301 Nosocomial Pneumonia

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SHORT VIEW SUMMARY

Diagnosis

- Classic clinical signs of ventilator-assisted pneumonia (VAP) include fever, leukocytosis, purulent secretions, worsening oxygenation, infiltrates, and pathogenic cultures. These signs are neither sensitive nor specific. Paucity of neutrophils or lack of organisms on Gram stain makes VAP unlikely, but their presence is not specific. Stable oxygenation/ventilator settings argue against clinically significant disease.
- Quantitative bronchoalveolar lavage (BAL) cultures are 57% sensitive, are 80% specific, and have a positive predictive value of 77% for histologically confirmed VAP.
- Randomized controlled trials of quantitative BAL cultures versus endotracheal aspirates for diagnosis have found no difference between these sampling strategies on duration of mechanical ventilation, length of stay, mortality, superinfection, or acquired resistance rates. Endotracheal aspirates are therefore preferred.
- Diagnostic studies are performed to guide therapy: blood and endotracheal aspirate cultures, urine pneumococcal and *Legionella* antigens, with or without viral studies are recommended.

Microbiology

- The most common pathogens are *Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella* spp., and *Acinetobacter* spp. Drug resistance in VAP is common; 25% to 40% of *S. aureus* isolates are methicillin resistant, 20% to 30% of *Pseudomonas* and *Klebsiella* isolates are ceftazidime and cefepime resistant, and 55% to 70% of *Acinetobacter* isolates are carbapenem resistant. Drug resistance is less common in early hospital-acquired pneumonia (HAP), particularly in patients who have not spent time in an intensive care unit. Risk factors for methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant gram-negative pathogens include recent broad-spectrum antibiotic use, prolonged hospitalization, poor functional status, hemodialysis, and severe illness.

Treatment

- Initiate broad-spectrum antibiotics as soon as pneumonia is suspected. Tailor coverage to the local distribution of pathogens and susceptibilities associated with HAP and VAP. In the absence of local data, use vancomycin or linezolid plus two antipseudomonal agents for empirical therapy. Narrower-spectrum regimens are appropriate if local antibiotic resistance rates are low and there are no patient-level risk factors for MRSA or other antibiotic resistant pathogens. Consider a loading dose of vancomycin 25 to 30 mg/kg for seriously ill patients. Include anaerobic coverage only if there is frank aspiration.
- Reassess the likelihood of pneumonia daily; if the diagnosis no longer seems likely, then stop antibiotics.
- Narrow treatment as soon as susceptibilities are available. Avoid double coverage once pathogens and susceptibilities are known. If cultures are negative and the patient's condition is improving, trim or stop antibiotics.
- Vancomycin and linezolid are similarly effective for MRSA. Vancomycin is administered at 15 to 20 mg/kg every 8 to 12 hours. The goal trough is 15 to 20 mg/L. There is an increased risk of clinical failure with underdosage and increased risk of nephrotoxicity with supratherapeutic doses.
- Treat patients for 7 to 8 days, or for a shorter duration in those with rapid clinical improvement, and longer in those who are slow to improve or who have complications such as abscess or empyema. Daily procalcitonin monitoring can be used to safely shorten the duration of antibiotics.
- Adjunctive aerosolized antibiotics in addition to intravenous therapy enhance clearance of pulmonary cultures and may improve clinical cure rates, but they do not affect more objective patient outcomes such as duration of mechanical ventilation, nephrotoxicity, or mortality. Vibrating mesh plate is preferred for delivery. Data are sparse.

Prevention

- VAP rates are subjective and nonspecific. Therefore preferentially select interventions proven to improve concrete outcomes such as duration of mechanical ventilation, mortality, and/or antibiotic utilization.
- Noninvasive positive pressure ventilation, minimizing sedation, and ventilator-weaning protocols (especially paired daily spontaneous awakening and breathing trials) shorten the average duration of mechanical ventilation.
- Digestive decontamination decreases mortality, but there are ongoing concerns about the potential impact on antibiotic resistance rates, especially in units with high baseline resistance rates.
- Oral care with chlorhexidine reduces the frequency of positive pulmonary cultures but has no effect on objective outcomes. Some studies have found an association between oral care with chlorhexidine and higher mortality rates.

Nosocomial pneumonia refers to pneumonia acquired while in a hospital. It is classically divided into hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) but has also been applied to the concept of health care–associated pneumonia (HCAP). The majority of studies on nosocomial pneumonias focus on VAP; hence, this chapter also focuses primarily on VAP, but the principles developed from VAP are thought to be generally applicable.

HEALTH CARE–ASSOCIATED PNEUMONIA

Pneumonias acquired outside the hospital by patients with significant contact with the health care system (HCAP) have historically been conflated with HAP because some early case series found that their pathogen distribution, resistance profiles, and mortality rates were similar to pneumonias acquired by patients inside hospitals.[1–6] The equilibration of HCAP with HAP has been called into question, however, owing to the fear that the HCAP category is unnecessarily broad and drives substantial overuse of broad-spectrum antimicrobials.[7,8] Prospective case series do document higher rates of methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas, Acinetobacter,* and enteric gram-negative pathogens in patients with HCAP, but the overall prevalence of these pathogens is still low. The pooled prevalences of MRSA and *Pseudomonas* in HCAP patients across eight prospective studies, for example, were only 2.2% and 2.1%, respectively.[9] Investigators in some case series do report much higher prevalences, but this typically occurs when the analysis is restricted to patients with positive cultures, typically a sicker subset of the total pneumonia population.[10,11] Pathogen prevalences can also vary substantially by geography, hospital type, and population

characteristics. The local prevalence of drug-resistant pathogens, recent exposure to broad-spectrum antibiotics, hemodialysis, poor functional status, and severity of illness appear to be better predictors of drug-resistant pathogens and morbidity than patients' outpatient health care contacts.[6,10,12,13]

EPIDEMIOLOGY

"Official" VAP rates reported by infection control programs have fallen to extremely low levels over the past 15 years. According to the Centers for Disease Control and Prevention (CDC), the mean VAP rate for medical intensive care units (ICUs) fell from 4.9 to 0.9 VAPs per 1000 ventilator-days between 2002 and 2012.[14,15] During the same period, VAP rates in surgical ICUs fell from 9.3 to 2.2 events per 1000 ventilator days. Remarkably, the median VAP rate for US medical ICUs in 2012 (the last year for which data are available) was zero.[15] These incidence densities correspond to VAP incidence rates of less than 1 VAP per 100 ventilated patients.

The credibility of these rates has been questioned. They were generated by infection preventionists using the CDC's traditional surveillance definitions for nosocomial pneumonia, but the CDC's old definitions included many subjective criteria such as "new or progressive infiltrates," "change in the character of sputum," and "worsening oxygenation."[16–19,20] Many observers were therefore concerned that increasing pressures on US hospitals to report low VAP rates might have influenced surveyors to interpret these very subjective clinical signs more strictly over time.[21,22] An audit of chart diagnoses of VAP in ventilated patients conducted by the US Centers for Medicare and Medicaid Services found that the rate of clinically diagnosed and treated VAP was in fact stable at approximately 10 cases per 100 ventilated patients between 2005 and 2013.[23] Likewise, cross-sectional surveys of ICUs continue to suggest that about 15% of patients are on antibiotics for nosocomial respiratory infections at any given time.[19,20,22,24,25]

Fewer data are available on the incidence of nosocomial pneumonia outside ICUs. A 1-day point-prevalence survey of health care–associated infections in 183 hospitals in 10 US states identified 67 nosocomial pneumonias among 10,748 nonventilated patients (0.6% incidence).[26] A second study using discharge diagnosis codes from a 20% sample of US hospitals reported that 1.6% of hospitalized patients had secondary diagnosis codes for pneumonia.[27] A third set of investigators reviewed the charts of all patients with discharge diagnosis codes for pneumonia in 21 US hospitals. Nosocomial pneumonia rates in nonventilated patients ranged from 0.12 to 2.28 cases per 1000 patient-days.[28]

MORBIDITY AND MORTALITY

VAP is estimated to extend the duration of mechanical ventilation and intensive care by 4 to 6 days.[29,30] Crude mortality rates for VAP range between 16% and 78%.[31] Crude mortality rates for non-ICU nosocomial pneumonia range from 15% to 53%.[28,32–34] Identifying the fraction of these deaths attributable to pneumonia itself rather than to patients' underlying frailties, however, is controversial. Estimates have ranged from 0% to 50%.[35–40] More recent studies using multistate models to account for the time-dependent nature of VAP (the longer a patient remains on a ventilator, the higher his or her risk of both VAP and death) have found attributable mortality rates of 8% to 10%.[41–43] Dutch researchers calculated almost identical figures (9%–13%) using an entirely different method. They estimated attributable mortality as the ratio of the pooled mortality risk reduction to the pooled VAP risk reduction in the treatment versus control arms of randomized controlled trials of VAP prevention interventions.[44,45] Estimates using marginal structural models are even lower: 6% of ICU deaths are due to VAP, corresponding to a net-attributable mortality rate of 1.5%.[36]

PATHOPHYSIOLOGY

The histologic hallmark of VAP is heterogeneity. Autopsies of ventilated patients' lungs are often notable for widely scattered, patchy areas of inflammation.[46] The lesions vary significantly in age and severity, ranging from bronchiolitis to bronchopneumonia to frank abscess, often within the same lung. Dependent areas tend to be affected more often than nondependent areas. Different organisms can be cultured from different lung segments of the same patient in 25% to 37% of cases.[46,47] Cultures of histologically benign–appearing lung segments are often positive.[48,49] Taken together, these findings suggest that ventilated patients are prone to repeated microaspirations around the endotracheal tube cuff, some of which progress to clinically manifest pneumonia, whereas others resolve spontaneously.

Microbiologic, structural, humoral, and pharmacologic factors combine to increase the risk of pneumonia in critically ill patients. The flora of the oral tract rapidly shifts on admission from typical community respiratory organisms (streptococci, *Haemophilus*) toward "hospital-associated" pathogens such as *S. aureus,* Enterobacteriaceae, *Pseudomonas,* and *Acinetobacter* species. The likelihood of these organisms being drug resistant steadily increases with time in the hospital, exposure to antimicrobials, and severity of illness. Orogastric and nasogastric feeding tubes disrupt the lower esophageal sphincter and increase the risk of aspiration of gastric contents.[50] The presence of an endotracheal tube disrupts normal ciliary clearance of constitutive bronchial secretions and impairs patients' capacity to cough. Secretions therefore pool above the endotracheal tube cuff and intermittently seep around folds in the cuff, particularly if the cuff is underinflated or if it shifts during patient movement or repositioning.[51] Biofilm begins to form both inside and outside the endotracheal tube within a day of placement and serves as a bacterial reservoir within the trachea and oropharynx. Suctioning or instillation of aerosols through the endotracheal tube can mobilize and embolize bacteria from the biofilm into the lungs.[49] Critical illness, poor nutrition, sedation, and immobilization may increase patients' susceptibility to infection.[52,53] These factors interact with and reinforce one another to enhance the risk of microaspiration and the likelihood that pulmonary parenchymal colonization will lead to invasive infection.

RISK FACTORS

Understanding the pathophysiology of pneumonia helps predict HAP and VAP risk factors. Factors that enhance the risk of aspiration increase the likelihood of infection. These include mechanical factors such as emergency intubation, reintubation, duration of intubation, supine positioning, enteral feeding through use of orogastric or nasogastric tubes, use of paralytic agents, and underinflation of the endotracheal tube cuff[51,54–62]; factors that affect mental status such as central nervous system disease, impaired consciousness, and depth of sedation[55,59,60]; factors that increase bacterial bioburden in the upper respiratory and orogastric tracts, such as duration of hospitalization, nasogastric intubation, prolonged antibiotic exposures, and the use of proton pump inhibitors or other gastric acid suppressants[60,63,64]; factors that increase handling or breaking of the ventilator circuit, such as inhaled β-agonist therapy[65]; and patient factors such as age, preexisting lung disease, and severity of illness.[54,60,66] Intensive care staffing levels and transportation out of the ICU for diagnostic imaging or procedures are additional factors that can increase risk.[67–69] Surgical patients in general, and burn and trauma patients in particular, have higher VAP rates than medical patients.[55,70]

DIAGNOSIS

More than 100 years ago, Sir William Osler noted a striking discrepancy in pneumonia rates between the wards and the autopsy suite.[71] Contemporary autopsy series continue to confirm the limitations of bedside diagnosis for nosocomial pneumonia.[72] Tejerina and colleagues,[73] for example, evaluated common clinical definitions for VAP in a population of 253 patients, with histologic findings as the reference standard. Defining VAP as a new radiographic infiltrate and two additional signs—leukocytosis, fever, or purulent respiratory secretions—was 65% sensitive and 36% specific. Defining VAP more strictly by requiring radiographic infiltrates and all three of leukocytosis, fever, and purulent respiratory secretions increased specificity to 91% but dropped sensitivity to 16%. Further requiring positive cultures (tracheal aspirate culture with pathogenic organisms, no minimum growth threshold) raised the specificity of both the loose and the strict definitions to 93% and 99%, respectively, but with further cost in sensitivity.[73]

HAP and VAP diagnosis are challenging because the cardinal clinical signs of pneumonia are neither sensitive nor specific in hospitalized patients. Hospitalized patients in general, and critically ill ventilated patients in particular, are at risk for a host of pulmonary complications

including pulmonary edema, atelectasis, thromboembolic disease, acute respiratory distress syndrome (ARDS), hypersensitivity reactions, and hemorrhage, in addition to pneumonia. All of these complications tend to present with some combination of a common core set of clinical signs: fever, leukocytosis, impaired oxygenation, changes in the character and quantity of sputum production, and radiographic infiltrates. The problem is compounded by the fact that many hospitalized patients have abnormal lung conditions at admission that further complicate the interpretation of radiographs and result in impaired oxygenation and abnormal sputum production. These include cancers, scars from prior surgeries, bronchiectasis, obstructive lung disease, pulmonary fibrosis, and, in the case of trauma patients, contusions, lacerations, pulmonary hemorrhage, inhalation injuries, or combinations of these insults. Most patients are found to have two or more conditions contributing to their "pneumonia-like" syndrome.[74–76] Sometimes fever, leukocytosis, and inflammatory syndromes caused by extrapulmonary disease (e.g., bloodstream infections, surgical site infections, pancreatitis) can occur concurrently with noninfectious pulmonary conditions (e.g., atelectasis, pulmonary edema, ARDS) to render a net clinical picture that looks like pneumonia even though the contributing conditions in isolation would rarely be confused with pneumonia.[77] All told, VAP is confirmed at autopsy in only two-thirds of patients with clinically suspected pneumonia.[48,73,78–81]

Alveolar infiltrates and air bronchograms are the most sensitive radiographic signs for autopsy-proven VAP, but neither is specific (sensitivity 83% and 88%, specificity 58% and 26%, respectively).[75] Focal, unilateral infiltrates are more specific than bilateral infiltrates (specificities of 80% and 47%, respectively) but are present in only 21% of cases.[75] Radiographic progression alone is a poor predictor of the presence or absence of histologic pneumonia.[82] Accurate radiographic diagnosis is even more challenging in patients with ARDS.[75,83] In general, there is no correlation between the presence or absence of radiographic infiltrates and positive cultures on quantitative bronchoalveolar lavage (BAL) or autopsy.[47,82,84] Computed tomography (CT) is more accurate than portable radiographs to diagnose pneumonia,[85,86] but few studies have been published on the use of CT specifically for nosocomial pneumonias. On blinded comparison of immediate postmortem CT versus autopsy in 182 patients, radiologists missed 32% of pneumonias and overcalled 14%.[87]

Quantitative BAL cultures have been advocated to increase the accuracy of VAP diagnosis, but studies comparing quantitative bronchoscopic cultures and histologic findings only partially confirm this. Specimens are prone to contamination with organisms residing in the mouth and on the endotracheal tube; sampling the incorrect lung segment can generate both false positives (subclinical bronchiolitis rather than frank pneumonia) and false negatives (an uninfected lung segment instead of the infected segment); and recent antibiotic exposure can misleadingly suppress growth.[46,88] Bronchoscopy studies bear witness to the microbial complexity and diversity of intubated patients. There is little or no correlation between positive quantitative cultures and the presence of infiltrates or leukocytosis.[47,84] Cultures taken from different lung segments are discrepant in more than one-third of patients with suspected VAP.[47] There is little correlation between Gram stain characteristics (gram positive vs. gram negative) and final culture results.[89] In addition, VAP exists on a microbiologic and histologic spectrum that may not cross arbitrary quantitative thresholds for positivity.[90] Studies evaluating the accuracy of quantitative BAL for VAP relative to histologic findings have found sensitivities of 14% to 90% (weighted average, 57%), specificities of 42% to 100% (weighted average, 80%), and positive predictive values of 29% to 100% (weighted average, 77%).[79,82,91–94] Of note, negative cultures are not protective: Patients with culture-negative VAP have outcomes similar to or worse than those of patients with culture-positive VAP.[95–97]

Clinical Pulmonary Infection Score

Some workers have proposed scoring systems to aid diagnosis. The most common of these is the Clinical Pulmonary Infection Score (CPIS).[98] The original score was calculated by assigning 0 to 2 points for each of six clinical criteria, including temperature, white blood cell count, quantity and quality of respiratory secretions, Gram stain and culture findings, ratio of Pao_2 to Fio_2, and radiographic results. A score of more than 6 was considered diagnostic for pneumonia. Many workers have proposed modified versions of the CPIS to simplify application or make it more suitable for early diagnosis of VAP by deemphasizing cultures and increasing emphasis on dynamic changes in radiographs (Table 301.1).[99,100] Unfortunately, validation studies do not bear out the value of the CPIS.[92,99–104] In the autopsy series by Tejerina and colleagues,[73] for example, the sensitivity and specificity of a CPIS score of greater than 6 were 46% and 60%, respectively.

TABLE 301.1 Clinical Pulmonary Infection Score (CPIS) as Modified by Schurink and Colleagues

CPIS POINTS	0	1	2
Temperature, °C	≥36.1 and ≤38.4	≥38.5 and ≤38.9	≤36 or ≥39
White blood cell count, per 10^9/L	≥4 and ≤11	≤3.9 or ≥11.1	≥11.1 with band forms or ≥17.1
Tracheal secretions	Absent	Present but nonpurulent (white or light yellow)	Purulent (yellow, green, or brown)
Oxygenation (Pao_2 to Fio_2 ratio)	>240		<240 and no adult respiratory distress syndrome
Chest radiograph	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate
Tracheal aspirate culture result (semiquantitative growth amount)	None (0)	Moderate (1+ or 2+)	Heavy (3+)

From Schurink CA, Van Nieuwenhoven CA, Jacobs JA, et al. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med. *2004;30:217–224.*

SUMMARY AND RECOMMENDATIONS FOR CLINICAL DIAGNOSIS

The best available evidence suggests that clinical examination can alert physicians to the possibility of VAP but that it is insufficient to definitely rule in or rule out pneumonia.[105] Examination of sputum or BAL specimens can help refine clinical suspicions. The absence of organisms on Gram stain or less than 50% neutrophils in BAL fluid help exclude the diagnosis.[79,81,82,89] The presence of organisms or neutrophils, however, is not specific. Stable ventilator settings argue against a clinically impactful pneumonia.[106,107] The absence of new infiltrates makes pneumonia unlikely, but their presence is not specific. None of these findings are sufficiently powerful to establish or refute a diagnosis of VAP definitively. Clinicians caring for ventilated patients with a clinical syndrome consistent with VAP should therefore have a low threshold to consider additional diagnoses and further investigations, particularly if an empirical trial of antibiotics does not lead to improvement within 48 to 72 hours.

Microbiologic Evaluation

It is important to try to establish a microbiologic diagnosis in order to ensure coverage of the active pathogen(s), to minimize exposure to unnecessary agents, and to help define the distribution of pathogens and resistance profiles in one's practice setting with a view to informing local empiric treatment guidelines. Inappropriate and delayed therapy are associated with increased mortality risk.[108–111] Blood and respiratory cultures are indicated in all patients. Pneumococcal and *Legionella* urine antigen testing increase diagnostic yield compared with respiratory sampling alone.[32] Viruses account for up to one-quarter of nosocomial pneumonia cases.[34,112–116] Viral studies are therefore indicated during periods of endemicity, in immunocompromised patients, and in patients with diffuse ground-glass opacities on CT.[112–114]

Invasive Versus Noninvasive Respiratory Tract Sampling

A number of options for respiratory tract sampling are available, including endotracheal aspirates, BAL, and protected specimen brush. These in

turn can be analyzed qualitatively or quantitatively. There has been a great deal of controversy over whether clinicians should routinely acquire specimens by using invasive techniques (BAL or protected specimen brushes) or noninvasive techniques (endotracheal aspiration). This question has now been evaluated in five randomized trials.[117–121] Route of sampling made no difference in average duration of mechanical ventilation or intensive care length of stay. All but one trial[120] found no difference in mortality rates. A meta-analysis of all five trials also found no difference in any patient outcome, including the frequency of antibiotic changes.[122] Invasive sampling should consequently be reserved for patients with negative endotracheal aspirate cultures whose condition worsens despite empirical coverage or patients with positive endotracheal aspirate specimens whose condition worsens despite targeted antibiotics. Repeat sampling in patients in whom empirical treatment fails can lead to antibiotic switches or stops in 30% to 50% of patients.[3,123,124] Sampling is still worthwhile in patients on antibiotics. In one study, for example, BAL yield was 72% despite a mean 11.4 days of antibiotics before sample acquisition.[123] Not surprisingly, these patients are often found to be harboring multidrug-resistant pathogens.

