Hospital-acquired pneumonia (HAP) is usually caused by bacterial, viral, or fungal pathogens that occur ≥48 h after hospital admission. Overall, more than 80% of HAP episodes are related to invasive airway management (in patients with endotracheal intubation or tracheostomy) with mechanical ventilation, which is known as ventilator-associated pneumonia (VAP). VAP is defined as pneumonia developing more than 48 h after intubation and mechanical ventilation. Healthcare-associated pneumonia (HCAP) is part of the continuum of pneumonia, which includes patients who were hospitalized in an acute-care hospital for ≥2 days within 90 days of the infection; resided in a long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic. Although this document focuses more on HAP and VAP, many of the principles are also relevant to the management of HCAP. HAP, VAP, and HCAP are the second most common nosocomial infections after urinary tract infection, but are the leading causes of mortality due to hospital-acquired infections.

This chapter highlights the changing epidemiology, pathogenesis, and treatment of HAP, VAP, and, to a lesser extent, HCAP. Our primary focus is on bacterial pathogens causing HAP in immunocompetent adults. Readers are referred to other chapters for specific information on pulmonary infections related to immunodeficiency, mycobacteria, viruses, or fungal pathogens. Our major emphasis is on evidence-based patient management (diagnosis and treatment) and prevention strategies to improve patient outcomes.

### Epidemiology

Each year there are 5–10 episodes of HAP per 1,000 hospital admissions. HAP accounts for 15% of all healthcare-associated infections and approximately 25% of all intensive care unit (ICU) infections. Rates of HAP tend to be higher in university versus non-teaching hospitals. VAP rates in the Centers for Disease Control and Prevention’s (CDC) National Nosocomial Infections Surveillance (NNIS) system varied by the type of ICU with a pooled mean of 7.3/1,000 ventilator days for medicine versus 13.2 for surgical ICUs. The 50th percentile (median) was 6.0 ventilator days for medicine and 11.6/1,000 ventilator days for surgical ICUs.

Crude mortality rates range between 20 and 50% for VAP and vary by patient population and method of diagnosis. The mortality attributable to the pneumonia also varies between 10 and 30%, depending on the methodology used. Several studies have demonstrated that rates of VAP increase...
with the duration of mechanical ventilation and attack rates have been estimated to be approximately 3% per day during the first 5 days and 2% per day thereafter.8

We are entering an era with greater pressure for public reporting of healthcare-associated infections, but rates may depend on the definitions and denominators used. Eggimann et al. examined several ways to report healthcare-associated infection rates and suggested some caveats for benchmarking rates of VAP. In a prospective cohort of 1,068 medical ICU patients, 127 episodes of VAP developed in 106 (23.5%) of 451 mechanically ventilated patients.10 The incidence of first episode of VAP was 22.8/1,000 patient-days; 29.6/1,000 patient days at risk, 35.7/1,000 ventilator days, and 44.0/1,000 ventilator days at risk. When considering all 127 episodes of VAP, infection rates increased from 22.8 to 27.3 episodes/1,000 ICU days and from 35.7 to 42.8 episodes/1,000 ventilator days at risk. These data demonstrate the importance of the denominator chosen and may differ by as much as 40–60%. These rates have decreased in the past 3 years due to better prevention measures.

Crude mortality rates for VAP pneumonia range from 20 to 60%, reflecting, in large part, the severity of underlying disease, organ failure, and specific pathogen(s) and study populations.1,2,6,11,12 In two major studies of VAP, the mortality rate varied between 4% in patients without prior antibiotic exposure to 73% in those with VAP due to MDR pathogens (e.g., P. aeruginosa or A. baumannii), and attributable mortality ranged from 6 to 14%.13

Prevention programs for VAP are critically important for patient safety. Preventing VAP not only improves clinical outcomes, but also significantly reduces healthcare costs and liability. Rello et al. demonstrated that an average episode of VAP increased hospitalization by 12 days, mechanical ventilation by 10 days, ventilator days by 6 days, and ICU stay by 6 days at a hospital cost of $40,000; similar results have been reported from a suburban hospital by Warren et al.12,14

**Pathogenesis**

Pathogenesis of HAP involves the direct interaction between the pathogen(s) with the host and epidemiologic variables that facilitate this dynamic. There are several mechanisms that contribute to the pathogenesis of HAP, and the relative contribution of each pathway remains controversial and varies by population at risk and the infecting pathogen(s) (Fig. 29.1).1,2 Microaspiration in nonventilated patients is the primary route of bacterial entry into the lower respiratory tract.1,2 In addition, patients who are sedated, postoperative, or have abnormal swallowing are at higher risk for aspiration.1,2 Direct inoculation, bacteremic spread, or translocation of bacteria from the gastrointestinal tract are less common modes of acquisition.
High concentrations of bacteria refluxed from the gastric reservoir or infected sinuses may be aspirated and increase levels of bacteria colonizing the oropharynx, but the relative contribution of these sites remains controversial. The current practice of maintaining patients in the semi-upright position, especially while providing enteral feeding, probably reduces the contribution of gastric colonization to VAP. Bacterial adherence and colonization of the oropharynx clearly are important for bacterial entry into the lower respiratory tract.

Colonization with gram-negative bacilli was present in 16% of moderately ill patients versus 57% of critically ill patients, and rates of pneumonia increased sixfold in ICU patients with bacterial colonization. Host factors, types of bacteria colonizing the pharynx, and the use of antibiotics may alter colonization and adherence of gram-negative bacilli. Oral epithelial cells rich in fibronectin bind gram-positive organisms, such as streptococci and S. aureus; conversely, those poor in fibronectin preferentially bind gram-negative bacilli such as P. aeruginosa.

In the mechanically ventilated patient, inhalation of aerosols, contaminated tubing condensate, leakage of bacteria, and oral secretions around the endotracheal cuff are routes of bacterial entry into the lower respiratory tract (Fig. 29.2). In addition, local trauma and inflammation from the endotracheal tube increase tracheal colonization and reduce clearance of organisms and secretions from the lower respiratory tract. The development of biofilm-encased bacteria over time on the endotracheal tube lumen may increase the risk of bacterial embolization into the alveoli following suctioning or bronchoscopy (Fig. 29.3).

