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

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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.

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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.

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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].

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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*

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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)*.

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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)*.

INTRODUCTION

Despite advances in the understanding of contributing causes and prevention, HAP and VAP continue to be frequent complications of hospital care. Together, they are among the most common hospital-acquired infections (HAIs), accounting for 22% of all HAIs in a multistate point-prevalence survey [4]. Although hospital-reported data from the National Healthcare Safety Network suggest that VAP rates have been declining [5, 6], recently published data from a randomly selected national sample demonstrated that approximately 10% of patients who required mechanical ventilation were diagnosed with VAP and that this rate has not declined over the past decade [7].

These infections negatively impact important patient outcomes. While all-cause mortality associated with VAP has been reported to range from 20% to 50%, the mortality directly related to VAP is debated; a recent meta-analysis derived from randomized VAP prevention studies estimated the attributable mortality at 13% [8]. There is little controversy, however, regarding the tremendous resource use and prolonged hospital length of stay related to VAP. Two recent studies estimated that VAP prolongs length of mechanical ventilation by 7.6 to 11.5 days and prolongs hospitalization by 11.5 to 13.1 days compared to similar patients without VAP [9, 10]. The excess cost associated with VAP was estimated to be approximately $40 000 per patient [10].

Even in HAP, generally considered to be less severe than VAP, serious complications occur in approximately 50% of patients [11], including respiratory failure, pleural effusions, septic shock, renal failure, and empyema. This is particularly seen among patients who develop HAP in the intensive care unit (ICU), where the mortality rate approaches that of patients with VAP [11, 12].

The last American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) HAP/VAP guidelines, published in 2005 [1], provided evidence-based recommendations for the prevention, diagnosis, and treatment of HCAP, HAP, and VAP. Since 2005, new studies have provided additional insights into diagnosis and treatment of these conditions. Furthermore, in the 11 years since the publication of these guidelines, there have been advances in evidence-based guideline methodology. For these reasons, the ATS and the IDSA have collaborated to create updated guidelines for the diagnosis and treatment of HAP and VAP.

Scope and Purpose

The purpose of this document is to provide evidence-based guidance on the most effective diagnosis and management of nonimmunocompromised patients with HAP/VAP. Patients with immunosuppression who are at risk for opportunistic pulmonary infection represent a special population that often requires an alternative approach to diagnosis and treatment. While many of the concepts addressed in these guidelines

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might be applicable to immunosuppressed patients, the recommendations are not intended for such patients. The target audience for these guidelines includes healthcare professionals who care for patients at risk for HAP and 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. This document may also serve as the basis for development and implementation of locally adapted guidelines.

To determine the scope of the current guidelines, the panel considered whether or not there were new data that could lead to a change in recommendations since the last ATS/IDSA guidelines were published. We also considered the availability of more recent guidelines from other organizations to avoid needless redundancy. Based on these considerations, the panel agreed that the guidelines on the prevention of VAP initially published by the Society for Healthcare and Epidemiology of America (SHEA) in 2008 [13], and updated in 2014 [14], made it unnecessary to include prevention recommendations in the present guidelines. The panel initially agreed that updated recommendations regarding the diagnosis and treatment of HCAP, HAP, and VAP were needed, given the existence of important new evidence since the publication of the prior guidelines in 2005.

Healthcare-Associated Pneumonia

The rationale for inclusion of the HCAP designation with the HAP/VAP guidelines in 2005 was that patients with HCAP were thought to be at high risk for MDR organisms by virtue of their contact with the healthcare system. Therefore, due to both the patients' contact with the healthcare system and the presumed high risk of MDR pathogens, guidelines for these patients were included with guidelines for HAP and VAP, the HAPs. However, in subsequent years, these 2 rationales for including HCAP with the HAP/VAP recommendations have come into question. There is increasing evidence from a growing number of studies that many patients defined as having HCAP are not at high risk for MDR pathogens [15–19]. Furthermore, although interaction with the healthcare system is potentially a risk for MDR pathogens, underlying patient characteristics are also important independent determinants of risk for MDR pathogens [15–17]. Even if HCAP would be considered as a separate clinical entity, it was thought that this could be included in the upcoming community-acquired pneumonia (CAP) guidelines because patients with HCAP, like those with CAP, frequently present from the community and are initially cared for in emergency departments. Finally, in light of the more recent data regarding the HCAP population, the panel anticipated that recommendations regarding coverage for MDR pathogens among community-dwelling patients who develop pneumonia would likely be based on validated risk factors for MDR pathogens, not solely on whether or not the patient had previous contacts with the healthcare system. For these reasons, the panel unanimously decided that HCAP should not be included in the HAP/VAP guidelines.

Definitions

The panel agreed that the definitions of HAP and VAP, as delineated in the 2005 guidelines [1], are clinically useful and generally accepted; therefore, the panel did not consider amending them. Pneumonia was defined in the 2005 document as the presence of "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." Nonetheless, the panel recognizes that there is no gold standard for the diagnosis of HAP or VAP. Furthermore, in the 2005 document and this update, HAP is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission. VAP is defined as a pneumonia occurring >48 hours after endotracheal intubation.

Much of the literature on this subject is complicated by inconsistent usage of the term HAP, with some using the term to denote any pneumonia developing in the hospital, and others excluding VAP from the HAP designation. In this document, the term "HAP" will denote episodes of pneumonia not associated with mechanical ventilation. Thus, HAP and VAP patients will belong to 2 mutually exclusive groups. In using this definition, we can avoid the use of the cumbersome term "non-ventilator-associated HAP," with occasional exceptions in the interest of clarity (eg, section headings or key tables).

We note the new entities of ventilator-associated events (including ventilator-associated conditions and infection-related ventilator-associated complications) introduced by the US Centers for Disease Control and Prevention as potential metrics to assess the quality of care provided to ventilated patients [20]. While the measurement of these events may be a useful concept for trending and benchmarking quality, these definitions were designed for the purposes of surveillance and quality improvement at the population level and not to aid in diagnosis and treatment decisions at the bedside. The panel therefore did not consider these definitions for the purposes of these guidelines.

METHODOLOGY

Guideline Panel Composition

The IDSA and ATS each elected one co-chair to lead the guideline panel. Dr Andre Kalil was elected to represent the IDSA and Dr Mark Metersky was elected to represent the ATS. A total of 18 subject-matter experts comprised the full panel, which included specialists in infectious diseases, pulmonary medicine, critical care medicine, laboratory medicine, microbiology, and pharmacology as well as a guideline methodologist. Two other societies, the Society of Critical Care Medicine

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(SCCM) and the SHEA, provided representatives with expertise in HAP and/or VAP. An expert in guideline methodology, Dr Jan Brozek, oversaw all methodological aspects of the guidelines. Ms Peggy Cruse, MLIS, and Ms Shandra L. Knight, MS, worked as the librarians in charge of all issues related to the systematic identification of scientific evidence and literature for all PICO (Patient/Population [P]; Intervention/Indicator[I]; Comparator/Control[C]; Outcome[O]) questions. Ms Jennifer J. Padberg, MPH, Ms Judy Corn, and Mr John Harmon were in charge of all administrative and logistic issues related to the guideline panel. Mr Shane McDermott and Ms Jennifer J. Padberg, MPH, were in charge of all conflicts of interest (COI) issues.

Disclosure and Management of Potential Conflicts of Interest

All prospective panelists were required to disclose any actual, potential, or perceived COI prior to being placed on the panel. The disclosures were used to categorize the panelists as cleared for full participation, allowed to participate with recusal from certain aspects of guideline development, or disqualified from participation. The co-chairs remained free of any financial COI during the entire guideline development process. They therefore avoided any relationships with pharmaceutical or device companies that had products in development or being marketed for pneumonia. Furthermore, all panelists were precluded from participating in any marketing-related activities (ie, lectures or advisory boards directly funded by a pharmaceutical or device company with interests related to the subject of these guidelines) during the entire process. Panelists were required to disclose to the ATS and IDSA and the chairs any new activities that had the potential to be viewed as a COI prior to engaging in the activity. Staff and members of the societies determined if specific activities were allowed under the societies' COI rules. Assignments of panelists to specific PICO questions were made as to minimize any COI concerns. At the beginning of each meeting, whether face-to-face or by teleconference, panelists were required to disclose any new potential COI or prior relevant COI to the subject matter to be discussed.

Clinical Questions and Evidence Review

An initial list of relevant clinical questions for these guidelines was created by the co-chairs and then submitted to the whole panel for review and discussion. After the committee prioritized the proposed topics via an online poll, the final set of clinical questions to be addressed was approved by the whole committee. All outcomes of interest were identified a priori and the guideline committee explicitly rated their importance for decision making. Each clinical question was assigned to a pair of panelists.

Two expert health sciences librarians (P. C. and S. L. K.) designed literature searches to address all of the clinical questions (see supplementary materials [21] for full search details). Searches were limited to studies performed in adults and those published in English or containing an English abstract. No publication year limits were used. The initial literature searches were performed in 2012 and 2013, and then updated in July 2014. Studies published up to November 2015 were included if pertinent to these guidelines. To supplement the electronic searches, as needed, panelists contacted experts and hand-searched journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles. The titles and abstracts of all identified citations were screened and all potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria.

The results of the literature searches were thoroughly reviewed by the panelists followed by selection and evaluation of the relevant articles. Once the articles were selected, the panelists in conjunction with the co-chairs and the methodologist decided if a qualitative and/or a quantitative analysis was appropriate. Panelists were not required to update their recently performed meta-analyses with results of the last search unless there was likelihood that doing so would result in a change to the strength or direction of a recommendation.

Evidence summaries for each question were prepared by the panel members using the GRADE approach for rating the confidence in the evidence [2]. The summaries of evidence were discussed and reviewed by all committee members and edited as appropriate. The values and preferences for a specific outcome could have a higher or lower value placed on it for different PICO questions; this variation happened because the value was always evaluated in the context of all other outcomes relevant to each PICO question. Once the analyses were completed, the panelists presented their data and findings to the whole panel for deliberation and drafting of recommendations. Literature search strategies, evidence tables, evidence profiles, and additional data, including meta-analysis results, can be found in the supplementary materials [21].

Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "weak" (conditional) according to the GRADE approach. The words "we recommend" indicate strong recommendations and "we suggest" indicate weak recommendations. Table 1 provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policy makers. Although there is arguably ongoing need for research on virtually all of the topics considered in this guideline, "Research Needs" were noted for recommendations in which the need was believed by the panelists to be particularly acute. High-quality evidence was lacking for many of the recommendations. Strong recommendations were sometimes made in the setting of lower-quality evidence when the panelists believed that most individuals would desire the recommended course of action, and that most well-informed clinicians would agree, despite the low-

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quality evidence. All members of the panel participated in the preparation of the guideline and approved the final recommendations. Feedback was obtained from external peer reviewers. The American College of Chest Physicians (CHEST), SCCM and the SHEA reviewed and endorsed the guideline. The IDSA Standards and Practice Guidelines Committee, the IDSA Board of Directors, and the ATS Board of Directors reviewed and approved the guideline prior to dissemination.

RISK FACTORS FOR ANTIBIOTIC RESISTANCE IN VAP AND HAP

Because issues surrounding antibiotic resistance are fundamental to the consideration of many of the clinical questions addressed by this guideline, we undertook a series of systematic reviews and meta-analyses to better understand risk factors for MDR in both VAP and HAP. In these meta-analyses, we studied risk factors for MDR in general, in addition to risk factors for specific classes of organisms. The findings do not lead to any specific recommendations, rather they provided guidance for the panelists for several of the treatment recommendations. If more than one study was available for any risk factor, then random-effects modeling was used for the pooled estimates and their confidence intervals (CIs).

Risk Factors for VAP Caused by Any MDR Organism

Risk factors for MDR VAP have been addressed in several studies (Table 2). Overall, 54 studies were identified in the literature search, and 39 were excluded because of duplicate publication (n = 1), lack of a comparator (n = 34), or nonclinical focus (n = 4). Fifteen potential risk factors were included in the meta-analysis.

Factors associated with an increased risk of MDR VAP vs non-MDR VAP were use of intravenous antibiotics in the past 90 days (odds ratio [OR], 12.3; 95% CI, 6.48–23.35) [22–24], ≥5 days of hospitalization prior to the occurrence of VAP [23, 25–29], septic shock at the time of VAP (OR, 2.01; 95% CI, 1.12–3.61) [24, 30], acute respiratory distress syndrome (ARDS) before VAP (OR, 3.1; 95% CI, 1.88–5.1) [22, 24], and acute renal replacement therapy prior to VAP (OR, 2.5; 95% CI, 1.14–5.49) [22]. Coma present at the time of ICU admission was associated with lower risk of MDR VAP (OR, 0.21; 95% CI, .08–.52) [22]. Use of systemic corticosteroids was associated with an increased risk of MDR VAP in only one study [23], but due to the lack of reporting on specific dose and duration in addition to the lack of replication by other studies, corticosteroid use was not accepted by the panel as a risk factor for MDR VAP. Potential risk factors that were not found to be consistently associated with resistant organisms in our analysis are listed in the supplementary materials [21].

Prior exposure to intravenous antibiotics has been consistently identified as a predisposing factor to MDR pathogens in VAP. While early antimicrobial therapy has been reported to lessen the risk of VAP due to antibiotic-susceptible gram-positive cocci and *Haemophilus influenzae*, it has been implicated in the rise of MDR VAP due to MRSA, *Pseudomonas*, and other non-glucose-fermenting organisms late in the course of hospitalization [24, 31–33]. This emphasizes the need for judicious selection of patients for antibiotic therapy.

Other underlying clinical conditions may influence the microbiology of VAP. Sepsis may alter the response of cellular elements that comprise the innate immune system [34]. The protracted immunosuppressive phase following the hyperinflammatory response in sepsis diminishes the host ability to clear MDR pathogens that are selected following early administration of antibiotics. Studies of patients with ARDS have also noted a higher incidence of MRSA and non-glucose-fermenting gram-negative bacilli [35]. The onset of VAP appears to be delayed in ARDS patients, probably because of the near-universal use of antibiotics early in the course of ARDS. When VAP does occur, however, the microbial causes appear no different than those among patients without ARDS who have required mechanical ventilation for similar periods of time and who have experienced similar levels of exposure to antibiotic therapy [36]. In contrast, coma upon ICU admission had a protective effective against MDR VAP. This effect is related to the increased propensity of neurotrauma patients to develop VAP early in their ICU admission.

The concept of early- and late-onset pneumonia is based on data from the late 1980s demonstrating that about 50% of mechanically ventilated patients developed VAP within the first 4 days after admission [37]. This concept has been subject to validation in several subsequent studies. The study by Ewig et al comprehensively illustrates the pathogenesis and the rationale behind it [38]. First, it could be demonstrated that upper airway colonization was an independent predictor of subsequent tracheobronchial colonization. Second, colonization patterns in the upper and lower airways changed within the first 3–4 days from a community-like to a typical nosocomial pattern. Third, colonization with community-like patterns was associated with early-onset pneumonia, whereas nosocomial patterns were associated with a risk of late-onset pneumonia. Finally, antimicrobial prophylaxis with 1 or 2 dosages of a cephalosporin decreased the risk of colonization with community-like pathogens, and subsequently, early-onset VAP was a risk factor for subsequent colonization with typical nosocomial pathogens and increased the risk of late-onset VAP. Others found that the threshold may also be extended to 7 days [24].

Several subsequent studies have questioned the relationship between the timing of VAP and the risk of MDR organisms. No significant differences between pathogen patterns in early and late VAP were found [23, 25–29]. These studies, however, varied in their definitions of important concepts such as the definition of "time zero" and risk factors for MDR. In fact, the concept of early vs late VAP should be based on hospital

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admission as the starting point, rather than intubation, as intubation may have taken place after several days of hospitalization, thus resulting in a patient already colonized in the upper and lower airways with typically nosocomial pathogens. Moreover, the presence of risk factors for MDR should take precedence over the distinction between early- and late-onset pneumonia. Hence, timing of developing VAP should be evaluated in the context of other risk factors and recent antibiotic treatment. Nonetheless, the reviewed evidence suggests that overall, patients who develop VAP after >5 days of hospitalization are at higher risk of infection with MDR organisms than patients who develop VAP earlier in their hospitalization.

Risk Factors for MDR HAP

Risk factors for MDR HAP have only rarely been studied (Table 2). Fifteen potential risk factors were included in our meta-analysis. Only one risk factor was significantly associated with MDR HAP: prior intravenous antibiotic use (OR, 5.17; 95% CI, 2.11–12.67) [39, 40]. While other risk factors may be relevant, evidence is lacking. With regard to the early vs late pneumonia concept, no data are available for HAP.

Risk Factors for HAP/VAP Due to MRSA

A small number of studies have specifically addressed risk factors for nosocomial pneumonia due to MRSA (Table 2). Most studies analyzed risk factors for MRSA colonization. Overall, 14 variables have resulted in potential predictive factors in 3 studies [41–43].

While nosocomial pneumonia due to MRSA may be associated with several variables reflecting mainly patient characteristics, severity of disease, as well as specific treatments and interventions, the most consistent body of evidence regarding risk factors for MRSA was related to the prior use of intravenous antibiotics. Prior antibiotic treatment is a recognized risk factor for MRSA infection; however, less attention has been paid to the question of which specific antimicrobial classes are the most predictive. Furthermore, MRSA pneumonia is more often seen in late-onset pneumonia than in early-onset pneumonia [42].

Active case finding of colonized patients and implementation of isolation and decolonization strategies may also have a complementary role in the reduction of MRSA infections. Some studies have shown that MRSA colonization is associated with an increased likelihood of isolation of MRSA from respiratory samples [44], including samples exclusively from patients diagnosed with pneumonia [45], while at least one other study did not demonstrate this association [46]. However, to our knowledge, there are no studies that have prospectively evaluated the use of MRSA screening to inform empiric treatment choices.

While there are several potential risk factors for MRSA pneumonia, the published evidence for most of these is scarce and of low quality. Based on the limited data, the panel agreed that the prior use of intravenous antibiotics was the most predictive risk factor for MRSA pneumonia. There is also some evidence suggesting that a positive MRSA screen from nasal or respiratory samples may increase the risk of MRSA being cultured from respiratory samples, but not enough evidence to definitively list this as a risk factor for MRSA pneumonia (see section X).

Risk Factors for HAP/VAP Due to MDR *Pseudomonas aeruginosa*

Seven variables were evaluated in 2 studies investigating the association between *P. aeruginosa* and nosocomial pneumonia (Table 2) [30, 47]. Direct comparison of available studies is difficult owing to the varied definitions used for multidrug resistance. When focusing on case–control studies using more stringent definitions of multidrug resistance (ie, resistance to multiple classes of antipseudomonal antimicrobials), prior use of antibiotics, mechanical ventilation, and history of chronic obstructive pulmonary disease have been identified as potential risk factors for MDR P. aeruginosa infection. Furthermore, although there are limited data in HAP/VAP patients, patients with cystic fibrosis and bronchiectasis are more likely than patients with other pulmonary diseases to be chronically colonized with *P. aeruginosa* and are therefore also likely at increased risk for MDR *P. aeruginosa*. When looking specifically at antibiotics associated with the isolation of MDR P. aeruginosa, prior receipt of carbapenems, broad-spectrum cephalosporins, and fluoroquinolones have been identified as independent risk factors. While there are several potential risk factors, the published evidence is scarce and of low quality. Based on the limited analysis, the panel agreed that the prior use of intravenous antibiotics was the most predictive risk factor for MDR *Pseudomonas* pneumonia.

DETERMINING ETIOLOGY OF HAP AND VAP

Because of the growing frequency of MDR organisms as a cause of VAP, as well as the risks of initial ineffective therapy, experts believe that cultures of respiratory secretions should be obtained from virtually all patients with suspected VAP [1]. The panelists were in agreement with this practice. Given the widespread acceptance of this tenet at the bedside and the likelihood that few data would be found to address this question, panel members decided that this issue would not be formally addressed in this document. Therefore, the following sections related to VAP diagnosis presume that cultures of respiratory secretions would be obtained from all patients with suspected VAP.

The panelists recognized that the underlying evidence in support of blood cultures for patients with VAP is limited. However, approximately 15% of patients with VAP are bacteremic [48–50], and in these patients the definitive identification of a pathogen, often MDR, may alter management. Some studies have found that patients with bacteremic VAP are at higher risk of morbidity and mortality than nonbacteremic patients [49–51]. It should be recognized that at least 25% of

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positive blood cultures in suspected VAP patients are from a nonpulmonary source. Thus, blood cultures results might provide evidence of a nonpulmonary source of infection and might reveal bacteria that are not effectively treated by empiric VAP therapy, a potentially important finding given the nonprecise nature of VAP diagnosis [49, 50]. For these reasons, the panelists have not revised the 2005 ATS/IDSA guidelines recommendation and remain in favor of blood cultures for all patients with suspected VAP. Data are even more limited for patients with HAP, in whom sputum samples are less commonly available than in patients with VAP. However, bacteremic HAP is not unusual [52]; therefore, blood culture results may provide further guidance for both antibiotic treatment and treatment de-escalation for HAP and VAP.

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, BAL, PSB) and blind bronchial sampling (ie, mini-BAL). Noninvasive respiratory sampling refers to endotracheal aspiration.

Summary of the Evidence

Our systematic review identified 5 relevant randomized trials [53–57]. In 3 of the trials, invasive sampling (bronchoscopy or blind bronchial sampling) with quantitative cultures was compared to noninvasive sampling (endotracheal aspiration) with semiquantitative cultures [53, 54, 57]; in the remaining 2 trials, invasive sampling with quantitative cultures was compared to noninvasive sampling with quantitative cultures [55, 56]. No trials were identified that compared noninvasive sampling with quantitative cultures to noninvasive sampling with semiquantitative cultures.

The trials did not identify any significant differences in 28-day mortality, overall mortality, length of ICU stay, duration of mechanical ventilation, or antibiotic changes [53, 54, 57]. The 2 trials that compared invasive sampling with quantitative cultures to noninvasive sampling with quantitative cultures evaluated antibiotic changes; one demonstrated that invasive sampling led to more antibiotic changes than noninvasive sampling (42% vs 15%; relative risk [RR], 2.81, 95% CI, 1.01–7.81) [56], whereas the other found no difference [55]. Two of the trials that compared invasive sampling with quantitative cultures to noninvasive sampling with semiquantitative cultures measured antibiotic days: one demonstrated more antibiotic-free days in the invasive sampling group (5.0 days vs 2.2 days; $P < .001$) [54], whereas the other found no difference [53]. The trial that found no difference in antibiotic days excluded patients who were infected or colonized with *Pseudomonas* species or MRSA. Therefore, they were able to use monotherapy and there was less opportunity to deescalate antibiotics, potentially biasing the results toward no effect [53]. There was no difference in the emergence of antibiotic resistance in the only study that looked at this outcome [54]; no other information regarding adverse events was reported in any of the trials.

When the 5 trials were pooled via meta-analysis, sampling technique did not affect any clinical outcome, including mean duration of mechanical ventilation, ICU length of stay, or mortality [58].

Taken together, the evidence suggests that outcomes are similar regardless of whether specimens are obtained invasively or noninvasively, and whether cultures are performed quantitatively or semiquantitatively. The evidence provides low confidence in the effects estimated by the trials due to risk of bias (lack of blinding in some trials, possible selection bias), indirectness (differing protocols), and imprecision (3 of the trials included small numbers of patients) [55–57].

We summarized the performance characteristics of several sampling techniques—endotracheal aspirates (ETAs), BAL, and PSB—for informational purposes only; the performance characteristics were not used to inform our recommendation. The performance characteristics were estimated by pooling data from studies that used histopathology as the reference standard. Nine such studies were identified [59–67]. None of the tests had ideal performance characteristics. Generally, semiquantitative ETAs were the most sensitive, but least specific test [59–61, 64]. Quantitative ETAs and quantitative BAL had near-equivalent intermediate-level performance. Sensitivity ranged from 48% (95% CI, 38%–57%) for PSB with $\geq 10^3$ CFU/mL to 57% (95% CI, 47%–66%) for quantitative BAL to 75% (95% CI, 58%–88%) for ETA with any amount of growth. Specificity ranged from 47% (95% CI, 29%–65%) for ETA with any amount of growth to 80% (95% CI, 71%–88%) for quantitative BAL to 83% (95% CI, 70%–92%) for ETA with $\geq 10^5$ CFU/mL. Positive predictive values ranged from 60% (95% CI, 49%–71%) for PSB with $\geq 10^3$ CFU/mL and 61% (95% CI, 45%–76%) for ETAs with any amount of growth to 77% (95% CI, 66%–85%) for BAL with $\geq 10^4$ CFU/mL and 81% (95% CI, 67%–91%) for ETAs with $\geq 10^5$ CFU/mL.

Rationale for the Recommendation

There is no evidence that invasive microbiological sampling with quantitative cultures improves clinical outcomes

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compared with noninvasive sampling with either quantitative or semiquantitative cultures. 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 these reasons, noninvasive sampling with semiquantitative cultures is the microbiological sampling technique recommended by the panel.

The guideline panel acknowledged that there is a potential that invasive sampling with quantitative cultures could lead to less antibiotic exposure if growth below defined thresholds (eg, 10^3 CFU/mL for PSB, 10^4 CFU/mL for BAL) is used as a trigger to stop antibiotics [68]. This outcome is important due to the risks of acquiring antibiotic resistance, the risk of side effects, and the costs of unnecessary or excessive antibiotic therapy; however, the estimated effects of invasive sampling with quantitative culture on antibiotic exposure are inconsistent and, therefore, insufficient to guide therapy at this time [53–55]. Of note, lower respiratory (eg, BAL, mini-BAL, brush, wash, ETA) and sputum samples should be processed within 2 hours if kept at room temperature and within 24 hours if kept at 4 degrees Celsius [69].

Research Needs

The panel agreed that the question of whether or not invasive sampling with quantitative cultures reduces antibiotic use, antibiotic resistance, direct costs, and indirect costs should be a priority area for future research. In addition, the panel agreed that such trials should measure adverse outcomes, as most trials to date have only evaluated beneficial outcomes.

II. If Invasive Quantitative Cultures Are Performed, Should Patients With Suspected VAP Whose Culture Results Are Below the Diagnostic Threshold for VAP (PSB With $<10^3$ 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.

