Antimicrobial Resistance Among Epidemiologically Important Gram-Positive Bacteria

Cassandra D. Salgado

1 Introduction

The emergence of antimicrobial resistance among clinically relevant bacteria has resulted in profound changes in the approach to treatment of infections caused by these pathogens. This chapter will focus on three epidemiologically important gram-positive bacteria: *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Enterococcus* species. Common infections due to these organisms, common resistance mechanisms, and available treatment options will be reviewed.

2 *Streptococcus pneumoniae*

The pneumococcus, *S. pneumoniae*, is a gram-positive bacterium that replicates in chains when grown in a liquid medium. In the microbiology laboratory, pneumococci have been traditionally identified by four standard reactions: (1) α-hemolysis of blood agar media; (2) catalase negativity; (3) susceptibility to optochin, and (4) solubility in bile salts. Several characteristics of the organism allow it to produce infection in a susceptible host; however, it is the outer polysaccharide capsule that has received the greatest amount of study and description. The capsule protects the organism against phagocytosis and is responsible for the virulence characteristic of the strain. This capsular antigen provokes a type-specific protective immunity (anticapsular antibodies), which has served as the basis for the serotype identification system of the organism. There are currently 90 different serotypes that have been identified; however, serotypes 6, 14, 18, 19, and 23 are the most prevalent, accounting for the majority of disease worldwide [1]. The cell wall is covalently bound to the capsule and is composed primarily of glycopeptides. It is the antigens contained within the cell wall that cause the profound inflammatory reaction among

C.D. Salgado (✉)
Division of Infectious Diseases, Medical University of South Carolina, Charleston, SC, USA
e-mail: salgado@musc.edu

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infected hosts. Other components of the cell wall are responsible for attachment of the organism and then subsequent entry into activated host cells. Activated host cells up-regulate platelet-activating receptors on their surface. Phosphorylcholine, a key component in the pneumococcal cell wall, is responsible for inserting the bacteria into these receptors, later to be taken into the cell by an endocytic vacuole. Additionally, most clinically relevant pneumococcal isolates produce an important virulence factor, pneumolysin, which is an effective cytotoxin responsible for injuring neutrophils, endothelial cells, and alveolar epithelia.

S. pneumoniae is a common colonizing organism of the nasopharynx in humans. When cultured at any given single point in time, the prevalence varies by age group, with pneumococci present in 5–10% of adults and 20–40% of children. Infants become colonized with *S. pneumoniae,* on average, at the age of 6 months, and the initial serotype appears to persist for a mean of 4 months. Adults colonized with individual serotypes have been shown to harbor them for shorter periods of time, usually 2–4 weeks [2]. The worldwide rate of invasive pneumococcal disease, defined as isolation of the organism from a normally sterile body site, has been reported as 15 per 100,000 persons, per year [3], and is more common among the very young (less than 2 years of age) and the elderly (more than 65 years of age). Fortunately, recent data from the United States have suggested that the incidence of pneumococcal disease is decreasing, perhaps as a result of the use of the protein conjugate vaccine in children [4].

Because the organism may be present in the nasopharynx, *S. pneumoniae* has been recognized as a common cause of pneumonia, sinusitis, and otitis media. These infections likely occur via direct spread and invasion. Less frequently, *S. pneumo* has been reported as a cause of meningitis, endocarditis, peritonitis, or bone and joint infections. These infections likely occur via hematogenous spread of the organism from transient or persistent bacteremia.

Over the last 40 years, *S. pneumo* has developed resistance to a variety of antibiotics, including that to β-lactams, macrolides, tetracyclines, trimethoprim-sulfamethoxazole, and fluoroquinolones. Factors which increase a patient's risk for having an antibiotic-resistant strain of *S. pneumo* have been described as previous exposure to antibiotics; exposure to day care or pre-school; stay in a nursing home or other long-term care facility; and having a history of a recent respiratory infection (including viral infections). Of all the classes of antibiotic resistance, the most clinically relevant and most studied among *S. pneumo* isolates is that toward penicillin.

