Management and Prevention of Ventilator-associated Pneumonia Caused by Multidrug-resistant Pathogens

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Abstract and Introduction

Abstract

Ventilator-associated pneumonia (VAP) due to multidrug-resistant (MDR) pathogens is a leading healthcare-associated infection in mechanically ventilated patients. The incidence of VAP due to MDR pathogens has increased significantly in the last decade. Risk factors for VAP due to MDR organisms include advanced age, immunosuppression, broad-spectrum antibiotic exposure, increased severity of illness, previous hospitalization or residence in a chronic care facility and prolonged duration of invasive mechanical ventilation. Methicillin-resistant *Staphlococcus aureus* and several different species of Gram-negative bacteria can cause MDR VAP. Especially difficult Gram-negative bacteria include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, carbapenemase -producing *Enterobacteraciae* and extended-spectrum β-lactamase producing bacteria. Proper management includes selecting appropriate antibiotics, optimizing dosing and using timely de-escalation based on antibimicrobial sensitivity data. Evidence-based strategies to prevent VAP that incorporate multidisciplinary staff education and collaboration are essential to reduce the burden of this disease and associated healthcare costs.

Introduction

Ventilator-associated pneumonia (VAP), defined as a pneumonia that occurs 48 h after intubation, is the most frequently occurring healthcareassociated infection in mechanically ventilated patients. Incidence rates have been reported to range from 8 to 28%, with 10–20% of mechanically ventilated patients at risk for developing VAP. [1,2] Recent studies have shown lower rates of VAP over the past decade. This has been attributed to improved prevention strategies and widespread VAP prevention programs. [3–5] Incremental healthcare spending due to VAP ranges from US$20,000 to 40,000. [1,6–8] Morbidity due to VAP was described in a study of 99 hospitalized intensive care unit (ICU) patients who received long-term mechanical ventilation and survived for at least 1 year after hospital discharge. [9] These patients demonstrated a high rate of readmissions and discharges to various healthcare facilities. Additionally, they demonstrated a poor functional status and high degree of healthcare consumption, as only 9% had no dependency and the cost per survivor was US$3.4 million.

Most cases of VAP occur within 10 days of mechanical ventilation. [10] In contrast to early-onset VAP, late-onset VAP occurs after 5 days of ventilation and is most commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) Gram-negative pathogens. Multidrug resistance is defined as resistance to three or more antibiotic classes. [11] The emergence of MDR pathogens over the past decade and the associated negative impact on patient outcomes has been well documented. [12–14] In this review, the authors focus on the most common MDR pathogens causing VAP and outline preventative and treatment strategies to reduce mortality and improve patient outcomes.

Pathogenesis

Understanding the pathogenesis of VAP is important for establishing the principles for therapy and strategies for prevention. [2,6] The aerodigestive tract above the vocal cords is heavily colonized with bacteria. [15] A complex array of host defense mechanisms protects the trachea and lungs from bacterial infection. Mechanical host defenses filter and humidify air, while the cough response, mucus and cilia trap and clear bacteria entering the lower airway. In addition, a variety of humoral and cellular immune mechanisms are highly effective in preventing infection. [16,17] In critically ill patients, host defenses may be impaired due to malnutrition, chronic diseases or immunosuppression. Moreover, bacterial adherence is favored by reduced immunoglobin A, augmented protease production, denuded mucus membranes and elevated airway pH. [18]

In intubated critically ill patients, the endotracheal tube (ETT) facilitates bacteria entry into the lower respiratory tract by permitting leakage of secretions around the ETT cuff and prevents the exit of bacteria from the lower airway, creating a need for manual tracheobroncheal suctioning, as shown in Figure 1. [2,19] However, suctioning through the ETT, which may be encased with a biofilm, can increase the risk of biofilm embolization to the lung parenchyma, which can cause VAP. [20,21] Progression from colonization to infection depends on the number, type and virulence of pathogens entering the lower airway.

[18,22,23] VAP may be caused by endogenous flora or exogenous microorganisms originating from contaminated respiratory equipment, infected aerosols, the ICU environment and the hands of healthcare workers. [18,24] Risk factors for VAP include advanced age, high Acute Physiology and Chronic Health Evauluation II (APACHE II) score, trauma, surgery, prolonged intubation, use of a nasogastric tube and the number and type of bacteria entering the lower airway. [17,25–27]

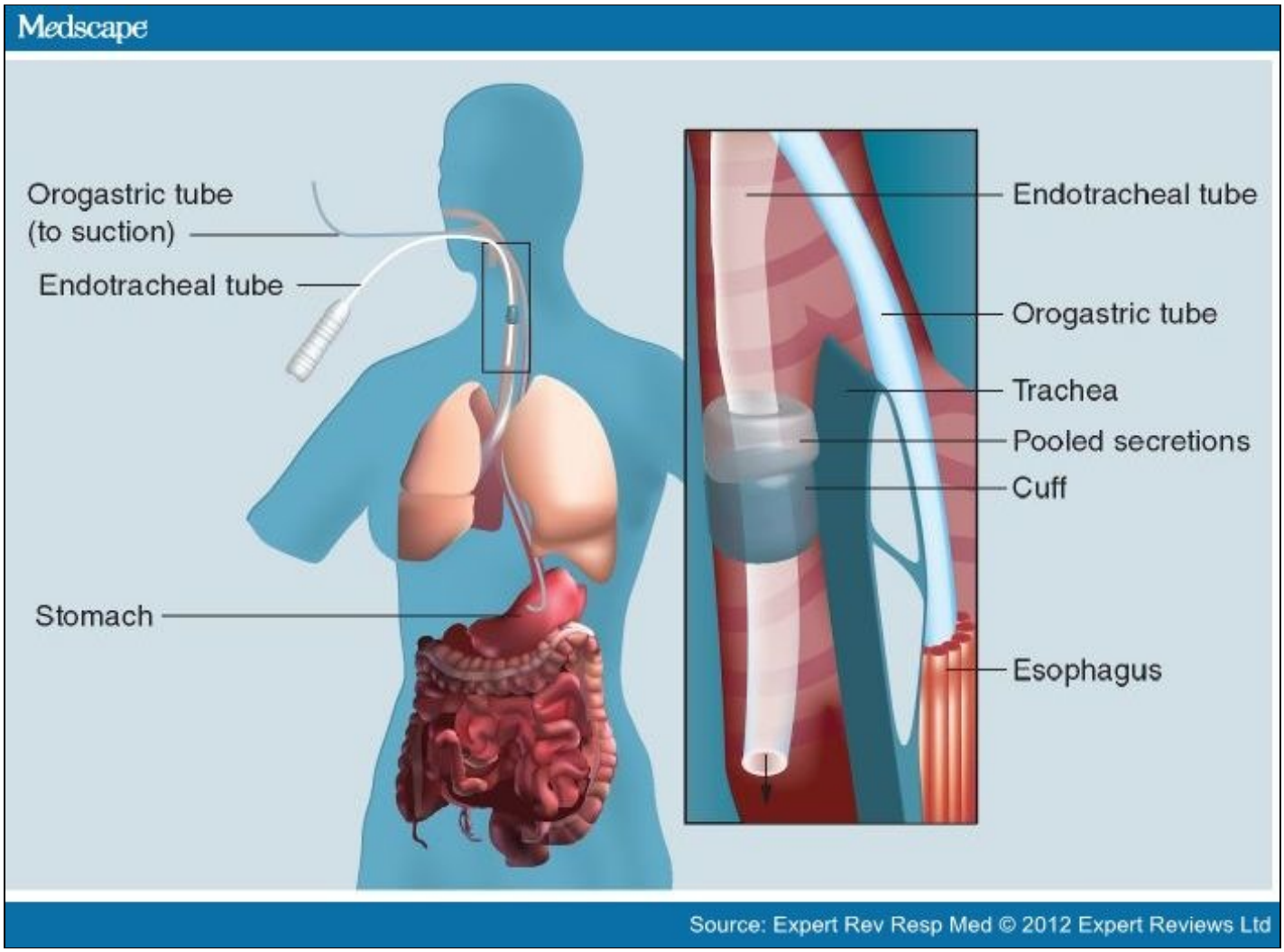

Figure 1.

Primary pathway of bacterial entry into the lower respiratory tract in intubated patients. Sources include pooled bacterial secretions that leak around the endotracheal tube cuff and biofilm-encased bacteria that colonize the endotracheal tube lumen.Redrawn with permission from [226].

The stomach may be an important, underappreciated reservoir for bacteria causing VAP. The gastric cavity is sterile under normal circumstances. With the use of acid-suppressive medications in critically ill intubated patients, gastric colonization may reach 10 $^{6–8}$ bacteria/ml. Colonized stomach contents may reflux to the oropharynx and subglottic space and then be aspirated to the tracheobronchial tree where they can cause pneumonia. [28–30] Reduction of gastric acidity due to the use of histamine-2 receptor antagonists or proton pump inhibitors for stress ulcer prophylaxis significantly increases gastric colonization with bacteria that can be refluxed into the oropharynx and subglotic space. [31] Recumbency and the presence of nasogastric tubes can facilitate orogastric reflux of colonized gastric contents. [31]

Criteria for Diagnosing VAP & Ventilator-Associated Tracheobronchitis

There is no gold standard for the diagnosis of VAP. [32–34] Clinical signs and microbiologic and radiologic criteria for the diagnosis of ventilator-associated tracheobronchitis (VAT) and VAP are summarized in . Microbiologic criteria may be based on the use of endotracheal aspirates (EA) or specimens obtained by bronchoalveolar lavage (BAL) or protected specimen brush (PSB) as shown in . VAP may also be diagnosed by a clinical pulmonary infection score ≥6. [35,36] A review comparing

various criteria of VAP diagnosis concluded that the most frequently used Johanson clinical criteria (new or progressive infiltrate on chest radiograph and at least two of the following three criteria: fever >38°C, leukocytosis or leukopenia and purulent secretions) resulted in only 69% sensitivity and 72% specificity when compared with postmortem lung biopsies. [32,37,38] Additional clinical criteria can increase specificity at the cost of sensitivity. The review also evaluated various microbiologic criteria versus histological references. Sensitivities for VAP diagnosis ranged from 22 to 50% and specificity from 45 to 100%. Diagnostic yield was higher but still limited when microbiologic criteria were added to histological references. Studies of BAL relative to histology report a wide range of positive-predictive values (range: 20–100) but the average is only approximately 60%. Invasive microbiologic diagnosis for VAP is not always readily available and is more costly. [39]

Table 1. Diagnosis of ventilator-associated tracheobronchitis and ventilator-associated pneumonia.

