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Methicillin-Resistant *Staphylococcus aureus* Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). MRSA pneumonia is associated with significant morbidity and mortality. Several virulence factors allow *S. aureus* to become an effective pathogen. The polysaccharide intracellular adhesin allows for the production of biofilms, some strains can produce capsular polysaccharides that protect against phagocytosis, microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) allow for colonization of epithelial surfaces, and *S. aureus* secretes several exotoxins that aid in tissue destruction. The α-hemolysin exotoxin secreted by *S. aureus* is one of the most important virulence factors for the bacteria. The diagnosis of MRSA pneumonia can be challenging; the infection may present as a mild respiratory infection or severe respiratory failure and septic shock. Many individuals are colonized with MRSA and thus a positive nasopharyngeal swab does not confirm infection in the lower respiratory tract. The management of MRSA pneumonia has evolved. Historically, vancomycin has been the primary antibiotic used to treat MRSA pneumonia. Over the past decade, prospective studies have shown that linezolid leads to higher rates of clinical cure. Monoclonal antibodies are being studied as potential therapeutic options. MRSA is an important cause of HAP/VAP; novel diagnostics may facilitate rapid diagnosis of this infection and the available literature should be used to make informed decisions on management.

Keywords

Methicillin-resistant *Staphylococcus aureus*; pneumonia; ventilator

Staphylococcus aureus pneumonia is the most common cause of gram-positive hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).[1,2] Up to 15% of VAP cases are caused by methicillin-resistant *S. aureus* (MRSA).[3] The incidence of nosocomial MRSA pneumonia varies, reportedly decreasing in tertiary care and large academic centers while increasing in community hospitals.[4,5] However, the mortality rate associated with MRSA HAP/VAP remains as high as 55%, depending on the population

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Conflict of Interest

None declared.

being studied.[6–8] Intensive care unit (ICU) and hospital length of stay, duration of mechanical ventilation, and cost are increased in patients with MRSA pneumonia compared with patients with methicillin-sensitive *S. aureus* (MSSA) pneumonia.[9,10]

For these reasons, the 2016 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines advise empirical therapy against MRSA in high-risk patients with suspected HAP/VAP.[11] However, the definition of high risk is complicated with only prior antibiotic therapy a defined risk in the ATS/IDSA guidelines. Unfortunately, this risk factor does not distinguish MRSA from resistant gram-negative pathogens. Even with this guidance, MRSA pneumonia remains a challenge and empirical overtreatment for MRSA HAP/VAP is common.[12] Diagnosis is difficult in nonintubated patients with HAP, especially because individuals may be colonized with MRSA without having a lower respiratory tract infection. Diagnosis is also difficult due to the prolonged turnaround time of standard diagnostic tools like semiquantitative culture. Management is equally challenging due to the lack of consensus on optimal antibiotic therapy and difficulty in eradicating the infection. In this review, we discuss various aspects of MRSA pneumonia and highlight relevant literature to help guide clinical decisions in the care of patients with this life-threatening infection.

Methicillin Resistance in *Staphylococcus aureus*

S. aureus are aerobic and facultative anaerobic gram-positive cocci, commonly identified in clusters. *S. aureus* is a commensal organism commonly found on human skin and in human respiratory and gastrointestinal tracts.[13] 20% of healthy individuals are chronically colonized with *S. aureus* and studies demonstrate that up to 80% of *S. aureus* isolates from bacteremic patients are clonally identical to isolates from the patient's nasopharynx.[14,15]

The cell wall of *S. aureus* is composed of peptidoglycan. Key parts of peptidoglycan synthesis are catalyzed by penicillin-binding proteins (PBPs). Beta-lactam antibiotics bind the transpeptidase site of PBPs, inhibiting their ability to catalyze the formation of glycan chains for peptidoglycan synthesis and thus preventing cell wall formation.[16] In the clinical setting, β-lactam antibiotics were initially highly effective bacteriocidal agents against *S. aureus*. However, *S. aureus* strains developed resistance by producing β-lactamases to hydrolyze penicillins.[16] To combat this issue, methicillin, a penicillin with resistance to hydrolysis by β-lactamases, was developed.[17] Yet in 1961, roughly only 1 year after methicillin was introduced as a treatment option for *S. aureus*, MRSA was identified.[18] Methicillin resistance in *S. aureus* results from the production of a unique PBP called PBP2a. This protein is not inhibited by β-lactams and thus cell wall synthesis catalyzed by PBP2a continues even in the presence of β-lactams. PBP2a is encoded by the *mecA* gene. The *mecA* gene is highly conserved in MRSA and is essential for methicillin resistance.

