Community-associated *Staphylococcus aureus* infections: pneumonia

Marios Karvouniaris,
Demosthenes Makris,
Epameinondas Zakyntinos

Critical Care Medicine Department,
University Hospital of Larissa, Greece

Abstract

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is an emerging health problem with distinct epidemiology. CA-MRSA colonization and infection is associated with risk factors different from healthcare-associated methicillin-resistant *S. aureus* infection. CA-MRSA strains present different characteristics to healthcare associated strains in terms of microbiology as well. Moreover, infection as a result of CA-MRSA may be associated with severe infections, in particular necrotizing pneumonia. CA-MRSA strains may produce Pantone-Valentine leukocidin, a protein that available data suggest to be associated with the severity of the infection. Although the incidence of CA-MRSA pneumonia is relatively low, it affects mostly young, immunocompetent individuals, and in this respect constitutes a serious and potentially lethal form of community-acquired pneumonia. Current treatment suggested by international consensus guidelines includes linezolid or vancomycin often combined with clindamycin and/or rifampicin. However, clinical studies are required to clarify further therapeutic issues on timing, dosing, and choice of optimum treatment, and whether new therapeutic strategies such as vaccination and immunoglobulins could be useful. In the present review we discuss the microbiology, epidemiology, pathogenesis, and clinical aspects of community-acquired pneumonia as a result of CA-MRSA in respect of management and prevention.

Introduction

During the last ten years an old pathogen, *Staphylococcus aureus*, has created new public health problems. Methicillin-resistant *S. aureus* (MRSA) is the cause of emerging infections in the community, a result of strains that differ from the usual healthcare-associated ones and are referred to as community-associated MRSA (CA-MRSA) strains. Based on recent definitions,¹ diagnosis of infection because of CA-

MRSA requires the following epidemiological criteria: i) the diagnosis was made in the outpatient setting or by a culture positive for MRSA within 48 hours after admission to hospital; ii) no medical history of colonization or infection with MRSA; iii) absence of hospitalization, admission to a nursing home, skilled nursing facility or hospice, dialysis, or surgery in the past year; iv) absence of permanent indwelling catheters or medical devices that pass through the skin into the body.

Currently, MRSA infection is considered a major public health issue because it affects young, immunocompetent individuals. CA-MRSA has the potential to cause severe skin and soft tissue infections and most notably, pneumonia (CAP-MRSA), which can be severe and necrotizing. Thus, CA-MRSA is associated with considerable morbidity and even mortality in the case of necrotizing CAP-MRSA. However, CAP-MRSA is a relatively novel entity and there are still unanswered questions in several aspects of CAP-MRSA.

In the present review we discuss the microbiology, epidemiology, pathogenesis and clinical aspects of CAP-MRSA in respect of its management and prevention.

Microbiology

CAP-MRSA is caused by community-acquired staphylococcus strains. These are ubiquitous bacteria and morphologically gram-positive *Staphylococcus* cocci.² Their main representative, *S. aureus* subsp. *aureus*, is highly resistant to extreme and adverse environmental conditions, such as drying as well as high NaCl concentrations,³ and can grow at a temperature range of 15 to 45 degrees.⁴ This explains its ability to colonize the nasal mucosa especially but also the pharyngeal mucosa and the skin (usually of the perineum and the axillae) of 50% of the general population. Thus, a high percentage of the population may chronically carry the microbe for years and such individuals are at increased and continuous risk of subsequent infection.^{5,6} Moreover, *S. aureus* strains produce a number of extracellular enzymes (such as coagulase, hyaluronidase, penicillinase) and toxins (hemolysins, staphylococcal superantigens, and leukocidins), which function as virulence factors. In addition, *S. aureus* strains produce catalase, which protects them from hydrogen peroxide produced by the phagocyte.⁷

The main mechanism of resistance to methicillin (MRSA strains) is not dependent on penicillinase, but on the production by *S. aureus* of a different penicillin-binding protein, PBP2a or PBP2', with low-binding affinity to β -lactams. This different protein is encoded by the *mecA* gene, which is situated on the

Correspondence: Demosthenes Makris, Lecturer of Critical Care Medicine, ICU, University Hospital of Larissa, Greece. E-mail: appollon7@hotmail.com; dimomakris@med.uth.gr

