Clinical Infectious Diseases

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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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

These guidelines are intended for use by healthcare professionals who care for patients at risk for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), including specialists in infectious diseases, pulmonary diseases, critical care, and surgeons, anesthesiologists, hospitalists, and any clinicians and healthcare providers caring for hospitalized patients with nosocomial pneumonia. The panel's recommendations for the diagnosis and treatment of HAP and VAP are based upon evidence derived from topic-specific systematic literature reviews.

EXECUTIVE SUMMARY

In this 2016 guideline, the term "hospital-acquired pneumonia" (HAP) denotes an episode of pneumonia not associated with mechanical ventilation. Thus, patients with HAP and ventilator-associated pneumonia (VAP) belong to 2 distinct groups. The major differences between this guideline and the 2005 version [1] include the following: the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for the evaluation of all available evidence (Table 1) [2]; the removal of the concept of healthcare-associated pneumonia (HCAP); and the recommendation that each hospital generate antibiograms to guide healthcare professionals with respect to the optimal choice of antibiotics. In an effort to minimize patient harm and exposure to unnecessary antibiotics and reduce the development of antibiotic resistance, we recommend that the antibiogram data be utilized to decrease the unnecessary use of dual gram-negative and empiric methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotic treatment. We also recommend short-course antibiotic therapy for most patients with HAP or VAP independent of microbial etiology, as well as antibiotic de-escalation.

Summarized below are the recommendations made in the 2016 guideline. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of this guideline.

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Table 1. Interpretation of Strong and Weak (Conditional) Recommendations

	Strong Recommendation	Weak (Conditional) Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

MICROBIOLOGIC METHODS TO DIAGNOSE VAP AND HAP

I. Should Patients With Suspected VAP Be Treated Based on the Results of Invasive Sampling (ie, Bronchoscopy, Blind Bronchial Sampling) With Quantitative Culture Results, Noninvasive Sampling (ie, Endotracheal Aspiration) With Quantitative Culture Results, or Noninvasive Sampling With Semiquantitative Culture Results?

Recommendation

1. We suggest noninvasive sampling with semiquantitative cultures to diagnose VAP, rather than invasive sampling with quantitative cultures and rather than noninvasive sampling with quantitative cultures *(weak recommendation, low-quality evidence)*.

   Remarks: Invasive respiratory sampling includes bronchoscopic techniques (ie, bronchoalveolar lavage [BAL], protected specimen brush [PSB]) and blind bronchial sampling (ie, mini-BAL). Noninvasive respiratory sampling refers to endotracheal aspiration.

II. If Invasive Quantitative Cultures Are Performed, Should Patients With Suspected VAP Whose Culture Results Are Below the Diagnostic Threshold for VAP (PSB With $<10^3$ Colony-Forming Units [CFU]/mL, BAL With $<10^4$ CFU/mL) Have Their Antibiotics Withheld Rather Than Continued?

Recommendation

1. Noninvasive sampling with semiquantitative cultures is the preferred methodology to diagnose VAP (see section I); however, the panel recognizes that invasive quantitative cultures will occasionally be performed by some clinicians. For patients with suspected VAP whose invasive quantitative culture results are below the diagnostic threshold for VAP, we suggest that antibiotics be withheld rather than continued *(weak recommendation, very low-quality evidence)*.

   Values and Preferences: This recommendation places a high value on avoiding unnecessary harm and cost.

   Remarks: Clinical factors should also be considered because they may alter the decision of whether to withhold or continue antibiotics. These include the likelihood of an alternative source of infection, prior antimicrobial therapy at the time of culture, degree of clinical suspicion, signs of severe sepsis, and evidence of clinical improvement.

III. In Patients With Suspected HAP (Non-VAP), Should Treatment Be Guided by the Results of Microbiologic Studies Performed on Respiratory Samples, or Should Treatment Be Empiric?

Recommendation

1. We suggest that patients with suspected HAP (non-VAP) be treated according to the results of microbiologic studies performed on respiratory samples obtained noninvasively, rather than being treated empirically *(weak recommendation, very low-quality evidence)*.

   Values and Preferences: The suggestion places a high value on the potential to accurately target antibiotic therapy and then deescalate antibiotic therapy based upon respiratory and blood culture results. Minimizing resource use by not obtaining respiratory cultures is given a lower value.

   Remarks: Noninvasive methods to obtain respiratory samples include the following: spontaneous expectoration, sputum induction, nasotracheal suctioning in a patient who is unable to cooperate to produce a sputum sample, and endotracheal aspiration in a patient with HAP who subsequently requires mechanical ventilation. The panel recognizes that for some patients in whom a respiratory sample cannot be obtained noninvasively, there may be factors which could prompt consideration of obtaining samples invasively.

