Complex Pneumonia Case

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Learning Objectives

At the conclusion of this session, given a patient case, the participant should be able to

1. Select the appropriate treatment and monitoring for a complex patient-case with multiple conditions, including healthcare-associated pneumonia, acute renal insufficiency, sepsis, COPD and dehydration.
2. Interpret clinical data, including lab, physical examination and vital signs.
3. Determine and prioritize pneumonia-related treatment goals.
4. Determine approaches to manage drug allergies and select next best drug therapy when primary drugs are precluded.
5. Discuss approaches to limiting antimicrobial over use by stewarding antibiotic usage appropriately.
6. Explain relevant Joint Commission pneumonia-related core measures.
7. Discuss economic and safety issues in patients receiving treatment for pneumonia.

Format: Today’s session will be a highly interactive discussion of the attached case studies.

Premise: Participants in this course are pharmacists who practice in clinical acute care settings. You are responsible for evaluating and monitoring the patient’s therapy. You are responsible for providing comprehensive patient management and education.
CC/HPI (including sx analysis for CC):
“I can’t breathe!”

AB with a PMH of COPD presented to the emergency department (ED) several hours ago complaining of SOB. Ten days prior to today’s admission, she presented to your ED with hypoxia and dehydration. She was found to have H3N2 influenza and was treated with intravenous fluids and oseltamivir 75 mg orally every 12 hours. She returned to her baseline state of health and was discharged home 3 days ago with a prescription for an additional 3 days of oseltamivir. On the day of discharge the patient displayed the following vital signs.

BP = 137/97 mm Hg  Pulse = 64 bpm, regular  R = 16  T = 98.2°F (oral)

Yesterday at home, she noted increased production of thick, yellow sputum, used her albuterol inhaler five times, and had “chills and sweats” so she came to the ED this morning. Vitals signs on presentation were: BP = 105/65 mmHg, T = 101.4°F. Her O₂ saturation was 88% on room air, so she was placed on 4 liters/min of O₂ via nasal cannula. Her O₂ saturation improved to 92% with this intervention. The ED physician ordered the following labs: CBC with differential, CMP, ABG, Blood cultures, Sputum cultures, and a CXR.

Past Medical History (major illnesses and surgeries)
HTN x 30 years
Dyslipidemia x 23 years
Chronic Obstructive Pulmonary Disease (x 5 years)
Osteoarthritis (knees, uses walker)
Obesity (BMI = 30 kg/m²)
Osteopenia

Current Prescription/OTC Medications

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Drug Name/Strength/Regimen</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>3/2012</td>
<td>HCTZ 50mg daily</td>
<td>HTN</td>
</tr>
<tr>
<td>1/2014</td>
<td>Lisinopril 20mg daily</td>
<td>HTN</td>
</tr>
<tr>
<td>2/2007</td>
<td>Pravastatin 20mg daily</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>2/2011</td>
<td>Tiotriipium 18mcg/cap, 1 cap inhaled daily</td>
<td>COPD</td>
</tr>
<tr>
<td>2/2011</td>
<td>Albuterol 90mcg per puff, 1-2 puffs every 4-6 hours prn</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>4/2013</td>
<td>Acetaminophen 500mg po TID prn</td>
<td>Pain</td>
</tr>
<tr>
<td>10/2013</td>
<td>Calcium 600mg + Vitamin D 400 units po BID</td>
<td>Osteopenia</td>
</tr>
</tbody>
</table>

Vaccinations:  Influenza vaccine fall 2014 (missed vaccination this year)  Preventative medicine
Pneumococcal polysaccharide vaccine (age 67)  Preventative medicine
**Objective Data (observations/vital signs/physical examination/labs)**

**Physical Exam**

General: Obese, moderate respiratory distress


Lungs: Tachypneic, increased respiratory effort, prolonged expirations with end-expiratory wheezing, decreased air movement, inspiratory crackles at the left lower lung base.

CV: Tachycardia, regular rhythm, no murmurs/rubs/gallops, no jugular venous distension > 10 cm, warm extremities with < 2 second capillary refill.

Abd: normal active bowel sounds, no abdominal tenderness to palpation, no distension

Ext: No lower extremity edema.

