So Long HCAP! The Updated IDSA Hospital-Acquired and Ventilator-Associated Pneumonia Treatment Guidelines

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Pharmacy Grand Rounds
11/14/2017
Abbreviations

- HAP: hospital-acquired pneumonia
- VAP: ventilator-associated pneumonia
- HCAP: healthcare-associated pneumonia
- IDSA: Infectious Diseases Society of America
- MDRO: multidrug-resistant organism
- CAD: coronary artery disease
- A-fib: atrial fibrillation
- BPH: benign prostatic hyperplasia
- CAP: community-acquired pneumonia
- RRT: renal replacement therapy
- CrCl: creatinine clearance
Objectives

• Describe the significant burden that VAP and HAP have on the United States healthcare system

• Identify the key differences between the 2005 and the 2016 IDSA guidelines

• Select appropriate antibiotic treatment regimens for patients who are diagnosed with HAP or VAP based off of individual and institutional factors
Definitions from 2016 HAP/VAP Guidelines

• HAP: an episode of pneumonia not associated with mechanical ventilation that develops 48 hours or more after admission and did not appear to be incubating at the time of admission.

• VAP: an episode of pneumonia that is associated with mechanical ventilation and develops 48-72 hours after endotracheal intubation.

Clin Infect Dis 2016; 63: e61-e111
What is the estimated additional cost per hospitalization in patients who develop VAP compared to patients who do not?

- A. $10,000
- B. $20,000
- C. $40,000
- D. $70,000
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- C. $40,000
- D. $70,000
HAP/VAP Epidemiology

• HAP/VAP account for 22% of all hospital acquired infections
• Some controversy regarding mortality rates
• ~50% of HAP develop serious complications
• Little debate on economic burden of VAP
  • Prolonged mechanical ventilation (7.6 vs 11.5 days)
  • Prolonged hospitalization (11.5 vs 13.1 days)
  • $40,000 in additional costs

Clin Infect Dis 2016; 63: e61-e111
Mechanism of VAP
## Updates in 2016 Guidelines

<table>
<thead>
<tr>
<th>Factor</th>
<th>2005</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence grading</td>
<td>Evidence quality</td>
<td>GRADE methodology</td>
</tr>
<tr>
<td>HCAP</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Biomarker use</td>
<td>N/A</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>Empiric antibiotic coverage</td>
<td>Narrow coverage in some cases</td>
<td>Broad coverage for all</td>
</tr>
<tr>
<td>Double-cover <em>Pseudomonas</em></td>
<td>Per risk factors</td>
<td>Reduced # of risk factors</td>
</tr>
<tr>
<td>Unit antibiograms</td>
<td>Local ok</td>
<td>Prefer individual units</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>8-15 days</td>
<td>7 days for all</td>
</tr>
</tbody>
</table>

Clin Infect Dis 2016; 63: e61-e111  
## GRADE Methodology

<table>
<thead>
<tr>
<th></th>
<th>Strong Recommendation</th>
<th>Weak (Conditional) Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Most patients would want the suggested course of action, but some would not.</td>
<td>Most patients would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td>Most individuals should receive the intervention.</td>
<td>Personalized interventions or decisions should be made for each patient in order to optimize care.</td>
</tr>
<tr>
<td><strong>Policy Makers</strong></td>
<td>The recommendation can be adopted as policy in most situations.</td>
<td>Policymaking will require substantial debate and involvement of various stakeholders.</td>
</tr>
</tbody>
</table>
Recommendations From the Evidence

Strong Recommendations
- Moderate Quality Evidence: 7
- Low Quality Evidence: 6
- Very Low Quality Evidence: 6

Weak Recommendations
- Moderate Quality Evidence: 1
- Low Quality Evidence: 13
- Very Low Quality Evidence: 10

Clin Infect Dis 2016; 63: e61-e111
### 2005 Guideline Definition of HCAP

#### Risk Factors for HCAP Per 2005 IDSA Guidelines

<table>
<thead>
<tr>
<th>Risk Factor</th>
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</thead>
<tbody>
<tr>
<td>Hospitalization for two or more days within 90 days of infection onset</td>
</tr>
<tr>
<td>Nursing home or long-term care facility resident</td>
</tr>
<tr>
<td>Intravenous infusion therapy (including antibiotics) within 30 days</td>
</tr>
<tr>
<td>Chronic dialysis within 30 days</td>
</tr>
<tr>
<td>Home wound care</td>
</tr>
</tbody>
</table>

