

Recommendations for Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia: Review of Recent International Guidelines

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Recently published guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia are reviewed for recommendations regarding diagnosis and antimicrobial therapy to assess the implications for development of future clinical trials. Despite some differences (mostly related to likely pathogens), there is a general agreement about the recommended approach to management. All of the reviewed guidelines invariably recommend early, appropriate antimicrobial therapy and avoidance of excessive antimicrobials by deescalation of therapy on the basis of microbiological culture results and the clinical response of the patient. Developers of future clinical trials will need to be mindful of these recommendations to maintain best practice care for each investigator.

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), subclassifications of nosocomial pneumonia, are considered to be the most serious hospital-acquired infections because of their relatively high associated morbidity and mortality. In light of the significance of these infections, several international organizations have published guidelines for appropriate management. The purpose of this review is to analyze recently published guidelines and to compare specific recommendations to assess the implication that they may have on the development of future clinical trials. The focus will be on recommendations regarding diagnosis, which will influence criteria for patient enrollment in studies, and antimicrobial therapy, which will have an effect on comparator agents for clinical trials.

Although practice guidelines cannot be considered as evidence to be used to develop future clinical trials, recommendations in guidelines are optimally based on best available evidence and, thus, reflect what can be

considered as best practice recommendations. Ideally, clinical trials will need to reflect such recommendations for optimal acceptance by investigators.

METHODS

Guidelines published from 1 January 2005 through 28 February 2009 were identified using the US National Institutes of Health, National Library of Medicine Medline database. A search strategy used a combination of the medical subject heading terms “hospital-acquired pneumonia,” “ventilator-associated pneumonia,” “pneumonia,” and “Guidelines.” These results were further filtered to identify guidelines published by a national professional society or professional medical association. Guidelines by the following organizations were identified: American Thoracic Society and Infectious Diseases Society of America [1], Latin American Thoracic Society [2], South African Thoracic Society [3], Japanese Respiratory Society [4], Portuguese Society of Pulmonology and Portuguese Intensive Care Society [5], Society Brasileira de Pulmonologia [6], Association of Medical Microbiology and Infectious Diseases of Canada [7], and British Society for Antimicrobial Chemotherapy [8]. Only articles that were published in an English version [1, 3, 5, 7, 8] are included in this review.

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Table 1. Recent Guidelines for the Management of Hospital-Acquired Pneumonia and/or Ventilator-Associated Pneumonia

Guideline	Evidence-based grading system
American Thoracic Society and Infectious Diseases Society of America (2005)	Level I: well-conducted, randomized controlled trials Level II: well-designed studies without randomization, large systemically analyzed case series Level III: case studies and expert opinion; in some instances from antibiotic susceptibility data without clinical observations
South African Thoracic Society (2006)	No grading indicated
Portuguese Society of Pulmonology and Portuguese Intensive Care Society (2007)	No grading indicated
Association of Medical Microbiology and Infectious Diseases of Canada (2008)	
Strength of recommendation	(A) Good evidence to support recommendation (B) Moderate evidence to support recommendation (C) Poor evidence to support recommendation
Quality of evidence	(I) Evidence from ≥ 1 properly randomized controlled trial (II) Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies; from multiple time series; or from dramatic results from uncontrolled experiments (III) Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
British Society for Antimicrobial Chemotherapy (2008)	(A) ≥ 1 Meta-analysis, systematic review, or randomized controlled trial (B) Studies rated 2++ demonstrating consistency (C) Studies rated 2+ (D) Studies rated 3 or 4++ (GPP) Recommended best practice based on clinical experience

NOTE. GPP, Good Practice Point.

RESULTS

In the 2005 American Thoracic Society and Infectious Diseases Society of America guidelines [1], HAP (or nosocomial pneumonia) was defined as pneumonia that occurs ≥ 48 h after admission that did not appear to be incubating at the time of admission, VAP was defined as a type of HAP that develops >48 h after endotracheal intubation, and health care–associated pneumonia (HCAP), a relatively new clinical entity, was defined as pneumonia that occurs in a nonhospitalized patient with extensive health care contact, as defined by ≥ 1 of the following modes: intravenous therapy, wound care, or intravenous chemotherapy during the prior 30 days, residence in a nursing home or other long-term care facility, hospitalization in an acute care hospital for ≥ 2 days during the prior 90 days, or attendance at a hospital or hemodialysis clinic during the prior 30 days. All of the reviewed guidelines shared similar definitions for HAP and VAP; however, although the South African guideline [3] used the same definition of HCAP, neither the Canadian [7] nor the UK [8] guidelines referred to this classification. The Portuguese guideline [5] mentions HCAP but did not come to a consensus for endorsing this as a specific classification; the statement indicated that the definition of HCAP was useful for epidemiological studies, but until studies were conducted in Portugal, it was preferable to make individual, patient-by-patient assessments of each HCAP criterion.

