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Managing Severe Community-Acquired Pneumonia Due to Community Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Abstract Community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) is a rare, but significant cause of community-acquired pneumonia (CAP). A number of virulence determinants have been implicated in the development of severe community MRSA pneumonia, characterized by multilobar cavitating necrosis in patients without usual risk-factors for pneumonia. Optimal management is uncertain, and is extrapolated from anecdotal experiences with small case series, randomized studies of hospital-acquired pneumonia, and laboratory investigations using *in vitro* experiments and animal models of MRSA pneumonia. Adequate clinical suspicion, early diagnosis and administration of appropriate antibiotics are necessary for best patient outcomes, although some patients will still do badly even with early anti-MRSA therapy. Vancomycin or linezolid have been recommended as first-line therapy, possibly in combination with other antibiotics. Newer antibiotics such as ceftaroline are still being evaluated.

Keywords Methicillin-resistant *Staphylococcus aureus* · MRSA · Community-acquired pneumonia · CAP · *Staphylococcus aureus* pneumonia · Necrotizing pneumonia · Community-acquired MRSA · NORSA · Panton-Valentine Leukocidin · PVL · Vancomycin · Linezolid · Ceftaroline

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Introduction

The emergence of rapidly progressive necrotizing pneumonia due to "community-associated" strains of methicillin-resistant *Staphylococcus aureus* (MRSA) has been notable for its high morbidity and mortality in relatively young and previously healthy patients. However, optimal management of these patients is not clear, and even the best available treatment may still result in poor outcomes. In this review, we discuss the epidemiology, clinical features and management of patients presenting with severe necrotizing community-acquired pneumonia (CAP) due to community MRSA.

Previously, the term "community-acquired MRSA" has been used interchangeably to describe the location of acquisition of the infection, the antibiotic resistance profile, and the genotype of the organism, while "hospital-acquired MRSA" has been used for the traditional multidrug-resistant MRSA associated with hospitalization. To avoid confusion, we have used the terminology "community MRSA" to refer to strains that usually cause community-onset infections and that are usually non-multidrug resistant.

Epidemiology

Traditionally, CAP due to *S. aureus* was thought to occur predominantly at the extremes of age following an episode of influenza, and represented approximately 1% to 5% of CAP in several prospective studies [1, 2, 3••]. Although it was known community strains of *S. aureus* could cause severe pneumonia in patients with underlying risk factors, the emergence of necrotizing pneumonia due to community MRSA isolates has been a rare, but significant occurrence in individuals not necessarily predisposed to severe pneumonia.

The exact incidence of pneumonia due to community MRSA is difficult to determine. Although there are a number of case reports and small case series in the literature, there are yet to be any substantial epidemiologic studies. In a multicenter, prospective study of 885 episodes of CAP, our group in Australia identified only a single case of MRSA pneumonia, along with ten methicillin-sensitive *S. aureus* cases (MSSA) [1]. More recently, a Spanish study found 11 cases of MRSA out of 3523 patients who presented with CAP [4].

Worldwide, there are a number of different strains of community MRSA with varying antimicrobial resistance phenotypes and likely different virulence potential [5, 6]. In North America, a highly successful epidemic strain, USA300 (ST8-MRSA-IV), is responsible for the majority of community MRSA infections while in other regions such as Europe and Australia, there is significant heterogeneity in the clonal epidemiology of community MRSA [7•].

Clinical Features and Diagnosis

A number of case reports and small case series describing the clinical features of necrotizing community MRSA pneumonia have been reported [3••, 8–11, 12•, 13, 14]. Though several strains have been reported in these cases, the features are common to many of the strains worldwide (Table 1).

In some cases, there may be a history of influenza-like illness prior to presentation with severe pneumonia marked by high fever, hypotension and hemoptysis [15]. This may lead to septic shock and progressive respiratory failure.

Table 1 Clinical features of severe community MRSA pneumonia

Patient characteristics
Preceding influenza-like illness
Young age
Known colonization/infection with community MRSA
Known risks for CA-MRSA infection e.g., intravenous drug use, indigenous or Pacific Islander populations, MSM,[a] prisoners, contact sports such as rugby or wrestling
Clinical Signs & Symptoms
Cough with hemoptysis
Dyspnea
Myalgia
Rigors
Fever
Hypotension
Investigations
Leukocytosis or leukopenia
Thrombocytopenia
Diffuse multilobar infiltrates on chest X-ray
Cavitating lesions on chest X-ray

[a] MSM—men who have sex with men

Other features of severe sepsis may be evident, including purpura fulminans, tissue necrosis, disseminated intravascular coagulation and lactic acidosis. Investigations may reveal either leukocytosis or leukopenia, the latter being associated with a poorer prognosis, as well as multilobar infiltrates with evolving cavitation.