*Am J Respir Crit Care Med 2005; 171: 388–416*
Removal of HCAP From 2016 Guidelines

• Originally felt that patients who were exposed to healthcare were at risk for MDROs

• Studies assessing these risks were of poor quality and were subject to publication bias

• Individual patient characteristics do play a role in risk of infection with MDROs
  • Some allusion to adding HCAP in the upcoming CAP guidelines
Patient Case

• 87 y/o male admitted for fever, productive cough and increasing shortness of breath

• PMH: CAD, A-fib, BPH, osteoarthritis, no allergies

• Labs: WBC 16, Temp 39 °C, O₂ sat 82% on room air, CrCl 50 ml/min
  • Sputum cx: pending

• History
  • Resides at local nursing home
  • Treated ~4 weeks ago successfully for cellulitis of right hand with cephalexin 500 mg PO q12hrs x 10 days
Which initial antibiotic regimen is the most appropriate for our patient?

• A: Vancomycin 15-20 mg/kg IV daily + cefepime 1 g IV q12hrs
• B: Amoxicillin/clavulanate 875 mg PO q12hrs
• C: Vancomycin 15-20 mg/kg IV daily + piperacillin/tazobactam 3.375 g IV q6hrs + levofloxacin 750 mg IV daily
• D: Ceftriaxone 1 g IV daily + azithromycin 500 mg IV daily
Which initial antibiotic regimen is the most appropriate for our patient?

- A: Vancomycin 15-20 mg/kg IV daily + cefepime 1 g IV q12hrs
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- D: Ceftriaxone 1 g IV daily + azithromycin 500 mg IV daily
Use of Biomarkers in HAP/VAP: Diagnosis

- Procalcitonin - no (*strong recommendation*, *moderate*-quality evidence)
- sTREM-1 - no (*strong recommendation*, *moderate*-quality evidence)
- CRP - no (*weak recommendation*, *low-quality evidence*)
Utility of Procalcitonin in Duration of Therapy

• Suggested to use procalcitonin in addition to clinical criteria vs. clinical criteria alone for antibiotic discontinuation *(weak recommendation, low-quality evidence)*.
  
  • Potential Benefit: reduced side-effects and costs
  
  • Potential Harm: inappropriate discontinuation of necessary therapy

Clin Infect Dis 2016; 63: e61-e111
Cochrane Database Syst Rev 2012; 9: CD007498
Empiric Coverage for HAP and VAP

- Cover for *S. aureus*, *P. aeruginosa*, and other GNRs in **ALL** patients (*strong recommendation, very low-quality evidence*)
- When covering MRSA, use vancomycin or linezolid (*strong recommendation, low quality evidence*)
- Do not use aminoglycosides as sole antipseudomonal agent (*strong recommendation, very low-quality evidence*)

Clin Infect Dis 2016; 63: e61-e111
### Empiric Antibiotic Coverage: MDRO Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors for MDRO VAP</th>
<th>Risk Factor for MDRO HAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior IV antibiotic use within 90 days</td>
<td>• Prior IV antibiotic use within 90 days</td>
</tr>
<tr>
<td>• OR 12.3 (95% CI 6.48-23.35)</td>
<td>• OR 5.17 (95% CI 2.11-12.67)</td>
</tr>
<tr>
<td>• Septic shock at time of VAP</td>
<td></td>
</tr>
<tr>
<td>• OR 2.01 (95% CI 1.12-3.61)</td>
<td></td>
</tr>
<tr>
<td>• ARDS preceding VAP</td>
<td></td>
</tr>
<tr>
<td>• OR 3.1 (95% CI 1.88-5.1)</td>
<td></td>
</tr>
<tr>
<td>• 5 or more days of hospitalization prior to VAP</td>
<td></td>
</tr>
<tr>
<td>• Acute RRT prior to onset of VAP</td>
<td></td>
</tr>
<tr>
<td>• OR 2.5 (95% CI 1.14-5.49)</td>
<td></td>
</tr>
</tbody>
</table>