Summary of the Evidence

Although we do not recommend routine performance of invasive quantitative cultures for patients with suspected VAP, the panel recognizes that many clinicians feel that they are of benefit in decreasing inappropriate antibiotic use and will likely continue performing them, given the low quality of evidence on which the recommendation against their performance was based. We therefore decided to address the issue of the safety of antibiotic discontinuation when quantitative cultures are below the diagnostic threshold. We identified 6 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 $<10^3$ CFU/mL, a BAL of $<10^4$ CFU/mL, and an ETA of $<10^5$ CFU/mL [54, 68, 70–73]. We excluded 20 studies that either did not withhold antibiotics on the basis of the culture results or did not measure the utilization of antibiotics once the culture results were known [53, 55–57, 74–88].

Only one of the selected studies was a randomized trial [54]. The trial randomly assigned patients with possible VAP to either bronchoscopic sampling with quantitative cultures or the use of clinical criteria alone to diagnose VAP. This trial found that bronchoscopic sampling with quantitative cultures decreased 14-day mortality and antibiotic use. However, it did not compare outcomes among those whose antibiotics were withheld on the basis of the culture results to those whose antibiotics were continued.

Because the randomized trial did not answer our question, we next evaluated the 5 observational studies [68, 70–73]. Only 2 of the studies compared outcomes among those whose antibiotics were withheld on the basis of the invasively obtained quantitative culture results to those whose antibiotics were continued despite the culture results. The first study was a prospective cohort study of 68 patients with suspected VAP, in which the prevalence of VAP among those undergoing invasive sampling was 51%. Patients whose antibiotics were discontinued on the basis of the quantitative cultures had a similar mortality and rate of new respiratory infection as those whose antibiotics were continued [71]. The second study was a retrospective cohort study of 89 patients with suspected VAP whose invasively obtained quantitative cultures were below the diagnostic threshold for VAP [68]. Similar to the other observational study, patients whose antibiotics were discontinued did not have a higher mortality or rate of new respiratory infection compared to patients whose antibiotics were continued. However, those whose antibiotics were withheld received a shorter duration of antibiotics, had a lower rate of total superinfection, and a lower rate of MDR superinfection.

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Taken together, the evidence indicates that patients whose antibiotics are withheld on the basis of an invasive quantitative culture below the diagnostic threshold for VAP have similar clinical outcomes, less antibiotic use, and better microbiologic outcomes compared to patients whose antibiotics are continued. The panel's confidence in these estimated effects (ie, the quality of evidence) was very low because they were derived from observational studies with imprecision (ie, small studies with few events) and high risk of bias (clinicians may have been more likely to stop antibiotics early in less sick patients).

Rationale for the Recommendation

Antibiotic discontinuation in patients with suspected VAP whose invasive quantitative culture results are below the diagnostic threshold for VAP may be beneficial. It decreases unnecessary antibiotic use, which should reduce antibiotic-related adverse events (eg, *Clostridium difficile* colitis and promotion of antibiotic resistance) and costs. Moreover, it improves microbiological outcomes (ie, fewer superinfections). While there is no evidence that this approach worsens clinical outcomes, in theory it could result in antibiotics being withdrawn from some patients who would benefit from antibiotic therapy because the quantitative culture results were misleadingly low due to sampling error or prior exposure to antibiotics.

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.

Summary of the Evidence

We found only one randomized trial that compared empiric antibiotic therapy with therapy based on the results of microbiologic studies in patients with suspected HAP [89]. Sixty-eight patients with HAP were randomly assigned to undergo bronchoscopy with protected specimen brushing vs noninvasive management. In the latter group, expectorated sputum samples were not obtained, so noninvasive management resulted in empiric therapy, which was supposed to adhere to the recommendations from the 2005 ATS/IDSA guidelines [1]. There was no difference among the 2 groups in either clinical cure at 28 days or hospital length of stay. There was lower 28-day mortality in the empirically treated group than the invasive group, but this was not statistically significant (10% vs 21.9%; RR, 0.46; 95% CI, .13–1.61). This evidence provided very low confidence in the estimated effects of microbiologic studies because there was very serious risk of bias (fewer patients in the invasive group received antibiotics than in the noninvasive group [76% vs 100%], lack of blinding, lack of concealment) and imprecision.

Rationale for the Recommendation

Despite a lack of evidence showing that respiratory cultures in patients with suspected HAP improve clinical outcomes, the panel agreed that an attempt should be made to obtain respiratory samples for culture. The rationale for this suggestion is that resistant pathogens lead to a significant risk of inadequate initial empiric antibiotic therapy [90, 91], which is associated with an increased risk of mortality in patients with HAP [92]. Having culture results means that the antibiotic regimen can be adjusted on the basis of those results if the patient does not respond to initial therapy. Furthermore, performing cultures of respiratory samples provides the opportunity to de-escalate antibiotic coverage based on the results, minimizing unnecessary antibiotic exposure. The panel acknowledges the potential for false-positive results related to oral contamination when noninvasive samples are obtained, but judged that the risks of inadequate initial coverage and the potential benefit of allowing de-escalation outweigh the negative impact of false-positive culture results.

The panel further agreed that the respiratory specimens should be obtained noninvasively rather than invasively. The panel considered potential advantages of invasive sampling, which might include less risk of inadequate initial antibiotic coverage [90–92] and facilitation of antibiotic de-escalation. However, there is no evidence in patients with HAP that either of these goals would be frequently realized with regular use of invasive sampling. Furthermore, routine use of invasive sampling via bronchoscopy would be associated with increased cost and increased risks to the patient. Although generally safe, bronchoscopy may rarely cause life-threatening complications [93] and BAL results in temporary worsening of gas exchange both due to sedating medications and the lavage itself [94], and this could result in the need for respiratory support. The potential advantages of obtaining invasive cultures (less risk of inadequate initial coverage, de-escalation of antibiotic therapy) may not outweigh the disadvantages (negative impact

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of false-positive culture) of noninvasive techniques once the costs and risks of the invasive procedure are added as potential disadvantages.

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

IV. In Patients With Suspected HAP/VAP, Should 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).*

Summary of the Evidence

PCT is a precursor of calcitonin that is constitutively secreted by C cells of the thyroid gland and K cells of the lung [95]. In healthy individuals, PCT is normally undetectable (<0.01 ng/mL). When stimulated by endotoxin, PCT is rapidly produced by parenchymal tissue throughout the body [96]; this PCT production has also been observed in diverse types of bacterial infections [97, 98]. PCT may increase in response to sterile inflammation or viral infection, but it is less common [99]. This characteristic makes PCT a potentially valuable diagnostic test for the diagnosis of HAP/VAP.

We sought studies that enrolled patients with suspected HAP/VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon serum PCT levels plus clinical criteria with outcomes among patients for whom therapy was based upon clinical criteria alone. We found no such studies; therefore, we selected 6 studies that reported the performance characteristics for serum PCT for the diagnosis of HAP/VAP, generally diagnosed according to the 2005 guideline definitions [1, 100–105]. Our underlying assumption was that serum PCT results indicative of HAP/VAP will prompt antibiotic therapy, which will improve clinical outcomes. The immunoluminometric method was used to measure serum PCT in 2 studies, and the Kryptor test using time-resolved amplified cryptate emission technology was used to measure serum PCT in 4 studies. The cutoffs used to distinguish patients who had HAP/VAP from those who did not varied among studies, ranging from 0.5 to 3.9 ng/mL. Some studies reported results for varying thresholds. None of the cutoffs used in the studies were subsequently validated.

We pooled the performance characteristics of serum PCT for the diagnosis of HAP/VAP via a meta-analysis using a bivariate regression approach. The 6 studies included 665 participants, among whom 335 (50.4%) were ultimately diagnosed with HAP/VAP. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic OR were 67% (95% CI, 53%–79%), 83% (95% CI, 43%–97%), 3.9 (95% CI, .9–17.5), 0.4 (95% CI, .25–.62), and 10 (95% CI, 2–59), respectively. The optimal PCT diagnostic thresholds differed according to the severity of presentation, clinical setting, and type of assay used. The summary receiver operating characteristic (SROC) curve resulted in an area under the curve (AUC) of 0.76 (95% CI, .72–.79), which indicates moderate overall test accuracy.

The panel's confidence in the accuracy of these pooled performance characteristics (ie, the quality of evidence) was moderate because they were derived from accuracy studies with a serious risk of bias. The risk of bias was multifactorial. Many studies did not report enrolling consecutive patients, did not report enrolling patients with a legitimate diagnostic uncertainty (some studies required prior microbiological confirmation of HAP/VAP), did not explain the reasons for withdrawals, did not report blinding the outcome assessor, and may have chosen diagnostic thresholds that gave more favorable results.

The meta-analysis revealed inconsistency of the evidence (heterogeneity analysis $I^2 = 87.9$; $P < .001$). However, the panel did not downgrade the quality of evidence due to the inconsistency because the performance characteristics were similar even after the heterogeneity was reduced by excluding certain studies. Causes of the heterogeneity included the methodological quality of the studies, the clinical setting (ie, whether the study was conducted in a surgical or medical unit), and the type of PCT assay. There was no evidence of potential publication bias according to Egger test for funnel plot asymmetry.

Rationale for the Recommendation

The systematic review identified no studies that enrolled patients with suspected HAP/VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon serum PCT levels plus clinical criteria vs outcomes among patients for whom therapy was based upon clinical criteria alone. Therefore, the guideline development panel used accuracy studies to inform its recommendations.

The panel decided a priori that it would recommend that antibiotics be initiated or withheld on the basis of serum PCT testing plus clinical criteria, rather than clinical criteria alone, if HAP/VAP can be confirmed or excluded by serum PCT with a sensitivity and specificity of >90%. These thresholds were set because, assuming a prevalence of HAP/VAP of 50% among those who undergo testing, then for every 1000 patients tested, only 50 patients (5%) would be incorrectly categorized as having or not having HAP/VAP.

The evidence indicates that serum PCT plus clinical criteria can diagnose HAP/VAP with a sensitivity and specificity of 67% and 83%, respectively. These findings failed to meet the panel's prespecified thresholds for recommending that serum PCT plus clinical criteria be used to decide whether or not to initiate

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antibiotics. The false-negative and false-positive rates of serum PCT testing plus clinical criteria are 33% and 17%, respectively. Thus, assuming a prevalence of HAP/VAP of 50%, then for every 1000 patients with suspected HAP/VAP who are evaluated with serum PCT plus clinical criteria, 165 patients (16.5%) would be incorrectly diagnosed as not having HAP/VAP and 85 patients (8.5%) will be incorrectly diagnosed as having HAP/VAP.

A recent trial that randomized ICU patients to a PCT-guided antibiotic escalation protocol vs standard of care, aiming to improve survival by increasing early appropriate antibiotic 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 [106].

In the view of the guideline panelists, patients who are incorrectly diagnosed with HAP/VAP are likely to receive antibiotics and, therefore, are at unnecessary risk for side effects and incur unnecessary costs. Perhaps more important, efforts to find the correct diagnosis may cease, increasing the time until correct diagnosis and therapy. Conversely, incorrectly excluding HAP/VAP delays the initiation of antibiotic therapy, which may lead to poorer clinical outcomes. The panel agreed that the frequency of such undesirable consequences due to misleading PCT results was unacceptable and, therefore, recommended not using PCT to guide antibiotic initiation.

V. In Patients With Suspected HAP/VAP, Should 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 BALF sTREM-1 plus clinical criteria, to decide whether or not to initiate antibiotic therapy *(strong recommendation, moderate-quality evidence)*.

Summary of the Evidence

Triggering receptor expressed on myeloid cells (TREM-1) has been studied as a biological marker of microbial infection. TREM-1 is a member of the immunoglobulin superfamily that has been shown to be strongly expressed on the neutrophils and monocytes infiltrating tissues invaded by bacteria or fungi [107]. However, its use in diagnosing infections is uncertain because several recent studies suggest sTREM-1 may also be elevated in noninfectious causes of inflammation [108, 109].

We sought studies that enrolled patients with suspected HAP/VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon soluble TREM-1 (sTREM-1) levels plus clinical criteria with outcomes among patients for whom therapy was based upon clinical criteria alone. We found no such studies; therefore, we selected 6 studies that reported the performance characteristics for sTREM-1 for the diagnosis of HAP/VAP [110–115]. Our underlying assumption was that sTREM-1 results indicative of HAP/VAP would prompt antibiotic therapy, which would improve clinical outcomes. The measurement of sTREM-1 was performed on BALF by immunoblot in one study [115], on BALF by enzyme-linked immunosorbent assay (ELISA) in 4 studies [110–114], and on mini-BALF by ELISA in one study [114]. The cutoff values used to distinguish patients who had HAP/VAP from those who did not varied widely among studies, ranging from 5 to 900 pg/mL.

We pooled the performance characteristics of sTREM-1 for the diagnosis of HAP/VAP via a meta-analysis using a bivariate regression approach. Our meta-analysis included 208 patients with clinically suspected pneumonia, of whom 108 (52%) were ultimately diagnosed with pneumonia. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic OR were 84% (95% CI, 63%–94%), 49% (95% CI, 18%–81%), 1.6 (95% CI, .8%–3.3), 0.33 (95% CI, .12–0.93), and 5 (95% CI, 1–24), respectively. The sensitivity and specificity of sTREM-1 were lower in studies that used ELISA [110–114] than in studies that used an immunoblot technique [115]. The optimal sTREM-1 diagnostic thresholds differed according to the severity of presentation, clinical setting, and type of assay used. The SROC curve resulted in an AUC of 0.78 (95% CI, .75–.82), which indicates moderate overall test accuracy.

The panel's confidence in the accuracy of these pooled performance characteristics (ie, the quality of evidence) was moderate because they are derived from accuracy studies with serious risk of bias. The risk of bias is due to the studies not enrolling consecutive patients with legitimate diagnostic uncertainty (one study used clinical plus microbiological results as inclusion criteria [115], whereas 5 studies used clinical, radiological, and microbiological findings as inclusion criteria [110–114]). Moreover, because the studies in the meta-analysis used BALF quantitative culture as the reference standard, the prior use of antibiotics may have resulted in more negative cases and participants with anaerobic infections may have been misclassified, which could have altered the performance characteristics of sTREM-1.

Rationale for the Recommendation

Our systematic review identified no studies that enrolled patients with suspected HAP/VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon soluble sTREM-1 levels plus clinical criteria vs outcomes among patients for whom therapy was based upon clinical criteria alone. Therefore, the guideline development panel used accuracy studies to inform its recommendations.

The panel decided a priori that it would recommend that antibiotics be initiated or withheld on the basis of BALF sTREM-1 testing plus clinical criteria, rather than clinical criteria alone, if HAP/VAP could be confirmed or excluded by BALF sTREM-1

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with a sensitivity and specificity of >90%. These thresholds were set because, assuming a prevalence of HAP/VAP of 50% among those who undergo testing, then for every 1000 patients tested, only 50 patients (5%) will be incorrectly categorized as having or not having HAP/VAP.

The evidence indicates that BALF sTREM-1 can diagnose HAP/VAP with a sensitivity and specificity of 84% and 49%, respectively. These findings failed to meet the panel's prespecified thresholds for recommending that BALF sTREM-1 plus clinical criteria be used to decide whether or not to initiate antibiotics. The false-negative and false-positive rates of BALF sTREM-1 are 16% and 51%, respectively. Thus, again assuming a prevalence of HAP/VAP of 50%, then for every 1000 patients tested, 80 patients (8%) will be incorrectly diagnosed as not having HAP/VAP and 255 patients (25.5%) will be incorrectly diagnosed as having HAP/VAP.

Patients who are incorrectly diagnosed with HAP/VAP are likely to receive antibiotics and, therefore, are at unnecessary risk for side effects and incur unnecessary costs. Perhaps more important, efforts to find the correct diagnosis may cease, increasing the duration until correct diagnosis and therapy. Conversely, incorrectly excluding HAP/VAP delays the initiation of antibiotic therapy, which may lead to poorer clinical outcomes. The panel agreed that the frequency of such undesirable consequences due to misleading BALF sTREM-1 results was unacceptable and, therefore, recommended not using BALF sTREM-1 to guide antibiotic therapy.

VI. In Patients With Suspected HAP/VAP, Should 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)*.

Summary of the Evidence

We sought studies that enrolled patients with suspected HAP/VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon CRP levels plus clinical criteria with outcomes among patients for whom therapy was based upon clinical criteria alone. We found no such studies; therefore, we selected 3 studies that evaluated the ability of CRP to identify patients with VAP [102, 115, 116].

One observational study enrolled 148 patients receiving mechanical ventilation and then found that the CRP levels in patients who had pneumonia were the same as in those who did not [115]. A similar study that enrolled 44 patients receiving mechanical ventilation found no differences in the CRP levels of patients who had VAP compared with those who did not [102]. Finally, in a study of 28 patients who had a return of spontaneous circulation after an out-of-hospital arrest, the CRP levels were the same among patients with and without VAP [116]. Taken together, these studies suggest that CRP cannot reliably distinguish patients with VAP from patients without VAP.

The panel's confidence in the findings that CRP levels are similar among patients with and without VAP was low because the findings are from observational studies with serious imprecision (ie, few patients and events).

Rationale for the Recommendation

For a diagnostic test to be helpful in deciding whether or not to initiate or withhold antibiotics for VAP, it must be capable of distinguishing patients with VAP from patients without VAP. All 3 studies suggest that CRP levels do not make this distinction. Therefore, the panel judged that CRP testing was just as likely to lead clinicians astray as it is to help clinicians and, therefore, the benefits of using CRP levels to inform decision making in patients with possible VAP does not outweigh the costs and burdens of testing.

VII. In Patients With Suspected HAP/VAP, Should the Modified 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*).

Summary of the Evidence

Clinical criteria have historically informed the need to start antibiotics in patients with suspected HAP/VAP. However, semiobjective measures such as the CPIS have emerged as a potential tool to assist clinicians in deciding whether or not to initiate antimicrobial therapy for patients with suspected VAP. The CPIS is a semiobjective assessment of several clinical factors predictive of pneumonia; temperature, white blood cell count, presence and character of respiratory secretions, PaO_2/FiO_2 (arterial oxygen partial pressure/inspired oxygen fraction) ratio, and chest radiograph findings.

We sought studies that enrolled patients with suspected HAP/VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon the CPIS plus clinical criteria with outcomes among patients for whom therapy was based upon clinical criteria alone. We found no such studies; however, we found a published systematic review with meta-analysis of 13 accuracy studies that reported the performance characteristics of the CPIS for the diagnosis of VAP [117–121]. The pooled prevalence of VAP in the studies was 48%. The meta-analysis found that the CPIS can confirm or exclude VAP with a sensitivity, specificity, and diagnostic OR of 65% (95% CI, 61%–69%), 64% (95% CI, 60%–67%), and 4.84 (95% CI, 2.42–9.71), respectively. The SROC curve resulted in an AUC of 0.748 (95% CI, .65–.85).

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The panel's confidence in the accuracy of these pooled performance characteristics (ie, the quality of evidence) was low because they are derived from accuracy studies with serious risk of bias (ie, many studies did not enroll consecutive patients with true diagnostic uncertainty, withdrawals were not explained) and inconsistency (heterogeneity analysis $I^2 > 87\%$ for all pooled analyses).

Rationale for the Recommendation

Our systematic review identified no studies that enrolled patients with suspected VAP and then compared outcomes among patients for whom the initiation of antibiotic therapy was based upon the CPIS plus clinical criteria vs outcomes among patients for whom therapy was based upon clinical criteria alone. Therefore, the guideline development panel used a published systematic review and meta-analysis of accuracy studies to inform its recommendations.

The panel decided a priori that it would recommend that antibiotics be initiated or withheld on the basis of the CPIS plus clinical criteria, rather than clinical criteria alone, if VAP can be confirmed or excluded by the CPIS with a sensitivity and specificity of >90%. These thresholds were set because, assuming a prevalence of VAP of 48% among those who undergo testing, then for every 1000 patients tested, only 48 patients (4.8%) will be incorrectly categorized as having or not having VAP.

The evidence indicates that the CPIS can diagnose VAP with a sensitivity and specificity of only 65% and 64%, respectively. These findings failed to meet the panel's prespecified thresholds for recommending that the CPIS plus clinical criteria be used to decide whether or not to initiate antibiotics. The false-negative and false-positive rates of the CPIS are 35% and 36%, respectively. Thus, again assuming a prevalence of VAP of 48%, then for every 1000 patients tested, 168 patients (16.8%) will be incorrectly diagnosed as not having HAP/VAP and 187 patients (18.7%) will be incorrectly diagnosed as having VAP.

Patients who are incorrectly diagnosed with HAP/VAP are likely to receive antibiotics and, therefore, are at unnecessary risk for side effects and incur unnecessary costs. Perhaps more important, efforts to find the correct diagnosis may cease, increasing the duration until correct diagnosis and therapy. Conversely, incorrectly excluding HAP/VAP delays the initiation of antibiotic therapy, which may lead to poorer clinical outcomes. The panel agreed that the frequency of such undesirable consequences due to misleading CPIS results was unacceptable and, therefore, recommended not using CPIS to guide antibiotic therapy.

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)*.

Summary of the Evidence

To determine whether or not treatment for VAT is warranted, we sought evidence that the treatment of VAT improves clinical outcomes. VAT has been defined as fever with no other recognizable cause, with new or increased sputum production, positive ETA culture (>10^6 CFU/mL) yielding a new bacteria, and no radiographic evidence of nosocomial pneumonia [122].

Our systematic review identified 3 randomized trials that compared the effects of antibiotics to either placebo or no antibiotics in patients with VAT [123–125]. However, the panel decided to exclude 2 of the trials because they were too indirectly related to the clinical question, as they defined VAT differently than all other studies and evaluated aerosolized antibiotics rather than intravenous antibiotics [124, 125]. The remaining randomized trial randomly assigned 58 patients to receive either intravenous antibiotics or no antibiotics for 8 days [123]. The group that received antibiotic therapy had lower ICU mortality (18% vs 47%; OR, 0.24, 95% CI, .07–.88), less subsequent VAP (13% vs 47%; OR, 0.17, 95% CI, .04–.70), and more mechanical ventilation–free days (median 12 vs 2 days; $P < .001$), but no difference in the duration of mechanical ventilation or length of ICU stay [123].

The panel was concerned about the randomized trial's risk of bias because it was unblinded and stopped early due to benefit. Therefore, the panel also evaluated 4 observational studies [122, 126–128]. When the observational studies were combined with the randomized trial, *P. aeruginosa* comprised 34% of the isolates; other common organisms included *Acinetobacter* (27%), *Klebsiella* (5%), and MRSA (32%). MDR organisms comprised 61% of all isolates, and polymicrobial infections comprised 31% of the episodes of VAT [122, 126–128].

The observational studies compared adult mechanically ventilated patients with VAT who received intravenous antibiotics to patients who did not receive antibiotics. Antibiotic therapy was associated with a shorter duration of mechanical ventilation (–3.5 days; 95% CI −6.88 to −.019 days); however, no significant differences were found for mortality or the duration of ICU stay [122, 126–128].

Taken together, the evidence suggests that antibiotic therapy for VAT may shorten the duration of mechanical ventilation; however, it is uncertain whether it improves other clinical outcomes due to inconsistent findings. The panel's confidence in the estimated effects of antibiotic therapy in VAT (ie, the quality of evidence) was low because it consisted of a randomized trial limited by very serious risk of bias as described above, observational studies, and inconsistent findings. Two other observational studies on VAT were published more recently, but their results did not change the panel's recommendations [129, 130].

Rationale for the Recommendation

The potential desirable consequence of antibiotic therapy is a decreased duration of mechanical ventilation; in contrast, the

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potential undesirable consequences of antibiotic therapy include side effects such as rash, *C. difficile* colitis, antibiotic resistance, and cost. The panel recognizes the potential desirable and undesirable consequences, but judged that the latter outweigh the former, given the uncertainty regarding the benefits. Furthermore, the panel recognizes that in some patients, VAT may occasionally result in mucus plugging, and resultant weaning difficulty. In such patients, antibiotic treatment might be considered, but no evidence for or against is available for this situation. Last, the panel also recognizes that the diagnosis of pneumonia is imperfect. The sensitivity and specificity of portable chest radiographs for pneumonia are lower than those of computed tomography and autopsy. Thus, in the presence of new respiratory signs of infection, such as an increased amount of purulent sputum and a high-quality sample with positive Gram stain, in conjunction with new systemic signs of infection plus worsening oxygenation and/or increasing ventilator settings, antibiotic treatment may be considered even in the absence of new or progressive persistent infiltrates on portable chest radiographs; the rationale for that is because of the high likelihood of a new VAP.

Research Needs

Randomized trials are needed to examine the effects of treating VAT on clinical outcomes, since the existing randomized trials have serious limitations. Such trials should use a concise definition that precludes overlap with VAP or, alternatively, combines the diagnosis of VAT and VAP and adjusts for severity of respiratory illness. Studies assessing the effect of inhaled and intravenous antibiotics on clinical outcomes are needed. In addition, such trials should measure days of systemic antibiotics and posttreatment antimicrobial resistance from both respiratory and nonrespiratory sites, as the high frequency of MDR pathogens in the existing studies suggests that antimicrobial resistance is increasing in the ICU.

INITIAL TREATMENT OF VAP AND HAP

Selecting an empiric antibiotic regimen for clinically suspected VAP is difficult because clinicians must balance the potential benefits of starting adequate antibiotics early (eg, decreased mortality) with the harms of superfluous coverage (eg, adverse drug effects, *C. difficile* infection, and increased antimicrobial resistance).

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 in order 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.

Summary of the Evidence

Antimicrobial flora and resistance patterns can vary considerably between and within countries, regions, hospitals, ICUs in a hospital, and specimen sources (ie, pulmonary vs other specimens) [32, 74, 131, 132]. This was illustrated by an observational study that compared quantitative culture results obtained by bronchoscopy from 229 patients with VAP at 4 different institutions; there was wide variation in both the frequency of pathogens and patterns of antibiotic resistance among the institutions [32]. Similarly, another observational study of patients with VAP found wide variation in both the frequency of pathogens and patterns of antibiotic resistance in different ICUs within a single institution [132]. However, another study found that resistance rates measured in overall hospital antibiograms are reflected in the resistance rates found in ICU-acquired infections, although the frequency of MRSA might be underestimated [133].