▪	Clinical signs and symptoms †	Radiograph	▪	Microbiology
VAT VAP	At least two parameters from points 1–3 1. Temperature: ≥38°C or 100.4°F 2. WBCs ≥12,000/mm ^{3} or ≤4000/mm ^{3} 3. Purulent sputum 4. Hypoxemia	No new infiltrate New and persistent infiltrate	No positive BAL or PSB BAL ≥10 ^{4} cfu/ml ‡ or PSB ≥10 ^{3} cfu/ml ‡	Endotracheal aspirate Semiquantitative culture: moderate to heavy growth or Quantitative ≥10 $^{5–6}$ cfu/ml

†Alternative diagnostic criteria: ≥1 of parameters 1.2 and ≥1 of parameters 3.4. VAP may be diagnosed by a CPIS ≥6 [28,29].

‡Applicable for VAP only.

BAL: Bronchoalveolar lavage (bronchoscopic or nonbronchoscopic); CPIS: Clinical pulmonary infection score; PSB: Protective specimen brush;

VAP: Ventilator-associated pneumonia; VAT: Ventilator-associated tracheobronchitis; WBC: White blood cell.

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Intubated patients have easy access for sputum EA that can be assessed by Gram stain and culture. Gram stain of an EA may provide rapid clues to the type of pathogen and the presence of polymorphonulcear leukocytes, which suggests infection. A positive BAL or PSB culture establishes the diagnosis of VAP. Two meta-analyses comparing invasive versus noninvasive culture techniques found similar outcomes, but use of invasive methods was associated with significantly reduced antibiotic use. [40,41]

Clinical and EA microbiologic criteria are similar for VAT and VAP, but for the diagnosis of VAP, patients must have a new and persistent infiltrate on chest radiograph or CT scan. Differentiating infiltrates for the diagnosis of pneumonia may be difficult in patients with congestive heart failure, shock or acute respiratory distress syndrome. In these patients, use of invasive diagnostics, such as BAL or PSB, may be more useful than noninvasive methods. [2] A management strategy for suspected VAP is outlined in Figure 2.

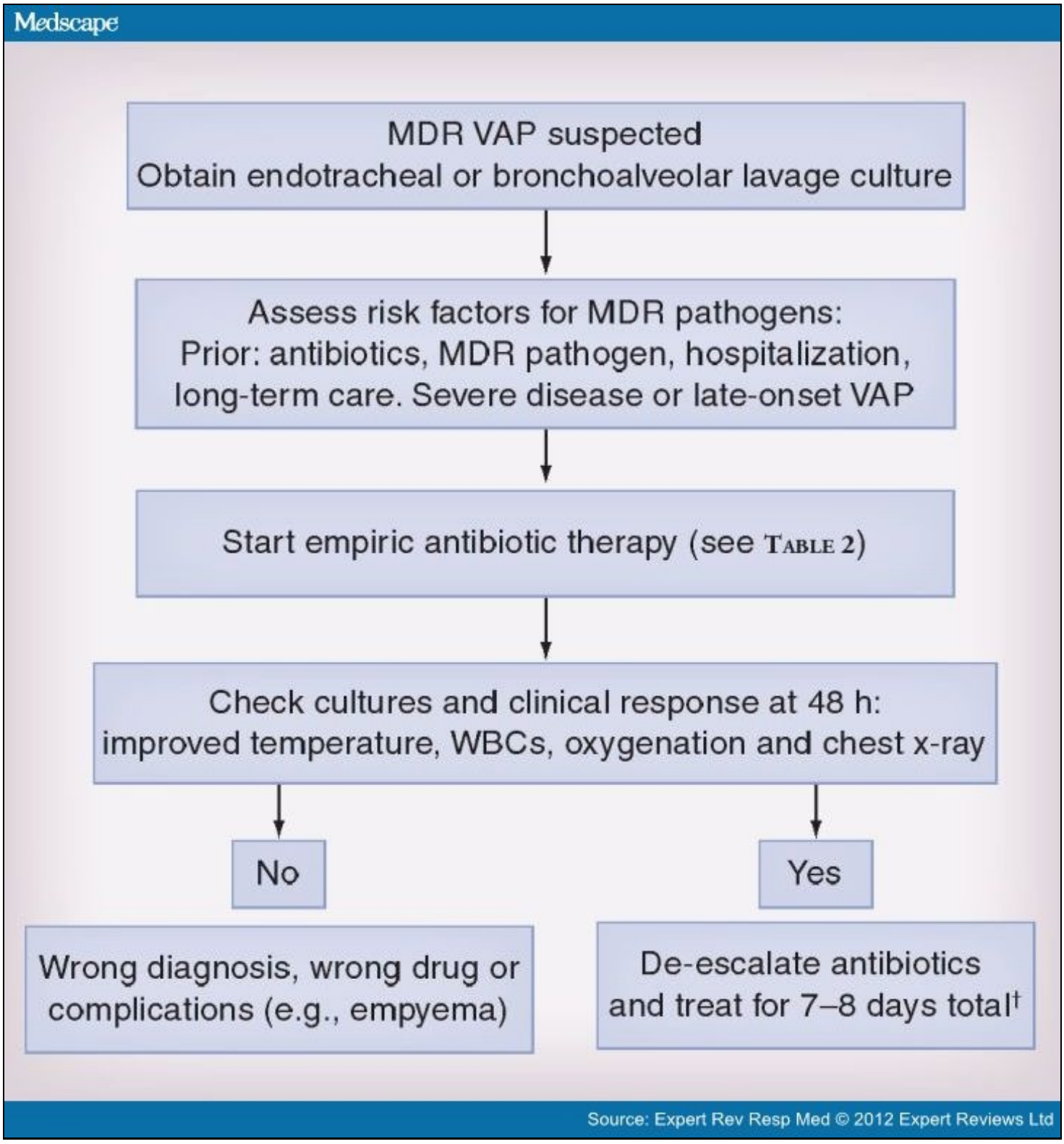

Figure 2.

Suggested algorithm for the management of ventilator-associated pneumonia caused by multidrug-resistant pathogens.

†De-escalate antibiotics and treat for 7–8 days in responders who are not infected with *Pseudomonas aeruginosa* or *Acinetobacter* species.

MDR: Multidrug resistant; VAP: Ventilator-associated pneumonia; WBC: White blood cell.

Management of VAP Due to MDR Pathogens

Principles for the management of patients with suspected VAP are discussed in the 2005 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) Guidelines for the Management of Adults with Hospital-Acquired, Ventilator-Associated and Healthcare-Associated Pneumonia and are summarized in . [6] The guidelines recommend early, broad-spectrum antibiotic therapy, including double coverage of Gram-negative bacteria (GNB), if risk factors for MDR pathogens are present; however, clinicians may consider narrower empiric coverage based on local microbiologic patterns. Some of these risk factors include prior hospitalization within 90 days, prior residence in a nursing home and prior antibiotic use. [6]

Table 2. Suggested empirical antibiotic therapy for ventilator-associated pneumonia in patients at risk for multidrug-resistant bacteria.

MRSA	**Vancomycin or linezolid** †
Gram-negative bacilli	Antipseudomonal cephalosporin (e.g., cefepime, ceftazidime) or Antipseudomonal β-lactam/β-lacatamase inhibitor (e.g., piperacillin–tazobactam) or Antipseudomonal carbapenem (e.g., meropenem, imipenem, doripenem) plus Aminoglycoside (e.g., gentamicin, tobramycin, amikacin) or Fluoroquinolone (e.g., ciprofloxacin, levofloxacin, moxifloxacin)

†Consider linezolid for the initial treatment of VAP in the case of severe pneumonia, shock, multiple risk factors for MRSA infection or a history of MRSA colonization or MRSA infection. See Table 4 for specific doses.

MRSA: Methicillin-resistant *Staphylococcus aureus;* VAP: Ventilator-associated pneumonia.

Adapted from the American Thoracic Society/Infectious Disease Society of America guidelines [3].

Initial broad-spectrum, empiric therapy should be followed by de-escalation 24–48 h after initiation when microbiologic cultures and antibiotic sensitivity data are available. Patients with uncomplicated infection should be treated for at least 7–8 days. In those who are nonresponders, and in selected patients with VAP due to *Pseudmonas aeruginosa* or MDR Gram-negative bacilli, such as *Acinetobacter* species, therapy should be extended up to 14 days. Procalcitonin concentration measurements can aid in shortening the duration of VAP treatment, but do not alter the rate of mortality. [42,43] In contrast to community-acquired pneumonia, in hospital-acquired pneumonia and healthcare-associated pneumonia, microbiologic identification with antibiotic sensitivity data are frequently available for intubated patients with suspected VAP. [44] Antibiotics used in the treatment of MDR VAP due to specific pathogens are shown in and doses are reviewed in .

Table 3. Treatment for ventilator-associated pneumonia caused by selected multidrug-resistant pathogens.

Pathogen	First-line treatment	Alternative treatment
Gram-positive pathogens		
Methicillin-resistant *Staphylococcus aureus*	Vancomycin or linezolid †	If vancomycin MIC >1: consider change to linezolid
Vancomycin intermediate *Staphylococcus aureus* Heteroresistant vancomycin intermediate *Staphylococcus aureus* Vancomycin-resistant *Staphylococcus aureus*	Linezolid	▪
Linezolid-resistant *Staphylococcus aureus*	Vancomycin	▪
Gram-negative pathogens		
Extended-spectrum β-lactamase producing *Enterobacteraciae*	Carbapenems	Fluoroquinolones, aminoglycosides and polymyxins
Carbapenemase-producing *Enterobacteraciae*	Polymyxins and aminoglycosides	Tigecycline ‡
Pseudomonas aeruginosa	Cefepime, ceftazidime, piperacillin/tazobactam, imipenem, meropenem and doripenem	Fluoroquinolones, aminoglycosides and polymyxins
Acinetobacter baumannii	Carbapenems	Polymyxin, aminoglycosides and sulbactam
Stenotrophomonas maltophilia	Trimethoprim–sulfamethoxazole	Fluoroquinolones and ceftazidime

Table 4. Antibiotic dosing for ventilator-associated pneumonia due to multidrug-resistant pathogens in patients with normal renal function.