In mechanically ventilated patients, the stomach and gastrointestinal tract may contribute to oropharyngeal and tracheal colonization with gram-negative bacilli, although some investigators question their importance. The stomach often is sterile when the pH is <2 because of the potent bactericidal activity of hydrochloric acid. An increase in gastric colonization occurs with achlorhydria, and various gastrointestinal diseases, malnutrition, or use of antacids or histamine-2 (H2) blockers. In mechanically ventilated patients, colonization may reach 1–100 million gram-negative bacilli/ml of gastric juice when the pH is >4.
The pathogenesis of lower respiratory tract infections often begins with tracheal colonization, which may progress to ventilator-associated tracheobronchitis (VAT), and, in selected patients, to VAP. In addition, discrimination between VAT and VAP may be difficult due to poor and overlapping definitions. VAT is defined as the presence of clinical signs of lower respiratory tract infection (fever, leukocytosis, and purulent sputum) with a quantitative endotracheal sputum sample with more than 106 organisms/ml of a respiratory pathogen, in the absence of a new or progressive infiltrate on chest X-ray (Fig. 29.2). Monitoring endotracheal aspirates used to identify pathogens colonizing the lower airway is needed to diagnose and initiate early, appropriate antibiotic therapy. Recent data suggest that VAT appears to be an important risk factor for VAP and that targeted antibiotic therapy for VAT may be a new paradigm for VAP prevention and better patient outcomes.

Immune Defenses in the Lung

The response of pulmonary host defenses to invading microorganisms plays an integral part in the pathogenesis and outcome of infection (Fig. 29.1). Mucociliary and mechanical clearances in the upper airway are important factors in the defense against infection. Bacterial antigens and cytokines that alter the activity and efficacy of ciliary cells in clearing bacteria from the lower airway need further study. The ability of macrophages and polymorphonuclear leukocytes to eliminate bacterial pathogens, and the interaction of these cells with inflammatory cytokines, probably play important roles in the pathogenesis of pneumonia. Cell-mediated immune response is controlled by a complex array of lipids, peptides, and cytokines, including interleukin-1 and -2 interferons, growth factors, and chemotactic factors. Leukotrienes complement components, and platelet-activating factor also assist in the inflammatory response and contribute to the pathogenesis of pneumonia.

Etiologic Agents

The wide spectrum of etiologic agents causing HAP/VAP varies by hospital, type of ICU, and patient population studied, emphasizing the importance of current local surveillance data. Bacteria causing HAP/VAP may originate from various sources, including the patient’s endogenous flora, other patients, staff, contaminated devices, or the environment. Prior hospitalization, exposure to chronic care facilities, and antibiotic therapy also are important predisposing factors for MDR pathogens. In the absence of these factors, early onset HAP, occurring during the first 5 days of the hospital stay, is usually caused by *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, or anaerobic bacteria (Table 29.1). In comparison, late-onset HAP is more commonly caused by MDR gram-negative bacilli (Klebsiella pneumoniae with extended-spectrum beta-lactamases (ESBL+) and MRSA or VISA). In children

| Table 29.1. Non-multidrug-resistant and multidrug-resistant (MDR) pathogens causing HAP. |
|-----------------------------------------------|-----------------------------------------------|
| **Non-MDR pathogens**                       | **MDR pathogens**                             | **Comments**                                   |
| **Gram-positive Cocci**                     |                                               |                                               |
| *Staphylococcus aureus*                     | Methicillin-resistant *S. aureus* (MRSA)      | MRSA is increasing in hospitals; community-acquired MRSA (CA-MRSA) isolates are rapidly emerging; less resistant; inducible resistance to clindamycin has been reported |
|                                               | Vancomycin or glycopeptide-intermediate *S. aureus* (VISA,GISA) | New definitions of vancomycin sensitivity (MICs) may increase prevalence of GISA, VISA isolates, currently rare. |
|                                               | Vancomycin-resistant *S. aureus* (VRSA)        | VRSA currently rare                             |
|                                               | Linezolid-resistant *S. aureus* (LRSA)         | LRSA strains are rare, but may increase with greater prescribing. Usually early onset HAP; PRSP strains increasing; resistant serotypes changing with use of protein–polysaccharide vaccine in children |
| **Streptococcus pneumoniae** (pneumococcus) | Penicillin-resistant *S. pneumoniae* (PRSP) and multidrug-resistant (MDR)*S. pneumoniae* |                                               |
| **Gram-negative Bacilli**                    |                                               |                                               |
| *Escherichia coli*                           | Extended-spectrum beta-lactamase (ESBL)+ *E. coli* | Not a common HAP pathogen                       |
| *Klebsiella pneumoniae*                     | ESBL+ *K. pneumoniae*                         | ESBL+ strains are increasing in the United States |
| *Enterobacter species*                      | Pseudomonas aeruginosa                        | Resistance to cephalosporins may develop on therapy |
| *Serratia marcescens*                       | Acinetobacter species                         | Some resistant isolates reported               |
|                                               | Burkholderia cepacia                          | Common MDR pathogen; resistant spectrum common |
|                                               | Stenotrophomonas maltophilia                  | Variable; may cause outbreaks of VAP           |
| **Gram-negative Cocacobacilli**             |                                               | Uncommon                                       |
| *Hemophilus influenzae*                     |                                               | Uncommon                                       |
| **Moraxella catarrhalis**                   |                                               |                                               |
| **Special pathogens**                       |                                               |                                               |
| *Legionella pneumophila*                    |                                               | Early onset HAP; more common chronic lung disease patients; resistant strains usually b-lactamase+ |

Check hospital water supply; cooling towers (airborne)
Gram-negative bacilli have been implicated in more than 60% of reported episodes of HAP, and *S. aureus* (often MRSA) accounts for 20–40% of episodes but is increasing rapidly in the United States.\(^1,^5,^9\) Isolation rates of these bacteria vary considerably depending on the population at risk, location, hospital size, ICU type, and method of diagnosis. However, overall rates of MDR pathogen infections are increasing rapidly in the United States and many other countries.\(^5,^37,^38\) Most episodes of bacterial nosocomial pneumonia are caused by more than one species of bacteria because of aspiration or leakage of mixed bacterial flora from the oropharynx.\(^1,^2,^6,^12\)