Rationale for the Recommendations

The panel recommends basing regimens for the empiric treatment of suspected VAP on the local prevalence of pathogens and antimicrobial susceptibilities associated with VAP. Because antimicrobial flora and resistance patterns can vary considerably between ICUs, hospitals, regions, and countries, the only way to know the local prevalence and resistance patterns of pathogens associated with VAP is to develop a local antibiogram. Ideally, the antibiogram should be specific for VAP patients, or failing that, specific for ICU patients, since there is wide variability between different settings and specimen sources. Nonetheless, the panel did recognize that developing a local antibiogram, especially one tailored to patients with VAP, will not be feasible in many settings. This is particularly the case for hospitals that do not routinely conduct surveillance for VAP, hospitals that have very few cases of VAP, and/or hospitals with relatively few positive ICU cultures regardless of specimen source. In the absence of local microbial epidemiology, clinicians can refer to large national and international surveys of organisms and resistance patterns. The survey closest to the local level should be utilized. An approved guideline for susceptibility testing is available [134].

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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, P. 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 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 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 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, *C. 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 one 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.

Summary of the Evidence

Surveillance studies suggest that the organisms most commonly associated with VAP in the United States are *S. aureus* (approximately 20%–30% of isolates), *P. aeruginosa* (approximately 10%–20% of isolates), enteric gram-negative bacilli (approximately 20%–40% of isolates), and *Acinetobacter baumannii* (approximately 5%–10% of isolates) [138]. These organisms are also the most frequent isolates identified in international surveillance programs, albeit with a higher fraction of cases attributable to *P. aeruginosa* and *A. baumannii* [139].

Many of these organisms, both in the United States and abroad, are resistant to common antibiotics. These same surveillance studies reported that almost 50% of *S. aureus* isolates were resistant to methicillin (MRSA), 28%–35% of *P. aeruginosa* isolates were resistant to cefepime, 19%–29% of *P. aeruginosa* were resistant to piperacillin-tazobactam, and 56%–61% of *A. baumannii* isolates were resistant to carbapenems [138, 139].

A large number of observational studies suggest that inadequate and/or delayed treatment is associated with higher mortality rates in patients with VAP [118, 140–143]. In a meta-analysis of 9 observational studies (813 patients), inadequate antibiotic therapy for VAP was associated with a higher risk of death (OR, 2.34; 95% CI, 1.51–3.62) [141].

Our systematic review did not identify randomized controlled trials (RCTs) comparing regimens with and without agents active against one or more of the potentially resistant pathogens commonly associated with VAP. Nonetheless, the

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breadth of studies associating inadequate and delayed therapy with poor outcomes suggests that empiric treatment regimens for VAP should include agents likely to be active against these pathogens.

Gram-Positive Coverage

There are limited data to inform the choice between different agents active against MRSA. Vancomycin and linezolid have been best studied. Meta-analyses of RCTs comparing vancomycin and linezolid suggest that they are associated with similar clinical outcomes [144–147] (see section XV). Other theoretical choices include teicoplanin, telavancin, ceftaroline, and tedizolid [148–150]. Two randomized clinical trials evaluated teicoplanin vs vancomycin or linezolid for gram-positive infections [151, 152]. However, multiple sites of infection were included in both studies and small numbers of patients with pneumonia were evaluated, and a small number of patients with documented MRSA pneumonia were evaluated. Thus, more evidence is needed to define the clinical role of teicoplanin in patients with HAP/VAP. Two RCTs comparing telavancin and vancomycin found similar outcomes for both agents, but <10% of patients in these trials had MRSA VAP, and patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min) randomized to telavancin had higher mortality rates [148, 153, 154]. There are no published RCTs evaluating ceftaroline or tedizolid for the treatment of MRSA VAP. Daptomycin is inactivated by surfactant and is therefore not used for treatment of pneumonia. RCTs comparing tigecycline to imipenem and ceftobiprole to ceftazidime noted significantly lower clinical cure rates among VAP patients randomized to tigecycline and ceftobiprole, respectively [155, 156].

Gram-Negative Coverage

Potential options to cover gram-negatives are more varied. We identified 29 RCTs comparing different gram-negative regimens for empiric treatment of VAP [155–183]. The regimens tested varied considerably but included comparisons within and between carbapenems, cephalosporins, antipseudomonal penicillins, aminoglycosides, quinolones, aztreonam, and tigecycline either alone or in combination. Individually, none of these trials reported significant differences in clinical response or mortality rates between comparator arms with the exceptions of tigecycline and doripenem, which were both associated with worse outcomes [155, 158]. We did not identify any RCTs assessing colistin as empiric therapy for VAP, but a systematic review and meta-regression of observational studies comparing colistin to other antibiotics found no differences in clinical response rates, mortality, or nephrotoxicity [184]. The US FDA recently approved 2 new cephalosporin–β-lactamase combinations, ceftolozane-tazobactam and ceftazidime-avibactam, for the treatment of complicated urinary tract and intra-abdominal infections. These agents are active against *Pseudomonas* and other gram-negative bacteria, but their effectiveness against VAP has yet to be determined [185].

We performed a series of meta-analyses comparing each class of antibiotics against all other classes to evaluate whether any particular class of antibiotics might be superior to another. For each class, we identified all RCTs that included the antibiotic class of interest in one study arm vs agents from any other class in the comparison arm. These trials were combined using random-effects models. Summary risk ratios for mortality, clinical response, acquired resistance, and adverse events are presented in the supplementary materials [21].

There were no significant differences in mortality, clinical response, acquired resistance, or adverse events for patients randomized to cephalosporin vs noncephalosporin regimens or antipseudomonal penicillin vs non-antipseudomonal penicillin regimens.

Our meta-analysis of 9 trials including 2174 patients on carbapenem-based regimens demonstrated a 22% relative decrease in mortality with carbapenem-based regimens compared to regimens without carbapenems (RR, 0.78; 95% CI, .65–.95; $I^2 = 0\%$; $P = .01$) [155, 159, 161, 163, 167, 168, 173, 182, 183]. The pooled mortality rate in the carbapenem arm was 13.9%, vs 17.8% in the noncarbapenem arm, for an absolute reduction of 3.9% (95% CI, .8–7.0). However, there were no differences between carbapenems vs noncarbapenems in clinical response rates or adverse event rates. In addition, the published studies did not consistently report the rates of subsequent *C. difficile* infection and acquired carbapenem resistance.

Patients randomized to aminoglycoside-containing regimens had similar mortality rates but lower clinical response rates compared to patients treated with aminoglycoside-free regimens (56% vs 68%; RR, 0.82; 95% CI, .71–.95). Patients randomized to quinolone-containing regimens had similar mortality and clinical response rates but slightly fewer adverse events compared to those randomized to quinolone-free regimens (24% vs 27%; RR, 0.88; 95% CI, .78–.99).

Combination Versus Monotherapy for Empiric Gram-Negative Coverage of Suspected VAP

We evaluated whether there was a difference in outcomes in patients randomized to one vs 2 antipseudomonal agents. We identified 7 eligible trials [160–162, 170, 171, 176, 181]. There were no differences in mortality, clinical response, adverse effects, or acquired resistance between the monotherapy and combination arms. However, many of these studies excluded patients with comorbid illnesses and patients known to be colonized with resistant pathogens. A number of the studies also allowed adjunctive empiric coverage for *Pseudomonas* until patients' actual pathogens were identified. These factors limit the applicability of these studies to the selection of empiric regimens in unselected patients with suspected VAP.

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Gram Stains

The role of Gram stains in guiding empiric therapy for VAP is unclear. Some studies suggest that the absence of gram-positive organisms on Gram stain makes it less likely that *S. aureus* will be cultured [186, 187]. A recent meta-analysis of observational studies, however, found relatively poor concordance between Gram stains and final cultures [188]. The pooled kappa was 0.40 (95% CI, .34–.46) for gram-positive organisms and 0.30 (95% CI, .25–.36) for gram-negative organisms [188]. We did not identify RCTs evaluating the use of Gram stains to inform empiric treatment choices.

S. aureus Surveillance Screening

Many hospitals perform surveillance screening for MRSA in some or all inpatients. The sensitivities of MRSA screens vary considerably by anatomical site and by method of isolation (nares vs oropharynx, conventional culture vs polymerase chain reaction) [189]. Observational data suggest that concurrent or recent positive MRSA screens increase the likelihood that clinical infection is due to MRSA [45, 190]. This association is strongest, however, for skin and soft tissue infections. Only about 30% of respiratory infections are due to MRSA in patients with positive MRSA surveillance studies [44, 46]. Likewise, negative MRSA surveillance studies need to be interpreted within the context of the local prevalence of MRSA. In settings with low prevalence of respiratory infections due to MRSA, a negative nasal screen further suggests that pneumonia is unlikely to be due to MRSA and that anti-MRSA coverage can be withheld [190]. In settings with higher prevalence rates of MRSA, a negative screen decreases the probability that infection is due to MRSA but does not rule out the possibility [44, 46]. In these settings, some studies have found that up to 75% of critically ill patients with MRSA lower respiratory tract infections have negative nasal culture surveillance screens for MRSA [46]. We did not identify any RCTs evaluating the use of MRSA screening to inform empiric treatment choices for VAP.

Rationale for the Recommendations

Selecting empiric treatments for clinically suspected VAP is a difficult balancing act between starting adequate antibiotics early and limiting superfluous coverage. Delaying treatment and failing to cover patients' causative pathogens are both associated with higher mortality rates Conversely, broader coverage and longer treatment courses increase the risks of adverse drug effects, *C. difficile* infections, and antimicrobial resistance [191, 192]. The generally recommended compromise is to pair early and aggressive treatment with early and aggressive de-escalation (see section XXIII) [68, 84, 120, 193–197].

National and international surveillance data suggest that a considerable fraction of VAP is attributable to MRSA and resistant gram-negatives. Unless local or regional data demonstrating pathogen and/or antimicrobial resistance patterns significantly different from the rates listed above are available, empiric coverage should include an agent active against MRSA and at least 2 agents active against gram-negative organisms, including *P. aeruginosa*. The rationale for including 2 gram-negative agents in empiric regimens is to increase the probability that at least one agent will be active against the patient's pathogen. On the other hand, if local or regional data suggest a low prevalence of MRSA and low antibiotic resistance rates among gram-negatives, then a single agent active against both *P. aeruginosa* and MSSA or one agent active against MSSA combined with one agent active against *Pseudomonas* and other gram-negatives is likely adequate [162].

Empiric therapies should be informed by patient-specific risk factors for antimicrobial-resistant pathogens and the distribution of pathogens and antibiotic resistance in the local practice environment [131, 133]. Not all patients require maximal empiric coverage (see Table 3 for specific antibiotic recommendations). Patient-specific factors to consider include prior culture results and antimicrobial resistance patterns, recent antibiotic exposures, time since hospital admission, and severity of illness. The risk factors for antibiotic-resistant pathogens are listed in Table 2. The positive predictive values of individual risk factors for drug resistance are variable and imperfect; hence, clinicians should also consider the local prevalence of drug-resistant pathogens when choosing empiric regimens. Coverage for MRSA and resistant gram-negative bacilli may still be appropriate in a patient without specific risk factors for resistant pathogens if the local prevalence of antibiotic-resistant pathogens is high. Conversely, narrow-spectrum coverage may be appropriate for patients without specific risk factors for antibiotic-resistant pathogens being treated in locations with a low prevalence of antibiotic-resistant organisms.

There are no data to pinpoint what specific organism frequencies or antibiotic resistance rates should be used when designing empiric regimens to assure coverage. The panel suggests that ICU-level *S. aureus* methicillin resistance rates of >10%–20% merit selecting a gram-positive agent active against MRSA, and that ICU-level gram-negative resistance rates of >10% to an agent being considered for empiric gram-negative monotherapy merit using 2 gram-negative agents for empiric therapy of suspected VAP. The reason for the lower threshold for gram-negatives compared with gram-positives is because gram-negatives are more frequently implicated in VAP; hence, there is increased risk for inadequate empiric gram-negative coverage. The panel recognizes that calculating the total VAP gram-negative resistance rate to a potential antibiotic choice may be challenging because it requires knowing both the local prevalence of organisms associated with VAP and their resistance rates to all potential antibiotic choices. For hospitals that are unable to calculate their gram-negative VAP resistance rate for each antibiotic, the resistance rate for *Pseudomonas* is a reasonable, albeit conservative, proxy as *Pseudomonas* is the most common gram-negative organism associated with VAP

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and tends to have higher resistance rates than other gram-negatives commonly causing VAP.

The thresholds selected by the panel were chosen to try to minimize the probability of inappropriate coverage while recognizing that indiscriminate use of broad-spectrum coverage for all patients in all settings is not necessary and is potentially harmful. In arriving at these thresholds, the panel considered the number of patients that would need to be treated to benefit one individual. For example, if the average prevalence of *S. aureus* in VAP is approximately 25%, then a methicillin resistance rate of 10%–20% implies that only 2.5%–5% of VAPs will be due to MRSA and the vast majority of patients will not benefit from MRSA coverage. Higher prevalence rates of MRSA, however, increase the percentage of patients likely to benefit from MRSA coverage. We acknowledge that, given the lack of data to inform optimal thresholds for broadening coverage, individual units can adjust these thresholds in accordance with local values and preferences. We note that other infectious disease guidelines have suggested a similar threshold to inform empiric antibiotic choices [198]. We believe that further research on optimal thresholds for selecting broad vs narrow empiric regimens is an important priority.

The panel recommended vancomycin or linezolid for empiric MRSA coverage, vs other agents, based on the many trials comparing these agents. Because the effects of vancomycin and linezolid on clinical outcomes appear to be similar, the final choice should rest upon other factors such as blood cell counts, renal function, concurrent prescriptions for serotonin-reuptake inhibitors, and cost.

The panel suggested that monotherapy with an agent active against both MSSA and *Pseudomonas* may be adequate in patients without risk factors for antimicrobial-resistant pathogens receiving treatment in units with low prevalence rates of MRSA and resistant gram-negatives. Possible agents include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem. The panel cautions clinicians that quinolone resistance is slightly more common in MSSA vs resistance to the other options. If infection is confirmed to be due to MSSA, the panel suggests selecting a narrower-spectrum agent with less likelihood of inducing resistance such as cefazolin, oxacillin, or nafcillin.

The panel suggested using 2 antipseudomonal agents from 2 different classes for empiric treatment of patients with risk factors for antibiotic-resistant pathogens as well as patients receiving care in units where >10% of VAPs are resistant to an agent being considered for monotherapy. We made this suggestion despite the panel's meta-analysis suggesting no difference in mortality, clinical response, adverse effects, or acquired resistance rates between regimens with one antipseudomonal agent vs 2. The panel was concerned that the trial data we reviewed do not apply to all patients with VAP because most of the studies specifically excluded patients colonized with resistant pathogens and patients at increased risk for resistant pathogens. It was the panel's belief that these data then are most applicable to patients at low risk for resistant pathogens or in whom resistant pathogens have been excluded. These data do suggest, however, that once a pathogen has been identified and susceptibilities are known, there is no reason to continue combination therapy.

The panel did not specifically recommend carbapenems as the empiric agent of choice for VAP despite our meta-analysis suggesting that carbapenems may be associated with lower mortality rates in VAP. The panel was concerned because all of the carbapenem studies only evaluated patients for short-term outcomes. Many studies now associate carbapenems with selection of *C. difficile* and antibiotic-resistant organisms at both the individual patient and hospital levels, including organisms resistant to agents other than carbapenems [199–209]. Furthermore, despite the lower number of studies collecting and reporting the development of carbapenem resistance (only 7 studies), our standard meta-analysis showed a trend for an increased risk of developing resistance (RR, 1.40; 95% CI, .95–2.06; $P = .08$), and our Bayesian analyses showed a 96% probability of developing carbapenem resistance with the use of empiric carbapenem. It is therefore possible that short-term mortality benefits may be outweighed by long-term harms. Of note, a significant increase in antibiotic resistance and a lack of survival benefits with carbapenems compared to other antibiotics was observed by our panel's analysis of the treatment of HAP/VAP due to *P. aeruginosa* (see section XVI). Finally, carbapenem resistance rates have risen since the publication of many of the studies included in our analysis [210–212], and hence a blanket recommendation in favor of carbapenems may not be suitable for many contemporary ICUs. We believe this is a critical area for future research.

The panel suggested avoiding aminoglycosides when alternative agents with adequate gram-negative activity are available because of aminoglycosides' poor lung penetration, increased risk of nephrotoxicity and ototoxicity, and our meta-analysis suggesting that they are associated with poorer clinical response rates compared with other classes.

Although there are no randomized trials assessing polymyxins (colistin or polymyxin B) as empiric therapy for VAP, polymyxins may yet be a reasonable component of empiric regimens in units with high rates of resistance to agents from other classes [184]. In some ICUs, organisms sensitive to colistin alone are responsible for >20% of gram-negative VAP [213]. In ICUs operating under these difficult conditions, including colistin in empiric regimens may increase the frequency of initially appropriate empiric antibiotic treatment. However, there are limited data on how this might affect nephrotoxicity rates, colistin resistance, and mortality rates over the long term. Overuse of polymyxins may jeopardize its current role as the gram-negative antibiotic of last resort.

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Finally, the panel strongly encourages clinicians to consider all relevant, available data about both their individual patient and their practice environment to tailor empiric choices for each patient. Factors to consider include the clinician's confidence about whether or not the patient truly has pneumonia, the patient's risk factors for drug-resistant pathogens, the patient's drug allergies and severity of illness, results from prior clinical cultures, results of MRSA screening, the morphology and quantity of organisms on Gram stains, and the local distribution of organisms and resistance patterns associated with VAP. Some of these factors could reasonably cause a clinician to include coverage for MRSA even if the local prevalence of methicillin resistance is <10%–20% (for example, if the patient is severely ill and has a good-quality ETA Gram stain dense with gram-positive cocci and a recent positive surveillance nasal screen for MRSA). Conversely, some factors could also reasonably support a decision to omit MRSA coverage even within a unit with relatively high rates of antibiotic resistance (eg, if the clinical suspicion for pneumonia is relatively low, the patient is not severely ill and has no risk factors for drug-resistant pathogens, and a good-quality Gram stain of pulmonary secretions shows gram-negative bacilli alone).

Research Needs

There is a pressing need for more data to guide the selection of broad- vs narrow-spectrum empiric regimens. More data are also needed on the differential impact of different empiric regimens on antimicrobial resistance rates and long-term outcomes at the individual and population levels, such as mortality and antibiotic resistance.

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.

Summary of the Evidence

We performed a systematic review of both randomized trials and observational studies to determine the prevalence of infecting organisms in HAP. Studies published prior to 2000 were excluded because of changes in resistance patterns and organism prevalence over time. We selected 24 studies that provided relevant data [11, 89, 92, 139, 155, 179, 214–231]. The studies enrolled patients predominantly in North America, Europe, and Asia, with a small percentage from South America. A meta-analysis determined the following frequencies of potentially drug-resistant pathogens: non-glucose-fermenting gram-negative bacilli (19% [95% CI, 15%–24%] of isolates, with *Pseudomonas* species accounting for 13% [95% CI, 10%–17%] and *Acinetobacter* species accounting for 4% [95% CI, 2%–6%]), enteric gram-negative bacilli (16% [95% CI, 13%–20%] of isolates), *S. aureus* (16% [95% CI, 12%–21%] of isolates), MRSA (10% [95% CI 6%–14%] of isolates), and MSSA (6% of isolates). There was considerable variation in the rates of isolation of specific pathogens across studies, but the study year and geographic area did not account for the variation, with the possible exception of *Acinetobacter* species. *Acinetobacter* species increased in prevalence from studies published between 1994 and 1999 to studies published between 2006 and 2012, and are a more common cause of HAP in Asia than in Europe and the United States. One study was not included in the meta-analysis because the number of observations could not be determined [139]; however, exclusion of the study was inconsequential as the results of the study and meta-analysis were concordant.

The systematic review had limitations that should be considered before applying the findings to clinical practice. There was significant variation among studies regarding whether or not patients who were immunosuppressed or did not have a confirmed pathogen were included; inclusion of only patients with positive microbiologic results may bias the data to reflect the sickest patients, as severely ill patients are more likely to have positive microbiology and more likely to have infection with drug-resistant organisms [27, 232, 233]. There was also variation in the unit of analysis (ie, the patient or the isolate). Because specific antibiotic sensitivities were not reported in most studies, the results reflect potentially antibiotic-resistant organisms, not actual antibiotic resistance rates.

Antimicrobial flora and resistance patterns can vary considerably among countries, regions, hospitals, ICUs within a hospital, and specimen sources (ie, pulmonary vs other specimens) [32, 131, 132]. This was illustrated by an observational study that enrolled 405 patients who were consecutively admitted to the medical, surgical, or trauma ICU of a large academic medical center and then followed prospectively for 3 months. There were significant differences in antibiotic susceptibility among ICUs for *S. aureus*, *Enterococcus* species, *Acinetobacter* species, *Enterobacter* species, *Klebsiella* species, and *Pseudomonas* species [132]. However, another study found that resistance rates measured in overall hospital antibiograms are reflected in the resistance rates found in ICU-acquired infections, although the frequency of MRSA might be underestimated [133].

Rationale for the Recommendations

To balance the competing goals of providing early appropriate antibiotic coverage and avoiding superfluous treatment

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that may lead to antibiotic resistance and other adverse consequences, one approach involves preferentially providing broad antimicrobial therapy to patients with the greatest need for such therapy, such as those with risk factors for antimicrobial-resistant pathogens and those in an environment where antibiotic-resistant pathogens are common [131, 133].

Identifying patients who are in an environment where antibiotic-resistant pathogens are common requires that both local prevalence and antibiotic resistance patterns be determined. The distribution of pathogens and antibiotic-resistance patterns associated with HAP should ideally be determined using local data from each medical unit, if possible, because antimicrobial flora and resistance patterns vary considerably among countries, regions, hospitals, ICUs, and specimen sources. The guideline panel agreed that the use of local antibiograms to inform antibiotic selection is the preferred approach to initiating early appropriate antibiotic coverage while avoiding superfluous treatment.

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 coverage for MSSA (and not MRSA) is indicated, we suggest a regimen including piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem. 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.

Summary of the Evidence

With respect to whether patients with HAP should be empirically treated for *S. aureus*, our meta-analysis of 23 studies described above (see section XI) found that MRSA and MSSA were associated with 10% and 6% of cases of HAP, respectively. Inadequate initial treatment of *S. aureus* may be associated with increased mortality according to an observational study of 165 patients with HAP. The study found that inadequate antibiotic

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therapy was associated with increased total mortality (75% vs 22%; RR, 10.41; 95% CI, 2.01–53.95) and increased mortality due to pneumonia (50% vs 15.1%; RR, 4.92; 95% CI, 1.31–18.49) [11]. This study is indirect evidence that failure to adequately target *S. aureus* increases mortality because the study identified the causative pathogen in only one-third of cases and, among the cases in which the pathogen was identified, <10% were due to *S. aureus*.

With respect to selection of an antibiotic once the decision is made to target MRSA, the guideline panel found limited evidence specific to patients with HAP that compared different regimens. The panel, therefore, decided that the most appropriate evidence to inform its judgments was the comparisons of various regimens described above for VAP, which found no differences in clinical outcomes when vancomycin was compared to linezolid (see section XV).

With respect to whether patients with HAP should be empirically treated for *P. aeruginosa* and other gram-negative bacilli, the meta-analysis of 23 studies described above found that *P. aeruginosa* was associated with 13% of cases of HAP, and other gram-negative bacilli were associated with 22% of cases. Inadequate initial treatment of *P. aeruginosa* and other gram-negative bacilli may be associated with increased mortality according to the observational study of 165 patients with HAP described above. [11]. However, this study constitutes indirect evidence that failure to adequately target *P. aeruginosa* and other gram-negative bacilli increases mortality because the study identified the causative pathogen in only one-third of cases; among the cases in which the pathogen was identified, <50% were due to *P. aeruginosa* or other gram-negative bacilli.

With respect to whether to use a single antibiotic or 2 antibiotics to target *P. aeruginosa* and other gram-negative bacilli in HAP, we found limited evidence that addressed this question in patients with HAP.

With respect to the preferred antibiotic regimen, our systematic review identified 10 randomized trials that compared empiric antibiotic regimens in adult populations in which at least two-thirds of the patients had HAP rather than VAP [153, 155, 177, 179, 183, 214, 229, 234–236]. Four trials compared carbapenems to piperacillin-tazobactam [179, 183, 229, 235], 5 trials compared a cephalosporin to various alternative antibiotics [177, 214, 237–239], and 2 compared a new antimicrobial (televancin or tigecycline) to an alternative antibiotic [153, 155]. Our meta-analysis of the 4 trials that compared carbapenems to piperacillin-tazobactam revealed no difference in mortality (RR for carbapenems, 0.94; 95% CI, .66–1.34). The remaining 6 trials could not be pooled; however, all of the trials found that no specific antimicrobial regimens demonstrated better outcomes than comparator regimens with the exception of one trial, which had important limitations and in which the difference may not have been clinically significant [177].

Given the association of aminoglycoside therapy with adverse effects in patients with VAP, the panel was concerned that similar effects may occur in HAP. Several of the antimicrobial regimens used in the trials included aminoglycosides. Although side effects were not compared to other regimens, the incidence of renal failure and vertigo/tinnitus in patients with HAP who received an aminoglycoside-containing regimen was 3% and 2%, respectively [229, 235].

Although not available in the United States, ceftobiprole is a new cephalosporin with in vitro activity against common HAP pathogens, including MRSA, *Enterobacter* species, and *P. aeruginosa*. In a study of 781 patients with nosocomial pneumonia, including 571 with HAP, ceftobiprole had a similar clinical cure rate and microbiological eradication rate to those of the combination of ceftazidime and linezolid for HAP (but not VAP). Adjunctive antipseudomonal therapy was provided to patients with suspected or proven *Pseudomonas* infection [156].