Neuro/Psych: A + O x 3, lethargic but arousable

**Vital Signs**

BP = 105/65 mm Hg  Pulse = 92 bpm  R = 24  T = 101.4°F (oral)

Height = 5’ 5”  Weight = 180 lb  BMI = 30 kg/m²  ECG = sinus tachycardia

**Laboratory Tests** (measured today)

ABG (room air):  pH = 7.32  /  PaCO₂ = 60  /  PaO₂ = 67  /  O₂ sat = 87%

CBC with Differential:  WBC = 16 X 10⁹/L (85% neutrophils), Hgb = 13.1 g/dL, Platelets = 365K

Na = 139 mEq/L  K = 4.5 mEq/L  Cl = 99 mEq/L  CO₃ = 27 mmol/L  BUN = 37 mg/dL  Cr = 1.2 mg/dL

Glucose = 107 mg/dL

AST = 22 units/L  ALT = 44 units/L

Blood culture: pending

Respiratory culture: pending

Urinary Legionella antigen: negative

Radiology:

CXR: Hyperexpanded lungs, mild cardiomegaly. Consolidation in left lower lobe concerning for pneumonia.
Presentation Questions
(* not in PowerPoint presentation)

Dehydration
1. AB progressively deteriorates and is transferred to the medical intensive care unit for maintenance of hemodynamic stability and intubation. Which of the following is an appropriate initial fluid regimen?
   a. Lactated Ringers at 125 mL/hr over 24 hours
   b. Lactated Ringers 1000 mL infused over 30 minutes
   c. D5W 1000 mL infused over 30 minutes
   d. Albumin 25 g (100 mL of 25% solution) infused over 24 hours

Healthcare-Associated Pneumonia and Sepsis
2. If AB is ventilated on the first day that she presents to your medical facility, which of the following would represent her pneumonia diagnosis?
   a. Community Acquired Pneumonia (CAP)
   b. Health Care Associated Pneumonia (HCA)
   c. Ventilator Associated Pneumonia (VAP)
   d. Complicated Pneumonia (CP)

COPD
3. Which of the following risk factors predisposes AB to pneumonia with Gram-positive and Gram-negative multidrug-resistant pathogens?
   a. Five-year history of COPD
   b. Status as a retired nurse
   c. Post influenza infection
   d. Recent hospitalization

Healthcare-Associated Pneumonia and Sepsis
4. In addition to fluid status correction and vasopressor initiation, which of the following is the next most important intervention to help AB regain hemodynamic stability?
   a. Early Ambulation
   b. Broad-spectrum antibacterial coverage
   c. Hydrocortisone
   d. Intravenous immune globulin

5. Which of the following is a guideline-approved, empiric drug regimen to provide coverage for Gram-negative organisms in AB?
   e. Doripenem 1 g intravenously every 8 hours
   f. Moxifloxacin 400 mg intravenously once daily + Gentamicin 500 mg intravenously once daily
   g. Piperacillin-tazobactam 4.5 g intravenously every 6 hours + Gentamicin 500 mg intravenously once daily
   h. Tigecycline 100 mg intravenously as a loading dose followed by 50 mg intravenously every 12 hours + Moxifloxacin 400 mg intravenously once daily
A blood culture that was drawn upon transfer to the MICU is now showing Gram positive cocci. Also, a bronchoscopic alveolar lavage (BAL) is performed and an initial report indicates that many Gram-positive cocci are visualized. The following fluid analysis is provided for the BAL fluid.

Fluid Specimen BAL
Fluid Turbidity 4+
Fluid Color Red
Fluid WBC 100 /UL
Fluid RBCs 32500 /UL
Fluid Segmented Neutrophils 74%
Fluid Lymphocytes 6%
Fluid Monocytes 9%
Fluid Macrophages 8%
Fluid Other Cells 3%

6. Which of the following would be an appropriate regimen for AB given the Gram positive cocci isolated from the BAL fluid?
   a. Vancomycin 1.5 g intravenously every 24 hours
   b. Vancomycin 2 g intravenously every 12 hours
   c. Daptomycin 650 mg intravenously every 24 hours
   d. Ceftaroline 600 mg intravenously every 12 hours
   e. Oxacillin 2 g intravenously every 6 hours

7. If you are giving both vancomycin and piperacillin-tazobactam, which should you infuse first if the patient only has a line with a single lumen?
   a. Piperacillin-Tazobactam because precipitation issues exist and Gram negatives are most likely to kill you first.
   b. Vancomycin because precipitation issues exist and S.aureus is most likely to kill you first.
   c. I would Y-site the Piperacillin-Tazobactam and Vancomycin together.