Therapy for Gram-positive pathogens	
Vancomycin	15–20 mg/kg iv. every 8–12 h. Consider loading dose of 25–30 mg/kg iv. × 1 in the critically ill
Linezolid	600 mg iv. every 12 h
Therapy for Gram-negative pathogens	
Antipseudomonal cephalosporins	
Cefepime	2 g iv. every 8 h
Ceftazidime	2 g iv. every 8 h
Antipseudomonal penicillin	
Piperacillin/tazobactam	4.5 g iv. every 6 h
Antipseudomonal carbapenems	
Meropenem	1000 mg iv. every 8 h
Imipenem	500 mg iv. every 6 h or 1000 mg iv. every 8 h

Fluoroquinolones	
Ciprofloxacin	400 mg iv. every 8 h
Levofloxacin	750 mg iv. every 24 h
Moxifloxacin	400 mg iv. every 24 h
Aminoglycosides	
Gentamicin	iv.: 5–7 mg/kg of dosing weight iv. every 24–48 h †
Tobramycin	iv.: 5–7 mg/kg of dosing weight every 24–48 h † Nebulized: 300 mg every 12 h
Amikacin	iv.: 15–20 mg/kg of dosing weight every 24–48 h † Nebulized: 250–500 mg every 12 h
Other antibiotics	
Trimethoprim-sulfamethoxazole (*Stenotrophomonas maltophilia* only)	5 mg/kg of trimethoprim iv. every 6–8 h
Tigecycline ‡	100 mg iv. × 1, then 50 mg iv. every 12 h
Sulbactam ‡ (*Acinetobacter baumannii* only)	Up to 6000 mg/day iv. in divided doses
Colistin	iv.: 2.5–5 mg/kg/day in 2–4 divided doses ¶ Nebulized: 50–75 mg every 8–12 h

Management of VAP Due to MRSA

MRSA is the most common Gram-positive pathogen that causes VAP in the USA. [45] From 1992 to 2003, the rate of MRSA infection in ICU patients increased from 36 to 64% across 1200 centers. [46] Data indicate that MRSA colonization persists for a median time of 7.4–8.5 months. [47,48] MRSA infections are associated with high mortality, morbidity and healthcare costs. [49,50] Complications are significantly increased in patients who experience delayed therapy or receive suboptimal antibiotics.

Current therapy options for MRSA VAP include vancomycin and linezolid. Daptomycin has activity against MRSA, but is not recommended for the treatment of pneumonia, as it binds to and is inactivated by pulmonary surfactant. Ceftaroline is a new cephalosporin with broad-spectrum activity, including MRSA, that has been approved for community-acquired pneumonia but not VAP.

Vancomycin is a glycopeptide antibiotic that was introduced in 1956 to treat *S. aureus* infections, but was quickly overshadowed by the less toxic semisynthetic penicillins, such as methicillin, and cephalosporins, such as cefazolin. Toxicity concerns associated with vancomycin have largely subsided with the introduction of a purer form of the drug, although nephrotoxicity can occur, especially with high doses. [51] With the rapid emergence of MRSA infections in the 1980s and 1990s, vancomycin became the cornerstone for MRSA therapy. Vancomycin dosing is weight-based, and dose reductions are necessary for patients with compromised renal function. Measurement of vancomycin serum levels is necessary to optimize efficacy and reduce renal toxicity. Recommended trough levels for the treatment of VAP due to MRSA are 15–20 µg/ml.

Because vancomycin use has increased over the last three decades, the minimum inhibitory concentrations (MICs) of vancomycin needed to treat *S. aureus* infections have increased. Vancomycin MICs exceeding 2 µg/ml correlate with lower clinical efficacy. [52] Studies have documented the emergence of *S. aureus* strains identified as vancomycin intermediate sensitivity, with MICs of 4–8 µg/ml, and vancomycin-resistant *S. aureus*, with MICs of at least 16 µg/ml. [53] In addition, some *S. aureus* isolates have shown heteroresistance. These strains are associated with poor response to vancomycin and are termed heteroresistant vancomycin-resistant *S. aureus*. These observations underscore the need to carefully evaluate patients treated with vancomycin therapy who are not responding.

In 2002, the oxazolidinone linezolid was introduced for treating MRSA pneumonia. Linezolid inhibits synthesis in the bacterial

50S ribosome, has excellent oral bioavailability, achieves high lung epithelial fluid levels, can be given both intravenously and orally and does not require serum monitoring. The main concerns with linezolid include thrombocytopenia, neuropathy and drug interactions with antidepressants, monoamine oxidase inhibitors, some analgesics and anticonvulsants. [54] Linezolid resistance is rare, but has been reported with widespread use. [55]

Over the past decade, there has been considerable controversy over the risks and benefits of vancomycin versus linezolid therapy for MRSA pneumonia. [46,56–59] Data from two prospective, randomized, controlled, double-blind trials of MRSA nosocomial pneumonia showed that linezolid was noninferior to vancomycin given at a dose of 1 g every 12 h for patients with normal renal function. A *post-hoc* analysis found that patients treated with linezolid had better survival (80 vs 64%; $p < 0.03$) and higher clinical cure rates (59 vs 36%; $p < 0.01$). [58,59] However, these data were limited by the low number of subjects treated, the subset design and the use of vancomycin at lower doses than recommended in consensus guidelines. [60]

Wunderink *et al.* recently published a multicenter, prospective, double-blind, randomized controlled trial comparing linezolid 600 mg intravenously every 12 h with vancomycin dosed 15 mg/kg every 12 h and adjusted to achieve trough levels of 15–20 µg/ml. [61] Clinical response and MRSA eradication rates were improved by approximately 10% at the end of the study in the linezolid group, but the lower bound of the 95% CI approached zero. There was no difference in mortality between the groups at 14 or 28 days. Renal toxicity was higher in the vancomycin group. Limitations of this study were nicely reviewed in an editorial that accompanied the study. [62] Given the marginally significant difference in clinical outcome and the lack of mortality benefit, current data suggest linezolid and vancomycin are both reasonable options for initial, empiric treatment of VAP in most patients ().

Table 5. Comparison of linezolid and vancomycin for methicillin-resistant *Staphylococcus aureus* ventilator-associated pneumonia.

Variable	Vancomycin	Linezolid
Class	Glycopeptide	Oxazolidinone
Active site	Cell wall	50S ribosome
Activity	Bactericidal	Bacteriostatic
Antitoxin activity	No	Yes
Oral therapy available	No	Yes
Weight-based dosing	Yes	No
Serum concentration monitoring required	Goal: 15–20 µg/ml	No serum concentration monitoring
Renal dose adjustment	Yes	No
Epithelial lung penetration	Low	High
Adverse drug reactions	'Red man syndrome', thrombocytopenia	Serotonin syndrome, thrombocytopenia, neuropathy
Significant drug interactions	No	Yes
Resistant strains	VISA, VRSA	LRSA
Heteroresistance	Yes	No
Increased MICs reported	Yes	Rare

Some patients may benefit from linezolid over vancomycin; however, it is important to consider the use of linezolid in light of the need to minimize the development of resistance arising from overuse. [63] Linezolid may be advantageous when enhanced lung penetration is desired, vancomycin MICs exceed 1 µg/ml and in the case of endotoxin-producing bacteria. Consequently, linezolid should be considered for initial treatment of VAP in patients who have severe pneumonia, shock, multiple risk factors for MRSA infection, or a history of MRSA colonization or MRSA infection. Therapy should be changed from vancomycin to linezolid in patients with an MRSA pneumonia that does not respond to initial vancomycin therapy or if an isolate with an MIC >1 µg/ml is identified. [64]

Management of VAP Due to Gram-negative Pathogens

Infections due to MDR GNB are increasing in frequency and are associated with significant morbidity, mortality and healthcare costs. [14,65,66] GNB can develop resistance through several mechanisms, including production of enzymes that destroy or degrade antibiotics, downregulation of outer membrane entry porins, upregulation of efflux pumps and mutations at antibiotic binding sites Figure 3. [11,13,67]