More recently, pneumonia due to community-acquired MRSA (CA-MRSA) has emerged in children and adults.\(^39–42\) In contrast to healthcare-associated (HA)-MRSA, CA-MRSA isolates are genetically distinct and almost uniformly carry the Panton–Valentine leukocidin (PVL), which may be associated with greater virulence. These strains also have been identified as an emerging source of infection spreading within hospitals. There is also concern over the evolution of vancomycin or glycopeptide-intermediate *S. aureus* (VISA/GISA) isolates of *S. aureus* that have been increasing.\(^39,^43\)

### Diagnosis

Accurate data regarding etiologic agents, epidemiology, and treatment of HAP/VAP are limited by the lack of a diagnostic gold standard. Although clinical criteria and semiquantitative sputum culture criteria for the diagnosis of VAP are the current standard for diagnosis in most hospitals, there are concerns about lack of diagnostic specificity.\(^2,^6,^44\) Atelectasis, pulmonary edema, pulmonary emboli, neoplastic processes, and some autoimmune diseases can mimic HAP and VAP and, therefore, microbiologic diagnosis is critical. In addition, chest radiographic changes may be difficult to evaluate due to adult respiratory distress syndrome (ARDS) or congestive heart failure, making the clinical diagnosis of pneumonia more difficult (Fig. 29.4a, b). The use of a computerized tomographic (CT) scan improves imaging but quality sputum samples for Gram stain and culture are also of paramount importance for providing clues to possible pathogens. Sputum may be produced spontaneously, induced by nebulized saline, or obtained by bronchoscopy in the non-intubated patient. For patients in mechanically ventilated ICUs, there has been considerable controversy regarding the benefits and risks of clinical diagnosis using semiquantitative evaluation of endotracheal aspirates versus quantitative cultures obtained from either bronchoscopic bronchoalveolar lavage (B-BAL) or protective specimen brush (B-PSB) or non-bronchoscopic BAL/PSB (NB-BAL or NB-PSB).\(^2\) These diagnostic approaches are discussed below.

### Clinical Diagnosis

The clinical diagnosis of pneumonia is defined as the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever >38°C, leukocytosis or leukopenia, and purulent secretions). While sensitivity for the presence of pneumonia is increased if only one criterion is used, specificity is reduced, leading to significantly increased use of antibiotics. Requiring all three clinical criteria is too insensitive, resulting in under-prescribing for patients with HAP.

The clinical pulmonary infection score (CPIS), used in some ICUs, gives points for clinical, radiographic, physiologic (\(\text{PaO}_2/\text{FiO}_2\)), and microbiologic data for a single numerical result.\(^46\) When the CPIS score was greater than 6, good correlation was found with the presence of pneumonia.\(^55\) Singh et al. used a modified CPIS score that did not rely on culture data to guide clinical management.\(^46\) Patients with a low clinical suspicion of VAP (CPIS ≤ 6) were randomized to therapy with ciprofloxacin compared to conventional therapy. The
ciprofloxacin group had antibiotics discontinued after 3 days if there was no deterioration in their clinical status or CPIS score. The modified CPIS score appears to be an objective measure to define patients who can receive shorter courses of therapy (3 days), achieving better overall outcomes.

**Microbiologic Diagnosis**

Most microbiology laboratories report sputum culture results in a semiquantitative fashion, describing growth as light, moderate, or heavy. Moderate to heavy growth is most consistent with a diagnosis of VAT or VAP, especially if the Gram stain has many polymorphonuclear leukocytes and bacteria. The presence of bacteria on Gram stain (smear) correlates with $10^5$ bacteria/ml by bronchoscopic alveolar lavage (BAL). Also, the morphology of the bacteria is a clue to the offending bacteria (i.e., gram-positive cocci in clusters suggest *S. aureus* and gram-negative bacilli may suggest *Klebsiella* spp., *E. coli*, or *P. aeruginosa*). It is also important to correlate these findings with aerobic culture results, because anaerobic cultures are not routinely performed. A Gram stain of sputum or tracheal aspirate without bacteria or inflammatory cells has a strong negative predictive value for VAP and may suggest another cause for the patient’s fever, leukocytosis, and infiltrate on chest X-ray.

Use of the endotracheal aspirates for the diagnosis of VAP allows prompt, empiric therapy, and may reduce mortality. However, it may not effectively separate lower airway colonization (purulent tracheobronchitis) from VAP (Table 29.2). Semiquantitative criteria suggesting VAP are moderate to heavy growth.

By comparison, quantitative endotracheal aspirates, or cultures of lower respiratory secretions using bronchoscopic or non-bronchoscopic BAL or PSB to define VAP, are more specific than semiquantitative endotracheal aspirates. VAP is defined as growth of $>10^5$ to $10^6$ CFU/ml for endotracheal aspirates, $>10^6$ CFU/ml for PSB, and $>10^5$ CFU/ml for BAL. Growth below the threshold suggests colonization or contamination with some exceptions. For example, patients who have had a recent change in antibiotics may have a false-negative BAL/PSB, perhaps early VAP, inadequate BAL technique, or other causes, such as *Legionella pneumophila*, viruses, or anaerobic bacteria. However, the quantitative approach may improve de-escalation of antibiotics by targeting the specific pathogens that are causing VAP. In one large, prospective, randomized trial of 413 patients with suspected VAP, patients receiving invasive management compared to those managed clinically had a lower mortality rate at day 14 (16 and 25%; $p=0.02$, but not at day 28), lower mean sepsis-related organ failure assessment scores ($p=0.04$), and significantly more antibiotic-free days (11 ± 9 vs. 7 ± 7; $p<0.001$). Multivariate analysis demonstrated significantly reduced mortality (hazard ratio, 1.54 [CI, 1.10–2.16]; $p=0.01$). Although a high percentage of patients in both arms received adequate initial antibiotics, more patients in the invasive group received adequate therapy than in the clinical group, and the impact of this difference on the observed mortality is of concern. This study suggests that the quantitative approach is safe, leads to less antibiotic use, and may potentially reduce mortality.

On the contrary, a recent randomized study by a Canadian Critical Care Trials group compared quantitative and semiquantitative techniques for diagnosing VAP in 740 patients who were randomized to specifically target antibiotic therapy. Although there were many patients excluded from the study, including those with MRSA and *P. aeruginosa* colonization, the clinical outcomes in terms of length of stay in the hospital/ICU and the 28-day mortality were similar between the two groups.