8. If vancomycin therapy is initiated, which of the following strategies is guideline supported to improve efficacy?
   a. Obtain a peak concentration after the first dose to ensure adequate exposure
   b. Obtain a serum trough concentration immediately before the second dose
   c. Obtain a trough concentration immediately before the fifth dose at steady state.
   d. Obtain a minimum of 3 randomly timed concentrations at steady state to calculate the area under the concentration curve

It is now two days later, and AB is now hemodynamically stable in the MICU. Only norepinephrine remains for vasopressor therapy and it is being infused at a rate of 5 mcg/minute. The culture and susceptibility results return for the blood culture and BAL. The following is reported to you:

BLOOD CULTURE: STAPHYLOCOCCUS AUREUS GROWTH AT 48 HOURS

<table>
<thead>
<tr>
<th>Tested</th>
<th>Interpretation Result (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINDAMYCIN</td>
<td>Susceptible &lt;=0.25</td>
</tr>
<tr>
<td>ERYTHROMYCIN</td>
<td>Susceptible &lt;=0.25</td>
</tr>
<tr>
<td>OXACILLIN</td>
<td>Susceptible 0.5</td>
</tr>
</tbody>
</table>
**Susceptibility Results**

<table>
<thead>
<tr>
<th>Tested</th>
<th>Interpretation</th>
<th>Result (mg/L)</th>
</tr>
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<tbody>
<tr>
<td>CLINDAMYCIN</td>
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</tr>
<tr>
<td>OXACILLIN</td>
<td>Susceptible</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>Susceptible</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>LINEZOLID</td>
<td>Susceptible</td>
<td>2</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>Susceptible</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>TETRACYCLINE</td>
<td>Susceptible</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>TRIMETHOPRIM/SULFAMETHOXAZOLE</td>
<td>Susceptible</td>
<td>&lt;=0.5/9.5</td>
</tr>
<tr>
<td>VANCOMYCIN</td>
<td>Susceptible</td>
<td>1</td>
</tr>
</tbody>
</table>

9. Given the above susceptibilities, which of the following would be most appropriate for AB?
   a. Vancomycin 1.5 g intravenously every 24 hours
   b. Vancomycin 2 g intravenously every 12 hours
   c. Linezolid 600 mg every 24 hours
   d. Ceftaroline 600 mg intravenously every 12 hours
   e. Oxacillin 2 g intravenously every 6 hours

10. Which of the following total durations of therapy would be most appropriate for AB if she has a favorable response to treatment?
   a. 3-5 days
   b. 7-21 days
   c. 21-28 days
   d. 42-56 days

11. After AB stabilizes, which of the following would be the most appropriate blood glucose target to balance safety and efficacy?
   a. <110 mg/dL
   b. <140 mg/dL
   c. <180 mg/dL
   d. <250 mg/dL
Acute Renal failure

12. AB is diagnosed with a type-1 mediated allergy to cephalosporin agents by the allergy service. Which of the following treatments for the MSSA infection would be best for AB given her development of renal failure and her newly diagnosed beta-lactam allergy?
   a. Oxacillin; there is insignificant cross reactivity between cephalosporins and penicillins
   b. Vancomycin; mortality data favor vancomycin for treatment of MSSA
   c. Linezolid; several trials found reduced rates of nephrotoxicity with linezolid when compared with vancomycin
   d. Daptomycin; daptomycin is the drug of choice in patients with bloodstream infections in whom vancomycin is not an option.
References / Resources

COPD/Dehydration
Relative to pneumonia, the interested reader should be familiar with the sepsis guidelines:


HCAP

Also CAP guidelines are very helpful.


Sepsis

Kidney Injury

The Joint Commission
The Joint Commission. Specifications Manual for National Hospital Inpatient Quality Measures. Available at:

Compatibility:
Disclosures

- I have received research support from Cubist Pharmaceuticals, now a wholly owned subsidiary of Merck.
- The views offered in the presentation are not necessarily the views of Midwestern University or Northwestern Memorial Hospital.