The natural history of necrotizing community MRSA pneumonia is rapidly progressive within hours to days, and is associated with significant morbidity and mortality, even with appropriate treatment [3••].

Virulence Determinants in Community MRSA Pneumonia

Many of the major global community MRSA clones, including USA300 carry the accessory genome element *lukSF-PV* which encodes for Panton-Valentine leukocidin (PVL) [7•, 16••]. PVL is a staphylococcal exotoxin that forms pores, causing lysis of polymorphonuclear leukocytes [17]. Clinically, it has been linked with severe staphylococcal pneumonia, including in young children [8, 10]. This epidemiological association with necrotizing pneumonia is not confined to MRSA isolates but also MSSA [10]. Although the role of PVL in the pathogenesis of community MRSA infection in experimental animal models is mired in controversy, some of this can be explained by differing susceptibility by host neutrophils to PVL [18–20]. Human neutrophils and rabbit neutrophils are rapidly lysed by PVL, whereas murine neutrophils are relatively resistant [19]. In addition, the importance of PVL is also likely to be dependent on site of infection. With specific regard to pneumonia, PVL positive USA300 and purified PVL were demonstrated to cause severe disease including lung necrosis and death in a rabbit pneumonia model [21].

Although much attention has been paid to PVL, other virulence factors such as α-hemolysin and α-type phenol soluble modulins have also been implicated in the pathogenesis of severe community MRSA infections, including pneumonia [6, 22]. The genes which encode these important exotoxins and surface proteins are carried in the staphylococcal core genome, and are present in all *S. aureus* [16••]. Some community MRSA strains including USA300, express increased levels of α-hemolysin and α-type phenol soluble modulins [6]. It is this increased expression of exotoxins that may be responsible for the severe clinical disease associated with certain community MRSA strains.

The arginine catabolic mobile element (ACME) was first described in the complete genome sequence of USA300 but this was found to have only small contribution to increased virulence of this strain [23–25].

It is therefore likely to be a combination of multiple factors including the presence of PVL and greater expression of α-hemolysin that is important in determining virulence in

severe community MRSA infections and necrotizing pneumonia [16••]. Testing and treating for a single virulence factor such as PVL may be misleading as the mere presence of a gene encoding a virulence factor may not necessarily correlate with severe disease [6].

Management

It is notable that most of the evidence for the management of necrotizing community MRSA pneumonia is from small case series and anecdotal case reports. Current antimicrobial therapy guidelines have drawn from in vitro data as well as clinical studies of nosocomial MRSA pneumonia and community MSSA pneumonia, and extrapolated data to form recommendations. However, there are significant differences between nosocomial MRSA pneumonia and community MRSA pneumonia [3••]. Table 2 summarizes the main antibiotic options for treatment.

For many years, vancomycin was the first choice antibiotic for treating MRSA pneumonia. However, a number of studies of nosocomial pneumonia have raised issues with its clinical efficacy [26, 27]. Despite bactericidal activity against *S. aureus* in vitro, glycopeptides have been observed to result in poorer clinical outcomes in treatment of MSSA bacteremia compared with beta-lactams [28•]. There is also evidence to suggest that vancomycin clears bacteremia more slowly than beta-lactams, resulting in more prolonged bacteremia [29, 30]. Similarly, a prospective study of treatment of community and nosocomial bacteremic *S. aureus* pneumonia reported substantially higher mortality with vancomycin compared with cloxacillin in the MSSA subgroup [27].

Several reasons have been suggested for reduced clinical efficacy of vancomycin, including inadequate dosing and monitoring of levels. However, comparisons in healthcare-associated MRSA pneumonia have not always shown improved outcomes with aggressive vancomycin dosing (i.e. trough concentrations of >15 μg/mL) versus more conservative dosing targets (5–15 μg/mL) [31]. Other studies have pointed towards poor vancomycin concentrations in lung tissue [32], and pulmonary lining fluid [33, 34], barely above the measured in vitro minimum inhibitory concentration (MIC) despite adequate serum concentrations.

