Severe Hospital-Acquired Pneumonia: A Review for Clinicians

John Dallas, MD, and Marin Kollef, MD, FCCP

Corresponding author
Marin Kollef, MD, FCCP
Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, Campus Box 8052, 660 South Euclid Avenue, St. Louis, MO 63110, USA.
E-mail: mkollef@dom.wustl.edu

Current Infectious Disease Reports 2009, **11**:349–356
Current Medicine Group LLC ISSN 1523-3847

Hospital-acquired pneumonia (HAP) is one of the most commonly encountered nosocomial infections. Patients who develop severe HAP experience considerable morbidity and mortality, and the condition results in a substantial expenditure of health care resources. A large body of scientific literature about HAP now exists. This article summarizes the current state of knowledge concerning severe HAP with an emphasis on recent advances in its diagnosis, treatment, and prevention.

Introduction

Hospital-acquired pneumonia (HAP) is defined as pneumonia that develops after more than 48 hours of hospitalization without suggestion that the process was arising at the time of admission. Ventilator-associated pneumonia (VAP) describes a subset of patients with HAP arising after more than 48 hours of mechanical ventilation [1].

HAP must be distinguished from community-acquired pneumonia (CAP) and health care–associated pneumonia (HCAP). CAP refers to pneumonia that develops outside the hospital or within the first 48 hours of admission in patients who do not meet the criteria for diagnosis of HCAP. HCAP is a newer term used to describe a subset of patients who traditionally were classified as having CAP but who have important risk factors for multidrug-resistant (MDR) pathogens as the causative organisms for pneumonia. These risk factors include hospitalization in an acute care facility within 90 days of presentation, residence in a nursing home, antibiotic treatment or chemotherapy within 30 days of presentation, undergoing hemodialysis at an outpatient clinic, home infusion therapy, a household contact known to be infected or colonized with a MDR pathogen, and the presence of an indwelling intravenous catheter [2•].

Previously, HAP onset was often classified as "early" or "late" depending on whether it arose within the first 4 days of hospitalization. This designation was used because it was thought that those with early-onset HAP were at less risk for infection with MDR pathogens. However, recent literature has moved away from this designation with the realization that many patients with early-onset HAP also have risk factors for MDR pathogens.

No formal definition of "severe" HAP exists. Most clinicians would agree that HAP should be considered severe in the following circumstances: all cases of VAP, requirement for ICU admission, need for vasopressor support, and need for ventilatory support (either invasive or noninvasive). The presence of identified risk factors for mortality in HAP should lead to suspicion of severe HAP. These risk factors include age greater than 65 years, altered mental status, and infection with methicillin-resistant *Staphylococcus aureus* (MRSA) or MDR *Pseudomonas aeruginosa* [3,4••].

Pathogenesis

The development of HAP requires potentially pathogenic microorganisms to gain entry into the lower respiratory tract. These pathogens may originate from medical staff, hospital equipment (including ventilator circuits and tubing), or fomites. Often, colonization occurs in the oropharyngeal cavity, sinuses, and perhaps the upper gastrointestinal tract before pathogens enter the lower respiratory tract.

Previously, the ventilator and its associated tubing and humidification agents were a major focus of investigations concerning VAP. In recent years, the focus shifted to the importance of the endotracheal tube (ETT) in VAP pathogenesis. In addition to the aspiration events that often accompany the intubation procedure, the ETT mitigates the cough reflex, leading to accumulation of infected secretions in the subglottic space [5].

Biofilms were implicated in the pathogenesis of many nosocomial infections, including urinary tract infections associated with bladder catheters and blood stream infections associated with central venous catheters. The ETT also represents an ideal surface for the formation of bacterial biofilm. Biofilms form on the inner surface of the ETT

Table 1. Causative pathogens of ventilator-associated pneumonia in the United States

Organism	Percentage, %
Gram-positive bacteria	
Staphylococcus aureus	24
Streptococcus spp	8
Streptococcus pneumoniae	4
Enterococcus spp	1
Coagulase-negative *Staphylococcus* spp	1
Other gram positives	1
Gram-negative bacteria	
Pseudomonas aeruginosa	16
Enterobacter spp	8
Acinetobacter baumannii	8
Klebsiella pneumoniae	7
Haemophilus spp	7
Escherichia coli	5
Stenotrophomonas maltophilia	2
Other gram negatives	3
Anaerobic bacteria	3
Fungi	
Candida spp	2

(*Adapted from* Centers for Disease Control and Prevention [11].)

quickly after intubation and can be easily dislodged by suction catheter use, leading to inoculation of the lower respiratory tract [6].

