Eur J Clin Microbiol Infect Dis (2005) 24: 794–803
DOI 10.1007/s10096-005-0053-3

CURRENT TOPIC: REVIEW

M. H. Kollef

Antibiotic management of ventilator-associated pneumonia due to antibiotic-resistant gram-positive bacterial infection

Published online: 9 December 2005

Abstract Gram-positive cocci, in particular *Staphylococcus aureus*, account for as much as one-third of all cases of hospital-acquired pneumonia, and treatment has become increasingly complex as the proportion of resistant isolates has increased. Methicillin-resistant *S. aureus* is of particular concern because this pathogen is now associated with hospital-acquired, ventilator-associated, community-acquired, and healthcare-associated pneumonia. Antibiotic therapy for ventilator-associated pneumonia is challenging because it can be caused by multiple pathogens, which can be resistant to multiple drugs. This article reviews the epidemiology of ventilator-associated pneumonia and describes options for antibiotic treatment. Particular attention is paid to pneumonia due to methicillin-resistant *S. aureus*. Studies suggest that vancomycin, the traditional treatment for ventilator-associated pneumonia, may not be the best option for this type of pneumonia and that other antibiotics, such as linezolid and clindamycin, might be better choices. New antibiotics with activity against methicillin-resistant *S. aureus* are under investigation and may soon become available for clinical use. Studies are needed to define the optimal choice of antibiotic for pneumonias caused by this organism, and these choices will need to be balanced with the need to minimize the emergence of resistance.

Introduction

Hospital-acquired pneumonia (HAP) accounts for 15% of all nosocomial infections [1], and treatment has become increasingly complex because of the continuing emergence of antibiotic-resistant bacteria. Of particular concern is methicillin-resistant *Staphylococcus aureus* (MRSA), a pathogen whose prevalence continues to grow and one that is now associated with all forms of pneumonia, including HAP, ventilator-associated pneumonia (VAP), and pneumonia acquired in the community setting. Healthcare-associated pneumonia was recently described as pneumonia developing in patients admitted to the hospital from high-risk environments such as nursing homes and extended-care facilities. High-risk environments include patients' homes if patients are receiving chronic dialysis, home infusion therapy, or home wound therapy, or if they were recently hospitalized. Healthcare-associated pneumonia is generally more similar microbiologically to HAP and VAP than community-acquired pneumonia.

Antibiotic therapy for pneumonia is challenging because the illness can be caused by multiple pathogens that can be resistant to multiple drugs. This article reviews the prevalence of pneumonia due to *S. aureus* and *Streptococcus pneumoniae*, describes the epidemiology of VAP, and discusses antibiotic treatment options for VAP. Particular attention is paid to VAP due to MRSA.

Resources for this article were obtained by searching the PubMed database (1966–present). English-language articles of relevance were selected and reviewed. Additional resources were obtained through the bibliographies of reviewed articles.

Pneumonia due to *S. aureus* and *S. pneumoniae*

Gram-positive cocci, in particular *S. aureus*, account for 20–30% of all HAP cases [1], and the proportion of resistant isolates continues to increase. Nosocomial strains of MRSA are distributed worldwide [2], and data from the U.S. National Nosocomial Infections Surveillance System show that MRSA now accounts for more than 55% of *S. aureus*-related infections in the intensive care setting [3]. Along with *Pseudomonas aeruginosa* and *Acinetobacter*, MRSA is also a common cause of late-onset pneumonia, particularly in patients who require mechanical ventilation [1].

M. H. Kollef (✉)
Washington University School of Medicine,
Campus Box 8052, 660 South Euclid Avenue,
St. Louis, MO 63110, USA
e-mail: mkollef@im.wustl.edu
Tel.: +1-314-4548764
Fax: +1-314-4545571

MRSA has also moved beyond the hospital setting and is emerging as a community-acquired pathogen among patients without established risk factors [4]. The MRSA strains originating in the community are microbiologically distinct from hospital-acquired MRSA (HA-MRSA) and thus have been labeled "community-acquired" MRSA (CA-MRSA). Although CA-MRSA is primarily associated with skin and soft tissue infections, it is increasingly causing more invasive infections, including fatal necrotizing pneumonia.

In what may be the first reported cases in North America, four healthy adults were admitted to a Baltimore, MD, hospital during the winter of 2003–2004 with severe necrotizing MRSA pneumonia [5]. All four patients lacked the typical risk factors associated with an MRSA infection, but all isolates carried the Panton–Valentine leukocidin (PVL) gene, which belongs to the synergohymenotropic class of toxins. These toxins damage membranes of host defense cells and erythrocytes by the synergistic action of two components that are secreted separately but combine to create lytic pores in the cell membranes of neutrophils. Carried on a bacteriophage, the PVL gene is encoded by two contiguous and cotranscribed genes, *lukF-PV* and *lukS-PV* [6]. Three of four patients eventually recovered, but they experienced significant morbidity and an intensive care unit stay of 1–3 months.

A second problematic resistant, gram-positive pathogen is *S. pneumoniae*. About 4 million cases of community-acquired pneumonia occur every year in the USA, and *S. pneumoniae* is still the most common causative pathogen [7]. Until the early 1990s, penicillin resistance was rare in clinical isolates of *S. pneumoniae* [8]. A national surveillance program conducted by the Centers for Disease Control and Prevention during the 1980s found that only 3–6% of strains of *S. pneumoniae* were not susceptible to penicillin. Among those strains, virtually none demonstrated a high level of resistance.

Over the past decade, however, a significant development in the pathogenesis of community-acquired pneumonia has been the rapid increase in penicillin-resistant *S. pneumoniae*. Thornsberry et al. [9], in a surveillance study performed during 1997–1998, found a high prevalence of penicillin-resistant *S. pneumoniae*, with only 65% of the isolates showing susceptibility to penicillin using current breakpoints.

Results from the first year of the Global Respiratory Antimicrobial Surveillance Project (GRASP) [10], published in February 2005, show that 30% of the 2,656 *S. pneumoniae* isolates had decreased susceptibility to penicillin (17% full resistance, 13% intermediate resistance). In addition, 31% of the isolates were resistant to erythromycin. Resistance to telithromycin and quinupristin-dalfopristin was "rare" (data not shown), and no resistance to linezolid or vancomycin was recorded. The isolates were collected from patients at 65 medical centers in 20 countries across Europe, eastern Asia, and southern Africa and were tested against 24 antimicrobial agents.