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staphylococcal cassette chromosome *mec* (SCC*mec*), an element of extra-chromosomal DNA. SCC*mec* has been characterized as a novel, mobile resistance element that differs from both transposons and bacteriophages.⁸ To date, five SCC*mec* types (I–V) have been distinguished.⁹ All SCC*mec* elements carry the gene *mecA*, which has identical nucleotide content irrespective of the SCC*mec* type and the methicillin MICs of the MRSA strains that may range from <2 mg/L to >1000 mg/L.¹⁰ The gene *mecA* codes for the penicillin-binding protein PBP2a, which allows for the synthesis of the peptidoglycan layer and cell wall synthesis in the presence of β -lactams.⁹

Thus, the study of the epidemiology of MRSA strains is based on screening for SCC*mec*, the *mecA* gene, and the genes *lukF* and *lukS* by polymerase chain reaction (PCR). For epidemiological reasons as well, screening of the MRSA genotype is done with pulsed-field gel electrophoresis. The genes *lukF* and *lukS* encode Pantone-Valentine leukocidin (PVL) and are present in the majority of CA-MRSA strains (overall in 77%). The PVL locus is situated in a bacteriophage that occurs in less than 5% of *S. aureus* strains worldwide. In addition to PVL, CA-MRSA strains are characterized by increased prevalence of other toxins (α -toxin and staphylococcal enterotoxin B).¹¹ Hence, these strains are considered rather more virulent than the hospital-acquired MRSA strains, and in this respect CAP-MRSA may present necrotizing characteristics and may be associated with an adverse outcome. Furthermore, unlike healthcare-associated methicillin-resistant *S. aureus* strains that gradually develop resistance to other antibiotic classes in

addition to all β -lactams (penicillins, cephalosporins, carbapenems) resistance, CA-MRSA resistance is confined mostly to β -lactam antibiotics (Table 1).¹² In this respect, epidemiological criteria have been established that distinguish CA-MRSA infection, and therefore CAP-MRSA, from infection as a result of healthcare-associated MRSA infection (*see definition*).

Epidemiology

It has been about 50 years since hospital strains of MRSA were first described.¹² However, in parallel with the presence of healthcare-associated MRSA, a new family of strains that caused infections in the community (CA-MRSA), including younger and healthier persons, without risk factors for the development of MRSA infection, has appeared. CA-MRSA strains have spread to the general population and MRSA is identified very often as a cause of skin and soft-tissue infections among patients presenting to emergency departments in the United States and Greece as well.^{13,14} CAP-MRSA is commonly encountered during the influenza season and usually occurs in children, adolescents, and young adults without underlying diseases (lung or hematologic disease, immunosuppression, diabetes mellitus). Previous studies have depicted risk factors for colonization with CA-MRSA and development of infections.¹⁵ Clinically, CA-MRSA strains are capable of causing serious invasive disease that is sometimes fatal.¹⁶ In a recent series of 51 patients from the United States with staphylococcal pneumonia in the community, 73% of the isolates were MRSA and only half of the patients have been given appropriate antibiotic therapy (linezolid or vancomycin).¹⁷

CA-MRSA strains are spreading to the hospitals as well and are replacing¹⁸ the traditional HA-MRSA strains. Thus, there is also an

emergence of the staphylococcal cassette chromosome mec type IV methicillin-resistant *S. aureus* as a cause of ventilator-associated pneumonia (VAP, pneumonia presented after 48 hours of endotracheal intubation). These CA-MRSA strains were responsible for 20% of the total MRSA-VAP cases in an academic institution. These were usually PVL-positive strains. In these strains, the presence of leukocidin was not associated with necrotizing pneumonia.¹⁹ CA-MRSA caused <1% of cases of CAP admitted to the hospital according to a recent retrospective study.²⁰

Pathogenesis

S. aureus infections are caused by strains that have already colonized nasal mucosa making the colonized persons a reservoir for the spread of the microbe.²¹ Pneumonia results (55% of cases) mainly from aspiration of nasopharyngeal secretions colonized by *S. aureus*, which usually occurs after infection with the influenza virus. The rest of the cases can occur by hematogenous dissemination, secondary to the infection of skin or soft tissues, as well as after septic abortion. The presentation is typically severe regardless of the previous health status of the patient.²²

In the case of CA-MRSA, however, a few striking differences compared to other MRSA and MSSA infections should be noted. In CA-MRSA cases, non-nasal colonization predominates in axillae, perineum, and rectum (the latter explaining the sexual transmission of the pathogen). In addition, in outbreaks CA-MRSA infection was associated with exposures to various contaminated fomites shared by athletes, relatives, or roommates, including whirlpools, shared razors, and shared towels.²³ These characteristics of MRSA pathogenesis of infection should be kept in mind.