The Case: Please let me introduce you to AB

<table>
<thead>
<tr>
<th>Vitals</th>
<th>AB</th>
<th>Sex</th>
<th>Race/Ethnicity</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP 102/65 mmHg</td>
<td>Pusker 64, regular</td>
<td>R=16 bpm</td>
<td>T=98.2°F</td>
<td>(oral)</td>
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<td>BP 137/97 mmHg</td>
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CC/HP (including sx analysis for CC):

“Can’t breathe!”

AB with a PMH of COPD presented to the Emergency Room several hours ago complaining of SOB. Ten days prior to today’s admission, she presented to your ED with hypoxia and dehydration. She was found to have H1N2 influenza A and was treated with intravenous fluids and oseltamivir 75mg orally every 12 hours. She returned to her baseline state of health and was discharged home 3 days ago with a prescription for an additional three days of oseltamivir.

The Case

Past Medical History (major illnesses and surgeries)

- HTN x 30 years
- Dyslipidemia x 23 years
- Chronic Obstructive Pulmonary Disease (x 5 years)
- Osteoarthritis (knees, uses walker)
- Obesity (BMI = 30 kg/m²)
- Osteopenia

The Case

On the day of discharge the patient displayed the following vital signs.

BP 127/97 mmHg  Pusker 64, regular  R=16 bpm  T=98.2°F (oral)

Yesterday at home, she noted increased production of thick, yellow sputum, used her albuterol inhaler five times, and had “chills and sweats” so she came to the ER this morning.

Vitals signs on presentation were:

BP 102/65 mmHg  Pusker 65, regular  R=28 bpm  T=100.2°F (oral)

Her O2 saturation was 88% on room air, so she was placed on 4 liters/min of O2 via nasal cannula. Her O2 saturations improved to 92% with this intervention.

The ED physician ordered the following labs: CBC with differential, comprehensive metabolic panel (CMP), ABG, Blood cultures, Sputum cultures, and a CXR.

Learning Objectives

- Select the appropriate treatment and monitoring of a complex patient-case with multiple conditions, including healthcare-associated pneumonia, acute renal insufficiency, sepsis, COPD and dehydration.
- Interpret clinical data, including lab, physical examination and vital signs.
- Determine and prioritize pneumonia-related treatment goals.
- Determine approaches to manage drug allergies and select next best therapy when primary drugs are precluded.
- Discuss approaches to limiting antimicrobial overuse by stewarding antibiotic usage appropriately.
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Current Medications

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<th>Start Date</th>
<th>Drug Name/Strength/Daily</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2014</td>
<td>HCTZ 50 mg daily</td>
<td>AM</td>
</tr>
<tr>
<td>2/2014</td>
<td>Losartan 50 mg daily</td>
<td>AM</td>
</tr>
<tr>
<td>3/2014</td>
<td>Prazosin 10 mg daily</td>
<td>AM</td>
</tr>
<tr>
<td>4/2014</td>
<td>Ibuprofen 300 mg daily</td>
<td>CV</td>
</tr>
<tr>
<td>1/2013</td>
<td>Furosemide 50 mg daily</td>
<td>CV</td>
</tr>
<tr>
<td>10/2013</td>
<td>Calcium 100 mg + Vitamin D 400 units daily</td>
<td>CV</td>
</tr>
</tbody>
</table>

Vaccinations
- Influenza vaccine fall 2014 (missed vaccination this year)
- Prophylactic pneumococcal vaccine (age 67)

Drug Allergy/Adverse Effects: BPA

Family Medical History: Non-contributory

Neuro/Psych, Ext:
- Abd:
  - CV:
  - Lungs:
    - HEENT:
  - General:
  - Distension
  - Dis
  - Lung expiratory and \( >2 \) second capillary refill.
  - Tachycardia, tachypnea, increased respiratory effort, decreased air movement, inspiratory crackles at the lower lung base.
  - CV: Tachycardia, regular rhythm, no murmur/rubs/gallop, no jugular venous distension \( >10 \) cm, warm extremities with \( <2 \) second capillary refill.
  - Abd: normal active bowel sounds, no abdominal tenderness to palpation, no distension
  - Ext: No lower extremity edema.
  - Neuro/Psyche: A + O x 3, lethargic but arousable

Surviving Sepsis, Volume Repletion

- Correction of the patient to euvolemia is paramount
- A shift toward crystalloid therapy in recent guidelines (grade 1B).
- Another key factor is the bolus amount… which is suggested at 30 mL/kg (grade 1C).
- Not discussed... crystalloid choice, but D5W becomes free water and is not available intravascularly. Some data now support LR > NS.