Epidemiology of ventilator-associated pneumonia

HAP is defined as pneumonia that occurs 48 or more hours after hospital admission. Although HAP is the second most common hospital-acquired infection, it leads to the highest number of deaths due to nosocomial infections. Pneumonia that occurs within 48 h of hospital admission can be difficult to distinguish from a community-acquired infection that might have been in progress before hospitalization (M.H. Kollef and S.T. Micek, unpublished data). Early-onset pneumonia may also be the result of aspiration that occurred during tracheal intubation.

VAP, a form of HAP, complicates the course of 8–28% of patients receiving mechanical ventilation [11]. It specifically refers to pneumonia that develops in mechanically ventilated patients more than 48 h after tracheal intubation. The attributable mortality rate appears to vary considerably, depending on the patient population and infecting pathogen. Studies have found the mortality rate to range from 24 to 50%, reaching as high as 76% in some cases [11].

Early-onset disease, which occurs within 48–72 h of the onset of ventilatory support, is frequently caused by antibiotic-sensitive bacteria, including methicillin-sensitive *S. aureus* (MSSA), *Haemophilus influenzae*, and *S. pneumoniae* [12]. Pathogens with strong intrinsic or acquired antimicrobial resistance are rarely found to be causative agents. In contrast, late-onset VAP, defined as occurring more than 72 h after the start of mechanical ventilation, tends to be caused by antibiotic-resistant pathogens, including MRSA, *P. aeruginosa*, *Acinetobacter* spp., and *Enterobacter* spp.

Over the past two decades, the prevalence of MRSA strains has steadily increased worldwide. A number of factors are associated with a higher risk of HA-MRSA, including lengthy hospitalization, an intensive care unit stay, prolonged antimicrobial therapy, surgical procedures, and close proximity to a hospitalized patient who is infected or colonized with MRSA [13]. Trouillet et al. [14], in reviewing 135 consecutive episodes of VAP, found *S. aureus* to be the most frequently isolated organism (21.3%), and multidrug-resistant bacteria were most prevalent among patients who had been ventilated 7 or more days (Table 1). Overall, 57% of VAP episodes were caused by potentially antibiotic-resistant pathogens, and a lengthy duration of mechanical ventilation, prior use of antibiotics, and prior use of broad-spectrum antibiotics were the three variables that remained independently associated with this type of infection. Rello et al. [15] also found that patients with MRSA VAP were more likely to have received corticosteroids before their infection, but cranioencephalic trauma was more common (58%) in patients with an MSSA infection than among those with an MRSA infection (18%).

The spread of MRSA among healthy persons in the community who lack established risk factors has been

Table 1 Numbers and percentages of microorganisms responsible for 135 episodes of VAP according to duration of mechanical ventilation (MV) and prior antibiotic therapy (ABT)

Pathogen	Group1 (MV<7 days, no ABT) (*n*=22)	Group 2 (MV<7 days, with ABT) (*n*=12)	Group 3 (MV≥7 days, no ABT) (*n*=17)	Group 4 (MV≥7 days, with ABT) (*n*=84)
Multidrug-resistant bacteria	0*	6 (30)	4 (12.5)**	89 (58.6)
Pseudomonas aeruginosa	0	4 (20)	2 (6.3)	33 (21.7)
Acinetobacter baumannii	0	1 (5)	1 (3.1)	20 (13.2)
Stenotrophomonas maltophilia	0	0	0	6 (3.9)
MRSA	0	1 (5)	1 (3.1)	30 (19.7)
Other bacteria	41 (100)	14 (70)	28 (87.5)	63 (41.4)
Enterobacteriaceae	10 (24.4)	4 (20)	7 (21.9)	23 (15.1)
Haemophilus spp.	8 (19.5)	2 (10)	1 (3.1)	4 (2.6)
MSSA	6 (14.6)	0	7 (21.9)	7 (4.6)
Streptococcus pneumoniae	3 (7.3)	0	0	0
Other streptococci	7 (17.1)	5 (25)	7 (21.9)	14 (9.2)
Neisseria spp.	5 (12.2)	2 (10)	4 (12.5)	3 (2)
Other pathogens	2 (4.9)	1 (5)	2 (6.3)	12 (7.9)
Total no. of bacteria	41 (100)	20 (100)	32 (100)	152 (100)

Reprinted from Trouillet et al. [14]
*p<0.02 vs. groups 2, 3, or 4
**p<0.0001 vs. group 4

characterized by clusters of cases or outbreaks, which have occurred among diverse groups of people. Recent outbreaks have occurred in Pacific Islanders, in Native Americans, among members of athletic teams, and in prison inmates [16–20].

In a study that compared the epidemiological and microbiological characteristics of CA-MRSA and HA-MRSA cases identified at 12 laboratory facilities in Minnesota, USA, community-associated cases comprised 12% of 1,100 MRSA infections [19]. Skin and soft tissue infections accounted for 75% of all CA-MRSA cases, and the community-acquired strains were far less likely than healthcare-associated strains to involve the respiratory or urinary tract. CA-MRSA isolates also tended to possess different exotoxin gene profiles than the healthcare-associated isolates. However, in contrast to HA-MRSA strains, which are generally multidrug resistant, CA-MRSA strains tended to be susceptible to agents other than β-lactams, including ciprofloxacin, clindamycin, gentamicin, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin.

Virulence of pneumonia due to methicillin-resistant *S. aureus*

MRSA infections require more complex medical management and may result in greater morbidity and mortality as compared with infections caused by susceptible strains. Studies have demonstrated that the associated morbidity and mortality of HA-MRSA is at least equal to, if not greater than, the morbidity and mortality of infections caused by MSSA. A meta-analysis of nine studies comparing the risk of mortality between HA-MRSA and HA-MSSA found that patients with MRSA bacteremia had twice the risk of death as those with an MSSA-associated infection [21]. Rello et al. [15] also reported that the mortality rate directly related to VAP was significantly higher for those with an MRSA infection as opposed to an MSSA infection.