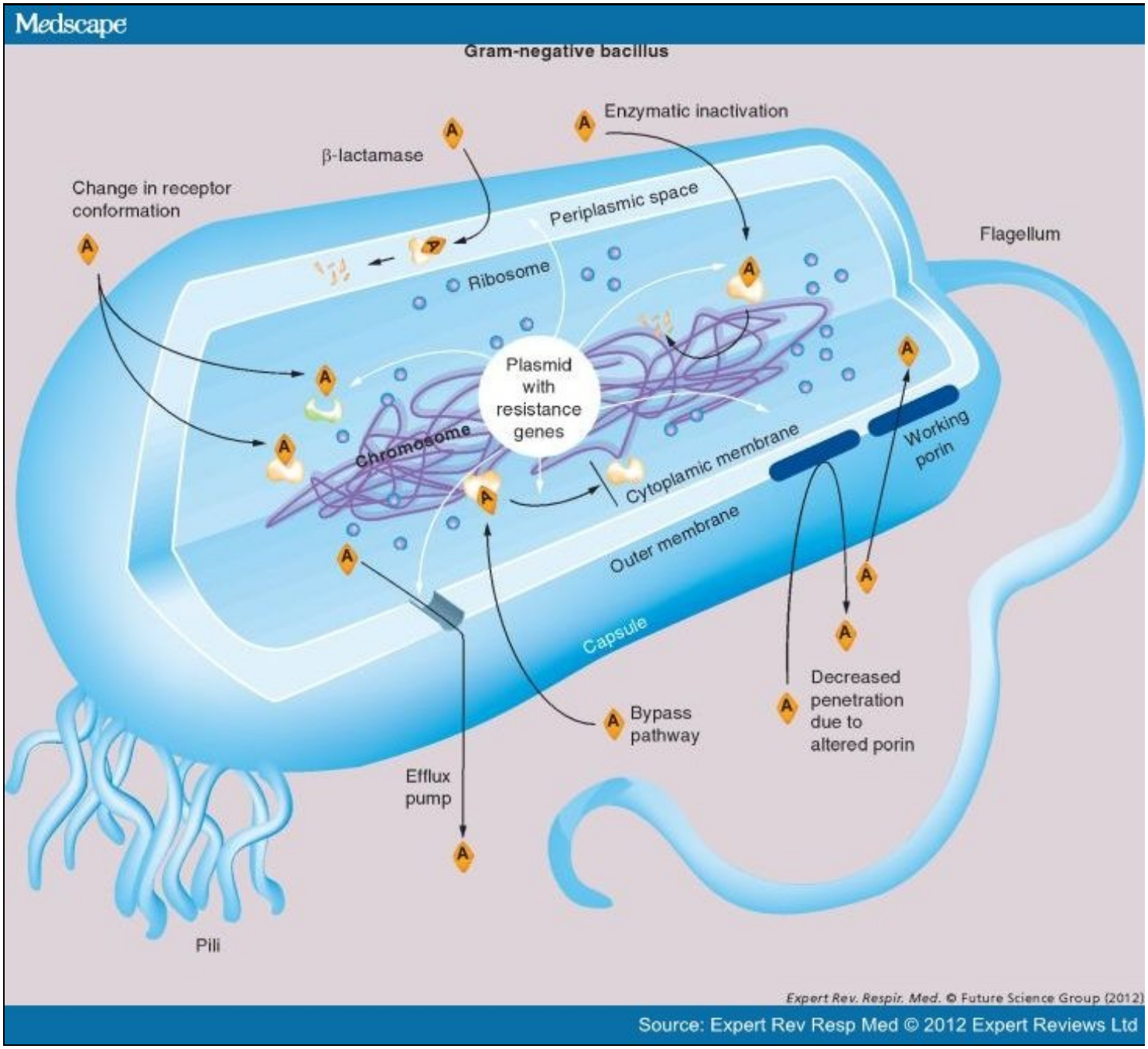

Figure 3.

Mechanisms of resistance to antibiotics in Gram-negative bacilli.

β-lactamases, enzymes that hydrolyze the β-lactam structure of penicillins and cephalosporins, are commonly implicated in antibiotic resistance. Aminoglycoside-modifying enzymes contribute to aminoglycoside resistance while binding site mutations in DNA gyrases are responsible for resistance to quinolones. Downregulation of outer-membrane proteins prevent antibiotics from penetrating to the cytoplasmic space and are responsible for the mechanisms of *Pseudomonas* resistance. Efflux pumps confer resistance to quinolones, antipseudomonal penicillins and third-generation cephalosporins by removing the antibiotic from the cytoplasmic space before it can attach to its target site. Initial management of these infections should follow

established guidelines with antibiotic optimization and de-escalation as indicated. [6] Management of specific pathogens is detailed later.

Extended-Spectrum β-lactamases

Extended-spectrum β-lactamases (ESBLs) represent a major source of antimicrobial resistance in GNB. The most common bacteria that produce ESBLs are *Klebsiella* species, *Escherichia coli*, *P. aeruginosa* and *Acinteobacter* species. Although some β-lactams may appear sensitive *in vivo*, ESBLs confer resistance to all penicillins and aztreonam. ESBL-producing organisms are also frequently resistant to fluorquinolones, trimethoprim–sulfamethoxazole and aminoglycosides since other mechanisms of resistance can be carried on genes encoding for ESBLs on bacterial plasmids. [11] Carbapenems have greater stability against ESBLs and are a good choice to treat infections due to ESBL-producing organisms. [11] Although cephalosporins have been avoided in the past for the treatment of ESBL-producing bacteria, revised MIC breakpoints (discussed later) will result in increased susceptibility to cephalosporins. Thus, if an organism is susceptible to a cephalosporin when using the new breakpoints, these drugs may be used for treatment.

Hospitalized patients can become colonized by MDR GNB. It is estimated that 85% of uncolonized patients admitted to a general medical ward become carriers of ESBL-producing *Enterobacteriaceae* during their hospitalization. [68] Risk factors for rectal carriage include nursing home residence, recent antibiotic therapy and prior carriage of an MDR pathogen. The median duration of ESBL carriage has been reported to be 132 days, and more than 50% of patients readmitted from 6 to 12 months after hospitalization still carry ESBL-producing *Enterobacteriaceae*. [68,69]

Carbapenemase-Producing Enterobacteraciae

Carbapenemases are broad-spectrum β-lactamases that cause resistance to all β-lactams, β-lactamase inhibitors and carbapenems. Many reports of carbapenemase-producing enterobacteraciae (CPEs) have involved *Klebsiella pneumoniae* infections. Thus, the term *K. pneumoniae* carbapenemases has been used in the literature to describe this subset of CPE isolates. *Enterobacteriaceae*, such as *E. coli*, *Enterobacter* species, *P. aeruginosa* and *Acinetobacter baumannii*, can also be CPEs. [70–72] Alarmingly, healthcare-associated infections due to CPEs are on rise in the USA and worldwide. [73] In the USA, CPEs have been reported most commonly in the northeast. High-dose carbapenem therapy has been reported to select for CPE strains. [74]

CPE isolates may be reported as susceptible to some β-lactam antibiotics, but these agents should be avoided because additional resistance mechanisms may be expressed and *in vitro* susceptibility may not translate into *in vivo* efficacy due to ESBL production. [75]

Treatment options for VAP due to infections from CPEs may include fluoroquinolones, trimethoprim–sulfamethoxazole, polymyxins and aminoglycosides. [11,70,76–78] Given the limited *in vivo* data regarding the treatment of CPE infections, appropriate antimicrobial choices for individual isolates should be determined based on susceptibility testing and patient-specific criteria. [76,79–81] A recent review evaluated 15 studies that reported a total of 57 treatment courses for CPE infections. The authors concluded that aminoglycosides or combination regimens containing polymyxins and tigecycline were most effective while carbapenems and polymyxin monotherapy were less effective. [70] Nonetheless, tigecycline is not recommended for the treatment of VAP based on data showing a high rate of mortality during treatment. [305] Results of studies evaluating treatment of CPEs are limited because the papers are largely case reports, definitions are inconsistent or unreported, different types of infections are combined for analysis and publication bias may exist.

Other experts caution that while combination therapy for CPEs may appear beneficial based on *in vitro* testing, clinical data are lacking. [79,82] When considering treatment options, reports of resistance developing during treatment, antimicrobial tissue penetration and medication-related adverse effects should be taken into account. Poor lung penetration has been observed with intravenous polymyxins, but clinical outcome data relating to this finding are conflicting. [83–87] Additionally, polymyxins have historically been associated with increased nephrotoxicity and occasional neurotoxicity. Use of aminoglycosides may potentiate both nephrotoxicity and ototoxicity.

Pseudomonas Aeruginosa

P. aeruginosa is a ubiquitous Gram-negative bacillus responsible for a broad spectrum of nosocomial infections in critically ill and immunocompromised patients. It possesses intrinsic virulence factors that alter immune clearance and increase tissue damage. Healthy humans may be colonized, but are rarely infected. The respiratory tract is the most common site of *P. aeruginosa* infections and the organism is one of the most frequently encountered VAP pathogens. [88,89] Patients previously

colonized or infected by *P. aeruginosa* or those with previous exposure to antibiotics during ICU stay are at greatest risk. [90] Strains that produce exotoxins have been associated with excess mortality. [91]

P. aeruginosa has been more frequently associated with resistance to fluoroquinolones, which were once the preferred antipseudomal agents. [11,92] A systematic literature review reported significant increases in imipenem resistance, from 15% at initiation of imipenem treatment for VAP to 54% during treatment. [93] While resistance to imipenem results from loss of membrane proteins, production of metallo-β-lactamases confers resistance to all carbapenems and antipseudomonal β-lactams. [11]

Acinetobacter Baumannii

Acinetobacter is a Gram-negative coccobacillus that has evolved from a low pathogenic bacteria to an important MDR nosocomial pathogen in the USA. [94] The respiratory tract is the most common site of *Acinetobacter* infections and most infected patients are elderly, critically ill, severely debilitated or chronically ventilator dependant.

Epidemiologic data emphasize the importance and spread of MDR *Acinetobacter* species in the USA. Data from the Centers for Disease Control and Prevention collected from more than 300 hospitals in the USA show that rates of carbapenem resistance in 3601 isolates of *A. baumanni* infections increased from 9% in 1995 to 40% in 2004. [94] Outbreaks of *Acinetobacter* have been reported in ICUs throughout the USA and Canada. [94] *A. baumannii* isolates account for approximately 80% of *Acinetobacter* infections. Of great concern to clinicians is the intrinsic resistance of many *Acinetobacter* isolates to commonly available antibiotics used for treating pneumonia. [95,96] These mechanisms include β-lactamases, porins and efflux pumps.

Infections caused by antibiotic-susceptible *Acinetobacter* species have been treated with antipseudomonal carbapenems and β-lactamase inhibitors such as ampicillin/sulbactam or sulbactam alone. [97] Aminoglycosides may be used as adjunctive antibiotics for *A. baumannii* pneumonia based on sensitivity results. [98] Infections caused by MDR isolates are often treated with polymyxin B or polymyxin E (colistin), with doses adjusted for renal function. Patients treated with intravenous colistin should be carefully monitored for nephrotoxicity and neurotoxicity. The use of polymyxins plus rifampin, imipenem or azithromycin has been reported. Aerosolized polymyxin has also been utilized as an adjunctive antibiotic for VAP as discussed later. [99,100] Antibiotic combinations used for the treatment of *Acinetobacter* infections are reviewed elsewhere. [96]

Stenotrophomonas Maltophilia

Stenotrophomonas maltophilia has become a more frequent pathogen in ICUs in the USA over the past 20 years. It is most common in ventilated patients with a recent history of multiple trauma, broad-spectrum antibiotic exposure, tracheostomy or immunocompromise. [101,102]

VAP due to *S. maltophilia* is associated with increased length of ICU stay, longer duration of mechanical ventilation and greater mortality. [103] Increased mortality may be related to inadequate empiric antibiotic therapy due to intrinsic resistance to the empiric antibiotic regimens commonly prescribed and recommended in the ATS/IDSA Guidelines. [6] High-dose trimethoprim-sulfamethoxazole is the drug of choice for *S. maltophilia* based on its excellent *in vitro* activity. Some clinical isolates are sensitive to fluoroquinolones or ceftazidime. [102] After treatment, patients should be carefully monitored as recurrence is not uncommon, especially in ventilated patients. Recent investigations have emphasized that VAP due to *S. maltophilia* may be polymicrobial and less virulent than other Gram-negative pathogens. In some patients, inadequate initial antibiotic therapy may not significantly alter clinical outcomes. [102]

General Considerations in the Treatment of VAP Due to MDR Pathogens

Pharmacokinetic & Pharmacodynamic Optimization of β-lactams

Pharmacokinetics (PK) describes the absorption, distribution, metabolism and excretion of medications in the body over time while pharmacodynamics (PD) considers the effect of drug concentration at the receptor level on outcomes. Relevant PK–PD parameters include peak drug concentration relative to MIC (C_{max}/MIC), area under the concentration–time curve to MIC (AUC/MIC) and time above MIC (T > MIC). These parameters are illustrated in Figure 4.