Of the 5 reviewed guidelines, 3 indicated an evidence-based

grading system (Table 1). Key recommendations from each guideline about diagnosis of HAP and VAP are listed in Table 2. Each guideline acknowledged the relative unreliability of current diagnostic methods; however, there was general agreement about clinical criteria for suspecting HAP or VAP (Table 3). Recommendations for bacteriological diagnosis were variable, but all guidelines suggested some method of obtaining lower respiratory tract samples. Quantitative cultures were discussed in each guideline, with recognition that each technique (eg, bronchoscopic vs nonbronchoscopic) has its own methodological limitations.

Recommendations for empirical antimicrobial therapy for HAP and VAP are listed in Table 4. All guidelines recommend stratification of patients by presence or absence of risk factors for multidrug-resistant pathogens. The durations of therapy suggested in each guideline are listed in Table 5.

DISCUSSION

The recommendations for the general approach to the management of HAP and VAP are similar in the reviewed guidelines. All of the guidelines invariably emphasize the need to use early, appropriate antimicrobial therapy and to avoid excessive use of antibiotics by deescalation of initial antibiotic therapy on the basis of microbiological culture results and the clinical response of the patient.

Diagnosis. Each of the guidelines acknowledges the prob-

Table 2. Key Recommendations for Diagnosis of Hospital-Acquired Pneumonia (HAP) and/or Ventilator-Associated Pneumonia (VAP) from Recent Guidelines

Guideline	Key recommendations for diagnosis
American Thoracic Society and Infectious Diseases Society of America (2005)	<ul style="list-style-type: none"> ● All patients should have comprehensive evaluation to define severity and exclude other sources of infection and reveal conditions that can influence the likely etiology (II) ● A new or progressive pulmonary infiltrate and ≥ 2 of fever, leukocytosis, or sputum purulence is most accurate clinical criteria (II) ● Patients should have blood cultures performed (II) ● Obtain LRT secretions for culture before initiating antimicrobial therapy (II) ● Negative culture result of appropriate LRT specimen in absence of change in antimicrobial therapy in preceding 72 h virtually rules out pyogenic bacterial infection; exception includes Legionella (II) ● Reliable tracheal aspirate Gram stain can be used to direct initial antimicrobial therapy and may increase the diagnostic value of CPIS (II) ● Quantitative cultures can be performed on endotracheal samples collected bronchoscopically or no bronchoscopically (the choice depends on local expertise, experience, availability, and cost (II) ● Modified CPIS of ≤ 6 for 3 days is a criterion to select patients at low risk for early discontinuation of empirical therapy of HAP (I)
Association of Medical Microbiology and Infectious Diseases of Canada (2008)	<ul style="list-style-type: none"> ● CPIS score should be calculated to improve sensitivity and specificity for the diagnosis of HAP and VAP (B2) ● Invasive diagnostic testing has not been demonstrated to improve clinical outcomes and is not recommended except for in immunocompromised hosts (A1) ● Recommended that, for most patients, a clinical approach supplemented by noninvasive quantitative cultures of respiratory samples is sufficient to guide appropriate antibiotic choices (C3) ● Low CPIS score may allow careful observation of the patient without antibiotics (by the third day of calculating the CPIS, a score of < 6 may allow discontinuation of antibiotics)
South African Thoracic Society (2006)	<ul style="list-style-type: none"> ● Invasive diagnostic techniques not essential or routinely recommended ● Fresh specimen of lower respiratory tract secretions should be submitted for culture (for patients who are intubated this should be through a sterile catheter)
Portuguese Society of Pulmonology and Portuguese Intensive Care Society (2007)	<ul style="list-style-type: none"> ● Combination of clinical and microbiological strategies is recommended ● If nosocomial pneumonia is suspected, obtain blood and respiratory samples for culture; consider the risk/benefit of invasive procedures individually ● BAL or PSB should be done in intubated patients if feasible
British Society for Antimicrobial Chemotherapy (2008)	<ul style="list-style-type: none"> ● CPIS is useful for selecting patients for short-course therapy (C) ● Chest radiograph should be performed and compared with previous chest radiographs (D) ● CT may assist in diagnosis of HAP (GPP) ● Endotracheal aspirate samples are not useful for diagnosis of VAP (A) ● There is no evidence that any 1 invasive method is best (A) ● Recommend the least expensive, least invasive method requiring minimal expertise be used for microbiological diagnosis (GPP) ● Quantitative culture of PSB or BAL specimen should not be relied on for diagnosis of HAP/VAP (A) ● Quantification of intracellular organisms in BAL specimen can be used to guide therapy (A)