All MRSA strains contain a *mecA* gene and regulatory sequences that encode for the production of penicillin-binding protein 2a, which is not found in MSSA isolates [22]. The presence of penicillin-binding protein 2a renders *S. aureus* insensitive to all β-lactams that have been developed, including cephalosporins, cephamycins, and carbapenems. Hospital-acquired strains also tend to be multidrug resistant and may exhibit reduced susceptibility or complete resistance to erythromycin, clindamycin, gentamicin, tobramycin, and ciprofloxacin. Conversely, CA-MRSA isolates usually exhibit resistance only to β-lactams and are susceptible to many non-β-lactam agents (see above).

S. aureus strains can express many potential virulence factors, including surface proteins that promote colonization of host tissues, exotoxins and superantigens that cause tissue damage and the symptoms of septic shock, and invasins that promote bacterial spread in tissues (e.g., leukocidin, kinases, hyaluronidase). PVL is a cytotoxin produced by fewer than 5% of *S. aureus* strains, and it has been associated with primary skin infections and severe necrotizing pneumonia [6]. In a study in which investigators screened 172 strains of *S. aureus*, PVL genes were detected in 93% of strains associated with furunculosis and in 85% of those associated with severe necrotic hemorrhagic pneumonia, both of which were community acquired [23]. PVL genes were not detected in strains causing

other types of infections, such as HAP, toxic-shock syndrome, infective endocarditis, or mediastinitis.

Gillet et al. [6] compared 16 cases of PVL-positive *S. aureus* pneumonia with 36 cases that were PVL negative. Patients in the PVL-positive cohort tended to be much younger than those infected with PVL-negative *S. aureus*. Twelve of 16 PVL-positive patients experienced an influenza-like illness during the 2 days prior to hospital admission, compared with only three individuals with PVL-negative strains. Rapid progression to severe pneumonia was also seen in PVL-positive patients, and 48 h after admission, their survival rate was 63%, compared with 94% for PVL-negative individuals. Postmortem histopathologic examination of the lungs showed extensive necrotic ulcerations of the tracheal and bronchial mucosa and massive hemorrhagic necrosis of interalveolar septa.

S. pneumoniae, one of the most significant pathogens affecting the respiratory tract, is increasingly being found to be resistant to multiple drugs. For example, in the GRASP study [10], 21% of the *S. pneumoniae* isolates tested (563 of 2,656) were multidrug resistant (defined as intermediate or full resistance to penicillin plus intermediate or full resistance to at least two of the following agents: chloramphenicol, erythromycin, tetracycline, or trimethoprim-sulfamethoxazole). Penicillin, erythromycin, tetracycline, trimethoprim-sulfamethoxazole was the most prevalent phenotype (8% of all *S. pneumoniae*).

In Canada, the prevalence of pneumococci with reduced susceptibility to fluoroquinolones rose from 0% in 1993 to 1.7% in 1997 and 1998 [24]. In the USA, the prevalence of ofloxacin-nonsusceptible isolates increased from 2.6% in 1995 to 3.8% in 1997 [25]. Levofloxacin resistance was reported in 0.2% of isolates in 1998 (7 of 3,120) and 1999 (8 of 3,432), and 13 of those 15 (87%) isolates also were nonsusceptible to trovafloxacin. Most fluoroquinolone-resistant isolates were found to be resistant to other antimicrobial agents (including penicillin, cefotaxime, erythromycin, and trimethoprim-sulfamethoxazole), and prevalence was highest in persons over 65 years of age. The finding that the vast majority of levofloxacin-nonsusceptible isolates also were nonsusceptible to trovafloxacin is concerning, given that fluoroquinolones are recommended for treatment of pneumococcal infections in cases of suspected resistance to penicillin or other antimicrobial agents [25].

In addition, co-resistance of *S. pneumoniae* also is becoming a concern. In a study of 1,601 isolates collected from patients at 34 U.S. medical centers conducted from November 1997 to April 1998, Doern et al. [26] observed that 5.4% of *S. pneumoniae* isolates (87 of 1,601) were co-resistant to penicillin, macrolides, tetracycline, trimethoprim-sulfamethoxazole, and chloramphenicol. An additional 3.7% of strains were co-resistant to the first four drugs but not chloramphenicol. The authors suggest that clonal spread of organisms resistant to more than one class of drugs is a possible explanation for the increase in multidrug-resistant strains and caution that "under such circumstances, regardless of the antimicrobial drug used to select for resistance, multidrug-resistant organisms may become more prevalent" [26].

Specific issues of antibiotic treatment

Antimicrobial selection for VAP can be difficult because the pneumonia can be polymicrobial and caused by pathogens that are multidrug resistant. Even in mild to moderate cases, the presence of highly resistant gram-negative bacilli such as *P. aeruginosa* and *Acinetobacter* spp. needs to be considered if the patient has known risk factors, such as a prolonged stay in the intensive care unit. In its 1995 consensus statement, the American Thoracic Society recommended that patients with severe HAP, either early onset with risk factors or late onset, receive an antimicrobial regimen effective against core organisms as well as the more resistant and virulent gram-negative bacilli [27]. If a patient is at high risk for an MRSA infection, or if MRSA is endemic to an institution, then vancomycin needs to be considered [27]. Initial treatment usually needs to be combination therapy.

The updated consensus statement, issued jointly with the Infectious Diseases Society of America in February 2005, notes that the presence of multidrug-resistant pathogens needs to be considered in patients with healthcare-associated pneumonia because these patients are at a higher risk [28]. They should be treated for resistant organisms regardless of when their pneumonia began or the length of hospital stay. Monotherapy is recommended whenever possible to avoid exposure to unnecessary antibiotics as well as to reduce costs, but combination therapy should be used if the patient is likely to have a multidrug-resistant pathogen. In addition, efforts should be made to decrease the duration of an initially appropriate antibiotic regimen, from the traditional 14–21 days to periods as short as 7 days, if there is a good clinical response and the infecting organism is not *P. aeruginosa*.

Until recently, the glycopeptides, vancomycin and teicoplanin, were the only antibacterial compounds available to which MRSA strains remained uniformly susceptible. In 1996, the first clinical isolate of *S. aureus* with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus*, or VISA) was reported in Japan [29], and since then similar cases have been reported around the world [30–34]. Only a few years later, clinical isolates of *S. aureus* that were fully resistant to vancomycin were reported in South Africa [35] and Michigan, USA [36]. The emergence of MRSA strains with reduced vancomycin susceptibility has limited treatment options and increased the incidence of treatment failure [37], and infection with one of these strains may be an independent predictor of mortality [38].