The guideline panel had very low confidence in the following bodies of evidence: (1) the estimated prevalence of various pathogens, because the estimates are based upon a meta-analysis that included studies with risk of bias; (2) the estimated effects of inadequate antibiotic therapy on non–mechanically ventilated patients with HAP due to *P. aeruginosa* and other gram-negative bacilli, since the study was an observational study that was limited by indirectness of the population (the population of interest was patients with HAP due to *P. aeruginosa* and other gram-negative bacilli, but the population studied was patients with HAP due to a variety of pathogens) [11]; (3) the estimated effects of various empiric regimens (including monotherapy vs combination therapy) because they were based upon meta-analyses of randomized trials with risk of bias and very serious indirectness (the indirectness reflects the fact that the trials were performed in patients with HAP in different settings using different protocols and different regimens); (4) the estimated adverse effects of aminoglycosides because they were not compared to a control group (ie, a case series within a randomized trial [229, 235]); (5) the study that evaluated the effects of inadequate antibiotic therapy on patients with HAP due to *S. aureus*, as the study was an observational study that was limited by indirectness of the population (the population of interest was patients with HAP due to *S. aureus*, but the population studied was patients with HAP due to a variety of pathogens [11]); and (6) the estimates derived from comparisons of vancomycin to linezolid because they were determined by a meta-analyses of randomized trials, which were limited by a risk of bias and indirectness (see section XV). The indirectness refers to the meta-analyses including patients with VAP, whereas the population of interest was patients with HAP.

Rationale for the Recommendations

The evidence indicated that 16% (95% CI, 12%–21%) of HAP cases are caused by *S. aureus*. The guideline panel agreed that

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this frequency was sufficient to recommend that all empiric regimens include an antibiotic with activity against *S. aureus*, particularly in light of evidence that inadequate treatment of *S. aureus* may increase mortality. In other words, the panel judged that the benefit of potentially decreasing mortality outweighs the additional side effects, burdens, and cost of including an antibiotic with activity against *S. aureus*. The recommendation is strong despite the very low quality of evidence because the panel judged that the upsides of the recommendation are more important to patients than the downsides and, therefore, most well-informed patients would want to receive the additional antibiotic.

The guideline panel agreed that the finding that 10% (95% CI 6%–14%) of HAP cases are attributable to MRSA was insufficient justification to use an antibiotic that targets MRSA in all patients with HAP. Factors that the panel considered included the following: HAP patients tend to be less severely ill than VAP patients and, therefore, the negative consequences of initial inappropriate antibiotic therapy are likely less severe than with VAP patients [92, 219, 222]; culture data are often not obtained in patients with HAP because adequate sputum samples can be difficult to obtain and, therefore, clinicians are likely to continue the initial broad-spectrum antibiotic regimen for the entire course of therapy as there are no culture data to support de-escalation; and lack of de-escalation increases the likelihood of acquiring antibiotic resistance.

Instead, the panel agreed that empiric coverage of MRSA should be reserved for patients with HAP who have either factors increasing the likelihood for MRSA infection or a high risk for mortality. Our analyses revealed intravenous antibiotic treatment during the prior 90 days as a risk factor for MRSA nosocomial pneumonia. Other factors that probably increase likelihood of MRSA pneumonia include prior known MRSA colonization detected via nasal or respiratory cultures or non-culture screening [45, 190] and a high-quality Gram stain showing numerous and predominant gram-positive cocci in clusters with the morphology of *Staphylococcus* species [187, 240]. Hospitalization in a unit where >20% of *S. aureus* isolates are methicillin resistant or the prevalence of MRSA is not known increases a priori the risk of MRSA compared with hospitals where MRSA is known to be rare. The 20% threshold for deciding whether or not to target MRSA or MSSA was arbitrarily chosen by the panel in an attempt to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use. A high risk for mortality was defined by the guideline panel as requiring ventilatory support due to pneumonia and having septic shock.

The guideline panel prefers vancomycin or linezolid for patients whose empiric antibiotic regimen will include an agent that targets MRSA. This is based upon extensive clinical experience with these agents and the effects of these agents in patients with VAP. Because the effects of vancomycin and linezolid on clinical outcomes are similar, the final choice rests upon factors such as blood cell counts, concurrent prescriptions for serotonin-reuptake inhibitors, renal function, and cost.

Patients with HAP who have no risk factors for either MRSA infection or a poor clinical outcome may receive an empiric regimen that includes an antibiotic targeting MSSA. Of note, some agents that may be included in empiric regimens for HAP due to their activity against *P. aeruginosa* and gram-negative bacilli are also suitable for empiric coverage against MSSA. These include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, and meropenem. An empiric antimicrobial regimen that includes one of these agents does not require an additional agent to target MSSA. If infection with MSSA alone is confirmed, oxacillin, nafcillin, and cefazolin are narrow-spectrum intravenous antibiotics that are optimal for treating MSSA.

The evidence indicated that approximately 35% of HAP cases are caused by gram-negative bacilli. The panel agreed that this high prevalence, combined with the possibility that inadequate treatment increases mortality, dictates that all empiric regimens target *P. aeruginosa* and other gram-negative bacilli. In other words, the panel judged that the benefit of potentially decreasing mortality outweighs the side effects, burdens, and cost of targeting *P. aeruginosa* and other gram-negative bacilli. The recommendation is strong despite the very low quality of evidence, because the panel judged that the upsides of the recommendation are more important to patients than the downsides and, therefore, most well-informed patients would want antibiotics with activity against *P. aeruginosa* and other gram-negative bacilli.

With respect to whether the empiric regimen should include one antibiotic or 2 antibiotics with activity against *P. aeruginosa*, the guideline panel considered indirect evidence from patients with VAP. Similar to its decision making with VAP, the panel was concerned about applying this evidence to all patients with HAP because most of the studies excluded patients at increased risk for resistant pathogens. It was the panel's impression that the data are most applicable to patients who are at low risk for resistant pathogens or in whom resistant pathogens have been excluded. The panel concluded that patients with HAP with factors increasing the likelihood of gram-negative infection, including *Pseudomonas*, or increased risk for mortality should receive antibiotics from 2 different classes with activity against *P. aeruginosa*, whereas patients without these factors should receive only one such antibiotic. The panel agreed that this approach was an appropriate balance between the competing goals of providing early appropriate antibiotic coverage to improve clinical outcomes such as mortality while avoiding superfluous treatment that may lead to antibiotic resistance, side effects, and increased cost.

Factors likely increasing the probability of gram-negative infection, including *Pseudomonas*, are a high-quality Gram stain

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from a respiratory specimen with numerous and predominant gram-negative bacilli [240], and having structural lung disease that is associated with *Pseudomonas* infection (ie, bronchiectasis and cystic fibrosis). Risk factors for mortality include the requirement for ventilatory support due to pneumonia and having septic shock.

This approach will likely decrease the number of patients with HAP for whom 2 antibiotics with activity against *P. aeruginosa* would be recommended for initial empiric therapy, compared with the recommendations from the 2005 ATS/IDSA HAP/VAP guidelines [1]. The panel agreed that this change is warranted, particularly in light of the growing prevalence of *C. difficile* induced by antibiotics, the public health concerns related to increasing antibiotic resistance, and the dearth of new antibiotics. The evidence suggests that non-glucose-fermenting gram-negative bacilli (eg, *Pseudomonas and Acinetobacter*) and enteric gram-negative bacilli account for 19% (95% CI, 15%–24%) and 16% (95% CI, 13%–20%), respectively, of cases of HAP. This means that even in a hospital with a high rate of antibiotic resistance (eg, 20% for non-glucose-fermenting gram-negative bacilli and 10% for enteric gram-negative bacilli), the rate of HAP caused by antibiotic-resistant gram-negative bacilli will be approximately 5%. Thus, gram-negative monotherapy would be expected to be adequate for 95% of patients with HAP. Of course, in hospitals with a high rate of antibiotic resistance to the agent being considered for monotherapy, the use of 2 antipseudomonal agents should be considered.

The panel elected to not recommend a specific antibiotic class to target *P. aeruginosa* and other gram-negative bacilli due to the lack of evidence that any regimen is superior to another. The only exceptions are the aminoglycosides. The panel chose to recommend against aminoglycosides in most situations because of the poor lung penetration and risk of nephrotoxicity and ototoxicity in the absence of improved outcomes in patients with HAP, coupled with the indirect evidence from patients with VAP of inferior clinical outcomes and increased adverse effects.

Patients with early-onset HAP (variably defined as pneumonia occurring within 4–7 days of hospital admission) have a lower rate of MDR pneumonia than patients with late-onset HAP [228]. Still, a number of patients with early-onset HAP are infected with MDR pathogens [228, 241], probably because many have risks for resistant pathogens, such as prior receipt of intravenous antibiotics. Thus, the panel did not recommend different antibiotic regimens for early-onset HAP, preferring to address the specific risk factors that confer increased risk in patients independent of the timing of the HAP.

Although not available in the United States, ceftobiprole may be an option for HAP monotherapy where it is available, given the results of the study described above [156].

PHARMACOKINETIC/PHARMACODYNAMIC OPTIMIZATION OF ANTIBIOTIC THERAPY

XIII. Should Antibiotic Dosing Be Determined by 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.

Summary of the Evidence

Our systematic review identified 3 randomized trials [242–244] and 4 observational studies [245–248] that measured the effects of PK/PD-optimized dosing (ie, dosing guided by therapeutic drug monitoring or extended continuous intravenous infusion) on clinical outcomes. A meta-analysis of 3 studies (one randomized trial [244] and 2 observational studies [246, 248]) determined that PK/PD-optimized dosing reduced both mortality (12% vs 24%; RR, 0.49; 95% CI, .34–.72) and the ICU length of stay (mean difference, −2.48 days; 95% CI, −3.09 to −1.87 days). A meta-analysis of 5 studies (2 randomized trials [242, 243] and 3 observational studies [246–248]) found that PK/PD-optimized dosing improved the clinical cure rate (81% vs 64%; RR, 1.40; 95% CI, 1.16–1.69). These benefits from PK/PD optimization have also been detected during the treatment of infections other than HAP/VAP [249].

PK/PD targets associated with improved clinical outcomes have been reported in observational studies. Generally speaking, the PK/PD targets reported for quinolones and aminoglycosides are fairly consistent, whereas the PK/PD targets reported for β-lactams are highly variable.

The guideline panel's confidence in the estimated effects on mortality, ICU length of stay, and clinical cure rate in patients with HAP/VAP was very low, because most of the studies included in the meta-analyses were observational studies with a risk of bias due to the excess influence of one observational study [248]. In the mortality and ICU length-of-stay meta-analyses, the study contributed 638 of 741 patients (86%), and in the clinical cure rate meta-analysis, the study contributed 638 of 908 patients (70%). In addition, the evidence is indirect for any specific class of antibiotics or any specific approach to PK/PD optimization, as several antibiotic classes and dosing strategies (eg, extended or continuous infusion [242–244, 246, 247] and monitoring serum concentrations [245, 248]) were included in the studies in the meta-analyses.

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Finally, the meta-analysis for clinical cure was also limited by inconsistency.

Rationale for the Recommendation

The guideline panel carefully weighed the potential advantages of PK/PD-optimized dosing (decreased mortality, decreased ICU length of stay, and increased clinical cure rate) against the potential downsides (more burdensome and costly, possibly more toxicity among patients who require higher doses due to augmented clearance). In addition, the panel considered the possibility that the increased clinical cure rate might lead to shorter courses of antibiotics and, subsequently, less antibiotic toxicity and less antibiotic resistance. On the basis of this information, the panel decided that patients with HAP/VAP should have PK/PD-optimized dosing of their antimicrobial regimens, rather than simply following the dosing described in the manufacturer's prescribing information. The panel agreed that the potential benefits were far more important to patients than the inconveniences and costs associated with the approach, and agreed that their low confidence in the estimated effects of PK/PD-optimized dosing was insufficient to justify an alternative approach.

The rationale for using PK/PD-optimized dosing rather than following the manufacturer's prescribing information is sound. The distribution of many antibiotics can be severely altered by pathophysiological changes that are common to critically ill patients, leading to altered pharmacokinetics [250]. Because the ICU is also commonly associated with less susceptible pathogens, the likelihood of standard antibiotic dosing achieving desired PK/PD targets is probably reduced in critically ill patients, which may partially explain suboptimal clinical outcomes observed in HAP/VAP [251, 252].

PK/PD-optimized dosing is probably more burdensome and costly than conventional dosing. As an example, the most accurate approach to dosing in patients with HAP/VAP requires measurement of the blood concentration of the antibiotic and then incorporation of the result into a dosing software package [253]. Costs and burdens include education, blood sampling, performing the drug assay, and acquiring and updating the software. Alternative interventions, such as routine extended infusions of β-lactams or weight-based dosing of aminoglycosides, are probably less burdensome and costly than management using the blood concentration of antibiotics, but still more burdensome than conventional dosing, because clinical staff must be trained and educated.

No published studies describing the PK/PD of piperacillin-tazobactam or polymyxins (colistin or polymyxin B) in patients with HAP/VAP are available at this time and so these drugs were not included in this recommendation. However, the most optimal dosing of these drugs, based on limited evidence and extrapolation from similar drug classes, is provided in Table 3 (see section X).

More recently, the Agency for Healthcare Research and Quality (AHRQ) published a report on the use of PK/PD for HAPs, which concluded that the evidence does not favor the routine use of PK/PD [254]. This contrasts with our guideline recommendation. We suggest that the reasons for the different conclusions between the AHRQ report and ours are related to the following: (1) We used a distinct research question where we consolidated the studied issue into a singular PICO question, rather than 3 questions that were considered separately in the AHRQ report; (2) given this difference from the AHRQ methods, we were able to use the meta-analytic methodology to analyze the combined effects of studies, which may have given further confidence for interpreting the relative effects of identified studies; and (3) the ATS/IDSA guideline also evaluated noninterventional studies that analyzed patient outcomes associated with optimized drug exposure; these studies were not evaluated by the AHRQ report.

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 MDR.

Summary of the Evidence

Our systematic review identified 9 studies of inhaled antibiotics as adjunctive therapy for VAP due to gram-negative bacilli. Five of the studies were randomized trials and 4 were observational studies [125, 255–262]. Three different inhaled antibiotics were administered in the 9 investigations—tobramycin, gentamicin, and colistin. Most of the studies provided minimal information about the device and method used to deliver the inhaled antibiotic. The predominant organisms isolated in the studies were MDR *Klebsiella pneumoniae*, *P. aeruginosa*, and *A. baumannii*.

Our meta-analyses found that the addition of an inhaled antibiotic to a systemic antibiotic regimen improved the clinical cure rate (ie, resolution of signs and symptoms of respiratory infection) (RR, 1.29; 95% CI, 1.13–1.47), but had no definitive effects on mortality (RR, 0.84; 95% CI, .63–1.12) or nephrotoxicity (RR, 1.11; 95% CI, .78–1.57). There were no other harmful

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effects attributed to the inhaled antibiotics. When only the trials that evaluated colistin were pooled, the clinical cure rate similarly improved (RR, 1.28; 95% CI, 1.11–1.47).

Several outcomes were reported by a few studies. One trial found that inhaled antibiotics reduced the frequency of requiring additional intravenous antibiotics [125]. Two studies looked for, but did not find, increased antibiotic resistance among patients who received an adjunctive inhaled antibiotic [125, 256]. Two studies reported that inhaled colistin reduces the duration of mechanical ventilation [260, 261]. The effects of adjunctive inhaled antibiotics on the ICU length of stay and hospital length of stay were not evaluated.

The panel's confidence in the estimated effects of adjunctive inhaled antibiotics was very low because a large proportion of the evidence used to derive the estimates was observational data limited by imprecision (ie, most of the studies were small, with the largest study including 208 patients).

Rationale for the Recommendation

The guideline panel weighed the evidence for advantages of adjunctive inhaled antibiotic therapy in patients with VAP due to gram-negative bacilli (increased clinical cure rate) against the potential downsides (increased burden and cost) in the context of no proven effects on mortality, side effects, or antibiotic resistance. The panel agreed that the potential benefits were more important to patients than inconvenience and cost. However, the panel acknowledged having very low confidence in the estimated effects of adjunctive inhaled antibiotic therapy and recognized that there are many important unknowns (eg, optimum dosing, optimum delivery method, population most likely to benefit). For these reasons, the panel elected to recommend adjunctive inhaled antibiotic therapy for patients who are most likely to benefit: specifically, those who have VAP caused by bacteria that are only susceptible to the classes of antibiotics for which evidence of efficacy by the intravenous alone route is the most limited (ie, aminoglycosides or colistin). However, 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 intravenous antibiotics alone, whether the infecting organism is or is not MDR.

The rationale for adjunctive inhaled antibiotic therapy is based in part upon the observation that antibiotic efficacy against bacteria within purulent secretions may require antibiotic concentrations >10–25 times the minimum inhibitory concentration (MIC); these levels cannot be achieved with intravenous therapy alone and, therefore, the addition of inhaled antibiotic therapy may be beneficial [263]. The finding of low antibiotic concentrations in the secretions and epithelial lining fluid of the lung during intravenous therapy with aminoglycosides is well known [264–266]. However, it also occurs with other antibiotics and its correlation with clinical outcomes remains unknown. Studies of high-dose intravenous colistin have shown that the concentration in the serum is approximately the MIC of *Acinetobacter* and *Pseudomonas* [267, 268]; concentrations in the lung and airway are lower and, therefore, subtherapeutic. The ongoing use of antibiotics at subtherapeutic levels may lead to the selection of antibiotic-resistant organisms.

Research Needs

There is an urgent need for information about the optimal delivery and dosing of inhaled antibiotic therapy. In addition, clinical trials are needed that evaluate the concentrations of antibiotics that ensure efficacy in the context of viscous purulent secretions. The duration of systemic antibiotic therapy and antibiotic resistance are important endpoints for future studies. If future investigations demonstrate that adjunctive inhaled therapy decreases the duration of systemic antibiotics and lessens the emergence of resistance, this could have a relevant impact on treatment decisions.

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.

Summary of the Evidence

Our systematic review identified 7 randomized trials that addressed the selection of antibiotics for HAP/VAP caused by MRSA [153, 269–274]. Four trials compared linezolid to vancomycin [271–274]. The remaining 3 trials compared telavancin [153], quinupristin plus dalfopristin [269], or vancomycin plus rifampin [270] to vancomycin alone.

Linezolid is the most extensively studied alternative to vancomycin for MRSA pneumonia [271–274]. Our meta-analyses of the 4 trials found no difference in mortality when analyzed using an intention-to-treat strategy (RR, 0.91; 95% CI, .71–1.16) or a modified intention-to-treat strategy (RR, 0.82; 95% CI, .37–1.80). We also found no difference in the clinical cure rate when analyzed using an intention-to-treat strategy; however, there was improvement of the clinical cure rate among patients who received linezolid when analyzed using a modified intention-to-treat strategy (RR, 1.18; 95% CI, 1.00–1.40). Use of a modified intention-to-treat analysis is controversial because it involves excluding patients following randomization [275]. Linezolid and vancomycin appear to confer no clear difference in nephrotoxicity, thrombocytopenia, serious adverse events, or need for treatment discontinuation due to an adverse event.

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None of the other trials demonstrated a clear superiority of an alternative antibiotic or regimen over vancomycin alone. The study that compared telavancin to vancomycin combined 2 smaller trials that were conducted in patients with gram-positive nosocomial pneumonia. In the combined population of 1503 patients, there were no differences in clinical cure rate, mortality, or adverse effects, although there was a trend toward increased all-cause mortality with telavancin in one of the component studies (21.5% vs 16.6%; mean difference, 4.9%; 95% CI, −.7% to 10.6%) [153]. This primarily occurred among patients with creatinine clearance values <30 mL/minute, prompting an FDA advisory panel to recommend limiting the use of telavancin to patients with creatinine clearance levels above this threshold [276]. Increases in serum creatinine were more common in the telavancin group (16% vs 10%) [153].

A nonblinded trial that compared quinupristin plus dalfopristin to vancomycin in 298 patients with gram-positive nosocomial pneumonia found similar clinical response rates in both treatment groups. This was also true for the subgroup of 51 patients with MRSA pneumonia [269]. Another nonblinded trial compared vancomycin plus rifampin to vancomycin alone in 83 patients with MRSA nosocomial pneumonia [270]. It found that vancomycin plus rifampin increased the 14-day clinical cure rate and decreased the 60-day mortality rate, but had no effect on 28-day mortality. Of note, 34.1% of the patients who were treated with rifampin developed resistance to the antibiotic [270]. Although this trial did not report significant adverse effects, other studies have reported an association of rifampin with hepatotoxicity, acute renal failure, and hemolytic anemia [277].

Two randomized clinical trials evaluated teicoplanin vs vancomycin or linezolid for gram-positive infections [151, 152]. However, multiple sites of infection were included in both studies and small numbers of patients with pneumonia were evaluated, and a small number of patients with documented MRSA pneumonia were evaluated. Thus, more evidence is needed to define the clinical role of teicoplanin in patients with HAP/VAP.

Taken together, the evidence suggests that there are no important differences among the antibiotics available to treat HAP/VAP due to MRSA with 2 exceptions: vancomycin plus rifampin may improve the short-term clinical cure rate at the expense of more rifampin resistance and possibly other side effects, and telavancin may be harmful in the setting of a creatinine clearance <30 mL/minute. Our confidence in the accuracy of these estimated effects was diminished by risk of bias, which included lack of blinding, ineffective randomization (ie, baseline differences), missing data, failure to follow an intention-to-treat analysis, and protocols that allowed outcomes to be overridden "by the sponsor . . . all revisions were made before unblinding" [274, 278]. It was also decreased by indirectness of the population, as our population of interest was patients with HAP/VAP due to MRSA but many of the trials enrolled patients with HAP/VAP due to a variety of gram-positive organisms or patients with healthcare-associated non-HAP/VAP pneumonia. The panel decided that its overall confidence in the evidence was moderate, electing to downgrade due to the serious risk of bias, but not the indirectness.

There has been concern related to the potential phenomenon known as "MIC creep," referring to reports of a trend of increasing vancomycin MICs among MRSA isolates in some institutions [279, 280]. This has not been a universal phenomenon, and surveillance studies from different countries have not demonstrated such an overall increase; in general, MRSA isolates with intermediate vancomycin MICs remain uncommon [281–285]. Furthermore, although there are theoretical reasons for concern when treating MRSA pneumonia if the isolate has intermediate MICs, there is evidence that outcomes are not worse in such patients [286–288]. As with any other organism defined as intermediate to the selected antibiotic, a lack of clinical improvement despite appropriate antibiotic dosing and duration should prompt consideration of a change in antibiotic therapy.

Rationale for the Recommendation

The evidence indicates that vancomycin and linezolid are roughly equivalent, and no alternative agent or regimen is clearly superior to vancomycin or linezolid; additionally, alternative regimens may be more harmful. Given these observations, the guideline panel had a high level of confidence that the benefit-risk ratio of using vancomycin or linezolid to treat patients with HAP/VAP caused by MRSA is higher than the ratio for alternative regimens.

While a difference in nephrotoxicity risk between vancomycin and linezolid was not identified using the measure of absolute risk difference, there was an increased RR of nephrotoxicity associated with vancomycin compared with linezolid. The lack of double-blinding in about half of the randomized studies may have led to ascertainment bias with respect to nephrotoxicity, which could have favored linezolid. It should be noted that a variety of definitions for nephrotoxicity were used across studies and that there were no differences in terms of serious adverse events, or need for treatment discontinuation between the 2 antibiotics. Nonetheless, based on observational evidence, the selection of vancomycin vs linezolid may depend upon factors such as blood cell counts, concurrent prescriptions for serotonin-reuptake inhibitors, renal function and cost. The panel agrees with a prior consensus recommendation to achieve a vancomycin trough level of 15–20 mg/L in patients being treated for pneumonia [289], although the panel did not review the related evidence systematically.

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

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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.

Summary of the Evidence

Our systematic review identified no RCTs that compared antibiotic regimens in patients with HAP/VAP caused by *P. aeruginosa*. The panel therefore considered 2 bodies of evidence: evidence from randomized trials that compared antibiotic regimens in patients with HAP/VAP due to any pathogen, and evidence from subgroup analyses on patients with HAP/VAP caused by *P. aeruginosa*.

With respect to studies that compared antibiotic regimens in patients with HAP/VAP due to any pathogen, a systematic review of 41 randomized trials found that no specific antimicrobial regimen decreased mortality and treatment failure more than any other regimen [290], and 33 randomized trials found that no specific antimicrobial regimen improved a variety of clinical outcomes more than any other regimen [155–183, 229, 291–293]. The panel's confidence in applying these estimated effects to the clinical question was low because they are derived from randomized trials limited by risk of bias (ie, many trials were not blinded) and indirectness (ie, the question is specific to patients with HAP/VAP caused by *P. aeruginosa*, but the studies were conducted with patients who had HAP/VAP due to any pathogen).

The prevalence of antibiotic resistance among patients with HAP/VAP due to *P. aeruginosa* is high. An observational study of 314 patients with VAP caused by *P. aeruginosa* determined that susceptible, MDR, and extensively drug-resistant *P. aeruginosa* represented 54%, 32%, and 14% of *P. aeruginosa* isolates, respectively [294]. In another observational study of 91 episodes of VAP caused by *P. aeruginosa*, it was found that susceptible, MDR, and extensively drug-resistant *P. aeruginosa* represented 34%, 20%, and 46% of *P. aeruginosa* isolates, respectively [295]. Antibiotic resistance has been associated with an increased ICU length of stay, but not mortality or recurrence of HAP/VAP; however, the lack of statistical power is a common issue with the published evidence [294]. Mortality due to HAP/VAP is more closely associated with severity of illness than antibiotic resistance [296].

With respect to studies that performed subgroup analyses on patients with HAP/VAP caused by *P. aeruginosa*, the evidence is probably best understood by considering each antibiotic class separately. A review of 36 RCTs confirmed that it was only possible to perform this analysis for the carbapenem antibiotic class, due to lack of comparative studies within a specific antibiotic class or lack of specific data for the *P. aeruginosa* subgroup for fluoroquinolones and β-lactams.

Doripenem: Three randomized trials were identified that compared doripenem to other antibiotic regimens in a subgroup of patients with *P. aeruginosa* [157, 158, 179]. The comparisons were to either imipenem [157, 158] or piperacillin-tazobactam [179]. We pooled the subgroup analyses and found no significant differences between doripenem and the other regimens in terms of mortality (28% vs 21%; RR, 1.07; 95% CI, .49–2.35) and treatment failure rate (45% vs 63%; RR, 0.76; 95% CI, .40–1.42). The panel's confidence in these estimated effects was very low because they are derived from randomized trials limited by risk of bias (ie, many trials were unblinded), inconsistency (ie, I^2 test for heterogeneity >25%), and imprecision (ie, few events and wide CIs). In addition, the doripenem FDA label was recently modified due to this drug's association with increased risk of death in patients with VAP due to *P. aeruginosa* [297].