Methicillin-Resistant *S. aureus* Pathogenesis

MRSA has multiple virulence factors that allow for the development of infection in lower respiratory tract. *S. aureus* synthesizes polysaccharide intracellular adhesin which allows for the production of biofilms.[19] Biofilm formation aids in persistent and relapsing infection even in the presence of appropriate antimicrobial therapy. *S. aureus* strains can also produce

capsular polysaccharides that protect against phagocytosis.[20] The cell wall adhesion surface proteins on *S. aureus* known as microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) allow for colonization of epithelial surfaces which can predispose the host to invasive infection.[21] Colonization is primarily achieved via binding to the extracellular matrix of host cells. Binding to fibrinogen in the extracellular matrix also allows for evasion of immune cells.[22] Additionally, *S. aureus* secretes several exotoxins in the form of proteases, lipases, and metalloproteases aiding in tissue destruction.[19]

The α-hemolysin exotoxin secreted by *S. aureus* is perhaps the most important virulence factor for the bacteria and has been the subject of much research over the past several decades. Alpha-hemolysin is a water-soluble cytokine that binds to host cell membranes, and undergoes molecular transformation leading to perforation of the host cell membrane and cell lysis. The *hla* gene that encodes α-toxin is highly conserved in strains of MSSA and MRSA isolated from respiratory samples of hospitalized patients.[23] The α-toxin secreted by *S. aureus* most notably leads to lysis of red blood cells, but additional research has demonstrated the ability of the toxin to destroy a variety of immune cells including neutrophils, macrophages, and T lymphocytes.[24,25] The ability of α toxin to bind to a wide range of cells is facilitated by ADAM10, a transmembrane surface protein on multiple host cells. ADAM10 is a metalloprotease that acts as a cell receptor for α-hemolysin toxin.[26] Once bound by α toxin, ADAM10 metalloprotease activity is upregulated and downstream signaling leads to vascular endothelial injury, increased vascular permeability, and pulmonary edema.[27] The hemorrhagic and necrotic pulmonary lesions seen in MRSA pneumonia are believed to be the result of the activity of α toxin causing alveolar-capillary destruction. Studies have demonstrated that mouse models deficient in ADAM10 are unable to induce endovascular injury.[28]

Risk Factors for MRSA HAP/VAP

While *S. aureus* has multiple virulence factors, the presence of the bacteria alone is not sufficient to cause infection in the alveolar space. *S. aureus* transitions from a commensal bacteria to a respiratory pathogen when dysbiosis in the pulmonary microenvironment leads to microbial overgrowth, low α- and β-diversity, and a host inflammatory response.[29,30] Several clinical factors disrupt the normal, healthy lung microbiome and allow MRSA to cause pulmonary infection.

One of the most important risk factors for the development of VAP is endotracheal intubation. Endotracheal intubation predisposes the host to pneumonia via several mechanisms, none of which are unique to MRSA but are important to mention.[31] The endotracheal tube acts as surface for bacteria to reside and proliferate away from host immune cells. The endotracheal tube bypasses several upper respiratory defense mechanisms, making it more difficult for microbes in the lower respiratory tract to be cleared. Airway mucosa is often injured by the presence of the endotracheal tube and may become sites for bacteria to adhere to and cause infection.

The 2016 ATS/IDSA guidelines identify several risk factors for multidrug-resistant VAP/HAP, and cite intravenous antibiotic use within the past 90 days as the most consistent

risk factor for MRSA HAP/VAP. A subsequent single-center prospective study assessed the ability of these risk factors to predict multidrug-resistant infections and adequate antibiotic therapy for patients with nosocomial pneumonia in the ICU.[12] In this study, IV antibiotic use within the past 90 days was associated with a negative predictive value of 91% for the development of nosocomial MRSA pneumonia but had a positive predictive value of only 8%. These operating characteristics suggest that prior antibiotic exposure is helpful for identifying patients who would benefit from empirical anti-MRSA antibiotics in the ICU. However, use of this risk factor alone, even in units where greater than 10 to 20% of *S. aureus* isolates are methicillin resistant, results in substantial overtreatment.