THE USE OF BIOMARKERS AND THE CLINICAL PULMONARY INFECTION SCORE TO DIAGNOSE VAP AND HAP

IV. In Patients With Suspected HAP/VAP, Should Procalcitonin (PCT) Plus Clinical Criteria or Clinical Criteria Alone Be Used to Decide Whether or Not to Initiate Antibiotic Therapy?

Recommendation

1. For patients with suspected HAP/VAP, we recommend using clinical criteria alone, rather than using serum PCT plus clinical criteria, to decide whether or not to initiate antibiotic therapy *(strong recommendation, moderate-quality evidence)*.

V. In Patients With Suspected HAP/VAP, Should Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1) Plus Clinical Criteria or Clinical Criteria Alone Be Used to Decide Whether or Not to Initiate Antibiotic Therapy?

Recommendation

1. For patients with suspected HAP/VAP, we recommend using clinical criteria alone, rather than using bronchoalveolar lavage fluid (BALF) sTREM-1 plus clinical criteria, to

decide whether or not to initiate antibiotic therapy *(strong recommendation, moderate-quality evidence)*.

VI. In Patients With Suspected HAP/VAP, Should C-Reactive Protein (CRP) Plus Clinical Criteria, or Clinical Criteria Alone, Be Used to Decide Whether or Not to Initiate Antibiotic Therapy?

Recommendation

1. For patients with suspected HAP/VAP, we recommend using clinical criteria alone rather than using CRP plus clinical criteria, to decide whether or not to initiate antibiotic therapy *(weak recommendation, low-quality evidence)*.

VII. In Patients With Suspected HAP/VAP, Should the Modified Clinical Pulmonary Infection Score (CPIS) Plus Clinical Criteria, or Clinical Criteria Alone, Be Used to Decide Whether or Not to Initiate Antibiotic Therapy?

Recommendation

1. For patients with suspected HAP/VAP, we suggest using clinical criteria alone, rather than using CPIS plus clinical criteria, to decide whether or not to initiate antibiotic therapy *(weak recommendation, low-quality evidence)*.

TREATMENT OF VENTILATOR-ASSOCIATED TRACHEOBRONCHITIS

VIII. Should Patients With Ventilator-Associated Tracheobronchitis (VAT) Receive Antibiotic Therapy?

Recommendation

1. In patients with VAT, we suggest not providing antibiotic therapy *(weak recommendation, low-quality evidence)*.

INITIAL TREATMENT OF VAP AND HAP

IX. Should Selection of an Empiric Antibiotic Regimen for VAP Be Guided by Local Antibiotic-Resistance Data?

Recommendations

1. 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.
2. We recommend that empiric treatment regimens be informed by the local distribution of pathogens associated with VAP and their antimicrobial susceptibilities.

   Values and preferences: These recommendations place a high value on targeting the specific pathogens associated with VAP as narrowly as possible to assure adequate treatment while minimizing overtreatment and its undesirable consequences.

   Remarks: The frequency with which the distribution of pathogens and their antimicrobial susceptibilities are updated should be determined by the institution. Considerations should include their rate of change, resources, and the amount of data available for analysis.

X. What Antibiotics Are Recommended for Empiric Treatment of Clinically Suspected VAP?

Recommendations (See Table 3 for Specific Antibiotic Recommendations)

1. In patients with suspected VAP, we recommend including coverage for *S. aureus, Pseudomonas aeruginosa,* and other gram-negative bacilli in all empiric regimens *(strong recommendation, low-quality evidence)*.
   i. We suggest including an agent active against MRSA for the empiric treatment of suspected VAP only in patients with any of the following: a risk factor for antimicrobial resistance (Table 2), 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 *(weak recommendation, very low-quality evidence)*.
   ii. We suggest including an agent active against methicillin-sensitive *S. aureus* (MSSA) (and not MRSA) for the empiric treatment of suspected VAP in patients without risk factors for antimicrobial resistance, who are being treated in ICUs where <10%–20% of *S. aureus* isolates are methicillin resistant (*weak recommendation, very low-quality evidence)*.
2. If empiric coverage for MRSA is indicated, we recommend either vancomycin or linezolid *(strong recommendation, moderate-quality evidence)*.
3. When empiric treatment that includes coverage for MSSA (and not MRSA) is indicated, we suggest a regimen including piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem *(weak recommendation, very low-quality evidence)*. Oxacillin, nafcillin, or cefazolin are preferred agents for treatment of proven MSSA, but are not necessary for the empiric treatment of VAP if one of the above agents is used.
4. We suggest prescribing 2 antipseudomonal antibiotics from different classes for the empiric treatment of suspected VAP only in patients with any of the following: a risk factor for

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.