Penicillin inhibits *S. pneumo* by binding to proteins on the cell wall. These penicillin-binding proteins (PBPs) are enzymes needed for synthesis of peptidoglycan. When these PBPs become altered, they have much less affinity for penicillin (and often other β-lactams). Traditionally, resistance to penicillin has been described as concentration-dependent. This definition has been based upon achievable drug concentrations in the cerebral spinal fluid (CSF); however, it has been determined that achievable drug concentrations in the CSF are often much lower than what can be achieved in the plasma, inner-ear fluid, or alveolar fluid. Thus, it is important to realize this when considering whether or not an isolate is resistant and may depend

upon where the infection is located. In the microbiology laboratory, *S. pneumo* is defined as susceptible to penicillin when the MIC ≤0.06 μg/mL; intermediately resistant to penicillin when the MIC is 0.10–1.0 μg/mL; and highly resistant to penicillin when the MIC ≥2.0 μg/mL. In the United States, approximately 60% of *S. pneumo* are susceptible to penicillin, 20% have intermediate resistance, and 20% are highly resistant, but this percentage may vary depending on the region [5]. Children are colonized and infected with more resistant strains compared to adults and in general, invasive isolates tend to be more susceptible than those that cause otitis media. Fortunately, in the United States, use of the 7-valent protein conjugate pneumococcal vaccine has resulted in an 80% reduction in invasive disease and a >95% decrease in invasive *S. pneumo* isolates which are covered by the vaccine [4]. However, not entirely unexpected, there has been an increase among strains that are not covered in the vaccine (type 6 (non-B), 19 (non-F), 35, 11, and 15) and, unfortunately, these strains have demonstrated resistance to antibiotics, as well. Resistance to cephalosporins follows a similar concept and susceptibility to ceftriaxone, a common third-generation cephalosporin used for treatment of *S. pneumo* infections, is defined in the microbiology lab as follows: susceptible if the MIC <1.0 μg/mL; intermediately resistant if the MIC = 2.0 μg/mL; and resistant if the MIC >4.0 μg/mL.

Also important to consider when making treatment decisions is that in the United States, almost 30% of *S. pneumo* isolates are resistant to macrolides, but this varies dramatically depending on the region; up to 10% are resistant to clindamycin; less than 5% are resistant to fluoroquinolones (although this may be higher among long-term care facility residents); 20% are resistant to tetracyclines; and almost one-third are resistant to trimethoprim-sulfamethoxazole [5, 6].

Because the achievable drug concentration differs depending on the body site, therapeutic decisions may differ, depending on the site infected. For Example, to treat all but the most resistant *S. pneumo* isolates, recommended first-line antibiotic therapy for otitis media and sinusitis has been higher dose amoxicillin given at 90 mg/kg per day, divided into twice or thrice daily doses. If treatment failure occurs or the patient has a penicillin allergy, one might consider a macrolide antibiotic, and if one suspects cross-resistance to penicillin as well as the macrolide class of antibiotics, alternatives such as clindamycin or a third-generation cephalosporin should be considered. For pneumonia and bacteremia, there is debate regarding whether or not infection due to penicillin-resistant strains is associated with a worse outcome when compared to infection due to susceptible strains. Some studies have shown that the elderly and those with underlying co-morbid conditions do worse when suffering from pneumonia due to a β-lactam-resistant *S. pneumo* and, thus, many recommend a β-lactam plus a macrolide for patients presenting with community-acquired pneumonia where *S. pneumo* is a consideration [7]. For bacteremia in a normal host, most experts recommend cefuroxime, cefotaxime, or ceftriaxone at standard doses, as the plasma levels achievable typically exceed the desired MIC. Meningitis can be associated with extremely poor outcomes when not treated appropriately and the achievable drug concentration in the CSF is lower than that achievable in plasma or alveoli. Thus, the treatment recommendations for meningitis suspected to be due

to *S. pneumo* in an area where isolates exist with intermediate or high resistance to penicillin and/or ceftriaxone (or the patient has risk factors for an antibiotic-resistant strain) are for higher dose third-generation cephalosporins such as cefotaxime 2 g IV q4h or ceftriaxone 2 g IV q12h, plus vancomycin. Of note, vancomycin does not penetrate the blood–brain barrier well, so, once susceptibilities return, if treatment can be continued with a β-lactam, this is desirable.

Unlike many bacteria that cause significant disease, there are vaccines available for prevention of *S. pneumo* infection. The 7-valent pneumococcal conjugate vaccine (Prevnar®), released in 2000, is recommended for children under the age of 2 years. Pneumococcal vaccines for the prevention of disease among children and adults who are 2 years and older are the Pneumovax® and the Pnu-Immune®. These vaccines are 23-valent polysaccharides currently recommended for use in all adults who are older than 65 years and for persons who are 2 years and older and at high risk for disease (e.g., sickle cell disease, HIV infection, or other immunocompromising condition).