Question 1:
AB progressively deteriorates and is transferred to the medical intensive care unit for maintenance of hemodynamic stability and intubation. Which of the following is an appropriate initial fluid regimen?

A. Lactated Ringers at 125 mL/hr over 24 hours
B. Lactated Ringers 1000 mL infused over 30 minutes
C. DSW 1000 mL infused over 30 minutes
D. Albumin 25 grams (100 mL of 25% solution) infused over 24 hours
**Goals of Initial Resuscitation**

“Protocolized, quantitative resuscitation of patients with sepsis-induced hypotension (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L).”

Goals during the first 6 hr of resuscitation (Grade 1C):
- Central venous pressure 8–12 mm Hg
- Mean arterial pressure (MAP) ≥ 65 mm Hg
- Urine output ≥ 0.5 mL/kg/hr
- Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively.


**Question 2:**
If AB is ventilated on the first day that she presents to your medical facility, which of the following would represent her pneumonia diagnosis?

A. Community Acquired Pneumonia (CAP)
B. Health Care Associated Pneumonia (HCAP)
C. Ventilator Associated Pneumonia (VAP)
D. Complicated Pneumonia (CP)

---

**First, HCAP**

- Any patient who ...
  - Was hospitalized in an acute care hospital for two or more days within 90 days of the infection
  - Resided in a nursing home or long-term care facility
  - Received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the infection
  - Attended a hospital or hemodialysis clinic


**HAP, CAP, HCAP, VAP, ... different letters... different treatments**

Pathogens may vary on the basis of pneumonia classification

- **HAP:** Hospital acquired pneumonia - a pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission
- **VAP:** pneumonia that arises more than 48–72 hours after endotracheal intubation
- **CAP:** Now a pneumonia diagnosis of exclusion


**Question 3:**
Which of the following risk factors predisposes AB to pneumonia with Gram-positive and Gram-negative multidrug-resistant pathogens?

A. Five year history of COPD
B. Status as a retired nurse
C. Post influenza infection
D. Recent hospitalization

---

**HAP, VAP, HCAP guideline revisions in progress, many participating**

- American College of Chest Physicians
- American College of Emergency Physicians
- American Thoracic Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- Infectious Diseases Society of America
- Society of Critical Care Medicine
- ... and many more international groups.
Risk factors for MDRO include:

- HCAP designation
- Antimicrobial therapy in last 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Home infusion therapy (including antibiotics)
- Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy


HCAP Criteria... one more time

- Was hospitalized in an acute care hospital for two or more days within 90 days of the infection
- Resided in a nursing home or long-term care facility
- Received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection
- Attended a hospital or hemodialysis clinic


“CAP” before 2005, is now “HCAP”... the trade-off

HCAP: Overtreatment?
- Fewer missed cases?
- Higher individual resistance?

CAP: Undertreatment?
- More missed cases?
- Lower individual resistance?

Incidence of Pathogens, Overlap

The experts can agree... on disagreeing

*Clinical and microbiological features of HCAP are more similar to HAP and VAP than CAP*

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Question 4:
In addition to fluid status correction and vasopressor initiation, which of the following is the next most important intervention to help AB regain hemodynamic stability?

A. Early ambulation
B. Broad-spectrum antibiotic coverage
C. Hydrocortisone
D. Intravenous immune globulin

---

Even more important in Septic Shock

Average survival if active therapy was started within hour “x” of shock

---

National Hospital Inpatient Quality Measures... one example for CAP, Non-ICU

- β-lactam (IV or IM) + Macrolide (IV or PO)
- Anti-pneumococcal Quinolone monotherapy (IV or PO)
- Or β-lactam (IV or IM) + Doxycline (IV or PO)
- Or Tigecycline monotherapy (IV)

Acceptable drugs:
- β-lactam: Ceftriaxone, Cefotaxime, Amoxicillin/Sublactam, Ertapenem, Cefazolin
- Macrolide:ERYTHROMYCIN, CLARITHROMYCIN, AZITHROMYCIN
- Anti-pneumococcal Quinolones: Levofoxacin, Moxifloxacin, Gemifloxacin

---

Oversight is in place

... for CAP... not HCAP

- PN 3a: Blood cultures within 24 hours of hospital arrival
- PN 3b: Blood cultures prior to antibiotic
- PN 6: Antibiotic treatment selection

- make sure your empiric/formulary choices are "approved!"

