Severe community acquired pneumonia pdf

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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. Keywords: HAP, VAP, hospital, ventilator, pneumonia, antibiotics, mortality, antibiotic therapy 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. 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? 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 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). 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). 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. 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). 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). 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. 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? 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? 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? 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? 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). For patients with HAP/VAP due to P. aeruginosa, we recommend against aminoglycoside monotherapy (strong recommendation, very low-quality evidence). Remarks: Routine antimicrobial susceptibility testing should include assessment of the sensitivity of the P. aeruginosa isolate to polymyxins (colistin or polymyxin B) in settings that have a high prevalence of extensively resistant organisms. XVII. Should Monotherapy or Combination Therapy Be Used to Treat Patients With HAP/VAP Due to P. aeruginosa? 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). 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). 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 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. 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 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 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. 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 ≥103 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 ≥105 CFU/mL. Positive predictive values ranged from 60% (95% CI, 49%–71%) for PSB with ≥103 CFU/mL and 61% (95% CI, 45%–76%) for ETAs with any amount of growth to 77% (95% CI, 66%–85%) for BAL with ≥104 CFU/mL and 81% (95% CI, 67%–91%) for ETAs with ≥105 CFU/mL. Rationale for the Recommendation There is no evidence that invasive microbiological sampling with quantitative cultures improves clinical outcomes 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, 103 CFU/mL for PSB, 104 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 106 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 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 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. 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. 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]. X. What Antibiotics Are Recommended for Empiric Treatment of Clinically Suspected VAP? Recommendations (See Table 3 for specific antibiotic recommendations) 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). 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). 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% 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). 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). In patients with suspected VAP, we suggest avoiding aminoglycosides if alternative agents with adequate gram-negative activity are available (weak recommendation, low-quality evidence). 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. 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 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

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