Imipenem: We identified a published systematic review of 20 randomized trials that compared imipenem to an alternative antibiotic in patients with *P. aeruginosa* [298]. Patients who received imipenem had a lower clinical cure rate (45% vs 75%; RR, 0.60; 95% CI, .48–.75) and microbiological cure rate (48% vs 53%; RR, 0.91; 95% CI, .73–1.13) than patients who received an alternative antibiotic. Among patients who received imipenem, antibiotic resistance increased from 15% to 39%; among patients who received an alternative antibiotic, antibiotic resistance increased from 2.5% to 22%. The panel's confidence in these estimated effects was low because they are derived from randomized trials limited by risk of bias (ie, many trials were unblinded) and imprecision (ie, few events).

Other carbapenems: We identified a published systematic review of 12 randomized trials that compared a carbapenem (alone or in combination with an aminoglycoside) to an alternative antibiotic in patients with *P. aeruginosa* [299]. Most of the trials compared a carbapenem to either a fluoroquinolone or a β-lactam. Our meta-analyses found that patients treated with a carbapenem had a lower treatment success rate (6 randomized trials: OR, 0.42; 95% CI, .22–.82) [159, 161, 169, 183, 300, 301], a lower eradication rate (7 randomized trials: OR, 0.50; 95% CI, .24–.89) [159, 161, 169, 173, 183, 299, 300], and a higher incident antibiotic resistance rate (4 randomized trials: OR, 5.17; 95% CI, 1.96–13.65) [173, 291, 293, 301]. Exceptions to the lower eradication rate existed when the carbapenem was meropenem (3 randomized trials: OR, 1.10; 95% CI, .39–3.14) [159, 161, 300]. The panel's confidence in these estimated effects was very low because they are derived from randomized trials limited by risk of bias (ie, many trials were unblinded), inconsistency (ie, low I^2 test for heterogeneity), and imprecision (ie, few events). Ertapenem has no or limited activity against

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P. aeruginosa and is therefore not recommended for treatment of pneumonia due to this organism.

Aminoglycosides: Our systematic review identified no recent trials comparing aminoglycoside monotherapy to other antimicrobial regimens in HAP/VAP and, therefore, there were no data related to the effects of such therapy in patients with HAP/VAP due to *P. aeruginosa*.

Rationale for the Recommendations

The evidence synthesis failed to identify an antipseudomonal agent that is clearly preferable to the others, due to either greater benefit or less harm. Thus, the panel did not recommend a preferred antibiotic regimen for patients with confirmed HAP/VAP caused by *P. aeruginosa*. Some of the outcomes described above suggest that imipenem may have outcomes that are inferior to other regimens (ie, a lower cure rate); however, the panel's confidence in these results was so low that it was unwilling to suggest not using this agent.

The panel recognized that as many as two-thirds of patients with HAP/VAP caused by *P. aeruginosa* have antibiotic resistance and that the prevalence of antibiotic resistance is widely variable. This variability was the primary reason that the panel agreed that antibiotic choices should be based upon antimicrobial susceptibility testing. The benefits of this approach include assurance that the patient is being treated with an antibiotic with activity against the pathogen, while the downsides are the costs, burdens, and delays associated with testing. The recommendation is strong despite the low quality of evidence because the panel agreed that the importance of avoiding ineffective therapy (ie, potential for harms without benefits) far outweighs the costs, burdens, and time for antibiotic susceptibility testing.

The aminoglycosides are the only exceptions with regard to the panel not making a recommendation for or against a specific antibiotic class in HAP/VAP due to *P. aeruginosa*. The panel chose to recommend against aminoglycoside monotherapy for 2 reasons. First, aminoglycosides penetrate the lung poorly; therefore, high peak serum concentrations are necessary to obtain microbiologically active concentrations in the alveoli, which increases the risk of nephrotoxicity and ototoxicity [266, 302, 303]. Studies have found no detectable antipseudomonal activity within bronchial secretions despite therapeutic aminoglycoside levels in the serum of patients with *Pseudomonas* pulmonary infection [304]. Second, there is a lack of studies evaluating the effects of aminoglycoside monotherapy in HAP/VAP.

Occasionally, routine antimicrobial susceptibility testing identifies no antibiotics to which *P. aeruginosa* is susceptible. Intravenous polymyxins (colistin or polymyxin B) [305–310] may be an option for the treatment of such extensively resistant *P. aeruginosa* [184]. For this reason, the panel agreed that polymyxin susceptibility should be routinely assessed for *Pseudomonas* isolates in settings with a high prevalence of extensively resistant organisms.

Research Needs

There is a lack of trials that enrolled patients with HAP/VAP caused by *P. aeruginosa* and compared antibiotic regimens, and subgroup analysis from trials that enrolled patients with HAP/VAP caused by any pathogen are limited by the small sizes of the subgroups. There is an urgent need for multicenter trials that enroll patients with HAP/VAP caused by *P. aeruginosa* and then evaluate the benefits and harms of various antibiotic regimens. Such trials should measure mortality, treatment failure, side effects, and antibiotic resistance as outcomes, and should control for variables such as severity of illness, bacteremia, organ failure, and aminoglycoside use.

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 were known, continued combination therapy is not recommended.

Summary of the Evidence

Our systematic review identified one published systematic review [290] and 7 randomized trials [159, 161, 162, 170, 171, 181, 311] that compared monotherapy to combination therapy in the treatment of HAP/VAP due to any pathogen. The published systematic review included 41 randomized trials (7015 patients) [290]. HAP/VAP caused by *P. aeruginosa* represented 13.8% of cases. Our meta-analysis of trials that reported mortality determined that combination therapy offered no benefit beyond monotherapy (RR, 0.94; 95% CI, .76–1.16); similarly, a meta-analysis of trials that reported the treatment failure rate determined that combination therapy was not associated with a lower rate of treatment failure than monotherapy. Among the 7 randomized trials, 5 trials found that patients treated with combination therapy and monotherapy had similar

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clinical outcomes which, depending upon the study, included mortality, clinical treatment success, microbiological treatment success, and ICU and hospital length of stay [159, 161, 162, 170, 171, 181, 311]. Two trials, however, demonstrated superior outcomes among those who received carbapenem monotherapy compared with those who received combination therapy [159, 161]. The different findings in these trials might be attributable to the combination of the broad spectrum of carbapenems and increased nephrotoxicity due to aminoglycoside-containing combination therapy.

Taken together, the efficacy information provided by the systematic review and most randomized trials was remarkably similar, finding no differences between monotherapy and combination therapy for mortality, treatment failure, ICU and hospital length of stay, duration of mechanical ventilation, and acquisition of resistance. The panel's confidence that these estimates apply to the clinical question was low because there was a risk of bias (many trials were unblinded) and because the trials enrolled patients with HAP/VAP due to any pathogen. The latter introduces indirectness of the population, as the clinical question was about patients with HAP/VAP due to *P. aeruginosa*, but only 6%–23% of the population in the trials had HAP/VAP due to *P. aeruginosa*. Additional limitations that the panel was aware of, but did not consider serious enough to warrant further downgrading of the quality of evidence, were that most of the studies were conducted more than a decade ago and the antimicrobial agent was often not the only independent variable, as the duration of therapy also varied.

More direct evidence (ie, studies that specifically evaluated patients with HAP/VAP due to *P. aeruginosa*) was available from the 2 observational studies [312, 313]. The first was a multicenter observational study that included 183 episodes of VAP caused by *P. aeruginosa* [312]. Inappropriate empiric therapy was associated with increased mortality (adjusted hazard ratio [HR], 1.85; 95% CI, 1.07–3.10), and the initial use of combination therapy reduced the likelihood of inappropriate therapy. Once patients who received inappropriate empiric treatment were excluded, however, mortality was similar among those who received definitive treatment using monotherapy and combination therapy (23.1% vs 33.2%; adjusted HR, 0.90; 95% CI, .50–1.63). The second was a single-center observational study that enrolled 100 consecutive patients with bacteremic *P. aeruginosa* pneumonia [313]. It found that a decreased all-cause 28-day mortality was associated with the absence of septic shock at the time of bacteremia (OR, 0.07; 95% CI, .01–.49) and adequate combination therapy (OR, 0.05; 95% CI, .01–.34).

The observational studies suggest that combination therapy is beneficial for initial empiric therapy; however, once the antibiotic susceptibilities are known, there are no differences in outcome among patients who receive definitive treatment using monotherapy or combination therapy. Nonetheless, there is a possibility that a subset of patients with *P. aeruginosa* pneumonia complicated by septic shock may benefit from combination therapy [313, 314]. The panel's confidence in these effects was also low because they were based upon observational studies.

Septic shock: The panel sought additional evidence that patients with septic shock may benefit from combination therapy by looking at evidence from patients who had septic shock from sources other than just HAP/VAP caused by *P. aeruginosa*. The studies identified had inconsistent results. A meta-analysis of 64 randomized and quasi-randomized trials (7586 patients with culture-positive bacterial septic shock) that compared β-lactam monotherapy to combination therapy with a β-lactam and aminoglycoside in hospitalized patients with sepsis determined that there was no difference in mortality, regardless of whether the trial arms included the same β-lactam (RR, 1.01; 95% CI, .75–1.35) or different β-lactams (RR, 0.85; 95% CI, .71–1.01) [315]. In contrast, a propensity-matched analysis (2446 patients) found that early combination therapy was associated with decreased mortality in septic shock [314].

A potential reason for the discordant results is that the studies did not require specific criteria to define the patients as having septic shock. It is possible that the benefits of combination therapy were diluted by including less severely ill patients in the studies. This is supported by a meta-analysis of randomized trials and observational studies that determined that combination antimicrobial therapy decreased mortality only among patients with severe sepsis or septic shock and a high risk of death (31% vs 41%; HR, 0.71; 95% CI, .57–.89 among patients with sepsis due to pneumonia, who comprised 36% of the study population), with potentially harmful consequences in low-risk patients [316].

The guideline panel had very low confidence that the estimated effects of monotherapy and combination therapy from these studies of sepsis and septic shock from any cause are accurate in patients with sepsis or septic shock due to HAP/VAP caused by *P. aeruginosa*, because much of the evidence base is observational and the results are both inconsistent and indirect (the question is about patients with septic shock due to *P. aeruginosa* pneumonia, but the evidence is from patients with septic shock from any cause). To be consistent with the approach described above, the panel did not further downgrade the quality of evidence due to the age of the studies [317] or the variability of the duration of antibiotic therapy.

Bacteremia: Approximately 20% of patients with *P. aeruginosa* bacteremia develop septic shock according to an observational study of 709 episodes of *P. aeruginosa* bacteremia, and those who develop septic shock are at increased risk for mortality (OR, 6.6; 95% CI, 4.0–10.0) [318]. Given the strong relationship between shock and bacteremia, the panel also sought additional evidence that patients with bacteremia may benefit from combination therapy by looking at evidence from patients who had bacteremia from sources other than just HAP/VAP caused by *P. aeruginosa*.

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An initial meta-analysis from 2004 comparing combination antimicrobial therapy with monotherapy for *Pseudomonas* bacteremia demonstrated a mortality benefit from combination antimicrobial therapy (OR, 0.50; 95% CI, .32–.79) [319]. However, more recent studies have not confirmed this finding. Three meta-analyses that included more recent studies compared the use of combination therapy to monotherapy for definitive therapy in patients with *P. aeruginosa* bacteremia and found no differences in all-cause mortality [320–322]. The largest individual study was a post hoc analysis of an observational study that compared monotherapy to combination therapy in 593 patients with a single episode of *P. aeruginosa* bacteremia; it demonstrated that combination therapy was not associated with a reduction in the 30-day mortality risk compared with monotherapy (adjusted HR, 1.34; 95% CI, .73–2.47) [323]. A potential explanation for the different findings in the initial meta-analysis and the subsequent studies is that many of the studies in the initial meta-analysis included patients who received aminoglycoside monotherapy.

The guideline panel had very low confidence that the estimated effects of monotherapy and combination therapy from these studies apply to patients with *P. aeruginosa* bacteremia due to HAP/VAP. The reasons for the very low confidence are that a large proportion of the evidence base is observational with inconsistent results, and because of indirectness of the population (the question is about patients who are severely ill with septic shock and bacteremia due to *P. aeruginosa* pneumonia, but the evidence is from patients whose severity of illness was unspecified and who have *P. aeruginosa* bacteremia from any source).

Rationale for the Recommendations

The evidence synthesis found no differences in the effects of monotherapy and combination therapy as definitive treatment (ie, treatment once the antibiotic susceptibility results are known) on mortality, treatment failure, ICU and hospital length of stay, duration of mechanical ventilation, and acquisition of resistance, regardless of whether the results derived from observational studies that enrolled patients with HAP/VAP caused by *P. aeruginosa* or meta-analyses of randomized trials that enrolled patients with HAP/VAP due to any pathogen. The panel felt strongly that, in the absence of any demonstrable benefit, the costs and potential side effects of an additional antibiotic were not warranted. Therefore, the recommendation is strong despite the low quality of evidence.

There was an important exception, however. The panel judged that combination therapy is warranted as definitive therapy for patients with HAP/VAP due to *P. aeruginosa* who have septic shock or a high risk for death. The decision was based upon the evidence that combination therapy was associated with decreased mortality among patients with pneumonia complicated by septic shock. The panel agreed that the potential for decreased mortality outweighs the additional costs, inconveniences, and possible side effects attributable to an additional antibiotic. The potential upsides of the recommendation seemed more important to patients than the potential downsides.

The panel chose to recommend against aminoglycoside monotherapy as definitive therapy for 2 reasons. First, aminoglycosides penetrate the lung poorly; therefore, high peak serum concentrations are necessary to obtain microbiologically active concentrations in the alveoli, which increases the risk of nephrotoxicity and ototoxicity [266, 302, 303]. Studies have found no detectable antipseudomonal activity within bronchial secretions despite therapeutic aminoglycoside levels in the serum of patients with *Pseudomonas* pulmonary infection [304]. Second, there is a lack of studies evaluating the effects of aminoglycoside monotherapy in HAP/VAP. Given this lack of empirical evidence, the recommendation is based upon the committee's collective clinical experience.

Research Needs

The potential benefit of combination therapy in patients with septic shock is based upon studies in septic shock from any cause. These findings need to be confirmed by randomized trials in patients with septic shock due to *P. aeruginosa* pneumonia. Outcomes for such trials should include mortality, treatment failure, ICU and hospital length of stay, side effects, and development of antibiotic resistance.

XVIII. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to 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.

Summary of the Evidence

Comparative antibiotic data for HAP/VAP caused by ESBL-producing gram-negative organisms is extremely limited. There are no randomized trials or observational studies that specifically enrolled patients with HAP/VAP due to ESBL-producing gram-negative organisms; furthermore, trials that enrolled patients with HAP/VAP due to any pathogen had an insufficient number of cases due to ESBL-producing gram-negative organisms to make subgroup analyses possible [291, 324–326].

The only evidence that exists is a few case series that describe the failure of third-generation cephalosporins in treating ESBL-producing pathogens [327, 328]. In the absence of any randomized

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trials or observational studies, the guideline panel relied upon the case series and its collective clinical experience to formulate its judgments, which constitutes very low-quality evidence.

Rationale for the Recommendation

Our evidence synthesis failed to identify an agent that is clearly preferable to others in the treatment of HAP/VAP due to ESBL-producing gram-negative bacilli. Thus, the panel did not recommend a preferred antibiotic regimen for patients with confirmed HAP/VAP caused by ESBL-producing gram-negative bacilli. The panel was aware that carbapenems are sometimes considered the agents of choice for treating such infections, in light of the case series describing failure of third-generation cephalosporin therapy. One recent study favored carbapenems but also suggested that the use of β-lactam/β-lactamase inhibitors may be beneficial [329], and another suggested that either cefepime or piperacillin-tazobactam may be used against ESBL infections if the MICs are within susceptible ranges [330]. However, the panel's confidence in those data was so low that it did not want to use the series as the basis of a recommendation either for carbapenems or against cephalosporins or β-lactam/β-lactamase inhibitors.

The panel agreed that antimicrobial susceptibility testing provides the best information to inform antibiotic choices. However, the panel recognized that such testing often provides clinicians with several choices and, therefore, agreed that patient-specific factors such as allergies and comorbidities should also be considered. The recommendation is strong despite the very low quality of evidence because the panel agreed that the importance of identifying an effective therapy far outweighs the costs, burdens, and time for antibiotic susceptibility testing. Of note, the Clinical and Laboratory Standards Institute no longer recommends specific ESBL testing; thus, this recommendation also applies when the ESBL phenotype is suspected.

Research Needs

There is an urgent need for studies comparing various antibiotic regimens in the treatment of pneumonia due to ESBL-producing gram-negative bacilli. Appropriate clinical outcomes include mortality, treatment failure rate, ICU and hospital length of stay, acquired antibiotic resistance, and 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.

Summary of the Evidence

Our systematic review identified 6 randomized trials [155, 259, 331–334] and 6 observational studies [256, 257, 261, 335–337] that evaluated the impact of specific antibiotics on clinical outcomes in critically ill patients with VAP/HAP due to *Acinetobacter* species. The studies found no differences in mortality, length of ICU stay, or clinical response when standard-dose ampicillin-sulbactam was compared with imipenem [335], intravenous colistin [332], or high-dose ampicillin-sulbactam [333], or when imipenem was compared to intravenous colistin [337]. In contrast, a trial found that tigecycline decreased clinical cure rates compared with imipenem [155], and an observational study demonstrated that tigecycline-based therapy was associated with higher mortality than was colistin-based therapy, although the latter was associated with more nephrotoxicity [336]. The panel had low confidence that the estimated effects from these studies are an accurate reflection of the effects in patients with HAP/VAP due to *Acinetobacter* species because the estimates were derived from observational studies, as well as randomized trials with both a risk of bias (ie, some studies were not blinded) and indirectness of the population (ie, the question is about patients with HAP/VAP due to *Acinetobacter* species, but the studies enrolled patients with HAP/VAP due to a variety of gram-negative bacilli). Evidence on polymyxin B for the treatment of HAP/VAP is growing, but also limited by low-quality evidence [305–308, 338].

Adjunctive therapies have also been studied. Two observational studies [257, 261] suggested that the combination of aerosolized colistin plus intravenous colistin was associated with a higher clinical response than intravenous colistin alone, although no significant difference in mortality was observed. In contrast, the addition of rifampicin to intravenous colistin did

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not improve clinical outcomes such as mortality in 2 randomized trials (even though it improved microbiological eradication) [331, 334]. The addition of aerosolized colistin to an intravenous antibiotic other than colistin resulted in no change in mortality in a randomized trial [259]. The panel had low confidence in most of these estimated effects for the same reasons as described above; however, it had moderate confidence in the estimated effects of the addition of rifampicin because the effects were derived from 2 randomized trials with a risk of bias.

Rationale for the Recommendations

The evidence suggests that the carbapenems (including imipenem), ampicillin-sulbactam, and colistin are equally effective at treating *Acinetobacter* species that are determined by antimicrobial sensitivity testing to be sensitive to those agents. The guideline panel agreed that the carbapenems and ampicillin-sulbactam are preferred due to fewer side effects, whereas colistin should be reserved for *Acinetobacter* species that are sensitive only to colistin due to the risk of nephrotoxicity from colistin therapy. The recommendation to use colistin to treat *Acinetobacter* species that are sensitive only to colistin was strong despite the low quality of evidence because, for such patients, there are no other therapeutic options, so colistin therapy may be lifesaving.

The use of adjunctive therapies was discussed at length by the guideline panel. Adjunctive aerosolized colistin improved clinical outcomes without increasing harms; the panel agreed that the additional benefits outweighed the additional burdens and costs of such therapy and, therefore, opted to recommend adjunctive aerosolized colistin. In contrast, adjunctive rifampicin did not improve outcomes and, therefore, was not recommended because its burdens, costs, and risks clearly exceed the benefits.

Finally, the evidence synthesis indicated that the current label dose of tigecycline worsened clinical outcomes compared with several other therapies. The panel's strong recommendation against tigecycline despite low-quality evidence is intended to emphasize the importance of avoiding potentially harmful therapies, particularly when alternative choices exist.

Research Needs

There is an urgent need for studies comparing various antibiotic regimens in the treatment of pneumonia due to *Acinetobacter* species. Appropriate clinical outcomes include mortality, treatment failure rate, ICU and hospital length of stay, acquired antibiotic resistance, and side effects.

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 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.

Summary of the Evidence

Our systematic review identified 5 observational studies [256, 257, 261, 339, 340] and 4 randomized trials [259, 331, 332, 334] relevant to the clinical question. *Acinetobacter baumannii* was the only organism or predominant organism in most studies, and intravenous colistin monotherapy was the comparator in most studies.

Most of the studied antibiotics conferred similar effects when given intravenously. A trial that randomly assigned patients to ampicillin-sulbactam or intravenous colistin found no difference in mortality or clinical response [332]. An observational study that similarly compared intravenous colistin and sulbactam to intravenous colistin alone detected no difference in the clinical response or microbiological response [340]. Two randomized trials comparing rifampicin plus intravenous colistin to intravenous colistin alone found no difference in mortality, clinical response, or hospital length of stay [331, 334].

In contrast, the addition of inhaled colistin to intravenous colistin appeared beneficial. Three observational studies [256, 257, 261] and one randomized trial [259] evaluated the effects of combination therapy with inhaled and intravenous colistin. Our meta-analysis of these 4 studies showed an improved clinical cure rate (RR, 1.29; 95% CI, 1.11–1.51) and trend toward improved mortality (RR, 0.75; 95% CI, .52–1.09) when the combination of adjunctive inhaled colistin plus intravenous colistin was compared to intravenous colistin monotherapy. Of note, the meta-analysis was repeated after removing one of the studies deemed to have a high risk of bias because carbapenem-resistant infections were not equally distributed between the 2 study arms and nearly 50% of patients may have had carbapenem-sensitive infections [257]. The repeat meta-analysis found

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that combination therapy with inhaled and intravenous colistin was still superior to intravenous colistin monotherapy in terms of clinical cure (RR, 1.28; 95% CI, 1.07–1.55). Inhaled colistin was not associated with nephrotoxicity, bronchospasm, or neurotoxicity, although this outcome was not systematically evaluated across studies. The risk for the development of resistant strains with inhaled colistin was addressed in one study, and no such cases were identified [256].

Nephrotoxicity is the most common side effect of intravenous colistin. In 3 studies, the frequency of colistin-associated nephrotoxicity ranged from 19% to 33% [256, 261, 332]. This degree of renal dysfunction may be unavoidable when treating critically ill patients. In fact, a meta-regression analysis showed no difference in the rate of nephrotoxicity in patients with VAP who were treated with colistin compared with more traditional agents [184]. The addition of inhaled colistin did not increase the risk of renal injury or the emergence of colistin-resistant infections. The development of *Acinetobacter* resistance to inhaled colistin has only been described in spontaneously breathing patients, probably because drug concentrations in the airway are significantly lower in these patients compared with patients on mechanical ventilation [341]. Recommendations regarding the frequency of administration and the total daily dose of intravenous colistin or polymyxin B and whether a loading dose should be administered are evolving and are beyond the scope of these guidelines, but a suggestion is made in Table 3 (see section X). These issues should be addressed with the assistance of a critical care pharmacist. Similar concerns surround the use of inhaled colistin, as neither the dose nor method of delivery is standardized. Evidence on polymyxin B for the treatment of HAP/VAP is growing, but also limited by low-quality evidence [305–308, 338].

The panel had moderate confidence in the finding of no difference among most antibiotic regimens because the finding derived from randomized trials with indirectness of the intervention (ie, colistin dosing was highly variable). In contrast, the panel had low confidence in the estimated effects of inhaled plus intravenous colistin compared with intravenous colistin alone because the effects derived from observational studies with indirectness of the intervention, as well as from randomized trials with a risk of bias (lack of blinding) and imprecision (wide CIs for the outcome of mortality).

Rationale for the Recommendation

Intravenous colistin or polymyxin B is standard therapy for HAP/VAP caused by a carbapenem-resistant pathogen because such pathogens commonly demonstrate in vitro susceptibility to only the polymyxin antibiotic class. Our systematic review found no alternative antibiotic regimen with effects superior to intravenous colistin; the panel judged that intravenous polymyxins should remain the preferred therapy until an alternative antimicrobial regimen is definitively shown to be more beneficial or less harmful, as clinical experience is becoming more
extensive.

The panel agreed that the benefits of inhaled colistin plus intravenous colistin or polymyxin B combination therapy outweighed the downsides in most patients with HAP/VAP caused by a carbapenem-resistant pathogen. The benefits considered by the panel were an improved clinical cure rate and trend toward improved mortality, while the downsides included potential harms (ie, nephrotoxicity, acquisition of colistin resistance, and other less severe side effects), increased burdens, and increased costs.

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.

Summary of the Evidence

We identified 2 published systematic reviews of randomized trials [342, 343] and an observational study [344] that compared short-course antibiotic therapy to prolonged-course therapy for VAP.

One systematic review [342] included 6 randomized trials [120, 158, 345–348] that enrolled 508 patients with HAP/VAP and compared fixed durations of antibiotic therapy. Nearly all of the patients had VAP, rather than HAP. Short courses of antibiotics (ie, 7–8 days) increased 28-day antibiotic-free days (mean difference, 4.02 days; 95% CI, 2.26–5.78 days) and reduced recurrent VAP due to MDR pathogens (42.1% vs 62.3%; OR, 0.44; 95% CI, .21–.95) compared with long courses of antibiotics (ie, 10–15 days). There were no differences in mortality, recurrent pneumonia, treatment failure, hospital length of stay, or duration of mechanical ventilation. In the subgroup of patients with VAP due to a non-glucose-fermenting gram-negative bacillus including *Pseudomonas* and *Acinetobacter* (33% of patients), short courses of antibiotics were associated with recurrent infection (OR, 2.18; 95% CI, 1.14–4.16), but no other differences.

