Guideline Updates in Hospital-Acquired Pneumonia (HAP), Ventilator-Associated Pneumonia (VAP) and Candidiasis

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Disclosures

• No disclosures to report

Learning Objectives

• Explain the major updates to the 2016 IDSA/ATS Hospital-acquired and Ventilator-associated Pneumonia Guidelines and the 2016 IDSA Candidiasis Guidelines

• Describe the empiric treatment regimens for patients with Hospital-acquired and Ventilator-associated Pneumonia

• Identify patient risk factors for invasive candidiasis and appropriate empiric therapy
2016 IDSA/ATS Guidelines for Hospital-acquired Pneumonia and Ventilator-associated Pneumonia

- Update of previous iteration of guidelines by ATS/IDSA on HAP/VAP/HCAP published in 2005

- **HAP Definition:** Pneumonia not incubating at the time of hospital admission and occurring ≥48 hours after admission

- **VAP Definition:** Pneumonia occurring >48 hours after endotracheal intubation

Removal of Healthcare-associated Pneumonia (HCAP)

- **HCAP Definition (2005 ATS/IDSA HAP/VAP/HCAP Guidelines):**
  - Patients with pneumonia who have any of the following risk factors:
  - Hospitalized for ≤3 days within 90 days
  - Residence in a nursing home or prolonged care facility
  - Home infection therapy (including antibiotics) within 7–30 days of the infection
  - Home wound care
  - Family member with a multidrug resistant (MDR) pathogen

  **Rationale:** Patients with HCAP were thought to be at high risk for MDR organisms due to their contact with the healthcare system.

  **Recent studies have demonstrated that patients meeting criteria for HCAP are not at high risk for MDR pathogens.**

Risk Factors for MDR Pathogens in HAP and VAP

- Guideline authors performed systematic reviews and meta-analyses to determine risk factors for MDR pathogens in both HAP and VAP.

<table>
<thead>
<tr>
<th>Risk Factors for MDR HAP</th>
<th>Risk Factors for MDR VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to antibiotic use within 30 days</td>
<td>Prior to antibiotic use within 90 days</td>
</tr>
<tr>
<td>ARDS preceding VAP</td>
<td>Acute renal replacement therapy prior to VAP onset</td>
</tr>
<tr>
<td>Hospital days prior to VAP</td>
<td>Hospital days prior to VAP</td>
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<tr>
<td>≥90 days</td>
<td>≥90 days</td>
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<tr>
<td>Septic shock at time of VAP</td>
<td>Septic shock at time of VAP</td>
</tr>
<tr>
<td>Prior to antibiotic use within 90 days</td>
<td>Prior to antibiotic use within 90 days</td>
</tr>
<tr>
<td>Pseudomonas VAP/HAP</td>
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</tr>
<tr>
<td>Acute renal replacement therapy prior to VAP onset</td>
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Empiric Treatment for HAP and VAP

- Must balance potential benefits of starting adequate antibiotics early with the harms of excessive coverage
- Development of a local antimicrobial stewardship program to guide clinicians on the optimal choice of antibiotics for HAP and VAP
  - Including an antibiotic specific to the ICU population
- Clinicians should consider all available data about their individual patient and their practice environment to tailor antibiotic choices for each patient