3 *Staphylococcus aureus*

S. aureus, a member of the Micrococcaceae, are named after their ability to grow in grape-like clusters in solid media. In the microbiology laboratory, staphylococci are characterized by a positive catalase test and identified as *S. aureus* by a positive coagulase test (indicating the presence of coagulase enzymes). Several virulence factors have been described which may contribute to *S. aureus'* ability to cause clinical disease in a susceptible host. These include toxins which act on cell membranes; exotoxins such as toxic shock syndrome toxin and enterotoxins; leukocidin, which mediates the destruction of phagocytes; and catalases, coagulases, and hyaluronidases, which promote invasion and survival in tissue. Of particular interest is the Panton Valentine leukocidin (PVL) gene, which encodes for release of a cytotoxin responsible for tissue necrosis and leukocyte destruction. The presence of this gene has been associated with infections of greater severity [8]. *S. aureus* is a common colonizer of human skin and mucosa. It preferentially colonizes the anterior nares, particularly in adults, and at any given time 10–40% of the population is transiently colonized with the organism. A small proportion may become chronically colonized with *S. aureus* and, as such, is often at increased risk for clinical disease.

The discovery of penicillin proved to be extremely valuable in the treatment of infections due to staphylococci; however, resistance to this agent developed rapidly. Currently, susceptibility rates to penicillin are in single digits and thus, use of synthetic penicillins has become commonplace since the development of methicillin in the 1960s. Unfortunately, development of methicillin resistance among *S. aureus* was detected within months of its release. Resistance to methicillin develops once *S. aureus* acquires a large mobile genetic element, the staphylococcal cassette chromosome *mec* (SCC*mec*). Within this cassette the genes *ccrA* and *ccrB* mediate mobilization, and the *mec*A gene mediates β-lactam resistance. Specifically, *mec*A

encodes for an altered penicillin-binding protein, PBP2a. This protein, when found on the surface of the bacteria, has little affinity for β-lactam antibiotics and confers resistance to the entire class. Additionally, the *mec*A gene is often flanked by IS431, an insertion sequence that acts as a "collector" for additional antibiotic-resistance genes, thus promoting multidrug-resistant strains of MRSA. At least five different varieties of the SCC*mec* have been described (types I–V), based largely upon their corresponding *mec*A genes. Types I–III are large in size and tend to carry multiple antibiotic-resistance encoding genes. Types IV and V are smaller in size, are likely more mobile, and contain fewer antibiotic-resistance encoding genes. *S. aureus* resistant to methicillin has been defined in the laboratory as isolates with an MIC of $\geq$ 16 mg/L to methicillin or an MIC of $\geq$ 4 mg/L to oxacillin; however, more rapid and often more dependable methods for laboratory identification of methicillin resistance are those that actually detect the *mec*A gene, or the product of the gene, PBP2a.

MRSA has traditionally been considered an organism acquired within the healthcare system, but over the past several years, an increasing number of reports have described MRSA occurring among patients without this history. This emerging epidemiology has led many to describe MRSA as either healthcare-associated or community-associated, and the prevalence, resistance patterns, and clinical syndromes associated with the organism depend on this classification.

3.1 Healthcare-Associated MRSA

MRSA may be defined as healthcare-associated using a time-based definition such as being isolated from a patient after at least 72 h of admission to a healthcare facility. Additionally, healthcare-associated strains of MRSA tend to harbor the SCC*mec* types I, II, or III and are therefore usually multidrug-resistant. MRSA among hospitalized patients continues to be isolated with increased frequency and is an important cause of hospital-acquired infections. These infections include pneumonia (including ventilator-associated pneumonia), device-associated infections such as central-line associated bacteremia, and surgical site infections. According to data collected from US hospitals, the proportion of hospital-acquired infections due to *S. aureus* that were resistant to methicillin has continued to increase over the past two decades, and in 2004 approached 60% among ICU patients [9]. Experts suggest that evolutionary changes in the microorganism, combined with ineffective (or noncompliance with) infection-control measures and selective pressure from antibiotic use have all likely contributed to the continued rise of MRSA.