Biofilms are also associated with antimicrobial resistance. Mechanisms for this resistance include impaired access of antibiotics to bacteria because of a protective matrix encasing the biofilm, reduced growth rate of bacteria within hypoxic zones of the biofilm, and biofilm-induced expression of resistance genes [7]. Ongoing research focuses on novel methods of preventing biofilm formation and disrupting the biofilm once it has been established.

Epidemiology

Incidence

HAP is one of the most common nosocomial infections, and VAP is the most common nosocomial infection diagnosed in the ICU [1]. By the best estimates, VAP occurs in 10% to 20% of patients receiving mechanical ventilation for more than 48 hours [8].

Impact on outcome

The crude mortality rate of HAP is between 30% and 70%. The extent of this mortality directly attributable to HAP is controversial. Pneumonia may occur as part of the "end-of-life" process in many patients. A thorough systemic review found a twofold increase in mortality directly attributable to VAP [8]. Little doubt exists that development of HAP increases total hospital and ICU length of stay and overall health care costs. Additionally, VAP significantly increases the duration of mechanical ventilation [1].

Etiology

Knowledge of typical pathogens associated with HAP is critical when deciding on empiric antibiotic therapy. Most data concerning the microbiology of HAP refer specifically to the VAP population, but available studies suggest that the microbiology of HAP is similar enough to VAP to warrant similar approaches to empiric treatment regimens [9]. Typical bacterial pathogens associated with VAP are described elsewhere, and recent data reveal no major changes in these patterns (Table 1) [10,11].

The etiologic agents of VAP may change depending on the duration of hospitalization and mechanical ventilation. So-called late VAP is often associated with a higher rate of polymicrobial infection and infection with MDR pathogens. This trend was confirmed recently in the population residing in long-term acute care hospitals [12].

In many cases the etiologic agent of HAP is unknown, and the role of nonbacterial pathogens in the pathogenesis of HAP is incompletely understood. Recent reports indicate that viral pathogens (eg, herpes simplex virus, cytomegalovirus, and mimivirus) may have a role as etiologic agents of VAP [13,14]. Further study is needed to identify the role of viral pathogens in HAP.

The role of fungal pathogens in the pathogenesis of HAP was investigated recently. *Candida* spp are frequently isolated from lower respiratory tract specimens in patients receiving mechanical ventilation but were thought to represent colonization rather than infection. However, a recent retrospective analysis associated the presence of *Candida* spp in respiratory tract secretions of patients with VAP with worse clinical outcomes and increased hospital mortality [15]. It is unknown if these findings are due to a potential role of *Candida* in the pathogenesis of VAP or are a marker of a more severely ill patient population.

Interestingly, a potential pathogenic interaction between *Candida* spp and *P. aeruginosa* (the two most commonly isolated organisms from the lower respiratory tract in mechanically ventilated patients) was suggested [16]. Retrospective data suggest that antifungal treatment of candidal colonization may decrease the rate of VAP associated with *P. aeruginosa* [17].

Diagnosis

The diagnosis of HAP is suspected based on the triad of clinical signs of infection (fever, tachycardia, and leukocy-

tosis), a new or progressive pulmonary infiltrate on chest radiograph, and purulent pulmonary secretions. The diagnosis may be confirmed with microbiologic evidence of infection in the appropriate clinical setting.

In practice, the diagnosis of HAP is often difficult and diagnostic criteria remain controversial. Important problems include the multitude of other conditions occurring in hospitalized patients that present with similar clinical signs, the poor specificity of portable chest radiographs in identifying a pneumonic infiltrate, and the decision to use invasive or noninvasive means to obtain respiratory specimens for culture. Consensus has not been reached regarding the optimal algorithm for HAP diagnosis.

Probably the greatest controversy involving the diagnosis of HAP concerns the decision to use an invasive or noninvasive strategy to obtain culture specimens. The noninvasive strategy involves obtaining a culture of expectorated sputum in nonintubated patients or of endotracheal tube aspirate in intubated patients. The invasive strategy involves performing bronchoalveolar lavage (BAL) or using a protected specimen brush device to obtain cultures from the lower respiratory tract, thereby bypassing potential contamination from colonizers of the upper respiratory tract. Most studies do not show improved patient outcomes with an invasive diagnostic strategy. However, this is not surprising because clinical criteria alone are overly sensitive for the diagnosis of HAP, and most patients with suspected HAP are aggressively treated with antibiotics.