Prior nasopharyngeal colonization is highly associated with the risk of MRSA pneumonia. Factors associated with this colonization, particularly when persistent despite attempts to decolonize with mupirocin, are poorly understood but include genetic risks and may be independent of prior antibiotic exposure.

Diagnosing MRSA HAP/VAP

The 2016 guidelines also discuss the role of *S. aureus* surveillance screening for inpatients; positive nasopharyngeal swabs are known to increase the likelihood of MRSA pneumonia.[32] The negative predictive value of nasal screening ranges from 76 to 99% and be useful to rule out pneumonia in nonintubated patients with suspected HAP. However, the test has a poor positive predictive value, as only a minority of colonized patients actually develop MRSA pneumonia and nasal MRSA colonization does not exclude a gram-negative pathogen causing pneumonia. Therefore, in intubated patients, sampling of the lower respiratory tract is superior to nasopharyngeal swabs for ruling out MRSA VAP.[33]

Because of chronic nasal colonization and the tendency of MRSA to form biofilms on endotracheal tubes, growth of MRSA in endotracheal aspirates (ETAs) is problematic for diagnosis. In a prospective study, *S. aureus* was cultured from twice as many cases using ETAs compared with bronchoscopic cultures (19 vs. 9.8%).[34] The corresponding use of anti-MRSA drugs was significantly decreased. Despite this, the 2016 ATS/IDSA HAP/VAP guidelines suggest patients with suspected VAP be treated based on results of noninvasive sampling like ETAs rather than invasive sampling like bronchoscopy or blind bronchial sampling. Conversely, the international HAP/VAP guidelines give a weak recommendation for use of invasive quantitative cultures to avoid overtreatment of pathogens such as MRSA.[35] Both suggest that MRSA treatment can be stopped with either a negative culture or growth below an established threshold.

As culture-independent molecular techniques have been incorporated into clinical microbiology laboratories over the last few years, the diagnostic algorithms may be changing. The most common culture-independent tools for the diagnosis of MRSA pneumonia are limited and multiplex nucleic-acid amplification tests detect a unique *S. aureus* gene and also detect the presence of *mec*A. *MecA* is contained within a mobile genetic element called the “staphylococcal chromosomal cassette,” SCCmec.[36] This mobile genetic element is specific to *S. aureus*. Detection of a highly conserved portion of the SCCmec, for example, the major right extremity junction (MREJ) of SCCmec, identifies

S. aureus and detection of mecA identifies methicillin resistance. Multiple studies have concluded that the use of a NAAT to identify mecA/MREJ is a rapid and sensitive way to diagnose MRSA pneumonia.[33] Cultures may be adversely affected by delays in transport to the microbiology laboratory, errors in preparation, receipt of antibiotics prior to the sample being cultured, suboptimal growth media, and metabolic impairment of growth of certain bacteria in polymicrobial infections. NAATs are more sensitive than standard cultures; thus, it is not uncommon for clinicians to have a positive NAAT and negative culture from the same respiratory sample. In these cases, deviation from the 2016 guidelines may be warranted and antibiotic therapy may be indicated.

Treatment of MRSA HAP/VAP

Many critically ill patients with suspected HAP/VAP are treated with empirical anti-MRSA therapy due to the frequent presence and nonspecificity of risk factors. Definitive treatment of diagnosed MRSA pneumonia is usually with vancomycin or linezolid.

Vancomycin is a glycopeptide antibiotic that inhibits cell wall synthesis in gram-positive bacteria. Due to complex pharmacokinetics and a narrow therapeutic window, vancomycin must be monitored by trough levels to achieve an effective dose and to avoid nephroand ototoxicity. There is some concern that vancomycin may not achieve optimal concentrations in lung tissue,[37,38] especially when the minimal inhibitory concentration (MIC) is 1 to 2 μg/mL. Vancomycin has been the standard empirical treatment for suspected MRSA infections for decades, leading to progressive increases in MICs and the recent emergence of vancomycin-resistant *S. aureus*.