It should be noted that the breakpoints used to define susceptibility to vancomycin vary between countries. In the USA, the National Committee for Clinical and Laboratory Standards, now the Clinical Laboratory and Standards Institute, has developed the following guidelines: suscep-

tible, minimum inhibitory concentration (MIC)≤4 μg/ml; intermediate, MIC 8–16 μg/ml; and resistant, MIC≥32 μg/ml [39]. However, the British Society for Antimicrobial Chemotherapy defines resistant as an MIC≥8 mg/l [40]. In addition, terminology may differ. The Centers for Disease Control and Prevention notes that even though the acronym "VISA" is often used, particularly in the USA, "GISA" (glycopeptide-intermediate *S. aureus*) is technically more accurate, because all VISA isolates have been shown to have intermediate-level susceptibility to both vancomycin and teicoplanin [41].

Although vancomycin traditionally has been considered the antimicrobial agent of choice for treating MRSA infections, a number of reports suggest that treatment with vancomycin can be variable and sometimes ineffective despite laboratory data showing susceptibility of the pathogen to the drug [42]. Treatment results are often less than optimal compared with results of β-lactam treatment of nonresistant strains of *S. aureus* [43].

In one study evaluating treatment outcomes in patients with vancomycin-susceptible *S. aureus*-associated lower respiratory tract infections, 25 of 70 patients did not clinically respond to treatment [42]. Two patients died from their respiratory infection, one after 21 days of treatment and the other after 12 days. Eight others died of underlying disease. Vancomycin was discontinued in 15 patients after a lack of clinical response.

A study by Gonzalez et al. [44] showed a relationship between mortality and vancomycin treatment in patients with bacteremic pneumonia caused by *S. aureus*. The mortality rate was high both for patients with MSSA and for those with MRSA, and it was also quite high for MRSA patients who were correctly treated with vancomycin (50%). Patients with MSSA who were treated with oxacillin had a much lower death rate than those who received vancomycin therapy (0 vs. 47%).

These results are consistent with results reported earlier by Levine et al. [45], who found persistent bacteremia in patients with MRSA-associated endocarditis who were treated with vancomycin. Forty-two consecutive patients with MRSA endocarditis were randomly assigned to receive either vancomycin or vancomycin plus rifampin for 28 days. The median duration of bacteremia was 9 days. Therapy failed in six patients, three of whom died and three of whom required valve surgery. Clinical response to vancomycin was slow, although most patients eventually did respond. Few complications were seen in either group. Table 2 lists additional clinical success rates of vancomycin therapy.

Table 2 Clinical success rates with vancomycin in patients with hospital-acquired MRSA pneumonia

Study	No. of patients with clinical cure (%)
Fagon et al. [52]	8/18 (44.4)
Wunderink et al. [46]	22/62 (35.5)
Moise et al. [42]	53/70[a] (57.7)

[a]Thirty-five with MRSA

The suboptimal performance of vancomycin in many cases of MRSA infection has led to it being used in combination with other antimicrobial agents, notably rifampin and aminoglycosides. However, results of in vitro studies have been contradictory, and there is a lack of clinical data to support this practice. Shelburne et al. [43] evaluated the effects of vancomycin alone and in combination with gentamicin and rifampin on vancomycin-susceptible isolates of CA-MRSA, HA-MRSA, and MSSA. Strains of CA-MRSA were more likely to be susceptible to gentamicin (90%) than were HA-MRSA strains (50%) [43]. The mean killing time for vancomycin alone was similar in all specimens. When vancomycin was combined with gentamicin, however, killing was nearly 100 times greater at each point. Conversely, combining rifampin with vancomycin decreased bactericidal activity. No evidence of a synergistic effect was noted for any of the isolates, and it was found to be antagonistic in nine strains.

Some studies suggest that linezolid may be associated with better survival and clinical cure rates than vancomycin in patients with HA-MRSA pneumonia. In a retrospective analysis of data from two prospective, randomized, double-blind studies, treatment outcomes with linezolid (600 mg q12 h) and with vancomycin (1 g q12 h) were compared in patients with HA-MRSA [46]. Kaplan–Meier survival rates for linezolid were 80.0% (60/75 patients), as opposed to 63.5% (54/85 patients) for vancomycin, in the MRSA subset of patients (p=0.03).

Etiology of vancomycin clinical failure

Vancomycin treatment failures and slow clinical responses in patients with MRSA and MSSA infections are not uncommon despite the organism being fully susceptible. The degree of protein binding of vancomycin relative to unbound or free drug concentrations in serum appears to limit the ability of vancomycin to adequately penetrate the lung tissue of patients with MRSA pneumonia. This explanation is supported by a study by Lamer et al. [47], who determined the concentration of vancomycin in epithelial lining fluid (ELF) in 14 critically ill, ventilated patients treated with vancomycin (15 mg/kg body weight, adjusted to obtain trough concentrations of approximately 15–20 μg/ml). Using the albumin concentration in ELF as a marker of inflammation, vancomycin penetration was higher in patients with ELF albumin values >3.4 mg/ml, and increased albumin concentration in ELF was associated with greater antimicrobial penetration into the alveoli. The mean vancomycin level in ELF (4.5±2.3 μg/ml) represented only 18% of the simultaneous plasma level (24±10 μg/ml). Patients with more pronounced lung inflammation tended to have better drug penetration, and an increased albumin concentration in ELF was associated with enhanced vancomycin penetration into the alveoli.

Glycopeptide-intermediate strains are also a cause of vancomycin treatment failure, although this is still relatively rare. More common is heteroresistance to vancomycin (hVISA), in which subpopulations within the strain

exhibit reduced susceptibility to vancomycin even if the overall MIC for the entire isolate remains within the susceptible range. In an Australian study, patients with hVISA-associated bacteremia were significantly more likely to have a high bacterial load infection and experience vancomycin treatment failure [48]. Although the rate of hVISA was low (5 of 53 episodes, 9.4%), the number was significantly higher than expected based on prior MIC data alone.