The primary advantage of an invasive diagnostic strategy likely lies in its ability to limit unnecessary antibiotic use. A recently published study confirmed that endotracheal aspirate statistically overdiagnosed VAP when compared with BAL and demonstrated a 21% decrease in antibiotic use after a practice change initiative designed to encourage increased use of BAL [18]. Studies indicate that discontinuing antibiotics in low-risk patients with a negative culture of BAL fluid is a safe strategy [19].

Clinical scoring systems such as the clinical pulmonary infection score (CPIS) were introduced to overcome some of the difficulties in diagnosing VAP. A recent review on the utility of the CPIS concluded that although its role in clinical practice remains undefined, it may hold promise as a tool to decide which patients can tolerate early discontinuation of antibiotics [20•]. Caution is urged when using CPIS alone as a diagnostic tool because it may underestimate VAP incidence.

Measurement of several biomarkers including procalcitonin (PCT), C-reactive protein (CRP), and soluble triggering receptor expressed on myeloid cells (sTREM)-1 in serum and BAL fluid was evaluated for potential diagnostic and prognostic information in VAP. In general, recent evidence indicates these measurements have poor sensitivity and limited diagnostic value [21•]. However, serum PCT levels show promise as a method to limit antibiotic use in low-risk patients with community-acquired pneumonia [22], and this intriguing concept deserves more evaluation in HAP.

Treatment

Guidelines

Studies consistently reveal improved patient outcomes and decreased antibiotic use patterns when formal guidelines for the management of HAP are used [23]. Many different sets of regional and country-specific guidelines for the treatment of HAP were published [1,24–27]. Additionally, references are available to assist in implementing evidence-based guidelines modified for local antimicrobial resistance patterns [28].

Empiric therapy

Inappropriate initial antibiotic therapy for HAP is associated with increased mortality and other adverse outcomes [23,29]. Conversely, excess antimicrobial use inevitably leads to increasing problems with antibiotic resistance.

To select an appropriate regimen, one must decide if risk factors for MDR pathogens are present. Previously, this decision was based solely on the length of hospitalization before the development of pneumonia. Other risk factors for MDR pathogens now include antimicrobial therapy in the previous 90 days, current hospitalization ≥ 5 days, high frequency of antibiotic resistance in the community or specific hospital unit, or presence of other HCAP risk factors (see Introduction) [2•].

The most important causative organisms of HAP that are considered as MDR include oxacillin-resistant *S. aureus*, *P. aeruginosa*, *Acinetobacter baumannii*, and the extended-spectrum β-lactamase–producing Enterobacteriaceae. Specific treatment recommendations for these organisms are outside the scope of this review but are available in published guidelines. Figure 1 depicts a suggested treatment algorithm for suspected HAP.

Duration of therapy and de-escalation

Most patients with HAP who receive appropriate initial antimicrobial therapy show a good response within 6 days. Prolonged therapy leads to colonization with resistant bacteria that could cause recurrent disease [30]. A relatively large, nonblinded, randomized trial published in 2003 demonstrated no adverse outcomes for patients treated with 8 versus 15 days of antimicrobial therapy although those with inappropriate initial antibiotic therapy were excluded [31]. The practice of discontinuing antibiotics when signs of infection improve also was shown to not worsen patient outcomes [32]. This information has led to a general consensus that "routine" VAP can be treated with a shorter duration of antibiotics (6–8 days) rather than the longer duration (14–21 days) previously recommended.