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].

antimicrobial resistance (Table 2), 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 *(weak recommendation, low-quality evidence)*.

5. We suggest prescribing one antibiotic active against *P. aeruginosa* for the empiric treatment of suspected VAP in patients without risk factors for antimicrobial resistance who are being treated in ICUs where ≤10% of gram-negative isolates are resistant to the agent being considered for monotherapy *(weak recommendation, low-quality evidence)*.
6. In patients with suspected VAP, we suggest avoiding aminoglycosides if alternative agents with adequate gram-negative activity are available *(weak recommendation, low-quality evidence)*.
7. In patients with suspected VAP, we suggest avoiding colistin if alternative agents with adequate gram-negative activity are available *(weak recommendation, very low-quality evidence)*.

Values and Preferences: These recommendations are a compromise between the competing goals of providing early appropriate antibiotic coverage and avoiding superfluous treatment that may lead to adverse drug effects, *Clostridium difficile* infections, antibiotic resistance, and increased cost.

Remarks: Risk factors for antimicrobial resistance are provided in Table 2. The 10%–20% threshold for deciding whether or not to target MRSA and the 10% threshold for deciding whether or not to prescribe 1 antipseudomonal agent or 2 were chosen by the panel with a goal of trying to assure that ≥95% of patient receive empiric therapy active against their likely pathogens; when implementing these recommendations, individual ICUs may elect to modify these thresholds. If patient has structural lung disease increasing the risk of gram-negative infection (ie, bronchiectasis or cystic fibrosis), 2 antipseudomonal agents are recommended.

XI. Should Selection of an Empiric Antibiotic Regimen for HAP (Non-VAP) Be Guided by Local Antibiotic Resistance Data?

Recommendations

1. We recommend that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is tailored to their HAP population, if possible.
2. We recommend that empiric antibiotic regimens be based upon the local distribution of pathogens associated with HAP and their antimicrobial susceptibilities.

Remarks: The frequency with which the distribution of pathogens and their antimicrobial susceptibilities are updated should be determined by the institution. Considerations should include their rate of change, resources, and the amount of data available for analysis.

XII. What Antibiotics Are Recommended for Empiric Treatment of Clinically Suspected HAP (Non-VAP)?

Recommendations (See Table 4 for Specific Antibiotic Recommendations)

1. For patients being treated empirically for HAP, we recommend prescribing an antibiotic with activity against *S. aureus (strong recommendation, very low-quality evidence)*. (See below for recommendations regarding empiric coverage of MRSA vs MSSA.)
   i. For patients with HAP who are being treated empirically and have either a risk factor for MRSA infection (ie, prior intravenous antibiotic use within 90 days, hospitalization in a unit where >20% of *S. aureus* isolates are methicillin resistant, or the prevalence of MRSA is not known, or who are at high risk for mortality, we suggest prescribing an antibiotic with activity against MRSA *(weak recommendation, very low-quality evidence)*. (Risk factors for mortality include need for ventilatory support due to HAP and septic shock).
   ii. For patients with HAP who require empiric coverage for MRSA, we recommend vancomycin or linezolid rather than an alternative antibiotic *(strong recommendation, low-quality evidence)*.
   iii. For patients with HAP who are being treated empirically and have no risk factors for MRSA infection and are not at high risk of mortality, we suggest prescribing an antibiotic with activity against MSSA. When empiric treatment that includes coverage for MSSA (and not MRSA) is indicated, we suggest a regimen including piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem.

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].

Oxacillin, nafcillin, or cefazolin are preferred for the treatment of proven MSSA, but are not necessary for empiric coverage of HAP if one of the above agents is used *(weak recommendation, very low-quality evidence)*.

2. For patients with HAP who are being treated empirically, we recommend prescribing antibiotics with activity against *P. aeruginosa* and other gram-negative bacilli *(strong recommendation, very low-quality evidence)*.

   i. For patients with HAP who are being treated empirically and have factors increasing the likelihood for *Pseudomonas* or other gram-negative infection (ie, prior intravenous antibiotic use within 90 days; also see Remarks) or a high risk for mortality, we suggest prescribing antibiotics from 2 different classes with activity against *P. aeruginosa (weak recommendation, very low-quality evidence)*. (Risk factors for mortality include need for ventilatory support due to HAP and septic shock). All other patients with HAP who are being treated empirically may be prescribed a single antibiotic with activity against *P. aeruginosa*.

   ii. For patients with HAP who are being treated empirically, we recommend not using an aminoglycoside as the sole antipseudomonal agent *(strong recommendation, very low-quality evidence)*.