The other systematic review [343] similarly included 4 randomized trials [345, 346, 348] that enrolled 883 patients with VAP and compared short-course antibiotic regimens (ie, 7–8 days) to long-course regimens (ie, 10–15 days). Short-course regimens increased antibiotic-free days, but there was no difference in mortality, recurrent pneumonia, ventilator-free days, duration of mechanical ventilation, or length of ICU stay.

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We conducted our own meta-analyses using the trials that were included in the published systematic reviews, as well as data provided by these trials' authors. We also found no differences between short-course antibiotic regimens (ie, 7–8 days) and long-course regimens (ie, 10–15 days) in terms of mortality, clinical cure, and recurrent pneumonia. Of note, the specific subpopulation with VAP due to non-glucose-fermenting gram-negative bacilli was analyzed, and no differences were observed for pneumonia recurrence (OR, 1.42; 95% CI, .66–3.04; $P = .37$) or mortality (OR, 0.94; 95% CI, .56–1.59; $P = .83$).

The observational study enrolled patients with VAP due to non-glucose-fermenting gram-negative bacilli, which included 27 patients who were treated with antibiotics for 3–8 days and 127 patients who were treated for ≥9 days. There were no differences in mortality or recurrence rate among patients who received a short course of antibiotics compared to those who received a long course [344].

Taken together, the evidence indicates that short courses of antibiotics reduce antibiotic exposure and recurrent pneumonia due to MDR organisms. Other clinical outcomes such as mortality do not appear to be affected by the duration of antibiotic therapy, with the exception of short courses, which were associated with recurrence of the initial VAP due to a non-glucose-fermenting gram-negative bacillus in some previous studies, but not in our updated meta-analysis. The panel's confidence in these results was moderate, reflecting that they derive from meta-analyses of randomized trials that have a risk for bias. The risk of bias is due to many of the trials not being blinded and recurrence being measured at 30 days, which allows more time for recurrence to occur in the short-course arms of the trials, potentially biasing the studies in favor of long-course antibiotics. There was also indirectness; the question is for all patients with VAP, but the largest trial excluded patients with early VAP.

Rationale for the Recommendation

The desirable consequences of a short-course antibiotic regimen are that it decreases antibiotic exposure and antibiotic resistance, without increasing recurrent disease or mortality. The decreased antibiotic exposure almost certainly reduces costs and side effects. The undesirable consequence of a short-course antibiotic regimen is that occasionally antibiotics will be discontinued in a patient who needs them, resulting in recurrent VAP. The evidence suggests that this is very uncommon and, therefore, the panel had a high level of confidence that the benefits of a short-course antibiotic regimen outweighed the harms, leading to their recommendation to use antibiotics for 7 days rather than 8–15 days in patients with VAP.

The panel considered whether a separate recommendation was indicated for patients with VAP due to non-glucose-fermenting gram-negative bacilli, in light of the previous evidence suggesting that recurrence may be increased in such patients who receive a short course of antibiotics. The panel agreed that a different recommendation was not indicated because, even if there is a small increased recurrence rate, mortality and clinical cure do not appear to be affected; in addition, the evidence for recurrence is from subgroup analyses with important limitations. These include all of the following: There was potential bias in favor of long-course therapy due to the differential time period during which recurrence was assessed; there was the possibility that the second episode of VAP is incorrectly being considered a recurrence because of persistent colonizing organisms being cultured; many studies reported superinfections from both lung and other organ sites (eg, urinary tract infection) as recurrence; pulmonary infiltrates are known to persist on imaging studies and lag behind clinical resolution, leading to false identification of a new or recurrent pneumonia; and many subgroup analyses were performed, raising the possibility of multiple hypothesis testing.

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.

Summary of the Evidence

The guideline panel found no studies that provided useful data for comparing short-term to long-term antibiotic therapy in HAP; however, the duration of therapy has been studied in VAP. Short courses of antibiotics (ie, 7–8 days) increased 28-day antibiotic-free days (mean difference, 4.02 days; 95% CI, 2.26–5.78 days) and reduced recurrent VAP due to MDR pathogens (42.1% vs 62.3%; OR, 0.44; 95% CI, .21–.95) compared with long courses of antibiotics (ie, 10–15 days). There were no differences in mortality, recurrent pneumonia, treatment failure, hospital length of stay, or duration of mechanical ventilation. In the subgroup of patients with VAP due to a non-glucose-fermenting gram-negative bacillus, including *Pseudomonas and Acinetobacter* (33% of patients), short courses of antibiotics were associated with recurrence (41.8% vs 24.7%; OR, 2.18; 95% CI, 1.14–4.16), but no mortality or other clinical differences were found [342, 345–347]. The increased risk of recurrence might have been in part due to bias created by how the time to recurrence was defined. A more recent and larger body of evidence comparing short-course vs long-course antibiotic treatment found no differences in mortality, recurrent pneumonia, treatment failure, hospital length of stay, or duration of mechanical ventilation (see section XXI).

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Rationale for the Recommendation

Due to the absence of studies comparing short-term to long-term antibiotic therapy in patients with HAP, the guideline panel used evidence from patients with VAP to inform its judgments. The evidence suggests that antibiotic therapy for ≤7 days does not reduce the benefits of antibiotic therapy; however, the shorter duration of therapy almost certainly reduces antibiotic-related side effects, *C. difficile* colitis, the acquisition of antibiotic resistance, and costs. Given these potential benefits of a shorter duration of therapy without known harms, the panel decided that empiric antibiotic therapy should be prescribed for ≤7 days. The recommendation is strong, reflecting the panel's belief in the importance of avoiding therapies that are potentially harmful and costly if there is no evidence of benefit.

The guideline panel agreed that it is reasonable to empirically de-escalate the antimicrobial regimen to a single broad-spectrum antibiotic in patients who have a negative sputum culture and are clinically improving, provided that there is ongoing coverage according to a local HAP antibiogram, or, if not available, for enteric gram-negative bacilli and MSSA. Patients who have not had sputum cultures performed, have factors that diminish the reliability of the sputum culture (eg, antibiotic therapy prior to obtaining the sample or a poor-quality sample), or are at high risk for MDR infections may not be appropriate candidates for de-escalation.

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.

Summary of the Evidence

We identified 6 relevant studies that enrolled patients with nosocomial pneumonia [194, 196, 229, 349–351]. One of the studies was a randomized trial [229], and the remaining 5 were observational studies [196, 349–351]. One study found lower mortality with de-escalation therapy [196], 3 studies found a non–statistically significant reduction in mortality with de-escalation therapy [349–351], and 2 studies found an increase in mortality with de-escalation therapy [194, 229]. When the studies were pooled, there was no difference in mortality for the de-escalation group vs the fixed-regimen group (19.7% vs 22.6%; OR, 0.81; 95% CI, .64–1.1).

Other outcomes were similarly inconsistent or unaffected by the antimicrobial strategy. For ICU length of stay, the randomized trial found that de-escalation caused a non–statistically significant decrease in the length of stay [229], whereas one of the observational studies found that de-escalation was associated with a non–statistically significant increase in the length of stay [349]. Recurrence of pneumonia was the same in both the de-escalation and fixed-regimen groups in 2 observational studies [194, 350]. One of the studies reported an increase in emergence of resistant pathogens, particularly MRSA, in the de-escalation group (37.9% vs 16.7%; $P < .05$) [229].

Following our systematic review, a randomized trial was reported that specifically compared a de-escalation strategy of antimicrobial management to a fixed strategy. It defined de-escalation as narrowing the spectrum of initial antimicrobial therapy and a fixed strategy as the continuation of appropriate antimicrobial therapy until therapy was complete. The trial randomly assigned 116 patients with sepsis in the ICU to receive either a de-escalation strategy or fixed strategy. Pneumonia was a more common cause of sepsis in the de-escalation group (58% vs 40%). De-escalation increased the number of antimicrobial days (9 days vs 7.5 days; $P = .03$) and the risk of superinfection (27% vs 11%; RR, 2.58; 95% CI, 1.09–6.12). There was no difference in mortality or ICU length of stay [352]. In a subgroup analysis of the 56 patients with pneumonia, there were no differences in any of the outcomes measured.

Taken together, the evidence indicates the following: There are no differences between de-escalation and a fixed antimicrobial regimen in terms of mortality or ICU length of stay; there is conflicting evidence about the effect of de-escalation on the incidence of recurrent pneumonia; and de-escalation may increase antimicrobial days, superinfection, and the emergence of MRSA. The panel's confidence in these estimated effects is very low. The panel's systematic review consisted mostly of observational studies that were limited by risk of bias, indirectness (different definitions of de-escalation, different antimicrobial regimens and protocols), and inconsistent results. The subsequent randomized trial was limited by both serious risk of bias (not blinded, failure of randomization [ie, baseline differences]) and probably also indirectness (the question is about patients with HAP/VAP, but the trial may have included patients with healthcare-associated non-HAP/VAP pneumonia).

Rationale for the Recommendation

De-escalation is widely considered the preferable approach to antimicrobial management and has become a principle of antimicrobial stewardship. National guidelines and numerous papers contend that de-escalation is beneficial because it likely reduces antimicrobial resistance, side effects, and costs [1, 195, 353–358]. However, there is very little evidence that substantiates these presumed benefits, and there is some evidence (albeit very poor-quality evidence) that de-escalation may have some undesirable effects. These undesirable effects may, in part, be the result of changing an appropriate antimicrobial regimen

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to an inappropriate regimen due to misinterpretation of microbiological tests, misleading microbiological tests (eg, poor-quality specimens reflecting contamination), or erroneous decision making.

The panelists felt that the evidence was poor and that they had essentially no confidence in the estimated effects of a de-escalation strategy compared with a fixed regimen. Therefore, the panel elected to inform its recommendation with unsystematic observations (ie, clinical experience) and clinical rationale. They had a high level of confidence that de-escalation reduces costs, burdens, and side effects, and that it is very likely that de-escalation also reduces antimicrobial resistance. In contrast, they thought it may be possible that recurrent pneumonia could be increased by de-escalation, but had serious doubts that de-escalation could increase superinfection or antimicrobial days. When these factors were considered together, the panel judged that the potential benefits of de-escalation outweigh the possible harms and, therefore, recommended de-escalation.

Research Needs

Well-done randomized trials comparing the effects of de-escalation and fixed antimicrobial regimens on clinical outcomes are urgently needed. With antibiotic resistance considered one of the most significant threats of the current era and de-escalation a potential way to combat resistance, such research demands a high priority.

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.

Summary of the Evidence

We identified a published systematic review that selected randomized trials that enrolled patients with acute respiratory infections and compared PCT-based antibiotic decision making with conventional (ie, no PCT) decision making. The review selected 14 trials with 4221 patients and found that PCT-based decision making decreased antibiotic exposure (adjusted mean difference, −3.47 days; 95% CI, −3.78 to −3.17 days) and was not associated with increased mortality or treatment failure [359, 360]. The generalizability of these findings is limited by indirectness, as the question is about the discontinuation of antibiotics in patients with VAP, but the trials included patients with any type of acute respiratory infection and evaluated both the initiation and discontinuation of antibiotics. The evidence is predominantly from patients with VAP, so our recommendations for HAP are mostly based on VAP studies.

In addition, we identified 2 published randomized trials [361, 362] and an abstract of a randomized trial [363], all of which specifically evaluated the discontinuation of antibiotic therapy for VAP on the basis of PCT levels plus clinical criteria vs clinical criteria alone. When pooled, the trials included 308 patients with VAP and found that those patients whose antibiotics were either continued or discontinued on the basis of PCT levels plus clinical criteria had a shorter duration of antibiotic therapy (9.1 days vs 12.1 days; $P < .00001$), but no difference in mortality. Other outcomes were reported by only some of the trials, but included no effects on the duration of mechanical ventilation, length of ICU stay, length of hospital stay, incidence of recurrent pneumonia, or development of resistance.

Taken together, the evidence suggests that discontinuing antibiotics on the basis of PCT levels plus clinical criteria decreases antibiotic exposure compared with using clinical criteria alone; all other outcomes remain unchanged. The panel had low confidence in these results because they derive from a meta-analysis of 14 randomized trials with both a serious risk of bias (the trials were not blinded) and indirectness, as well as from a meta-analysis of 3 randomized trials with a serious risk of bias (the trials were not blinded) and some inconsistency ($I^2 = 21\%$). Moreover, the control groups in the trials had routinely received 9–15 days of antibiotics; it is uncertain if a benefit would also be seen in hospitals that have a lower baseline duration of antibiotic therapy [342, 345].

Rationale for the Recommendation

The desirable consequence associated with the use of PCT levels to guide the discontinuation of empiric antibiotic therapy is that it decreases antibiotic exposure without increasing treatment failure or mortality. The decreased antibiotic exposure almost certainly reduces costs and side effects. The undesirable consequences of using PCT levels to guide the discontinuation of empiric antibiotic therapy are that PCT testing is more costly and burdensome than clinical criteria alone. Moreover, falsely low PCT levels may encourage inappropriate discontinuation of necessary antibiotic therapy and falsely high PCT levels may lead to the continuation of unnecessary antibiotic therapy. When all these factors were considered, the panel felt that the benefits of decreased antibiotic exposure outweighed the costs, burdens, and uncertain results associated with PCT testing.

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)*.

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Summary of the Evidence

Use of the CPIS as a diagnostic tool was discussed above. The CPIS has also been studied as a management tool to aid in the decision of whether or not to discontinue antibiotics. Our systematic review identified 3 such studies [120, 193, 364]. The evidence is predominantly from patients with VAP, so our recommendations for HAP are mostly based on VAP studies.

In the first study, 81 ICU patients with pulmonary infiltrates and a CPIS ≤6 (low risk of pneumonia) were randomly assigned to standard therapy (choice and duration of antibiotic therapy at the discretion of the clinician) or ciprofloxacin monotherapy with reevaluation at 3 days. If the CPIS remained ≤6 at 3 days, ciprofloxacin was discontinued; otherwise, it was continued. Patients in the standard therapy group were more likely to receive ≥3 days of antibiotic therapy than patients in the CPIS group (90% vs 28%; $P = .0001$). There was no difference in mortality or ICU length of stay; however, patients in the CPIS group had a shorter duration of antibiotic therapy (3.0 days vs 9.8 days; $P = .0001$), a less expensive treatment course ($259 vs $640; $P = .0001$), and less antibiotic resistance and fewer superinfections (14% vs 38%; RR, 0.36; 95% CI, .14–.89) [120].

In the second study, 290 patients with VAP were assigned to have the duration of empiric antibiotic therapy for VAP determined using an antibiotic discontinuation policy (discontinuation group) or according to the clinical judgment of the treating ICU physicians (conventional group). The discontinuation policy required discontinuation of antibiotics if a noninfectious etiology for the infiltrates was identified or the symptoms and signs of infection resolved; the symptoms and signs overlapped with the CPIS, but were slightly different. The duration of antibiotic therapy was reduced in the discontinuation group compared with the conventional therapy group (6 days vs 8 days; $P = .001$), but there were no differences in mortality, ICU length of stay, development of resistance, or incidence of superinfections [193, 364].

The third study was an observational study of 102 patients with VAP that compared outcomes among patients managed prior to the implementation of an antimicrobial guideline with outcomes among patients managed after implementation of the guideline. The guideline set standard antibiotic therapy to 7 days and encouraged a longer duration of therapy only for patients with evidence of ongoing active infection; this evidence closely overlapped with the CPIS (ie, fever, leukocytosis, persistent infiltrates, ongoing purulent sputum). Following implementation of the guideline, the duration of antibiotic therapy was shorter (8.6 days vs 14.8 days; $P < .001$), and recurrent VAP was less common (7.7% vs 24%; RR, 0.32; 95% CI, .11–.93) [193, 364].

Taken together, the evidence is inconsistent. One study suggests that use of the CPIS to determine antibiotic duration decreases cost, antibiotic resistance, and superinfection [120], but 2 other studies suggest that use of the CPIS has no effect on most clinical outcomes [193, 364]. The panel had low confidence in these estimated effects because, although 2 of the studies were randomized trials, the evidence was limited by inconsistency and indirectness (the question is about the use of CPIS in patients with VAP, but one trial enrolled patients with a low likelihood of VAP and the other studies used criteria slightly different from the CPIS).

Rationale for the Recommendation

This recommendation illustrates the panel's belief that an unproven intervention should not be recommended. Implementation of the CPIS is not costly and is minimally burdensome; however, it may be harmful if it does not reliably discriminate patients who can safely have their antibiotics discontinued from patients who should have their antibiotics continued, since it may lead to the discontinuation of antibiotics in patients who need ongoing antimicrobial therapy.

Notes

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References

1. American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med **2005**; 171:388–416.

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on 15 May 2018

2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ **2008**; 336:924–6.
3. US Food and Drug Administration (FDA). Information for healthcare professionals: colistimethate (marketed as Coly-Mycin M and generic products). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124896.htm. Accessed September 2014.
4. Magill SS, Edwards JR, Fridkin SK; Emerging Infections Program Healthcare-Associated Infections Antimicrobial Use Prevalence Survey Team. Survey of health care-associated infections. N Engl J Med **2014**; 370:2542–3.
5. Dudeck MA, Weiner LM, Allen-Bridson K, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, device-associated module. Am J Infect Control **2013**; 41:1148–66.
6. Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) report, data summary for 2009, device-associated module. Am J Infect Control **2011**; 39:349–67.
7. Wang Y, Eldridge N, Metersky ML, et al. National trends in patient safety for four common conditions, 2005–2011. N Engl J Med **2014**; 370:341–51.
8. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis **2013**; 13:665–71.
9. Muscedere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis **2010**; 51(suppl 1):S120–5.
10. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol **2012**; 33:250–6.
11. Sopena N, Sabria M; Neunos Study Group. Multicenter study of hospital-acquired pneumonia in non-ICU patients. Chest **2005**; 127:213–9.
12. Esperatti M, Ferrer M, Giunta V, et al. Validation of predictors of adverse outcomes in hospital-acquired pneumonia in the ICU. Crit Care Med **2013**; 41:2151–61.
13. Coffin SE, Klompas M, Classen D, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. Infect Control Hosp Epidemiol **2008**; 29 (suppl 1):S31–40.
14. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol **2014**; 35(suppl 2):S133–54.
15. Chalmers JD, Rother C, Salih W, Ewig S. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clin Infect Dis **2014**; 58:330–9.
16. Gross AE, Van Schooneveld TC, Olsen KM, et al. Epidemiology and predictors of multidrug-resistant community-acquired and health care-associated pneumonia. Antimicrob Agents Chemother **2014**; 58:5262–8.
17. Yap V, Datta D, Metersky ML. Is the present definition of health care-associated pneumonia the best way to define risk of infection with antibiotic-resistant pathogens? Infect Dis Clin North Am **2013**; 27:1–18.
18. Jones BE, Jones MM, Huttner B, et al. Trends in antibiotic use and nosocomial pathogens in hospitalized veterans with pneumonia at 128 medical centers, 2006–2010. Clin Infect Dis **2015**; 61:1403–10.
19. Valles J, Martin-Loeches I, Torres A, et al. Epidemiology, antibiotic therapy and clinical outcomes of healthcare-associated pneumonia in critically ill patients: a Spanish cohort study. Intensive Care Med **2014**; 40:572–81.
20. Hayashi Y, Morisawa K, Klompas M, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. Clin Infect Dis **2013**; 56:471–7.
21. Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS). Supplemental material for the 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. Available at: http://www.idsociety.org/Organ_System/#HospitalAcquiredVentilatorAssociatedPneumoniaHAPVAP. Accessed 9 June 2016.
22. Depuydt P, Benoit D, Vogelaers D, et al. Systematic surveillance cultures as a tool to predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. Intensive Care Med **2008**; 34:675–82.
23. Giantsou E, Liratzopoulos N, Efraimidou E, et al. Both early-onset and late-onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. Intensive Care Med **2005**; 31:1488–94.
24. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med **1998**; 157:531–9.
25. Gastmeier P, Sohr D, Geffers C, Ruden H, Vonberg RP, Welte T. Early- and late-onset pneumonia: is this still a useful classification? Antimicrob Agents Chemother **2009**; 53:2714–8.
26. Ibrahim EH, Ward S, Sherman G, Kollef MH. A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. Chest **2000**; 117:1434–42.
27. Martin-Loeches I, Deja M, Koulenti D, et al. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. Intensive Care Med **2013**; 39:672–81.
28. Restrepo MI, Peterson J, Fernandez JF, Qin Z, Fisher AC, Nicholson SC. Comparison of the bacterial etiology of early-onset and late-onset ventilator-associated pneumonia in subjects enrolled in 2 large clinical studies. Respir Care **2013**; 58:1220–5.
29. Verhamme KM, De Coster W, De Roo L, et al. Pathogens in early-onset and late-onset intensive care unit-acquired pneumonia. Infect Control Hosp Epidemiol **2007**; 28:389–97.
30. Parker CM, Kutsogiannis J, Muscedere J, et al. Ventilator-associated pneumonia caused by multidrug-resistant organisms or *Pseudomonas aeruginosa*: prevalence, incidence, risk factors, and outcomes. J Crit Care **2008**; 23:18–26.
31. George DL, Falk PS, Wunderink RG, et al. Epidemiology of ventilator-acquired pneumonia based on protected bronchoscopic sampling. Am J Respir Crit Care Med **1998**; 158:1839–47.
32. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J. Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. Am J Respir Crit Care Med **1999**; 160:608–13.
33. Leroy O, Meybeck A, d'Escrivan T, Devos P, Kipnis E, Georges H. Impact of adequacy of initial antimicrobial therapy on the prognosis of patients with ventilator-associated pneumonia. Intensive Care Med **2003**; 29:2170–3.
34. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol **2013**; 13:862–74.
35. Markowicz P, Wolff M, Djedaini K, et al. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. Am J Respir Crit Care Med **2000**; 161:1942–8.
36. Chastre J, Trouillet JL, Vuagnat A, et al. Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med **1998**; 157(4 pt 1):1165–72.
37. Langer M, Cigada M, Mandelli M, Mosconi P, Tognoni G. Early onset pneumonia: a multicenter study in intensive care units. Intensive Care Med **1987**; 13:342–6.
38. Ewig S, Torres A, El-Ebiary M, et al. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. Am J Respir Crit Care Med **1999**; 159:188–98.
39. Leroy O, Giradie P, Yazdanpanah Y, et al. Hospital-acquired pneumonia: microbiological data and potential adequacy of antimicrobial regimens. Eur Respir J **2002**; 20:432–9.
40. Leroy O, d'Escrivan T, Devos P, Dubreuil L, Kipnis E, Georges H. Hospital-acquired pneumonia in critically ill patients: factors associated with episodes due to imipenem-resistant organisms. Infection **2005**; 33:129–35.
41. Bouza E, Giannella M, Bunsow E, et al. Ventilator-associated pneumonia due to meticillin-resistant *Staphylococcus aureus*: risk factors and outcome in a large general hospital. J Hosp Infect **2012**; 80:150–5.
42. Moreira MR, Cardoso RL, Almeida AB, Gontijo Filho PP. Risk factors and evolution of ventilator-associated pneumonia by *Staphylococcus aureus* sensitive or resistant to oxacillin in patients at the intensive care unit of a Brazilian university hospital. Braz J Infect Dis **2008**; 12:499–503.
43. Wooten DA, Winston LG. Risk factors for methicillin-resistant *Staphylococcus aureus* in patients with community-onset and hospital-onset pneumonia. Respir Med **2013**; 107:1266–70.
44. Robicsek A, Suseno M, Beaumont JL, Thomson RB Jr, Peterson LR. Prediction of methicillin-resistant *Staphylococcus aureus* involvement in disease sites by concomitant nasal sampling. J Clin Microbiol **2008**; 46:588–92.
45. Dangerfield B, Chung A, Webb B, Seville MT. Predictive value of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal swab PCR assay for MRSA pneumonia. Antimicrob Agents Chemother **2014**; 58:859–64.
46. Sarikonda KV, Micek ST, Doherty JA, Reichley RM, Warren D, Kollef MH. Methicillin-resistant *Staphylococcus aureus* nasal colonization is a poor predictor of intensive care unit-acquired methicillin-resistant *Staphylococcus aureus* infections requiring antibiotic treatment. Crit Care Med **2010**; 38:1991–5.
47. Montero M, Sala M, Riu M, et al. Risk factors for multidrug-resistant *Pseudomonas aeruginosa* acquisition. Impact of antibiotic use in a double case-control study. Eur J Clin Microbiol Infect Dis **2010**; 29:335–9.
48. Agbaht K, Diaz E, Munoz E, et al. Bacteremia in patients with ventilator-associated pneumonia is associated with increased mortality: a study comparing bacteremic vs. nonbacteremic ventilator-associated pneumonia. Crit Care Med **2007**; 35:2064–70.
49. Kunac A, Sifri ZC, Mohr AM, Horng H, Lavery RF, Livingston DH. Bacteremia and ventilator-associated pneumonia: a marker for contemporaneous extra-pulmonic infection. Surg Infect (Larchmt) **2014**; 15:77–83.
50. Luna CM, Videla A, Mattera J, et al. Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. Chest **1999**; 116:1075–84.