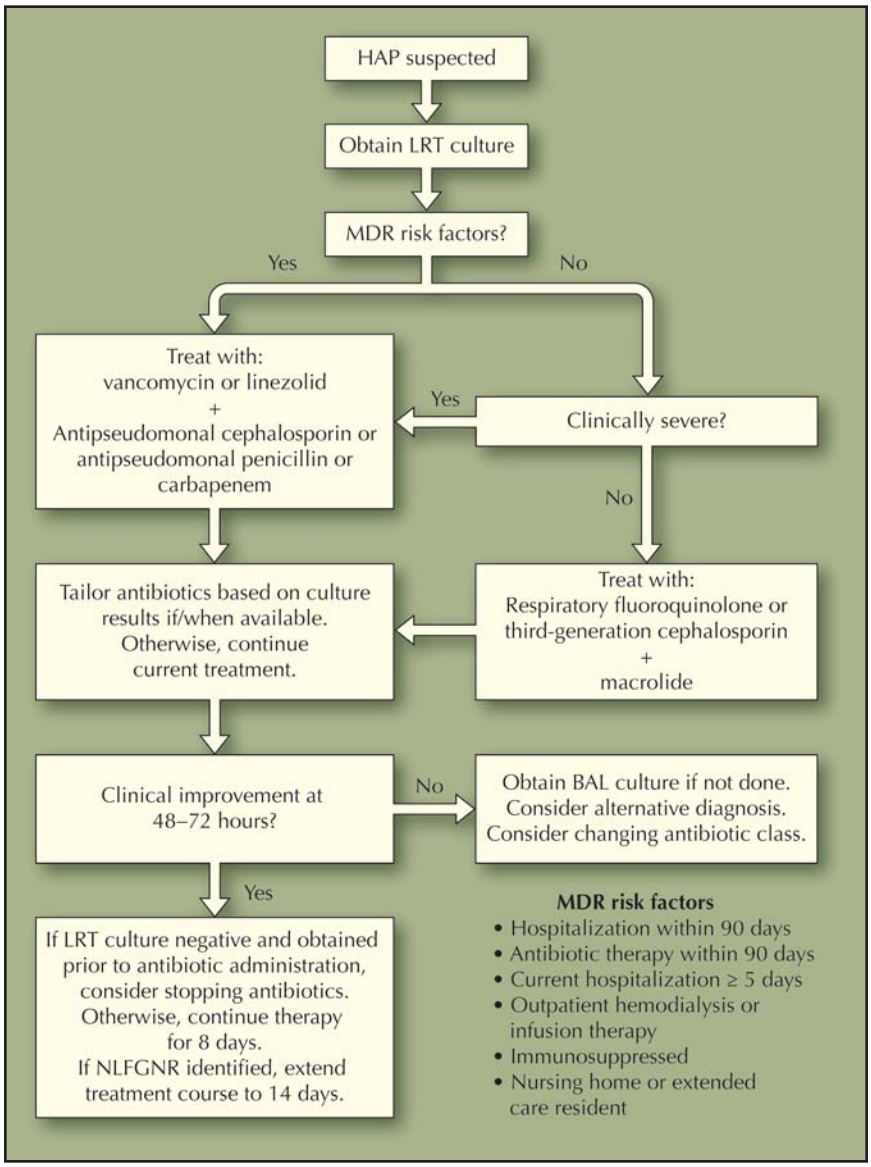

Figure 1. Suggested treatment algorithm for hospital-acquired pneumonia (HAP). BAL—bronchoalveolar lavage; LRT—lower respiratory tract; MDR—multidrug resistant; NLFGNR—non-lactose fermenting gram-negative rod.

Patients with VAP caused by nonfermenting gram-negative bacilli such as *A. baumannii*, *Stenotrophomonas maltophilia*, and particularly *P. aeruginosa* are at risk for relapse [33]. Treating these patients with a longer course of antibiotics (≥ 14 days) is recommended, although prospective data supporting this are lacking.

In addition to limiting the duration of therapy, antimicrobial use can be decreased by using the most narrow-spectrum antimicrobial available once sensitivity results are known. This strategy decreased antibiotic use without adverse effects on patient outcome [34•].

Continuous intravenous antibiotics

Many antibiotics commonly used to treat HAP (β-lactams, oxazolindones, vancomycin) exhibit time-dependent bacterial killing characteristics. This implies that maximal bacterial killing is accomplished by maintaining the antibiotic concentration above the minimum inhibitory concentration for the longest period of time, rather than depending on a high peak concentration for maximum effectiveness. This can be achieved by extended dosing intervals or continuous antibiotic infusion. Clinical outcomes data for this approach are limited, but small studies demonstrate higher rates of clinical cure for VAP with continuous infusion of piperacillin/tazobactam, meropenem, and ceftazidime [35]. Further prospective studies in larger groups are needed to verify this approach.

Aerosolized antibiotics

The most recent American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines [1] for the management of HAP concluded that aerosolized antibiotics were not proven to have value in VAP treatment but can be considered as adjunctive treatment for VAP caused by MDR pathogens that are unresponsive to standard therapy. Most studies evaluated inhaled antibiotics (often aminoglycosides or colistin) as adjuncts to systemic therapy rather than as stand-alone therapy. Since the ATS/IDSA guidelines were published, several other