   Values and Preferences: These recommendations are a compromise between the competing goals of providing early appropriate antibiotic coverage and avoiding superfluous treatment that may lead to adverse drug effects, *C. difficile* infections, antibiotic resistance, and increased cost.

   Remarks: The 20% threshold for deciding whether or not to target MRSA or MSSA was chosen in an effort to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use; when implementing these recommendations, individual units may elect to modify this threshold. 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.

PHARMACOKINETIC/PHARMACODYNAMIC OPTIMIZATION OF ANTIBIOTIC THERAPY

XIII. Should Antibiotic Dosing Be Determined by Pharmacokinetic/Pharmacodynamic (PK/PD) Data or the Manufacturer's Prescribing Information in Patients With HAP/VAP?

Recommendation

1. For patients with HAP/VAP, we suggest that antibiotic dosing be determined using PK/PD data, rather than the manufacturer's prescribing information *(weak recommendation, very low-quality evidence)*.

   Values and Preferences: This recommendation places a high value on improving clinical outcome by optimization of therapy; it places a lower value on burden and cost.

   Remarks: PK/PD-optimized dosing refers to the use of antibiotic blood concentrations, extended and continuous infusions, and weight-based dosing for certain antibiotics.

ROLE OF INHALED ANTIBIOTIC THERAPY

XIV. Should Patients With VAP Due to Gram-Negative Bacilli Be Treated With a Combination of Inhaled and Systemic Antibiotics, or Systemic Antibiotics Alone?

Recommendation

1. For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), we suggest both inhaled and systemic antibiotics, rather than systemic antibiotics alone *(weak recommendation, very low-quality evidence)*.

   Values and Preferences: This recommendation places a high value on achieving clinical cure and survival; it places a lower value on burden and cost.

   Remarks: It is reasonable to consider adjunctive inhaled antibiotic therapy as a treatment of last resort for patients who are not responding to intravenous antibiotics alone, whether the infecting organism is or is not multidrug resistant (MDR).

PATHOGEN-SPECIFIC THERAPY

XV. What Antibiotics Should Be Used for the Treatment for MRSA HAP/VAP?

Recommendation

1. We recommend that MRSA HAP/VAP be treated with either vancomycin or linezolid rather than other antibiotics or antibiotic combinations *(strong recommendation, moderate-quality evidence)*.

   Remarks: The choice between vancomycin and linezolid may be guided by patient-specific factors such as blood cell counts, concurrent prescriptions for serotonin-reuptake inhibitors, renal function, and cost.

XVI. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to *P. aeruginosa*?

Recommendations

1. For patients with HAP/VAP due to *P. aeruginosa,* we recommend that the choice of an antibiotic for definitive (not empiric) therapy be based upon the results of antimicrobial susceptibility testing *(strong recommendation, low-quality evidence)*.
2. For patients with HAP/VAP due to *P. aeruginosa,* we recommend against aminoglycoside monotherapy *(strong recommendation, very low-quality evidence)*.

   Remarks: Routine antimicrobial susceptibility testing should include assessment of the sensitivity of the *P. aeruginosa*

isolate to polymyxins (colistin or polymyxin B) in settings that have a high prevalence of extensively resistant organisms.

XVII. Should Monotherapy or Combination Therapy Be Used to Treat Patients With HAP/VAP Due to *P. aeruginosa*?

Recommendations

1. For patients with HAP/VAP due to *P. aeruginosa* who are not in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, we recommend monotherapy using an antibiotic to which the isolate is susceptible rather than combination therapy *(strong recommendation, low-quality evidence)*.
2. For patients with HAP/VAP due to *P. aeruginosa* who remain in septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known, we suggest combination therapy using 2 antibiotics to which the isolate is susceptible rather than monotherapy *(weak recommendation, very low-quality evidence)*.
3. For patients with HAP/VAP due to *P. aeruginosa,* we recommend against aminoglycoside monotherapy *(strong recommendation, very low-quality evidence)*.

   Remarks: High risk of death in the meta-regression analysis was defined as mortality risk >25%; low risk of death is defined as mortality risk <15%. For a patient whose septic shock resolves when antimicrobial sensitivities are known, continued combination therapy is not recommended.

XVIII. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to Extended-Spectrum β-Lactamase (ESBL)–Producing Gram-Negative Bacilli?

Recommendation

1. For patients with HAP/VAP due to ESBL-producing gram-negative bacilli, we recommend that the choice of an antibiotic for definitive (not empiric) therapy be based upon the results of antimicrobial susceptibility testing and patient-specific factors *(strong recommendation, very low-quality evidence)*.

