ in IL-10 production

- Increased production of pro-inflammatory cytokines
- SASP
- Necrotic cells
- Damage response
- Neutrophils
- Monocytes
- Dendritic cells
- NK cells

- ↑ CD56dim CD16+ cytotoxic cells
- ↓ expression and function of cytotoxicity receptors

Age-Associated Alterations in Adaptive Immunity

Young — Aging — Older

B cells
- Memory B cell responses
- Production and secretion of antibodies in response to extracellular pathogens

CD4+ cells
- T helper functions, such as differentiation to Th1 cells for responses to intracellular pathogens
- Cytokine production to regulate inflammation and B cell function

CD8+ cells
- Cytotoxic T cells that lyse target cells e.g. virus-infected or tumor cells

CMV
- Impaired signal transduction
- ↓ production of naïve cells
- ↑ memory cells (role of CMV)
- ↓ TCR repertoire diversity
- Oligoclonal expansion
- Loss of CD28 expression

- ↑ production of antibody secreting cells
- ↓ class switching

- ↑ memory cells
- ↑ production of naïve cells
- Impaired helper functions

- Impaired signal transduction
- Impaired helper functions

Shaw and Bandaranayake 2016
Pneumococcal Polysaccharide (PS) vs. Conjugate Vaccines

23-Valent Polysaccharide (PS) Vaccine:
- T cell-independent
- No immunological memory
- 23 serotypes account for ~60% of adult pneumococcal infection

13-Valent Conjugate PS Vaccine:
- PS conjugated to CRM$_{197}$ (mutant non-toxic form of Diphtheria toxoid)
- +memory T cell responses
- ~28-42% of invasive pneumococcal disease (probably decreasing)

Potential Advantages of Pneumococcal Conjugate Vaccine in Older Adults

- Induction of immunologic memory permits boosting of responses
- Potential for hyporesponsiveness associated with 23-valent PS vaccine in some studies
- Appears preferable for initial vaccination of naïve older adult, and likely for re-vaccination of adults previously immunized with the 23-valent PS vaccine
Potential Advantages of Pneumococcal Conjugate Vaccine in Older Adults

Adults ≥ 70 years, all received 23-valent PS vaccine ≥ 5 years ago

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Group B (range)</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>6A</th>
<th>6B</th>
<th>7F</th>
<th>9V</th>
<th>14</th>
<th>18C</th>
<th>19A</th>
<th>19F</th>
<th>23F</th>
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<tbody>
<tr>
<td>70-74</td>
<td>13vPnc (171 - 180)</td>
<td>81</td>
<td>55</td>
<td>658</td>
<td>68</td>
<td>1111</td>
<td>1309</td>
<td>316</td>
<td>234</td>
<td>311</td>
<td>961</td>
<td>497</td>
<td>364</td>
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<tr>
<td></td>
<td>23vPS (173 - 197)</td>
<td>66</td>
<td>59</td>
<td>295</td>
<td>44</td>
<td>98</td>
<td>507</td>
<td>210</td>
<td>114</td>
<td>371</td>
<td>685</td>
<td>255</td>
<td>234</td>
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<tr>
<td>75-79</td>
<td>13vPnc (171 - 180)</td>
<td>101</td>
<td>67</td>
<td>603</td>
<td>92</td>
<td>930</td>
<td>1478</td>
<td>217</td>
<td>198</td>
<td>249</td>
<td>945</td>
<td>343</td>
<td>331</td>
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<tr>
<td></td>
<td>23vPS (178 - 190)</td>
<td>52</td>
<td>44</td>
<td>149</td>
<td>36</td>
<td>113</td>
<td>397</td>
<td>164</td>
<td>103</td>
<td>339</td>
<td>534</td>
<td>176</td>
<td>201</td>
</tr>
<tr>
<td>80+</td>
<td>13vPnc (92 - 101)</td>
<td>59</td>
<td>42</td>
<td>333</td>
<td>56</td>
<td>599</td>
<td>944</td>
<td>182</td>
<td>98</td>
<td>274</td>
<td>769</td>
<td>296</td>
<td>284</td>
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<tr>
<td></td>
<td>3vPS (89 - 95)</td>
<td>41</td>
<td>41</td>
<td>156</td>
<td>24</td>
<td>65</td>
<td>226</td>
<td>289</td>
<td>85</td>
<td>134</td>
<td>254</td>
<td>147</td>
<td>197</td>
</tr>
</tbody>
</table>

FDA Vaccines and Related Biological Products Advisory Committee Meeting Nov. 16, 2011

The 13-Valent Conjugate Pneumococcal Vaccine Prevents Pneumococcal Disease (Including Pneumococcal Pneumonia) in Older Adults

A. Vaccine-Type CAP

VE 46%

B. NB and NI CAP

VE 75%

Community Acquired Pneumonia Immunization Trial in Adults (CAPITA):
– a randomized placebo-controlled trial (n=85,000) of the 13-valent conjugate vaccine in vaccine naïve adults ≥ 65 in the Netherlands
– primary outcome is first episode of vaccine-serotype specific pneumococcal CAP.