MICROBIOLOGY

The microbiology of nosocomial pneumonia varies considerably depending on the duration of hospitalization before pneumonia, the severity of illness, comorbid conditions, the reason for admission, and prior antibiotic exposures. *Streptococcus pneumoniae,* β-hemolytic streptococci, and *Haemophilus influenzae* are the most frequent organisms in patients just admitted to the hospital (≤2 days).[125] Thereafter, *S. aureus, Pseudomonas aeruginosa,* Enterobacteriaceae, and *Acinetobacter* species begin to predominate. The risk of *S. aureus* being methicillin resistant rises progressively with duration of hospitalization.[126] Patients hospitalized for extended periods or exposed to prolonged courses of antibiotics, or both, are also susceptible to *Stenotrophomonas maltophilia, Burkholderia cepacia,* and other difficult-to-treat organisms. Some VAP cases are polymicrobial, especially in aspiration pneumonia and ARDS.[127–129] *Candida* species, enterococci, and coagulase-negative staphylococci are almost always colonizers rather than invaders.[130–132]

Although clinicians have long recognized that the distribution of causative pathogens evolves over the course of hospitalization, the breakpoint at which microbial ecology shifts has been subject to debate.[133] Different investigators have used different cutoffs to define early versus late pneumonia (4, 5, and 7 days) and have variously counted these days from hospital admission, ICU admission, or initiation of mechanical ventilation. A number of studies note little or no differences in pathogen mix between early- versus late-onset pneumonias.[134,135] It is clear, however, that the ecology of respiratory flora can shift within 1 to 2 days of hospital admission, so even studies using breakpoints of 4 days or less to define early-onset pneumonia may still be lumping together patients who have their native flora with those who have begun to acquire hospital spectrum flora.[22,136] Duration of hospitalization before pneumonia is probably a better predictor of microbiology than duration of mechanical ventilation.[125] However, it is clear from studies comparing early- versus late-onset pneumonia that just as so-called late pathogens can be isolated early in the course of hospitalization, so too is it possible to isolate so-called early pathogens late in the course of hospitalization.[22,128] The median numbers of ventilator days and hospital days until the appearance of various pathogens at bronchoscopy in a series of 346 patients in a Swedish ICU are summarized in Table 301.2.

Certain comorbidities predispose to particular pathogens.[127] Patients with cystic fibrosis are prone to *S. aureus* and *P. aeruginosa*. Patients with chronic obstructive pulmonary disease have higher rates of *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.* Diabetes and head trauma are risk factors for *S. aureus.*

The prevalence of nosocomial pneumonias attributable to resistant pathogens has risen over the past 2 decades.[137–139] The overall distribution of pathogens among VAP cases reported to the CDC's National Healthcare Safety Network in the years 2011 and 2012 is shown in Table 301.3, along with their antibiotic resistance patterns.[139] Risk factors for drug-resistant bacteria include severe illness, prolonged mechanical ventilation, recent broad-spectrum antibiotic exposure, recent hospitalization or residence in an extended-care facility, and immunosuppression.[94,128,140,141] The findings

TABLE 301.2 Median Number of Hospital Days and Ventilator Days Until First Isolation of Different Pathogens With Bronchoscopy

PATHOGEN	VENTILATOR DAYS MEDIAN (IQR)	HOSPITAL DAYS MEDIAN (IQR)
β-Hemolytic streptococci	0.26 (0.01–1.91)	1.15 (0.38–2.24)
Streptococcus pneumoniae	1.20 (0.45–1.79)	1.33 (0.78–2.03)
Haemophilus influenzae	1.94 (1.20–2.88)	2.12 (1.44–3.12)
Staphylococcus aureus	0.96 (1.15–2.24)	2.70 (1.68–5.36)
Escherichia coli	2.01 (0.45–5.11)	4.26 (2.18–6.85)
Klebsiella species	2.10 (0.53–5.65)	4.83 (2.43–10.94)
Other Enterobacteriaceae	2.55 (0.39–5.76)	4.40 (2.27–13.32)
Acinetobacter species	2.86 (0.24–5.90)	4.25 (1.61–5.90)
Pseudomonas aeruginosa	3.79 (1.09–10.48)	5.29 (2.85–18.66)
Stenotrophomonas maltophilia	5.73 (2.70–15.72)	11.09 (5.75–34.35)

IQR, Interquartile range.
From Hyllienmark P, Martling CR, Struwe J, et al. Pathogens in the lower respiratory tract of intensive care unit patients: impact of duration of hospital care and mechanical ventilation. Scand J Infect Dis. *2012;44:444–452.*

of studies on whether or not drug-resistant pathogens increase attributable morbidity and mortality are inconsistent.[126,140,142–146]

There is a correlation between severity of pneumonia and culprit organisms. Patients who require intubation are more likely to harbor MRSA and resistant gram-negative pathogens than patients who do not (Table 301.4).[6,10,147] Likewise, among patients with ICU-acquired pneumonia, there is a linear trend between severity of illness score and progressive likelihood of MRSA, extended-spectrum β-lactamase producers, and gram-negative pathogens resistant to third-generation cephalosporins.[140] This parallels the early work of Johanson and colleagues,[136] who compared the frequency of gram-negative pathogens in oropharyngeal cultures from healthy community dwellers, healthy clinicians working in a hospital setting, psychiatric inpatients, "moderately ill" orthopedic patients, and moribund medical patients. The prevalence of gram-negative pathogens was less than 5% in the first three groups, 22% in the moderately ill orthopedic patients, and 66% in the moribund patients.[136]

Viruses can account for up to one-third of severe pneumonias, including HAP, particularly in immunocompromised hosts.[112–116] There are reports of influenza and other respiratory virus outbreaks in hospitalized patients, including patients on mechanical ventilation.[148–150] Reactivation disease secondary to cytomegalovirus (CMV) can also manifest well after admission. The mortality rate for viral pneumonias that merit intensive care is similar to that for bacterial pneumonias.[113]

The causative pathogens for non-ICU pneumonia are less often identified, presumably because of prior antibiotic exposures, the difficulty of obtaining adequate sputum specimens in nonintubated patients, and some rate of misdiagnosis due to aspiration pneumonitis and other pneumonia mimickers. For example, a causative pathogen was identified in only one-third of patients with 165 cases of HAP of any severity versus two-thirds of 96 cases of HAP that necessitated ICU admission (see Table 301.4).[32,33] The microbiology of severe HAP necessitating ICU admission is similar to that of VAP.[32] Severe HAP necessitating ICU admission is more likely due to "nosocomial" pathogens such as MRSA and *P. aeruginosa,* whereas patients with less severe HAP not necessitating ICU care are more likely to have *S. pneumoniae* and *H. influenzae* pneumonia (see Table 301.4).[32,33] There is considerable overlap, however, between these two populations. Anaerobic bacteria are common in patients with frank aspiration but are otherwise rarely implicated.[151,152]

Knowledge of the microbiology of nosocomial pneumonia is limited by the sensitivity of conventional culture methods. Molecular diagnostic studies that use 16S and 18S polymerase chain reaction (PCR)

TABLE 301.3 Distribution of Pathogens and Their Antibiotic Resistance Patterns Among VAP Cases Reported to the CDC's National Healthcare Safety Network, 2011–2012, and ICU-Acquired Pneumonias Reported to the European Center for Disease Prevention and Control, 2015

PATHOGEN	FREQUENCY USA	FREQUENCY Europe	ANTIBIOTIC-RESISTANCE PROFILE[a]
Staphylococcus aureus	24.7%	17.0%	Methicillin/oxacillin resistant—USA 42%, Europe 23%
Pseudomonas aeruginosa	16.5%	20.1%	Ciprofloxacin/levofloxacin resistant—USA 32% Imipenem/meropenem resistant—USA 28%, Europe 24% Cefepime/ceftazidime resistant—USA 26%, Europe 24% Piperacillin-tazobactam resistant—USA 19% Aminoglycoside resistant—USA 18% Resistant to ≥3 of the above classes—USA 20%
Klebsiella species	10.2%	14.9%	Cefepime/ceftazidime/ceftriaxone resistant—USA 21%, Europe 43% Imipenem/meropenem resistant—USA 10%, Europe 11% Resistant to ≥3 classes—USA 13%
Enterobacter species	8.3%	10.5%	Cefepime/ceftazidime/ceftriaxone resistant—USA 27%, Europe 42% Imipenem/meropenem resistant—USA 3%, Europe 2.2% Resistant to ≥3 classes—USA 3%
Acinetobacter baumannii	6.1%	5.2%	Imipenem/meropenem resistant—USA 55%, Europe 69% Resistant to ≥3 classes—USA 54%
Escherichia coli	5.4%	13.2%	Ciprofloxacin/levofloxacin resistant—USA 31% Cefepime/ceftazidime/ceftriaxone resistant— SA 17%, Europe 20% Imipenem/meropenem resistant—USA 2%, Europe 0.5% Resistant to ≥3 classes—USA 10%

[a]Resistance rates for USA specifically for VAP, resistance rates for Europe for all health care–associated infections in ICUs.
CDC, Centers for Disease Control and Prevention; *ICU,* intensive care unit; *VAP,* ventilator-assisted pneumonia.
From Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol. *2016;37:1288–1301 and European Center for Disease Prevention and Control (ECDC). Healthcare-associated infections acquired in intensive care units. In: ECDC. Annual epidemiological report for 2015. Stockholm: ECDC; 2017.*

TABLE 301.4 Causative Pathogens of Nosocomial Pneumonia Acquired in Non-ICU Settings as a Function of Severity of Illness

	165 HAP CASES OF VARIABLE SEVERITY[31]	96 CASES OF SEVERE HAP NECESSITATING ICU ADMISSION[36]
No pathogen identified	105 (64%)	32 (33%)
Pathogen identified	60 (36%)	64 (67%)
Gram-positive pathogens:		
Streptococcus pneumoniae	16 (27%)	11 (17%)
Staphylococcus aureus	4 (6.7%)	9 (14%)
methicillin susceptible	3 (5.0%)	8 (13%)
methicillin resistant	1 (1.7%)	1 (1.6%)
Gram-negative pathogens:		
Pseudomonas aeruginosa	7 (12%)	18 (28%)
Enterobacteriaceae	8 (13%)	6 (9.4%)
Haemophilus influenzae	2 (3.3%)	2 (3.1%)
Acinetobacter species	5 (8.3%)	1 (1.6%)
Legionella pneumophila	7 (12%)	12 (19%)
Aspergillus species	7 (12%)	13 (20%)

HAP, Hospital-acquired pneumonia; *ICU,* intensive care unit.

amplification suggest that the microbiota of nosocomial pneumonia is far broader than current conventional wisdom. One evaluation of BAL fluid from 185 patients with ICU pneumonia, for example, identified 160 different organisms.[153] Almost half of these organisms had not been previously associated with pneumonia. The extent to which these agents are colonizers versus invaders, however, remains to be determined.

TREATMENT

Treating nosocomial pneumonia is a delicate balancing act between factors that favor more antibiotics and those that favor less. Concern that therapeutic delay is associated with worse outcomes, recognition of the limited sensitivity of clinical examination for VAP, and awareness of the frequent presence of multidrug-resistant pathogens favor early, aggressive treatment with broad-spectrum agents for most patients.[124,154,155] On the other hand, recognition that one-third to one-half of patients labeled as having VAP have been misdiagnosed, fear of catalyzing *Clostridioides difficile* (formerly *Clostridium difficile*) infection and other adverse effects of antibiotics, and hesitancy to drive further patient- and unit-level antibiotic resistance warrant restraint in prescribing.[73,156–162] The current solution to this dilemma is diagnostic and therapeutic humility. In practice, this means early coverage with broad-spectrum agents as soon as pneumonia seems likely, active microbiologic investigation to facilitate antibiotic narrowing, and continual reevaluation of the likelihood of pneumonia with a view to rapidly withdrawing antibiotics if the patient's clinical evolution is not consistent with pneumonia. If the evidence for pneumonia is equivocal and the patient is not in septic shock, observational data suggest that it is reasonable to forestall treatment while obtaining more diagnostic data.[163,164]

Empirical Therapy

Empirical therapy for VAP should include both gram-positive and gram-negative coverage. Specific antibiotic choices should be informed by the local distribution of pathogens and their drug resistance profiles.[165–167] US guidelines recommend designing a regimen with a 95% or greater probability of covering the patient's likely pathogens based on the patient's specific risk factors for resistant organisms and the prevailing organism and resistance profiles in one's ICU.[94] The US guidelines list the following risk factors for drug-resistant pathogens:

- Prior intravenous antibiotic use within 90 days
- Septic shock at the time of VAP
- ARDS preceding VAP
- ≥5 days since admission to hospital
- Acute renal replacement therapy before VAP onset

In the absence of local data, national surveillance data can guide antibiotic choices. In both Europe and the United States, the most common VAP pathogens are *S. aureus, P. aeruginosa,* and Enterobacteriaceae.[22,139,168] Approximately 25% to 40% of *S. aureus* isolates are resistant to methicillin, 20% to 30% of *P. aeruginosa* isolates are resistant to at least one class of antipseudomonals, and 20% to 40% of *Klebsiella pneumoniae* isolates are resistant to ceftazidime and cefepime (see Table 301.2).[139,168] Other gram-negative organisms are similarly likely to be resistant to at least one class of gram-negative agents. An ideal empirical regimen should therefore include an agent active against MRSA and two antipseudomonal agents from two different classes in order to increase the likelihood that at least one antibiotic will be active. Reasonable empirical choices are shown in Table 301.5.

The choices presented in Table 301.5 should be modified or supplemented depending on specific patient or hospital circumstances. For

TABLE 301.5 Empirical Treatment Options for Ventilator-Associated Pneumonia

GRAM-POSITIVE AGENTS (CHOOSE ONE)	ANTIPSEUDOMONAL AGENTS (CHOOSE ONE AGENT FROM COLUMN 1; IF PATIENT HAS RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS, INCLUDING HIGH LOCAL PREVALENCE OF MULTIDRUG PATHOGENS, THEN ALSO CHOOSE AN AGENT FROM COLUMN 2)	
Vancomycin *or* Linezolid	Antipseudomonal cephalosporin (ceftazidime or cefepime) Antipseudomonal carbapenem (imipenem or meropenem) Antipseudomonal β-lactam (piperacillin-tazobactam) Monobactam (aztreonam)	Antipseudomonal quinolone (ciprofloxacin or levofloxacin) Antipseudomonal aminoglycoside (amikacin, tobramycin, or gentamicin) Polymyxin (colistin, polymyxin B)

[a]Select one gram-positive agent and two gram-negative agents.

example, if a patient previously colonized with a resistant organism develops pneumonia, then empirical treatment should include coverage for that pathogen. Similar special circumstances might include local outbreaks or high local prevalence of multidrug-resistant *Acinetobacter,* multidrug-resistant *Pseudomonas,* or carbapenem-resistant Enterobacteriaceae.[165] Empirical treatment choices in these cases should be informed by the antibiograms of previously isolated pathogens and might include ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, colistin, tigecycline, or ampicillin-sulbactam if needed to ensure coverage. Some units customize this approach on a patient-by-patient basis by obtaining regular surveillance cultures.[169–171] Clinicians should also consider covering for *Legionella* or influenza if the clinical presentation or local epidemiologic findings suggest that one of these pathogens is possible. Anaerobic coverage is generally not required except after an episode of frank aspiration.[129,151,152,172] Empirical antifungal coverage is not typically indicated for immunocompetent individuals. New oral ulcers or vesicles consistent with herpes simplex virus merit empirical addition of acyclovir.

Treatment for HAP outside the ICU should also be informed by patient risk factors and the local distribution of pathogens and resistance rates. The major risk factor for multidrug-resistant pathogens for nonventilator HAP per US guidelines is intravenous antibiotic use in the preceding 90 days.[94] Other potential risk factors mentioned in the literature include prolonged hospitalization, hemodialysis, poor functional status, and severe pneumonia.[94,128,140,141] It may be possible to treat patients with none of these risk factors more narrowly. US and European guidelines both suggest that monotherapy may be adequate for patients without septic shock who do not need ventilator support and do not have any risk factors for MRSA.[94,173] As with VAP, continual reevaluation of the decision to treat and expeditious antibiotic narrowing or withdrawal in patients whose condition rapidly improves can help minimize superfluous antibiotic exposures.

Vancomycin Versus Linezolid for MRSA Coverage

Vancomycin and linezolid are both reasonable choices for empirical or directed treatment of MRSA nosocomial pneumonia. There are theoretical and/or logistic grounds in favor of each. Linezolid has superior lung penetration, may reduce biofilm formation on endotracheal tubes, does not need dose adjustment based on body mass or renal function, is less nephrotoxic, and is available in an oral formulation for patients with limited intravenous access in the hospital or at discharge.[174,175] On the other hand, the threshold for linezolid resistance appears lower, patients are more likely to develop thrombocytopenia and gastrointestinal symptoms, and it interacts with serotonin reuptake inhibitor medications.[176,177]

There appears to be little difference in clinical effectiveness between vancomycin and linezolid.[178] Early work suggested a possible advantage to linezolid on the basis of retrospective subgroup analysis of the MRSA population in two trials of empirical therapy for nosocomial pneumonia.[179,180] Prospective randomized trials, however, have not confirmed this initial signal.[178] Wunderink and colleagues[181] randomized 448 patients to linezolid versus dose-optimized vancomycin (15 mg/kg every 12 hours). The authors concluded that linezolid was superior to vancomycin on the basis of clinical cure rates (58% vs. 47%, $P = .04$); however, this result was based on a *per-protocol* analysis that only included 339 out of the 448 study patients.[182] Broadening the analysis to include all 448 patients eliminated the apparent difference in clinical response rates (46% vs. 41%, $P = .34$) and there was no difference in 60-day mortality rates between study arms.

Vancomycin has a narrow therapeutic window. Underdosage increases the probability of clinical failure, and overdosage increases the risk of nephrotoxicity.[183] Initial vancomycin trough levels less than 15 mg/L increase the risk for clinical failure, relapse, or both.[166–168,184,185] Conversely, higher vancomycin trough levels and longer treatment courses increase the risk of nephrotoxicity.[186] Concurrent treatment with aminoglycosides or piperacillin-tazobactam further potentiates the risk of acute kidney injury.[186,187] The net incidence of nephrotoxicity in critically ill patients treated with vancomycin for pneumonia is approximately 15%, although the extent to which this risk is due to vancomycin versus underlying illness and concomitant therapies is unclear.[176,186]

The current recommended dosage strategy for vancomycin is 15 to 20 mg/kg every 8 to 12 hours, with a goal of achieving serum trough concentrations of 15 to 20 mg/L.[188] In seriously ill patients, clinicians can also consider a loading dose of 25 to 30 mg/kg to speed attainment of target trough concentrations.[188]

The results of observational studies differ on whether elevated MICs are associated with worse outcomes or not.[189–191] Prospective randomized trials comparing vancomycin and linezolid for treatment of MRSA pneumonia due to isolates with elevated vancomycin MICs have not been conducted.

Ceftaroline is the only FDA-approved cephalosporin with activity against MRSA. It is approved for the treatment of MRSA soft tissue infections and methicillin-susceptible *S. aureus* (MSSA) pneumonia. Whether the drug is effective in MRSA pneumonia remains to be determined.[192] Ceftobiprole is also active against MRSA but is not currently approved in the United States. A randomized controlled trial comparing ceftobiprole versus linezolid plus ceftazidime for the treatment of nosocomial pneumonia reported comparable clinical cure rates for patients with non–ventilator-associated HAP but significantly lower cure rates with ceftobiprole for patients with VAP.[193]

Combination Versus Monotherapy for Gram-Negative Pathogens

Three reasons have been proposed for double covering gram-negative bacteria: (1) to increase the probability that an empirical regimen includes an agent active against the infecting pathogen, (2) to achieve synergy between agents and thereby enhance treatment effectiveness, and (3) to decrease the probability that the organisms will acquire resistance during treatment.[194] An increasing body of literature speaks to these claims.