Clin Infect Dis 2016; 63: e61-e111
Additional HAP Treatment Considerations

- Cover MRSA if: *(weak recommendation, very low-quality evidence)*
  - >20% prevalence of MRSA among S. aureus isolates
  - local resistance patterns are unknown
  - high risk of mortality (need for ventilator support and septic shock)

- Treat *Pseudomonas* with two antibiotics from different classes if: *(weak recommendation, very low-quality evidence)*:
  - structural lung disease (i.e., bronchiectasis, cystic fibrosis)
  - high risk of mortality (need for ventilator support, septic shock)

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Additional VAP Treatment Considerations

• Cover MRSA if: *(weak recommendation, very low-quality evidence)*
  • >10-20% prevalence of MRSA among S. aureus isolates
  • local resistance patterns are unknown

• Treat *Pseudomonas* with two antibiotics from different classes if: *(weak recommendation, low quality evidence):*
  • >10% of Gram-negative isolates are resistant to monotherapy options
Which Antibiotics Should Be Used?

- *Pseudomonas*, MSSA, and gram- coverage for all
  - Anti-pseudomonal \(\beta\)-lactam or levofloxacin
- Vancomycin or linezolid for MRSA
  - consider patient-specific factors (i.e. blood cell count, use of SSRIs, renal function, cost)
- When 2 anti-pseudomonal agents are needed
  - Fluoroquinolone
  - Aminoglycosides (no monotherapy)
  - Polymixins (considered for VAP only)

Clin Infect Dis 2016; 63: e61-e111
<table>
<thead>
<tr>
<th>Broad-Spectrum Antibiotics With MSSA, Gram negative, and Antipseudomonal Activity</th>
<th>Gram-Positive Antibiotics With MRSA Activity</th>
<th>Gram-Negative Antibiotics With Antipseudomonal Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipseudomonal penicillins</strong>&lt;br&gt;• Piperacillin-tazobactam 4.5 g IV q6h</td>
<td><strong>Glycopeptides</strong>&lt;br&gt;• Vancomycin 15 mg/kg IV q8–12h (consider a 25–30 mg/kg loading dose in severe illness)</td>
<td><strong>Fluoroquinolones</strong>&lt;br&gt;• Ciprofloxacin 400 mg IV q8h&lt;br&gt;• Levofloxacin 750 mg IV q24h</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Antipseudomonal Cephalosporins</strong>&lt;br&gt;• Cefepime 2 g IV q8h&lt;br&gt;• Ceftazidime 2 g IV q8h</td>
<td><strong>Oxazolidinones</strong>&lt;br&gt;Linezolid 600 mg IV q12h</td>
<td><strong>Aminoglycosides</strong>&lt;br&gt;• Amikacin 15–20 mg/kg IV q24h&lt;br&gt;• Gentamicin 5–7 mg/kg IV q24h&lt;br&gt;• Tobramycin 5–7 mg/kg IV q24h</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Antipseudomonal Carbapenems</strong>&lt;br&gt;• Imipenem 500 mg IV q6hd&lt;br&gt;• Meropenem 1 g IV q8h</td>
<td><strong>Monobactams</strong>&lt;br&gt;• Aztreonam 2 g IV q8h</td>
<td><strong>Polymyxins</strong>&lt;br&gt;• Colistin 5 mg/kg IV loading dose followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h maintenance dose&lt;br&gt;• Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong>&lt;br&gt;• Levofloxacin 750 mg IV q24h</td>
<td></td>
<td></td>
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</tbody>
</table>

Adapted from Clin Infect Dis 2016; 63: e61-e111
2005 IDSA *Pseudomonas* Double-Coverage

- Previous guideline recommendations of when to cover *Pseudomonas*
  - Antimicrobial therapy in preceding 90 d
  - Current hospitalization of 5 d or more
  - High frequency of antibiotic resistance in the community or in the specific hospital unit
  - Immunosuppressive disease and/or therapy