Drifting MICs of vancomycin for MRSA may also result in treatment failure. Sakoulas et al. [49] found a relationship between vancomycin treatment failure and an elevated vancomycin MIC in patients with MRSA bacteremia. The clinical success rate was only 9.5% when the vancomycin MIC was 1–2 μg/ml. At MICs of ≤0.5 μg/ml, the clinical success rate was significantly higher at 55.6%.

Moise et al. [42] evaluated whether a particular area under the inhibitory curve/MIC ratio ($AUIC_{24}$/MIC) was predictive of successful clinical and microbiological outcomes with vancomycin in patients with *S. aureus*-associated lower respiratory tract infection. The median calculated average $AUIC_{24}$/MIC in patients who did not respond to vancomycin treatment was 306, in contrast to 491 for patients who were successfully treated. Three quarters of the patients with calculated $AUIC_{24}$/MICs of >345 experienced a clinical success, compared with 24% of those with a calculated $AUIC_{24}$/MIC of ≤345. The authors suggest that the $AUIC_{24}$/MIC may need to be adjusted for the protein binding of vancomycin and recommend an $AUIC_{24}$/MIC for unbound drug of about 125 when the total $AUIC_{24}$/MIC is >866. It is important to note that Moise et al. [42] assumed a vancomycin protein binding level of ≥80%. However, other investigators studying the relation between vancomycin protein binding and serum concentrations of albumin and alpha 1-acid glycoprotein have reported vancomycin protein binding levels of only 50% [50, 51].

Comparator studies

New classes of antibiotics with demonstrated activity against MRSA and other resistant gram-positive pathogens have recently become available. Quinupristin/dalfopristin, the first formulation of the streptogramin class of antibiotics, is active against a range of gram-positive bacteria that are usually resistant to other agents, including vancomycin-resistant *Enterococcus faecium*. In a head-to-head trial studying treatment of HAP caused by gram-positive pathogens, investigators reported that quinupristin/dalfopristin had a clinical success rate equivalent to that of vancomycin in bacteriologically evaluable patients (54.2 vs. 53.7%) and in the all-treated population (56.3 vs. 58.3) [52]. The clinical success rate in both groups for MRSA was relatively low: 30.9% for quinupristin/dalfopristin and 44.4% for vancomycin in the bacteriologically evaluable population, and 19.4 and 40%, respectively, for the all-treated population with a baseline pathogen.

Linezolid, the first member of the oxazolidinone class of antibiotics, is highly active against gram-positive bacteria, including drug-resistant strains, and has nearly 100% oral bioavailability. Two large, prospective, randomized, double-blind studies that compared initial empiric treatment with either linezolid or vancomycin in patients with gram-positive HAP reported similar outcomes between the two treatment groups. There were no differences in outcome in the overall population, but a subset analysis showed improved survival for patients treated with linezolid when they were stratified by Acute Physiology and Chronic Health Evaluation (APACHE) II scores [46]. Wunderink et al. [46] performed a retrospective analysis to assess the survival and clinical cure rates in patients with HA-MRSA using data that had been collected prospectively. Kaplan–Meier survival rates for all patients with HAP were 80.9% for linezolid and 77.8% for vancomycin. When narrowed to the MRSA subset, survival rates for linezolid were 80%, compared with 63.5% for vancomycin. In the same subset, clinical cure rates for linezolid were 59.0% versus 35.5% for vancomycin (Fig. 1). The survival and cure rates remained significant even after adjusting for baseline variables.

Using the same data, Kollef et al. [53] assessed treatment efficacy, including clinical cure and survival rates, in the subset of patients with VAP, which included 91 patients with MRSA-associated infections. Clinical cure rates were higher for all VAP patients treated with linezolid as compared with standard-dose vancomycin therapy, particularly for those with MRSA-associated VAP (62.2 vs. 21.2%) (Table 3).

Two large trials have also compared linezolid with teicoplanin, a glycopeptide that is available in a number of countries but has not been approved in the USA. The first study was a randomized, controlled, multicenter trial of 430 patients with gram-positive infections, 27% of which

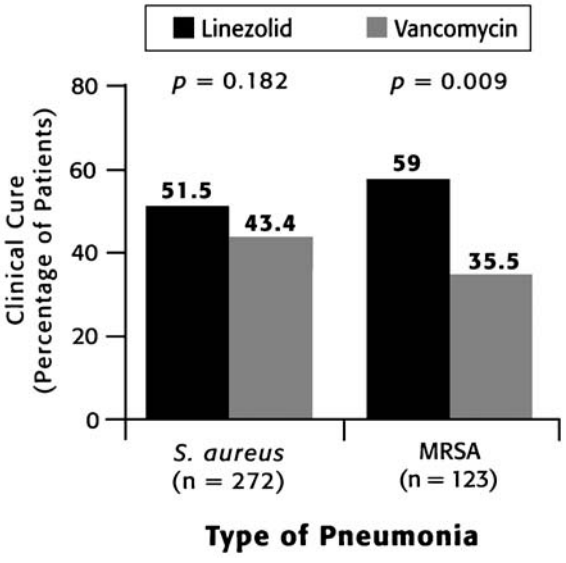

Fig. 1 Clinical cure rates in patients with *S. aureus*-associated nosocomial pneumonia treated with linezolid vs. vancomycin. Reprinted from Wunderink et al. [46]

Table 3 Comparison of clinical cure rates in patients with *Staphylococcus aureus*-associated VAP treated with linezolid vs. vancomycin

	Linezolid (%)	Vancomycin (%)
VAP (*n*=434)	45.4	36.7
Gram-positive VAP (*n*=214)	53.7	37.7
S. aureus VAP (*n*=179)	48.9	35.2
MRSA VAP (*n*=70)	62.2	21.2

Data from Kollef et al. [53]

were pneumonia [54]. The predominant baseline pathogen in both treatment groups was *S. aureus*. Clinical cure rates in the intent-to-treat population were 95.5% with linezolid and 87.6% in the teicoplanin group for all infections combined. Cure rates for bacteremia were statistically significant for linezolid (88.5 vs. 56.7%), but this was not seen for other infection categories, including pneumonia (96.2 vs. 92.9%) (Fig. 2). Bacterial eradication rates for linezolid exceeded those of teicoplanin for all infection sites combined but did not reach statistical significance.