Multiple studies have suggested that inappropriate initial therapy (defined as failure to prescribe an antibiotic active against the causative pathogen) increases mortality risk.[110,111] Initiating two gram-negative agents rather than one increases the likelihood that initial therapy will include an active agent, which in turn is associated with lower mortality risk.[195–199] There are no differences in clinical outcomes, however, between patients receiving definitive therapy with one versus two active agents once susceptibilities are available.[196,198,200,201] Indeed, with some regimens, particularly β-lactam and aminoglycoside combinations, double coverage is associated with more clinical failure, more nephrotoxicity, and greater risk of nurturing antimicrobial resistance and superinfection.[201–203] Adding an aminoglycoside even for a brief period may increase the risk of clinical failure and nephrotoxicity.[203] Definitive treatment with a carbapenem and fluoroquinolone may mitigate the short-term risk of acquired resistance in some patients,[200] but this risk is generally small[200,204] and likely outweighed by greater long-term risk for multidrug-resistant pathogens at the population level.[157–161]

These findings were borne out in the largest randomized trial to date of empirical monotherapy versus combination therapy for suspected VAP. Heyland and colleagues[204] randomized 740 patients with suspected VAP to meropenem alone versus meropenem plus ciprofloxacin. Combination therapy was more likely to be active than monotherapy (93% vs. 85%, $P = .01$), but there were no differences in patients' outcomes, including duration of mechanical ventilation, intensive care length of stay, hospital length of stay, or mortality. Similarly, there were no differences in rates of acquired antimicrobial resistance, sputum colonization, or *C. difficile* infections. This study specifically excluded patients at high risk for multidrug-resistant pathogens (including patients known to be colonized with MRSA or *Pseudomonas* or those recently treated with a carbapenem or ciprofloxacin), however, so the majority of patients were infected with pathogens susceptible to both the monotherapy and combination therapy agents. This study design limits the generalizability of this study to routine practice. The authors did, however, conduct a subgroup analysis among the subset of patients infected with *Pseudomonas, Acinetobacter,* or multidrug-resistant gram-negative bacilli. There were only 56 patients in this subset (8% of this study population vs. 30% or more in an unselected VAP population). Among these patients, empirical double coverage was much more likely to include an active agent (84% vs. 19%, $P < .001$) and to achieve microbiologic cure (64% vs. 29%, $P = .05$) compared with monotherapy. There were also trends toward shorter duration of mechanical ventilation and intensive care length of stay and decreased mortality with combination therapy.

Taken together, these studies suggest that combination therapy is appropriate for empirical treatment of severe pneumonia, particularly in patients at high risk for multidrug-resistant pathogens. Once the culprit pathogen's antibiotic susceptibilities are known, however, coverage should rapidly be tapered to a single agent.

Aerosolized Versus Intravenous Drug Delivery

Aerosolizing antibiotics is theoretically attractive to improve pulmonary penetration while limiting systemic toxicities, particularly for nephrotoxic agents with poor lung penetration such as colistin and the aminoglycosides. Optimal delivery of aerosolized agents requires vibrating mesh plate nebulizers rather than ultrasonic or jet nebulizers and careful coordination of nebulization, ventilator settings, and sedation.[205,206] Aerosolized antibiotics have been studied both as an adjunct and as an alternative to intravenous treatment. There is a paucity of randomized controlled trials evaluating these strategies, but available data suggest that adjunctive aerosolized antibiotics may enhance microbiologic clearance but have little or no impact on patients' duration of mechanical ventilation, length of stay, or mortality.[207–209] Less is known about aerosolization as an alternative to intravenous therapy. Lu and colleagues[210] randomized 40 patients with *P. aeruginosa* VAP to intravenous amikacin and ceftazidime versus aerosolized amikacin and ceftazidime. They found no difference in clinical response or superinfection rates but less acquired resistance in the aerosolized antibiotic group. The same investigators also followed 165 patients with VAP caused by *P. aeruginosa* or *Acinetobacter baumannii*.[211] Patients with isolates sensitive to β-lactams, aminoglycosides, or quinolones were treated with intravenous antibiotics for 14 days. Patients with multidrug-resistant strains were treated with aerosolized colistin. Clinical response, mortality, and nephrotoxicity rates were similar between the two groups. Of note, there is risk associated with aerosolizing antibiotics. Up to 10% of patients treated with nebulized antibiotics develop cardiorespiratory complications, some of which can be life-threatening.[209] Nebulized antibiotics should therefore be reserved for the treatment of patients with multidrug-resistant pathogens for whom other options are limited.[212]

Tailoring and Deescalating Therapy

Tailoring treatment to the single narrowest-spectrum agent available is critical as soon as antimicrobial susceptibility data are available, not only because sustained double coverage is unnecessary but because continuing treatment with superfluous agents is expensive, liable to drive population-level antibiotic resistance, and potentially harmful.[157–161,202,213–215]

There appears to be little difference in clinical effectiveness among most available agents. A meta-analysis of 41 treatment trials of 29 different treatment regimens found no difference in mortality rates among the regimens studied.[201] There is a possible signal toward lower short-term mortality rates when VAP is treated with carbapenems versus other classes, but the impact of this strategy on long-term mortality and population-level resistance rates has not been adequately characterized.[94] Clinicians can therefore select the narrowest-spectrum agent available for definitive treatment. Non-aminoglycosides should be preferentially selected if possible, given the poor lung penetration and nephrotoxicity of aminoglycosides.[94]

Narrowing treatment for patients with negative cultures requires careful clinical judgment. Some proportion of patients with negative cultures probably do not have pneumonia at all but rather mimicking conditions such as mucous plugging, pulmonary edema, atelectasis, thromboembolic disease, ARDS, and others. If an alternative diagnosis is established or if the patient's clinical course does not seem consistent with pneumonia, then antibiotics should be stopped.[216–218] There are fewer data on how to manage culture-negative patients whose clinical course does still seem consistent with pneumonia. The findings of observational studies suggest that antibiotics can be safely stopped as soon as the patient's condition clinically improves, but more data are necessary.[97,219–222]

Duration of Therapy

Chastre and colleagues[223] randomized 401 patients with culture-positive VAP to 8 versus 15 days of antibiotics. They found no difference in ventilator-free days, intensive care length of stay, mortality, or recurrent infection between short-course and long-course therapy. The one exception was pneumonia due to nonfermenting gram-negative bacilli, including *P. aeruginosa*. Patients with these pathogens had higher rates of microbiologic recurrence when randomized to 8-day therapy (41% vs. 25%). There was no difference, however, in ventilator-free days, length of stay, or mortality rates in patients with nonfermenting gram-negative bacilli randomized to 8 days versus 15 days. Other studies mirror these findings.[224,225] The default treatment course for HAP and VAP for all pathogens is therefore 7 to 8 days.[94] This treatment regimen can be modified, however, depending on clinical evolution and complicating factors such as bacteremia, empyema, or lung abscess.

Clinicians can also use clinical and laboratory data to shorten treatment duration. Antibiotics can be safely stopped even before 8 days of treatment if all clinical signs and symptoms completely resolve (defervescence, improvement in white blood cell count, resolution of purulent secretions, normalization of oxygenation, and stabilization or regression of infiltrates).[107,217,219] Multiple randomized controlled trials have suggested that measuring procalcitonin levels daily or every other day can shorten the average duration of antimicrobial therapy without adversely affecting pneumonia patients' ventilator-free days, intensive care length of stay, or mortality.[226–229] Indeed, a patient-level meta-analysis of randomized controlled trials suggested that measuring procalcitonin levels daily to guide antibiotic discontinuations may lower mortality rates.[229] CT or ultrasound quantification of reaeration after several days of treatment can help measure antibiotic response, but this strategy has not yet been studied as a means of guiding antibiotic deescalation.[230]

PREVENTION

Interpreting the literature on nosocomial pneumonia prevention is challenging because of circularity between clinical definitions for pneumonia and the mechanisms by which most prevention measures work.[231] Most pneumonia definitions incorporate some assessment of the quality or quantity of pulmonary secretions or the results of pulmonary cultures acquired via the oropharynx or endotracheal tube (expectorated sputum, endotracheal aspirates, or BAL), or both. Most prevention strategies in turn are designed to decrease the volume of regurgitant secretions or decrease the bacterial burden in and around the oropharynx and endotracheal tube, or both. There is consequently a risk that some observed decreases in "pneumonia" better reflect fewer secretions or less colonization of the oral-respiratory tract, rather than a decline in true invasive infections. Evidence for this effect is apparent in a striking paradox of the VAP prevention literature: Many interventions lower VAP rates, but very few improve concrete outcomes such

TABLE 301.6 Interventions Proposed to Lower Ventilator-Assisted Pneumonia Rates

MECHANISM	INTERVENTIONS AND SELECTED REFERENCES	IMPACT ON DURATION OF MECHANICAL VENTILATION AND/OR MORTALITY[a]
Avoid intubation	Noninvasive positive pressure ventilation[266]	Lower mortality rates
Minimize duration of intubation[b]	Ventilator weaning protocols[267–270]	Less time to extubation
	Daily spontaneous breathing trials[271,272]	Less time to extubation, possibly lower mortality rates
	Daily spontaneous awakening trials[271,273,274]	Less time to extubation, possibly lower mortality rates
	Early mobility[275–278]	Conflicting data
Decrease pathogen burden in the upper gastrointestinal and respiratory tract	Regular oral care with antiseptics, especially chlorhexidine[241,242]	May increase mortality rates
	Tooth brushing[279]	Insufficient data
	Selective digestive decontamination with topical and parenteral antibiotics[235,280,281]	Lower mortality rates
	Probiotics[282,283]	Insufficient data
	Saline instillation before tracheal suctioning[284]	Insufficient data
Decrease pathogen burden on endotracheal tubes	Silver-coated endotracheal tubes[285]	No impact
	Mucous shaving of the endotracheal tube[286]	Insufficient data
Decrease pooling, seepage, and aspiration of secretions	Elevation of the head of the bed[287]	Insufficient data
	Optimization of endotracheal tube cuff pressures[51]	Insufficient data
	Endotracheal tubes with ultrathin polyurethane cuff membranes[288–291]	Insufficient data
	Tapered endotracheal tube cuffs[291,292]	No impact
	Subglottic secretion drainage[236]	No impact

[a]Conclusions regarding impact on duration of mechanical ventilation and mortality drawn from Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014;35:915–936.
[b]These interventions have been shown to decrease average duration of mechanical ventilation, but their impact on ventilator-assisted pneumonia rates has not yet been adequately studied.

as duration of mechanical ventilation, intensive care length of stay, or hospital mortality.[231–234]

Given the risk of misclassification bias favoring the intervention arm in VAP prevention trials, studies reporting lower VAP rates should be interpreted with caution. Objective outcomes such as duration of mechanical ventilation, intensive care or hospital length of stay, mortality, and antibiotic dispensing are more credible and reliable metrics to measure the impact of prevention interventions. Table 301.6 lists selected interventions proposed to lower VAP rates. The only interventions that have been shown to affect the concrete outcomes listed earlier, however, are noninvasive positive pressure ventilation, ventilator weaning protocols (especially paired daily sedative interruptions and spontaneous breathing trials), and selective oral and digestive decontamination.[234–236] Digestive decontamination has not been widely adopted owing to concern that the intervention will increase *C. difficile*–associated diarrhea and antibiotic resistance rates; the latter does not appear to be a concern in ICUs with low baseline resistance rates but has not yet been adequately studied in ICUs with high baseline resistance rates.[237–239] Additional interventions, such as elevation of the head of the bed in patients receiving enteral nutrition and optimizing endotracheal tube cuff pressures, appear promising but have not yet been sufficiently studied to affirm an impact on objective patient outcomes.[240] Emerging evidence suggests the possibility that routine oral care with chlorhexidine may be harmful in ventilated patients. Two meta-analyses of randomized, controlled trials and one large observational study have reported a possible association with increased mortality rates.[240–242]

Ventilator-Associated Pneumonia Prevention Bundles

Grouping multiple interventions (see Table 301.6) into VAP prevention "bundles" may enhance their effectiveness by exploiting synergies between interventions (e.g., conducting spontaneous breathing trials during spontaneous awakening trials to maximize patients' capacity for participation) or by enhancing their visibility, immediacy, and hence performance by frontline providers.[243] VAP prevention bundles have become a standard of care in most hospitals, but there is wide variability in their components and definitions for adherence.[244] Nonetheless, many hospitals have reported substantial and sustained drops in VAP rates after bundle implementations.[245–247] Very few hospitals have reported improvements in ventilator days, hospital length of stay, or mortality rates, however, raising concern that some of the apparent decline in VAP may be due to surveillance bias.[21] Bundles have mostly been studied in unblinded, longitudinal observational studies that compare rates before and after implementation. Lack of blinding and surveyors' expectations of what effect bundles should be having on VAP rates may have influenced their interpretations of ambiguous clinical signs.[21]

VENTILATOR-ASSISTED PNEUMONIA AS A QUALITY METRIC

The complexity, subjectivity, and questionable accuracy of VAP surveillance definitions have limited the utility of VAP as a metric to measure and compare quality of care across hospitals. These concerns prompted the CDC to develop a new framework called ventilator-associated events (VAEs) to measure quality of care for ventilated patients.[248,249] VAEs broaden the focus of surveillance from pneumonia alone to complications of mechanical ventilation in general. The new system includes a hierarchy of definitions that use quantitative criteria to make surveillance more objective, reproducible, and potentially electronic. The first tier of the VAE definition set flags episodes of nosocomial respiratory deterioration ("ventilator-associated conditions" [VACs]) on the basis of sustained increases in ventilator settings. The second tier seeks to identify the subset of VACs that may be infection related ("infection-related ventilator-associated complications" [IVACs]) on the basis of concurrent abnormalities in temperature or white blood cell count and sustained new antibiotic starts. The third tier flags IVACs that might be possible VAPs on the basis of culture results and Gram stain neutrophil counts.[106,250,251] VAEs are strongly associated with increased morbidity, mortality, and antibiotic utilization.[69,106,250–253] The crude mortality rate in patients with VAEs is 31%.[254]

There is limited overlap between VAEs and traditionally defined VAP; by design, VAEs focus on an expanded set of ICU complications and include only pneumonias that required a sustained increase in ventilator support.[255,256] The most common clinical events that trigger VAEs include pneumonia, volume overload, atelectasis, and ARDS.[251,257,258] Risk factors for VAEs include prolonged mechanical ventilation; deep sedation, particularly with benzodiazepines; positive fluid balance; red blood cell transfusions; and high tidal volume ventilation.[250,259–262] Strategies to prevent VAEs therefore include avoiding intubation, minimizing sedation, pairing daily spontaneous awakening with spontaneous breathing trials, using intravenous fluids conservatively to maintain euvolemia, ventilating with low tidal volumes, and setting conservative thresholds for blood transfusions.[262–265]

Key References

The complete reference list is available online at Expert Consult.

9. Chalmers JD, Rother C, Salih W, et al. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis*. 2014;58:330–339.
20. Metersky ML, Wang Y, Klompas M, et al. Trend in ventilator-associated pneumonia rates between 2005 and 2013. *JAMA*. 2016;316:2427–2429.
26. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198–1208.
28. Baker D, Quinn B. Hospital Acquired Pneumonia Prevention Initiative-2: incidence of nonventilator hospital-acquired pneumonia in the United States. *Am J Infect Control*. 2018;46:2–7.
45. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis*. 2013;13:665–671.
69. Bouadma L, Sonneville R, Garrouste-Orgeas M, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. *Crit Care Med*. 2015;43:1798–1806.
73. Tejerina E, Esteban A, Fernandez-Segoviano P, et al. Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. *J Crit Care*. 2010;25:62–68.
85. Claessens YE, Debray MP, Tubach F, et al. Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. *Am J Respir Crit Care Med*. 2015;192:974–982.
94. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.
97. Raman K, Nailor MD, Nicolau DP, et al. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med*. 2013;41:1656–1663.
106. Klompas M, Magill S, Robicsek A, et al. Objective surveillance definitions for ventilator-associated pneumonia. *Crit Care Med*. 2012;40:3154–3161.
107. Klompas M, Li L, Menchaca JT, et al; Centers for Disease C, Prevention Epicenters P. Ultra-short-course antibiotics for patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings. *Clin Infect Dis*. 2017;64:870–876.
115. Chow EJ, Mermel LA. Hospital-acquired respiratory viral infections: incidence, morbidity, and mortality in pediatric and adult patients. *Open Forum Infect Dis*. 2017;4:ofx006.
116. Shorr AF, Zilberberg MD, Micek ST, et al. Viruses are prevalent in non-ventilated hospital-acquired pneumonia. *Respir Med*. 2017;122:76–80.
121. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med*. 2006;355:2619–2630.
122. Berton DC, Kalil AC, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2012;(1):CD006482.
125. Hyllienmark P, Martling CR, Struwe J, et al. Pathogens in the lower respiratory tract of intensive care unit patients: impact of duration of hospital care and mechanical ventilation. *Scand J Infect Dis*. 2012;44:444–452.
139. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
162. Tamma PD, Avdic E, Li DX, et al. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med*. 2017;177:1308–1315.
163. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis*. 2012;12:774–780.
164. Ramsamy Y, Muckart DJ, Bruce JL, et al. Empirical antimicrobial therapy for probable v. directed therapy for possible ventilator-associated pneumonia in critically injured patients. *S Afr Med J*. 2016;106:196–200.
168. European Center for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In: ECDC, ed. *Annual Epidemiological Report for 2015*. Stockholm: ECDC; 2017.
173. Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). *Eur Respir J*. 2017;50.
178. Kalil AC, Klompas M, Haynatzki G, et al. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. *BMJ Open*. 2013;3:e003912.
188. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
190. Ruiz-Ramos J, Vidal-Cortes P, Diaz-Lamas A, et al. Ventilator-associated pneumonia by methicillin-susceptible *Staphylococcus aureus*: do minimum inhibitory concentrations to vancomycin and daptomycin matter? *Eur J Clin Microbiol Infect Dis*. 2017;36:1569–1575.
200. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. *JAMA*. 2012;307:2390–2399.
201. Aarts MA, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2008;36:108–117.
203. Ong DSY, Frencken JF, Klein Klouwenberg PMC, et al. Short-course adjunctive gentamicin as empirical therapy in patients with severe sepsis and septic shock: a prospective observational cohort study. *Clin Infect Dis*. 2017;64:1731–1736.
204. Heyland DK, Dodek P, Muscedere J, et al. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med*. 2008;36:737–744.
206. Rello J, Rouby JJ, Sole-Lleonart C, et al. Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients. *Clin Microbiol Infect*. 2017;23:640–646.
208. Zampieri FG, Nassar AP Jr, Gusmao-Flores D, et al. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care*. 2015;19:150.
209. Sole-Lleonart C, Rouby JJ, Blot S, et al. Nebulization of antiinfective agents in invasively mechanically ventilated adults: a systematic review and meta-analysis. *Anesthesiology*. 2017;126:890–908.
212. Rello J, Sole-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect*. 2017;23:629–639.
223. 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.
224. Pugh R, Grant C, Cooke RP, et al. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev*. 2015;(8):CD007577.
228. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis*. 2016;16:819–827.
229. Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis*. 2018;18:95–107.
234. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:915–936.
235. Roquilly A, Marret E, Abraham E, et al. Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis. *Clin Infect Dis*. 2015;60:64–75.
236. Caroff DA, Li L, Muscedere J, et al. Subglottic secretion drainage and objective outcomes: a systematic review and meta-analysis. *Crit Care Med*. 2016;44:830–840.
237. Daneman N, Sarwar S, Fowler RA, et al. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13:328–341.
240. Klompas M, Li L, Kleinman K, et al. Associations between ventilator bundle components and outcomes. *JAMA Intern Med*. 2016;176:1277–1283.
241. Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ*. 2014;348:g2197.
242. Klompas M, Speck K, Howell MD, et al. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med*. 2014;174:751–761.
249. Magill SS, Klompas M, Balk R, et al. Developing a new, national approach to surveillance for ventilator-associated events. *Crit Care Med*. 2013;41:2467–2475.
254. Magill SS, Li Q, Gross C, et al. Incidence and characteristics of ventilator-associated events reported to the National Healthcare Safety Network in 2014. *Crit Care Med*. 2016;44:2154–2162.
262. Mekontso Dessap A, Katsahian S, Roche-Campo F, et al. Ventilator-associated pneumonia during weaning from mechanical ventilation: role of fluid management. *Chest*. 2014;146:58–65.
263. Klompas M, Anderson D, Trick W, et al. The preventability of ventilator-associated events. The CDC prevention epicenters wake up and breathe collaborative. *Am J Respir Crit Care Med*. 2015;191:292–301.
271. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371:126–134.