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Other Therapies?¹

- IV Immune Globulin: One large RCT in adults and 1 large RCT in infants showed no benefit (2B)
- Hydrocortisone 200 mg should only be considered if fluid resuscitation and vasopressors do not restore hemodynamic stability (2C)
  - French RCT: benefit in patients with vasopressor unresponsive shock
  - CORTICUS: enrolled patients with vasopressor responsive shock, no benefit.
  - The use of ACTH is no longer recommended due to a lack of ability to predict resolution of shock (2B)

Question 5:
Which of the following is a guideline-approved, empiric drug regimen to cover Gram-negative organisms in AB?

A. Doripenem 1 g IV every 8 hr
B. Moxifloxacin 400 mg IV once daily + Gentamicin 500 mg IV once daily
C. Piperacillin-tazobactam 4.5 g IV every 6 hr + Gentamicin 500 mg IV once daily
D. Tigecycline 100 mg IV as a loading dose followed by 50 mg IV every 12 hr + Moxifloxacin 400 mg IV once daily

Revisiting MDRO, AB in Mind

- Risk factors for MDRO include:
  - HCAP designation
  - Antimicrobial therapy in last 90 days
  - Current hospitalization of 5 days or more
  - High frequency of antibiotic resistance in the community or in the specific hospital unit
  - Home infusion therapy (including antibiotics)
  - Family member with multidrug-resistant pathogen
  - Immunosuppressive disease and/or therapy

No Doripenem

<table>
<thead>
<tr>
<th>VAP Clinical Care Rates and All-Cause 28-Day Mortality Rate, Doripenem vs. Imipenem</th>
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</thead>
<tbody>
<tr>
<td>Doripenem</td>
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<tr>
<td>1 g every 8 hr, 4-hr infusion</td>
</tr>
<tr>
<td>Microbiologically evaluable</td>
</tr>
<tr>
<td>Microbiologically evaluable</td>
</tr>
<tr>
<td>All-Cause 28-day Mortality Rate (MITT)</td>
</tr>
</tbody>
</table>

Note: Modern pathogens should be aware that Doripenem is not approved to treat any type of pneumonia; nor is it approved for doses greater than 500 mg every eight hours.

**MRSA Pneumonia Coverage**

<table>
<thead>
<tr>
<th>MRSA Pneumonia Coverage</th>
<th>MDRO risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Antibacterial Combination (ceftazidime, cefepime)</td>
</tr>
<tr>
<td></td>
<td>Antibacterial Combination (impipenem or meropenem)</td>
</tr>
<tr>
<td></td>
<td>B-lactam/β-lactamase inhibitor (piperacillin–tazobactam)</td>
</tr>
<tr>
<td></td>
<td>Antibacterial Combination (ciprofloxacin or levofloxacin)</td>
</tr>
<tr>
<td></td>
<td>Carbapenem (imipenem, doripenem)</td>
</tr>
<tr>
<td></td>
<td>Vancomycin or linezolid</td>
</tr>
</tbody>
</table>

**Pre-2012**
- Post-hoc analyses of RCTs
- Observational Studies
- Meta-analyses

**2012 and beyond**
- RCT

**Quick Summary of Pre-2012...**
other observational studies support and refute

<table>
<thead>
<tr>
<th>Linezolid Efficacy, n (%)</th>
<th>Vancomycin Efficacy, n (%)</th>
<th>Reported p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>Microbiologic Efficacy</td>
<td>Therapy</td>
</tr>
<tr>
<td>Preclinical</td>
<td>Postclinical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>A</td>
<td>15/23 (65.2)</td>
<td>7/9 (77.8)</td>
</tr>
<tr>
<td>B</td>
<td>12/19 (63.2)</td>
<td>10/23 (43.5)</td>
</tr>
<tr>
<td>C</td>
<td>27/42 (64.3)</td>
<td>17/32 (53.1)</td>
</tr>
<tr>
<td>D</td>
<td>36/61 (59)</td>
<td>22/62 (35.5)</td>
</tr>
</tbody>
</table>