   Remarks: Patient-specific factors that should be considered when selecting an antimicrobial agent include allergies and comorbidities that may confer an increased risk of side effects.

XIX. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to *Acinetobacter* Species?

Recommendations

1. In patients with HAP/VAP caused by *Acinetobacter* species, we suggest treatment with either a carbapenem or ampicillin/sulbactam if the isolate is susceptible to these agents *(weak recommendation, low-quality evidence)*.
2. In patients with HAP/VAP caused by *Acinetobacter* species that is sensitive only to polymyxins, we recommend intravenous polymyxin (colistin or polymyxin B) *(strong recommendation, low-quality evidence)*, and we suggest adjunctive inhaled colistin *(weak recommendation, low-quality evidence)*.
3. In patients with HAP/VAP caused by *Acinetobacter* species that is sensitive only to colistin, we suggest not using adjunctive rifampicin *(weak recommendation, moderate-quality evidence)*.
4. In patients with HAP/VAP caused by *Acinetobacter* species, we recommend against the use of tigecycline *(strong recommendation, low-quality evidence)*.

   Values and Preferences: These recommendations place a relatively higher value on avoiding potential adverse effects due to the use of combination therapy with rifampicin and colistin, over achieving an increased microbial eradication rate, as eradication rate was not associated with improved clinical outcome.

   Remarks: Selection of an appropriate antibiotic for definitive (nonempiric) therapy requires antimicrobial susceptibility testing.

XX. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to Carbapenem-Resistant Pathogens?

Recommendation

1. In patients with HAP/VAP caused by a carbapenem-resistant pathogen that is sensitive only to polymyxins, we recommend intravenous polymyxins (colistin or polymyxin B) *(strong recommendation, moderate-quality evidence)*, and we suggest adjunctive inhaled colistin *(weak recommendation, low-quality evidence)*.

   Values and Preferences: These recommendations place a high value on achieving clinical cure and survival; they place a lower value on burden and cost.

   Remarks: Inhaled colistin may have potential pharmacokinetic advantages compared to inhaled polymyxin B, and clinical evidence based on controlled studies has also shown that inhaled colistin may be associated with improved clinical outcomes. The clinical evidence for inhaled polymyxin B is mostly from anecdotal and uncontrolled studies; we are therefore not suggesting use of inhaled polymyxin B. Colistin for inhalation should be administered promptly after being mixed with sterile water. This recommendation was made by the US Food and Drug Administration (FDA) after a report that a cystic fibrosis patient died after being treated with a premixed colistin formulation [3]. Intravenous polymyxin B may have potential pharmacokinetic advantages compared to intravenous colistin, but clinical data are lacking in patients with HAP/VAP.

LENGTH OF THERAPY

XXI. Should Patients With VAP Receive 7 Days or 8–15 Days of Antibiotic Therapy?

Recommendation

1. For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration *(strong recommendation, moderate-quality evidence)*.

Remarks: 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.

XXII. What Is the Optimal Duration of Antibiotic Therapy for HAP (Non-VAP)?

Recommendation

1. For patients with HAP, we recommend a 7-day course of antimicrobial therapy *(strong recommendation, very low-quality evidence).*
   Remarks: 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.

XXIII. Should Antibiotic Therapy Be De-escalated or Fixed in Patients With HAP/VAP?

Recommendation

1. For patients with HAP/VAP, we suggest that antibiotic therapy be de-escalated rather than fixed *(weak recommendation, very low-quality evidence).*
   Remarks: De-escalation refers to changing an empiric broad-spectrum antibiotic regimen to a narrower antibiotic regimen by changing the antimicrobial agent or changing from combination therapy to monotherapy. In contrast, fixed antibiotic therapy refers to maintaining a broad-spectrum antibiotic regimen until therapy is completed.

XXIV. Should Discontinuation of Antibiotic Therapy Be Based Upon PCT Levels Plus Clinical Criteria or Clinical Criteria Alone in Patients With HAP/VAP?

Recommendation

1. For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone *(weak recommendation, low-quality evidence).*
   Remarks: It is not known if the benefits of using PCT levels to determine whether or not to discontinue antibiotic therapy exist in settings where standard antimicrobial therapy for VAP is already 7 days or less.

XXV. Should Discontinuation of Antibiotic Therapy Be Based Upon the CPIS Plus Clinical Criteria or Clinical Criteria Alone in Patients With Suspected HAP/VAP?

Recommendation

1. For patients with suspected HAP/VAP, we suggest not using the CPIS to guide the discontinuation of antibiotic therapy *(weak recommendation, low-quality evidence).*

Notes

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