References

1. Gaynes R. Health care–associated bloodstream infections: a change in thinking. *Ann Intern Med*. 2002;137:850–851.
2. El-Solh AA, Sikka P, Ramadan F, et al. Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):645–651.
3. El-Solh AA, Aquilina AT, Dhillon RS, et al. Impact of invasive strategy on management of antimicrobial treatment failure in institutionalized older people with severe pneumonia. *Am J Respir Crit Care Med*. 2002;166:1038–1043.
4. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137:791–797.
5. 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.
6. Shorr AF, Zilberberg MD, Micek ST, et al. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med*. 2008;168:2205–2210.
7. Ewig S, Welte T, Chastre J, et al. Rethinking the concepts of community-acquired and health-care-associated pneumonia. *Lancet Infect Dis*. 2010;10:279–287.
8. Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? *Curr Opin Infect Dis*. 2012;25:166–175.
9. Chalmers JD, Rother C, Salih W, et al. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis*. 2014;58:330–339.
10. Shorr AF, Zilberberg MD, Reichley R, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis*. 2012;54:193–198.
11. Giannella M, Pinilla B, Capdevila JA, et al. Pneumonia treated in the internal medicine department: focus on healthcare-associated pneumonia. *Clin Microbiol Infect*. 2012;18:786–794.
12. Lim WS, Macfarlane JT. A prospective comparison of nursing home acquired pneumonia with community acquired pneumonia. *Eur Respir J*. 2001;18:362–368.
13. Ewig S, Klapdor B, Pletz MW, et al. Nursing-home-acquired pneumonia in Germany: an 8-year prospective multicentre study. *Thorax*. 2012;67:132–138.
14. Centers for Disease Control and Prevention. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control*. 2004;32:470–485.
15. Dudeck MA, Weiner LM, Allen-Bridson K, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, Device-associated module. *Am J Infect Control*. 2013;41:1148–1166.
16. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;36:309–332.
17. Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. *Am J Infect Control*. 2010;38:237–239.
18. Stevens JP, Kachniarz B, Wright SB, et al. When policy gets it right: variability in U.S. hospitals' diagnosis of ventilator-associated pneumonia. *Crit Care Med*. 2014;42:497–503.
19. Klompas M. Eight initiatives that misleadingly lower ventilator-associated pneumonia rates. *Am J Infect Control*. 2012;40:408–410.
20. Metersky ML, Wang Y, Klompas M, et al. Trend in ventilator-associated pneumonia rates between 2005 and 2013. *JAMA*. 2016;316:2427–2429.
21. Coello R, Brannigan E, Lawson W, et al. Prevalence of healthcare device-associated infection using point prevalence surveys of antimicrobial prescribing and existing electronic data. *J Hosp Infect*. 2011;78:264–268.
22. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302:2323–2329.
23. Koulenti D, Lisboa T, Brun-Buisson C, et al. Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units. *Crit Care Med*. 2009;37:2360–2368.
24. Fihman V, Messika J, Hajage D, et al. Five-year trends for ventilator-associated pneumonia: correlation between microbiological findings and antimicrobial drug consumption. *Int J Antimicrob Agents*. 2015;46:518–525.
25. Nora D, Povoa P. Antibiotic consumption and ventilator-associated pneumonia rates, some parallelism but some discrepancies. *Ann Transl Med*. 2017;5:450.
26. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198–1208.
27. Giuliano KK, Baker D, Quinn B. The epidemiology of nonventilator hospital-acquired pneumonia in the United States. *Am J Infect Control*. 2017.
28. Baker D, Quinn B. Hospital Acquired Pneumonia Prevention Initiative-2: incidence of nonventilator hospital-acquired pneumonia in the United States. *Am J Infect Control*. 2018;46:2–7.
29. Beyersmann J, Gastmeier P, Grundmann H, et al. Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. *Infect Control Hosp Epidemiol*. 2006;27:493–499.
30. 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.
31. Melsen WG, Rovers MM, Bonten MJ. Ventilator-associated pneumonia and mortality: a systematic review of observational studies. *Crit Care Med*. 2009;37:2709–2718.
32. Sopena N, Sabria M. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest*. 2005;127:213–219.
33. Valles J, Mesalles E, Mariscal D, et al. A 7-year study of severe hospital-acquired pneumonia requiring ICU admission. *Intensive Care Med*. 2003;29:1981–1988.
34. Micek ST, Chew B, Hampton N, et al. A case-control study assessing the impact of nonventilated hospital-acquired pneumonia on patient outcomes. *Chest*. 2016;150:1008–1014.
35. Heyland DK, Cook DJ, Griffith L, et al. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. *Am J Respir Crit Care Med*. 1999;159(4 Pt 1):1249–1256.
36. Bekaert M, Timsit JF, Vansteelandt S, et al. Attributable mortality of ventilator associated pneumonia: a reappraisal using causal analysis. *Am J Respir Crit Care Med*. 2011;184:1133–1139.
37. Fagon JY, Chastre J, Hance AJ, et al. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med*. 1993;94:281–288.
38. Rello J, Quintana E, Ausina V, et al. Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest*. 1991;100:439–444.
39. Papazian L, Bregeon F, Thirion X, et al. Effect of ventilator-associated pneumonia on mortality and morbidity. *Am J Respir Crit Care Med*. 1996;154:91–97.
40. Fagon JY, Chastre J, Vuagnat A, et al. Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA*. 1996;275:866–869.
41. Nguile-Makao M, Zahar JR, Francais A, et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. *Intensive Care Med*. 2010;36:781–789.
42. Wolkewitz M, Beyersmann J, Gastmeier P, et al. Modeling the effect of time-dependent exposure on intensive care unit mortality. *Intensive Care Med*. 2009;35:826–832.
43. Schumacher M, Wangler M, Wolkewitz M, et al. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. *Methods Inf Med*. 2007;46:595–600.
44. Melsen WG, Rovers MM, Koeman M, et al. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med*. 2011;39:2736–2742.
45. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis*. 2013;13:665–671.
46. Rouby JJ, Martin De Lassale E, Poete P, et al. Nosocomial bronchopneumonia in the critically ill. Histologic and bacteriologic aspects. *Am Rev Respir Dis*. 1992;146:1059–1066.
47. Jonker MA, Sauerhammer TM, Faucher LD, et al. Bilateral versus Unilateral Bronchoalveolar Lavage for the Diagnosis of Ventilator-Associated Pneumonia. *Surg Infect (Larchmt)*. 2012.
48. Fabregas N, Torres A, El-Ebiary M, et al. Histopathologic and microbiologic aspects of ventilator-associated pneumonia. *Anesthesiology*. 1996;84:760–771.
49. Estes RJ, Meduri GU. The pathogenesis of ventilator-associated pneumonia: I. Mechanisms of bacterial transcolonization and airway inoculation. *Intensive Care Med*. 1995;21:365–383.
50. File TM Jr, Tan JS, Thomson RB Jr, et al. An outbreak of *Pseudomonas aeruginosa* ventilator-associated respiratory infections due to contaminated food coloring dye–further evidence of the significance of gastric colonization preceding nosocomial pneumonia. *Infect Control Hosp Epidemiol*. 1995;16:417–418.
51. Nseir S, Zerimech F, Fournier C, et al. Continuous control of tracheal cuff pressure and microaspiration of gastric contents in critically ill patients. *Am J Respir Crit Care Med*. 2011;184:1041–1047.
52. Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA*. 2011;306:2594–2605.
53. Caroff DA, Szumita PM, Klompas M. The relationship between sedatives, sedative strategy, and healthcare-associated infection: a systematic review. *Infect Control Hosp Epidemiol*. 2016;37:1234–1242.
54. Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA*. 1993;270:1965–1970.
55. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med*. 1998;129:433–440.
56. Tejada Artigas A, Bello Dronda S, Chacon Valles E, et al. Risk factors for nosocomial pneumonia in critically ill trauma patients. *Crit Care Med*. 2001;29:304–309.
57. Ibrahim EH, Tracy L, Hill C, et al. The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. *Chest*. 2001;120:555–561.
58. Akca O, Koltka K, Uzel S, et al. Risk factors for early-onset, ventilator-associated pneumonia in critical care patients: selected multiresistant versus nonresistant bacteria. *Anesthesiology*. 2000;93:638–645.
59. Metheny NA, Clouse RE, Chang YH, et al. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. *Crit Care Med*. 2006;34:1007–1015.
60. Bornstain C, Azoulay E, De Lassence A, et al. Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clin Infect Dis*. 2004;38:1401–1408.
61. Torres A, Serra-Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med*. 1992;116:540–543.
62. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet*. 1999;354:1851–1858.
63. Herzig SJ, Howell MD, Ngo LH, et al. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301:2120–2128.
64. Ewig S, Torres A, El-Ebiary M, et al. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 1999;159:188–198.
65. Jaillette E, Nseir S. Relationship between inhaled beta(2)-agonists and ventilator-associated pneumonia: a cohort study. *Crit Care Med*. 2011;39:725–730.
66. Tejerina E, Frutos-Vivar F, Restrepo MI, et al. Incidence, risk factors, and outcome of ventilator-associated pneumonia. *J Crit Care*. 2006;21:56–65.
67. Hugonnet S, Uckay I, Pittet D. Staffing level: a determinant of late-onset ventilator-associated pneumonia. *Crit Care*. 2007;11:R80.
68. Bercault N, Wolf M, Runge I, et al. Intrahospital transport of critically ill ventilated patients: a risk factor for ventilator-associated pneumonia–a matched cohort study. *Crit Care Med*. 2005;33:2471–2478.
69. Bouadma L, Sonneville R, Garrouste-Orgeas M, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. *Crit Care Med*. 2015;43:1798–1806.
70. Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. *Am J Infect Control*. 2011;39:798–816.
71. Osler W. *The Principles and Practices of Medicine*. 6th ed. New York, NY: Appleton & Co.; 1907.
72. Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review. *Histopathology*. 2005;47:551–559.
73. Tejerina E, Esteban A, Fernandez-Segoviano P, et al. Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. *J Crit Care*. 2010;25:62–68.
74. Petersen IS, Aru A, Skodt V, et al. Evaluation of pneumonia diagnosis in intensive care patients. *Scand J Infect Dis*. 1999;31:299–303.
75. Wunderink RG, Woldenberg LS, Zeiss J, et al. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. *Chest*. 1992;101:458–463.

76. Rao VK, Ritter J, Kollef MH. Utility of transbronchial biopsy in patients with acute respiratory failure: a postmortem study. *Chest*. 1998;114:549–555.
77. Meduri GU, Mauldin GL, Wunderink RG, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest*. 1994;106:221–235.
78. Rouby JJ, Rossignon MD, Nicolas MH, et al. A prospective study of protected bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. *Anesthesiology*. 1989;71:679–685.
79. Marquette CH, Copin MC, Wallet F, et al. Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am J Respir Crit Care Med*. 1995;151:1878–1888.
80. Bregeon F, Papazian L, Thomas P, et al. Diagnostic accuracy of protected catheter sampling in ventilator-associated bacterial pneumonia. *Eur Respir J*. 2000;16:969–975.
81. Balthazar AB, Von Nowakonski A, De Capitani EM, et al. Diagnostic investigation of ventilator-associated pneumonia using bronchoalveolar lavage: comparative study with a postmortem lung biopsy. *Braz J Med Biol Res*. 2001;34:993–1001.
82. Kirtland SH, Corley DE, Winterbauer RH, et al. The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. *Chest*. 1997;112:445–457.
83. Winer-Muram HT, Steiner RM, Gurney JW, et al. Ventilator-associated pneumonia in patients with adult respiratory distress syndrome: CT evaluation. *Radiology*. 1998;208:193–199.
84. Butler KL, Sinclair KE, Henderson VJ, et al. The chest radiograph in critically ill surgical patients is inaccurate in predicting ventilator-associated pneumonia. *Am Surg*. 1999;65:805–809, discussion 809–810.
85. Claessens YE, Debray MP, Tubach F, et al. Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. *Am J Respir Crit Care Med*. 2015;192:974–982.
86. Self WH, Courtney DM, McNaughton CD, et al. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. *Am J Emerg Med*. 2013;31:401–405.
87. Roberts IS, Benamore RE, Benbow EW, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet*. 2012;379:136–142.
88. Johanson WG, Dever LL. Nosocomial pneumonia. *Intensive Care Med*. 2003;29:23–29.
89. O'Horo JC, Thompson D, Safdar N. Is the gram stain useful in the microbiologic diagnosis of VAP? A meta-analysis. *Clin Infect Dis*. 2012;55:551–561.
90. Niederman MS. The argument against using quantitative cultures in clinical trials and for the management of ventilator-associated pneumonia. *Clin Infect Dis*. 2010;51(suppl 1):S93–S99.
91. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax*. 1999;54:867–873.
92. Papazian L, Thomas P, Garbe L, et al. Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 1995;152(6 Pt 1):1982–1991.
93. Torres A, Fabregas N, Ewig S, et al. Sampling methods for ventilator-associated pneumonia: validation using different histologic and microbiological references. *Crit Care Med*. 2000;28:2799–2804.
94. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.
95. Timsit JF, Chevret S, Valcke J, et al. Mortality of nosocomial pneumonia in ventilated patients: influence of diagnostic tools. *Am J Respir Crit Care Med*. 1996;154:116–123.
96. Muscedere JG, McColl C, Shorr A, et al. Determinants of outcome in patients with a clinical suspicion of ventilator-associated pneumonia. *J Crit Care*. 2008;23:41–49.
97. Raman K, Nailor MD, Nicolau DP, et al. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med*. 2013;41:1656–1663.
98. Pugin J, Auckenthaler R, Mili N, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1991;143(5 Pt 1):1121–1129.
99. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, et al. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. *Intensive Care Med*. 2004;30:217–224.
100. Lauzier F, Ruest A, Cook D, et al. The value of pretest probability and modified clinical pulmonary infection score to diagnose ventilator-associated pneumonia. *J Crit Care*. 2008;23:50–57.
101. Fartoukh M, Maitre B, Honore S, et al. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. *Am J Respir Crit Care Med*. 2003;168:173–179.
102. Luyt CE, Chastre J, Fagon JY. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. *Intensive Care Med*. 2004;30:844–852.
103. Zilberberg MD, Shorr AF. Ventilator-associated pneumonia: the clinical pulmonary infection score as a surrogate for diagnostics and outcome. *Clin Infect Dis*. 2010;51(suppl 1):S131–S135.
104. Croce MA, Swanson JM, Magnotti LJ, et al. The futility of the clinical pulmonary infection score in trauma patients. *J Trauma*. 2006;60:523–527, discussion 527–528.
105. Klompas M, Platt R. Ventilator-associated pneumonia–the wrong quality measure for benchmarking. *Ann Intern Med*. 2007;147:803–805.
106. Klompas M, Magill S, Robicsek A, et al. Objective surveillance definitions for ventilator-associated pneumonia. *Crit Care Med*. 2012;40:3154–3161.
107. Klompas M, Li L, Menchaca JT, et al; Centers for Disease C, Prevention Epicenters P. Ultra-short-course antibiotics for patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings. *Clin Infect Dis*. 2017;64:870–876.
108. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118:146–155.
109. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest*. 2002;122:262–268.
110. Kuti EL, Patel AA, Coleman CI. Impact of inappropriate antibiotic therapy on mortality in patients with ventilator-associated pneumonia and blood stream infection: a meta-analysis. *J Crit Care*. 2008;23:91–100.
111. Muscedere JG, Shorr AF, Jiang X, et al. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: an important determinant of outcome. *J Crit Care*. 2012;27:322 e327–322 e314.
112. Garbino J, Soccal PM, Aubert JD, et al. Respiratory viruses in bronchoalveolar lavage: a hospital-based cohort study in adults. *Thorax*. 2009;64:399–404.
113. Choi SH, Hong SB, Ko GB, et al. Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med*. 2012;186:325–332.
114. Jouneau S, Poineuf JS, Minjolle S, et al. Which patients should be tested for viruses on bronchoalveolar lavage fluid? *Eur J Clin Microbiol Infect Dis*. 2012.
115. Chow EJ, Mermel LA. Hospital-acquired respiratory viral infections: incidence, morbidity, and mortality in pediatric and adult patients. *Open Forum Infect Dis*. 2017;4:ofx006.
116. Shorr AF, Zilberberg MD, Micek ST, et al. Viruses are prevalent in non-ventilated hospital-acquired pneumonia. *Respir Med*. 2017;122:76–80.
117. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. *Am J Respir Crit Care Med*. 1998;157:371–376.
118. Sole Violan J, Fernandez JA, Benitez AB, et al. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. *Crit Care Med*. 2000;28:2737–2741.
119. Ruiz M, Torres A, Ewig S, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. *Am J Respir Crit Care Med*. 2000;162:119–125.
120. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med*. 2000;132:621–630.
121. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med*. 2006;355:2619–2630.
122. Berton DC, Kalil AC, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2012;(1):CD006482.
123. Pereira Gomes JC, Pedreira WL Jr, Araujo EM, et al. Impact of BAL in the management of pneumonia with treatment failure: positivity of BAL culture under antibiotic therapy. *Chest*. 2000;118:1739–1746.
124. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. *Chest*. 1998;113:412–420.
125. Hyllienmark P, Martling CR, Struwe J, et al. Pathogens in the lower respiratory tract of intensive care unit patients: impact of duration of hospital care and mechanical ventilation. *Scand J Infect Dis*. 2012;44:444–452.
126. Rello J, Torres A, Ricart M, et al. Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. *Am J Respir Crit Care Med*. 1994;150(6 Pt 1):1545–1549.
127. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165:867–903.
128. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med*. 1998;157:531–539.
129. Dore P, Robert R, Grollier G, et al. Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. *Am J Respir Crit Care Med*. 1996;153(4 Pt 1):1292–1298.
130. el-Ebiary M, Torres A, Fabregas N, et al. Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. *Am J Respir Crit Care Med*. 1997;156(2 Pt 1):583–590.
131. Meersseman W, Lagrou K, Spriet I, et al. Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study. *Intensive Care Med*. 2009;35:1526–1531.
132. Lambotte O, Timsit JF, Garrouste-Orgeas M, et al. The significance of distal bronchial samples with commensals in ventilator-associated pneumonia: colonizer or pathogen? *Chest*. 2002;122:1389–1399.
133. Gastmeier P, Sohr D, Geffers C, et al. Early- and late-onset pneumonia: is this still a useful classification? *Antimicrob Agents Chemother*. 2009;53:2714–2718.
134. Giantsou E, Liratzopoulos N, Efraimidou E, et al. Both early-onset and late-onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. *Intensive Care Med*. 2005;31:1488–1494.
135. Verhamme KM, De Coster W, De Roo L, et al. Pathogens in early-onset and late-onset intensive care unit-acquired pneumonia. *Infect Control Hosp Epidemiol*. 2007;28:389–397.
136. Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. *N Engl J Med*. 1969;281:1137–1140.
137. Klevens RM, Edwards JR, Gaynes RP. The impact of antimicrobial-resistant, health care-associated infections on mortality in the United States. *Clin Infect Dis*. 2008;47:927–930.
138. Sanchez GV, Master RN, Clark RB, et al. *Klebsiella pneumoniae* antimicrobial drug resistance, United States, 1998-2010. *Emerg Infect Dis*. 2013;19:133–136.
139. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
140. Damas P, Layios N, Seidel L, et al. Severity of ICU-acquired pneumonia according to infectious microorganisms. *Intensive Care Med*. 2011;37:1128–1135.
141. Garnacho-Montero J, Ortiz-Leyba C, Fernandez-Hinojosa E, et al. *Acinetobacter baumannii* ventilator-associated pneumonia: epidemiological and clinical findings. *Intensive Care Med*. 2005;31:649–655.
142. Kollef MH, Silver P, Murphy DM, et al. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. *Chest*. 1995;108:1655–1662.
143. Zahar JR, Clec'h C, Tafflet M, et al. Is methicillin resistance associated with a worse prognosis in *Staphylococcus aureus* ventilator-associated pneumonia? *Clin Infect Dis*. 2005;41:1224–1231.
144. Shorr AF, Combes A, Kollef MH, et al. Methicillin-resistant *Staphylococcus aureus* prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. *Crit Care Med*. 2006;34:700–706.
145. Vidaur L, Planas K, Sierra R, et al. Ventilator-associated pneumonia: impact of organisms on clinical resolution

and medical resources utilization. *Chest*. 2008;133:625–632.