NOTE. See Table 1 for grading system. BAL, bronchoalveolar lavage; CPIS, Clinical Pulmonary Infection Score; GPP, Good Practice Point; LRT, lower respiratory tract; PSB, protected specimen brush.

lem with diagnosis of HAP and/or VAP and the relative difficulty in using clinical criteria to differentiate from other conditions that can mimic pneumonia. Such conditions include pulmonary infarction, adult respiratory distress syndrome, pulmonary edema with another infection site, pulmonary hemorrhage, vasculitis, malignancy, drug toxicity, radiation pneumonitis, and preexisting lung disease (eg, fibrosing alveolitis).

Nevertheless, the guidelines similarly recognize a clinical diagnosis of pneumonia when there is a new or progressive pulmonary infiltrate and 2 of the following signs or symptoms: fever, leukocytosis, or purulence (Table 3). Although the sensitivity for the presence of pneumonia is increased if only one criterion is used, this would lower specificity; if all these clinical criteria are required, the sensitivity will be poor.

Table 3. Criteria for Clinical Diagnosis of Ventilator-Associated Pneumonia from Recent Guidelines

Guideline	Criteria
American Thoracic Society and Infectious Diseases Society of America	New infiltrate and 2 of fever, increase in WBC count, and purulence (II)
Canadian (Association of Medical Microbiology and Infectious Diseases)	New infiltrate and 2 of fever, increase in WBC count, and purulence (not graded)
South African	New infiltrate and 2 of fever, increase in WBC count, and purulence
Portuguese	New infiltrate, fever, and increase in WBC count or purulence
British	New infiltrate and consider if purulent secretions, increase in oxygen requirement, fever, increase in WBC count (C)

NOTE. See Table 1 for grading system. WBC, white blood cell.

There is also a general consensus that inadequate evidence exists to definitely recommend the need for quantitative culture to establish the diagnosis. However, there is a trend suggesting that such studies are more reflective of true pneumonia when quantitative criteria are used. Most of the guidelines consider that use of either a clinical or a bacteriologic strategy is acceptable, provided that there is an effort to use the culture data to achieve appropriate therapy and that this is done with the least exposure to antibiotics possible. There is a consensus for recommending acquisition of a lower respiratory tract sample for culture before initiation or change of therapy and to use the results, in addition to serial evaluations of the clinical course, to modify therapy. However, the collection of a sample for culture should not delay the initiation of therapy, because delay of antimicrobial therapy is associated with poor outcomes.

Several of the guidelines suggest that a potential means to improve the clinical diagnosis of pneumonia is to combine all of the features into a single score, as has been done with the Clinical Pulmonary Infection Score [9]. This tool has been accurate for separating patients receiving mechanical ventilation who have pneumonia from those who do not have pneumonia, by measuring (on a scale from 0–2) each of the following signs and parameters: fever, leukocytosis, purulence of respiratory secretions, radiographic abnormalities, and oxygenation. In addition, either a Gram stain or a culture of a deep respiratory tract sample can be added to the scoring system, leading to improvements in its sensitivity and specificity [10]. With use of this approach, pneumonia is more likely in those with a Clinical Pulmonary Infection Score of ≥ 6 than in those with a score of < 6 .

Antimicrobial therapy. All the reviewed guidelines recommend patient risk stratification based on variable factors, including clinical presentation, time of onset relative to admission, and the potential for multidrug-resistant pathogens based on prior antibiotic exposure, previous hospital admission, or exposure to a health care setting (eg, long-term care facility). Initial, empirical therapy is based on the relative risk that a

patient has for being infected with a drug-resistant pathogen. In addition, the recommended choice of therapy should be guided by knowledge of local patterns of microbiology and drug resistance that are present in the hospital where the patient is being treated. Thus, an awareness of the drug susceptibility patterns of nosocomial pathogens in a given health care setting is important for achieving appropriate empirical antimicrobial therapy. This may have a confounding effect for guidelines, because specific susceptibility patterns for pathogens will differ among investigator sites.