Table 2. Strategies for the prevention of ventilator-associated pneumonia

Considered effective	Considered ineffective	Controversial
Avoidance of nasotracheal intubation	Scheduled ventilator circuit changes	Early tracheostomy
Change of ventilator circuit when visibly contaminated	Bacterial filters	Prophylactic antimicrobials (parenteral, oral, or inhaled)
Use of closed endotracheal suction system	Routine use of heat moisture exchangers	Stress ulcer prophylaxis
Subglottic secretion drainage	Routine use of parenteral nutrition without other reason	Early gastrostomy
Semirecumbent positioning	Probiotics	Antimicrobial therapy for tracheobronchitis
Oral cleansing with chlorhexidine	Oral cleansing with iseganan	Chest physiotherapy
Use of noninvasive ventilation when appropriate		Intensive glycemic control
Use of silver-coated endotracheal tubes		Use of kinetic beds
Conservative blood transfusion strategy		
Aggressive infection-control measures (hand disinfection, isolation gowns)		
Daily sedation holidays		
Staff education initiatives and prevention bundles		
Use of orogastric rather than nasogastric tubes		
Avoidance of reintubation		

small studies supported using inhaled antibiotics for VAP and tracheobronchitis [36–38]. Unfortunately, the literature in this area is plagued by small numbers of enrollees and lack of control groups. Data are lacking to support the use of inhaled antibiotics as more than an adjunctive therapy is nonimproving patients.

Prevention Strategies

Much literature exists concerning the prevention of VAP. However, the literature available to guide HAP prevention strategies for nonintubated patients is relatively sparse. Preventive strategies for VAP often focus on modifiable risk factors for oropharyngeal colonization with potentially pathogenic organisms and subsequent aspiration of these organisms. Several evidence-based guidelines for the prevention of VAP were published [39•,40]. Table 2 shows practices that are generally considered effective and ineffective in preventing VAP, and strategies that are still considered controversial. Several topics that have received particular attention recently are discussed next.

Oral and digestive decontamination

Selective digestive decontamination (SDD) describes a prophylactic antimicrobial regimen that typically includes nonabsorbable antibiotics applied to the oropharynx and gastrointestinal tract along with a short course of intravenous antibiotics in the hope of preventing HAP by eradicating commensal respiratory flora and preventing oropharyngeal colonization with potentially pathogenic organisms. SDD has been studied for more than 25 years and more than 10 meta-analyses have been performed. Despite fairly consistent demonstration of modest decreases in mortality and rate of blood stream infections, SDD is not widely used. This is primarily because of concerns about promoting antimicrobial resistance and uncertain cost-effectiveness. More recently, significant reductions in VAP were seen when oral and gastric decontamination were used without the parenteral antibiotic component.

A large, randomized trial of more than 6000 patients comparing SDD, oral decontamination with only topical agents, and standard care was published recently [41••]. Compared with standard care, SDD led to a 28-day mortality decrease from 27.5% to 26.9%. The 28-day mortality in the oral decontamination group was similar to the SDD group at 26.6%. Although the overall decrease in mortality with SDD was slight, the similar benefit seen in the oral decontamination group lends weight to the concept of forgoing parenteral antibiotics in this strategy. Because antimicrobial resistance may take time to develop, its emergence may not be noticed in clinical trials; this remains a major concern with the widespread implementation of SDD.

Continuous aspiration of subglottic secretions

Continuous aspiration of subglottic secretions (CASS) refers to the use of a specialized ETT with a suction port

above the ETT cuff that can be attached to a continuous suction system. This allows the removal of potentially infected secretions that may pool in the subglottic space. Previous trials of CASS for the prevention of VAP yielded promising but occasionally mixed results. A meta-analysis published in 2005 concluded that CASS decreased the incidence of VAP by nearly 50% [42]. The largest randomized trial evaluating CASS was published recently [43••]. In patients who were intubated for more than 48 hours, CASS led to significantly lower rates of VAP, shorter duration of mechanical ventilation, and decreased ICU stay. In addition, even though the initial cost of an ETT capable of CASS was more expensive than a traditional ETT, the overall cost decreased. Despite these data, CASS is not used frequently. Its use should be encouraged in high-risk patients whose expected duration of mechanical ventilation is longer than 48 hours.

Coated endotracheal tubes

Using an ETT or tracheostomy device coated with a substance that disrupts the formation of bacterial biofilm, thereby decreasing the dislodgement and aspiration of infectious particles, represents an attractive method for decreasing VAP. This method may be particularly attractive because it requires minimal to no intervention once the tube is placed. Preliminary animal data suggest that coated ETTs are effective at blocking biofilm formation and decreasing upper respiratory tract colonization.