### Should we double-cover *Pseudomonas*?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Study</th>
<th># of Patients</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez et al</td>
<td>2001</td>
<td>RCT</td>
<td>124 (HAP)</td>
<td>Pip/tazo + amikacin <strong>vs</strong> ceftazidime + amikacin</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Sieger et al</td>
<td>1997</td>
<td>RCT</td>
<td>211 (HAP)</td>
<td>Meropenem + tobramycin <strong>vs</strong> ceftazidime + tobramycin</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Heyland et al</td>
<td>2008</td>
<td>RCT</td>
<td>740 (VAP)</td>
<td>Meropenem + ciprofloxacin <strong>vs</strong> meropenem alone</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Damas et al</td>
<td>2006</td>
<td>RCT</td>
<td>74 (VAP)</td>
<td>Cefepime <strong>vs</strong> cefepime + levofloxacin or amikacin</td>
<td>No difference in mortality</td>
</tr>
</tbody>
</table>

* Clin Infect Dis 2016; 63: e61-e111
Unit Antibiotics

- Recommended by guidelines to have ICU antibiogram in addition to general hospital antibiogram
- Goal is to target pathogens specific to the ICU and to minimize overtreatment
- Likely to be differences between units in the hospital

Clin Infect Dis 2016; 63: e61-e111
## Rochester 2016 ICU Antibiogram

### Aerobic Gram-Positive Bacteria (% Susceptible)

<table>
<thead>
<tr>
<th>Microorganism (number tested)</th>
<th>Oxacillin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Vanco&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Secondary Drugs</th>
<th>Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Levo&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Floxacin le&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMP/SMX le&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minocycline le&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rifampin le&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinda le&lt;sup&gt;0.5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mupirocin le&lt;sup&gt;256&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Daptomycin le&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

- **Staphylococcus aureus (242)**
  - Oxacillin: 68%
  - Vanco: 99%
  - Levo: 69%
  - Floxacin: 97%
  - Rifampin: 95%
  - Clinda: 70%
  - Mupirocin: 99%
  - Daptomycin: 98%

- **Methicillin-Susceptible Staphylococcus aureus (163)**
  - Oxacillin: 100%
  - Vanco: 100%
  - Levo: 90%
  - Floxacin: 99%
  - Rifampin: 100%
  - Clinda: 82%
  - Mupirocin: 100%
  - Daptomycin: 97%

- **Methicillin-Resistant Staphylococcus aureus (78)**
  - Oxacillin: 0%
  - Vanco: 98%
  - Levo: 21%
  - Floxacin: 94%
  - Rifampin: 98%
  - Clinda: 41%
  - Mupirocin: 98%
  - Daptomycin: 94%

- **Staphylococcus coagulase negative (97)**
  - Oxacillin: 42%
  - Vanco: 100%
  - Levo: 61%
  - Floxacin: 71%
  - Rifampin: 98%
  - Clinda: 62%
  - Mupirocin: 97%
  - Daptomycin: 94%