It has also been suggested that respiratory viral infections make the bronchial surface

more vulnerable to secondary bacterial infection by facilitating the attachment of bacteria, such as staphylococci, on the destroyed respiratory epithelia, allowing the aspiration of oropharyngeal contents contaminated with *S. aureus*. Thus, previous studies found a positive association between influenza infection and staphylococcal pneumonia. This relationship might also be present between CAP-MRSA and the influenza virus. However, available epidemiological studies are few and results are not consistent. In a recent study that included cases with CAP-MRSA, 33% of those examined were positive for the influenza virus. However, a rapid influenza test with low sensitivity was used and thus one might argue that this incidence rate might underestimate the actual number of subjects with influenza. In addition, the presence of other respiratory viruses – which might also favor bacterial infections – have not been assessed.¹⁷ On the other hand, in a recent study from Australia²⁴ that examined co-infection with the new pandemic H1N1 influenza virus and CAP-MRSA, there were only five co-infections out of 252 H1N1 cases.

In addition, it has been suggested that the presence of a preceding influenza infection might be associated with the necrotizing character of CAP-MRSA. Thus, patients with ventilator-associated pneumonia because of CA-MRSA who did not present a preceding influenza infection, did not develop a necrotizing infection as well.¹⁹ However, as it was pointed out, more studies are required to clarify the potential contribution of a respiratory virus infection in the course of CAP-MRSA.

Another important issue in the pathogenesis of CA-MRSA infections that has been highlighted previously is the role of an extracellular toxin (leukocidin) described by Pantón-Valentine. PVL was first described in 1932 and is also referred to in the literature with the abbreviations Luk-PV.³ The presence of PVL has been considered to correlate with increased severity of infections as a result of *S. aureus*.³ Apart from CAP-MRSA, these can be

Table 1. Main characteristics of HA-MRSA and CA-MRSA strains.

Characteristic	HA-MRSA	CA-MRSA
Origin	Hospital, hospice etc.	Community
Infections	Surgical site infections, line- or device-associated infections, ventilator-associated pneumonia	Skin and soft tissue infections, necrotizing community-acquired pneumonia, necrotizing fasciitis
Epidemiology	Hospitalized, elderly	Young, athletes, injection drug users, military personnel
Antimicrobial resistance	Multidrug resistance	Mainly β -lactams
PVL	Absent	Usually present
Methicillin resistance elements	SCCmec I-III	SCCmec IV-V
Genotype	USA 100	USA 300
Active antibiotics	Vancomycin, linezolid, daptomycin	Vancomycin, linezolid, daptomycin trimethoprim/sulphomethoxazole, doxycycline, clindamycin

HA-MRSA, hospital-acquired methicillin-resistant *Staphylococcus aureus*; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*.

skin and soft tissue infections that need surgical debridement and septic, potentially fatal infections such as osteomyelitis, necrotizing fasciitis, and the Waterhouse-Friderichsen syndrome.¹² The severity of these infections and thus of CAP-MRSA has been attributed to the varying leukocytolytic, erythrocytolytic, and dermonecrotic properties of the toxin. The toxin forms heptameric pores in the leukocyte membrane and destroys the leukocyte, with the release of inflammatory enzymes and cytokines.³ At lower concentrations it induces the apoptosis of leukocytes.²⁵ In a mouse staphylococcal pneumonia model only PVL-positive (PVL+) strains caused necrotizing pneumonia.²⁶ Moreover, PVL acts differentially on neutrophils of various species, which suggests that PVL has an important cytotoxic role in human neutrophils. This has major implications for the pathogenesis of CA-MRSA infections.²⁷ Based on this data, the role of PVL for the severity of infections is potentially important. However, we should also underline here that severe CAMRSA infections may be present even in the absence of PVL, as it was demonstrated in studies with PVL-strains.²⁸ It is therefore likely that not only PVL but also other microbial or host factors might contribute to the severity of CAP-MRSA.²⁹