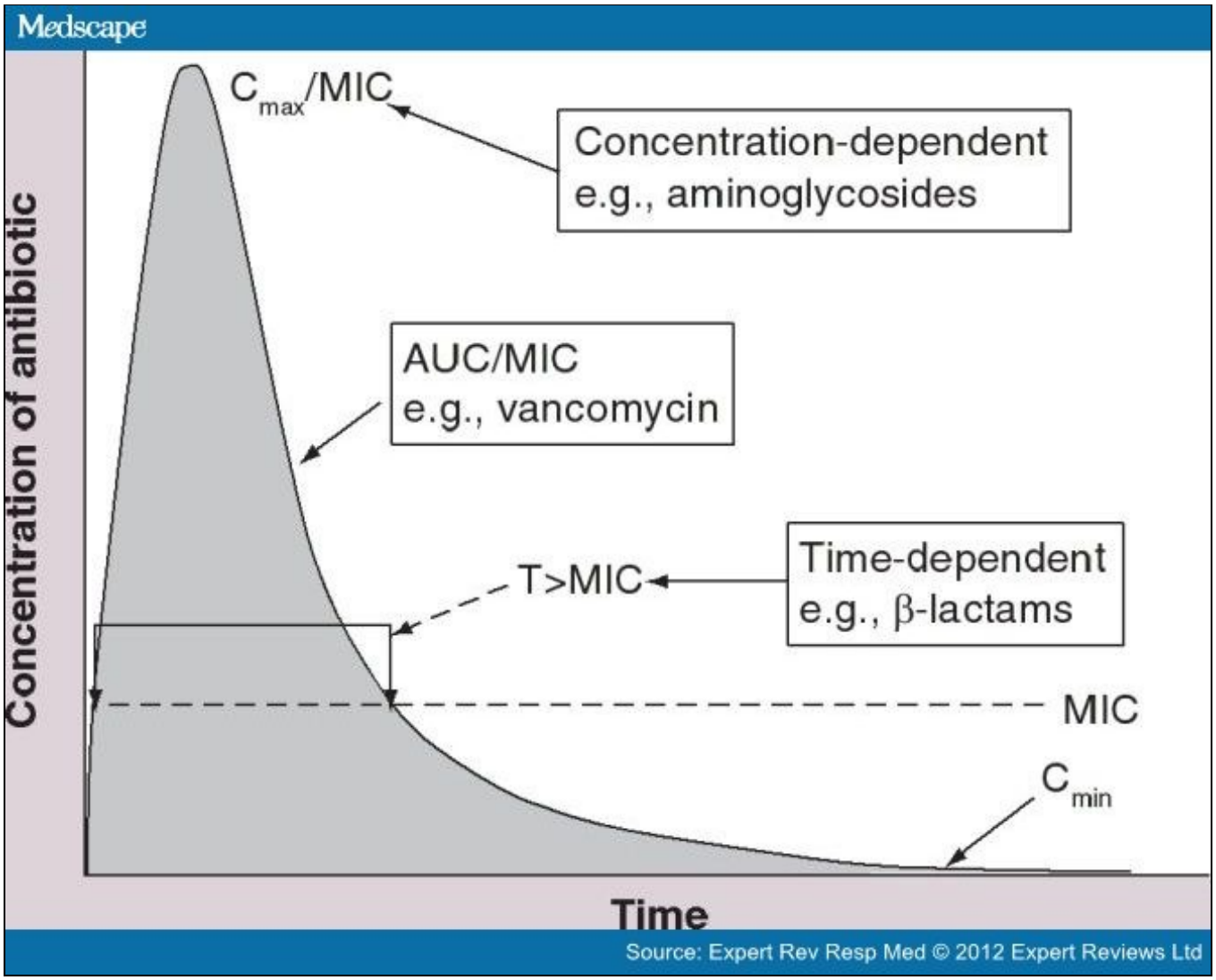

Figure 4.

Pharmacokinetic–pharmacodynamic kill parameters for different antimicrobials.

AUC: Area under the curve; C_{max}: Peak drug concentration; C_{min}: Minimum drug concentration; T: Time.

Optimization of C_{max}/MIC may be beneficial for concentration-dependent antibiotics such as aminoglycosides, while lengthening T > MIC may increase the effectiveness of time-dependent antibiotics like β-lactams. AUC/MIC should be targeted for agents that exhibit both concentration- and time-dependent characteristics, including vancomycin. PK–PD considerations may be particularly important in critically ill patients with increased volumes of distribution arising from fluid administration and capillary leak, alterations in drug clearance and renal function, and decreased protein binding. [104–110]

PK–PD simulations have demonstrated that optimization may be beneficial against resistant organisms, in patients with normal renal function and in cases of increased volume of distribution. [111–113] Specifically, piperacillin–tazobactam given as a 3.375 g infusion over 4 h allows for goal PK–PD attainment against *P. aeruginosa* with an MIC of 16 µg/ml whereas traditional bolus dosing of 3.375 g every 6 h results in suboptimal target attainment for organisms with MICs of 8 µg/ml. [114] Similar PK–PD optimization against more resistant bacteria have been suggested based on modeling of continuous infusions of cefepime and extended infusions of meropenem. [115,116]

Clinical studies have evaluated continuous and extended interval (i.e., over 3–4 h) β-lactam infusions and reported mixed results. One evaluation of extended infusion piperacillin–tazobactam demonstrated lower 14-day mortality and median length of stay in patients with *P. aeruginosa* infections and an APACHE II score of at least 17. No benefit was observed in the overall cohort. [114] Another historical cohort study of piperacillin–tazobactam showed a higher rate of clinical cure with the continuous infusion regimen when bacteria with an MIC of ≥8 µg/ml were treated. [117] However, no difference was found in

30-day mortality with extended infusion piperacillin–tazobactam in another study. [118]

A retrospective study of continuous infusion cefepime demonstrated a higher rate of clinical cure after logistic regression (89.3 vs 52.3%), while another retrospective study showed higher rates of clinical cure and bacteriologic eradication when T >MIC of 100% was attained for resistant organisms. [119,120] A study of continuous infusion meropenem demonstrated a higher rate of clinical cure as compared with traditional dosing, particularly against infections due to *P. aeruginosa* and bacteria with an MIC ≥0.5. [121] No significant difference was found in clinical cure when an extended infusion of doripenem was compared with conventional imipenem, but a subgroup analysis showed that *P. aeruginosa* resistance developed less often in the doripenem cohort. A meta-analysis of nine randomized, controlled trials evaluating extended and continuous infusions of β-lactams found no difference in survival or clinical cure with the longer infusions. [122]

Given the conflicting findings of individual studies and the nonsignificant difference observed in a meta-analysis, extended and continuous infusion antibiotics are most appropriate in patients who have resistant pathogens, normal renal function, high APACHE II scores or increased volumes of distribution. Additionally, because lengthier infusions may reduce the total number of antibiotic doses required per day, extended and continuous infusions may be considered as an opportunity to decrease total drug cost.

Changes to MIC Breakpoints & Effects on Resistance

Clinical laboratories rely on disk diffusion interpretive criteria, commonly referred to as 'MIC breakpoints', to determine whether bacteria are sensitive to antibiotics in daily practice. In the USA, breakpoints are set by the Clinical Laboratory and Standards Institute (CLSI) and the US FDA. Although CLSI breakpoints are updated regularly to reflect contemporary literature and epidemiology, updates to the FDA breakpoints may lag behind. Commercially available automated testing systems must adhere to breakpoints published by the FDA; however, clinical laboratories may choose to utilize either FDA or CLSI breakpoints.

Recently, the CLSI updated breakpoints in response to data characterizing the MIC distribution of wild-type bacteria, PK and PD analyses, and studies associating MICs with clinical outcomes. [123–127] In many cases, these breakpoints were lowered. Consequently, fewer bacteria are considered susceptible when updated, lower breakpoints are used. Clinicians should be aware of these breakpoint changes because laboratories may implement them as they deem appropriate. Additionally, clinicians may wish to take CLSI breakpoint changes into consideration when choosing antibiotics based on susceptibility data even if their local laboratory has not updated susceptibility reporting to reflect the most current CLSI criteria.

Changes made in 2010 included lower breakpoints for aztreonam, cephalosporins, ertapenem, imipenem and meropenem. In addition, breakpoints for doripenem were published for the first time. Changes to CLSI breakpoints for 2012 include a slightly higher breakpoint for ertapenem (MIC ≤0.5 µg/ml considered susceptible) and lower breakpoints for piperacillin, piperacillin/tazobactam, ticarcillin, ticarcillin/clavulanate, imipenem and meropenem when used for *P. areginosa* infections. [126] Upcoming CLSI breakpoint modifications may include fluoroquinolone breakpoints for several bacteria and cefepime and colistin breakpoints for *Enterobacteraciae*.