In the second study, Cepeda et al. [55] found similar overall clinical success rates in critically ill patients with gram-positive infections (83.3% for linezolid and 82.8% for teicoplanin). Unlike in the first study, clinical success rates for bacteremia were equal for both treatment groups (81.8 vs. 81.3%), but linezolid was superior to teicoplanin at initially clearing MRSA colonization at the end of treatment (51.1 vs. 18.6%). Overall, the researchers did not find a difference between linezolid and teicoplanin in either safety or effectiveness.

Daptomycin is the first member of a new class of bactericidal antibiotics, the cyclic lipopeptides. Daptomycin has been shown to be effective against significant gram-positive pathogens (including MRSA, glycopeptide-intermediate *S. aureus*, and vancomycin-resistant *Enterococcus faecalis* and *E. faecium*) and is approved in the USA for treatment of complicated skin and skin structure infections due to *S. aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* subsp. *equisimilis*. However, in phase III studies of severe community-acquired pneumonia, the rates of serious cardiorespiratory events and death were higher in daptomycin-treated patients than in those treated with the comparator (ceftriaxone), so the drug is contraindicated in pneumonia patients [56].

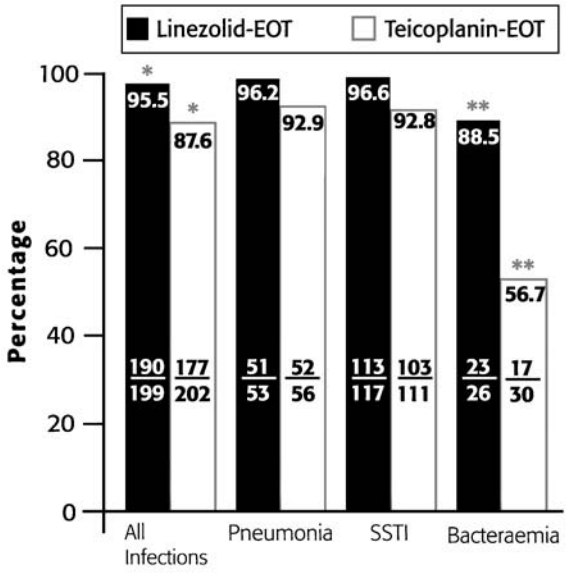

Fig. 2 Clinical success rates in patients with gram-positive infections treated with linezolid vs. teicoplanin. SSTI, skin/soft tissue infection; **p*=0.005; ***p*=0.009. Reprinted from Wilcox et al. [54]

Treating resistant infections due to methicillin-resistant *S. aureus*

Treating VAP due to MRSA is becoming an increasing challenge because of antibiotic resistance and the overall virulence of this pathogen. MRSA pneumonia frequently fails to respond to vancomycin, in part because of the agent's slower bactericidal activity as compared with β-lactam antibiotics and its inadequate penetration into lung tissue.

One possibility may be to use higher doses of vancomycin to increase efficacy, but there have no been no clinical trials to evaluate this possibility, and toxicity remains an issue. In pneumonia, however, vancomycin levels achieved at the site of infection may be less than effective because of a low $AUIC_{24}$/MIC, resulting in clinical failure (see discussion of Moise et al. [42] study in "Etiology of Vancomycin Clinical Failure").

For MRSA strains that produce toxins, linezolid or clindamycin may be a more appropriate selection. The alpha toxin, encoded by the *hla* gene, is a major virulence factor of *S. aureus*. In a study that evaluated the influence of subinhibitory doses of 31 antibiotics on the expression of the gene, vancomycin and teicoplanin did not have any effect [57]. Conversely, low concentrations of clindamycin reduced *hla* expression by 98%, and other studies have shown that clindamycin also inhibits production of toxic shock syndrome toxin 1 [58]. Clindamycin has been used successfully to treat MRSA pneumonia, although no clinical series have been published. In addition, concern over the possibility of resistance has discouraged some clinicians from prescribing that agent [59]. The erythromycin–clindamycin "D zone" test [60–62] can separate strains that have the genetic potential to become resistant during therapy from strains that are fully susceptible to clindamycin.

The expression of virulence factors in *S. aureus* has also been found to be vulnerable to sub-growth-inhibitory concentrations of linezolid. Bernardo et al. [63] tested subinhibitory concentrations of linezolid (12.5, 25, 50, and 90% of MIC) in *S. aureus* cultures. At all MICs, linezolid reduced the secretion of several specific virulence factors, including staphylococcal enterotoxin A, bifunctional autolysin, autolysin, protein A, and α- and β-hemolysins.

Linezolid may be an appropriate alternative for patients failing vancomycin therapy because of reduced pathogen susceptibility. In 25 patients with serious MRSA infections with reduced susceptibility to vancomycin, glycopeptide treatment failed in 76% [37]. Eighteen of these patients subsequently received linezolid, which was effective in 14 (78%), including four with endocarditis.

Importance of using shorter courses of therapy to avoid emergence of resistance

The optimal duration of antibiotic therapy for VAP has not been established. Guidelines from the American Thoracic Society recommend treating VAP due to *H. influenzae* and MSSA for 7–10 days and cases caused by *P. aeruginosa* and *Acinetobacter* spp. for at least 14–21 days. The guidelines, however, are not based on the results of prospective studies [64]. Clinicians in the critical care setting must deal with the conundrum of having to prescribe broad initial empiric antimicrobial therapy to patients with suspected VAP while at the same time attempting to minimize the emergence of further resistance.

Several studies have reported on strategies that allow practitioners to successfully and safely shorten the course of treatment in patients with suspected or microbiologically proven HAP and VAP. In one clinical trial involving 290 patients with VAP, Micek et al. [65] determined the impact and safety of a formalized antibiotic discontinuation policy. Initial empiric antibiotic treatment for suspected VAP was based on the clinical judgment of the treating physicians, and the VAP antibiotic discontinuation policy was developed on the basis of prior clinical experience.

The severity of illness was similar for patients receiving conventional management and for those in the discontinuation group. The duration of antibiotic treatment for VAP was statistically shorter among patients in the discontinuation group (6.0±4.9 vs. 8.0±5.6 days), and there were no statistically significant differences in hospital mortality or the durations of intensive care and hospitalization. MRSA and *P. aeruginosa* were the most common pathogens causing secondary episodes of VAP in both treatment groups.