Bonten et al., 2015
Limitations of the CAPITA Study

- Immunocompromised adults excluded (in subgroup analyses, older adults who developed immunocompromise did not show evidence of protection)
- No comparison to the polysaccharide vaccine
- Unclear if benefit will be as clear in the US, where conjugate vaccine is routinely given to children

Hospitalization for Pneumonia After the Introduction of PCV7

<table>
<thead>
<tr>
<th>Age Reduction</th>
<th>US Pop.</th>
<th>% Reduction</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>8.6</td>
<td>43</td>
<td>47,000</td>
</tr>
<tr>
<td>2-4</td>
<td>12.7</td>
<td>12</td>
<td>7,000</td>
</tr>
<tr>
<td>5-17</td>
<td>53.2</td>
<td>4.5</td>
<td>2,000</td>
</tr>
<tr>
<td>18-39</td>
<td>92.5</td>
<td>7.8</td>
<td>8,000</td>
</tr>
<tr>
<td>40-64</td>
<td>100.4</td>
<td>-10.1</td>
<td>-34,000</td>
</tr>
<tr>
<td>65-74</td>
<td>20.8</td>
<td>6.6</td>
<td>18,000</td>
</tr>
<tr>
<td>75-84</td>
<td>13.1</td>
<td>13.0</td>
<td>47,000</td>
</tr>
<tr>
<td>≥ 85</td>
<td>5.6</td>
<td>22.8</td>
<td>168,000</td>
</tr>
</tbody>
</table>

(Comparing 3 Yrs. before vs. 7-9 Yrs. after) Griffin et al., 2013
ACIP Recommendations for pneumococcal vaccination under age 65

- Persons 18-64 with
  - Chronic heart disease (not HTN)
  - Chronic lung disease
  - Chronic liver disease (including EtOH abuse)
  - Chronic renal failure, nephrotic syndrome
  - Diabetes
  - Smoking
  - Asplenia (functional or anatomic)
  - HIV
  - Other immunodeficiency
  - Hematologic malignancy
  - Solid organ transplantation
  - Long-term steroids, radiation, immunosuppressive agents
  - CSF leak
  - Cochlear implant

Kobayashi et al., MMWR 2015
ACIP Recommendations for 13-valent conjugate pneumococcal vaccine

- Adults with immunocompromising conditions who are naïve to pneumococcal vaccine should receive the 13-valent conjugate vaccine, followed by the 23-valent vaccine ≥ 8 weeks later.

- For adults with immunocompromising conditions who have received the 23-valent vaccine previously should receive the conjugate vaccine ≥ 1 year after the last dose of the 23-valent vaccine.

Questions and Considerations on Pneumococcal Vaccine

- While conceptually appealing, clear benefit for addition of conjugate to polysaccharide vaccine in adults (beyond effect of decreased colonization in children resulting from pediatric vaccination) unclear.

- Revaccination remains largely unsettled: ACIP recommends a single revaccination with the PS vaccine ≥ 5 years after the first dose. No recommendations for conjugate vaccine.

- Vaccinating individuals with a history of invasive pneumococcal disease (Yes, though no ACIP recommendation)?

- Consider conjugate/PS vaccination in older adults planning travel to countries without required childhood conjugate vaccination programs
Currently Used Influenza Vaccines for Adults 18-64

- Inactivated quadrivalent (H1N1, H3N2, two B strains) or trivalent (H1N1, H3N2, B)
- Inactivated quadrivalent intradermal
- Inactivated trivalent, needle-free injector device
- Inactivated trivalent, cell culture-based vaccine
- Inactivated quadrivalent, baculovirus-based recombinant HA vaccine

- Live attenuated vaccine approved for adults ≤ 50 not recommended this year on the basis of poor vaccine effectiveness from 2015-2016 season.

Influenza-Associated Deaths by Age Group, 1976-1999

Adapted from Thompson W et al. JAMA. 2003;289:179-186.
Hospitalization Rates for Confirmed Influenza 2012-2013

Influenza Vaccine Outcomes in Community Dwelling Elderly

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Vu et al.</th>
<th>Jefferson et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab confirmed influenza</td>
<td>--</td>
<td>49% (33-62%)</td>
</tr>
<tr>
<td>Clinical ILI</td>
<td>35% (19%-47%)</td>
<td>-5% (-89%-42%)</td>
</tr>
<tr>
<td>Hospitalizations for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia &amp; influenza</td>
<td>33% (27%-38%)</td>
<td>27% (21%-33%)</td>
</tr>
<tr>
<td>Respiratory conditions</td>
<td>30% (25%-35%)</td>
<td>22% (15%-28%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>--</td>
<td>24% (18%-30%)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>50% (45%-56%)</td>
<td>47% (39%-54%)</td>
</tr>
</tbody>
</table>

Potential Bias in Estimates of Influenza Vaccine Effectiveness?

Jackson et al., Int. J. Epidemiol. 2006 35: 337-344

Recent multicenter (n=31,899), randomized, double-blind controlled study of vaccine efficacy (DiazGranados et al., 2014) showed a relative efficacy of 24% for high-dose compared to standard vaccine in adults over 65 with primary outcome of laboratory-confirmed influenza.

Currently available only in trivalent form.
Inactivated, Adjuvanted Standard-Dose Trivalent Vaccine (Fluad)

- Approved for adults ≥ 65 years.
- Uses MF-59 adjuvant, an emulsion containing squalene and non-ionic detergents that promotes chemokine production in antigen presenting cells.
- Approved in Europe.
- In some studies appeared to yield increased antibody titers compared to unadjuvanted vaccine in older adults (DeDonato et al., 1999), but FDA licensing study showed equivalent titers.
- No efficacy studies in older adults available.

Novel Vaccines in Development

- Anti-HA stalk antibodies can provide broad protection across most influenza strains.
- Identification of HA targets that can stimulate production of broadly neutralizing antibodies.
- Other universal antigenic targets (e.g. M2e protein) in clinical development.