**Antimicrobial Management**

Current management principles for HAP and VAP summarized in the 2005 American Thoracic Society & Infectious Diseases Society (ATS/IDSA) Guidelines include early, appropriated, initial antibiotic therapy, followed by de-escalating antibiotics based on clinical response and microbiologic data and reducing duration of therapy to 7–8 days in responders. An alternative management strategy has been suggested that focuses on treating VAT before the development of VAP using targeted antibiotic therapy when a quantitative endotracheal aspirate has a pathogen(s) $\geq 10^6$ organisms/ml, but such a strategy needs further investigation.

**Early, Appropriate, and Adequate Initial Empiric Antibiotic Therapy**

As soon as HAP/VAP is suspected, the collection of respiratory samples and the prompt initiation of appropriate antibiotics, in adequate doses, are suggested (Fig. 29.5 and Table 29.2). It has been shown that the shorter the time between diagnosis and initiation of treatment the better the impact on prognosis, length of hospital stay, and cost. Appropriately therapy means that the pathogen is susceptible to the chosen regimen, whereas adequate therapy means that appropriate drugs, with good lung penetration, are given in optimal doses via the correct route. Choosing an initial, appropriate intravenous antibiotic regimen depends on the likelihood of infection with MDR pathogens, such as *P. aeruginosa*, *A. baumannii*, ESBL+ *K. pneumonia*, or MRSA.

Risk factors for MDR pathogens include prior hospitalization, late-onset infection, prior antibiotic therapy, and chronic dialysis, and are more for residents of chronic care facilities and for immunocompromised patients. Patients without MDR risk factors and early onset HAP or VAP usually can be treated with a more limited spectrum of antibiotics, such as ceftriaxone plus azithromycin, a third- or fourth-generation quinolone (i.e., levofloxacin), or ampicillin–sulbactam (Table 29.2). By comparison, broader initial antibiotic therapy is suggested if patients are at risk for MDR pathogens (Table 29.3). Finally, it is important to use doses of antibiotics that will achieve adequate concentrations in the lung parenchyma, which are outlined in the ATS/IDSA Guideline.
Assessing Clinical Response, Cultures, and Antibiotic De-escalation

While initial antibiotic coverage should be liberal and broad enough to cover all suspected pathogens, de-escalation or streamlining antibiotic therapy, based on the patient’s clinical response and microbiologic data, is of critical importance to improve patient outcomes and minimize antibiotic use. Patients without evidence of HAP or VAP should have their antibiotics stopped. If necessary, further work-up and treatment for other sources of fever should be initiated.

Limiting Duration of Therapy

In a recent randomized trial of patients with VAP, patients randomized to 8 days of antibiotic therapy had fewer recurrences and less resistance overall than those randomized to 15 days of therapy. No significant differences were noted in mortality or clinical response parameters, but rates of recurrence for those patients with VAP due to *P. aeruginosa* infection were higher in the group treated for 8 rather than 15 days. The ATS/IDSA guideline recommends 7–8 days of therapy for uncomplicated HAP or VAP with close follow-up for any signs of relapse, especially for patients with HAP or VAP due to *P. aeruginosa* (Fig. 29.5).

Management of Selected MDR Pathogens

**Pseudomonas Aeruginosa**

This pathogen is distinguished by its capacity to develop resistance to all known classes of antibiotics even while the patient is still on therapy. It is unclear if this problem could be avoided with the use of combination therapy. The only supporting data comes from a study of *P. aeruginosa* bacteremia (few cases...
of which were due to pneumonia), which showed that patients receiving combination therapy were less likely to die.66

Cometta et al.,65 in a prospective study, compared combination therapy of an aminoglycoside and a carbapenem versus monotherapy with carbapenem, which did not show improved outcomes, or a difference in the rate of developing resistance. Of note is that no study has used single daily dosing of the aminoglycoside, or the maximal effective dose recommended by ATS/IDSA. Also, no data are available comparing a fluoroquinolone-based combination therapy, with b-lactam monotherapy. However, if P. aeruginosa is isolated, combination therapy should be used until antibiotic sensitivity is available.

**Acinetobacter Species**

The choices of treatment of Acinetobacter species pneumonia are limited because of its native resistance to many classes of antibiotics. Carbapenems, polymyxins, and the sulfactam component of ampicillin–sulfactam are considered the most effective antibiotic classes. Wood and coworkers demonstrated equivalent rates of clinical cure in a population with trauma surgery with ampicillin–sulfactam, compared with imipenem, including patients with imipenem-resistant isolates.37 The emergence of carbapenem-resistant clones suggests the need for use of optimal doses of carbapenem. Polymyxins are significantly nephrotoxic, limiting their widespread intravenous use; there may be some benefit from aerosolized polymyxin.58,59

**Extended-Spectrum β-Lactamase Producers**

The hallmark of ESBL-producing enterobacteriaceae, such as Klebsiella pneumoniae, Escherichia coli, and Enterobacter species, is a variable response to cephalosporins, and therefore third- and fourth-generation agents should be avoided as monotherapy when these pathogens are suspected or isolated.60 Third-generation cephalosporins (e.g., cefotaxime) should not be used for treatment of Enterobacter spp. because of the high frequency of resistance of this pathogen to this therapy.61 The use of the fourth-generation cephalosporin (e.g., cefepime) is also not recommended.60,62 A most reliable empiric choice is a carbapenem, such as imipenem, meropenem, or etrapenem.63

**MRSA**

Although vancomycin is considered the standard therapy for MRSA pneumonia, clinical trials and studies from different centers have reported clinical failure rates of greater than 40% with a standard dose of 1 g every 12 h.64–66 This treatment failure may be related to inadequate dosing.64 Many physicians have therefore tried to achieve a trough concentration of 15 mg/l or more, but without prospective clinical data supporting this practice. Combination therapy with rifampin, aminoglycosides, and other agents has been tried, but without well-documented value.67 The use of continuous vancomycin infusions has not been proved to be advantageous compared with twice-daily dosing in severe MRSA infections.68