Risk factors for acquisition of healthcare-associated MRSA include prolonged hospital stay, particularly those in ICUs; exposure to and prolonged use of antibiotics; presence of severe underlying illness; receipt of invasive Procedures or foreign bodies; and being in close proximity to other MRSA-colonized or infected patients. Spread of MRSA in hospitals is thought to be largely due to patient-to-patient transmission from the contaminated equipment and hands of healthcare providers. MRSA is important because when patients develop infection due to the organism,

they suffer increased morbidity, mortality, and greater hospital costs than those who develop infection due to susceptible strains of the organism [10, 11]. A meta-analysis of studies of patients with *S. aureus* bacteremia reported that those with MRSA died almost twice as often, compared to those with methicillin-susceptible *S. aureus* [10], and another study of patients with *S. aureus* surgical site infections found that those with MRSA died more than three times as often, compared to those with methicillin-susceptible *S. aureus*, and had a 1.9-fold increase in hospital costs [11].

4 Community-Associated MRSA

MRSA may also be defined as community-associated, using the time-based approach described above, such as if the organism is isolated from a patient at the time of admission or within 48–72 h of admission to the hospital. Additionally, one may classify MRSA as community-associated if it is isolated from a patient presenting in the outpatient clinical setting or emergency department. Community-associated strains of MRSA usually harbor SCC*mec* IV and, less often, SCC*mec* V, and thus may retain some susceptibility to other classes of antibiotics. Also of note, MRSA isolates of community origin are more likely to possess the gene responsible for encoding PVL, a recognized virulence factor, and are often identified as the USA 300 clone when subjected to pulsed-field gel electrophoresis. Recent studies have described the frequency with which CA-MRSA has been occurring, as well as important characteristics among individuals with infections due to the organism [12, 13]. A study of patients with MRSA infections from Baltimore, Atlanta, and Minnesota reported that from 2001 through 2002, 8–20% of the MRSA isolates were classified as community-associated. The annual incidence of CA-MRSA disease was significantly higher among those less than 2 years old, and sometimes among blacks. Furthermore, the majority of infections (77%) were skin or soft tissue, but 6% were invasive in nature (e.g., bacteremias) and almost a quarter of patients with CA-MRSA infections required hospitalization. Also of interest was that among patients with CA-MRSA, many had contact with the healthcare system, such as visiting their physician within the previous year, or receiving antimicrobial therapy [12]. Another recent study documented that MRSA was the single most common identifiable cause of skin and soft-tissue infections among patients presenting to emergency departments in 11 US cities. The overall prevalence of MRSA was 59% and, among those, 97% were the USA 300 clone and 98% harbored SCC*mec* IV and were PVL positive [13]. Even though the majority of infections due to CA-MRSA have involved skin and soft tissue, the organism may also be a cause of more invasive infections, such as necrotizing fasciitis, bacteremia, or necrotizing pneumonia.

An important study was recently published and was the first to document the incidence and characteristics of invasive MRSA infections in nine US cities [14]. This population-based active case-finding study reported that, in 2005, more than 94,000 invasive MRSA infections occurred, for an estimated incidence rate

of 31.8 per 100,000 persons. These infections were associated with more than 18,000 deaths, for an estimated mortality rate of 6.3 per 100,000 persons. There was geographic variability, but in general most invasive MRSA infections were healthcare-associated; 58.4% were healthcare-associated community-onset infections and 26.6% were healthcare-associated hospital-onset infections. Only 13.7% of invasive MRSA infections were community-associated. Additionally, molecular analysis provided evidence that strains of community origin do cause a measurable amount of hospital-onset disease and in fact, 16% of invasive hospital-onset MRSA infections were due to the USA 300 clone [14].

Treatment for serious infections due to MRSA had been somewhat limited to agents such as vancomycin; however, newer agents with activity against the organism are now available. Vancomycin therapy requires an intravenous route, as well as monitoring of blood levels in order to assure adequate dosing and to avoid potential toxicity. Daptomycin, also given intravenously, is indicated for use in MRSA- and MSSA-complicated skin infections (at 4 mg/kg daily dose) and bacteremia, including right-sided endocarditis (at 6 mg/kg daily dose). Daptomycin levels do not need to be monitored; however, patients receiving the drug should be followed for the onset of muscle pain or weakness and weekly CPK levels should be measured. Another recently released intravenous agent with activity against MRSA is tygecycline. Regarding MRSA, this agent has clinical indications only for treatment of complicated skin and skin-structure infections at an initial dose of 100 mg, followed by 50 mg every 12 h. Linezolid, which can be given orally, has demonstrated pathogen-eradication rates and clinical efficacy comparable to that of vancomycin for commonly encountered infections, including skin and soft-tissue infections [15], and it may be associated with a more favorable outcome when used for treatment of MRSA nosocomial pneumonia (including ventilator-associated pneumonia) [16]. Additionally, older agents such as trimethoprim-sulfamethoxazole, clindamycin, and often tetracyclines may have activity and are often used for outpatient management of CA-MRSA infections, particularly those involving the skin and soft tissue.