### Recommendations for Empiric Antibiotic Therapy for HAP

<table>
<thead>
<tr>
<th>High Risk of Mortality &amp; No Risk Factors for MRSA</th>
<th>High Risk of Mortality &amp; No Risk Factors for MRSA or MRSA Isolation</th>
<th>High Risk for Mortality or Disease of the Airways, Vascular Access, or IV Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>One of the Following:</td>
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<td>One of the Following:</td>
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<tr>
<td>Piperacillin/tazobactam 4.5g IV</td>
<td>Vancomycin 15mg/kg IV q24h or Cefepime 2g IV</td>
<td>Meropenem 2g IV q8h or Piperacillin/tazobactam 4.5g q8h or Cefepime 2g q8h</td>
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<tr>
<td>Imipenem 2g IV q8h or</td>
<td>Vancomycin 15mg/kg IV q24h or Cefepime 2g IV</td>
<td>Vancomycin 15mg/kg q24h or Cefepime 2g q8h or Cefazolin 2g q8h</td>
</tr>
<tr>
<td>Colistin 1.5mg/kg IV q12h or Levofloxacin 750mg IV</td>
<td>Vancomycin 15mg/kg IV q24h or Cefepime 2g IV</td>
<td>Vancomycin 15mg/kg q24h or Cefepime 2g q8h or Cefazolin 2g q8h</td>
</tr>
<tr>
<td>Amikacin 7.5mg/kg IV q24h or</td>
<td>Vancomycin 15mg/kg IV q24h or Cefepime 2g IV</td>
<td>Vancomycin 15mg/kg q24h or Cefepime 2g q6h or Cefazolin 2g q6h</td>
</tr>
</tbody>
</table>

### Recommendations for Empiric Antibiotic Therapy for VAP

1. Choose one Gram-positive option from column A and two Gram-negative options, one from column B and one from column C.

<table>
<thead>
<tr>
<th>A. Gram-positive pathogens with MRSA Activity</th>
<th>B. Gram-negative pathogens with MRSA Activity</th>
<th>C. Gram-negative pathogens without MRSA Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid + β-lactam antibiotics</td>
<td>Piperacillin/tazobactam + β-lactam antibiotics</td>
<td>Imipenem or meropenem + β-lactam antibiotics</td>
</tr>
<tr>
<td>Teicoplanin + β-lactam antibiotics</td>
<td>Cefepime or imipenem + β-lactam antibiotics</td>
<td>Cefepime or imipenem + β-lactam antibiotics</td>
</tr>
<tr>
<td>Vancomycin + β-lactam antibiotics</td>
<td>Cefepime or meropenem + β-lactam antibiotics</td>
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</tr>
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</table>

For critically ill patients, being treated in a unit where >10% of S. aureus isolates are MRSA, or being treated in units where the MRSA prevalence is unknown.

- In the absence of local data, select the following empiric options for aerobic pathogens, with structural lung disease, being treated in a unit where >10% of gram-negative isolates are MDR.
- Optimize to an agent with minimal toxicity, being treated in units with increased susceptibility data as available.

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De-escalation of Empiric Therapy to Definitive Therapy

- Antibiotic therapy for patients with HAP/VAP should be de-escalated rather than fixed (weak recommendation, very low-quality evidence)
  - No difference in mortality or ICU length of stay
- Once a pathogen has been identified and susceptibilities are known, combination therapy can be de-escalated
  - Exception: Patients with HAP/VAP due to P. aeruginosa who remain in septic shock or a high risk of death (mortality risk >25%), continuation of combination therapy is suggested (weak recommendation, very low-quality evidence)

Duration of Treatment

- VAP: Recommended duration is a 7 day course of antimicrobials (strong recommendation, moderate-quality evidence)
  - No difference in mortality, clinical cure or recurrent pneumonia in meta-analysis when compared with long-course regimens
  - No difference in pneumonia recurrence or mortality in meta-analysis of a subpopulation of patients with VAP due to non-glucose fermenting gram-negative bacilli
- HAP: Recommended duration is a 7 day course of antimicrobials (strong recommendation, very low-quality evidence)
- Procalcitonin levels plus clinical criteria should be used to guide discontinuation of antibiotic therapy for patients with HAP/VAP (weak recommendation, low-quality evidence)

Other Important Recommendations

- Recommendation for use of antibiotic dosing based on PK/PD data rather than the manufacturer’s prescribing information (weak recommendation, very low-quality evidence)
- Recommendation for both inhaled and systemic antibiotics in patients with VAP due to gram-negative bacilli that are susceptible only to aminoglycosides and polymyxins (weak recommendation, very low-quality evidence)
Question 1

Which of the following antibiotic combinations would provide appropriate empiric therapy for a patient diagnosed with Ventilator-associated Pneumonia with risk factors for MRSA and MDR gram-negative organisms?