Linezolid is another agent that has been used in the treatment of patients with MRSA VAP. Two large multicenter trials demonstrated equivalence to vancomycin in the treatment of these patients.69,70 When these studies were combined and analyzed by multivariate techniques, linezolid was associated with a better clinical cure and lower mortality. Although the superiority of linezolid over vancomycin needs further validation in randomized trials, it has higher lung penetration, as measured by epithelial lining fluid analysis when compared with vancomycin.58,71 Linezolid should be considered in patients with renal failure or a documented lack of response to vancomycin. Dosing vancomycin in patients with fluctuating renal function is difficult, and requires frequent monitoring of drug levels. Notably, the presence of renal insufficiency was a significant predictor of vancomycin failure in a multivariate analysis of patients with VAP,69 and there is also concern about increased nephrotoxicity in patients receiving vancomycin and other nephrotoxic medications, such as aminoglycosides.58,72,73

Other approved new agents for nosocomial MRSA infections are quinupristin/dalfopristin. Daptomycin should not be used in the treatment of MRSA pneumonia, as it was found inferior in clinical trials. Tigecycline has excellent activity against MRSA in vitro, and clinical studies of VAP are in progress. Ceftobiprole and dalbavancin also have in vitro activity against MRSA, but are not currently approved for use in the United States.74–76

There are also new concerns over the emergence and rapid spread of a new strain of community-acquired MRSA that can cause serious pneumonia in healthy children and adults, and superinfection in individuals with influenza A virus infection.77–79 Community-acquired MRSA has caused outbreaks in nursing homes, hospitals, schools, prisons, athletic teams, and the military. This strain may continue to spread in the community and is likely to become a major healthcare-associated pathogen.39,79,80 Community-acquired MRSA isolates have increased virulence that may be related, in part, to the presence of the Panton–Valentine leukocidin. Furthermore, the combination of increasing hospital-acquired MRSA in healthcare settings and the rapid spread of community-acquired MRSA in selected high-risk populations and in acute and chronic healthcare settings requires close attention. Finally, the encapsulated pathogens S. pneumoniae and S. aureus, which may cause HAP, are common causes of bacterial superinfection following the yearly influenza outbreaks, and there is even greater concern over both hospital-acquired and community-acquired MRSA in the setting of a future bird flu pandemic.81

**Lack of Response to Initial Therapy**

In most patients, clinical improvement takes 24–48 h. Therefore, the selected antimicrobial regimen should not be changed during this time unless there is evidence of progressive deterioration.
Possible causes of rapid deterioration or failure to improve include three possibilities:

1. **Wrong diagnosis** – pulmonary embolism with infarction, atelectasis, pulmonary hemorrhage, neoplastic or connective tissue disease, chemical pneumonitis from aspiration, acute respiratory distress syndrome (ARDS) with diffuse alveolar damage, other source of infection.

2. **Wrong antimicrobial therapy** – drug-resistant pathogen, inadequate dosing, wrong antimicrobial agent.

3. **Wrong pathogen** – tuberculosis, fungal or viral infection, opportunistic infection, Legionella infection – or complication of pneumonia (empyema or lung abscess, *Clostridium difficile* colitis, bacterial or *Candida albicans* superinfection, drug fever).\(^2\)

### Prevention

Detailed, evidence-based prevention measures are well summarized in the 2004 CDC Healthcare Infection Control Prevention Advisory Committee (HICPAC) and ATS/IDSA Guidelines, as well as several review articles and in Table 29.4.\(^{1,2,82,83}\)

| Intervention/strategy | Support/evidence | Comments |
|-----------------------|------------------|----------|
| **Infrastructure**    |                  |          |
| Multidisciplinary team | Programs developed by team consensus more effective | Input by critical care staff and respiratory therapists crucial |
| “Champion” of the cause | Recognized leader/expert increases “buy-in” by staff and hospital administration | Leadership needed to set benchmarks, maintain efforts and secure resources |
| Targeted staff education | Staff education-awareness programs shown to reduce VAP | Such programs are adaptable to local needs and are cost-effective |
| Infection control      | Data supports importance in reducing spread of multidrug-resistant (MDR) organisms and associated costs | Coordinate with quality improvement efforts; feedback data to staff |
| Antibiotic control     | Reduces inappropriate antibiotic use | Designated pharmacist optimal; computer programs good alternative |
| Adequate staffing       | Critical for maintaining patient safety and adherence to protocols | Particularly important in critical care units; current nursing shortages exist |
| Benchmarking/quality    | Current recommendations from ICHI and local multidisciplinary teams | Benchmarks should be evaluated routinely and data communicated |

| **Patient care** |                  |          |
| Sedation vacation    | Supported by clinical data; accessible and feasible; part of VAP bundle | Implement standard protocols |
| Semi-upright position | Supported by early data; recent data suggest lower elevation target indicated | Few outcome data; poor compliance with strategy. Further studies needed |
| Noninvasive positive pressure ventilation | Supported by several clinical trials in recent review by Cochrane | Experience with technique is suggested for patients with COPD and CHF |
| Oral care            | Evidence is limited, but risk and cost are low | Further studies are needed |
| Stress bleeding prophylaxis | Data support use of proton pump inhibitors (PPIs) and histamine type 2 (H2) blockers; limit to high-risk patients | PPIs and H2 are more effective than sucralfate in preventing bleeding; *C. difficile* may be increases with PPIs |
| Deep vein thrombosis prophylaxis | Evidence supportive, part of VAP bundle | Recommended in the VAP 100.000 Lives Campaign VAP “bundle” |
| Standardized protocols for weaning and enteral feedings | Rates of VAP lowered by reduced duration of intubation and enteral feeding | Protocols help standardize implementation and provide standards for monitoring |
| Chlorhexidine with or without colistin | Randomized controlled trials (RCTs) demonstrate efficacy | More data needed |
| Selective decontamination of the digestive tract | VAP and mortality decreased with intravenous and topical antibiotics | Concerns about antibiotic resistance limit “routine” use |
| Targeting ventilator-associated tracheobronchitis (VAT) to prevent VAP | One randomized trial | Further studies are needed on VAT |
| Orotracheal intubation and use of orogastric tubes | Several small clinical trials report decreased sinusitis | Recommended, but limited impact on VAP |
| Continuous aspiration of subglottic secretions or | Decreased VAP shown in at least four RCTs | Optional; cost and impact on staffing are of concern |
| Silver-coated endotracheal tube (ETT) | One randomized trial demonstrated reduced VAP | Cost and identifying high-risk patients are needed |

(continued)
General Prevention Strategies

Most hospitals are using the Institute for Healthcare Improvement (IHI) bundles to reduce VAP (Table 29.4). This quality improvement effort, coupled with other measures regarding reduced reimbursement for healthcare-associated infections, has decreased rates of reported VAP in the United States and Europe.