5 Vancomycin-Intermediate *Staphylococcus aureus* and Vancomycin-Resistant *Staphylococcus aureus*

The past decade has seen first the emergence of *S. aureus* with intermediate resistance to and later frank resistance to vancomycin. Vancomycin-intermediate *S. aureus* (VISA) is defined in the microbiology lab as having an MIC toward vancomycin of 8–16 mg/L and has been described as a cause of infection primarily among patients on hemodialysis receiving long courses of vancomycin for MRSA infections [17]. The mechanism of resistance has been described as due to cell-wall thickening, which may cause the large vancomycin molecule to become trapped and unable to reach its functional targets. Vancomycin-resistant *S. aureus* (VRSA) is defined in the microbiology lab as having an MIC toward vancomycin of $\geq$64 mg/L. The mechanism of resistance for this extremely worrisome pathogen is acquisition

of the *vanA* gene from vancomycin-resistant *Enterococcus* (VRE). Emergence of this organism has originated in areas where MRSA and VRE have co-existed, and at least seven cases have been described in the United States [18]. Fortunately, these VISA and VRSA strains have retained susceptibility to many alternative antibiotic agents, but their mere existence highlights the importance of controlling their spread in healthcare facilities.

6 *Enterococcus* Species

Enterococcus, a resident normal flora of the gastrointestinal and genitourinary tract, was once classified as a group D *streptococcus*; however, advancements in nucleic acid analysis revealed that enterococci were not closely related to streptococci and a new genus was proposed [19]. Enterococci are facultative anaerobic organisms that grow at extreme temperatures and hydrolyze esculin in the presence of bile. Once thought to be of insignificant consequence to humans, *Enterococcus* is now the second- to third-most common cause of nosocomial infections in US hospitals and two species, *Enterococcus faecalis* and *E. faecium,* cause 90% of these infections.

Enterococci exhibit intrinsic resistance of varying degrees to many antibiotics traditionally used to treat infections due to gram-positive pathogens. Enterococci are much less susceptible to β-lactams than streptococci. For Example, *E. faecalis'* MIC toward ampicillin is 1 μg/mL, and its MIC toward penicillin and piperacillin is 2 μg/mL. Additionally, the cephalosporins are essentially ineffective against enterococci. Intrinsic resistance to β-lactams results from the reduced affinity of the penicillin-binding protein of the organism. Also of note, even if enterococci are susceptible to penicillins, if they are exposed to this class of antibiotics, they may develop tolerance to the drug's killing effect [19]. Acquired resistance among enterococci is an additional concern, particularly toward the aminoglycosides (streptomycin and gentamicin) and toward the glycopeptide, vancomycin. The most common and best described mechanism for enterococci to become resistant to vancomycin is by acquisition of the *vanA* gene cluster found on the transposable genetic element Tn*1546*. When enterococci possess this gene cluster and are exposed to vancomycin, they produce the enzymes necessary to cross-link peptides with altered terminal sequences (D-Ala-D-lactate instead of D-Ala-D-Ala). These altered sites have much less affinity for binding glycopeptides.

Unfortunately, just as we have seen the continued increase in other antibiotic-resistant organisms, VRE has followed suit. Data from US hospitals suggest that the prevalence of enterococci causing nosocomial infections that were vancomycin-resistant has continued to increase over the past decade and now has surpassed 30% among ICU patients [9]. Emergence of the organism in the healthcare system has been facilitated by the overuse of broad-spectrum antibiotics. Patients acquire colonization or infection and subsequently contaminate their hospital environment with this hardy organism. Just as is the case for other resistant organisms, such as MRSA, spread from patient to patient occurs almost always by contaminated hands and equipment of healthcare workers. Risk factors for VRE acquisition have

been described and include the presence of an underlying co-morbid condition such as diabetes, renal failure, or malignancy; lengthy hospital stay; receipt of broad-spectrum antibiotics such as cephalosporins and vancomycin; having indwelling devices; and being in close proximity to another VRE-colonized or infected patient. VRE colonization increases the risk of VRE infection. The most common site of infection has been described as the urinary tract (cystitis, pyelonephritis, prostatitis), but more invasive infections occur, such as bloodstream infections and endocarditis.