Clinical Presentation

On the whole, the clinical presentation of CAP-MRSA is one of a septic syndrome, and if it begins as influenza it continuously deteriorates and rapidly progresses to pneumonia, which is sometimes fatal. The presentation of the disease is unique and not that of a biphasic illness (influenza-like illness and then pneumonia) as it was formerly described.¹⁷ In the majority of cases, the disease is characterized by symptoms of the respiratory system – of the influenza type – that either precede or coexist with pneumonia, such as fever, cough, or sore throat. Fever is usually high ($>39^{\circ}\text{C}$). Symptoms indicating involvement of the lower respiratory system such as tachypnea (>30 breaths per minute), cyanosis, and cough are common. The cough is often productive and it is more likely for hemoptysis than for purulent sputum to be present. A common complication of CAP-MRSA is empyema. General symptoms including circulatory signs and symptoms of encephalopathy are also commonly observed especially in more severe disease. Tachycardia, often >140 beats per minute, and hypotension indicate risk of circulatory collapse. Symptoms of encephalopathy such as lethargy, confusion, or even coma are commonly observed during the course of the disease. Sometimes rash, boils, or diarrhea are also observed.^{17,30-33}

The most characteristic laboratory finding is leukopenia although leukocytosis is more commonly found. Chest X-ray findings are usually bilateral with rather symmetric consolidation. Cavitations, nodules, or pleural effusions are not often found. In subsequent chest X-ray examinations the areas of consolidation become progressively confluent.³⁴ The most common chest computer tomography (CT) scan findings are bilateral, rather symmetric consolidation as well as bilateral, rather ground-glass opacities, centrilobular nodules, and cavitations (either in regions of consolidation or in large nodules). Pleural effusions and mediastinal lymphadenopathy are found in the majority of cases.³⁴

Examination of necrotic materials in patients with necrotic PVL-positive pneumonias has shown tracheal and bronchial mucosal ulceration with a gray-white necrotic appearance. Abundant hemorrhagic secretions were found in the main bronchi while the lungs were solidified, congestive, and hemorrhagic. Microscopic examination revealed infiltration of the respiratory epithelium by inflammatory cells, and ulcerations coated by extensive gram-positive cocci colonies throughout the respiratory tract (larynx to lobar bronchi). The lung parenchyma was characterized by alveolar hemorrhage, necrosis of the interalveolar septa, and large clusters of gram-positive cocci.³⁰

Diagnosis

Diagnosis of CAP-MRSA might be difficult owing to the fact that CA-MRSA infections have not been considered as likely in the past. The fact that only half of the 51 US patients with staphylococcal pneumonia in the community were given appropriate antibiotic therapy (73% of the isolates were CA-MRSA)¹⁷ and, in addition, the potential fulminant course of CAP-MRSA underlined the necessity to clearly define CAP-MRSA and to achieve prompt diagnosis and therefore management. According to the guidelines for the community-acquired pneumonia in adults,³⁵ CAP-MRSA should be considered in cases with pneumonia when: i) influenza-like illness preceded, and ii) cavitations are found in chest X-ray without risk factors for the development of aspiration pneumonia owing to anaerobic microbes. Other authors^{15,36,37} point out that the clinical diagnosis of CAP-MRSA should be considered when influenza-like illness precedes and the following factors are present: young patients with hemoptysis, respiratory failure, tachypnea of >30 breaths/min, high fever, leukopenia, hypotension, tachycardia of >140 beats/min, and pneumatoceles, abscesses, or multilobar involvement in the chest X-ray. In general, CAP-

MRSA should be considered in subjects with risk factors for infection or known to be colonized by CA-MRSA when clinical symptoms indicate acute gram-positive coccal pneumonia.

The finding of clusters of gram-positive cocci in bronchoalveolar lavage (BAL) fluid, a tracheal aspirate sample, in proper sputum samples, or in pleural fluid may be diagnostic. Gram staining in blood samples might also indicate contamination.^{35,36} Thus, in a retrospective analysis that included patients with CAP-MRSA,²⁰ 73% of them had positive cultures in specimens obtained from the respiratory track (BAL, bronchial secretions, sputum), 33.3% had positive pleural fluid cultures while 33% had positive blood cultures. In this respect, it has been suggested that negative gram stain and culture results of an adequate sputum specimen should be sufficient to withhold or stop treatment for MRSA infection.³⁵

On the other hand, recently developed molecular methods³⁸ have the potential to improve diagnosis further. Molecular methods are rapid diagnostic tests that reduce the time of detection of MRSA from days to hours. Many tests have high sensitivity and specificity that exceeds 90%.³⁸ Recently molecular methods³⁹ have been validated and were highly accurate (with a sensitivity and specificity that are close to 100%) in the detection of MRSA in clinical samples, such as blood, pus, wounds, cerebrospinal fluid, and urine. These methods can also give useful information for the presence of PVL protein.³⁹ However, the authors have not tested sputum samples. In addition, the diagnostic yield of PCR techniques in CAP-MRSA is not yet known as there is a lack of studies in this field, and thus this is an issue that offers the opportunity to be explored in the future.