Staff education is needed for all clinicians and staff who manage HAP and VAP. Zack et al.96 used successfully a self-study module, in-service teaching programs that were coordinated with ICU staff meetings, along with fact sheets and posters, which were placed in the ICU and respiratory care departments. Rates of VAP dropped nearly 58%, and the cost savings were estimated to be between $425,606 and >$4,000,000. Babcock et al., using an extension of this program in an Integrated Health Care System, reported a 46% reduction in VAP over an 18-month period.97 Staffing in the ICU is important, which is under-appreciated,1,4, and must be sufficient for patient care and compliance with infection control practices.85-87

Use of proper isolation techniques and effective infection control practices are cornerstones for prevention of HAP.1,7,96 Infection control programs have repeatedly demonstrated efficacy in reducing infection and colonization due to MDR organisms.1,4,30,88-90 Unfortunately, staff compliance with proven infection control measures, such as hand hygiene, remains inconsistent in many hospitals. Also, surveillance of ICU infections to identify and quantify endemic and new MDR organisms with timely feedback of data is critical.10,88,91-93 Timely communication of current data among clinical, laboratory, pharmacy, and infection control staff is essential. Organism-specific strategies may need to be complemented by more aggressive eradication methods.43,93,94

Studies are beginning to implicate the inanimate environment as an indirect contributor to pathogen acquisition.98 Special interventions, including targeted environmental sampling and more aggressive environmental disinfection, may be indicated during outbreaks, particularly those involving MDR organisms or organisms that are more resistant to routine cleaning.95

Antibiotic stewardship programs play an extremely important role in the overall effort to control healthcare-associated infections, reduce emergence of MDR organisms, and control spiraling healthcare costs.96 Antibiotic stewardship should be focused, dynamic, and carefully monitored in order to adjust for specific MDR pathogens.2,97 An infectious disease pharmacist in the ICU, or a computerized decision support program to optimize drug regimens, has reduced inappropriate antibiotic use.1,2 By comparison, antibiotic cycling or rotation programs are more difficult to evaluate because of study design issues.2,97-100

Modifiable Risk Factors

Risk factors for the development of HAP can be differentiated into modifiable and non-modifiable conditions as will be discussed later. Aspiration – the primary route of bacterial entry into the lung – is common and increased during hospitalization, with sedation, neuromuscular blockers, head trauma, intubation, enteral feeding, and following surgery.1,101-106 Supine patient positioning may facilitate aspiration, which can be decreased by maintaining a semirecumbent patient position. One randomized trial demonstrated a threfold reduction in the incidence of ICU-acquired VAP in patients kept in a semirecumbent position versus supine position.106 VAP rates reached 50% in patients maintained in the supine position while simultaneously receiving enteral nutrition.

Although maintaining mechanically ventilated and/or enterally fed patients in a 30–45° position continues to be strongly recommended,1,2,106 recent studies have suggested that this may not be practical, at least at the levels currently recommended. A study by van Nieuwenhoven et al. in ventilated patients who were randomly assigned to backrest elevation of 45° versus the standard of 10°, demonstrated barriers to implementing this strategy.107 The targeted backrest elevation of 45° was not reached and the actual achieved difference was 28° versus 10°, which did not reduce VAP. Perhaps, further studies measuring the impact of maintaining ventilated and/or enterally fed patients in a semirecumbent position are more attainable targets.
Modulation of Bacterial Colonization

Oral Care

Oral care has been studied and recommended to prevent VAP.\textsuperscript{108–111} In a recent study, Mori et al. compared rates of VAP in a nonrandomized group compared to historic controls.\textsuperscript{112} The incidence of VAP in the oral care group was 3.9 episodes/1,000 days versus 10.4 in the control group. Although there are concerns about the study design, oral care has intuitive benefits and limited cost, but more randomized, controlled studies are needed.

Antiseptics

Oropharyngeal colonization is the primary source of pathogens causing HAP and VAP, and therefore reducing levels of colonization or eliminating potential pathogens is an obvious risk-reduction strategy. In a randomized trial, DeRiso et al. demonstrated that the use of the oral antiseptic chlorhexidine (CHX) significantly reduced rates of hospital-acquired infections in patients undergoing coronary artery bypass graft surgery.\textsuperscript{113} Although topical antiseptics, such as chlorhexidine (CHX), provide an attractive alternative to antibiotics, the initial reported success in patients who have undergone cardiac surgery could not be confirmed by other studies. A recent study by Koeman et al. provides important data from a multicenter, double-blind, randomized clinical trial of VAP outcomes for subjects treated with 2% CHX paste versus patients randomized to 2% CHX + 2% colistin (COL) paste to provide greater activity against gram-negative bacilli compared to placebo.\textsuperscript{114} Compared to the placebo group, the daily risk of VAP was reduced by 65% in the CHX group (p=0.01) and 55% in the CHX–COL group (p<0.03). This impressive result for an inexpensive, nontoxic, topically applied modality warrants further attention, but is difficult to reconcile with the absence of effect on ventilator days, length of stay, or mortality. It is important to measure how prophylactic use of CHX and CHX–COL complement other effective prevention strategies, and resistance could become an important issue over time.

Data from seven randomized controlled trials by Chan et al., involving 2,144 patients, showed that topical antiseptics are beneficial in preventing VAP; the benefit is most marked in patients who have undergone cardiac surgery.\textsuperscript{115} These findings are comparable to those of another recently published review study\textsuperscript{116} (limited to topical CHX), which also included seven trials but only 1,650 patients. However, both reviews found that oropharyngeal antiseptics had no impact on mortality or length of stay in the intensive care unit.

Antibiotic Prophylaxis Strategies

Modulation of oropharyngeal colonization by combinations of oral antibiotics, with or without systemic therapy, or selective decontamination of the digestive tract (SDD) is effective in preventing HAP/VAP, although the methodologic study quality, specific regimens used, study populations, and clinical impact differ widely among studies.\textsuperscript{1,2,108,110,117,118}

In two recently published prospective randomized trials, SDD was associated with a higher ICU survival among patients receiving SDD.\textsuperscript{118,119} Also, in two meta-analyses and one additional study, decreased mortality was demonstrated in critically ill surgical patients receiving SDD, including both systemic and local prophylactic antibiotics,\textsuperscript{117,120,121} raising questions about the relative importance of systemic rather than non-absorbed antibiotics.