Table 2 Antimicrobial options in treatment of community MRSA pneumonia

Antibiotic	Form	Pregnancy[a]	Adverse effects	Advantages	Disadvantages
Vancomycin	IV	C/B2	Nephrotoxicity	Traditional gold-standard treatment of invasive MRSA infections	Poor lung penetration
			Rash		Anecdotal evidence of clinical failure
			Hematologic abnormalities		Requires target therapeutic level
Linezolid	IV/oral	C/B3	Bone marrow suppression	Switches off toxin/PVL production (theoretical)	Not proven in bacteremia
			Lactic acidosis Neuropathy	Good lung penetration	Possibly better clinical efficacy than vancomycin in nosocomial pneumonia, but equivalent mortality
Rifampicin/Rifampin	IV/oral	C/C	Hepatotoxicity	Good lung penetration	Significant drug-drug interactions
			Cutaneous reactions Mild hematologic abnormalities	Bactericidal Some anti-toxin effects	Resistance develops quickly with monotherapy
Clindamycin	IV/oral	B/A	Gastrointestinal symptoms	Good lung penetration	Bacteriostatic
				Good anti-toxin effects	Not studied in bacteremia
					Variable susceptibility
Fluoroquinolones	IV/oral	C/B3	Gastrointestinal symptoms	Good lung penetration	Variable susceptibility
			Prolonged QT interval Tendinitis		Resistance may develop with monotherapy
Trimethoprim-Sulfamethoxazole	IV/oral	C/C	Rash Gastrointestinal symptoms Bone marrow suppression	Good lung penetration Most isolates susceptible	Not proven in severe/invasive *Staphylococcal* infections – thought to be inferior to vancomycin
			Renal impairment		
Ceftaroline	IV	B/–	Limited experience	Bactericidal	Limited experience, though Phase III trials completed
			Presumed class side-effects from cephalosporins	Adequate lung penetration	Not yet proven in severe *Staphylococcal* infections
			Rash Gastrointestinal symptoms	FDA approved for community-acquired pneumonia	
Telavancin	IV	C/–	Limited experience	Thought to be more potent than vancomycin in vitro	Similar pharmacokinetics to vancomycin
			Presumed class side-effects from glycopeptides e.g. nephrotoxicity		Does not appear to offer significant benefit over vancomycin
			Gastrointestinal symptoms Prolonged QT interval?		Not FDA approved for pneumonia

[a] US Food & Drug Administration category/Australian Therapeutic Goods Administration category

The oxazolidinone, linezolid, has been suggested as an alternative to vancomycin, given the issues with dosing and subtherapeutic tissue levels [35]. Linezolid has a unique mechanism of action, binding to the 50S ribosomal subunit with bacteriostatic activity against *S. aureus*. The perceived clinical advantages were its ability to achieve adequate levels in alveolar lining fluid, and the option of an oral formulation with almost 100% bioavailability, though a number of serious adverse effects including myelosuppression, neurotoxicity, serotonin syndrome and lactic acidosis can occur with high dose or prolonged therapy [36, 37].

Much of the literature supporting linezolid has been published by a group of investigators based in the United States investigating healthcare-associated pneumonia. Initial data published by this group suggested equivalent efficacy for linezolid and vancomycin in treatment of hospital-acquired Gram-positive pneumonia [38, 39]. In an analysis of the MRSA subgroup, the same authors concluded that clinical outcomes with linezolid were superior to those with vancomycin treatment [40]. However this analysis was criticized for using a non-pre-specified, non-randomized post-hoc subgroup analysis to draw conclusions [41]. Others pointed out that linezolid failed to show a significant advantage over vancomycin in the larger intention-to-treat MSSA subgroup, and that the authors did not attempt to optimise vancomycin dosing [42, 43].

In a well-designed follow-up study to address these criticisms, Wunderink et al. reported that more patients responded clinically with linezolid (57.6%) compared with vancomycin (46.6%) [44••]. However, there were twice as many patients with bacteremic pneumonia and more patients requiring mechanical ventilation allocated to the vancomycin group. Patients with bacteremic pneumonia were treated for 21 days (7–14 days without bacteraemia), even though current consensus guidelines would suggest 4–6 weeks of treatment is required [45]. It is also unclear whether a vancomycin loading dose was utilised in patients with high bacterial load to attempt to achieve therapeutic levels quickly. Patients in the vancomycin group had a similar degree of clinical response irrespective of vancomycin trough levels and vancomycin susceptibility, though this data was not included for all patients, and there was no assessment for the presence of heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA), which may be associated with clinical treatment failure with vancomycin [46]. Despite this, there was no statistical difference in 60-day mortality between the two groups, though the study was not designed to assess this, and clinical cure rates were suboptimal overall.

A recent review and meta-analysis of linezolid versus glycopeptides for the treatment of nosocomial pneumonia did not show any significant difference in terms of clinical or microbiological cure, though it did not include the recent study by Wunderink et al. [47•]. To our knowledge, there are yet to be any human comparator trials of treatment for community MRSA pneumonia.