146. McClure JR, Cooke RP, Lal P, et al. Outcome of late-onset hospital-acquired pneumonia related to causative organism. *J Hosp Infect*. 2009;71:348–352.
147. Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia? *Chest*. 2010;137:1283–1288.
148. Mohan S, Hamid NS, Cunha BA. A cluster of nosocomial herpes simplex virus type 1 pneumonia in a medical intensive care unit. *Infect Control Hosp Epidemiol*. 2006;27:1255–1257.
149. Sartor C, Zandotti C, Romain F, et al. Disruption of services in an internal medicine unit due to a nosocomial influenza outbreak. *Infect Control Hosp Epidemiol*. 2002;23:615–619.
150. Centers for Disease Control and Prevention. Suspected nosocomial influenza cases in an intensive care unit. *MMWR Morb Mortal Wkly Rep*. 1988;37:3–4, 9.
151. Bartlett JG, O'Keefe P, Tally FP, et al. Bacteriology of hospital-acquired pneumonia. *Arch Intern Med*. 1986;146:868–871.
152. El-Solh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med*. 2003;167:1650–1654.
153. Bousbia S, Papazian L, Saux P, et al. Repertoire of intensive care unit pneumonia microbiota. *PLoS ONE*. 2012;7:e32486.
154. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest*. 1997;111:676–685.
155. Luna CM, Aruj P, Niederman MS, et al. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. *Eur Respir J*. 2006;27:158–164.
156. Klompas M. Does this patient have ventilator-associated pneumonia? *JAMA*. 2007;297:1583–1593.
157. Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA*. 2003;289:885–888.
158. Lewis GJ, Fang X, Gooch M, et al. Decreased resistance of *Pseudomonas aeruginosa* with restriction of ciprofloxacin in a large teaching hospital's intensive care and intermediate care units. *Infect Control Hosp Epidemiol*. 2012;33:368–373.
159. Lafaurie M, Porcher R, Donay JL, et al. Reduction of fluoroquinolone use is associated with a decrease in methicillin-resistant *Staphylococcus aureus* and fluoroquinolone-resistant *Pseudomonas aeruginosa* isolation rates: a 10 year study. *J Antimicrob Chemother*. 2012;67:1010–1015.
160. Swaminathan M, Sharma S, Poliansky Blash S, et al. Prevalence and risk factors for acquisition of carbapenem-resistant Enterobacteriaceae in the setting of endemicity. *Infect Control Hosp Epidemiol*. 2013;34:809–817.
161. Ogutlu A, Guclu E, Karabay O, et al. Effects of Carbapenem consumption on the prevalence of *Acinetobacter* infection in intensive care unit patients. *Ann Clin Microbiol Antimicrob*. 2014;13:7.
162. Tamma PD, Avdic E, Li DX, et al. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med*. 2017;177:1308–1315.
163. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis*. 2012;12:774–780.
164. Ramsamy Y, Muckart DJ, Bruce JL, et al. Empirical antimicrobial therapy for probable v. directed therapy for possible ventilator-associated pneumonia in critically injured patients. *S Afr Med J*. 2016;106:196–200.
165. 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.
166. Rello J, Sa-Borges M, Correa H, et al. Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. *Am J Respir Crit Care Med*. 1999;160:608–613.
167. Namias N, Samiian L, Nino D, et al. Incidence and susceptibility of pathogenic bacteria vary between intensive care units within a single hospital: implications for empiric antibiotic strategies. *J Trauma*. 2000;49:638–645, discussion 645-636.
168. European Center for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In: ECDC, ed. *Annual Epidemiological Report for 2015*. Stockholm: ECDC; 2017.
169. Michel F, Franceschini B, Berger P, et al. Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. *Chest*. 2005;127:589–597.
170. Jung B, Sebbane M, Chanques G, et al. Previous endotracheal aspirate allows guiding the initial treatment of ventilator-associated pneumonia. *Intensive Care Med*. 2009;35:101–107.
171. Chan JD, Dellit TH, Choudhuri JA, et al. Active surveillance cultures of methicillin-resistant *Staphylococcus aureus* as a tool to predict methicillin-resistant S. aureus ventilator-associated pneumonia. *Crit Care Med*. 2012;40:1437–1442.
172. Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. *Chest*. 1999;115:178–183.
173. Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). *Eur Respir J*. 2017;50.
174. Conte JE Jr, Golden JA, Kipps J, et al. Intrapulmonary pharmacokinetics of linezolid. *Antimicrob Agents Chemother*. 2002;46:1475–1480.
175. Fernandez-Barat L, Ferrer M, Sierra JM, et al. Linezolid limits burden of methicillin-resistant *Staphylococcus aureus* in biofilm of tracheal tubes. *Crit Care Med*. 2012;40:2385–2389.
176. Kalil AC, Murthy MH, Hermsen ED, et al. Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2010;38:1802–1808.
177. Sanchez Garcia M, De la Torre MA, Morales G, et al. Clinical outbreak of linezolid-resistant *Staphylococcus aureus* in an intensive care unit. *JAMA*. 2010;303:2260–2264.
178. Kalil AC, Klompas M, Haynatzki G, et al. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. *BMJ Open*. 2013;3:e003912.
179. Wunderink RG, Rello J, Cammarata SK, et al. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789–1797.
180. Kollef MH, Rello J, Cammarata SK, et al. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med*. 2004;30:388–394.
181. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54:621–629.
182. Alaniz C, Pogue JM. Vancomycin versus linezolid in the treatment of methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: implications of the ZEPHyR trial. *Ann Pharmacother*. 2012;46:1432–1435.
183. Patel N, Pai MP, Rodvold KA, et al. Vancomycin: we can't get there from here. *Clin Infect Dis*. 2011;52:969–974.
184. Haque NZ, Zuniga LC, Peyrani P, et al. Relationship of vancomycin minimum inhibitory concentration to mortality in patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired, ventilator-associated, or health-care-associated pneumonia. *Chest*. 2010;138:1356–1362.
185. Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis*. 2011;52:975–981.
186. Cano EL, Haque NZ, Welch VL, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. *Clin Ther*. 2012;34:149–157.
187. Luther MK, Timbrook TT, Caffrey AR, et al. Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. *Crit Care Med*. 2018;46:12–20.
188. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
189. Choi EY, Huh JW, Lim CM, et al. Relationship between the MIC of vancomycin and clinical outcome in patients with MRSA nosocomial pneumonia. *Intensive Care Med*. 2011;37:639–647.
190. Ruiz-Ramos J, Vidal-Cortes P, Diaz-Lamas A, et al. Ventilator-associated pneumonia by methicillin-susceptible *Staphylococcus aureus*: do minimum inhibitory concentrations to vancomycin and daptomycin matter? *Eur J Clin Microbiol Infect Dis*. 2017;36:1569–1575.
191. Machado DP, Goldani LZ, Paiva RM, et al. The impact of serum vancomycin levels and minimum inhibitory concentrations of methicillin-resistant *Staphylococcus aureus* on mortality in patients with nosocomial pneumonia. *Can J Infect Dis Med Microbiol*. 2013;24:e75–e79.
192. Pasquale TR, Tan MJ, Trienski TL, et al. Methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. *J Chemother*. 2013;1973947813Y0000000156.
193. Awad SS, Rodriguez AH, Chuang YC, et al. A Phase 3 Randomized Double-blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime plus Linezolid for the Treatment of Hospital-acquired Pneumonia. *Clin Infect Dis*. 2014;59:51–61.
194. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev*. 2012;25:450–470.
195. Micek ST, Lloyd AE, Ritchie DJ, et al. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. *Antimicrob Agents Chemother*. 2005;49:1306–1311.
196. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med*. 2007;35:1888–1895.
197. Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother*. 2010;54:1742–1748.
198. Chamot E, Boffi El Amari E, Rohner P, et al. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother*. 2003;47:2756–2764.
199. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med*. 2010;38:1773–1785.
200. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. *JAMA*. 2012;307:2390–2399.
201. Aarts MA, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2008;36:108–117.
202. Paul M, Lador A, Grozinsky-Glasberg S, et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2014;(1):CD003344.
203. Ong DSY, Frencken JF, Klein Klouwenberg PMC, et al. Short-course adjunctive gentamicin as empirical therapy in patients with severe sepsis and septic shock: a prospective observational cohort study. *Clin Infect Dis*. 2017;64:1731–1736.
204. Heyland DK, Dodek P, Muscedere J, et al. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med*. 2008;36:737–744.
205. Rouby JJ, Bouhemad B, Monsel A, et al. Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies. *Anesthesiology*. 2012;117:1364–1380.
206. Rello J, Rouby JJ, Sole-Lleonart C, et al. Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients. *Clin Microbiol Infect*. 2017;23:640–646.
207. Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. *Am J Respir Crit Care Med*. 2014;189:1225–1233.
208. Zampieri FG, Nassar AP Jr, Gusmao-Flores D, et al. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care*. 2015;19:150.
209. Sole-Lleonart C, Rouby JJ, Blot S, et al. Nebulization of antiinfective agents in invasively mechanically ventilated adults: a systematic review and meta-analysis. *Anesthesiology*. 2017;126:890–908.
210. Lu Q, Yang J, Liu Z, et al. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by

Pseudomonas aeruginosa. *Am J Respir Crit Care Med*. 2011;184:106–115.
211. Lu Q, Luo R, Bodin L, et al. Efficacy of High-dose Nebulized Colistin in Ventilator-associated Pneumonia Caused by Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology*. 2012;117:1335–1347.
212. Rello J, Sole-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect*. 2017;23:629–639.
213. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis*. 2011;11:181–189.
214. Ewig S. Nosocomial pneumonia: de-escalation is what matters. *Lancet Infect Dis*. 2011;11:155–157.
215. Niederman MS, Craven DE, Chastre J, et al. Treatment of hospital-acquired pneumonia. *Lancet Infect Dis*. 2011;11:728, author reply 731-722.
216. 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.
217. 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.
218. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med*. 2000;162(2 Pt 1):505–511.
219. Kollef MH, Morrow LE, Niederman MS, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest*. 2006;129:1210–1218.
220. 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.
221. Labelle AJ, Arnold H, Reichley RM, et al. A comparison of culture-positive and culture-negative health-care-associated pneumonia. *Chest*. 2010;137:1130–1137.
222. Joung MK, Lee JA, Moon SY, et al. Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia. *Crit Care*. 2011;15:R79.
223. 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.
224. Pugh R, Grant C, Cooke RP, et al. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev*. 2015;(8):CD007577.
225. Dimopoulos G, Poulakou G, Pneumatikos IA, et al. Short- versus long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. *Chest*. 2013;144:1759–1767.
226. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J*. 2009;34:1364–1375.
227. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375:463–474.
228. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis*. 2016;16:819–827.
229. Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis*. 2018;18:95–107.
230. Bouhemad B, Liu ZH, Arbelot C, et al. Ultrasound assessment of antibiotic-induced pulmonary reaeration in ventilator-associated pneumonia. *Crit Care Med*. 2010;38:84–92.
231. Klompas M. The paradox of ventilator-associated pneumonia prevention measures. *Crit Care*. 2009;13:315.
232. Bonten MJ. Healthcare epidemiology: Ventilator-associated pneumonia: preventing the inevitable. *Clin Infect Dis*. 2011;52:115–121.
233. Bouadma L, Wolff M, Lucet JC. Ventilator-associated pneumonia and its prevention. *Curr Opin Infect Dis*. 2012;25:395–404.
234. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:915–936.
235. Roquilly A, Marret E, Abraham E, et al. Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis. *Clin Infect Dis*. 2015;60:64–75.
236. Caroff DA, Li L, Muscedere J, et al. Subglottic secretion drainage and objective outcomes: a systematic review and meta-analysis. *Crit Care Med*. 2016;44:830–840.
237. Daneman N, Sarwar S, Fowler RA, et al. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13:328–341.
238. Oostdijk EA, de Smet AM, Bonten MJ. Effects of decontamination of the digestive tract and oropharynx in intensive care unit patients on 1-year survival. *Am J Respir Crit Care Med*. 2013;188:117–120.
239. Houben AJ, Oostdijk EA, van der Voort PH, et al. Selective decontamination of the oropharynx and the digestive tract, and antimicrobial resistance: a 4 year ecological study in 38 intensive care units in the Netherlands. *J Antimicrob Chemother*. 2014;69:797–804.
240. Klompas M, Li L, Kleinman K, et al. Associations between ventilator bundle components and outcomes. *JAMA Intern Med*. 2016;176:1277–1283.
241. Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ*. 2014;348:g2197.
242. Klompas M, Speck K, Howell MD, et al. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med*. 2014;174:751–761.
243. Resar R, Pronovost P, Haraden C, et al. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Jt Comm J Qual Patient Saf*. 2005;31:243–248.
244. Klompas M. Ventilator-associated pneumonia: is zero possible? *Clin Infect Dis*. 2010;51:1123–1126.
245. Bouadma L, Deslandes E, Lolom I, et al. Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. *Clin Infect Dis*. 2010;51:1115–1122.
246. Berenholtz SM, Pham JC, Thompson DA, et al. Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the intensive care unit. *Infect Control Hosp Epidemiol*. 2011;32:305–314.
247. Rosenthal VD, Rodrigues C, Alvarez-Moreno C, et al. Effectiveness of a multidimensional approach for prevention of ventilator-associated pneumonia in adult intensive care units from 14 developing countries of 4 continents: findings of the International Nosocomial Infection Control Consortium (INICC). *Crit Care Med*. 2012;40:3121–3128.
248. Klompas M. Complications of mechanical ventilation–the CDC's new surveillance paradigm. *N Engl J Med*. 2013;368:1472–1475.
249. Magill SS, Klompas M, Balk R, et al. Developing a new, national approach to surveillance for ventilator-associated events. *Crit Care Med*. 2013;41:2467–2475.
250. Klompas M, Kleinman K, Murphy MV. Descriptive epidemiology and attributable morbidity of ventilator-associated events. *Infect Control Hosp Epidemiol*. 2014;35:502–510.
251. Klein Klouwenberg PM, van Mourik MS, Ong DS, et al. Electronic implementation of a novel surveillance paradigm for ventilator-associated events: feasibility and validation. *Am J Respir Crit Care Med*. 2014;189:947–955.
252. Muscedere J, Sinuff T, Heyland D, et al. The clinical impact and preventability of ventilator-associated conditions in critically ill mechanically ventilated patients. *Chest*. 2013;144:1453–1460.
253. Hayashi Y, Morisawa K, Klompas M, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. *Clin Infect Dis*. 2013;56:471–477.
254. Magill SS, Li Q, Gross C, et al. Incidence and characteristics of ventilator-associated events reported to the National Healthcare Safety Network in 2014. *Crit Care Med*. 2016;44:2154–2162.
255. Fan Y, Gao F, Wu Y, et al. Does ventilator-associated event surveillance detect ventilator-associated pneumonia in intensive care units? A systematic review and meta-analysis. *Crit Care*. 2016;20:338.
256. Klompas M. Ventilator-associated conditions versus ventilator-associated pneumonia: different by design. *Curr Infect Dis Rep*. 2014;16:430.
257. Klompas M, Khan Y, Kleinman K, et al. Multicenter Evaluation of a Novel Surveillance Paradigm for Complications of Mechanical Ventilation. *PLoS ONE*. 2011;6:e18062.
258. Boyer AF, Schoenberg N, Babcock H, et al. A prospective evaluation of ventilator-associated conditions and infection-related ventilator-associated conditions. *Chest*. 2015;147:68–81.
259. Klompas M, Li L, Szumita P, et al; Program CDCPE. Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated. *Chest*. 2016;149:1373–1379.
260. Ogbu OC, Martin GS, Sevransky JE, et al. High tidal volumes are independently associated with development of a ventilator-associated condition in the ICU. *Am J Respir Crit Care Med*. 2015;191:A3117.
261. Cocoros NM, Priebe G, Gray JE, et al. Factors associated with pediatric ventilator-associated conditions in six U.S. hospitals: a nested case-control study. *Pediatr Crit Care Med*. 2017;18:e536–e545.
262. Mekontso Dessap A, Katsahian S, Roche-Campo F, et al. Ventilator-associated pneumonia during weaning from mechanical ventilation: role of fluid management. *Chest*. 2014;146:58–65.
263. Klompas M, Anderson D, Trick W, et al. The preventability of ventilator-associated events. The CDC prevention epicenters wake up and breathe collaborative. *Am J Respir Crit Care Med*. 2015;191:292–301.
264. Rawat N, Yang T, Ali KJ, et al. Two-state collaborative study of a multifaceted intervention to decrease ventilator-associated events. *Crit Care Med*. 2017;45:1208–1215.
265. Klompas M. Potential strategies to prevent ventilator-associated events. *Am J Respir Crit Care Med*. 2015;192:1420–1430.
266. Burns KE, Meade MO, Premji A, et al. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. *CMAJ*. 2014;186:E112–E122.
267. Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med*. 1997;25:567–574.
268. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999;27:2609–2615.
269. Marelich GP, Murin S, Battistella F, et al. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. *Chest*. 2000;118:459–467.
270. Dries DJ, McGonigal MD, Malian MS, et al. Protocol-driven ventilator weaning reduces use of mechanical ventilation, rate of early reintubation, and ventilator-associated pneumonia. *J Trauma*. 2004;56:943–951, discussion 951-942.
271. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371:126–134.
272. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*. 1996;335:1864–1869.
273. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342:1471–1477.
274. Schweickert WD, Gehlbach BK, Pohlman AS, et al. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med*. 2004;32:1272–1276.
275. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373:1874–1882.
276. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. *JAMA*. 2016;315:2694–2702.
277. Wright SE, Thomas K, Watson G, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax*. 2017.
278. Schaller SJ, Anstey M, Blobner M, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet*. 2016;388:1377–1388.

279. Alhazzani W, Smith O, Muscedere J, et al. Toothbrushing for critically ill mechanically ventilated patients: a systematic review and meta-analysis of randomized trials evaluating ventilator-associated pneumonia. *Crit Care Med*. 2013;41:646–655.
280. 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.
281. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Notice of Retraction and Replacement: oostdijk et al. Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs: a Randomized Clinical Trial. *JAMA*. 2014;312:1429–1437. JAMA. 2017;317(15):1583-1584.
282. Siempos II, Ntaidou TK, Falagas ME. Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. *Crit Care Med*. 2010;38:954–962.
283. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. *Am J Respir Crit Care Med*. 2010;182:1058–1064.
284. Caruso P, Denari S, Ruiz SA, et al. Saline instillation before tracheal suctioning decreases the incidence of ventilator-associated pneumonia. *Crit Care Med*. 2009;37:32–38.
285. 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.
286. Berra L, Coppadoro A, Bittner EA, et al. A clinical assessment of the Mucus Shaver: a device to keep the endotracheal tube free from secretions. *Crit Care Med*. 2012;40:119–124.
287. Wang L, Li X, Yang Z, et al. Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. *Cochrane Database Syst Rev*. 2016;(1):CD009946.
288. Lorente L, Lecuona M, Jimenez A, et al. Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. *Am J Respir Crit Care Med*. 2007;176:1079–1083.
289. Poelaert J, Depuydt P, De Wolf A, et al. Polyurethane cuffed endotracheal tubes to prevent early postoperative pneumonia after cardiac surgery: a pilot study. *J Thorac Cardiovasc Surg*. 2008;135:771–776.
290. Blot SI, Rello J, Koulenti D. The value of polyurethane-cuffed endotracheal tubes to reduce microaspiration and intubation-related pneumonia: a systematic review of laboratory and clinical studies. *Crit Care*. 2016;20:203.
291. Philippart F, Gaudry S, Quinquis L, et al. Randomized intubation with polyurethane or conical cuffs to prevent pneumonia in ventilated patients. *Am J Respir Crit Care Med*. 2015;191:637–645.
292. Jaillette E, Girault C, Brunin G, et al. Impact of tapered-cuff tracheal tube on microaspiration of gastric contents in intubated critically ill patients: a multicenter cluster-randomized cross-over controlled trial. *Intensive Care Med*. 2017;43:1562–1571.

302 Health Care–Associated Urinary Tract Infections

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SHORT VIEW SUMMARY

Definitions
- Health care–associated urinary tract infection (UTI) refers to symptomatic UTI acquired in any institutional setting providing health care.
- Catheter-associated UTI (CAUTI) refers to symptomatic UTI in a patient currently or recently catheterized with an indwelling transurethral, suprapubic, intermittent, or external catheter.
- Catheter-associated bacteriuria is composed mostly of asymptomatic bacteriuria (ASB) but also includes CAUTI.
- In this chapter, "bacteriuria" encompasses both ASB and CAUTI. The terms *catheter-associated urinary tract infection* and *asymptomatic bacteriuria* are used when referring specifically to one of these conditions.

Epidemiology
- UTIs are the most commonly reported health care–associated infections in the United States. However, many reported CAUTIs are actually catheter-associated ASBs.
- 75% of UTIs acquired in the hospital are associated with urinary catheters.
- The incidence of bacteriuria associated with indwelling urethral catheterization with a closed drainage system is approximately 3% to 8% per day.
- The duration of catheterization is the most important risk factor for catheter-associated bacteriuria.
- Although bacteremia is a rare complication of catheter-associated bacteriuria, catheter-associated bacteriuria is so common that it is the most common source of gram-negative bacteremia in hospitalized patients.
- Catheter-associated bacteriuria is a frequent target for inappropriate antimicrobial therapy.