Preventive effects of intravenous antibiotics were evaluated in only one randomized trial: Administration of cefuroxime for 24 h at the time of intubation reduced the incidence of early onset HAP in patients with closed head injury.\textsuperscript{122} The role of the gastrointestinal tract in the pathogenesis of VAP and the clinical evidence for the efficacy of SDD were recently reviewed by Kallet and Quinn\textsuperscript{123} and in a Cochrane review by Liberati et al.\textsuperscript{115} In the latter study, the authors concluded that for topical and systemic antibiotic prophylaxis, five patients would need to be treated to prevent one infection and 21 patients would need to be treated to prevent one death. No recommendation was made for topical prophylaxis. In a large study of SDD by de Jonge et al. in 2003, SDD was highly effective in preventing pneumonia without an increase in antibiotic resistance.\textsuperscript{119}

However, citing concerns over rapid increases in antimicrobial resistance in the hospital setting, coupled with the association between MDR pathogens and poorer patient outcomes, recent guidelines have suggested that SDD should be considered for selected ICU populations and in targeted clinical scenarios, but not be employed “routinely” for VAP prevention.\textsuperscript{1,2,124}

Since VAT appears to be a precursor to VAP, recently there has been greater interest in collecting serial endotracheal aspirates and using targeted antibiotic therapy to treat VAT as a method of preventing VAP and not delaying therapy in patients with chest X-rays that are difficult to interpret.\textsuperscript{34,25} Although these approaches need further investigation, they could be a new paradigm for early treatment, VAP prevention, and better patient outcomes.

Endotracheal Tube and Mechanical Ventilation

Several devices have been identified as risk factors for HAP. Many of these devices are used in mechanically ventilated patients and increase the risk of VAP; intervention strategies are summarized in several review articles.\textsuperscript{1,2,125}

Subglottic Secretion Drainage

Continuous aspiration of subglottic secretions (CASS) through use of specially designed endotracheal tubes (ETTs) with a wider elliptic hole helps facilitate drainage (Fig. 29.3) and has significantly reduced the incidence of early onset VAP in several studies.\textsuperscript{12} In a recent meta-analysis, CASS reduced the incidence of VAP by half (risk ratio 0.51, 95% CI 1.7–2.3), shortened ICU stay by 3 days (95% CI 2.1–3.9), and delayed the onset of VAP by 6 days. CASS also was cost effective,
saving $4,992 per episode of VAP prevented or $1,872 per patient, but mortality was not affected.\textsuperscript{126}

Silver

Biofilm-encased bacteria that form on the ETT and are protected against killing by antibiotics and host defenses may be a risk factor for VAP. A large, randomized study of 1,509 patients intubated for more that 24 h compared the use of colloidal silver-coated ETT (Bard Pharmaceuticals) – designed to prevent endotracheal tube colonization and biofilm formation – to a conventional ETT.\textsuperscript{127} Diagnosis of VAP required confirmation of VAP by a BAL\textsuperscript{3} \textsuperscript{10} organisms/ml. The silver-ETT group had a lower incidence of VAP (4.8% vs. 7.5%, \(p=0.03\)), with a relative risk reduction of 35.9% and an absolute reduction of 2.7%, but did not reduce mortality rates, duration of intubation, ICU stay, or hospital stay. Like CASS, the silver-ETT delayed the onset of VAP, had its greatest effect in patients ventilated for more than 48 h, and was highly active against pathogens, such as \textit{P. aeruginosa} and MRSA.

Non-invasive Positive Pressure Ventilation

Non-invasive positive pressure ventilation (NPPV) provides ventilatory support without the need for intubation and for earlier removal of the endotracheal tube to reduce complications related to prolonged intubation. NPPV using a face mask is an attractive alternative for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) or acute hypoxemic respiratory failure, and for some immunosuppressed patients with pulmonary infiltrates and respiratory failure.\textsuperscript{1,2} Burns et al., in a recent Cochrane review, reported significant benefits: decreased mortality (RR 0.41, 95% CI 0.22–0.76), lower rates of VAP (RR 0.28, 95% CI 0.90–0.85), decreased length of ICU stay and shorter hospital stays, and lower duration of mechanical support.\textsuperscript{128} The impact of NPPV is greater in patients with COPD exacerbations or congestive heart failure than for patients with VAP. Recent data also indicate that NPPV may not be a good strategy to avoid re-intubation after initial extubation and is recommended for hospitals with staff who are experienced in this technique.\textsuperscript{129}

Sedation and Weaning

Efforts to reduce the likelihood of aspiration of oropharyngeal bacteria around the endotracheal tube cuff into the lower respiratory tract include limiting the use of sedative and paralytic agents that depress cough and other host-protective mechanisms, and maintaining endotracheal cuff pressure at \(>20\) cm H\(_2\)O.\textsuperscript{130} Re-intubation should be avoided, if possible, as it increases the risk of VAP.\textsuperscript{131} Efforts to reduce acute lung injury by using smaller tidal volumes and lower pressures have been suggested.\textsuperscript{132} Other strategies to reduce the duration of mechanical ventilation include improved methods of sedation and the use of protocols to facilitate and accelerate weaning.\textsuperscript{1,133–135} These interventions clearly are dependent on adequate ICU staffing.\textsuperscript{136,137}

Dries et al., using a standardized weaning protocol, reduced the proportion of days of mechanical ventilation (total ICU days) from 0.47 to 0.33%, number of patients failing extubation (25 vs. 43), and the rates of VAP (15–5%).\textsuperscript{138} Schweickert et al. evaluated seven complications in 128 patients receiving mechanical ventilation and continuous infusions of sedative drug, who were randomized to daily interruption of sedative infusions (\(N=66\)) versus sedation directed by the MICU team without this strategy (\(N=60\)).\textsuperscript{7,133} Daily interrupted sedative infusions reduced the length of stay in ICU (6.2 days vs. 9.9, \(p<0.01\)), duration of mechanical ventilation (4.8 vs. 7.3 days, \(p<0.003\)), and the incidence of complications per patient (13/12 patients vs. 26/19 patients, \(p<0.04\)).