Combination Therapy

Although there is a paucity of clinical evidence, some current guidelines recommend consideration of combination treatment for necrotizing community MRSA pneumonia, for increased bactericidal effect as well as anti-toxin effects. Most guidelines utilize either vancomycin or linezolid as the backbone of the therapeutic regimen, together with rifampicin, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX) or fluoroquinolones used in varying combinations [48–52].

In vitro studies of potential synergy between vancomycin and rifampicin have produced indeterminate results [53, 54], though there was a small clinical study in hospital-acquired MRSA pneumonia that suggested vancomycin with rifampicin was more effective than vancomycin alone [55]. A major concern with the combination of vancomycin and rifampicin is the rapid development of resistance to rifampicin, due to a single point mutation [46]. The use of linezolid and rifampicin in combination has not been demonstrated to show synergy in vitro, though there may be some additive effect. Unlike vancomycin, linezolid appears to prevent selection of rifampicin-resistant mutants [37]. However, the high bactericidal activity of rifampicin against *S. aureus*, together with its excellent tissue penetration and ability to inhibit PVL production have given good reason to include it in many empirical treatment regimens of serious staphylococcal infections, usually in combination with an additional agent, such as fusidic acid or ciprofloxacin where susceptible [56, 57]. Differing strain resistance profiles have resulted in varied approaches to combination use with rifampicin. For example, in the United States, the USA300 (ST8-MRSA-IV) strain is frequently not susceptible to fluoroquinolones [58], and fusidic acid is yet to be licensed.

Clindamycin has been used as sole therapy and in combination therapy for treatment of community MRSA pneumonia [12•, 59]. Its antitoxin properties have led to recommendations for including it in combination treatment for rapidly progressive, necrotizing pneumonia, with anecdotal evidence of success [60]. While vancomycin with clindamycin has demonstrated significant in vitro antagonism [61, 62], studies of linezolid and clindamycin in combination have not shown definite synergy, though there does not appear to be antagonistic effects [63]. However, use of clindamycin has been limited by its bacteriostatic activity and clindamycin resistance, either inducible or direct, in several community strains around the world e.g. USA400 (ST1-MRSA-IV) in North America, and ST59-MRSA-V/IV in Asia [64•].

Fluoroquinolones with activity against *S. aureus* have generally not been used as monotherapy due to concerns about the development of resistance. *In vitro* studies have demonstrated some synergy with vancomycin against *S. aureus* [65, 66], though slight antagonism in combination with linezolid has been observed [67]. Their effect on toxin production is unknown. In prosthetic joint infections, fluoroquinolones in combination with rifampicin have been used with success [68]. However, their efficacy in staphylococcal pneumonia remains uncertain.

Although many community strains of MRSA have retained susceptibility to TMP-SMX, experience in treatment of severe infections has suggested TMP-SMX is inferior to vancomycin monotherapy [69]. In vitro data suggests combination therapy with vancomycin, rifampicin and TMP-SMX is superior to vancomycin alone, though the role of TMP-SMX was largely to protect against rifampicin resistance [70]. One small clinical trial found prophylaxis with TMP-SMX in patients with severe burns was effective in preventing ventilator-associated MRSA pneumonia [71], but its efficacy and role in the treatment of *S. aureus* pneumonia remains unknown.

Synergy with vancomycin against MRSA in vitro has also been observed with gentamicin, cephalosporins and carbapenems regardless of individual susceptibility, though these combinations have not been evaluated clinically in the treatment of pneumonia [66]. Quinupristin-dalfopristin has shown variable interactions with vancomycin in vitro and its role in treating MRSA pneumonia appears limited [66].

Synergy using linezolid with carbapenems has been demonstrated against MRSA in vitro and in a rabbit model of endocarditis [72, 73]. This combination is currently being evaluated in the treatment of MRSA pneumonia [74]. Other combinations with linezolid have generally not shown synergy or antagonism [63, 67], though two separate studies have noted antagonism with vancomycin and linezolid [67, 75].

Newer Antimicrobials

Ceftaroline fosamil is a cephalosporin with in vitro bactericidal activity against MRSA, vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) due to the addition of a 1,3-thiazole ring to the cephem ring, resulting in enhanced binding to penicillin-binding protein 2a (PbP2a) expressed by MRSA, which normally has reduced affinity for beta-lactams. Multicenter, randomized, double-blind phase III studies have shown non-inferiority to ceftriaxone in the treatment of moderate-to-severe community-acquired bacterial pneumonia. However, clinical efficacy against severe invasive community MRSA infections, including necrotizing pneumonia, has not yet been reported [76]. Another fifth-generation cephalosporin, ceftobiprole, has also demonstrated in vitro activity against MRSA [77], though its application to the US Food and Drug Administration was rejected due to concerns surrounding study data integrity.