Although many substances have been studied as potential coatings for ETTs, only polyurethane and silver were studied in humans. A large, randomized, controlled, multicenter study using silver-coated ETTs was published recently [44••]. About 2000 patients expected to undergo mechanical ventilation for at least 24 hours were randomly allocated to either a standard ETT or a silver-coated tube. Relative RR of 35.9% and absolute RR of 2.7% were demonstrated for VAP with the use of a silver-coated ETT. No differences in patient outcomes including mortality, length of ICU stay, or duration of mechanical ventilation were demonstrated. Even though the absolute RR in this trial was small, silver-coated ETTs should be considered for patients at high risk of developing VAP given the relatively low cost of the intervention and limited potential of causing harm.

Treatment of ventilator-associated tracheobronchitis

Ventilator-associated tracheobronchitis (VAT) is defined as the development of purulent tracheal secretions in the setting of systemic signs of infection without evidence of a new or progressive infiltrate on chest radiograph in a patient intubated for more than 48 hours. No standard diagnostic criteria exist, but most definitions require a positive culture of the tracheal aspirate. The organisms that cause VAT are similar to those that cause VAP, and VAT may represent an intermediary condition between oropharyngeal colonization and VAP. Treatment of VAT represents a potential target to prevent VAP. VAT might be treated with either shorter courses of antibiotics than VAP or inhaled antibiotics in an attempt to decrease overall antimicrobial use [45].

Two randomized trials were published recently analyzing the treatment of VAT. Palmer et al. [38] performed a randomized, double-blind study of aerosolized antimicrobials targeted to Gram stain of the tracheal aspirate versus aerosolized saline placebo in 43 patients, and demonstrated improved CPIS score and progression to VAP in the treatment group with no difference in mortality. However, this study was severely limited by the use of a nonstandard definition of VAT that did not require the absence of VAP, and the majority of patients in both arms of the trial met criteria for VAP at inclusion. Nseir et al. [46] published a randomized, unblinded, multicenter study of no antibiotics versus 8 days of intravenous antibiotic therapy, and demonstrated a statistically significant decrease in the rate of progression to VAP in the group that received antibiotic treatment. The trial was stopped early at a planned 2-year interim analysis because of a statistically significant difference in ICU mortality between the two groups, raising the question of whether early, untreated VAP was present in the nontreatment group.

The diagnosis of VAT is complicated in clinical practice because of difficulties in prospectively classifying an abnormality on chest radiograph as a new or progressive infiltrate versus effusion, atelectasis, or pulmonary edema. The treatment of VAT deserves further study as a potential strategy to decrease VAP.

Tracheostomy timing

The optimal timing of tracheostomy in ICU patients is controversial, with some studies demonstrating benefit with early tracheostomy and others revealing none. A meta-analysis published in 2005 identified only 5 randomized trials encompassing 406 patients, and concluded that early tracheostomy (defined as tracheostomy up to 7 days after ICU admission) led to significant reductions in the durations of mechanical ventilation and ICU stay, but did not affect mortality or incidence of HAP [47]. An unblinded, multicenter, randomized trial of 123 patients was subsequently published and demonstrated no difference in any clinical outcome including mortality, incidence of VAP, or duration of mechanical ventilation [48]. Unfortunately, as the authors pointed out, the trial was significantly underpowered and had low recruitment rates. Recently published retrospective data continue to indicate a possible lower rate of VAP in patients undergoing early tracheostomy [49]. Additional well-designed trials are needed to determine more accurately the relationship between early tracheostomy and VAP before firm recommendations can be made.

Prevention bundles

Bundles of evidence-based directives implemented together decrease rates of VAP [50]. Despite considerable evidence of their effectiveness, studies continue to show that prevention

bundles are underused and knowledge of health care professionals in this area is lacking [51]. Further efforts should be made to expand the role of VAP prevention bundles and health care provider education initiatives.

Conclusions

HAP is a common problem in hospitalized patients, and its development is associated with considerable morbidity, mortality, and increased use of health care resources. Despite more than two decades of intense study, controversies remain in its diagnosis, treatment, and prevention. Evidence-based guidelines are readily available and represent the best available in-depth resource for clinicians managing patients with this devastating illness [1,24–27].

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. American Thoracic Society and 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.
2.• Anand N, Kollef MH: **The alphabet soup of pneumonia: CAP, HAP, HCAP, NHAP, and VAP.** *Semin Respir Crit Care Med* 2009, **30:**3–9.

This article is a current review of the classification of pneumonia, and is part of an entire journal issue devoted to HCAP.