Miscellaneous Strategies

Enteral Feeding

Enteral nutrition has been considered a risk factor for the development of HAP, mainly secondary to the increased risk of aspiration of gastric contents.\textsuperscript{1,139} Parenteral nutrition is associated with a higher risk of intravascular-device-associated infection and complications from central venous catheter insertion, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. Accurate assessment of the patient’s nutritional status and the use of enteral feeding, rather than parenteral nutrition, appear to reduce the risk of HAP.\textsuperscript{1,140} Early initiation of enteral feeding may help maintain the gastrointestinal epithelium and prevent bacterial translocation, but it is not without risk. Enteral feeding protocols have been suggested to reduce complications.\textsuperscript{1,141} Early gastrostomy for enteral feedings has been considered as a strategy to reduce VAP in patients with head injury and stroke.\textsuperscript{142}

Intensive Insulin Therapy

Hyperglycemia, relative insulin deficiency, or both may directly or indirectly increase the risk of complications and poor outcomes in critically ill patients. Van den Berghe et al. randomized patients in surgical ICUs to receive either intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dl or to receive conventional treatment.\textsuperscript{143} The group receiving intensive insulin therapy had reduced mortality (4.6% vs. 8%, \(p<0.04\)), and the difference was greater in patients who remained in the ICU for more than 5 days (10.6% vs. 20.2%, \(p=0.005\)). When compared to the control group, those treated with intensive insulin therapy had a 46% reduction of bloodstream infections, decreased frequency of acute renal failure requiring dialysis by 41%, fewer days with antibiotic treatment, and significantly shorter length of mechanical ventilation and ICU stay. While the same degree of benefit may not be seen in VAP as in other populations, aggressive treatment of hyperglycemia has both theoretical and clinical support for SICU patients.
A recent study of intensive insulin therapy in 1,200 medical ICU patients did not significantly reduce overall hospital mortality and actually increased mortality in patients with ICU stays less than 3 days. However, the intensive insulin therapy group had reduced acquired renal failure, duration of mechanical ventilation, and length of ICU and hospital stay. Unfortunately, predicting the length of stay is difficult, and coupled with concerns about the risks of hypoglycemia and with increased resource implications, the benefit of intensive insulin therapy for specific hospital or MICU patients will require further evaluation.

**Stress Bleeding Prophylaxis**

Histamine-type 2 (H2) antagonists and antacids have been identified as independent risk factors for ICU-acquired HAP. Sucralfate has been used for stress bleeding prophylaxis, as it does not increase intragastric acidity or gastric volume, but is less effective in preventing gastrointestinal bleeding.1,2

Numerous randomized trials, using different doses and various study populations, have provided controversial results on the benefits of specific stress bleeding prophylaxis agents in relation to the increased risk of VAP and bleeding.25,145 One large randomized trial comparing antacids, H2 blockers, and sucralfate reported no differences in rates of early onset VAP, but rates of late-onset VAP were lower in patients treated with sucralfate.25

More recently, Bornstein et al. examined risk factors for early onset VAP (from 3 to 7 days) in 747 patients.146 Several different variables were identified in the univariate analysis, but only sucralfate used in the first 48 h of ICU stay and unplanned extubation were predictors of VAP in the multivariate analysis, and antibiotics were protective. In an earlier multicenter study of VAP in patients with ARDS, sucralfate and duration of exposure to sucralfate were associated with an increased risk of VAP.147

A recent, large, double-blind, randomized trial comparing ranitidine to sucralfate demonstrated a trend toward lower rates of VAP with sucralfate, but clinically significant gastrointestinal bleeding was 4% higher in the sucralfate group.145

Data indicate that H2 blockers and protein pump inhibitors are associated with lower rates of gastrointestinal bleeding when compared to sucralfate, which may be doubly important, as transfusion also is a possible risk factor for VAP.

Concerns have been raised over reports of increased rates of *C. difficile* infections among persons receiving proton pump inhibitors.148 A cohort study from a database of 1,187 inpatients at a Montreal teaching hospital showed that patients who had also received proton pump inhibitors other than antibiotics were at increased risk for *C. difficile* diarrhea.

**Transfusion Risk**

Multiple studies have identified exposure to allogeneic blood products as a risk factor for postoperative infection and postoperative pneumonia, and the length of time of blood storage as another factor modulating risk.1 In one prospective randomized control trial, the use of leukocyte-depleted red blood cell transfusions resulted in a lower incidence of postoperative infections and, specifically, a reduced incidence of pneumonia in patients undergoing colorectal surgery.149 Routine red blood cell transfusion should therefore be conducted with a restricted transfusion trigger policy.

**Prevention Strategies at Discharge**

The focus of prevention has been on ICU patients while in the ICU, but these patients are also at increased risk for relapse or re-infection during their rehabilitation. Therefore, efforts should be directed at risk reduction at discharge, such as routine vaccinations and patient education aimed at reducing lifestyle risks, such as smoking cessation, exercise, and weight control.

**Conclusion**

In spite of the progress in the diagnosis, prevention, and management of HAP/VAP, these diseases still have a significant effect on outcome. Immediate administration of adequate antimicrobials is now considered a critical element in the effort to improve survival in HAP/VAP. The choice of the initial antibiotic regimen should be patient-oriented and guided by directed staining of respiratory samples. Prior hospitalization, presence of comorbidities, and the pressure of index cases are helpful indicators in order to anticipate the presence of MRSA, *A. baumanii* and *P. aeruginosa*. Local surveillance data and prior exposure to specific antibiotics (which should be avoided in the initial regimen) help in the choice of the initial antibiotic treatment. Antimicrobial therapy should be adjusted 48–72 h after the onset of pneumonia, based on a combination of quantitative respiratory cultures and resolution assessment. The duration of treatment should also be individualized; however, courses longer than 1 week are rarely justified.

Investing in prevention can pay great dividends in improved quality of life and reduced morbidity and mortality.12 In addition, prevention can have a huge impact in reducing length of hospital stay and healthcare costs during acute care. Spreading the seeds of prevention into chronic care and rehabilitation facilities also is vitally needed in the increasing diversity of our healthcare settings.

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