Microbiology
- Catheter-associated bacteriuria is caused by a broad range of bacteria, including *Escherichia coli, Pseudomonas aeruginosa, Klebsiella* spp., and *Enterococcus* spp.
- Many of these organisms are resistant to multiple antimicrobial agents.
- *Candida albicans* is also a common cause of catheter-associated funguria.

Diagnosis
- Significant bacteriuria: $\geq 10^3$ colony-forming units per milliliter (CFU/mL) in a symptomatic person is an indicator of CAUTI, whereas $\geq 10^5$ CFU/mL in an asymptomatic person is an indicator of ASB.
- The majority of patients with catheter-associated bacteriuria are asymptomatic, and signs and symptoms commonly associated with UTI, such as fever, dysuria, urgency, flank pain, or leukocytosis, are either nonspecific or not apparent in catheterized patients.
- In the catheterized patient, pyuria does not differentiate ASB from CAUTI, but its absence suggests that CAUTI is not the cause of symptoms.

Prevention
- Reducing exposure to urinary catheterization is the most effective way to prevent catheter-associated bacteriuria.
- A closed catheter drainage system is indicated in all catheterized patients who have an indwelling transurethral catheter.
- Routine use of antimicrobial-coated urinary catheters is not supported by available data.
- Routine use of systemic antimicrobial agents to prevent catheter-associated bacteriuria should be discouraged.
- Use of multiple infection control techniques and strategies simultaneously (*bundling*) is recommended.

Health Care–Associated Asymptomatic Bacteriuria
- Routine screening for and treatment of ASB in health care settings is discouraged, other than for pregnant women and patients undergoing urologic procedures that cause mucosal bleeding.
- Overtreatment of ASB is a major contributor to unnecessary antimicrobial use in acute and long-term care.

Management (See Table 302.7)
- Urine cultures should be obtained before treatment of CAUTI, ideally after catheter change.
- Recommended treatment duration for CAUTI ranges from 5 to 14 days, depending on the severity and choice of drug.

Fungal Urinary Tract Infection
- Asymptomatic health care–associated candiduria rarely requires treatment.

DEFINITIONS

Health care–associated urinary tract infection (UTI) refers to UTI that is acquired while a patient is receiving medical treatment in a health care setting.[1] The majority of health care–associated UTIs occur in patients whose urinary tracts are currently or were recently catheterized. All types of urinary catheters (indwelling, suprapubic, intermittent, and external or condom catheters) increase the risk of acquisition of bacteriuria and thus UTI. The focus of this chapter is on catheter-associated bacterial UTIs occurring in adults in hospitals and long-term care facilities (LTCFs). Candiduria, the most common type of health care–associated fungal UTI, is discussed in a separate section of the chapter.

There are major differences in the epidemiology, pathogenesis, treatment, and prevention of health care–associated UTI and acute uncomplicated cystitis, which are shown in Table 302.1. *Urinary tract infection* is a nonspecific term that generally refers to symptomatic bacterial or fungal infection of the bladder or kidney, or both, in a patient. Although this term is often used without regard to the presence or absence of urinary symptoms, a strict definition of UTI requires the presence of symptoms related to the urinary tract (Table 302.2). Unfortunately, *catheter-associated bacteriuria* is a nonspecific term frequently used in the urinary catheter literature that encompasses two more specific terms, *catheter-associated asymptomatic bacteriuria* (ASB) and *catheter-associated urinary tract infection* (CAUTI).[2] Catheter-associated bacteriuria is composed mostly of ASB, but in most publications one cannot discern what proportion of patients have CAUTI.

The relationship between ASB and CAUTI and other clinical outcomes remains unclear. Most patients with ASB do not progress to CAUTI, and factors that trigger a symptomatic event in patients with ASB are not known. Thus even though the presence of bacteriuria is presumably necessary for the development of CAUTI, the development of urinary

TABLE 302.1 Comparison of Uncomplicated Cystitis/Pyelonephritis and Health Care–Associated Urinary Tract Infections

	UNCOMPLICATED CYSTITIS AND PYELONEPHRITIS	HEALTH CARE–ASSOCIATED UTI
Age	Younger	Older
Sex	Female, rare in males	Male and female, female predominance
Main risk factor	Intercourse	Urinary catheter
Pathogenesis	Fecal organisms ascend urethra to bladder	Extraluminal: fecal organisms ascend catheter-urethra interface to bladder Intraluminal: fecal or exogenous (cross-infection) organisms enter drainage system that has been disconnected, ascend through catheter to bladder
Uropathogen virulence	More virulent: pyelonephritis > cystitis > ASB or fecal	Generally less virulent than in uncomplicated UTI
Microbiology	Single pathogen, usually *Escherichia coli;* yeast rare	Single (short-term catheter) to multiple (long-term catheter) organisms; diverse flora with gram-negatives, gram-positives, *Candida* spp.
Clinical	ASB in about 5% of women, but prevalence a function of culture frequency; transient, benign Cystitis: dysuria, frequency, or urgency Pyelonephritis: fever, back pain/tenderness	Catheter-associated bacteriuria in about 5% per day of catheterization; >90% is ASB, usually persistent, most do not progress to CAUTI CAUTI: fever, delirium, other nonspecific signs/symptoms, may have no lower tract symptoms
Diagnosis	ASB: $\geq 10^5$ CFU/mL Cystitis/pyelonephritis: $\geq 10^3$ CFU/mL	Catheter-associated ASB: $\geq 10^5$ CFU/mL CAUTI: $\geq 10^3$ CFU/mL
Resistance	Common but predictable; fluoroquinolone and trimethoprim/sulfamethoxazole resistance increasing; ESBL uropathogens more common	Multidrug resistance common and less predictable; ESBL uropathogens and fluoroquinolone resistance common; CRE uropathogens still uncommon in most places.
Treatment	Short-course (single-dose to 5-day regimen, depending on drug)	5- to 10-day regimen, depending on severity
Prevention	Education about risk factors; abstinence; antimicrobial prophylaxis	Reduce urinary catheterization; use condom or intermittent vs. indwelling urethral catheter; strict closed system with indwelling urethral catheter
Public health	Strains spread via food chain and within family units	Large reservoir of multidrug-resistant uropathogens; cross-infection a concern

ASB, Asymptomatic bacteriuria; *CAUTI,* catheter-associated urinary tract infection; *CRE,* carbapenem-resistant Enterobacteriaceae; *ESBL,* extended-spectrum β-lactamase; *UTI,* urinary tract infection.

TABLE 302.2 Definitions for Urinary Tract Infection Terminology

TERM	DEFINITION
Urinary tract infection (UTI)	Nonspecific term that generally refers to symptomatic bacterial or fungal infection of the urinary tract
Acute, uncomplicated cystitis	Symptomatic cystitis in a person with no signs or symptoms suggestive of infection outside the bladder
Catheter-associated bacteriuria	Presence of significant bacteriuria[a] in a catheterized or recently catheterized patient without regard to the presence or absence of urinary symptoms
Catheter-associated asymptomatic bacteriuria (ASB)	Presence of significant bacteriuria[a] in a catheterized or recently catheterized patient without symptoms referable to the urinary tract
Catheter-associated UTI (CAUTI)	Presence of significant bacteriuria[a] in a catheterized or recently catheterized patient with symptoms or signs referable to the urinary tract
Catheter-associated funguria	Presence of funguria in a catheterized or recently catheterized patient. Fungal colony counts have not been shown to be meaningful in interpreting the significance of funguria. Catheter-associated funguria should be distinguished as asymptomatic or symptomatic.

[a]Quantity of bacteria in the urine suggestive of infection rather than contamination (see text).

symptoms must require some facilitating event(s), such as tissue invasion, that we do not yet understand. On the other hand, even if ASB itself is benign, there are several reasons that may justify efforts to prevent it. For example, it may predispose the person to CAUTI through a common pathogenic pathway, in which case interventions that prevent ASB would be expected to prevent CAUTI. Additionally, catheter-associated bacteriuria (mostly ASB) is the source of many episodes of health care–associated bacteremia and may be associated with increased mortality,[3,4] although this latter point is controversial. In hospitals and LTCFs, catheter-associated bacteriuria represents a large reservoir of antimicrobial-resistant urinary pathogens in patients that increases the risk of cross-infection among catheterized patients. ASB also provides a scapegoat infection for physicians who have a low threshold for using antimicrobial therapy (inappropriately), and detection of ASB can terminate the diagnostic evaluation prematurely. The relationships between ASB and clinical outcomes, including CAUTI, are difficult to demonstrate in most studies, given the large sample sizes needed to demonstrate such a benefit.

Treatment of ASB is not recommended except in certain circumstances, such as pregnancy and urologic procedures that cause mucosal bleeding.[5] Antimicrobial treatment of ASB, particularly in catheterized persons, typically leads only to short-term suppression of bacteriuria, and clearly increases the likelihood of emergence of resistant urinary organisms.[6,7] Antimicrobial exposure also increases the patient's risk for developing *Clostridioides difficile* (formerly *Clostridium difficile*) colitis.[8] Bacteremia can arise from bacteriuria in patients with both ASB and CAUTI,[9] and at this point it is not possible to predict which patients with bacteriuria will develop bacteremia. Therefore a policy of widespread treatment of ASB is likely to be detrimental rather than beneficial. On the other hand, prevention of ASB might lead to fewer episodes of CAUTI, bacteremia, fever episodes, cross-infection, and inappropriate antimicrobial use. In fact, the greatest impact of effective CAUTI prevention interventions may be that removing unnecessary urinary catheters will also prevent episodes of ASB, and their sequelae, rather than the few episodes of CAUTI that occur in these patients. The subset of patients who have an ongoing need for urinary catheters for bladder drainage will be persistently bacteriuric. In these patients, CAUTI prevention efforts should focus on avoiding overdiagnosing CAUTI in patients who are asymptomatic and thus have ASB.

EPIDEMIOLOGY

Incidence and Prevalence

Approximately 75% of UTIs acquired in the hospital are associated with urinary catheters. In one study of 1453 health care–associated, symptomatic UTIs, 72% were CAUTIs and 28% were not catheter associated.[10] Almost half of the CAUTIs (45%) occurred among intensive care unit (ICU) patients. The National Healthcare Safety Network (NHSN) is the United States' national health care infection surveillance system, maintained by the Centers for Disease Control and Prevention (CDC). Of note, the current NHSN surveillance and reporting for UTI includes only CAUTI, and the only catheter type that meets surveillance definitions is the indwelling urethral (Foley) catheter; UTIs not associated with indwelling urinary catheters and episodes of ASB are not reported. Despite national emphasis on decreasing CAUTI, CAUTI rates did not

decrease between 2009 and 2014.[11] Whether the lack of change relates to changes in the surveillance definitions, which have changed often, or to an overall decrease in use of urinary catheters, thus shrinking the denominator, is unclear.[12] Per the 2015 NHSN report on device-related infections, which included data from calendar year 2013, the ratio of urinary catheter-days to patient-days decreased from the prior report in 2010.[13]

Urinary catheters are placed for different reasons in acute-care facilities and LTCFs. Common indications for urinary catheter use in acute care are discussed later under "Reduction of Unnecessary Catheterization" (see Table 302.6). Most of these patients are catheterized for only 2 to 4 days.[14] The most common appropriate reason for urinary catheterization in LTCFs is to relieve bladder outlet obstruction, and these catheters are often in place for years. Management of incontinence is no longer considered an appropriate justification for urinary catheterization.[15]

The incidence of bacteriuria associated with indwelling urethral catheterization with a closed drainage system is approximately 3% to 8% per day[16–18] and, thus, many patients catheterized for short periods of time and almost all those catheterized for a month or more will have catheter-associated bacteriuria. One month, or 30 days, is a convenient dividing line between short-term and long-term catheterization,[14] and it is used as such in this chapter, except where stated otherwise.

NHSN data from 2013–2014 showed the mean incidence of CAUTI per 1000 catheterized days was 1.3% to 4.8% in adult critical care units, 1.3% in inpatient medical-surgical wards, 2.0% to 2.5% in long-term acute care hospitals, and 2.6% in inpatient rehabilitation facilities.[13] Compared to data from 2012, CAUTI rates increased in the majority of critical care locations while decreasing in most non–critical care locations. Organisms causing CAUTI and reported to the NSHN are often resistant, with *Escherichia coli* fluoroquinolone resistance reported at 34.8% in 2014.[19]

CAUTI Risk Factors

The duration of catheterization is the most important risk factor for the development of catheter-associated bacteriuria.[14,20,21] Other risk factors for catheter-associated bacteriuria include the lack of systemic antimicrobial therapy, female sex, meatal colonization with uropathogens, microbial colonization of the drainage bag, catheter insertion outside the operating room, catheter care violations, absence of use of a drip chamber, rapidly fatal underlying illness, older age, diabetes mellitus, and elevated serum creatinine at the time of catheterization.[16,21–23] Risk factors in patients with health care–associated UTIs not associated with catheterization include other forms of instrumentation of the urinary tract. Many noncatheterized patients with health care–associated UTI are probably also at increased risk for UTI in the community, due to host behavioral or genetic factors associated with increased risk for UTI.[24]

Complications

Most episodes of catheter-associated bacteriuria occur in asymptomatic patients, with studies showing that less than one-fourth of patients with catheter-associated bacteriuria develop UTI symptoms.[25–28] In one study of 235 new cases of catheter-associated bacteriuria, more than 90% of the patients were asymptomatic and afebrile.[28] In another study of catheterized and bacteriuric female patients in an LTCF, the incidence of febrile episodes of possible urinary origin was only 1.1 episodes per 100 catheterized patient-days, and most of these episodes were low grade, lasted for less than a day, and resolved without antimicrobial treatment.[29]

However, as noted previously, there are significant consequences of catheter-associated bacteriuria. Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients.[30] Of 7217 episodes of bloodstream infection in acute-care hospitals across Canada, 21% were associated with the urinary tract; 71% of these episodes were associated with the presence of a urinary device.[31] However, one study of 1497 newly catheterized hospitalized patients found that only 1 of the 235 episodes of catheter-associated bacteriuria was unequivocally associated with secondary bloodstream infection.[28] Similarly, a retrospective cohort study of 444 episodes of catheter-associated bacteriuria in 308 patients found that only 3 episodes of bacteremia (0.7% of bacteriuric subjects) were directly attributed to bacteriuria.[32] Both of these studies demonstrated that bacteremia in catheterized patients can arise from either CAUTI or ASB (i.e., with or without urinary tract symptoms). Risk factors for urinary catheter–associated bacteremia include male sex, immunosuppression, and urinary tract procedures.[33] Urinary tract organisms are also the most common source of bacteremia in LTCFs, accounting for 40% to 55% of bacteremias,[34,35] and bacteremia is often polymicrobial in these patients.

Patients undergoing long-term indwelling catheterization, in addition to almost universal polymicrobial bacteriuria, may develop symptomatic lower and upper UTI, bacteremia, frequent febrile episodes, catheter obstruction, renal and bladder stone formation associated with urease-producing uropathogens, local genitourinary infections, fistula formation, incontinence, and bladder cancer.[14] Chronic renal inflammation and pyelonephritis are often found at autopsy in patients who had been on long-term urinary catheterization, many of whom were afebrile at the time of death.[36] Catheter blockage can be a recurrent problem in long-term catheterized patients and results from encrustation formed by urease-producing organisms, especially *Proteus mirabilis,* which hydrolyze urea to ammonia with formation of struvite and apatite crystals in the catheter lumen.

The effect of catheter-associated bacteriuria, either CAUTI or ASB, on mortality remains controversial. Inability to fully adjust for confounding variables probably explains some of the association, because patients who require an indwelling catheter tend to be sicker or have comorbidities. A review and meta-analysis of the relationship of CAUTI (defined as bacteriuria) to mortality and length of stay in ICU patients found that CAUTI was associated with increases in both mortality and length of stay, but the significant association disappeared when the analysis was restricted to studies that adjusted for other predictors of mortality.[37] Increased mortality has also been reported in residents of LTCFs with chronic indwelling catheters,[38] but catheterized patients in long-term care also tend to be sicker and more functionally impaired.[39,40]

One of the most serious adverse effects of catheter-associated bacteriuria is that bacteriuria is a frequent target for unnecessary antimicrobial therapy, which contributes to the problem of antimicrobial resistance in hospitals and LTCFs. Inappropriate treatment of ASB in hospitalized patients is well documented. For example, in a prospective, multicenter study of inpatients, 72% of 961 patients with ASB were treated with antimicrobial therapy unnecessarily.[41] Of those treated inappropriately, 14% received over 14 days of antimicrobials. Inappropriate treatment is associated with older age, predominantly gram-negative bacteriuria, and pyuria.[41,42] Inappropriate antimicrobial use also unnecessarily exacerbates the growing problem of health care–associated *C. difficile* colitis,[43] by 8.5-fold in a study of ASB treatment in nursing homes.[44] Catheter-associated bacteriuria is also harmful in that it comprises a large reservoir of antimicrobial-resistant organisms that may be transmitted between patients who have urinary catheters or other invasive devices.[21,45–48]

MICROBIOLOGY

Unlike the narrow and predictable spectrum of causative agents in uncomplicated UTI,[49] a broad range of bacteria can cause health care–associated UTI, and many are resistant to multiple antimicrobial agents.[40] Most episodes of bacteriuria in short-term catheterized patients are caused by single organisms, mostly gram-negative bacilli and enterococci.[28] NSHN surveillance data from 2011 to 2014 provide the most comprehensive picture of the organisms causing CAUTI in acute-care, long-term acute care, and inpatient rehabilitation facilities.[19] *E. coli* was the most common pathogen, accounting for 23% of 153,805 pathogens from CAUTIs reported in the surveillance network, although it is not as dominant as in uncomplicated UTI. The second-ranked pathogen was *Candida albicans* (11.7%). However, all species of *Candida* and unidentified yeast isolates from CAUTIs combined account for 23.9% of CAUTI pathogens. After 2015, CAUTI surveillance definitions changed to exclude yeast, reflecting the clinical uncertainty about whether *Candida* in the urine of catheterized patients represents infection or colonization. After *Candida,* the most commonly isolated bacterial pathogens, in order of relative rank, were *Pseudomonas aeruginosa, Klebsiella pneumoniae/oxytoca,* and *Enterococcus faecalis.* Other organisms reported include *Proteus, Enterobacter,* coagulase-negative *Staphylococci,* and *Staphylococcus aureus.* New gram-positive uropathogens that are

rarely reported, yet have been identified through improved culture techniques or newly recognized as pathogens through microbiome studies of the bladder, include *Actinotignum schaalii* and *Aerococcus urinae*.[50] Health care–associated UTIs arising from external catheters (condom drainage systems) are not reported to the NHSN, so less is known about their epidemiology. A single-center study of urine cultures collected from both indwelling and condom catheters in men found equivalent prevalence of Enterobacteriaceae and enterococci in both catheter types.[32] However, *Pseudomonas* and *Candida* were more prevalent in cultures from indwelling catheters.

Bacteriuria in long-term catheterized patients is usually polymicrobial and, in addition to the pathogens commonly seen in short-term catheterized patients, commonly includes less familiar species such as *P. mirabilis, Providencia* spp., and *Morganella morganii*.[40] In these patients, new episodes of infection often occur periodically in the presence of existing infection with organisms that may persist for months.[51,52] A urine culture obtained from a patient whose catheter has a biofilm may not accurately reflect the status of bacteriuria in the bladder,[53,54] and it is recommended that urine cultures from chronically catheterized patients be obtained from a freshly placed catheter.

PATHOGENESIS

In noncatheterized patients the usual origin of uropathogens is their own fecal microflora, which colonize the periurethral area and ascend to the bladder, resulting in bacteriuria with or without symptoms. In the mouse model of UTI, inoculation of *E. coli* into the bladder is followed by invasion of the superficial bladder cells and the formation of large intracellular bacterial colonies that, in response to infection, exfoliate and are removed with the flow of urine.[55] To avoid clearance by exfoliation, these intracellular uropathogens can reemerge and eventually establish a persistent, quiescent bacterial reservoir within the bladder mucosa that may serve as a source for recurrent acute infections.[55] Although internalization of uropathogenic *E. coli* into bladder and renal epithelial cells has been observed in vitro and in vivo,[56] there is only sparse evidence that this phenomenon occurs in humans[57,58] and only indirect evidence that the intracellular bacterial colonies observed in the mouse occur in humans.[59] Specifically, intracellular bacterial clusters have been seen in desquamated bladder epithelial cells shed from children and adults with UTIs.[59,60] It is possible that invasion of uropathogens into uroepithelial cells is the trigger for urinary symptoms, but an inflammatory response is not sufficient to cause urinary symptoms because pyuria often accompanies ASB in both catheterized and noncatheterized patients.