A. Cefepime 2g IV q8h + Levofoxacin 750mg IV q24h
B. Vancomycin 15 mg/kg IV q12h + Ceftazidine 2g IV q8h
C. Linezolid 600mg IV q12h + Meropenem 1g IV q8h + Amikacin 15mg/kg IV q24h
D. Piperacillin/Tazobactam 4.5g IV q6h + Levofoxacin 750mg IV q24h + Polymyxin B 1.5mg/kg IV q12h

Question 2

What is the recommended duration of therapy for patients with Hospital-acquired and Ventilator-associated Pneumonia?

A. 5 days
B. 7 days
C. 10 days
D. 14 days

2016 IDSA Guidelines for Candidiasis

- Update of previous iteration of guidelines by IDSA on Candidiasis published in 2009
- Invasive infections due to Candida species are major causes of morbidity and mortality in humans
  - Candidemia is one of the most common healthcare-associated bloodstream infections in the United States with an attributable mortality up to 47%
- Non-albicans Candida species constitute ~50% of all candidemia and other forms of invasive candidiasis
**Diagnosis and Risk Factors for Invasive Candidiasis (IC)**

- Sensitivity of blood cultures for diagnosing IC is ~50% and cultures can become positive late in the disease course
- Other non-culture diagnostic tests (i.e. β-D-glucan, PCR) may be useful as adjuncts to cultures
- Risk factors for IC include:

<table>
<thead>
<tr>
<th>Candida colonization</th>
<th>Skin lesion</th>
<th>Fever, neutropenia</th>
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<tbody>
<tr>
<td>Severity of illness</td>
<td>Necrotizing pancreatitis</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Exposure to broad-spectrum antibiotics</td>
<td>Recent major surgery</td>
<td>Central venous catheter (CVC)</td>
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**Antifungal Susceptibility Testing**

- Susceptibility of Candida to currently available antifungal agents is generally predictable if the species of the isolate is known
  - Surveillance studies of C. glabrata isolates have demonstrated increasing resistance to azoles and some resistance to echinocandins
  - Resistance of C. tropicalis and C. parapsilosis to fluconazole has been reported
- Echinocandin susceptibility testing recommended for all bloodstream and other relevant Candida isolates (strong recommendation, low-quality evidence)
- Echinocandin susceptibility testing to be considered in patients who have had prior treatment with an echinocandin and those with infection due to C. glabrata or C. parapsilosis (strong recommendation, low-quality evidence)

**Recommendations for Empiric Treatment of Candidemia in Non-Neutropenic Patients**

- An echinocandin is recommended as initial therapy (strong recommendation, high-quality evidence)
  - Caspofungin: 70mg IV x 1 dose, then 50mg IV q24h OR
  - Micafungin: 100mg IV q24h OR
  - Anidulafungin: 200mg IV x 1 dose, then 100mg IV q24h
- Fluconazole 800mg IV q24h or an alternative if the patient has not received fluconazole recently due to high fluconazole-resistant Candida species (strong recommendation, high-quality evidence)
- Transition from an echinocandin to fluconazole for patients who are clinically stable, have isolates susceptible to fluconazole and have negative repeat blood cultures (strong recommendation, moderate-quality evidence)
- CVCs should be removed as early as possible in the course of candidemia (strong recommendation, moderate-quality evidence)
- Recommended duration of therapy is 2 weeks after documented clearance of Candida species and resolution of symptoms (strong recommendation, moderate-quality evidence)
### Recommendations for Empiric Treatment of Candidemia in Neutropenic Patients

- An echinocandin is recommended as initial therapy (strong recommendation, moderate-quality evidence)
  - Caspofungin 70mg IV x 1 dose, then 50mg IV q24h OR
  - Micafungin 100mg IV q24h OR
  - Anidulafungin 200mg IV/PO x 1 dose, then 100mg IV q24h
- Fluconazole 400mg IV/PO q24h is a step-down therapy during persistent neutropenia in clinically stable patients, with isolates susceptible to fluconazole and bloodstream clearance (weak recommendation, low-quality evidence)
- CVC removal to be considered on an individual basis as other sources (GI tract) predominate (strong recommendation, low-quality evidence)

Recommended duration of therapy is 2 weeks after documented clearance of Candida provided neutropenia and symptoms have resolved (strong recommendation, moderate-quality evidence).