Inhaled Antibiotics

Local delivery of antibiotics to the respiratory tree has been investigated for nearly 40 years. [128] Theoretical benefits of local delivery include increased antibiotic concentration at the site of infection and low systemic absorption leading to decreased adverse effects and superinfections. [129–132] The most compelling data for local antibiotics come from studies of their use for cystic fibrosis in pediatric patients, where use has been shown to decrease hospitalizations and preserve lung function. [133,134] Considering that both cystic fibrosis and VAP involve airway inflammation and injury, impaired bronchial mucous clearance, and the formation of biofilms, clinicians have considered combining aerosolized antibiotics with systemic antimicrobials for the treatment of VAP. [135,136] However, few antibiotics have been specifically formulated for nebulized administration. As many nebulizers fail to produce drug particles that are small enough to penetrate to the distal airways, significant amounts may deposit in the oropharynx, tracheobronchial tree and ventilatory circuit, resulting in inadequate delivery of antibiotics into the aleveolar compartment. [137] The ATS/IDSA guidelines stated "adjunctive therapy with an inhaled aminoglycoside or polymyxin for MDR Gram-negative pneumonia should be considered, especially in patients not improving with systemic therapy" but called for more studies to evaluate this strategy. [138]

Three types of nebulizer systems may be used: jet, ultrasonic and vibrating-mesh nebulizers. Jet nebulizers combine high-pressure air with a drug to produce an aerosol, resulting in variations of particle size from device to device. [139] Excessive humidity in the device can decrease drug delivery, and microbial growth may be a concern if jet nebulizers are not cleaned

properly. Breath enhanced jet nebulizers may increase distal lung delivery of medications. [140] Ultrasonic nebulizers utilize a vibrating piezo-electric crystal to produce an aerosol and permit control of droplet size and drug output. They produce larger particles that are less likely to penetrate to the small airways. [139] Ultrasonic nebulizers have many other unfavorable characteristics, including high cost, maintenance requirements and possible denaturation of active molecules during aerosolization. [140] Vibrating-mesh nebulizers rely on a mesh or plate with multiple apertures to produce an aerosol. [141] They can synchronize with the inspiratory limb of the ventilator to deliver aerosol during a particular segment of inspiration. Vibrating-mesh nebulizers have been reported to be very efficient, with 50–70% of drug reaching the lung. [139] Vibrating-mesh nebulizers are associated with higher output, less drug loss due to evaporation and less risk of protein denaturation. [140]

Three small randomized trials have evaluated the use of currently available inhaled aminoglycosides for the treatment of hospital-acquired pneumonia (HAP). [142–144] Two of these trials reported greater success with the addition of inhaled aminoglycosides to systemic treatment. [142,143] The third trial was underpowered to show a benefit with inhaled therapy, but, notably, obstruction of the ventilator expiratory filter due to nebulization was reported in three patients receiving inhaled antibiotics. In one case, this obstruction resulted in cardiac arrest. [145] Several case series have reported successful use of aerosolized and endotracheally instilled aminoglycosides for the treatment of pneumonia. [146–152] Small observational trials have reported use of aerosolized colistin for the treatment of MDR *Pseudomonas* and *Acinetobacter* species. [99,148,149,153–161] Although treatment has been described in only approximately 360 patients and some patients were chronically colonized with these pathogens, response rates ranged from 24 to 100%, and from 76 to 100% after removal of the least favorable study.

Taken together, these reports of aerosolized aminoglycosides and colistin support consideration for patients with VAP who fail to respond to intravenous therapy and those infected with MDR organisms. Consideration should be given to the optimal nebulizer system and measures should be taken to improve the amount of drug delivered. [140] Clinicians should be aware that bronchoconstriction and chest tightness may occur when nebulized antibiotics are administered and pretreatment with an inhaled β-2 agonist should be utilized.

Surveillance Cultures & Empiric Treatment versus Targeted Treatment

Microbiologic surveillance in the form of serial EA sample analysis is based on an assumption that colonization of the tracheobronchial tree with MDR pathogens predisposes patients to infection with the colonizing organisms. The purpose of serial EA sample analysis is to identify likely pathogen(s) and antibiotic sensitivities before the development of VAP and to facilitate targeted antibiotic treatment and de-escalation. [162–167] Antibiotic de-escalation is of upmost importance since widespread use of antibiotics may be associated with increased emergence of MDR pathogens while inadequate treatment leads to worse patient outcomes. [168,169]

Some experts have suggested empiric antibiotic regimens determined by risk stratification for probability of VAP secondary to MDR organisms as an alternative to the double Gram-negative coverage advocated in the ATS/IDSA guidelines. [170] This approach may decrease unnecessary exposure to antibiotics and potentially reduce development of resistance. One strategy of targeted therapy involves systematic surveillance cultures.

Several studies have examined the use of serial respiratory surveillance cultures. Michel *et al.* obtained quantitative EA (Q-EA) twice weekly in an intubated cohort and compared these cultures with the results of BAL performed at the time of VAP diagnosis. In this study, the causative organism was identified by surveillance Q-EA in 83% of study patients. [162] Depuydt *et al.* used systemic surveillance cultures coupled with three-times weekly semiquantitative EA (SQ-EA) and Q-EA to detect VAP due to MDR pathogens. Overall, sensitivity of VAP pathogen prediction was 69% by EA and 82% for all surveillance cultures. Surveillance cultures contributed to early (within 48 h) appropriate antibiotic therapy in 96% of patients who developed VAP and in 89% of patients with MDR VAP. [163] Yang *et al*. used daily Q-EA cultures to evaluate for EA colonization and subsequent evolution of VAP. Out of 1868 screened patients, only 75 were included in the study. This study showed that once patients became colonized, VAP developed more rapidly in patients colonized with MDR *P. aeruginosa* compared with patients colonized with other organisms but MDR *P. aeruginosa* VAP occurred later than non-MDR *P. aeruginosa* VAP. [164] Finally, the introduction of a de-escalation strategy for treatment of VAP was shown to increase the rates of initially appropriate antibiotic therapy and decrease duration of treatment in a prospective observational study. [171] Episodes of superinfection were significantly reduced (from 24 to 7.7%; p = 0.03), presumably secondary to fewer new infections with highly resistant GNB. [172]

In contrast to these studies, Haydon and coworkers found limited value in using routine surveillance cultures to guide

antibiotic treatment in patients with VAP. These investigators used bronchoscopic techniques combined with systemic cultures as surveillance. Of the 220 organisms responsible for VAP, only 33% were recovered from any body site before VAP. When an organism was isolated from multiple sites, including at least one invasive respiratory culture, the predictive value was higher than when isolated from multiple sites other than the lungs ($p < 0.01$). Among 102 VAP episodes with prior respiratory samples, causative organisms were identified in only 35% of specimens. [165] Further studies are needed to clarify these results and define optimal intervals between surveillance cultures.

A strategy of surveillance cultures carries a risk of lowering the threshold to diagnose and treat VAT or VAP. Some clinicians may misinterpret colonization as infection while others may be uncomfortable simply observing a patient harboring pathogens such as MRSA or *Pseudomonas*. It is of paramount importance to distinguish colonization from infection to avoid antibiotic exposure in noninfected patients. The purpose of surveillance cultures is not to simply treat colony counts but to appropriately initiate early therapy in patients exhibiting signs of infection, target causative pathogens and minimize the use of unnecessary or redundant antibiotics.

Strategies to Minimize the Development of VAP

ETT With Subglottic Secretion Drainage

Aspiration of oropharyngeal and subglottic secretions is a major contributor to the pathogenesis of VAP. ETTs with subglottic secretion drainage (SSD) are specially designed tubes with a separate lumen that opens immediately above the ETT cuff. They drain subglottic secretions that accumulate above and leak around the ETT cuff (Figure 1).

ETTs with SSD have been shown to reduce the incidence of VAP by up to 50%. [173] A recently published meta-analysis reviewed 13 randomized clinical trials including 2442 patients. [174] This study showed that subglottic secretion drainage reduced the ICU length of stay, decreased duration of mechanical ventilation and lengthened time to first episode of VAP. There was, however, no significant change in ICU or hospital mortality.

ETTs with SSD appear to primarily reduce VAP occurring between 3 and 7 days after intubation. Because the pathogenesis of late onset VAP involves tracheal colonization that is not preceded by oropharyngeal subglottic secretion contamination and mechanisms such as ETT biofilms and hematogenous spread of organisms, ETTs with SSD are less effective in preventing late-onset VAP.

Routine use of SSD ETT is significantly costlier than use of standard ETTs but the higher cost of these ETTs may be offset by cost savings from the prevention of VAP. One VAP is prevented for every 11 patients intubated with ETTs with SSD. Although the use of ETTs with SSD may seem most attractive in patients requiring longer-term mechanical ventilation, identification of this population at the time of intubation is often difficult.

Silver-Coated ETT

Silver has antimicrobial properties. Silver-coated ETTs are designed to reduce VAP by decreasing bacterial colonization and biofilm formation in the ETT lumen that may lead to biofilm dislogement into the distal airway during suctioning or bronchoscopy.

A large prospective, randomized, single-blinded controlled study of 2003 patients in 54 North American centers demonstrated significant reduction of VAP in patients intubated for 24 h or longer with silver-coated ETTs. [19] The rates of microbiologically confirmed VAP were 4.8% in the silver-coated ETT group versus 7.5% in the control group. The silver-coated ETT also delayed occurrence of VAP. However, there was no statistically significant difference noted in the duration of intubation, length of stay in the ICU or hospital, or mortality. The number of patients needed to treat with the silver-coated ETT to prevent one case of VAP was approximately 37. A cost–effectiveness analysis of silver-coated ETT showed a savings of US$12,800 per case of VAP prevented. [175] However, identifying high-risk patients at the time of intubation is difficult.

Oral Care With Chlorhexidine

A number of studies have examined the use of chlorhexidine for the prevention of pneumonia. Chlorhexidine is a topical antiseptic with activity against a wide spectrum of bacteria that colonize the oropharyx. Numerous studies have been performed with mixed results in the prevention of nosocomial pneumonia. Chlorhexidine has been shown to reduce the incidence of nosocomial pneumonia in cardiothoracic ICU patients. Its role is less well established for medical and surgical patients and for the prevention of VAP as compared with HAP. [176,177] However, results in nosocomial pneumonia and VAP

have been variable. [178,179]

Staff Education & Adherence

Educating critical care staff about best practices and process optimization can substantially decrease rates of VAP. [180,181] There are many effective ways to educate healthcare workers. This can be achieved through self-study modules, Internet-based learning programs, lectures, focused small group teaching, workshops and informative posters summarizing VAP prevention guidelines. The United States Department of Health and Human Services website with resources on implementing a Comprehensive Unit Based Safety program to prevent healthcare infections is very useful and educational. [301] Other websites contain information that can assist in providing effective staff education. [302–304] Healthcare workers should undergo competency training in VAP prevention, and adherence to infection prevention guidelines should be monitored and reinforced.