Strains of *E. coli* associated with lower or upper tract UTI in healthy hosts are more likely to have certain putative virulence determinants, such as P fimbriae, compared with colonic strains and those causing ASB.[61,62] However, many UTIs are caused by *E. coli* with a virulence profile similar to that in strains causing ASB, and these putative virulence factors can be found in strains causing ASB or in colonic flora.

The most important predisposing factor for nosocomial UTI is urinary catheterization, which perturbs host defense mechanisms and provides easier access of uropathogens to the bladder. The indwelling urethral catheter introduces an inoculum of bacteria into the bladder at the time of insertion; facilitates ascension of uropathogens from the meatus to the bladder via the catheter-mucosa interface; provides a pool of organisms in the drainage bag, if the closed system is not maintained, which can ascend intraluminally to the bladder; compromises complete voiding; and constitutes a frequently manipulated foreign body on which pathogens are deposited via the hands of personnel. Indwelling urinary catheters provide a surface for the attachment of host cell binding receptors that are recognized by bacterial adhesins, thus enhancing microbial adhesion, as well as disrupting the uroepithelial mucosa to expose new binding sites for bacterial adhesins.[56] Bacteria attached to the catheter surface form exopolysaccharides that entrap bacteria, which replicate and form microcolonies that mature into biofilms on the inner and outer surfaces of the catheter.[22,56] These biofilms protect uropathogens from antimicrobials and the host immune response and facilitate transfer of antimicrobial resistance genes.[56] Some uropathogens in biofilms, such as *Proteus* spp., have the ability to hydrolyze urea to free ammonia and raise the urinary pH, which facilitates precipitation of minerals such as hydroxyapatite or struvite, creating encrustations that can block catheter flow.[22,56]

Whether external (condom) catheters also contribute to an increased risk of health care–associated UTI is unclear, because NHSN surveillance omits catheter types other than indwelling, transurethral catheters. A single center study in both acute and long-term care wards of 1009 sequential positive urine cultures collected from male veterans with either an indwelling (transurethral), external, suprapubic, or intermittent urinary catheter found that external catheters accounted for 37.4% of positive cultures.[63] Indwelling catheters accounted for 57.8% of these cultures, and the other two catheter types combined accounted for the remaining 4.9%.

The source of uropathogens in catheterized patients includes patients' endogenous flora, health care personnel, or inanimate objects.[22,45,64,65] Not unexpectedly, uropathogen virulence determinants such as P fimbriae appear to be of much less importance in the pathogenesis of health care–associated UTIs compared with uncomplicated UTIs.[61,62,66] Microbial pathogens can enter the catheterized bladder extraluminally (ascending outside the catheter along the urethral mucosa interface) or intraluminally (through the internal lumen from a contaminated drainage bag or break in the closed drainage system).[67] Rectal and periurethral colonization with the infecting strain often precedes catheter-associated bacteriuria, especially in women.[65] The negative impact of the catheter is demonstrated by the finding that, despite the continuous drainage of urine through the catheter, in patients with catheter urine colony counts as low as 3 to 4 colony-forming units per milliliter (CFU/mL) who are not given antimicrobials, the level of bacteriuria or candiduria uniformly rises to greater than 10^5 CFU/mL within 24 to 48 hours in those who remain catheterized.[68]

DIAGNOSIS

The clinical diagnosis of CAUTI is based on the presence of significant bacteriuria in a catheterized or recently catheterized person who has signs or symptoms of UTI not explainable by another condition after a thorough evaluation. Bacteriuria, urinary signs and symptoms, and pyuria in a catheterized patient are all nonspecific, and thus the clinician must exercise clinical judgment as to whether treatment is warranted. The latest NSHN definition (from January 2019) does not permit attribution of symptoms such as fever to another cause—if the patient has a urinary catheter and a positive urine culture that meets NHSN criteria for a CAUTI on the same day as the fever, a CAUTI must be reported. Mixed bacterial cultures and funguria in the absence of a bacterial organism do not meet the NHSN CAUTI definition.

Significant Bacteriuria

Significant bacteriuria is the level of bacteriuria that suggests bladder bacteriuria rather than contamination and is based on growth from a urine specimen collected in a manner to minimize contamination and transported to the laboratory in a timely fashion to limit bacterial growth. Definitions for significant bacteriuria are summarized in Table 302.3. The preferred method of obtaining a urine culture in patients with short-term catheterization is by sampling through a needleless catheter port in catheter tubing that is well cleaned with a disinfectant before accessing. If a port is not present, puncturing the catheter tubing with a needle and syringe is satisfactory.[40] In those patients with long-term indwelling catheters, the catheter urine may be unreliable,[53,54] so a urine specimen should be obtained from a freshly placed catheter. Cultures should not be obtained from the drainage bag. Although data are lacking, placing a fresh condom catheter prior to urine specimen collection makes intrinsic sense.

The level of bacteriuria considered significant in an asymptomatic noncatheterized woman is derived from studies in which colony counts in voided urine specimens were compared with paired catheter or suprapubic aspirate specimens.[69] In these studies, a bacterial count of 10^5 CFU/mL or greater in a catheterized specimen was confirmed by a repeat catheterized specimen in more than 95% of cases. On the other hand, 10^5 CFU/mL or greater in a voided urine specimen was confirmed in a second voided specimen in only 80% of cases. However, two consecutive positive voided urine cultures predicted a third positive voided urine culture with 95% confidence. Therefore two consecutive voided

TABLE 302.3 Definitions for Significant Bacteriuria

Noncatheterized, Clean-Catch Voided Specimen
Symptomatic Female or Male
$\geq 10^3$ CFU/mL (based on data with coliforms; sparse data on gram-positive organisms)
Asymptomatic
Female: $\geq 10^5$ CFU/mL of same species in two consecutive voided specimens Male: $\geq 10^5$ CFU/mL in single voided specimen
Catheterized: Urine From Freshly Placed Catheter Preferable
Symptomatic Female or Male
$\geq 10^3$ CFU/mL
Asymptomatic Female or Male
$\geq 10^5$ CFU/mL

[a]See text for details.

TABLE 302.4 Signs and Symptoms Compatible With Catheter-Associated Urinary Tract Infection (CAUTI)

For all symptoms attributed to CAUTI, other causes should be considered and ruled out:
- New onset or worsening of fever
- Altered mental status
- Flank pain
- Costovertebral angle tenderness
- Rigors
- Pelvic discomfort
- Malaise or lethargy
- Suprapubic pain or tenderness
- Dysuria[a]
- Urgent or frequent urination[a]

Patients with spinal cord injury may, in addition, demonstrate the following:
- Increased spasticity
- Autonomic dysreflexia
- Sense of unease

[a]In patients whose catheters have been removed.

specimens with 10^5 CFU/mL or greater of the same uropathogen predict bladder bacteriuria with the same degree of accuracy as a single urine specimen obtained through a catheter. Nevertheless, for practical purposes and cost containment, a single urine specimen with 10^5 CFU/mL or greater is often used to define significant bacteriuria in clinical practice and many studies.[5] The finding of a single voided urine specimen with 10^5 CFU/mL or greater of an Enterobacteriaceae was reproducible in 98% of asymptomatic ambulatory noncatheterized men when the culture was repeated within 1 week.[70] Thus a single, clean-catch voided urine specimen with 10^5 CFU/mL or greater of a uropathogen identifies ASB in men.[5] Based on a comparison of voided urine specimens (from freshly applied condom catheters) and paired urethral catheter specimens, 10^5 CFU/mL or greater is also the appropriate quantitative criterion for ASB in a man with a condom catheter.[71]

In symptomatic, noncatheterized men and women, lower colony counts of coliforms (e.g., *E. coli, K. pneumoniae*) have been shown to be significant.[72] A recent study of 236 symptomatic episodes of acute, uncomplicated cystitis in 226 women confirmed that the presence of even 10^2 *E. coli* in a midstream urine specimen was highly predictive of bladder bacteriuria (as determined by in-and-out catheterization).[73] This study also found that enterococci and group B streptococci growing in voided urine generally were not found in the bladder urine, suggesting that they were usually contaminants—in fact, when these organisms were found in the midstream urine specimen, *E. coli* was present in the bladder urine in 61% of these episodes. In men with urinary symptoms, a quantitative count of 10^3 CFU/mL or greater in a voided specimen best defines UTI.[74]

In urine specimens obtained by urethral catheterization from symptomatic or asymptomatic men and women, periurethral contamination is less of a problem, and lower quantitative counts of 10^2 CFU/mL or greater are considered to be significant in both men and women.[5,75] However, most clinical laboratories do not routinely quantify urine cultures to 10^2 CFU/mL, so it is reasonable to use a quantitative count of 10^3 CFU/mL or greater in a symptomatic person, whether catheterized or not, as an indicator of CAUTI, because this threshold is a reasonable compromise between sensitivity in detecting bladder bacteriuria and feasibility for the microbiology laboratory in quantifying organisms. Of note, the level of bacteriuria or candiduria rapidly increases from small quantities to greater than 10^5 CFU/mL in catheterized individuals.[68] In asymptomatic men and women, a colony count of 10^5 CFU/mL or greater is a reasonable criterion for the diagnosis of ASB, even though lower counts probably represent true bladder bacteriuria in catheter specimens, because increased specificity is desirable.

Symptoms and Signs

The majority of patients with catheter-associated bacteriuria lack symptoms, as demonstrated in a study of 1497 newly catheterized patients who were followed prospectively with daily urine cultures, urine leukocyte counts, and symptom assessment.[28] Only 8% of 194 patients with catheter-associated bacteriuria (defined as $>10^3$ CFU/mL; 85% of patients had $>10^5$ CFU/mL in at least one culture) who could respond to symptom assessment reported symptoms referable to the urinary tract, although bacteriuria and pyuria had been present in most for many days. Additionally, there were no significant differences between patients with and without bacteriuria in signs or symptoms commonly associated with UTI—fever, dysuria, urgency, or flank pain—or in leukocytosis. The lack of an association between fever and catheter-associated bacteriuria has also been convincingly demonstrated in other studies.[29,39] An ICU study found no relationship between fever and a UTI (defined as $\geq 10^5$ CFU/mL of urine).[76] Thus in the presence of an indwelling urinary catheter, symptoms referable to the urinary tract are unreliable, and fever or peripheral leukocytosis have little predictive value for the diagnosis of CAUTI. Likewise, no studies have demonstrated that malodorous or cloudy urine in a catheterized individual has clinical significance.

Nevertheless, catheterized patients with symptoms or signs compatible with UTI that are not explainable by another condition after a thorough evaluation warrant treatment. Signs and symptoms compatible with CAUTI are listed in Table 302.4. Patients with CAUTI who are currently catheterized usually do not manifest the classic symptoms of dysuria, frequency, and urgency.

Noncatheterized adult residents of LTCFs are also at risk for health care–associated UTI. Most available evidence about what constitutes symptoms and signs of UTI in nursing home residents is from studies performed in women. Symptoms in older women that should prompt further urinary testing are fever, acute dysuria (<1 week in duration), new or worsening urinary urgency, frequency, new urinary incontinence, gross hematuria, suprapubic pain or tenderness, and costovertebral angle pain or tenderness.[77] In a patient with cognitive impairment who is unable to express symptoms, a persistent change in mental status plus change in character of the urine that is not responsive to other interventions (i.e., hydration) may suggest a need for urine testing, among other evaluations.[77]

Pyuria

Pyuria is evidence of inflammation in the genitourinary tract and is present in almost all persons with symptomatic UTIs. It is also common in persons with ASB,[4] including 30% to 75% of bacteriuric patients with short-term indwelling urethral catheters and 50% to 100% of individuals with long-term indwelling catheters. In 761 newly catheterized patients in a university hospital, the specificity of pyuria for catheter-associated bacteriuria ($>10^5$ CFU/mL—almost all were asymptomatic) was 90%, but the sensitivity was only 47%.[78] In a longitudinal study of patients with long-term urinary catheters, bacteriuria and pyuria were common, even during asymptomatic periods, and did not change during symptomatic UTI episodes.[79] Thus in the catheterized patient, the presence

or absence or degree of pyuria alone does not, by itself, differentiate catheter-associated ASB from CAUTI, but in a symptomatic patient its absence suggests that CAUTI is not the cause of the symptoms.

PREVENTION

Prevention of symptomatic CAUTI is the main objective of prevention strategies in patients for whom urinary catheterization is being considered or has been performed. However, there may also be benefits to preventing catheter-associated ASB in such patients, although such benefits have usually not been evaluated as end points in clinical trials. In the discussion that follows, the impact of interventions on catheter-associated ASB and CAUTI are mentioned when data are available, but most studies use catheter-associated bacteriuria (composed mostly of ASB) as the outcome of interest. Of note, interventions that reduce the risk of catheter-associated ASB are likely to also reduce the risk of CAUTI.

The following text discusses in detail those practices for which published data suggest that they should be implemented, those for which there are some positive data but not enough to warrant routine implementation, and those that do not warrant routine implementation on the basis of interpretation of currently available data. Prevention of one of the most significant harms of catheter-associated bacteriuria, inappropriate antimicrobial use to treat ASB, is addressed under "Health Care–Associated Asymptomatic Bacteriuria" later.

Prevention Strategies That Should Be Routine

Prevention Components of Infection Control Programs

Intensive infection surveillance and control programs in US hospitals are strongly associated with reductions in rates of nosocomial UTI.[80] The decision in 2008 by the Centers for Medicare and Medicaid Services to stop reimbursing US hospitals for CAUTIs that develop during hospitalization[81,82] has made CAUTI reduction a key component of many quality improvement programs, both state-wide and nationwide.[83–85] Several evidence-based comprehensive guidelines have been published for prevention of CAUTIs, with an emphasis on infection prevention in hospitals.[86,87] CAUTI prevention strategies that are strongly recommended for hospitals to incorporate into their infection control programs are shown in Table 302.5. UTI bundles that combine several prevention techniques to accomplish reduction in CAUTI have been described.[88–91]

It should be noted that our ability to prevent catheter-associated ASB or CAUTI in patients who have appropriate indications for catheterization is quite limited, especially in those patients requiring long-term bladder drainage.[92] Many of the key evidence-based prevention strategies are being used more widely, although significant gaps in implementation exist. A national study of US hospitals in 2009 to ascertain the practices used to prevent CAUTI showed that although 79% of hospitals performed CAUTI surveillance, only 39% monitored duration or catheter removal or both.[93] Another survey in 2009 in acute-care hospitals that participate in a geriatric nursing quality program showed that only 89% of respondents routinely wash hands before urinary catheter placement.[94] In contrast, a survey in acute-care hospitals in 2013 found significant increases from 2005 to 2013 in use of catheter stop orders, use of bladder ultrasound to assess for urinary retention, and facility-wide monitoring of CAUTI rates ($P \leq .001$ for all comparisons).[95]

Interestingly, a study of 398 health systems found no evidence that the 2008 Centers for Medicare and Medicaid Services policy to reduce payments for CAUTI has had any measurable effect on infection rates in US hospitals from 2006 to 2011 (incidence-rate ratio [IRR] in the postimplementation vs. preimplementation period, 1.03; $P = .08$).[96] These findings align with those of the CDC summary report of NHSN surveillance in acute-care hospitals, which likewise found no change overall in CAUTI from 2009 to 2014.[11]

Residents of LTCFs have a risk of developing health care–associated infections similar to that in acute-care hospital patients, and in the United States almost as many such infections occur annually in LTCFs as in hospitals.[97] To address this problem, guidelines for infection prevention and control in LTCFs have been published.[97] There has been less research on the efficacy of infection control strategies in LTCFs compared with hospitals, but guidelines for prevention of CAUTIs in hospitalized patients are thought to be generally applicable to catheterized residents in LTCFs.[97] A systematic review of strategies to reduce CAUTI in nursing home residents found a variety of effective interventions, often implemented in bundles, including strategies to minimize catheter use, strategies to improve catheter care, and also general infection prevention strategies (such as hand hygiene).[98] NHSN surveillance for health care–associated infections, including CAUTI, is currently optional for LTCFs.

TABLE 302.5 Catheter-Associated Urinary Tract Infection (CAUTI) Prevention and Monitoring Strategies Strongly Recommended for Acute-Care Hospitals

- Develop and implement written guidelines for insertion, use, maintenance, and removal of urinary catheters.
- Ensure that only trained personnel insert urinary catheters.
- Ensure that supplies necessary for aseptic-technique catheter insertion are available.
- Implement a medical record documentation system for catheter use.
- Ensure sufficient trained personnel and resources for surveillance of catheter use and outcomes.
- Perform surveillance for CAUTI using standardized criteria (NHSN definitions).
- Educate health care personnel about CAUTI prevention techniques.
- Monitor health care professional competency in catheter use, catheter care, and catheter maintenance.
- Insert urinary catheters only when necessary and remove them when appropriate.
- Consider alternatives, such as condom catheters or intermittent catheterization, when appropriate.
- Practice hand hygiene on insertion and any manipulation of the catheter and site.
- Insert catheters using aseptic technique and sterile equipment.
- Use sterile gloves, a drape, and sponges; a sterile or antiseptic solution for cleaning the urethral meatus; and a single-use packet of sterile lubricant jelly for insertion.
- Use as small a catheter as appropriate to reduce urethral trauma.
- Properly secure catheter to prevent movement.
- Maintain a sterile, continuously closed drainage system.
- Replace the catheter and the collecting system when breaks in the drainage system occur.
- To examine urine, aspirate a small sample from the sampling port with a sterile syringe.
- Collect larger volumes of urine for special analyses aseptically from the drainage bag.
- Maintain unobstructed urine flow.
- Empty collecting bag regularly; use separate collecting container for each patient.
- Keep the collecting bag and tubing below the level of the bladder at all times.
- Keep catheter and collecting tube free from kinking.
- Routine hygiene is appropriate for cleaning the meatal area.
- In locations or populations with unacceptably high CAUTI rates despite the above:
  - Implement a program to systematically identify and remove catheters that are no longer necessary.
  - Develop a protocol for management of postoperative urinary retention.
  - Establish a system for analyzing and reporting data on catheter use and adverse events.

NHSN, National Healthcare Safety Network.
Modified from Yokoe DS, Anderson DJ, Berenholtz SM, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. Infect Control Hosp Epidemiol. *2014;35 Suppl 2:S21–31.*

Reduction of Unnecessary Catheterization

Reducing unnecessary catheterization is the most effective way to prevent catheter-associated ASB and CAUTI. Other reasons to reduce urinary catheterization are that catheters cause discomfort, restrict mobility, and delay hospital discharges.[99] Catheter-related trauma can occur on both insertion and removal, may necessitate urologic intervention, and is probably underappreciated, because CAUTI surveillance does not include noninfectious harms of catheterization.[100]

Studies have repeatedly documented that urinary catheters are often inserted for inappropriate reasons or remain in place longer than necessary. In studies of hospitalized patients with urinary catheters, the initial indication for catheter use was judged inappropriate in up to 50% of

cases, and continued catheterization was judged inappropriate for almost half of catheter-days.[27,101–103] Additionally, the reason for catheter placement is often not stated and orders for catheterization are often not written.[104] In the medical ICU, many unjustified catheter-days are due to monitoring of urine output when it is no longer indicated, and on medical wards, urinary incontinence is a major reason for unjustified initial and continued urinary catheterization. One problem is that clinicians are often unaware that their patients are catheterized. In one study, providers were unaware of patient catheterization for 28% of the 319 provider-patient observations—21% for students, 22% for interns, 27% for residents, and 38% for attending physicians.[105] For patients who were inappropriately catheterized, providers were unaware of catheter use for 41% of the 108 provider-patient observations.

Several strategies have been demonstrated to be effective in reducing inappropriate insertion of catheters and duration of catheterization. Strategies shown to reduce inappropriate insertion of catheters include education and use of a catheter indication sheet in the emergency department,[106] use of a multifaceted intervention restricting urinary catheterization in the operating room and postanesthesia care unit and expedited catheter removal on the postoperative surgical ward,[107] use of an ultrasound bladder scanner to assess bladder volumes following surgery,[108] and use of in-and-out catheterization rather than short-term indwelling catheterization in postoperative patients with urinary retention.[109] Use of portable bladder ultrasound devices to reduce unnecessary catheterization warrants further study in the care of oliguric patients.[110,111] Operating room and emergency department personnel are appropriate targets for educational efforts to enhance use of appropriate indications for catheter insertion given that approximately three-fourths of catheters are inserted there.[112]

A systematic review of interventions to minimize the initial use of indwelling urinary catheters in acute care concluded that there was insufficient evidence to support or rule out the effectiveness of interventions due to the small number of studies, limitations in study design, and variation in clinical environments.[113] Moreover, the reviewed studies also showed a lack of consensus as to the appropriate indications for placing an indwelling catheter.