The continued increase in VRE is concerning because patients who develop infection with VRE suffer increased morbidity, mortality, and greater hospital costs than those who develop infection caused by vancomycin-susceptible *Enterococcus* (VSE).

A large retrospective-matched case–control study comparing patients with VRE bloodstream infections to those with VSE bloodstream infections reported that those with VRE had significantly greater mortality (RR 2.13, 95% CI 1.05–4.37); greater length of stay (RR 1.73, 95% CI 1.43–2.10); greater mean cost (RR 1.40, 95% CI 1.26–1.59); greater need for surgery (RR 2.74, 95% CI 1.52–4.92); greater need for ICU admission (RR 3.47, 95% CI 1.75–6.85); and greater need to be discharged to a long-term care facility (RR 2.01, 95% CI 1.34–3.02) [20]. Additionally, data from multiple studies comparing patients with VRE bloodstream infection to those with VSE bloodstream infection suggest that VRE bacteremia has been associated with higher rates of recurrent BSI (16.9% vs. 3.7%, $p<0.0001$); higher crude case fatality rates (RR=2.57, 95% CI = 2.27–2.91); higher mortality due to bacteremia (RR = 1.79, 95% CI = 1.28–2.50); and greater hospital costs of $27,000 per episode of bloodstream infection ($p = 0.04$) [21].

The treatment of infections due to vancomycin-resistant strains of *Enterococcus* is a challenge because there are a limited number of agents available with sufficient activity against the organism and fewer agents have actually been studied in clinical trials. Quinupristin-dalfopristin has activity against *E. faecium*, but not most strains of *E. faecalis*. This, accompanied by the fact that it has significant side effects and must be given through a central venous catheter, significantly limits its use. Linezolid has activity against VRE [22], but this drug is bacteriostatic and thus must be used with caution among patients with bacteremia or endocarditis where bactericidal therapy is preferred. Linezolid is also associated with myelosuppression and thus is not typically considered a good choice for infections where long-term therapy (i.e., greater than 2 weeks) is needed. Daptomycin is bactericidal against VRE and may be considered for these more invasive infections; however, there are no comparative clinical studies specifically directed toward its use against VRE. Additionally, some strains of *E. faecium* have higher MICs toward daptomycin. Tigecycline has in vitro activity against VRE and has been studied for complicated skin and soft-tissue infections and intra-abdominal infections where VRE was isolated, but there is no formal indication for use of this drug for VRE infections [23]. Thus, each patient must be approached individually and much must be taken into consideration, such as type of infection and ability to remove foreign bodies or drain areas of infection, as well as underlying host factors. For patients with VRE infections with MICs to ampicillin ranging between 16 and 64 μg/mL, high doses of the drug may

be used (24 g a day divided q4h) plus gentamicin or streptomycin for severe invasive infections such as endocarditis. For invasive disease due to ampicillin-resistant VRE, off-label use of daptomycin or tigecycline should be considered. For endocarditis, these agents should be used in combination with another agent, based upon susceptibilities. These normally would include gentamicin or streptomycin; however, in vitro data support the use of doxycycline, rifampin, imipenem, or a fluoroquinolone.

7 Conclusion

Antibiotic resistance among gram-positive organisms continues to be a growing concern. Patients who acquire invasive infections due to these pathogens often stay sicker longer, have excess costs associated with their care, and more importantly, have increased risk of mortality. Treatment options are often limited for infections due to resistant gram positives and thus, efforts expended for control are needed.

Reducing the use of unnecessary antibiotics, particularly in the outpatient setting, coupled with vaccination efforts, will be important if the emergence of resistant *S. pneumo* is to be halted. Additionally, guidelines exist regarding control of antibiotic-resistant organisms, such as MRSA and VRE, and include reducing emergence of the organism by antibiotic control or effective stewardship, reducing patient-to-patient spread by reducing contamination of the environment (disinfection, terminal cleaning, dedicated pt equipment), and reducing contamination of the healthcare worker (hand hygiene, gowns, and gloves). Additionally, healthcare-acquired infections can be effectively controlled by closely following institutional infection-control measures, as well as published prevention guidelines for central venous catheter-associated bloodstream infections and ventilator-associated pneumonia.

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