3. Gastmeier P, Sohr D, Geffers C, et al.: **Risk factors for death due to nosocomial infection in intensive care unit patients: findings from the Krankenhaus Infektions Surveillance System.** *Infect Control Hosp Epidemiol* 2007, **28:**466–472.
4.•• Venditti M, Falcone M, Corrao S, et al.: **Outcomes of patients hospitalized with community-acquired, health care-associated, and hospital-acquired pneumonia.** *Ann Intern Med* 2009, **150:**19–26.

These authors compare the epidemiology of HAP, CAP, and HCAP in Italian hospitals.

5. Ramirez P, Ferrer M, Torres A: **Prevention measures for ventilator-associated pneumonia: a new focus on the endotracheal tube.** *Curr Opin Infect Dis* 2007, **20:**190–197.
6. Pneumatikos IA, Dragoumanis CK, Bouros DE: **Ventilator-associated pneumonia or endotracheal tube-associated pneumonia? An approach to the pathogenesis and preventive strategies emphasizing the importance of endotracheal tube.** *Anesthesiology* 2009, **110:**673–680.
7. Stewart PS, Costerton JW: **Antibiotic resistance of bacteria in biofilms.** *Lancet* 2001, **358:**135–138.
8. Safdar N, Dezfulian C, Collard HR, et al.: **Clinical and economic consequences of ventilator-associated pneumonia: a systematic review.** *Crit Care Med* 2005, **33:**2184–2193.
9. Weber DJ, Rutala WA, Sickbert-Bennett EE, et al.: **Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia.** *Infect Control Hosp Epidemiol* 2007, **28:**825–831.
10. Chastre J, Fagon JY: **Ventilator-associated pneumonia.** *Am J Respir Crit Care Med* 2002, **165:**867–903.
11. Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN): **Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the NHSN at CDC, 2006–2007.** Available at http://www.cdc.gov/nhsn/dataStat.html. Accessed June 2009.
12. Walkey AJ, Reardon CC, Sulis CA, et al.: **Epidemiology of ventilator-associated pneumonia in a long-term acute care hospital.** *Infect Control Hosp Epidemiol* 2009, **30:**319–324.
13. Luyt CE, Combes A, Nieszkowska A, et al.: **Viral infections in the ICU.** *Curr Opin Crit Care* 2008, **14:**605–608.
14. Vincent A, La Scola B, Forel JM, et al.: **Clinical significance of a positive serology for mimivirus in patients presenting a suspicion of ventilator-associated pneumonia.** *Crit Care Med* 2009, **37:**111–118.
15. Delisle MS, Williamson DR, Perreault MM, et al.: **The clinical significance of Candida colonization of respiratory tract secretions in critically ill patients.** *J Crit Care* 2008, **23:**11–17.
16. Roux D, Gaudry S, Dreyfuss D, et al.: **Candida albicans impairs macrophage function and facilitates Pseudomonas aeruginosa pneumonia in rat.** *Crit Care Med* 2009, **37:**1062–1067.
17. Nseir S, Jozefowicz E, Cavestri B, et al.: **Impact of antifungal treatment on Candida-Pseudomonas interaction: a preliminary retrospective case-control study.** *Intensive Care Med* 2007, **33:**137–142.
18. Morris AC, Kefala K, Simpson AJ, et al.: **Evaluation of diagnostic methodology on the reported incidence of ventilator-associated pneumonia.** *Thorax* 2009, **64:**516–522.
19. 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:**2706–2713.
20.• Rosbolt MB, Sterling ES, Fahy BG: **The utility of the clinical pulmonary infection score.** *J Intensive Care Med* 2009, **24:**26–34.

This article provides an excellent evaluation of the CPIS with a discussion of the controversies in its use.

21.• Rea-Neto A, Youssef NC, Tuche F, et al.: **Diagnosis of ventilator-associated pneumonia: a systematic review of the literature.** *Crit Care* 2008, **12:**R56.

These authors concisely review the considerable amount of literature pertaining to VAP diagnosis.

22. Christ-Crain M, Stolz D, Bingisser R, et al.: **Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial.** *Am J Respir Crit Care Med* 2006, **174:**84–93.
23. Nachtigall I, Tamarkin A, Tafelski S, et al.: **Impact of adherence to standard operating procedures for pneumonia on outcome of intensive care unit patients.** *Crit Care Med* 2009, **37:**159–166.
24. Torres A, Ewig S, Lode H, et al.: **Defining, treating and preventing hospital acquired pneumonia: European perspective.** *Intensive Care Med* 2009, **35:**9–29.
25. Song JH; Asian Hospital Acquired Pneumonia Working Group: **Treatment recommendations of hospital-acquired pneumonia in Asian countries: first consensus report by the Asian HAP Working Group.** *Am J Infect Control* 2008, **36(4 Suppl):**S83–S92.
26. Masterton RG, Galloway 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:**5–34.