**Linezolid vs. Vancomycin**

**The long anticipated RCT**
- Study took 5.5 yr; 1,255 patients randomized to find 448 patients with MRSA infections
- After exclusions, which ranged between 20-25% of the patients, 172 linezolid patients were compared to 176 vancomycin patients (Per Protocol analysis)
- Arguments about the baseline differences between the groups will be endless... but they were reasonably well matched.
- Most surrogate endpoints (e.g. clinical cure, microbiologic eradication) favored linezolid at pre-planned analysis times (e.g. end of study, end of therapy)
- Kaplan-Meier mortality curves were super-imposable (see supplementary materials online) and not different at 60 days... raising the question of the validity of the surrogate endpoints

**Question 7:**
If you are giving both vancomycin and piperacillin-tazobactam, which should you infuse first if the patient only has a line with a single lumen?

A. Piperacillin-Tazobactam because precipitation issues exist and Gram negatives are most likely to kill you first.
B. Vancomycin because precipitation issues exist and S.aureus is most likely to kill you first.
C. I would Y-site the Piperacillin-Tazobactam and Vancomycin together.
**Question 8:**
If vancomycin therapy is initiated, which of the following strategies for serum concentration monitoring is guideline-supported to improve efficacy?

A. Obtain a peak concentration after the first dose to ensure adequate exposure
B. Obtain a serum trough concentration immediately before the second dose
C. Obtain a trough concentration immediately before the fifth dose at steady state
D. Obtain a minimum of 3 randomly timed concentrations at steady state to calculate the area under the concentration curve

**Vancomycin Guidelines, continue**

**Variable**
- Optimal trough concentrations—complicated infections (e.g., pneumonia, meningitis, and hospital-acquired pneumonia caused by methicillin-resistant Staphylococcus aureus)
- Criteria for monitoring

**Optimal trough concentrations**
- Vancomycin serum trough concentration of 15–20 mg/L is recommended. Trough serum concentrations are the most accurate and practical method for monitoring efficacy, which can improve outcomes.
- Monitoring is recommended for patients receiving aggressive dosing (e.g., to achieve sustained trough levels of 15–20 mg/L) and at patients at high risk of nephrotoxicity (e.g., patients receiving concurrent nephrotoxins).

**Criteria for monitoring**
- Trough monitoring is recommended for patients receiving aggressive dosing (e.g., to achieve sustained trough levels of 15–20 mg/L) and at patients at high risk of nephrotoxicity (e.g., patients receiving concurrent nephrotoxins). Monitoring is also recommended for patients with unstable (i.e., deteriorating or significantly improving) renal function and those receiving prolonged courses of therapy (more than three to five days).

**Question 9**
It is now two days later, and AB is now hemodynamically stable in the MICU. Only norepinephrine remains for vasopressor therapy, and it is being infused at a rate of 5 mcg/minute. The culture and susceptibility results return for the blood culture and BAL.

The following is reported to you:
**Question 9, cont.**

- **Susceptible**
- **Result**

<table>
<thead>
<tr>
<th>AB</th>
<th>Reference</th>
<th>mg/L</th>
<th>&lt;0.5</th>
<th>&lt;0.5</th>
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<tbody>
<tr>
<td>Vancomycin</td>
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<tr>
<td>Trimethoprim</td>
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<tr>
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<tr>
<td>Gentamicin</td>
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</tbody>
</table>

**Duration... one of the toughest questions to answer**

- I am not aware of a RCT that compares treatment duration for HCAP MSSA pneumonia... nor will one likely be conducted for a while.
  - A large trial randomizing 633 VAP patients to 8 vs. 15 days of treatment has been performed.1
    - MSSA equally represented in the 8- and 15-day groups 13.6% vs. 11.7% of total, respectively
    - Death from all causes did not differ significantly
    - For all patients, 37/397 (9.9%) vs. 35/204 (17%), respectively
    - For MRSA patients, 6/21 (29%) vs. 5/21 (24%), respectively
    - For "other bacteria" patients, 16/112 (14%) vs. 11/120 (9%), respectively
  - MRSA guidelines suggest therapy durations of 7-21 days.2