Table 5 lists specific antimicrobials recommended for empirical therapy in the various guidelines. The agents included reflect the experience and rate of antimicrobial resistance in each area. In each guideline, monotherapy is listed for patients not considered to be at risk of infection with multidrug-resistant pathogens, whereas most guidelines recommend various combinations of therapy for patients at risk of infection with multidrug-resistant pathogens. Although numerous randomized clinical trials have been undertaken for evaluation of HAP and VAP (extensively reviewed in the Canadian Guidelines [7]), a number of limitations preclude demonstration of superiority of one agent over another; these include inclusion of heterogeneous patient populations, use of different combination treatment regimens in addition to a study agent, and relatively small sample sizes. In general, the British guidelines recommend less-broad-spectrum regimens than do the other guidelines. For purposes of choosing active drug comparators, these recommendations will need to be considered when designing future clinical trials.

All guidelines recommend a deescalation process after results of appropriate cultures are determined. Such an approach will be difficult to implement in a standard method in clinical trials.

The standard duration of therapy that is listed in the guidelines is 7–8 days for most pathogens and longer (usually 14 days) for nonfermenting gram-negative bacilli. These recommendations are primarily based on the results of a large random controlled trial involving patients with VAP and other studies suggesting that long-term therapy may not provide additional

Table 4. Summary of Recommendations for Empirical Antimicrobial Therapy from Recent Guidelines

Guideline	No risk for MDR pathogen	Risk for MDR pathogen
American Thoracic Society and Infectious Disease Society of America	Ceftriaxone or fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin), or ertapenem, or ampicillin-sulbactam (III)	Antipseudomonal β lactam (eg, ceftazidime, imipenem, meropenem, piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside plus linezolid or vancomycin (if MRSA risk) (III)
Canadian (Association of Medical Microbiology and Infectious Diseases)	Third-generation cephalosporin or fourth-generation cephalosporin (cefepime) or piperacillin-tazobactam or levofloxacin (750 mg every 24 h) or moxifloxacin (400 mg every 24 h) (C-3)	Not severe: third-generation cephalosporin or fourth-generation cephalosporin (cefepime) or piperacillin-tazobactam or levofloxacin (750 mg every 24 h) or moxifloxacin (400 mg every 24 h) or carbapenem (imipenem or meropenem) plus/minus vancomycin or linezolid (if MRSA present or suspected); severe: ^a antipseudomonal β lactam (eg, ceftazidime, imipenem, meropenem, piperacillin-tazobactam) plus aminoglycoside plus/minus vancomycin or linezolid (if MRSA present or suspected) (C-3)
South African	Third- or fourth-generation cephalosporin (ceftazidime, ceftriaxone, or cefotaxime, cefepime) or piperacillin-tazobactam or ertapenem or ciprofloxacin or levofloxacin	Risk factors include recent antibiotic therapy (90 days), hospitalization for ≥ 5 days, structural lung disease, high level of resistance in community or unit, immunosuppression, HCAP, severe HAP (particularly in ICU): cefepime or piperacillin-tazobactam or meropenem or imipenem-cilastatin or ciprofloxacin or levofloxacin plus/minus aminoglycoside; add vancomycin only if MRSA strongly suspected (alternatives include teicoplanin or linezolid; some emerging evidence of possible advantage of linezolid)
Portuguese	Amoxicillin-clavulanate or ceftriaxone or cefotaxime or levofloxacin	Risk factors include recent antibiotic therapy, late-onset pneumonia or hospitalization in preceding 3 months, structural lung disease, immunosuppression; 1 risk factor: antipseudomonal β lactam plus aminoglycoside or antipseudomonal β lactam plus quinolone; ≥ 2 risk factors: add MRSA coverage—continuous infusion vancomycin preferred (linezolid if prior vancomycin or kidney dysfunction or inability to monitor vancomycin levels)
British	If < 5 days in hospital, no prior antibiotics and absence of comorbidities, amoxicillin-clavulanate or cefuroxime (GPP)	<5 days in hospital, prior antibiotics, or significant comorbidities: cefotaxime or ceftriaxone or a fluoroquinolone or piperacillin-tazobactam; choice of empirical antibiotic therapy should be based on knowledge of the nature and susceptibility patterns of the pathogens that are prevalent in that unit; definitive therapy should be determined by culture; for <i>Pseudomonas</i> : ceftazidime, ciprofloxacin, meropenem or piperacillin-tazobactam; for MRSA: either linezolid or glycopeptide (no firm conclusion of which is optimal) (GPP)

NOTE. See Table 1 for grading system. HAP, hospital-acquired pneumonia; HCAP, health care-associated pneumonia; ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

^a Hypotension, need for intubation, sepsis syndrome, rapid progression of infiltrates, and end organ dysfunction.

clinical benefit and can increase emergence of drug resistance [11].