Strategies shown to reduce the duration of indwelling urethral catheterization, some of which were associated with a reduction in CAUTI in clinical trials, include physician reminders by the nursing staff, reminder stickers on medical charts or computer prompts to remove unnecessary catheters after admission, and prewritten orders for the removal of urinary catheters if predetermined criteria are not met.[99,114–123] A systematic review found that interventions to routinely prompt physicians or nurses to remove unnecessary urinary catheters reduced the rate of CAUTI (not clearly defined as symptomatic or not) by 52% ($P < .001$) and reduced the mean duration of catheterization by 1.06 days overall, although the significant decrease in duration was seen only in studies that used stop orders, rather than reminders.[124] Hospitals have responded to the evidence supporting stop orders, in that a national survey in 2013 found that 53% of hospitals surveyed were using catheter reminders or stop orders, up from 9% in 2005 ($P < .001$).[95]

Hospitals and LTCFs should develop institution-specific indications for inserting indwelling urinary catheters, monitor adherence to use of such indications in catheterizing patients, implement reminder systems for nurses and physicians as to which patients are catheterized, and consider implementing automatic catheter stop orders. Generally accepted indications for use of indwelling urinary catheters are shown in Table 302.6.

TABLE 302.6 Indications for Use of Indwelling Urinary Catheters

Perioperative use for selected surgical procedures
Use during prolonged surgical procedures with general or spinal anesthesia
Urine output monitoring in critically ill patients
Management of urinary retention and urinary obstruction
Assistance in pressure ulcer healing for incontinent patients
Prolonged immobilization
Improve comfort for end-of-life care or patient preference

Modified from Gould et al.[86] and Lo et al.[87]

Alternatives to Indwelling Urethral Catheterization

Although comparative studies are sparse, the consensus is that indwelling urethral catheterization places the patient at the greatest risk for catheter-associated bacteriuria and traumatic complications, and that alternative bladder drainage modalities should be used when appropriate.[86,87] Alternatives to indwelling urethral catheterization include the use of external collection devices, including condom catheters, intermittent catheterization, and suprapubic catheterization. Each of these alternative catheterization methods has been shown in selected populations to reduce the risk of catheter-associated bacteriuria, compared with indwelling catheterization, over the short term.[125,126] For patients requiring long-term catheterization, there are no trials comparing indwelling urethral catheterization, suprapubic catheterization, or intermittent catheterization.[127]

Condom Catheterization

In nonrandomized studies, use of condom catheters has been shown to result in a lower incidence of catheter-associated bacteriuria compared with indwelling urethral catheters.[20] In a prospective, randomized trial of 75 men at a Veterans Administration hospital, patients without dementia who had an indwelling catheter were about five times as likely to develop catheter-associated bacteriuria, develop CAUTI, or die (catheter-associated bacteriuria was the predominant outcome in this combined outcome variable) compared with those who had appropriately sized condom catheters.[128] No difference was seen in those patients with dementia, which may have to do with the increased risk of catheter-associated bacteriuria in patients who manipulate their condom catheters.[20] Thus in men with low postvoid residual volume who are not cognitively impaired, condom catheters are preferable to indwelling urethral catheters for short-term catheterization and probably for long-term catheterization. Although condom catheter–associated bacteriuria is not included in NSHN CAUTI surveillance and reporting, the positive urine cultures from condom catheters still trigger inappropriate antimicrobial use.[63] Some men may not be able to wear a condom catheter, such as those with a small or ulcerated penis. External catheters suitable for use in women are under development and testing.

Intermittent Catheterization

Intermittent catheterization is a technique in which the bladder is drained of urine by catheterization usually every 4 to 6 hours, so the amount of urine obtained with each collection is generally no more than 500 mL.[129] The schedule of intermittent catheterization is tailored for each individual to minimize the number of catheterizations while not allowing the bladder to become overdistended. Guttman and Frankel[130] in 1966 described intermittent catheterization using sterile technique, and Lapides and colleagues[131] later demonstrated that the clean (nonsterile) technique was safe and associated with a low incidence of complications in patients with neurogenic bladders. Intermittent catheterization is widely viewed to be associated with fewer complications than indwelling catheterization, including catheter-associated bacteriuria, hydronephrosis, bladder and renal calculi, bladder cancer, and autonomic dysreflexia,[132,133] and it has become the standard of care for appropriate women and men with spinal cord injury (SCI). It is also a commonly used alternative in patients without SCI who need long-term assistance with voiding.[40,134] No randomized controlled trials have compared intermittent urethral, indwelling urethral, and suprapubic or condom catheterization in patients on long-term catheterization, including those with neurogenic bladders.[132,135] On the other hand, a meta-analysis of trials comparing catheterization methods in patients (mostly postsurgical) undergoing short-term catheterization found no difference in ASB between indwelling and intermittent catheterization (20% vs. 22%; risk ratio [RR], 1.04; 95% confidence interval [CI], 0.85–1.28), although urinary retention was lower in patients with indwelling compared with intermittent catheterization (RR, 0.45; 95% CI, 0.22–0.91).[125] Nevertheless, intermittent catheterization is not commonly used for short-term catheterization because of the educational, motivational, and staff-time requirements necessary for its implementation.

Among patients undergoing long-term intermittent catheterization, randomized controlled studies in adults in hospitals, LTCFs, and outpatient settings with or without neurogenic bladders have shown no

difference in risk of catheter-associated ASB or CAUTI with use of sterile technique compared with clean (nonsterile) technique, with use of sterile catheters versus multiple-use catheters with the clean technique, or with daily or weekly replacement of multiple-use catheters.[134,136] Different techniques have been studied to reduce the microbial contamination of multiple-use catheters, including rinsing with tap water, air-drying, keeping dry until reuse, and microwaving or soaking the catheter in disinfectants, but there are no published trials evaluating the effectiveness of these methods in preventing catheter-associated bacteriuria. Although there are no data that reuse of catheters increases infection risk, catheter reuse is inconvenient for many patients who find it difficult to clean their catheters away from home, and others find it nonaesthetic.

Complications associated with long-term intermittent catheterization, although apparently less common than with indwelling urethral catheterization, include catheter-associated bacteriuria, prostatitis, epididymitis, urethritis, urethral trauma with bleeding, urethral strictures, and false passages.[129,133] Hydrophilic catheters, compared with standard catheters, reduce the friction of catheter insertion and urethral inflammation and are associated with improved patient satisfaction. These catheters have been widely used in Europe for many years in patients on intermittent catheterization. Systematic reviews and meta-analyses have come to different conclusions on whether hydrophilic catheters confer an advantage over standard catheters plus lubricant gel. A recent meta-analysis of hydrophilic versus standard catheters for intermittent catheterization included both children and adults with voiding difficulties, mostly from neurogenic bladders. This meta-analysis found a decreased risk ratio of UTIs associated with hydrophilic catheters in comparison with nonhydrophilic ones (RR, 0.84; 95% CI, 0.75–0.94; $P = .003$).[137] However, this analysis used an "antimicrobial-treatment given" definition of UTI, and the largest study included was in persons with traumatic SCI of less than 3 months' duration.[138]

Limitations to intermittent catheterization include limited availability of staff to perform the procedure or educate patients, inability or unwillingness of patients to perform frequent catheterizations, or abnormal urethral anatomy such as stricture, false passages, or bladder neck obstruction. UTIs and urethral trauma are the main complications.[137] Upper extremity impairment due to cervical SCI or other abnormality, obesity, and spasticity also make intermittent catheterization challenging for both males and females.

Suprapubic Catheterization

Potential advantages of suprapubic catheters in patients who need bladder drainage, compared with indwelling urethral catheters, include lower risk of catheter-associated bacteriuria because abdominal skin is less likely to be colonized with uropathogens compared with the urethra, reduced risk of urethral trauma and stricture, less interference with sexual activity, and, in those undergoing short-term catheterization, ability to more easily assess the appropriate time for catheter removal. A meta-analysis of randomized trials in primarily surgical patients undergoing short-term catheterization found insufficient evidence to determine whether indwelling urethral catheterization, compared with suprapubic catheterization, was associated with higher risk of UTI.[125] On the other hand, fewer patients with suprapubic catheters developed ASB (RR, 2.25; 95% CI, 1.63–3.10). Recatheterization was more common with indwelling urethral catheters (RR, 2.21; 95% CI, 1.19–4.09). Pain and discomfort were not included in this meta-analysis because the measurements were too heterogeneous.[125] Suprapubic catheters appear to be commonly used in gynecologic surgery in some centers, but their use is limited, presumably because their insertion is an invasive procedure, and they are harder to change when necessary. Potential complications include visceral injury (rare) and less serious complications, such as leakage, catheter blockage, and hematuria.[139] As mentioned previously, different catheterization methods have not been compared in patients with neurogenic bladders[132,135] or other patient groups on long-term catheterization.

Techniques for Catheter Insertion and Maintenance

Although use of aseptic technique for inserting indwelling urethral catheters is widely recommended,[140] few data exist to support such a recommendation. Some studies have shown that catheter insertion outside the operating room (where adherence to aseptic technique may be less than optimal) is associated with a higher risk of catheter-associated bacteriuria.[67] However, no significant difference in risk of catheter-associated bacteriuria was found in a study of 156 patients undergoing preoperative urethral catheterization who were randomized to sterile versus clean technique for catheter insertion.[141] Moreover, in patients managed with intermittent catheterization who are catheterized multiple times daily, there appears to be no difference in infection risk with nonsterile compared with sterile technique. Nevertheless, given the ubiquity of multidrug-resistant pathogens in the health care environment, it seems prudent to use aseptic technique for inserting indwelling urethral catheters in patients in the hospital or LTCF.[140]

Introduction of the closed catheter drainage system, in which the collecting bag is attached to the distal end of the collecting tube, was perhaps the most important advance in prevention of catheter-associated bacteriuria.[14,17,20] In patients managed with catheter drainage into open containers, 95% of patients develop catheter-associated bacteriuria by 96 hours.[142] By comparison, about 50% of patients managed with closed drainage systems develop catheter-associated bacteriuria by 14 days of continuous catheterization.[17] Based on such historical comparisons, closed systems have become the standard for bladder drainage. Disconnections at the catheter–collecting tube junctions have been shown to increase the risk of catheter-associated bacteriuria,[4,16,143] so many hospitals use preconnected urinary drainage systems in which the catheter, tubing, and drainage bag are supplied as a single connected unit. Diagnostic urine samples should be aspirated using aseptic technique through ports in the distal catheter, and larger volumes of urine for special analyses (not microbiologic studies) should be collected aseptically from the drainage bag with care not to contaminate the end of the drainage tube from potentially contaminated measuring containers.[64] The catheter should be properly anchored to minimize movement because movement of urethral catheters may cause urethral trauma and may facilitate the ascension of organisms up the urethra-catheter interface. Importantly, the drainage tube should not be allowed to move above the level of the bladder or below the level of the collection bag.[21]

Bundled CAUTI Prevention Programs

Two widespread, successful CAUTI prevention programs sponsored by the Agency for Healthcare Research and Quality have led to a decrease in CAUTI rates among participating facilities despite the overall lack of change in CAUTI rates per NSHN reports to the CDC over the same time period. One was performed in 926 units in 603 acute-care hospitals, representing more than 10% of acute-care hospitals in the United States,[84] while the other reported results from 404 nursing homes.[85] Both programs explicitly focused on both technical and socioadaptive components of CAUTI prevention. Technical components involved education in proper catheter insertion and maintenance techniques, and avoiding unnecessary catheter use, for example. The socioadaptive components focused on improving attitudes and behaviors related to infection prevention and patient safety. Facilities were also provided regular feedback on their rates of CAUTI and urinary catheter utilization. In acute-care units, CAUTI rates decreased from 2.4 to 2.05 per 1000 catheter-days, in adjusted analysis (IRR, 0.86; 95% CI, 0.76–0.96; $P = .009$).[84] In nursing homes, CAUTI rates in the adjusted analysis decreased from 6.42 to 3.33 per 1000 catheter-days (IRR, 0.46; 95% CI, 0.36–0.58; $P < .001$).[85] The effort from both the project team and the participants at the health care facilities was considerable and included in-person and virtual teaching sessions, coaching calls, webinars, educational materials, manuals, tools, and checklists. Of note, changes in the safety culture as measured by the Hospital Survey on Patient Safety Culture did not show any association with improvements in CAUTI rates at participating acute-care facilities.[144] Which aspects of these interventions are necessary for success and whether these interventions would succeed in facilities that did not volunteer to be part of this type of project is not known. However, these interventions are presented here as evidence that change in CAUTI rates is possible through national collaboratives.

Prevention Strategies With Possible Benefit

Although these practices might have benefit, they are not recommended for routine use.

Antiseptic- and Antimicrobial-Coated Catheters

In vitro studies have shown antiadherence or antimicrobial activity associated with silver-, minocycline- and rifampin-, and nitrofurazone-coated catheters,[145–147] although nitrofurazone appears to be the most inhibitory.[148,149] Currently two types of coated or impregnated catheters are available in the United States: catheters with an antiseptic silver alloy coating, and catheters impregnated with the antibiotic nitrofurazone (related to nitrofurantoin). Both are intended for short-term (<14 days) use. Silver oxide urinary catheters were inferior to silver alloy catheters at preventing bacteriuria in meta-analysis and are no longer manufactured in the United States.[150–152] There are no data to show that antimicrobial-coated catheters are beneficial in patients managed with long-term catheterization (>30 days).[153]

The largest and most clinically relevant trial of these coated catheters was a multicenter trial by Pickard and colleagues, in which 7102 patients undergoing short-term (1–14 days) catheterization were randomized to indwelling urethral catheterization with a silver alloy–coated catheter, a nitrofurazone-impregnated catheter, or a standard latex catheter.[154,155] In this trial 95% of the patients were catheterized for perioperative monitoring. The primary outcome was symptomatic UTI, defined as UTI symptoms and signs plus prescription of an antimicrobial for UTI, and the time frame for CAUTI was up to 6 weeks after catheter removal (unusually long for catheter trials). Compared to standard catheters, silver alloy–coated catheters showed no reduction in CAUTI, while nitrofurazone-coated catheters showed a minimal reduction in CAUTI (−2.1%; 95% CI, −4.2 to −0.1%). This reduction was less than the 3.3% reduction established a priori to be of clinical significance.[154]

In a meta-analysis of randomized trials comparing types of indwelling urinary catheters in hospitalized adults undergoing short-term catheterization, only the large, randomized, controlled trial by Pickard and colleagues measured symptomatic CAUTI as the primary outcome.[154,155] In a meta-analysis by Lam and coworkers, silver alloy catheters were associated with a slightly reduced risk of bacteriuria in comparison to standard catheters (RR, 0.82: 95% CI, 0.73–0.92).[156] However, the trial by Pickard and colleagues, judged to have low risk of bias in subject allocation, did not find that silver catheters significantly decreased ASB.[155] In the Lam and coworkers meta-analysis, nitrofurazone-impregnated catheters were associated with a lower risk of bacteriuria in comparison to standard catheters (RR, 0.73; 95% CI, 0.62–0.85) and in comparison to silver alloy catheters (RR, 0.78; 95% CI, 0.67–0.91).[156]

In summary, nitrofurazone-coated urinary catheters appear to have some benefit in the prevention of catheter-associated ASB in some trials of short-term catheterized patients, while silver alloy catheters have minimal effect. Whether the reduction in bacteriuria translates into reduction of secondary bloodstream infection or other health care–associated infections is unclear. Thus available data do not support routine use of antiseptic or antimicrobial urinary catheters to prevent CAUTI. Resistance to catheter-impregnated antimicrobial agents or antibiotics has not been demonstrated in published clinical trials, but this remains a concern.

Prophylaxis With Antimicrobial Agents

Systemic Antimicrobials

Systemic antimicrobial drug therapy has been shown repeatedly in prospective and retrospective studies to transiently prevent or delay the onset of catheter-associated bacteriuria, although development of antimicrobial resistance has been noted in some studies.[14,20,65] A meta-analysis of randomized controlled trials in surgical and nonsurgical patients undergoing short-term catheterization found limited evidence that postoperative antimicrobial prophylaxis for catheterized patients could reduce the risk of bacteriuria and other signs of infection, and limited evidence suggested that prophylactic antimicrobials reduce bacteriuria in catheterized nonsurgical patients.[157] However, resistance to the antibiotics used for prophylaxis (such as trimethoprim-sulfamethoxazole and ciprofloxacin) was observed in several trials. Meta-analysis of antimicrobial prophylaxis with long-term urinary catheter use only found one randomized, controlled trial in patients with indwelling catheters, and in this study, only 23 patients completed the 6-month study of norfloxacin suppression versus placebo.[132,158] Although this study demonstrated a significant decrease in symptomatic CAUTI, 25% of strains in placebo patients versus 90% of strains in norfloxacin patients were resistant to norfloxacin at the end of the prophylaxis period.[158] The other studies addressed in this meta-analysis were of patients performing intermittent catheterization, and results were inconsistent about whether prophylactic antimicrobials reduced UTIs.[132] Clinical trials in adults with neurogenic bladders secondary to SCI, using either indwelling[159] or intermittent catheterization,[160] and those in older adults with indwelling catheters,[161] have found that recurrent bacteriuria, after a course of targeted antimicrobials intended to sterilize the urine, is the rule rather than the exception.

Because of the potential for the development of antimicrobial resistance and adverse effects and cost, routine use of systemic antimicrobial agents to prevent catheter-associated bacteriuria or CAUTI should be discouraged. Unfortunately, up to 60% to 80% of hospitalized, catheterized patients receive antimicrobial therapy for a variety of reasons,[17,162] and not controlling for this important variable in the analyses of many intervention trials may explain why some interventions have not been shown to be effective in preventing catheter-associated bacteriuria.

Methenamine Salts

Methenamine salts (methenamine mandelate and methenamine hippurate) are hydrolyzed to ammonia and formaldehyde, which is responsible for the antibacterial activity of methenamine. Antimicrobial activity in urine is correlated with urinary concentrations of formaldehyde, and the urinary concentration of formaldehyde is dependent on the concentration of methenamine in the urine and the urine pH.[163] Maintaining a low urinary pH (below 6) is necessary to achieve bactericidal concentrations of formaldehyde, but the association between therapeutic efficacy and low urinary pH has not been confirmed consistently.[163] In addition, the optimal method to acidify the urine in a patient on methenamine is not known. Ascorbic acid is often used to acidify the urine, but up to 4 g/day have shown no significant effect on mean urinary pH, and doses as high as 12 g/day may be required to adequately acidify the urine.[163]

Methenamine salts have been shown to prevent uncomplicated cystitis in young women[163–165] but are not as effective or convenient as currently available regimens for prevention of UTI. In addition, methenamine salts are generally considered to have limited effectiveness in preventing CAUTI in patients with indwelling catheters for whom the time for hydrolysis to formaldehyde is limited.[20,163] A meta-analysis of 13 randomized or quasi-randomized controlled studies of methenamine hippurate for the prevention of UTIs suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR, 0.24; 95% CI, 0.07–0.89; bacteriuria: RR, 0.56; 95% CI, 0.37–0.83), but not in patients with known renal tract abnormalities (symptomatic UTI: RR, 1.54; 95% CI, 0.38–6.20; bacteriuria: RR, 1.29; 95% CI, 0.54–3.07).[166] The benefit in one study of women undergoing short-term catheterization following gynecologic surgery may have been due in part to the administration of methenamine for several days after the catheters had been removed in some cases.[167] Methenamine does not appear to prevent catheter-associated bacteriuria or CAUTI in SCI patients with neurogenic bladders irrespective of the method of bladder management.[166,168,169] There are no published data on the use of methenamine in patients using condom catheterization.

Overall, the data are unconvincing that methenamine is effective in reducing the risk of catheter-associated bacteriuria or CAUTI in patients managed with long-term indwelling catheterization—patients most in need of an effective agent that does not select for antimicrobial resistance. Methenamine does appear to be effective in post–gynecologic surgery patients undergoing short-term catheterization, and its use in this situation may be considered, although this group has little morbidity from catheter-associated bacteriuria. It may also be reasonable to consider a trial use of methenamine in patients on intermittent catheterization who have recurrent episodes of CAUTI, even though its benefit in such patients is unproven. If used, the recommended dose of methenamine hippurate is 1 g twice daily and that for methenamine mandelate is 1 g four times daily, and the urinary pH should be maintained below 6.[163]

Prevention Strategies With Little Benefit

These strategies have little or no demonstrated benefit and are not recommended for routine use.