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**The Options**

- **Vancomycin is inferior to anti-staphylococcal penicillins for treatment of MSSA.1**
- **Ceftriaxone has been studied in limited fashion for MSSA pneumonia**
  - MSSA subset analyses from clinical trials are insufficient to recommend use
  - Focus I: Ceftriaxone clinical cure 8/10 (80%) vs. ceftriaxone clinical cure 8/13 (69%)1, p=0.66 (my calc)
  - Focus II: Ceftriaxone clinical cure 10/15 (67%) vs. ceftriaxone clinical cure 8/15 (53%)1, p=0.46 (my calc)

**Question 10:** Which of the following total durations of therapy would be most appropriate for AB if she has a favorable response to treatment?

- A. Total of 3-5 days
- B. Total of 7-21 days
- C. Total of 21-28 days
- D. Total of 42-56 days

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**Question 9: cont.**

Given the above susceptibilities, which of the following would be most appropriate for AB?

- A. Vancomycin 1.5 g intravenously every 24 hours
- B. Vancomycin 2 g intravenously every 24 hours
- C. Linezolid 600 mg every 24 hours
- D. Ceftriaxone 600 mg intravenously every 12 hours
- E. Oxacillin 2 g intravenously every 6 hours
Stop the Madness! Time for Stewardship

- Vancomycin and Piperacillin-tazobactam are the second and third most utilized antibiotics in the hospital; second only to the entire class of fluoroquinolones.¹
- Respiratory infections (including CAP, HCAP, and VAP) are the most common indication for nosocomial antibiotics.¹
- Pneumonia can be a highly subjective empiric diagnosis with multiple causes for pulmonary decline, even when following algorithms/guidelines;² those without culture proven infection should be considered for antibiotic de-escalation.³

Question 11:
After AB stabilizes, which of the following would be the most appropriate blood glucose target to balance safety and efficacy?

A. <110 mg/dL
B. <140 mg/dL
C. <180 mg/dL
D. <250 mg/dL

The Study that led to 1A recommendations

The NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients

- n=3054 intensive control and n=3050 to conventional control


The Choices

- Oxacillin should not be given to patients experiencing hives to cephalosporins, cross reactivity going this way is ~25%¹
- Vancomycin is inferior to anti-staphylococcal penicillins for treatment of MSSA.² Less is known re: comparing vancomycin to linezolid.
- Daptomycin is inactivated by surfactant.³
- Several studies are now focusing on vancomycin nephrotoxicity with higher trough goals.

Question 12:
AB is diagnosed with a type-1 mediated allergy to cephalosporin agents by the allergy service. Which of the following treatments for the MSSA infection would be best for AB given her development of renal failure and her newly diagnosed beta-lactam allergy.

A. Oxacillin; there is insignificant cross reactivity between cephalosporins and penicillins
B. Vancomycin; mortality data favor vancomycin for treatment of MSSA
C. Linezolid; several trials found reduced rates of nephrotoxicity with linezolid when compared with vancomycin
D. Daptomycin; daptomycin is the drug of choice in patients with bloodstream infections in whom vancomycin is not an option


Conflicting Data

- Several randomized trials have assessed the target blood sugars
- The initial study found benefits from highly restrictive protocols (i.e. goals=80-110 mg/dL) in terms of mortality and decreased LOS when performed in a research setting although increased toxicity has become apparent in clinical settings (1A)
  - Clinical applicability is questionable especially given that severe hypoglycemia is a concern
  - Several recent trials stopped early for unacceptable adverse event rates
- Thus, expert opinion in the guidelines recommends targeting <180 mg/dL instead of <110 mg/dL

Dellinger RP et al. Crit Care Med. 2012; 41:832-47. URL in handout
Vancomycin Nephrotoxicity

Vancomycin appears to induce oxidative stress at the renal proximal tubule; free radical scavenging and antioxidant molecules have minimized this toxicity.

Risk-adjusted (controlled for contrast use and sex) probability of serum creatinine (SCr) increase of 0.5 mg/dL stratified by drug category. \( P = 0.02 \) for vancomycin 2 g versus linezolid and vancomycin 1 g categories.

Graphs by Treatment_days

Study Data

(purple=prospective, blue=retrospective)

Vancomycin Renal Toxicity by Trough