27. Muscedere J, Dodek P, Keenan S, et al.: **Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment.** *J Crit Care* 2008, **23:**138–147.
28. Beardsley JR, Williamson JC, Johnson JW, et al.: **Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia.** *Chest* 2006, **130:**787–793.
29. Kollef KE, Schramm GE, Wills AR, et al.: **Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant gram-negative bacteria.** *Chest* 2008, **134:**281–287.
30. Dennesen PJ, van der Ven AJ, Kessels AG, et al.: **Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia.** *Am J Respir Crit Care Med* 2001, **163:**1371–1375.
31. 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:**2588–2598.
32. Micek ST, Ward S, Fraser VJ, et al.: **A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia.** *Chest* 2004, **125:**1791–1799.
33. Nseir S, Deplanque X, Di Pompeo C, et al.: **Risk factors for relapse of ventilator-associated pneumonia related to nonfermenting Gram negative bacilli: a case-control study.** *J Infect* 2008, **56:**319–325.
34.• Joffe AR, Muscedere J, Marshall JC, et al.: **The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study.** *J Crit Care* 2008, **23:**82–90.
These authors confirm the safety of the strategy of de-escalating antibiotic therapy for VAP.
35. Roberts JA, Lipman J, Blot S, et al.: **Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients?** *Curr Opin Crit Care* 2008, **14:**390–396.
36. 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.
37. Michalopoulos A, Fotakis D, Virtzili S, et al.: **Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study.** *Respir Med* 2008, **102:**407–412.
38. Palmer LB, Smaldone GC, Chen JJ, et al.: **Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit.** *Crit Care Med* 2008, **36:**2008–2013.
39.• Muscedere J, Dodek P, Keenan S, et al.: **Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention.** *J Crit Care* 2008, **23:**126–137.
This article is a concise, current review of VAP prevention with evidence-based recommendations.
40. 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–S40.
41.•• de Smet AM, Kluytmans JA, Cooper BS, et al.: **Decontamination of the digestive tract and oropharynx in ICU patients.** *N Engl J Med* 2009, **360:**20–31.
This article reports a large, multicenter, randomized trial evaluating SDD. Limited benefit was demonstrated with addition of parenteral antibiotics to a regimen of oral decontamintion.
42. Dezfulian C, Shojania K, Collard HR, et al.: **Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis.** *Am J Med* 2005, **118:**11–18.
43.•• Bouza E, Perez MJ, Munoz P, et al.: **Continuous aspiration of subglottic secretions in the prevention of ventilator-associated pneumonia in the postoperative period of major heart surgery.** *Chest* 2008, **134:**938–946.
This article reports a large trial confirming the safety and efficacy of CASS for the prevention of VAP.
44.•• Kollef MH, Afessa B, Anzueto A, et al.: **Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial.** *JAMA* 2008, **300:**805–813.
This article reports the largest trial yet published evaluating antimicrobial-coated ETTs for the prevention of VAP.
45. Craven DE, Chroneou A, Zias N, et al.: **Ventilator-associated tracheobronchitis: the impact of targeted antibiotic therapy on patient outcomes.** *Chest* 2009, **135:**521–528.
46. Nseir S, Favory R, Jozefowicz E, et al.: **Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study.** *Crit Care* 2008, **12:**R62.
47. Griffiths J, Barber VS, Morgan L, et al.: **Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation.** *BMJ* 2005, **330:**1243.
48. Blot F, Similowski T, Trouillet JL, et al.: **Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients.** *Intensive Care Med* 2008, **34:**1779–1787.
49. Nseir S, Di Pompeo C, Jozefowicz E, et al.: **Relationship between tracheotomy and ventilator-associated pneumonia: a case control study.** *Eur Respir J* 2007, **30:**314–320.
50. Wip C, Napolitano L: **Bundles to prevent ventilator-associated pneumonia: how valuable are they?** *Curr Opin Infect Dis* 2009, **22:**159–166.
51. Krein SL, Kowalski CP, Damschroder L, et al.: **Preventing ventilator-associated pneumonia in the United States: a multicenter mixed-methods study.** *Infect Control Hosp Epidemiol* 2008, **29:**933–940.