CONCLUSION

Clinical practice guidelines are defined as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” [12, p 18]. They are widely used to help promote efficient and effective health care by improving process and patient outcomes. As described recently, “guidelines are a constructive response to the reality that the practicing physician requires assistance to assimilate and apply the exponentially expanding, often contradictory body of medical knowledge. For many clinicians, guidelines have become the final arbiters of care” [13, p 429].

The guidelines reviewed in this article reflect these principles. Because they are based on published evidence and developed

by consensus, they reflect what is considered as recommendations for optimal practice in each region of consideration. Thus, specific recommendations concerning appropriate diagnosis and empirical antimicrobial therapy that are listed in regional guidelines should have an impact in development of future clinical trials. Although recommendations for clinical and microbiological diagnosis are standard in the reviewed guidelines, there are differences in recommendations for empirical antimicrobial therapy. Such differences reflect a variation in likely pathogens and drug susceptibility patterns. Protocols for multinational studies will need to reflect these differences. In addition, all guidelines recommend reevaluation based on clinical response and results of appropriate microbiological data at 48–72 h, with recommendations to deescalate to pathogen-directed therapy. Such an approach may be difficult to implement in a standard method in clinical trials.

Despite some differences (mostly related to differences in

Table 5. Recommendations for Duration of Antimicrobial Therapy from Recent Guidelines

Guideline	Duration
American Thoracic Society and Infectious Disease Society of America	As short as 7 days, provided that the etiologic pathogen is not <i>Pseudomonas aeruginosa</i> and that the patient has a good clinical response (I)
Canadian (Association of Medical Microbiology and Infectious Diseases)	7–8 Days should suffice for most cases of HAP (C-3) and VAP (A-3); more prolonged period (14 days) for <i>P. aeruginosa</i> (C-3)
South African	Currently recommended treatment duration is 5–7 days
Portuguese	10–15 Days for nonfermenting gram-negative bacilli or Legionella and 7–8 days for other pathogens
British	When patients respond to therapy, the routine duration should be ≤8 days (C)

NOTE. See Table 1 for grading system. HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

likely pathogens), there is a general agreement about the recommended approach to general management of HAP and/or VAP in the reviewed guidelines. Developers of future clinical trials will need to be mindful of these recommendations to maintain best practice care for each investigator.

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References

- Niederman MS, Craven DE, Bonten MJ, et al. American Thoracic Society and the Infectious Diseases Society of America 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.
- Luna CM, Monteverde A, Rodriguez A, et al. Clinical guidelines for the treatment of nosocomial pneumonia in Latin America: an interdisciplinary consensus document. Recommendations of the Latin American Thoracic Society [in Spanish]. *Arch Broncopneumol* **2005**; 41:439–456.
- Brink A, Feldman C, Duse A, et al.; South African Thoracic Society. Guideline for the management of nosocomial infections in South Africa. *S Afr Med J* **2006**; 96:642–652.
- Japanese Respiratory Society. The JRS guideline for the management of hospital-acquired pneumonia in adults. *Nippon Naikai Gakkai Zasshi* **2008**; 97:2578–2583.
- Froes F, Paiva JA, Amaro P, et al.; Portuguese Society of Pulmonology and Intensive Care Society. Consensus document on nosocomial pneumonia [in Portuguese]. *Revisia Portuguesa de Pneumologia* **2007**; 13: 419–486.
- Sociedade Brasileira de Pneumologia e Tisiologia. Brazilian guidelines for treatment of hospital acquired pneumonia and ventilator associated pneumonia—2007. *J Bras Pneumol* **2007**; 33(suppl 1):S1–S30.
- Rotstein C, Evans G, Born A, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. *Can J Infect Dis Med Microbiol* **2008**; 19:19–53.
- Masterton RG, Gaooolway A, French G, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* **2008**; 62: 5–32.
- Pugin J, Auckenthaler R, Mili N, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic “blind” bronchoalveolar lavage fluid. *Am Rev Respir Dis* **1991**; 143:1121.
- Fartoukh M, Maitre B, Honore S, et al. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. *Am J Resp Crit Care Med* **2003**; 168:173–179.
- 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.
- Committee to Advise the Public Health Service on Clinical Practice Guidelines, Institute of Medicine. In: Field MJ, Lohr KN, eds. *Clinical practice guidelines: directions of a new program*. Washington, DC: National Academy Press, **1990**.
- Sniderman AD, Furberg CD. Why Guideline-making requires reform. *JAMA* **2009**; 301:429–431.