A large prospective, randomized, clinical trial conducted in 51 French intensive care units examined whether 8 days of antimicrobial therapy is as effective as 15 days in patients with VAP [66]. Mortality and rates of recurrent infections were similar between the two groups of patients. The number of mechanical ventilation-free days and organ failure-free days and the length of intensive care unit stay differed between the groups. Patients receiving 8 days of treatment had a higher number of antibiotic-free days (13.1 [7.4] vs. 8.7 [5.2] days), and multidrug-resistant pathogens were less likely to cause a recurrent infection in patients on the shorter regimen. However, even though patients with VAP caused by nonfermenting gram-negative bacilli did not experience a more unfavorable outcome, those on the 8-day regimen had a higher rate of recurrence (40.6 vs. 25.4%).

Finally, Ibrahim et al. [67] found that using a clinical guideline employing local microbiological data was useful not only in decreasing the length of antimicrobial therapy but also in improving overall antibiotic utilization in VAP patients. The rate of administering initial adequate therapy was statistically higher when using the guidelines (94.2 vs. 48.0%), and treatment duration was statistically shorter (8.6±5.1 vs. 14.8±8.1 days). Secondary VAP episodes also occurred less frequently in patients managed according to the guidelines (7.7 vs. 24.0%).

Conclusion

Management of VAP due to resistant gram-positive bacteria will continue to evolve as susceptibility patterns change and novel antimicrobial agents become available. A number of new antibiotics with activity against MRSA are currently under investigation and may soon become available for clinical use. Additional studies are needed to define the optimal antibiotic choices for treatment, but as always, clinicians must balance the need to provide adequate treatment with the need to minimize the emergence of resistance. The rising rates of resistance have heightened the need for more effective management, improvements in infection control, and new antimicrobial agents, as well as better stewardship of the antibiotics that are currently available.

References

1. Lynch JP (2001) Hospital-acquired pneumonia: risk factors, microbiology, and treatment. Chest 119(Suppl 2):373S–384S
2. Diekema DJ, Pfaller MA, Schmitz FJ et al (2001) Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. Clin Infect Dis 32(Suppl 2):S114–S132
3. Centers for Disease Control and Prevention (2003) National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992 through June 2003, issued August 2003. http://www.cdc.gov/ncidod/hip/NNIS/2003NNISReport_AJIC.PDF. Cited 14 March 2005
4. Centers for Disease Control and Prevention (1999) Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997–1999. JAMA 282:1123–1125
5. Francis JS, Doherty MC, Lopatin U et al (2005) Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton–Valentine leukocidin genes. Clin Infect Dis 40:100–107
6. Gillet Y, Issartel B, Vanhems P et al (2002) Association between *Staphylococcus aureus* strains carrying gene for Panton–Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359:753–759
7. Bartlett JG, Mundy LM (1995) Community-acquired pneumonia. N Engl J Med 333:1618–1624
8. Doern GV, Brueggemann A, Holley HP, et al (1996) Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. Antimicrob Agents Chemother 40:1208–1213

9. Thornsberry C, Jones ME, Hickey ML et al (1999) Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in the United States, 1997–1998. J Antimicrob Chemother 44:749–759
10. Beekmann SE, Heilmann KP, Richter SS et al (2005) Antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and group A â-haemolytic streptococci in 2002-2003: results of the multinational GRASP Surveillance Program. Int J Antimicrob Agents 25:148–156
11. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
12. Kollef MH (1999) The prevention of ventilator-associated pneumonia. N Engl J Med 340:627–634
13. Centers for Disease Control and Prevention (1996) National Nosocomial Infections Surveillance (NNIS) report, data summary from October 1986–April 1996, issued May 1996. Am J Infect Control 24:380–388
14. Trouillet JL, Chastre J, Vuagnat A et al (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 157:531–539
15. Rello J, Torres A, Ricart M et al (1994) Ventilator-associated pneumonia by *Staphylococcus aureus*: comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med 150 (6 Pt 1):1545–1549
16. Centers for Disease Control and Prevention (2003) Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. MMWR Morb Mortal Wkly Rep 52:793–795
17. Centers for Disease Control and Prevention (2003) Methicillin-resistant *Staphylococcus aureus* infections in correctional facilities—Georgia, California, and Texas, 2001–2003. MMWR Morb Mortal Wkly Rep 52:992–996
18. Centers for Disease Control and Prevention (2004) Community-associated methicillin-resistant *Staphylococcus aureus* infections in Pacific islanders—Hawaii, 2001–2003. MMWR Morb Mortal Wkly Rep 53:767–770
19. Naimi TS, LeDell KH, Como-Sabetti K, (2003) Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 290:2976–2984
20. Kazakova SV, Hageman JC, Matava M et al (2005) A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. N Engl J Med 352:468–475
21. Whitby M, McLaws ML, Berry G (2001) Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. Med J Aust 175:264–267
22. Foster TJ (2004) The *Staphylococcus aureus* "superbug". J Clin Invest 114:1693–1696
23. Lina G, Piemont Y, Godail-Gamot F et al (1999) Involvement of Panton–Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. Clin Infect Dis 29:1128–1132
24. Chen DK, McGeer A, de Azavedo JC et al (1999) Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N Engl J Med 341:233–239
25. Centers for Disease Control and Prevention (2001) Resistance of *Streptococcus pneumoniae* to fluoroquinolones—United States, 1995–1999. MMWR Morb Mortal Wkly Rep 50:800–804
26. Doern GV, Brueggemann AB, Huynh H et al (1999) Antimicrobial resistance with *Streptococcus pneumoniae* in the United States, 1997–98. Emerg Infect Dis 5:757–765
27. American Thoracic Society (1996) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies: a consensus statement. Am J Respir Crit Care Med 53:1711–1725
28. American Thoracic Society, Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416
29. Hiramatsu K, Hanaki H, Ino T et al (1997) Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 40:135–136
30. Centers for Disease Control and Prevention (1997) *Staphylococcus aureus* with reduced susceptibility to vancomycin—United States, 1997. MMWR Morb Mortal Wkly Rep 46:765–766
31. Ploy MC, Grelaud C, Martin C et al (1998) First clinical isolate of vancomycin-intermediate *Staphylococcus aureus* in a French hospital. Lancet 351:1212
32. Kim M-N, Pai CH, Woo JH et al (2000) Vancomycin-intermediate *Staphylococcus aureus* in Korea. J Clin Microbiol 38:3879–3881
33. Oliveira GA, Dell'Aquila AM, Masiero RL et al (2001) Isolation in Brazil of nosocomial *Staphylococcus aureus* with reduced susceptibility to vancomycin. Infect Control Hosp Epidemiol 22:443–448
34. Krzyszton-Russjan J, Gniadkowski M, Polowniak-Pracka H et al (2002) The first *Staphylococcus aureus* isolates with reduced susceptibility to vancomycin in Poland. J Antimicrob Chemother 50:1065–1069
35. Ferraz V, Duse AG, Kassel M et al (2000) Vancomycin-resistant *Staphylococcus aureus* occurs in South Africa. S Afr Med J 90:1113
36. Centers for Disease Control and Prevention (2002) *Staphylococcus aureus* resistant to vancomycin—United States, 2002. MMWR Morb Mortal Wkly Rep 51:565–567
37. Howden BP, Ward PB, Charles PGP et al (2004) Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. Clin Infect Dis 38:521–528
38. Fridkin SK, Hageman J, McDougal LK et al (2003) Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997–2001. Clin Infect Dis 36:429–439
39. National Committee for Clinical and Laboratory Standards (2003) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A6. NCCLS, Villanova, PA, USA
40. Brown DFJ (2001) Detection of methicillin/oxacillin resistance in staphylococci. In: Susceptibility testing guide. British Society for Antimicrobial Chemotherapy. http://bsac.test.tmg.co.uk/susceptibility_testing/guide_to_antimicrobial_susceptibility_testing.cfm. Cited 15 June 2005
41. Centers for Disease Control and Prevention (2000) *Staphylococcus aureus* with reduced susceptibility to vancomycin—Illinois, 1999. MMWR Morb Mortal Wkly Rep 48:1165–1167
42. Moise PA, Forrest A, Bhavnani SM et al (2000) Area under the inhibitory curve and a pneumonia scoring system for predicting outcomes of vancomycin therapy for respiratory infections by *Staphylococcus aureus*. Am J Health System Pharm 57(Suppl 2): S4–S9
43. Shelburne SA, Musher DM, Hulten K et al (2004) In vitro killing of community-associated methicillin-resistant *Staphylococcus aureus* with drug combinations. Antimicrob Agents Chemother 48:4016–4019
44. Gonzalez C, Rubio M, Romero-Vivas J et al (1999) Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis 29:1171–1177
45. Levine DP, Fromm BS, Reddy BR (1991) Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. Ann Intern Med 115:674–680
46. Wunderink RG, Rello J, Cammarata SK et al (2003) Linezolid vs. vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 124:1789–1797
47. Lamer C, de Beco V, Soler P et al (1993) Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. Antimicrob Agents Chemother 37:281–286