*Grey = not reported*

Adapted from Mayo Clinic 2016 ICU Antibiogram
# Rochester 2016 ICU Antibiogram

## Aerobic Gram-Negative Bacteria (% Susceptible)

| Microorganism (number tested) | Amp <20 | Cefazolin <2 | Ceftriaxone <1 | Ceftep <2 | Aztreon <4 | Meropenem <1 | Ertapenem <0.5 | Amp/Sulf <3/4 | Pip/Teicoplanin <16/4 | Gent <4 | Tobramycin <4 | Amikacin <16 | Ciproflaxacin <1 | Levofloxacin <2 | TMP/SMX <20/8 | Oral Cephalosporins and Aminopenicillins* | Nitrofurantoin <32 | Trimethoprim <64 |
|--------------------------------|---------|--------------|---------------|----------|------------|-------------|---------------|-------------|-------------------|--------|--------------|-------------|----------------|-------------|----------------|----------------|----------------|---------------------|------------------|-----------------|
| *Citrobacter spp (59)         | R | 93 ≤ | 98 | 94 | 100 | 100 | 74 | 98 | 94 | 96 | 100 | 94 | 94 | 89 | 87 ≤ |                       |                   |                  |
| *Enterobacter cloaceae complex (82) | R | R | 68 ≤ | 91 | 71 | 97 | 89 | R | 78 | 97 | 97 | 100 | 96 | 97 | 96 | 40 ≤ |                       |                   |                  |
| *Escherichia coli (196)       | 50 | 58 | 83 | 85 | 84 | 100 | 98 | 58 | 95 | 89 | 86 | 98 | 65 | 65 | 77 |                       |                   |                  |
| *Escherichia coli urine isolates only (59) | 54 | 61 ≤ | 84 | 88 | 84 | 100 | 98 | 64 | 98 | 91 | 88 | 100 | 59 | 59 | 77 | 97 ≤ | 98 ≤ | 98 ≤ |                       |                   |                  |
| *Klebsiella oxytoca (67)       | 13 | 89 | 100 | 92 | 100 | 100 | 61 | 92 | 98 | 97 | 100 | 94 | 94 | 94 | 100 ≤ |                       |                   |                  |
| *Klebsiella pneumoniae complex (105) | R | 71 | 89 | 95 | 92 | 99 | 98 | 69 | 92 | 95 | 95 | 98 | 92 | 94 | 85 | 95 ≤ | 38 ≤ |                       |                   |                  |
| *Proteus mirabilis (60)        | 81 | 6 | 98 | 98 | 98 | 100 | 90 | 91 | 98 | 60 | 63 | 76 | 91 ≤ | R |                       |                   |                  |
| *Pseudomonas aeruginosa* (125) | R | R | R | 84 | 80 ≤ | 72 ≤ | 81 ≤ | R | R | 82 | 87 | 94 | 96 | 76 | 70 | R |                       |                   |                  |
| *Serratia marcescens (67)      | R | R | 91 | 98 | 94 | 98 | 98 | R | 97 | 97 | 95 | 100 | 97 | 97 | 100 | R |                       |                   |                  |
| *Stenotrophomonas maltophilia* (53) | R | R | R | 15 | R | R | R | R | R | R | R | R | R | R | R | 84 | 99 | R |                       |                   |                  |

Grey = not tested; Grey "R" = intrinsic resistance

Adapted from Mayo Clinic 2016 ICU Antibiogram

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Patient Case #2

- 68 y/o female ICU day 5 for CHF exacerbation requiring mechanical ventilation for 4 days
  - In past 24 hours, patient has developed a fever and leukocytosis
  - Chest X-ray shows new infiltrate in left upper lobe of lung
- No IV antibiotics in the past 90 days
- Labs: CrCl ~65 ml/min, WBC 12.4, no allergies
- Cultures pending
While awaiting culture results, what would be appropriate empiric antibiotic therapy for this patient?

- A: Levofloxacin 500 mg IV daily
- B: Cefepime 2 g IV q8hrs
- C: Piperacillin/tazobactam 4.5 g IV q6hrs + vancomycin 15-20 mg/kg IV q12hrs + levofloxacin 750 mg IV daily
- D: Meropenem 1g IV q8hrs + linezolid 600 mg IV q12hrs
While awaiting culture results, what would be appropriate empiric antibiotic therapy for this patient?

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• D: Meropenem 1g IV q8hrs + linezolid 600 mg IV q12hrs
Length of Therapy

• HAP
  • 7 days (strong recommendation, very low-quality evidence)

• VAP
  • 7 days (strong recommendation, moderate-quality evidence)
  • Meta-analysis assessing VAP due to non-glucose-fermenting gram negative rods showed no difference in pneumonia recurrence (OR 1.42, 95% CI 0.66-3.04) or mortality (OR 0.94, 95% CI 0.56-1.59)

• ALWAYS assess the clinical picture

Clin Infect Dis 2016; 63: e61-e111
Conclusion

• The 2016 IDSA HAP/VAP Guidelines address differences in practice settings with significant differences in resistance patterns

• These are guidelines, not laws!
  • Clinical judgment should always be used

• Utilize antibiotics judiciously and carefully
  • Improve empiric treatment definitions and de-escalate when appropriate

• Shorter duration of therapy recommended
Questions & Discussion