An educational strategy utilizing a physician-led task force to educate respiratory therapists and critical care nurses about VAP prevention strategies was shown to reduce VAP rates from 12.6 to 5.7 per 1000 ventilator days ($p < 0.001$) ( ). [181] Another study reported a 46% decrease in the rates of VAP after an educational program for ICU nurses and respiratory therapists. [180]

Box 1. Selected prevention strategies for ventilator-associated pneumonia.

- Avoid mechanical ventilation if possible
- Use noninvasive ventilation and high-flow nasal cannula oxygen therapy
- Minimize duration of mechanical ventilation
- Practice hand hygiene and equipment sterilization
- Implement the Institute for Healthcare Improvement ventilator care bundle
- Daily interruption of sedation followed by assessment for readiness to wean and spontaneous breathing trials
- Semirecumbent positioning (30–45°)
- Oral care with chlorhexidine
- Use targeted treatment for VAP
- Educate healthcare staff, monitor adherence to VAP prevention strategies and reinforce as needed
- Checklists
- VAP surveillance data and reporting results to staff
- Use endotracheal tubes with subglottic secretion drainage or silver-coated endotracheal tubes

VAP: Ventilator-associated pneumonia.

Most VAP prevention strategies are focused on reducing bacterial colonization and microaspiration, but no single measure completely eliminates VAP. Guidelines have been established as ventilator bundles, but adherence has been poor. [182] This may be due to the lack of initial education, regular monitoring with feedback or use of daily checklists. There is also a need to invest in leadership, infection control teams and a strategic plan for continuous quality improvement. [7] Furthermore, educational initiatives must be ongoing and continually reinforced through monitoring of adherence and regular feedback to staff.

Daily ICU Checklist

An ICU checklist is a reminder document that prompts clinicians to evaluate specific medical interventions, prevention

measures and bundles and processes to enhance medical care and ensure consistency in a complex and stressful ICU environment. Thus, checklists aid in minimizing errors of omission and facilitate the delivery of safe and high-quality medical care through adherence to evidence-based best-practice guidelines.

The components of ICU checklists aimed at preventing VAP include reminders about the Institute for Healthcare Improvement (IHI) VAP prevention bundle as well as sedation vacations, daily spontaneous breathing trials and extubation as appropriate. Documentation of antibiotic use, re-evaluation of antibiotics, and appropriate de-escalation and discontinuation can be highlighted with checklists. The IHI bundle emphasizes maintaining patients in the semi-upright position (head of the bed elevation from 30 to 45°) to prevent reflux of bacteria from the gastric reservoir. [183] Patients who are transported outside of the ICU should also be maintained in this position. [184]

Use of daily ICU checklists has shown to help decrease the duration of mechanical ventilation. In a randomized, controlled single-site study, daily ICU checklist-based physician prompting was associated with a reduction in the number of ventilator-free days from 22 to 16 ($p = 0.028$) when compared with standard care. Additionally, ICU and hospital mortality rates were lower when daily ICU checklists were used. [185] The use of daily ICU checklists can help reduce the incidence of VAP and other nosocomial infections.

Although the use of an ICU checklist has resulted in improved patient outcomes and decreased healthcare cost, effective implementation remains a problem. [186] One study showed improvement in patient outcomes only in the prompted group with active as opposed to passive implementation of an ICU checklist. [171] There is also a potential for checklist fatigue. Checklists should be simple and easy to use. Effective use of checklists in ICUs requires a robust implementation strategy that emphasizes user buy in and, often, a clinician culture change. There is a need to establish accountability measures at the institutional as well as the state levels to ensure proper adherence.

Sedation Vacations & Spontaneous Breathing Trials

It has been over a decade since the link was made between improved patient outcomes and daily interruption of sedation infusions in mechanically ventilated patients. This action, termed 'sedation vacation,' has been shown to significantly reduce ventilator days and length of stay in the ICU. [187] IHI guidelines outline methods of implementing sedation vacations. [188] These include development of a ventilator weaning protocol, addition of sedation scoring tools to avoid over sedation and implementing hospital policies to encourage compliance. [188]

Sedation vacations should be followed by daily assessment for readiness to wean by patient awakening and trialing of spontaneous breathing trials (SBTs). The Awakening and Breathing Controlled trial demonstrated a significant decrease in ICU and ventilator days in study patients who were managed with a protocol of daily interruption of sedation followed by SBTs as compared with the control group. [189] Patients in the intervention group spent 3 fewer days on mechanical ventilation. Self-extubation rates were higher in the intervention group, but total reintubation rates were similar in both groups. The patients in the intervention group were discharged 4 days earlier from the ICU and the hospital on average. One-year survival rates were higher in the intervention group. For every seven patients treated with the daily awakening plus SBT protocol, one life was saved. [189]

In a blinded retrospective chart review, Schweickert *et al*. assessed 128 ventilated patients receiving continuous sedative infusions and compared the incidence of ventilator complications between patients who underwent daily strategized interruption of sedative infusions and those who were kept on sedation as ordered by a medical ICU team. [190] Overall, VAP rates decreased from 8.3% in the control group to 3% in the intervention group. [190] In addition, Dries *et al.* demonstrated a decrease in VAP incidence from 15% in the control group to 5% for patients with a sedation weaning protocol ($p < 0.001$). [191]

Strategies to Minimize Mechanical Ventilation

The colonization of the aerodigestive tract with pathogenic bacteria and subsequent aspiration of contaminated secretions in the lower airway is regarded as the most important mechanism for development of VAP. When endotracheal intubation and mechanical ventilation become necessary, premature extubation should be avoided, as reintubation significantly increases the risk of VAP. [192] The risk of VAP increases with duration of intubation. The risk per day is higher initially and decreases over time, being approximately 3% on day 5, 2% on day 10 and 1% on day 15. [17] Thus, strategies to lessen the duration of invasive mechanical ventilation, such as noninvasive positive pressure ventilation and high-flow oxygen therapy, should be utilized to reduce the incidence of VAP.

Noninvasive Positive Pressure Ventilation In a recent large study of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), a fourfold rise in the use of noninvasive positive-pressure ventilation (NIPPV) was associated with a significant decline in invasive mechanical ventilation and hospital mortality. [193] Other randomized controlled studies have also demonstrated efficacy of NIPPV in patients with acute respiratory failure secondary to COPD exacerbations and cardiogenic pulmonary edema. [194–196] NIPPV ventilation was shown to be effective in the treatment of early acute respiratory distress syndrome. [197] In patients with acute respiratory failure secondary to severe acute respiratory distress syndrome, enodotracheal intubation was avoided in 14 patients (70%) treated with NIPPV. [198] The efficacy of NIPPV is attributed to early recruitment of collapsed alveoli and resting of respiratory muscles while pharmacologic interventions take effect.

NIPPV can also facilitate extubation in a select group of patients with respiratory failure who have difficulty with weaning from mechanical ventilation. Nava *et al.* showed that NIPPV limited the duration of mechanical ventilation, decreased ICU length of stay, reduced nosocomial pneumonia and improved 60-day survival in patients being treated for COPD with hypercapnic respiratory failure. [199]

High-Flow Nasal Cannula Oxygen Therapy High-flow nasal cannula oxygen therapy (HFNC) is another modality available for oxygen delivery in the ICU. HFNC oxygen therapy provides warm humidified oxygen and FiO_2 up to 1.0 at high-flow rates (up to 50 l/min) using a specialized nasal cannula and delivery system. In addition to high oxygen flow rate, HFNC oxygen therapy generates clinically significant levels of continuous positive airway pressure. [200]

While this intervention has been in use for a long time in pediatric populations, its use in adult medical ICUs is increasing. A recently published prospective pilot study showed its beneficial effect on clinical signs and oxygenation in ICU patients with acute respiratory failure. [201] HFNC oxygen therapy can decrease the need for intubation and mechanical ventilation in patients with early acute hypoxemic respiratory failure. Use of HFNC oxygen therapy in patients with acute respiratory failure can result in a significant reduction in respiratory effort and improvement in the partial pressure of oxygen in the blood and oxygen saturation.

Antimicrobial Stewardship

Infections due to MDR pathogens have increased considerably over the last several decades while development of novel antimicrobials has slowed. [202–204] Meanwhile, rates of unnecessary antibiotic administration in hospitals have been documented to range from 30 to 50%. [203, 205,206] Cognizant of the imperative to rationally use antimicrobials to optimally treat individual patients, minimize unintended consequences arising from misuse and overuse, and limit the emergence of resistance, the IDSA recently published guidelines urging all hospitals to develop programs enhancing antimicrobial stewardship. [203] Such programs have been reported to save US$200,000–900,000 annually. [207–213]

Antimicrobial stewardship may include front-end approaches to restrict prescriptive authority and/or back-end approaches that utilize prospective review and feedback. [214] Both strategies have been associated with decreased drug expenditures, but drug cost may be shifted to unrestricted antimicrobials when the front-end approach is used. [215–218] Back-end approaches correlate with improved clinician satisfaction and may facilitate de-escalation. [214,219]

Some strategies that may foster rational antibiotic therapy by limiting available antibiotics include formulary restriction, the use of order sets and treatment algorithms, clinical guidelines, antibiotic approval programs and computer-assisted decision support systems ( ). [214] Many of these strategies have been shown to result in increased appropriate initial antibiotic selection and dosing, decreased antimicrobial misuse, lower drug costs and increased prescriber satisfaction. [135,172,220–223] Programs to drive antibiotic de-escalation include automatic stop orders with options to renew and mandatory prescriber reassessment of initial antibiotic orders after 48–72 h. Additionally, pharmacist-driven intravenous to oral interchange programs, pharmacy dosing programs, involvement of infectious disease pharmacists and the presence of a clinical pharmacist on rounds in ICUs have been associated with lower costs, more appropriate antimicrobial dosing and improved patient outcomes. [224] Education underlies any successful antimicrobial stewardship program. Specifically, multiple methods should be used to educate clinicians about order sets, treatment algorithms, supportive and collaborative services, and technology implemented to support decision-making. [214] A detailed review of antimicrobial stewardship techniques and steps to implement such programs has recently been published. [214]

Box 2. Summary of different antibiotic stewardship strategies.

• Clinical guidelines

• Treatment algorithms
• Formulary restriction programs
• Order sets with timed stop or renewal orders
• Antibiotic approval programs
• De-escalation of empiric antibiotics
• Infectious disease pharmacist participation in treatment decision-making and drug policy development
• Pharmacist rounding with ICU teams
• Pharmacist driven intravenous to oral interchange programs
• Pharmacist dosing programs
• Prescriber support via computerized provider order entry systems ICU: Intensive care unit.