48. Charles PG, Ward PB, Johnson PDR et al (2004) Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis 38:448–451
49. Sakoulas G, Moise-Broder PA, Schentag J et al (2004) Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 42:2398–2402
50. Albrecht LM, Rybak MJ, Warbasse LH et al (1991) Vancomycin protein binding in patients with infections caused by *Staphylococcus aureus*. DICP 25:713–715
51. Morita K, Yamaji A (1995) Changes in the serum protein binding of vancomycin in patients with methicillin-resistant *Staphylococcus aureus* infection: the role of serum alpha 1-acid glycoprotein levels. Ther Drug Monit 17:107–112
52. Fagon J, Patrick H, Haas DW, Nosocomial Pneumonia Group (2000) Treatment of gram-positive nosocomial pneumonia: prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Am J Respir Crit Care Med 161(3 Pt 1): 753–762
53. Kollef MH, Rello J, Cammarata SK et al (2004) Clinical cure and survival in gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intensive Care Med 30:388–394
54. Wilcox M, Nathwani D, Dryden M (2004) Linezolid compared with teicoplanin for the treatment of suspected or proven gram-positive infections. J Antimicrob Chemother 53:335–344
55. Cepeda JA, Whitehouse T, Cooper B et al (2004) Linezolid versus teicoplanin in the treatment of gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. J Antimicrob Chemother 53:345–355
56. Cubicin [prescribing information] (2003) Cubist Pharmaceuticals, Lexington, Mass, USA. http://www.cubicin.com/fullprescribing.htm#section06. Cited 10 June 2005
57. Ohlsen K, Ziebuhr W, Koller KP et al (1998) Effects of subinhibitory concentrations of antibiotics on alpha-toxin (*hla*) gene expression of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* isolates. Antimicrob Agents Chemother 42:2817–2823
58. van Langevelde P, van Dissel JT, Meurs CJ et al (1997) Combination of flucloxacillin and gentamicin inhibits toxic shock syndrome toxin 1 production by *Staphylococcus aureus* in both logarithmic and stationary phases of growth. Antimicrob Agents Chemother 41:1682–1685
59. Siberry GK, Tekle T, Carroll K et al (2003) Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. Clin Infect Dis 37:1257–1260
60. National Committee for Clinical Laboratory Standards (1997) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A4. NCCLS, Wayne, PA, USA
61. National Committee for Clinical and Laboratory Standards (2004) Performance standards for antimicrobial susceptibility testing. 14th informational supplement. Document M100-S14. NCCLS, Wayne, PA, USA
62. Steward CD, Raney PM, Morrell AK et al (2005) Testing for induction of clindamycin resistance in erythromycin-resistant isolates of *Staphylococcus aureus*. J Clin Microbiol 43:1716–1721
63. Bernardo K, Pakulat N, Fleer S et al (2004) Subinhibitory concentrations of linezolid reduce *Staphylococcus aureus* virulence factor expression. Antimicrob Agents Chemother 48:544–546
64. Dennesen PJ, van der Ven AJ, Kessels AG et al (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375
65. Micek ST, Ward S, Fraser VJ, Kollef MH (2004) A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 125:1791–1799
66. Chastre J, Wolff M, Fagon JY et al (2003) Comparison of 8 vs. 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290:2588–2598
67. Ibrahim EH, Ward S, Sherman G et al (2001) Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 29:1109–1115