The glycopeptide derivatives, telavancin, dalbavancin and oritavancin have all demonstrated in vitro bactericidal activity equivalent or superior to vancomycin, though their pharmacokinetic profiles differ. Telavancin has the most supporting data with randomized, double-blind phase III trials suggesting non-inferiority to vancomycin in treatment of hospital-acquired pneumonia [78]. However, along with a similar side-effect profile, like vancomycin, penetration into epithelial lining fluid is still suboptimal and the FDA has only approved it for use in treating MRSA skin infections [79]. Neither oritavancin nor dalbavancin appear likely to gain FDA approval at this stage.

Although most strains of community-MRSA are susceptible to tigecycline, it is yet to be approved for treatment of pneumonia due to concerns regarding efficacy in severe infections [80]. Serum levels are relatively low and it has not been generally recommended in treatment of bacteremia, which occurs frequently with severe necrotizing staphylococcal infections.

Daptomycin is inhibited by pulmonary surfactant in vitro [81], and clinical failure of daptomycin to prevent or treat MRSA pneumonia has been reported [82]. It has not been approved and is not recommended for treatment of pulmonary infections.

Non-Antibiotic Measures

In treatment of severe, necrotizing *S. aureus* pneumonia, most guidelines iterate the importance of early suspicion and early administration of antibiotics, in addition to adequate resuscitation measures and involvement of intensive care units, given the rapidly progressive nature of these infections. Utilization of non-conventional respiratory support strategies including extracorporeal membrane oxygenation (ECMO) have been used with encouraging results [83].

It has been suggested intravenous immunoglobulin (IVIG) containing anti-toxin antibodies may be able to replicate in vitro suppression of toxin-mediated effects [84], similar to its potential use in streptococcal toxic shock syndromes. However, there are no controlled trials on IVIG use in staphylococcal toxic shock. Case reports of IVIG use in PVL-producing community MRSA necrotizing pneumonia and disseminated sepsis have been published [85, 86].

In vitro studies have indicated that use of beta-lactams may actually induce toxin production [87–89], though a more recent investigation suggested cephalosporins may not have the same effect [90]. Some clinicians have thus advocated avoidance of beta-lactams in treatment of severe toxin-producing community MRSA infections [91].

Duration of Treatment

Ideal duration of therapy has not yet been established for community MRSA pneumonia. This is likely to be influenced by the burden and location of initial infection, development of complications such as bacteremia, endocarditis or empyema, and clinical response to treatment. Although experience is limited, cases reported in the literature have indicated the use of prolonged courses of antimicrobial treatment (compared with standard treatment of CAP) guided by clinical progress [3••, 8, 92]. This has also been accompanied by prolonged hospital stay [93].

Screening

Although upper airway colonization has been identified as a risk factor for invasive *S. aureus* infections including pneumonia [94], it has not been established whether nasal colonization with community MRSA is predictive of, or protective against severe necrotizing MRSA pneumonia. Similarly, the role of screening and decolonization in the community has not been established. Decolonization has predominantly been conducted in the hospital setting in the context of an outbreak, the intensive care unit, or pre-operatively, with subsequent reductions in MRSA infection rates [95]. However, there are numerous concerns regarding the effectiveness of screening and decolonization in the community setting, including the duration of effect, opportunity for re-colonization, potential adverse effects and development of resistance. Furthermore, studies showing that only 50% of colonized household members carry the same strain as the contact have suggested colonization frequently occurs by other means than direct household transmission [96]. At present, there does not appear to be a role for routine screening and decolonization of household contacts.

Conclusions

Severe necrotizing community MRSA pneumonia has emerged as a rare, but important cause of CAP, with significant morbidity and mortality even with adequate therapy. Although there are no prospective randomized trials to base guidelines upon, current empiric regimens for standard CAP are inadequate for these patients. Adequate clinical suspicion, prompt diagnosis and early administration of appropriate antibiotics are required for optimal management. Early referral to intensive care units may also be warranted.

Extrapolated data from studies of hospital-acquired pneumonia and other invasive MRSA infections has pointed towards the use of vancomycin or linezolid as the basis of therapy, possibly in combination with other antimicrobials for toxin-mediating and additional bactericidal effects. Selection of antibiotic combinations depends on regional MRSA strain susceptibility patterns. Anecdotal and observational data from small case series and case reports in the literature have indicated that management strategies are still suboptimal at present, though emerging antimicrobials such as ceftaroline appear promising.

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