Prognosis

CAP-MRSA is a potentially fatal infection and ICU admission was necessary in the vast majority (67-81%) of patients in previous studies. Among those admitted in the ICU more than 50% needed intubation and mechanical ventilation while their stay in ICU was often prolonged. Mortality in these populations is high (29-60%), depending on the study.^{17,31,33}

The poor prognosis of CAP-MRSA is linked to severity factors of pneumonia such as the development of adult respiratory distress syndrome (ARDS) or the need for inotropes or mechanical ventilation. The presence of hemoptysis (which likely reflects necrosis of the respiratory mucosa) is associated with rapid death. In a multivariate analysis, leukopenia and erythroderma (not associated with toxic shock syndrome) occurring within the

first 24 hours after admission to the hospital were independently associated with fatal outcome.⁴⁰ The presence of leukopenia (<4000/mL) has been pointed out by other authors as a significant independent risk factor as well.¹⁷ In the same study,¹⁷ co-infection with both influenza and *Staphylococcus* has been associated with a greater likelihood of death; however, this association did not remain significant in the multivariate analysis of data.

Prevention

Firstly, we should avoid the spread of *S. aureus* in the community by implementing the basic principles of hygiene and by the correct diagnosis and treatment of the infection that this pathogen causes (Table 2).⁴¹ Screening for nasal or skin carriers of the microbe is not necessary and decolonization should be avoided because of the fear of developing further antimicrobial resistance. Effectiveness of decolonization decreases after a few weeks, and concerning the pathogenesis of CA-MRSA (with the increased importance of non-nasal colonization), nasal mupirocin is not enough, making the undesirable use of systematic antibiotics necessary.⁵

A conjugated, bivalent vaccine against capsular antigens of *S. aureus* (StaphVAX),⁴² that can protect patients receiving hemodialysis from bacteremia and needs repeating the dose, was initially effective but a phase III trial failed to confirm the result.⁴³ A phase II clinical trial for the prevention of *S. aureus* in elective cardiothoracic surgery patients is under way. A vaccine against the cell wall protein IsdB is being tested.^{43,44} In terms of prevention with the use of passive immunization, a human immunoglobulin-G (IgG) preparation known as INH-A21 that contains elevated levels of antibodies to the staphylococcal surface adhesins ClfA and SdrG was given (phase III) to neonates but it failed to show a clinical benefit.⁴⁵ Staphylococcal infections have a complex pathogenesis through many toxins and enzymes. Thus, a multicomponent vaccine

is needed and the component antigens have to be highly conserved, thus include both toxins and surface antigens as well. Some candidate antigens are tested in pre-clinical trials.^{43,44} In two of them, mice were successfully vaccinated with α -hemolysin and PVL.^{46,47}

Treatment

The basic principles of CA-MRSA pneumonia treatment are not confined to antibiotic prescription (Table 3). It is advisable that the patients are admitted to the ICU with infectious disease consultation in order to make sure that the vital signs are properly supported and the patient is given the best possible antibiotic therapy. Despite the fact that sputum, pleural fluid, and blood cultures will support or confirm CAP-MRSA, their results should not delay treatment decisions, and thus patients should receive therapy as soon as possible, and in the case of empyema, the pleural cavity should be properly drained.^{35,36}

As has been underlined, antibiotic therapy should be given early, while the patient is still in the outpatient department after blood, sputum, and/or pleural fluid cultures have been done.^{15,35,36} Secondly, treatment should include drugs that combine anti-staphylococcal action with anti-MRSA activity and suppress the production of PVL toxin.³⁷ Unfortunately, there have been no well conducted randomized trials yet, especially for CAP-MRSA. Various combinations of vancomycin, clindamycin, linezolid, rifampicin, and cotrimoxazole have been used in various doses and with different success rates.¹⁵