### Empiric Treatment for Suspected Invasive Candidiasis in Non-Neutropenic Patients in the ICU

- Empiric antifungal therapy should be considered in ICU patients with IC risk factors and no other cause of fever (strong recommendation, moderate-quality evidence)
  - Should be based on clinical assessment of risk factors, surrogate markers for IC and/or culture data from nonsterile sites
- Empiric antifungal therapy should be started as soon as possible in ICU patients with IC risk factors and clinical signs of sepsis shock (strong recommendation, moderate-quality evidence)
- Preferred empiric treatment for suspected IC in non-neutropenic patients in the ICU is an echinocandin (strong recommendation, moderate-quality evidence)
- Recommended duration of empiric therapy for suspected IC is 2 weeks in those who improve (weak recommendation, low-quality evidence)
- For patients who have no clinical response to empiric antifungal therapy at 4-5 days and who do not have subsequent evidence of IC or have a negative surrogate marker for IC, consider stopping antifungal therapy (strong recommendation, low-quality evidence)

### Echinocandins

- Have become the preferred agents for candidemia and IC due to their fungicidal activity, efficacy, favorable safety profile, and limited drug interactions
  - Not to be used in Candida infections of the central nervous system, eye, or urinary tract as therapeutic concentrations are not achieved
  - C. parapsilosis has innately higher MICs to echinocandins
- Survival advantage associated with initial echinocandin therapy in IC
Other Important Recommendations

- Native valve Candida endocarditis
  - Lipid formulation of amphotericin B
  - Fluconazole or itraconazole (300 mg q24h)
  - Amphotericin B 3-5 mg/kg q24h, with or without flucytosine 25 mg/kg PO q6h OR high dose echinocandin (caspofungin 150 mg IV q24h, micafungin 150 mg IV q24h, or anidulafungin 200 mg IV q24h)
  - Recommended for initial therapy (strong recommendation, low-quality evidence)
  - Step down therapy to fluconazole 400-800 mg PO q24h in patients with susceptible isolates, clinical stability and cleared bloodstream (strong recommendation, low-quality evidence)

- Symptomatic Candida cystitis
  - Fluconazole susceptible isolate: Fluconazole 200 mg PO q24h x 2 weeks (strong recommendation, moderate-quality evidence)
  - Fluconazole-resistant C. albicans:
    - Amphotericin B deoxycholate 0.3-0.6 mg/kg IV q24h x 1-7 days OR fluconazole 25 mg/kg PO q24h x 7-10 days (strong recommendation, low-quality evidence)
  - C. krusei: Amphotericin B deoxycholate 0.3-0.6 mg/kg IV q24h x 1-7 days (strong recommendation, low-quality evidence)


Question 3

Which of the following are risk factors for invasive candidiasis?
A. Exposure to broad spectrum antibiotics
B. Presence of a central venous catheter
C. Receiving parenteral nutrition
D. Recent abdominal surgery
E. All of the above

Question 4

Which of the following antifungals would be most appropriate for initial empiric treatment of candidemia in neutropenic patients?
A. Caspofungin
B. Liposomal Amphotericin B
C. Voriconazole
D. Fluconazole
**Conclusion**

- Use local antibiograms to guide clinicians on the optimal choice of antibiotics for HAP and VAP
- Shorter durations of therapy (7 days) are recommended for HAP and VAP independent of causative pathogens
- Echinocandins are preferred agents for candidemia and most invasive Candida infections

**Guideline Updates in Hospital-Acquired Pneumonia (HAP), Ventilator-Associated Pneumonia (VAP) and Candidiasis**

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