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IDSA GUIDELINE

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

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Definitions

- Pneumonia: new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation.

- HAP (hospital-acquired pneumonia): pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission and not associated with mechanical ventilation.

- VAP (ventilator-associated pneumonia): pneumonia occurring >48 hours after endotracheal intubation and associated with mechanical ventilation.

- VAT (Ventilator-Associated Tracheobronchitis):fever with no other cause +increased sputum production +positive ETA culture (>106 CFU/mL) yielding a new bacteria+no RXevidence of nosocomial pneumonia

HAP/VAP: MICROBIOLOGIC METHODS TO DIAGNOSE

• We suggest noninvasive sampling (endotracheal aspiration, spontaneous expectoration, sputum induction, nasotracheal suctioning) with semiquantitative cultures to diagnose VAP: Noninvasive sampling can be done more rapidly than invasive sampling, with fewer complications and resources. Semiquantitative cultures can be done more rapidly than quantitative cultures, with fewer laboratory resources and less expertise needed.

• For some patients in whom a respiratory sample cannot be obtained noninvasively, there may be factors which could prompt consideration of obtaining samples invasively (BAL, protected specimen brush [PSB] and blind bronchial sampling [mini-BAL]). Six studies that enrolled patients with VAP, measured the discontinuation of antibiotics on the basis of quantitative culture results, and used the following thresholds to either diagnose or exclude VAP: a PSB of <103 CFU/mL, a BAL of <104 CFU/mL, and an ETA of <105 CFU/Ml. AB discontinuation in patients with VAP whose invasive quantitative culture results are below the diagnostic threshold for VAP may be beneficial.

• Despite a lack of evidence showing that respiratory cultures in HAP improve clinical outcomes, an attempt should be made to obtain respiratory samples for culture. The rationale for this suggestion is that R pathogens lead to a significant risk of inadequate initial empiric antibiotic therapy

HAP/VAP: Criteria to initiate AB therapy

- For patients with suspected HAP/VAP, is recommended using clinical criteria alone to decide whether or not to initiate antibiotic therapy

- A recent trial that randomized ICU patients to a PCT-guided AB escalation protocol vs standard of care, aiming to improve survival by increasing early appropriate AB therapy, showed that the PCT-guided protocol did not result in survival improvement, but resulted in a higher number of ventilator-days and prolonged ICU stay: *Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the ntensive care unit: a randomized trial. Crit Care Med 2011; 39:2048–58*.

Empiric Treatment of Clinically Suspected VAP

1) Patients who develop VAP after >5 days of hospitalization (late-onset-VAP) are at >risk of infection with MDR organisms than patients who develop VAP earlier in their hospitalization (early-onset-VAP).

2) Conditions of AB empirical treatment:

- Cover *S. aureus, Pseudomonas aeruginosa*, and other gram-negative bacilli in all empiric regimens
- Cover MRSA (vancomycin or linezolid) only in patients with any of the following: a risk factor for antimicrobial R, patients in units with >10%–20% MRSA, and patients in units where the prevalence of MRSA is not known
- Prescribe 2 antipseudomonal AB from different classes only in patients with any of the following: a risk factor for AB-R, patients in units with>10% of gram-negative isolates R to an agent being considered for monotherapy, and patients in an ICU with antimicrobial susceptibility rates no available
- Avoid aminoglycosides if alternative agents with adequate gram-negative activity are available
- Avoid colistin if alternative with adequate gram-negative activity is available

Ventilator-Associated Tracheobronchitis (VAT): not providing AB therapy

Risk Factors for MDR-Pathogens

Table 2. Risk Factors for Multidrug-Resistant Pathogens

Risk factors for MDR VAP
Prior intravenous antibiotic use within 90 d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90 d

Abbreviations: ARDS, acute respiratory distress syndrome; HAP, hospital-acquired pneumonia; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

Antibiotics for Empiric Treatment of Clinically Suspected VAP

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Drug levels and adjustment of doses and/or intervals required.

[b] Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.

[c] On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.

[d] The dose may need to be lowered in patients weighing <70 kg to prevent seizures.

[e] Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA); for example, One million IU of colistin is equivalent to about 30 mg of CBA, which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10 000 units) [136].

[f] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

Antibiotics for Empiric Treatment of Clinically Suspected HAP

Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily
		Gentamicin 5–7 mg/kg IV daily
		Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		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 treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.		

Abbreviations: HAP, hospital-acquired pneumonia; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a] Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock.

[b] Indications for MRSA coverage include intravenous antibiotic treatment during the prior 90 days, and treatment in a unit where the prevalence of MRSA among *S. aureus* isolates is not known or is >20%. Prior detection of MRSA by culture or non-culture screening may also increase the risk of MRSA. The 20% threshold was chosen to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use; hence, individual units can elect to adjust the threshold in accordance with local values and preferences. If MRSA coverage is omitted, the antibiotic regimen should include coverage for MSSA.

[c] If patient has factors increasing the likelihood of gram-negative infection, 2 antipseudomonal agents are recommended. If patient has structural lung disease increasing the risk of gram-negative infection (ie, bronchiectasis or cystic fibrosis), 2 antipseudomonal agents are recommended. A high-quality Gram stain from a respiratory specimen with numerous and predominant gram-negative bacilli provides further support for the diagnosis of a gram-negative pneumonia, including fermenting and non-glucose-fermenting microorganisms.

[d] Extended infusions may be appropriate.

[e] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

VAP:ROLE OF INHALED AB THERAPY

- The rationale for adjunctive inhaled AB therapy is based in part upon the observation that AB efficacy against bacteria within purulent secretions may require AB concentrations >10–25 MIC and these levels cannot be achieved with IV therapy alone and, therefore, the addition of inhaled AB therapy may be beneficial.

- The panel acknowledged having very low confidence in the estimated effects of adjunctive inhaled AB therapy and recognized that there are many important unknowns (optimum dosing, optimum delivery method, population most likely to benefit).

- For these reasons, the panel elected to recommend adjunctive inhaled AB therapy for patients who have VAP caused by bacteria that are only susceptible to AB for which evidence of efficacy by the IV alone route is the most limited (aminoglycosides or colistin), suggesting both inhaled and systemic AB rather than systemic alone

- The panel also believes that it is reasonable to consider adjunctive inhaled antibiotic therapy as a treatment of last resort for patients who are not responding to IV AB alone, whether the infecting organism is or is not MDR

HAP/VAP: Optimal Duration of AB Therapy

- The panel recommend a 7-day course of antimicrobial therapy rather than a longer duration

- There exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

- We suggest using PCT levels plus clinical criteria to guide the discontinuation of AB therapy, rather than clinical criteria alone