The impact of antimicrobial stewardship in critical care was reviewed in a comprehensive assessment of 24 published studies. These programs were shown to reduce antimicrobial utilization, total antimicrobial costs, average duration of antibiotic therapy, inappropriate use and antibiotic adverse effects. Stewardship strategies sustained beyond 6 months may be associated with less antibiotic resistance. These benefits were documented without increases in nosocomial infections, length of stay or mortality. [225]

Summary

Considering the dramatic increase in rates of MDR VAP, clinicians must be aware of current MDR pathogens, appropriate management and prevention strategies. Common MDR pathogens causing VAP are *S. aureus*, ESBL-producing *Enterobacteraciae*, carbapenemase-producing *Enterobacteraciae*, *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia*. Vancomycin and linezolid are recommended for the treatment of MRSA. β-lactams, fluoroquinolones and aminoglycosides are appropriate for most MDR Gram-negative pathogens that cause VAP. Polymixins should be reserved for highly resistant GNB that are not sensitive to other agents. Trimethoprim-sulfamethoxazole should be used for VAP due to *S. maltophilia*.

PK–PD optimization strategies are recommended for MDR VAP due to highly resistant organisms in patients with normal renal function or severe illness. Adjunctive inhaled antibiotics may be considered for very resistant pathogens and for patients who fail to respond to initial therapy. The use of targeted treatment based on surveillance cultures has been suggested to optimize initial antibiotic therapy.

VAP prevention strategies include avoiding intubation, liberating patients from mechanical ventilation as early as possible and using silver-coated ETTs or subglottic secretion drainage devices. Antibiotic stewardship strategies can also contribute to improved individual outcomes, decreased rates of resistance and lower overall treatment costs.

Expert Commentary

This article provides a detailed overview of current management and prevention strategies for VAP due to MDR bacteria. Over the past decade, there has been a dramatic increase in the incidence of VAP caused by MDR Gram-negative and Gram-positive pathogens. In contrast to hospital-acquired pneumonia (HAP) and healthcare associated pneumonia, VAP readily permits sampling of lower airway sputum that can be sent for Gram stain and culture. These microbiologic culture data provide valuable information about the likely bacteria causing VAP, the specific antibiotic sensitivity pattern and the need to either continue or alter initial broad-spectrum empiric therapy.

MDR pathogens causing VAP include MRSA and a spectrum of aerobic, Gram-negative bacilli. Optimal treatment of MRSA pneumonia involves vancomycin or linezolid. Over the past decade, experts have debated which of these two antibiotics is best. A recently published randomized, double-blind multicenter trial of linezolid and optimally dosed vancomycin to treat MRSA in patients with healthcare-associated pneumonia, HAP and VAP is discussed. In addition to reviewing the findings of this study, a perspective on use of linezolid for patients with VAP is added.

VAP is most often caused by aerobic Gram-negative bacilli that can manifest numerous antibiotic resistance mechanisms. The 2005 ATS/IDSA guidelines emphasize early, appropriate antibiotic therapy based on risk factors for MDR pathogens in order to reduce mortality and morbidity. Treatment of common MDR Gram-negative bacilli, such as *P. aeruginosa*, ESBL-producing *Enterobacteriaceae* and pathogens with carbapenemases is discussed.

Although *A. baumannii* is not a widespread pathogen, outbreaks in hospitals are occurring more frequently and have been difficult to control. Similarly, *S. maltophilia* is not widespread but is highly resistant to most antibiotics suggested for empiric therapy in the ATS/IDSA guidelines.

Specific recommendations in accordance with the 2005 ATS/IDSA guidelines are reviewed with some helpful insights to optimize antibiotic choices and reduce adverse effects. Effective initial therapy and improved antibiotic stewardship are emphasized.

Prevention of VAP has become an important focus in hospitals throughout the USA. Most hospitals have implemented the IHI bundle to reduce the incidence of VAP. This bundle includes daily interruption of sedation and assessment of readiness to wean. In addition, semirecumbent positioning is an inexpensive and important intervention that reduces reflux of gastric contents. Although often overlooked, semirecumbent positioning should be maintained when patients are being transferred from the ICU to other departments. Stress bleeding prophylaxis is also recommended in the bundle. However, we suggest that this intervention may not be necessary for all patients. Overuse of acid-suppression agents has been associated with a risk of VAP and other complications such as *Clostidium difficile* colitis.

The importance of either avoiding intubation or removing the ETT as soon as possible cannot be overemphasized. As discussed in this review, every effort should be directed at minimizing the duration of mechanical ventilation by pairing daily sedation interruption with an assessment of readiness to wean. In addition, data on the effectiveness of ETTs with subglottic secretion drainage and silver-coated ETTs, both of which have been demonstrated to reduce VAP, are reviewed. These tubes may not be used widely because they are expensive and it is difficult to identify patients who would benefit most.

One of the most important interventions to minimize the development of antibiotic-resistant pathogens is to reduce overuse of antibiotics. Regular education of ICU staff, evaluation of infection control practices and monitoring of adherence to VAP prevention strategies are recommended. It is important to regularly present and discuss data on infection rates, control of endemic MDR pathogens, and effective antibiotic usage and de-escalation. Antibiotic stewardship strategies are critical to reduce selection pressure for MDR pathogens and to limit healthcare and hospital pharmacy costs.

Although there has been an effort to have 'zero VAP' in hospitals, complete eradication of VAP may not be possible, especially in critically ill patients and patients who are ventilated for long periods of time. Furthermore, patients with early onset VAP may acquire infections at the time of intubation, especially during emergent intubations or when aspiration occurs at the time of intubation. In addition to efforts that aim to reduce mortality, measures that improve outcomes, such as duration of ventilation and ICU stay, antibiotic use and healthcare costs, are supported. The authors also encourage better collaboration between hospitals and chronic care facilities to prevent and reduce infections due to MDR pathogens. Prevention strategies outlined in this article are helpful for all groups interested in coordinated interventions that reduce VAP, decrease transmission of MDR pathogens causing VAP and decrease healthcare costs.

Five-year View

The prevalence of MDR organisms has increased dramatically over the last decade and is likely to grow. VAP will continue to cause significant mortality and morbidity, particularly in critically ill or debilitated patients. These infections are associated with great acute and chronic healthcare costs that will likely soar in the future. Because federal regulators are considering classifying VAP as a preventable event, treatment costs may no longer be reimbursable for hospitals in the USA. Consequently, future efforts should focus on preventing VAP, developing strategies that accurately identify patients at risk for MDR VAP and ensuring timely treatment and appropriate de-escalation.

To accomplish this, critical care staff should be thoroughly trained to utilize VAP prevention strategies in their daily practice. Adherence to these practices should be routinely monitored and encouraged through regular feedback. It is imperative that staff at hospitals and chronic care facilities practice good infection control to minimize transmission of MDR organisms.

Risk stratification methods and approaches that result in earlier identification of patients at high risk for VAP should be developed. More accurate and rapid diagnostic techniques to identify patients with VAP due to MDR bacteria are needed to

assure early, appropriate treatment and to permit more rapid de-escalation of initial therapy.

Considering the speed with which MDR bacteria have proliferated, the development of new antimicrobial agents effective against MDR pathogens is essential, but lacking. Hospitals should invest aggressively in antibiotic stewardship programs to minimize antibiotic misuse and overuse that contributes to higher morbidity, the development of resistance and greater healthcare costs. Future investigations and initiatives should focus on defining optimal treatment durations, decreasing morbidity, improving end-of-life care, achieving cost-effective therapy and creating novel antimicrobials directed at MDR pathogens.

Sidebar

Key Issues

- Disruption of mechanical host defenses and insults that compromise humoral and cellular immune mechanisms may predispose patients to ventilator-associated pneumonia (VAP) while endotracheal tube colonization with multidrug-resistant pathogens, aspiration and embolization of biofilm-encased bacteria introduce pathogenic bacteria into the lungs.
- There is no gold standard for the diagnosis of VAP, but clinical, quanitative and semiquantitative methods may be used.
- The treatment approach for VAP should center on timely and appropriate broad-spectrum antibiotic therapy coupled with efforts to obtain reliable cultures to permit de-escalation. The duration of therapy for Gram-negative bacteria other than *Pseudomonas areuginosa*and *Acinetobacter*species should be approximately 7–8 days if response to treatment has occurred.
- Vancomycin and linezolid may be used for methicillin-resistant *Staphylococcus aureus*(MRSA); however, a recent trial suggests linezolid may produce better outcomes. Linezolid should be considered for initial treatment of VAP in the case of severe pneumonia, critical illness, the presence of multiple risk factors for MRSA infection or a history of MRSA colonization or MRSA infection.
- Therapy should be changed from vancomycin to linezolid in patients with a MRSA pneumonia that does not respond to initial vancomycin therapy or if an isolate with an minimum inhibitory concentraton of >1 µg/ml is identified.
- Based on clinical and *in vitro*data, carbapenems should be used for extended spectrum β-lactamase-producing organisms and trimethoprim–sulfamethoxazole should be used for *Stenotrophomonas maltophilia*. Recommended treatment options for carbapenemase-producing *Enterobacteraciae*, *P. areuginosa*and *Acinetobacter*species are summarized but should be considered in light of culture and susceptibility data.
- Extended and continuous infusions of β-lactam antibiotics optimize pharmacokinetic–pharmacodynamic parameters and may result in better outcomes for severely ill patients, those with normal renal function and in the case of infections due to pathogens with high MICs.
- Aerosolized aminoglycosides and polymixins may be considered for multidrug-resistant Gram-negative infections in critically ill patients and those with slow response to treatment.
- Avoidance of mechanical intubation, shortened durations of intubation, the use of daily awakening and spontaneous breathing trial protocols, and mechanical ventilation with endotracheal tubes with subglottic secretion drainage and silver coatings prevent the development of VAP.
- Educational strategies and process optimization through the use of daily intensive care unit checklists have been shown to reduce the incidence of VAP and improve outcomes in critically ill patients.
- Antibiotic stewardship teams should collaborate to implement strategies in every hospital that reduce antibiotic misuse and overuse, minimize treatment-related adverse effects and reduce cost of care.

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Papers of special note have been highlighted as:

• of interest

•• of considerable interest

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