Linezolid is an oxazolidinone that inhibits bacterial protein synthesis, administered either orally or intravenously. The most common adverse effects associated with linezolid are thrombocytopenia, anemia, and transaminitis. The largest head-to-head comparison of vancomycin and linezolid for MRSA nosocomial pneumonia demonstrated both clinical and microbiologic superiority.[39] Smaller studies of the MRSA subgroup of more generic studies comparing vancomycin versus linezolid for the treatment of MRSA pneumonia provide mix results: some found no difference in clinical cure, duration, adverse effects, or hospital length of stay while more recent studies report increased rates of clinical cure and decreased all-cause mortality in patients treated with linezolid.[39–42] Differences in study design may explain some of the discrepancy in the findings. Since the 2016 guidelines were published, a meta-analysis of seven randomized controlled trials and eight retrospective studies found robust evidence to support superior clinical outcomes in patients with MRSA pneumonia treated with linezolid.[43]

Treatment of MRSA HAP/VAP

Tedizolid is a high-potency oxazolidinone with activity against MRSA through inhibition of bacterial protein synthesis by binding to the bacterial 23S ribosomal RNA.[44] Tedizolid has lower risks of gastrointestinal side effects, less interactions with commonly used medications like anti-depressants and less bone marrow toxicity compared to linezolid. In addition, compared to linezolid, tedizolid was found to be non-inferior regarding 28

all-cause mortality in hospitalized patients with hospital-acquired pneumonia and ventilator associated pneumonia.[45] Tedizolid is a promising drug for treatment of MRSA pneumonia, however it does not currently have FDA approval for use in pneumonia.

No alternative anti-MRSA therapies for pneumonia have been found to be superior to vancomycin or linezolid since the publication of the 2016 guidelines. Ceftaroline and ceftobiprole (where available) are cephalosporins with activity against MRSA. Ceftaroline has not specifically been studied for MRSA pneumonia, but case series suggests activity for MRSA HAP/VAP.[46] In a randomized clinical trial, ceftobiprole was equivalent or better to linezolid for MRSA HAP, but VAP outcomes were worse.[47]

One year after the guidelines were published, a study on inhaled vancomycin reported reduced sputum levels of MRSA and improvement in CPIS scores of patients treated with nebulized vancomycin compared with placebo.[48] Nebulized vancomycin has also been studied in the cystic fibrosis population, but has not been implemented into a broader clinical context likely due to the limited literature on efficacy and lack of large, prospective studies.[49]

Given a persistently high clinical and microbiological failure rate for MRSA pneumonia, adjunctive treatments are attractive. Adjunctive monoclonal antibodies are currently being studied.[50,51] An antibody directed against the α-toxin was safe and had a trend to better outcome in a study of *S. aureus* HAP/VAP.[52] *S. aureus*-specific lytic phages may also have a future role to play.[53]

Nosocomial MRSA Pneumonia in COVID-19

In December 2019, the SARS-CoV-2 virus was identified as the etiology of a severe respiratory syndrome now called “COVID-19 pneumonia.” The rapid spread of SARS-CoV-2 infection developed into a pandemic. Many patients with COVID-19 were hospitalized for prolonged periods of time and/or intubated, making them vulnerable to the development of superinfection nosocomial pneumonia. The current literature on COVID-19 and bacterial superinfection does not suggest increased mortality in patients with SARS-CoV and MRSA.[54,55] This is in contrast to robust literature on MRSA and influenza which demonstrates a significant increase in mortality.[56] However, higher incidence rates of VAP were reported, possibly due to increased lower respiratory tract sampling and use of a more sensitive diagnostic tool compared with previous studies investigating incidence of VAP.

Conclusions

The diagnosis and management of MRSA HAP/VAP is continually evolving. With the advent of culture-independent diagnostic tools, the diagnosis of nosocomial MRSA pneumonia can be made rapidly. With more literature on antibiotic therapy in MRSA, clinicians maychoose to shift away from vancomycin and use linezolid in the appropriate patient population. In the midst of the COVID-19 pandemic, concern was raised that bacterial superinfection would frequently complicate SARS-CoV-2 infection and adversely affect outcomes. However, the available literature demonstrates that superinfection with multidrug-resistant bacteria, including MRSA, is uncommon. We conclude that MRSA

remains an important cause of HAP/VAP; clinicians should take advantage of novel diagnostics to rapidly detect this infection and should use available literature to make informed decisions on antimicrobial therapy.

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