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51. O'Keefe GE, Caldwell E, Cuschieri J, Wurfel MM, Evans HL. Ventilator-associated pneumonia: bacteremia and death after traumatic injury. J Trauma Acute Care Surg **2012**; 72:713–9.
52. DeRyke CA, Lodise TP Jr, Rybak MJ, McKinnon PS. Epidemiology, treatment, and outcomes of nosocomial bacteremic *Staphylococcus aureus* pneumonia. Chest **2005**; 128:1414–22.
53. Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med **2006**; 355:2619–30.
54. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med **2000**; 132:621–30.
55. Ruiz M, Torres A, Ewig S, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. Am J Respir Crit Care Med **2000**; 162:119–25.
56. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. Am J Respir Crit Care Med **1998**; 157:371–6.
57. Sole Violan J, Fernandez JA, Benitez AB, Cardenosa Cendrero JA, Rodriguez de Castro F. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit Care Med **2000**; 28:2737–41.
58. Berton DC, Kalil AC, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database Syst Rev **2014**; 10:Cd006482.
59. Papazian L, Thomas P, Garbe L, et al. Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. Am J Respir Crit Care Med **1995**; 152(6 pt 1):1982–91.
60. Marquette CH, Copin MC, Wallet F, et al. Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. Am J Respir Crit Care Med **1995**; 151:1878–88.
61. Torres A, el-Ebiary M, Padro L, et al. Validation of different techniques for the diagnosis of ventilator-associated pneumonia. Comparison with immediate postmortem pulmonary biopsy. Am J Respir Crit Care Med **1994**; 149(2 pt 1):324–31.
62. Balthazar AB, Von Nowakonski A, De Capitani EM, Bottini PV, Terzi RG, Araujo S. Diagnostic investigation of ventilator-associated pneumonia using bronchoalveolar lavage: comparative study with a postmortem lung biopsy. Braz J Med Biol Res **2001**; 34:993–1001.
63. Sole-Violan J, Rodriguez de Castro F, Rey A, et al. Comparison of bronchoscopic diagnostic techniques with histological findings in brain dead organ donors without suspected pneumonia. Thorax **1996**; 51:929–31.
64. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax **1999**; 54:867–73.
65. Kirtland SH, Corley DE, Winterbauer RH, et al. The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. Chest **1997**; 112:445–57.
66. Bregeon F, Papazian L, Thomas P, et al. Diagnostic accuracy of protected catheter sampling in ventilator-associated bacterial pneumonia. Eur Respir J **2000**; 16:969–75.
67. Chastre J, Viau F, Brun P, et al. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. Am Rev Respir Dis **1984**; 130:924–9.
68. Raman K, Nailor MD, Nicolau DP, Aslanzadeh J, Nadeau M, Kuti JL. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. Crit Care Med **2013**; 41:1656–63.
69. Jorgensen JH, Pfaller MA, Carroll KC, et al. Manual of clinical microbiology. 11th edn. Washington: American Society of Microbiology, **2015**.
70. Bonten MJ, Bergmans DC, Stobberingh EE, et al. Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. Am J Respir Crit Care Med **1997**; 156:1820–4.
71. Brun-Buisson C, Fartoukh M, Lechapt E, et al. Contribution of blinded, protected quantitative specimens to the diagnostic and therapeutic management of ventilator-associated pneumonia. Chest **2005**; 128:533–44.
72. Marik PE, Lynott J, Croxton M, Palmer E, Miller L, Zaloga GP. The effect of blind-protected specimen brush sampling on antibiotic use in patients with suspected ventilator-associated pneumonia. J Intensive Care Med **2001**; 16:42–6.
73. Meduri GU, Wunderink RG, Leeper KV, Beals DH. Management of bacterial pneumonia in ventilated patients. Protected bronchoalveolar lavage as a diagnostic tool. Chest **1992**; 101:500–8.
74. Babcock HM, Zack JE, Garrison T, Trovillion E, Kollef MH, Fraser VJ. Ventilator-associated pneumonia in a multi-hospital system: differences in microbiology by location. Infect Control Hosp Epidemiol **2003**; 24:853–8.
75. Baker AM, Bowton DL, Haponik EF. Decision making in nosocomial pneumonia. An analytic approach to the interpretation of quantitative bronchoscopic cultures. Chest **1995**; 107:85–95.
76. Chastre J, Luyt CE, Combes A, Trouillet JL. Use of quantitative cultures and reduced duration of antibiotic regimens for patients with ventilator-associated pneumonia to decrease resistance in the intensive care unit. Clin Infect Dis **2006**; 43(suppl 2):S75–81.
77. Combes A, Luyt CE, Trouillet JL, Chastre J. Controversies in ventilator-associated pneumonia. Semin Respir Crit Care Med **2010**; 31:47–54.
78. Croce MA, Fabian TC, Waddle-Smith L, et al. Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. Ann Surg **1998**; 227:743–51; discussion 51–5.
79. Dreyfuss D, Mier L, Le Bourdelles G, et al. Clinical significance of borderline quantitative protected brush specimen culture results. Am Rev Respir Dis **1993**; 147:946–51.
80. Fujitani S, Yu VL. Quantitative cultures for diagnosing ventilator-associated pneumonia: a critique. Clin Infect Dis **2006**; 43(suppl 2):S106–13.
81. Giantsou E, Liratzopoulos N, Efraimidou E, et al. De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate. Intensive Care Med **2007**; 33:1533–40.
82. Grgurich PE, Hudcova J, Lei Y, Sarwar A, Craven DE. Diagnosis of ventilator-associated pneumonia: controversies and working toward a gold standard. Curr Opin Infect Dis **2013**; 26:140–50.
83. Heyland DK, Cook DJ, Marshall J, et al. The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. Canadian Critical Care Trials Group. Chest **1999**; 115:1076–84.
84. Kollef MH, Kollef KE. Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest **2005**; 128:2706–13.
85. Malhotra AK, Riaz OJ, Duane TM, et al. Subthreshold quantitative bronchoalveolar lavage: clinical and therapeutic implications. J Trauma **2008**; 65:580–8.
86. Rello J, Vidaur L, Sandiumenge A, et al. De-escalation therapy in ventilator-associated pneumonia. Crit Care Med **2004**; 32:2183–90.
87. Rodriguez de Castro F, Sole-Violan J, Aranda Leon A, et al. Do quantitative cultures of protected brush specimens modify the initial empirical therapy in ventilated patients with suspected pneumonia? Eur Respir J **1996**; 9:37–41.
88. Sterling TR, Ho EJ, Brehm WT, Kirkpatrick MB. Diagnosis and treatment of ventilator-associated pneumonia—impact on survival. A decision analysis. Chest **1996**; 110:1025–34.
89. Herer B, Fuhrman C, Gazevic Z, Cabrit R, Chouaid C. Management of nosocomial pneumonia on a medical ward: a comparative study of outcomes and costs of invasive procedures. Clin Microbiol Infect **2009**; 15:165–72.
90. Dorca J, Manresa F, Esteban L, et al. Efficacy, safety, and therapeutic relevance of transthoracic aspiration with ultrathin needle in nonventilated nosocomial pneumonia. Am J Respir Crit Care Med **1995**; 151:1491–6.
91. Dalhoff K, Braun J, Hollandt H, Lipp R, Wiessmann KJ, Marre R. Diagnostic value of bronchoalveolar lavage in patients with opportunistic and nonopportunistic bacterial pneumonia. Infection **1993**; 21:291–6.
92. Chung DR, Song JH, Kim SH, et al. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med **2011**; 184:1409–17.
93. Pereira W Jr, Kovnat DM, Snider GL. A prospective cooperative study of complications following flexible fiberoptic bronchoscopy. Chest **1978**; 73:813–6.
94. Gibson PG, Breit SN, Bryant DH. Hypoxia during bronchoalveolar lavage. Aust N Z J Med **1990**; 20:39–43.
95. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. Physiol Res **2000**; 49(suppl 1):S57–61.
96. Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab **1994**; 79:1605–8.
97. Charles PE, Kus E, Aho S, et al. Serum procalcitonin for the early recognition of nosocomial infection in the critically ill patients: a preliminary report. BMC Infect Dis **2009**; 9:49.
98. Muller F, Christ-Crain M, Bregenzer T, et al. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest **2010**; 138:121–9.
99. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet **1993**; 341:515–8.
100. Luyt CE, Combes A, Reynaud C, et al. Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. Intensive Care Med **2008**; 34:1434–40.
101. Dallas J, Brown SM, Hock K, et al. Diagnostic utility of plasma procalcitonin for nosocomial pneumonia in the intensive care unit setting. Respir Care **2011**; 56:412–9.
102. Ramirez P, Garcia MA, Ferrer M, et al. Sequential measurements of procalcitonin levels in diagnosing ventilator-associated pneumonia. Eur Respir J **2008**; 31:356–62.
103. Duflo F, Debon R, Monneret G, Bienvenu J, Chassard D, Allaouchiche B. Alveolar and serum procalcitonin: diagnostic and prognostic value in ventilator-associated pneumonia. Anesthesiology **2002**; 96:74–9.

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104. Liao X, Kang Y. Prognostic value of procalcitonin levels in predicting death for patients with ventilator-associated pneumonia. Intensive Care Med **2010**; 36: S102.
105. Zhou CD, Lu ZY, Ren NZ, Zhang GC. Diagnostic value of procalcitonin in ventilator associated pneumonia [in Chinese]. Chin Crit Care Med **2006**; 18:370–2.
106. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med **2011**; 39:2048–58.
107. Bouchon A, Dietrich J, Colonna M. Cutting edge: inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes. J Immunol **2000**; 164:4991–5.
108. Bopp C, Hofer S, Bouchon A, Zimmermann JB, Martin E, Weigand MA. Soluble TREM-1 is not suitable for distinguishing between systemic inflammatory response syndrome and sepsis survivors and nonsurvivors in the early stage of acute inflammation. Eur J Anaesthesiol **2009**; 26:504–7.
109. Ferat-Osorio E, Wong-Baeza I, Esquivel-Callejas N, et al. Triggering receptor expressed on myeloid cells-1 expression on monocytes is associated with inflammation but not with infection in acute pancreatitis. Crit Care **2009**; 13:R69.
110. Palazzo SJ, Simpson TA, Simmons JM, Schnapp LM. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as a diagnostic marker of ventilator-associated pneumonia. Respir Care **2012**; 57:2052–8.
111. Anand NJ, Zuick S, Klesney-Tait J, Kollef MH. Diagnostic implications of soluble triggering receptor expressed on myeloid cells-1 in BAL fluid of patients with pulmonary infiltrates in the ICU. Chest **2009**; 135:641–7.
112. Determann RM, Millo JL, Gibot S, et al. Serial changes in soluble triggering receptor expressed on myeloid cells in the lung during development of ventilator-associated pneumonia. Intensive Care Med **2005**; 31:1495–500.
113. Horonenko G, Hoyt JC, Robbins RA, et al. Soluble triggering receptor expressed on myeloid cell-1 is increased in patients with ventilator-associated pneumonia: a preliminary report. Chest **2007**; 132:58–63.
114. Ramirez P, Kot P, Marti V, et al. Diagnostic implications of soluble triggering receptor expressed on myeloid cells-1 in patients with acute respiratory distress syndrome and abdominal diseases: a preliminary observational study. Crit Care **2011**; 15:R50.
115. Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med **2004**; 350:451–8.
116. Oppert M, Reinicke A, Muller C, Barckow D, Frei U, Eckardt KU. Elevations in procalcitonin but not C-reactive protein are associated with pneumonia after cardiopulmonary resuscitation. Resuscitation **2002**; 53:167–70.
117. Fartoukh M, Maitre B, Honore S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med **2003**; 168:173–9.
118. Luna CM, Aruj P, Niederman MS, et al. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. Eur Respir J **2006**; 27:158–64.
119. Shan J, Chen HL, Zhu JH. Diagnostic accuracy of clinical pulmonary infection score for ventilator-associated pneumonia: a meta-analysis. Respir Care **2011**; 56:1087–94.
120. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med **2000**; 162(2 pt 1):505–11.
121. Veinstein A, Brun-Buisson C, Derrode N, et al. Validation of an algorithm based on direct examination of specimens in suspected ventilator-associated pneumonia. Intensive Care Med **2006**; 32:676–83.
122. Nseir S, Di Pompeo C, Soubrier S, et al. Effect of ventilator-associated tracheobronchitis on outcome in patients without chronic respiratory failure: a case-control study. Crit Care **2005**; 9:R238–45.
123. Nseir S, Favory R, Jozefowicz E, et al. Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. Crit Care **2008**; 12:R62.
124. Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am J Respir Crit Care Med **2014**; 189:1225–33.
125. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit Care Med **2008**; 36:2008–13.
126. Nseir S, Di Pompeo C, Pronnier P, et al. Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome. Eur Respir J **2002**; 20:1483–9.
127. Nseir S, Di Pompeo C, Soubrier S, et al. Outcomes of ventilated COPD patients with nosocomial tracheobronchitis: a case-control study. Infection **2004**; 32:210–6.
128. Dallas J, Skrupky L, Abebe N, Boyle WA 3rd, Kollef MH. Ventilator-associated tracheobronchitis in a mixed surgical and medical ICU population. Chest **2011**; 139:513–8.
129. Martin-Loeches I, Povoa P, Rodriguez A, et al. Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. Lancet Respir Med **2015**; 3:859–68.
130. Nseir S, Martin-Loeches I, Makris D, et al. Impact of appropriate antimicrobial treatment on transition from ventilator-associated tracheobronchitis to ventilator-associated pneumonia. Crit Care **2014**; 18:R129.
131. Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. Chest **2006**; 130:787–93.
132. Namias N, Samiian L, Nino D, et al. Incidence and susceptibility of pathogenic bacteria vary between intensive care units within a single hospital: implications for empiric antibiotic strategies. J Trauma **2000**; 49:638–45; discussion 45–6.
133. Fridkin SK, Edwards JR, Tenover FC, Gaynes RP, McGowan JE Jr. Antimicrobial resistance prevalence rates in hospital antibiograms reflect prevalence rates among pathogens associated with hospital-acquired infections. Clin Infect Dis **2001**; 33:324–30.
134. Clinical and Laboratory Standards Institute. Analysis and presentation of cumulative antimicrobial suseptibility test data. Approved guideline. 4th ed. CLSI document M39-A4. Wayne, PA: CLSI, **2014**.
135. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother **2011**; 55:3284–94.
136. Nation RL, Li J, Cars O, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. Lancet Infect Dis **2015**; 15:225–34.
137. Sader HS, Rhomberg PR, Jones RN. In vitro activity of beta-lactam antimicrobial agents in combination with aztreonam tested against metallo-beta-lactamase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. J Chemother **2005**; 17:622–7.
138. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol **2013**; 34:1–14.
139. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis **2010**; 51(suppl 1): S81–7.
140. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest **1998**; 113:412–20.
141. Kuti EL, Patel AA, Coleman CI. Impact of inappropriate antibiotic therapy on mortality in patients with ventilator-associated pneumonia and blood stream infection: a meta-analysis. J Crit Care **2008**; 23:91–100.
142. Muscedere JG, Shorr AF, Jiang X, Day A, Heyland DK; Canadian Critical Care Trials Group. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: an important determinant of outcome. J Crit Care **2012**; 27:322.e7–14.
143. Rello J, Ulldemolins M, Lisboa T, et al. Determinants of prescription and choice of empirical therapy for hospital-acquired and ventilator-associated pneumonia. Eur Respir J **2011**; 37:1332–9.
144. Vardakas KZ, Mavros MN, Roussos N, Falagas ME. Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: focus on the study design. Mayo Clin Proc **2012**; 87:349–63.
145. Walkey AJ, O'Donnell MR, Wiener RS. Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a meta-analysis of randomized controlled trials. Chest **2011**; 139:1148–55.
146. Kalil AC, Klompas M, Haynatzki G, Rupp ME. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. BMJ Open **2013**; 3:e003912.
147. Kalil AC, Murthy MH, Hermsen ED, Neto FK, Sun J, Rupp ME. Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: a systematic review and meta-analysis. Crit Care Med **2010**; 38:1802–8.
148. Torres A, Rubinstein E, Corey GR, Stryjewski ME, Barriere SL. Analysis of phase 3 telavancin nosocomial pneumonia data excluding patients with severe renal impairment and acute renal failure. J Antimicrob Chemother **2014**; 69:1119–26.
149. Pasquale TR, Tan MJ, Trienski TL, File TM Jr. Methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. J Chemother **2015**; 27:29–34.
150. Barber KE, Smith JR, Raut A, Rybak MJ. Evaluation of tedizolid against *Staphylococcus aureus* and enterococci with reduced susceptibility to vancomycin, daptomycin or linezolid. J Antimicrob Chemother **2016**; 71:152–5.
151. Cepeda JA, Whitehouse T, Cooper B, et al. Linezolid versus teicoplanin in the treatment of gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. J Antimicrob Chemother **2004**; 53:345–55.

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152. Wilcox M, Nathwani D, Dryden M. Linezolid compared with teicoplanin for the treatment of suspected or proven gram-positive infections. J Antimicrob Chemother **2004**; 53:335–44.
153. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clin Infect Dis **2011**; 52:31–40.
154. Corey GR, Kollef MH, Shorr AF, et al. Telavancin for hospital-acquired pneumonia: clinical response and 28-day survival. Antimicrob Agents Chemother **2014**; 58:2030–7.
155. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis **2010**; 68:140–51.
156. Awad SS, Rodriguez AH, Chuang YC, et al. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis **2014**; 59:51–61.
157. Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. Crit Care Med **2008**; 36:1089–96.
158. Kollef MH, Chastre J, Clavel M, et al. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care **2012**; 16:R218.
159. Alvarez Lerma F; Serious Infection Study Group. Efficacy of meropenem as monotherapy in the treatment of ventilator-associated pneumonia. J Chemother **2001**; 13:70–81.
160. Alvarez-Lerma F, Insausti-Ordenana J, Jorda-Marcos R, et al. Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. Intensive Care Med **2001**; 27:493–502.
161. Sieger B, Berman SJ, Geckler RW, Farkas SA. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. Crit Care Med **1997**; 25:1663–70.
162. Heyland DK, Dodek P, Muscedere J, Day A, Cook D; Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med **2008**; 36:737–44.
163. Polk HC Jr, Livingston DH, Fry DE, et al. Treatment of pneumonia in mechanically ventilated trauma patients. Results of a prospective trial. Arch Surg **1997**; 132:1086–92.
164. Croce MA, Fabian TC, Stewart RM, et al. Empiric monotherapy versus combination therapy of nosocomial pneumonia in trauma patients. J Trauma **1993**; 35:303–9; discussion 309–11.
165. Reeves JH, Russell GM, Cade JF, McDonald M. Comparison of ceftriaxone with cefotaxime in serious chest infections. Chest **1989**; 96:1292–7.
166. Thomas PD, Daly S, Misan G, Steele T. Comparison of the efficacy and adverse effect profile of cefotaxime, 3 g/day, and ceftriaxone, 2 g/day, in the treatment of nosocomial lower respiratory tract infections in ICU patients. Eur Respir Rev **1994**; 4:321–8.
167. Fink MP, Snydman DR, Niederman MS, et al. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. The Severe Pneumonia Study Group. Antimicrob Agents Chemother **1994**; 38:547–57.
168. Shorr AF, Zadeikis N, Jackson WL, et al. Levofloxacin for treatment of ventilator-associated pneumonia: a subgroup analysis from a randomized trial. Clin Infect Dis **2005**; 40(suppl 2):S123–9.
169. West M, Boulanger BR, Fogarty C, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. Clin Ther **2003**; 25:485–506.
170. Kljucar S, Heimesaat M, von Pritzbuer E, Olms K. Ceftazidime with and without tobramycin versus azlocillin plus tobramycin in the therapy of bronchopulmonary infections in intensive care patients [in German]. Infection **1987**; 15(suppl 4): S185–91.
171. Damas P, Garweg C, Monchi M, et al. Combination therapy versus monotherapy: a randomised pilot study on the evolution of inflammatory parameters after ventilator associated pneumonia [ISRCTN31976779]. Crit Care **2006**; 10:R52.
172. Hartenauer U, Weilemann LS, Bodmann KF, Ritzerfeld WW, Asmus S, Koch EM. Comparative clinical trial of ceftazidime and imipenem/cilastatin in patients with severe nosocomial pneumonias and septicaemias. J Hosp Infect **1990**; 15 (suppl A):61–4.
173. Torres A, Bauer TT, Leon-Gil C, et al. Treatment of severe nosocomial pneumonia: a prospective randomised comparison of intravenous ciprofloxacin with imipenem/cilastatin. Thorax **2000**; 55:1033–9.
174. Beaucaire G. Evaluation of the efficacy and safety of isepamicin compared with amikacin in the treatment of nosocomial pneumonia and septicaemia. J Chemother **1995**; 7(suppl 2):165–73.
175. Beaucaire G, Nicolas MH, Martin C, et al. Phare study. Comparative study of combined cefepime-amikacin versus ceftazidime combined with amikacin in the treatment of nosocomial pneumonias in ventilated patients. Multicenter group study [in French]. Ann Fr Anesth Reanim **1999**; 18:186–95.
176. Manhold C, von Rolbicki U, Brase R, et al. Outbreaks of *Staphylococcus aureus* infections during treatment of late onset pneumonia with ciprofloxacin in a prospective, randomized study. Intensive Care Med **1998**; 24:1327–30.
177. Saginur R, Garber G, Darling G, et al. Prospective, randomized comparison of intravenous and oral ciprofloxacin with intravenous ceftazidime in the treatment of nosocomial pneumonia. Can J Infect Dis **1997**; 8:89–94.
178. Ahmed SM, Choudhary J, Ahmed M, Arora V, Parul , Ali S. Treatment of ventilator-associated pneumonia with piperacillin-tazobactum and amikacin vs cefepime and levofloxacin: a randomized prospective study. Indian J Crit Care Med **2007**; 11:117–21.
179. Rea-Neto A, Niederman M, Lobo SM, et al. Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. Curr Med Res Opin **2008**; 24:2113–26.
180. Brun-Buisson C, Sollet JP, Schweich H, Briere S, Petit C. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. VAP Study Group. Clin Infect Dis **1998**; 26:346–54.
181. Brown RB, Lemeshow S, Teres D. Moxalactam vs carbenicillin plus tobramycin: treatment of nosocomial gram-negative bacillary pneumonias in non-neutropenic patients. Curr Ther Res **1984**; 36:557–64.
182. Maskin B, Fontan PA, Spinedi EG, Gammella D, Badolati A. Evaluation of endotoxin release and cytokine production induced by antibiotics in patients with gram-negative nosocomial pneumonia. Crit Care Med **2002**; 30:349–54.
183. Joshi M, Metzler M, McCarthy M, Olvey S, Kassira W, Cooper A. Comparison of piperacillin/tazobactam and imipenem/cilastatin, both in combination with tobramycin, administered every 6 h for treatment of nosocomial pneumonia. Respir Med **2006**; 100:1554–65.
184. Florescu DF, Qiu F, McCartan MA, Mindru C, Fey PD, Kalil AC. What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. Clin Infect Dis **2012**; 54: 670–80.
185. Liscio JL, Mahoney MV, Hirsch EB. Ceftolozane/tazobactam and ceftazidime/avibactam: two novel beta-lactam/beta-lactamase inhibitor combination agents for the treatment of resistant gram-negative bacterial infections. Int J Antimicrob Agents **2015**; 46:266–71.
186. Gottesman T, Yossepowitch O, Lerner E, et al. The accuracy of Gram stain of respiratory specimens in excluding *Staphylococcus aureus* in ventilator-associated pneumonia. J Crit Care **2014**; 29:739–42.
187. Tetenta S, Metersky ML. Tracheal aspirate Gram stain has limited sensitivity and specificity for detecting *Staphylococcus aureus*. Respirology **2011**; 16:86–9.
188. O'Horo JC, Thompson D, Safdar N. Is the Gram stain useful in the microbiologic diagnosis of VAP? A meta-analysis. Clin Infect Dis **2012**; 55:551–61.
189. McKinnell JA, Huang SS, Eells SJ, Cui E, Miller LG. Quantifying the impact of extranasal testing of body sites for methicillin-resistant *Staphylococcus aureus* colonization at the time of hospital or intensive care unit admission. Infect Control Hosp Epidemiol **2013**; 34:161–70.
190. Davis KA, Stewart JJ, Crouch HK, Florez CE, Hospenthal DR. Methicillin-resistant *Staphylococcus aureus* (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. Clin Infect Dis **2004**; 39: 776–82.
191. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother **2010**; 54:4851–63.
192. Swanson JM, Wells DL. Empirical antibiotic therapy for ventilator-associated pneumonia. Antibiotics **2013**; 2:339–51.
193. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest **2004**; 125:1791–9.
194. Joffe AR, Muscedere J, Marshall JC, Su Y, Heyland DK; Canadian Critical Care Trials Group. The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study. J Crit Care **2008**; 23:82–90.
195. Hibbard ML, Kopelman TR, O'Neill PJ, et al. Empiric, broad-spectrum antibiotic therapy with an aggressive de-escalation strategy does not induce gram-negative pathogen resistance in ventilator-associated pneumonia. Surg Infect (Larchmt) **2010**; 11:427–32.
196. Joung MK, Lee JA, Moon SY, et al. Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia. Crit Care **2011**; 15:R79.

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197. Weiss CH, Dibardino D, Rho J, Sung N, Collander B, Wunderink RG. A clinical trial comparing physician prompting with an unprompted automated electronic checklist to reduce empirical antibiotic utilization. Crit Care Med **2013**; 41:2563–9.
198. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis **2014**; 59:e10–52.
199. Mentzelopoulos SD, Pratikaki M, Platsouka E, et al. Prolonged use of carbapenems and colistin predisposes to ventilator-associated pneumonia by pandrug-resistant *Pseudomonas aeruginosa*. Intensive Care Med **2007**; 33:1524–32.
200. Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **2009**; 53:1983–6.
201. Marchaim D, Chopra T, Bhargava A, et al. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. Infect Control Hosp Epidemiol **2012**; 33:817–30.
202. Miyawaki K, Miwa Y, Seki M, Asari S, Tomono K, Kurokawa N. Correlation between the consumption of meropenem or doripenem and meropenem susceptibility of *Pseudomonas aeruginosa* in a university hospital in Japan. Biol Pharm Bull **2012**; 35:946–9.
203. McDougall DA, Morton AP, Playford EG. Association of ertapenem and anti-pseudomonal carbapenem usage and carbapenem resistance in *Pseudomonas aeruginosa* among 12 hospitals in Queensland, Australia. J Antimicrob Chemother **2013**; 68:457–60.
204. Routsi C, Pratikaki M, Platsouka E, et al. Risk factors for carbapenem-resistant gram-negative bacteremia in intensive care unit patients. Intensive Care Med **2013**; 39:1253–61.
205. Pena C, Guzman A, Suarez C, et al. Effects of carbapenem exposure on the risk for digestive tract carriage of intensive care unit-endemic carbapenem-resistant *Pseudomonas aeruginosa* strains in critically ill patients. Antimicrob Agents Chemother **2007**; 51:1967–71.
206. Ogutlu A, Guclu E, Karabay O, Utku AC, Tuna N, Yahyaoglu M. Effects of carbapenem consumption on the prevalence of *Acinetobacter* infection in intensive care unit patients. Ann Clin Microbiol Antimicrob **2014**; 13:7.
207. Armand-Lefevre L, Angebault C, Barbier F, et al. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother **2013**; 57:1488–95.
208. Moreira MR, Guimaraes MP, Rodrigues AA, Gontijo Filho PP. Antimicrobial use, incidence, etiology and resistance patterns in bacteria causing ventilator-associated pneumonia in a clinical-surgical intensive care unit. Rev Soc Bras Med Trop **2013**; 46:39–44.
209. Swaminathan M, Sharma S, Poliansky Blash S, et al. Prevalence and risk factors for acquisition of carbapenem-resistant Enterobacteriaceae in the setting of endemicity. Infect Control Hosp Epidemiol **2013**; 34:809–17.
210. European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report: antimicrobial resistance and healthcare-associated infections 2014. Stockholm: ECDC, **2015**.
211. Jacob J, Klein E, Laxminarayan R, et al. Carbapenem resistant enterobactereciae. MMWR Morb Mortal Wkly Rep **2013**; 62:165–70.
212. Thaden JT, Lewis SS, Hazen KC, et al. Rising rates of carbapenem-resistant enterobacteriaceae in community hospitals: a mixed-methods review of epidemiology and microbiology practices in a network of community hospitals in the southeastern United States. Infect Control Hosp Epidemiol **2014**; 35:978–83.
213. Luna CM, Sarquis S, Niederman MS, et al. Is a strategy based on routine endotracheal cultures the best way to prescribe antibiotics in ventilator-associated pneumonia? Chest **2013**; 144:63–71.
214. Yakovlev SV, Stratchounski LS, Woods GL, et al. Ertapenem versus cefepime for initial empirical treatment of pneumonia acquired in skilled-care facilities or in hospitals outside the intensive care unit. Eur J Clin Microbiol Infect Dis **2006**; 25:633–41.
215. Alsuraikh M, Hamdy G. Incidence, risk factors, and causative agents of hospital acquired pneumonia (nosocomial pneumonia) in adult hospitalized patients in medical wards of a general hospital in Kuwait. Kuwait Med J **2008**; 40:297–300.
216. Avci M, Ozgenc O, Coskuner A, Bozca B, Kidak L, Mermut G. Hospital-acquired pneumonia in nonintensive care unit wards. Turk J Med Sci **2010**; 40:357–63.
217. Cakir Edis E, Hatipoglu ON, Yilmam I, Eker A, Tansel O, Sut N. Hospital-acquired pneumonia developed in non-intensive care units. Respiration **2009**; 78:416–22.
218. Espejo E, Andres M, Torviso J, et al. Hospital-acquired bacteraemic pneumonia in non-ventilated patients. In: 21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)/27th International Congress of Chemotherapy (ICC) Posters 2011: S478.
219. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest **2005**; 128:3854–62.
220. Giannella M, Pinilla B, Capdevila JA, et al. Pneumonia treated in the internal medicine department: focus on healthcare-associated pneumonia. Clin Microbiol Infect **2012**; 18:786–94.
221. Piskin N, Aydemir H, Oztoprak N, et al. Inadequate treatment of ventilator-associated and hospital-acquired pneumonia: risk factors and impact on outcomes. BMC Infect Dis **2012**; 12:268.
222. Esperatti M, Ferrer M, Theessen A, et al. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. Am J Respir Crit Care Med **2010**; 182:1533–9.
223. Maruyama T, Niederman MS, Kobayashi T, et al. A prospective comparison of nursing home-acquired pneumonia with hospital-acquired pneumonia in non-intubated elderly. Respir Med **2008**; 102:1287–95.
224. Barreiro-Lopez B, Tricas JM, Mauri E, Quintana S, Garau J. Risk factors and prognostic factors in nosocomial pneumonia outside the intensive care units setting [in Spanish]. Enferm Infecc Microbiol Clin **2005**; 23:519–24.
225. Takano Y, Sakamoto O, Suga M, Muranaka H, Ando M. Prognostic factors of nosocomial pneumonia in general wards: a prospective multivariate analysis in Japan. Respir Med **2002**; 96:18–23.
226. Schussler O, Alifano M, Dermine H, et al. Postoperative pneumonia after major lung resection. Am J Respir Crit Care Med **2006**; 173:1161–9.
227. Watanabe A, Yanagihara K, Kohno S, Matsushima T; HAP Study Group. Multicenter survey on hospital-acquired pneumonia and the clinical efficacy of first-line antibiotics in Japan. Intern Med **2008**; 47:245–54.
228. Weber DJ, Rutala WA, Sickbert-Bennett EE, Samsa GP, Brown V, Niederman MS. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. Infect Control Hosp Epidemiol **2007**; 28:825–31.
229. Kim J, Chung J, Choi S-H, et al. Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. Crit Care **2012**; 16:1–9.
230. Kohlenberg A, Schwab F, Behnke M, Geffers C, Gastmeier P. Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database. Intensive Care Med **2010**; 36:971–8.
231. Herer B, Fuhrman C, Demontrond D, Gazevic Z, Housset B, Chouaid C. Diagnosis of nosocomial pneumonia in medical ward: repeatability of the protected specimen brush. Eur Respir J **2001**; 18:157–63.
232. Edis EC, Hatipoglu ON, Yilmam I, Eker A, Tansel O, Sut N. The importance of pathogen identification in the success of treatment of hospital acquired pneumonias. Turk Toraks Dergisi **2010**; 11:155–9.
233. Giunta V, Ferrer M, Esperatti M, et al. ICU-acquired pneumonia with or without etiologic diagnosis: a comparison of outcomes. Crit Care Med **2013**; 41:2133–43.
234. Fernandez-Guerrero M, Gudiol F, Rodriguez-Torres A, Arnau C, Valdes L, Vallve C. Nosocomial pneumonia: comparative multicentre trial between monotherapy with cefotaxime and treatment with antibiotic combinations. Infection **1991**; 19 (suppl 6):S320–5.
235. Schmitt DV, Leitner E, Welte T, Lode H. Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia—a double blind prospective multicentre study. Infection **2006**; 34:127–34.
236. Hoffken G, Barth J, Rubinstein E, Beckmann H; HAP Study Group. A randomized study of sequential intravenous/oral moxifloxacin in comparison to sequential intravenous ceftriaxone/oral cefuroxime axetil in patients with hospital-acquired pneumonia. Infection **2007**; 35:414–20.
237. Bhavnani SM, Rubino CM, Hammel JP, et al. Pharmacological and patient-specific response determinants in patients with hospital-acquired pneumonia treated with tigecycline. Antimicrob Agents Chemother **2012**; 56:1065–72.
238. Pea F, Di Qual E, Cusenza A, Brollo L, Baldassarre M, Furlanut M. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator-associated pneumonia. Clin Pharmacokinet **2003**; 42:589–98.
239. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother **2011**; 55:2704–9.
240. Anevlavis S, Petroglou N, Tzavaras A, et al. A prospective study of the diagnostic utility of sputum Gram stain in pneumonia. J Infect **2009**; 59:83–9.
241. Montravers P, Veber B, Auboyer C, et al. Diagnostic and therapeutic management of nosocomial pneumonia in surgical patients: results of the Eole study. Crit Care Med **2002**; 30:368–75.
242. Hanes SD, Wood GC, Herring V, et al. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg **2000**; 179:436–40.
243. Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents **2001**; 17:497–504.
244. Sakka SG, Glauner AK, Bulitta JB, et al. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin

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in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother **2007**; 51:3304–10.
245. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin Ther **2007**; 29:1107–15.
246. Lorente L, Jimenez A, Martin MM, Iribarren JL, Jimenez JJ, Mora ML. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. Int J Antimicrob Agents **2009**; 33:464–8.
247. Lorente L, Jimenez A, Palmero S, et al. Comparison of clinical cure rates in adults with ventilator-associated pneumonia treated with intravenous ceftazidime administered by continuous or intermittent infusion: a retrospective, nonrandomized, open-label, historical chart review. Clin Ther **2007**; 29:2433–9.
248. Scaglione F, Esposito S, Leone S, et al. Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia. Eur Respir J **2009**; 34:394–400.
249. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis **2014**; 58:1072–83.
250. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med **2009**; 37:840–51; quiz 59.
251. Roberts JA, Lipman J. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. Crit Care Med **2013**; 41:489–95.
252. Sinnollareddy MG, Roberts MS, Lipman J, Roberts JA. Beta-lactam pharmacokinetics and pharmacodynamics in critically ill patients and strategies for dose optimization: a structured review. Clin Exp Pharmacol Physiol **2012**; 39:489–96.
253. Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis **2014**; 14:498–509.
254. Lux LJ, Posey RE, Daniels LS, et al. Pharmacokinetic/pharmacodynamic measures for guiding antibiotic treatment for hospital-acquired pneumonia. Rockville, MD: Agency for Healthcare Research and Quality, **2014**. Comparative Effectiveness ?Reviews, No 136. Available at: http://www.ncbi.nlm.nih.gov/books/NBK266264/. Accessed 5 January 2015.
255. Hallal A, Cohn SM, Namias N, et al. Aerosolized tobramycin in the treatment of ventilator-associated pneumonia: a pilot study. Surg Infect (Larchmt) **2007**; 8:73–82.
256. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. Clin Infect Dis **2010**; 51:1238–44.
257. Korbila IP, Michalopoulos A, Rafailidis PI, Nikita D, Samonis G, Falagas ME. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. Clin Microbiol Infect **2010**; 16:1230–6.
258. Le Conte P, Potel G, Clementi E, et al. Administration of tobramycin aerosols in patients with nosocomial pneumonia: a preliminary study [in French]. Presse Med **2000**; 29:76–8.
259. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by gram-negative bacteria. J Antimicrob Chemother **2010**; 65:2645–9.
260. Doshi NM, Cook CH, Mount KL, et al. Adjunctive aerosolized colistin for multidrug resistant gram-negative pneumonia in the critically ill: a retrospective study. BMC Anesthesiol **2013**; 13:45.
261. Tumbarello M, De Pascale G, Trecarichi EM, et al. Effect of aerosolized colistin as adjunctive treatment on the outcomes of microbiologically documented ventilator-associated pneumonia caused by colistin-only susceptible gram-negative bacteria. Chest **2013**; 144:1768–75.
262. Brown RB, Kruse JA, Counts GW, Russell JA, Christou NV, Sands ML. Double-blind study of endotracheal tobramycin in the treatment of gram-negative bacterial pneumonia. The Endotracheal Tobramycin Study Group. Antimicrob Agents Chemother **1990**; 34:269–72.
263. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis **1985**; 132:761–5.
264. Panidis D, Markantonis SL, Boutzouka E, Karatzas S, Baltopoulos G. Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. Chest **2005**; 128:545–52.
265. Valcke YJ, Vogelaers DP, Colardyn FA, Pauwels RA. Penetration of netilmicin in the lower respiratory tract after once-daily dosing. Chest **1992**; 101:1028–32.
266. Boselli E, Breilh D, Djabarouti S, et al. Reliability of mini-bronchoalveolar lavage for the measurement of epithelial lining fluid concentrations of tobramycin in critically ill patients. Intensive Care Med **2007**; 33:1519–23.
267. Plachouras D, Karvanen M, Friberg LE, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother **2009**; 53:3430–6.
268. Markou N, Markantonis SL, Dimitrakis E, et al. Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, gram-negative bacilli infections: a prospective, open-label, uncontrolled study. Clin Ther **2008**; 30:143–51.
269. Fagon J, Patrick H, Haas DW, et al. Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. Am J Respir Crit Care Med **2000**; 161(3 pt 1):753–62.
270. Jung YJ, Koh Y, Hong SB, et al. Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant *Staphylococcus aureus* pneumonia. Crit Care Med **2010**; 38:175–80.
271. Kohno S, Yamaguchi K, Aikawa N, et al. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan. J Antimicrob Chemother **2007**; 60:1361–9.
272. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis **2002**; 34:1481–90.
273. Wunderink RG, Mendelson MH, Somero MS, et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*. Chest **2008**; 134:1200–7.
274. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis **2012**; 54:621–9.
275. Montedori A, Bonacini MI, Casazza G, et al. Modified versus standard intention-to-treat reporting: are there differences in methodological quality, sponsorship, and findings in randomized trials? A cross-sectional study. Trials **2011**; 12:58.
276. US Food and Drug Administration (FDA) Anti-Infective Drugs Advisory Committee. FDA advisory committee briefing document: telavancin for nosocomial pneumonia, **2012**. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329482.pdf. Accessed January 2013.
277. Ramsey KM, Mazer MA. Addition of rifampin to vancomycin for the treatment of pneumonias due to methicillin-resistant *Staphylococcus aureus*: caveat emptor. Crit Care Med **2010**; 38:326–7.
278. Lahey T. Questionable superiority of linezolid for methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: watch where you step. Clin Infect Dis **2012**; 55:159–60.
279. Holmes NE, Turnidge JD, Munckhof WJ, et al. Antibiotic choice may not explain poorer outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis **2011**; 204:340–7.
280. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05. J Antimicrob Chemother **2007**; 60:788–94.
281. Adam HJ, Louie L, Watt C, et al. Detection and characterization of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates in Canada: results from the Canadian Nosocomial Infection Surveillance Program, 1995–2006. Antimicrob Agents Chemother **2010**; 54:945–9.
282. Holmes RL, Jorgensen JH. Inhibitory activities of 11 antimicrobial agents and bactericidal activities of vancomycin and daptomycin against invasive methicillin-resistant *Staphylococcus aureus* isolates obtained from 1999 through 2006. Antimicrob Agents Chemother **2008**; 52:757–60.
283. Pitz AM, Yu F, Hermsen ED, Rupp ME, Fey PD, Olsen KM. Vancomycin susceptibility trends and prevalence of heterogeneous vancomycin-intermediate *Staphylococcus aureus* in clinical methicillin-resistant *S. aureus* isolates. J Clin Microbiol **2011**; 49:269–74.
284. Sader HS, Fey PD, Limaye AP, et al. Evaluation of vancomycin and daptomycin potency trends (MIC creep) against methicillin-resistant *Staphylococcus aureus* isolates collected in nine U.S. medical centers from 2002 to 2006. Antimicrob Agents Chemother **2009**; 53:4127–32.
285. van Hal SJ, Barbagiannakos T, Jones M, et al. Methicillin-resistant *Staphylococcus aureus* vancomycin susceptibility testing: methodology correlations, temporal trends and clonal patterns. J Antimicrob Chemother **2011**; 66:2284–7.
286. Honda H, Doern CD, Michael-Dunne W Jr, Warren DK. The impact of vancomycin susceptibility on treatment outcomes among patients with methicillin resistant *Staphylococcus aureus* bacteremia. BMC Infect Dis **2011**; 11:335.
287. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with

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Staphylococcus aureus bloodstream infections: a systematic review and meta-analysis. JAMA **2014**; 312:1552–64.
288. Walraven CJ, North MS, Marr-Lyon L, Deming P, Sakoulas G, Mercier RC. Site of infection rather than vancomycin MIC predicts vancomycin treatment failure in methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother **2011**; 66:2386–92.
289. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis **2009**; 49:325–7.
290. Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med **2008**; 36: 108–17.
291. Zanetti G, Bally F, Greub G, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. Antimicrob Agents Chemother **2003**; 47:3442–7.
292. Giamarellou H, Mandragos K, Bechrakis P, Pigas K, Bilalis D, Sfikakis P. Pefloxacin versus imipenem in the therapy of nosocomial lung infections of intensive care unit patients. J Antimicrob Chemother **1990**; 26(suppl B):117–27.
293. Jaccard C, Troillet N, Harbarth S, et al. Prospective randomized comparison of imipenem-cilastatin and piperacillin-tazobactam in nosocomial pneumonia or peritonitis. Antimicrob Agents Chemother **1998**; 42:2966–72.
294. Planquette B, Timsit JF, Misset BY, et al. *Pseudomonas aeruginosa* ventilator-associated pneumonia. Predictive factors of treatment failure. Am J Respir Crit Care Med **2013**; 188:69–76.
295. Pena C, Gomez-Zorrilla S, Oriol I, et al. Impact of multidrug resistance on *Pseudomonas aeruginosa* ventilator-associated pneumonia outcome: predictors of early and crude mortality. Eur J Clin Microbiol Infect Dis **2013**; 32:413–20.
296. Luyt CE, Aubry A, Lu Q, et al. Imipenem, meropenem, or doripenem to treat patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia. Antimicrob Agents Chemother **2014**; 58:1372–80.
297. US Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm. Accessed 5 January 2015.
298. Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. Imipenem resistance of *Pseudomonas* in pneumonia: a systematic literature review. BMC Pulm Med **2010**; 10:45.
299. Siempos II, Vardakas KZ, Manta KG, Falagas ME. Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia. Eur Respir J **2007**; 29:548–60.
300. Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. Meropenem Study Group. J Antimicrob Chemother **1995**; 36 (suppl A):145–56.
301. Norrby SR, Finch RG, Glauser M. Monotherapy in serious hospital-acquired infections: a clinical trial of ceftazidime versus imipenem/cilastatin. European Study Group. J Antimicrob Chemother **1993**; 31:927–37.
302. Carcas AJ, Garcia-Satue JL, Zapater P, Frias-Iniesta J. Tobramycin penetration into epithelial lining fluid of patients with pneumonia. Clin Pharmacol Ther **1999**; 65:245–50.
303. Levy J, Baran D, Klastersky J. Comparative study of the antibacterial activity of amikacin and tobramycin during *Pseudomonas* pulmonary infection in patients with cystic fibrosis. J Antimicrob Chemother **1982**; 10:227–34.
304. Mombelli G, Coppens L, Thys JP, Klastersky J. Anti-*Pseudomonas* activity in bronchial secretions of patients receiving amikacin or tobramycin as a continuous infusion. Antimicrob Agents Chemother **1981**; 19:72–5.
305. Furtado GH, d'Azevedo PA, Santos AF, Gales AC, Pignatari AC, Medeiros EA. Intravenous polymyxin B for the treatment of nosocomial pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa*. Int J Antimicrob Agents **2007**; 30:315–9.
306. Ouderkirk JP, Nord JA, Turett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant gram-negative bacteria. Antimicrob Agents Chemother **2003**; 47:2659–62.
307. Rigatto MH, Ribeiro VB, Konzen D, Zavascki AP. Comparison of polymyxin B with other antimicrobials in the treatment of ventilator-associated pneumonia and tracheobronchitis caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. Infection **2013**; 41:321–8.
308. Sobieszczyk ME, Furuya EY, Hay CM, et al. Combination therapy with polymyxin B for the treatment of multidrug-resistant gram-negative respiratory tract infections. J Antimicrob Chemother **2004**; 54:566–9.
309. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). J Antimicrob Chemother **2011**; 66:2070–4.
310. Sader HS, Rhomberg PR, Farrell DJ, Jones RN. Differences in potency and categorical agreement between colistin and polymyxin B when testing 15,377 clinical strains collected worldwide. Diagn Microbiol Infect Dis **2015**; 83:379–81.
311. Cometta A, Baumgartner JD, Lew D, et al. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. Antimicrob Agents Chemother **1994**; 38:1309–13.
312. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. Crit Care Med **2007**; 35:1888–95.
313. Park SY, Park HJ, Moon SM, et al. Impact of adequate empirical combination therapy on mortality from bacteremic *Pseudomonas aeruginosa* pneumonia. BMC Infect Dis **2012**; 12:308.
314. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med **2010**; 38:1773–85.
315. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev **2006**; CD003344.
316. Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. Crit Care Med **2010**; 38:1651–64.
317. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev **2012**; 25:450–70.
318. Morata L, Cobos-Trigueros N, Martinez JA, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother **2012**; 56:4833–7.
319. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis **2004**; 4:519–27.
320. Hu Y, Li L, Li W, et al. Combination antibiotic therapy versus monotherapy for *Pseudomonas aeruginosa* bacteraemia: a meta-analysis of retrospective and prospective studies. Int J Antimicrob Agents **2013**; 42:492–6.
321. Paul M, Leibovici L. Editorial commentary: combination therapy for *Pseudomonas aeruginosa* bacteremia: where do we stand? Clin Infect Dis **2013**; 57:217–20.
322. Vardakas KZ, Tansarli GS, Bliziotis IA, Falagas ME. Beta-lactam plus aminoglycoside or fluoroquinolone combination versus beta-lactam monotherapy for *Pseudomonas aeruginosa* infections: a meta-analysis. Int J Antimicrob Agents **2013**; 41:301–10.
323. Pena C, Suarez C, Ocampo-Sosa A, et al. Effect of adequate single-drug vs combination antimicrobial therapy on mortality in *Pseudomonas aeruginosa* bloodstream infections: a post hoc analysis of a prospective cohort. Clin Infect Dis **2013**; 57:208–16.
324. Balakrishnan I, Awad-El-Kariem FM, Aali A, et al. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC beta-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother **2011**; 66:2628–31.
325. Bassetti M, Righi E, Fasce R, et al. Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum beta-lactamase-producing organisms in an intensive care unit. J Antimicrob Chemother **2007**; 60:433–5.
326. Kaniga K, Flamm R, Tong SY, Lee M, Friedland I, Redman R. Worldwide experience with the use of doripenem against extended-spectrum-beta-lactamase-producing and ciprofloxacin-resistant Enterobacteriaceae: analysis of six phase 3 clinical studies. Antimicrob Agents Chemother **2010**; 54:2119–24.
327. Cheng WL, Hsueh PR, Lee CC, et al. Bacteremic pneumonia caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: appropriateness of empirical treatment matters. J Microbiol Immunol Infect **2014**; 49:208–15.
328. Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. Clin Infect Dis **2004**; 39:31–7.
329. Tsai HY, Chen YH, Tang HJ, et al. Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extended-spectrum beta-lactamase-producing *Proteus mirabilis*. Diagn Microbiol Infect Dis **2014**; 80:222–6.
330. Nguyen HM, Shier KL, Graber CJ. Determining a clinical framework for use of cefepime and beta-lactam/beta-lactamase inhibitors in the treatment of infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother **2014**; 69:871–80.

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331. Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Epidemiol Infect **2013**; 141: 1214–22.
332. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect **2008**; 56:432–6.
333. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii*. Scand J Infect Dis **2007**; 39:38–43.
334. Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis **2013**; 57:349–58.
335. Wood GC, Hanes SD, Croce MA, Fabian TC, Boucher BA. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of acinetobacter ventilator-associated pneumonia. Clin Infect Dis **2002**; 34:1425–30.
336. Chuang YC, Cheng CY, Sheng WH, et al. Effectiveness of tigecycline-based versus colistin- based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. BMC Infect Dis **2014**; 14:102.
337. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis **2003**; 36:1111–8.
338. Ramasubban S, Majumdar A, Das PS. Safety and efficacy of polymyxin B in multidrug resistant gram-negative severe sepsis and septic shock. Indian J Crit Care Med **2008**; 12:153–7.
339. Simsek F, Gedik H, Yildirmak MT, et al. Colistin against colistin-only-susceptible *Acinetobacter baumannii*-related infections: monotherapy or combination therapy? Indian J Med Microbiol **2012**; 30:448–52.
340. Kalin G, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Infection **2014**; 42:37–42.
341. Choi HK, Kim YK, Kim HY, Uh Y. Inhaled colistin for treatment of pneumonia due to colistin-only-susceptible *Acinetobacter baumannii*. Yonsei Med J **2014**; 55:118–25.
342. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev **2015**; 8:Cd007577.
343. Dimopoulos G, Poulakou G, Pneumatikos IA, Armaganidis A, Kollef MH, ?Matthaiou DK. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. Chest **2013**; 144:1759–67.
344. Hedrick TL, McElearney ST, Smith RL, Evans HL, Pruett TL, Sawyer RG. Duration of antibiotic therapy for ventilator-associated pneumonia caused by nonfermentative gram-negative bacilli. Surg Infect (Larchmt) **2007**; 8:589–97.
345. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA **2003**; 290:2588–98.
346. Fekih Hassen M, Ayed S, Ben Sik Ali H, Gharbi R, Marghli S, Elatrous S. Duration of antibiotic therapy for ventilator-associated pneumonia: comparison of 7 and 10 days. A pilot study [in French]. Ann Fr Anesth Reanim **2009**; 28:16–23.
347. Medina J, Perez Protto S, Paciel D, Pontet J, Saldun P, Berro M. Antibiotic treatment for the ventilator-associated pneumonia: 8 vs. 12 days randomized trial preliminary data. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, **2007**:361.
348. Capellier G, Mockly H, Charpentier C, et al. Early-onset ventilator-associated pneumonia in adults randomized clinical trial: comparison of 8 versus 15 days of antibiotic treatment. PLoS One **2012**; 7:e41290.
349. Alvarez-Lerma F, Alvarez B, Luque P, et al. Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study. Crit Care **2006**; 10:R78.
350. Eachempati SR, Hydo LJ, Shou J, Barie PS. Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? J Trauma **2009**; 66:1343–8.
351. Kollef MH. Providing appropriate antimicrobial therapy in the intensive care unit: surveillance vs. de-escalation. Crit Care Med **2006**; 34:903–5.
352. Leone M, Bechis C, Baumstarck K, et al. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med **2014**; 40:1399–408.
353. Camargo LF. The "de-escalation concept" and antibiotic de-escalation: a missed opportunity? Shock **2013**; 39(suppl 1):29–31.
354. Dellit TH, Chan JD, Skerrett SJ, Nathens AB. Development of a guideline for the management of ventilator-associated pneumonia based on local microbiologic findings and impact of the guideline on antimicrobial use practices. Infect Control Hosp Epidemiol **2008**; 29:525–33.
355. Hoffken G, Niederman MS. Nosocomial pneumonia: the importance of a de-escalating strategy for antibiotic treatment of pneumonia in the ICU. Chest **2002**; 122:2183–96.
356. Kollef MH, Morrow LE, Niederman MS, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest **2006**; 129:1210–8.
357. Lisboa T, Rello J. De-escalation in lower respiratory tract infections. Curr Opin Pulm Med **2006**; 12:364–8.
358. Niederman MS, Soulountsi V. De-escalation therapy: is it valuable for the management of ventilator-associated pneumonia? Clin Chest Med **2011**; 32:517–34.
359. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis **2012**; 55:651–62.
360. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev **2012**; 9:CD007498.
361. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J **2009**; 34:1364–75.
362. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet **2010**; 375:463–74.
363. Pontet J, Paciel D, Olivera W, Bentancourt S, Cancela M, Gervas J. Procalcitonin (PCT) guided antibiotic treatment in ventilator associated pneumonia (VAP). Multi-centre, clinical prospective, randomized-controlled study. Am J Respir Crit Care Med **2007**; 175:A212.
364. Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med **2001**; 29:1109–15.

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