The pharmacokinetic/pharmacodynamic (pK/Pd) properties of vancomycin include limited volume of distribution, inability of passively diffusing through plasmatic membrane, and water solubility. These properties may not be advantageous in treating pneumonia and, in this respect, the most severe forms of CAP-MRSA especially.⁴⁸ Vancomycin's average levels in lung epithelial lining fluid (ELF) are only 20% of blood levels and the recommended dose

of the antibiotic (1 g twice daily) is likely to be suboptimal for treating pneumonia.⁴⁸ A clinical study of nosocomial MRSA pneumonia has shown that despite the appropriate regimen containing glycopeptides (vancomycin or teicoplanin), increased mortality was shown, apart from patients who received vancomycin by continuous intravenous infusion and had a better prognosis.⁴⁹ Therefore, for the treatment of MRSA pneumonia, plasma trough levels should be maintained higher than currently recommended (usually 15-20 mg/L and even 30-35 mg/L instead of 10-15 mg/L, with the risk of developing complications) and may be given by continuous infusion. Thus, it has been suggested⁴⁸ that vancomycin should start with a loading dose of 15 mg/kg followed by a continuous infusion of 30 mg/kg/day, and to add rifampicin as well.

In addition, MRSA strains with MIC levels for vancomycin equal to or less than 1mg/L indicate increased risk of treatment failure. Furthermore, heteroresistance might be developed where, despite the apparent susceptibility, there are subpopulations of bacteria with resistance to the drug.⁵⁰ In addition, vancomycin does not have any effect on toxin levels and the inappropriate administration of nafcillin (β -lactam) may increase PVL production.¹¹ These considerations limit the usefulness of vancomycin in the setting of CAP-MRSA and suggest that vancomycin may have to be replaced with other agents with adequate anti-MRSA activity and suppression of the production of PVL toxin such as linezolid or clindamycin.⁵¹

On the contrary, linezolid may dramatically reduce PVL levels through inhibition of protein synthesis.¹¹ Linezolid is a moderately lipophilic compound and presents pK/pD properties such as large volume of distribution, ability to diffuse easily through plasmatic membranes,⁴⁸ and at this point offers advantages in treating serious lung infections. It has shown drug ELF-to-plasma ratios on average >2 at different time intervals after administration.⁴⁸ Moreover, resistance to linezolid is extremely rare.⁵² A previous study of nosocomial MRSA pneumonia showed that linezolid was associated with significantly better survival and clinical cure

Table 2. Potential strategies for preventing transmission of *S. aureus* in the community.

Compliance with hand hygiene
Keep draining wounds covered
Sharing of personal items (razors, towels) should be avoided
Avoid contact sports if a potential participant has an open skin lesion
Do not allow use of whirlpools or saunas to persons with open skin lesions
Make sure that communal bathing facilities are clean

Table 3. Therapeutic principles for CAP-MRSA.

Antimicrobials	Other measures
Linezolid 600 mg twice daily	Cultures (blood, pleural fluid, sputum)
Vancomycin 1 g twice daily	Admission to the ICU
Clindamycin 1.2-1.8 g every six hours	Infectious disease physician consultation
Rifampicin 600 mg twice daily	Infection control measures
Linezolid*+clindamycin*± rifampicin* combination	Pleural drainage in case of empyema

CAP-MRSA, community-associated pneumonia methicillin-resistant *Staphylococcus aureus*; *doses as described in the table.

rates than vancomycin.⁵³ In another study,⁵⁴ despite CAP-MRSA patients having received appropriate treatment with vancomycin, they presented clinical deterioration. Vancomycin was therefore changed with success to linezolid plus rifampicin or clindamycin.

The ATS Consensus Statement on the Management of CAP in Adults³⁵ states that when suspecting CAP-MRSA, linezolid or vancomycin should be added to the basic regime. The need to administer linezolid or clindamycin for decreasing PVL production is also emphasized although the best possible therapy has not yet been defined because of the lack of clinical studies.

Other agents such as rifampicin⁵¹ have been used for treating CA-MRSA infections as they have excellent *in vitro* activity against CA-MRSA. Moreover, the pharmacokinetic profile of rifampicin includes high lipid solubility and a large volume of distribution.⁵⁵ Thus, some authors have suggested the routine addition of rifampicin 600 mg twice daily if PVL+ staphylococcal pneumonia is suspected.¹⁵ However, rifampicin cannot be used as a single agent because of the rapid emergence of resistance but rather used in combination with other agents. Before such a decision, the interaction of rifampicin with other agents should be considered. For instance, combinations of rifampicin with trimethoprim/sulfamethoxazole (TMP/SMX) have been shown to exhibit antagonism *in vitro*.⁵¹ Many isolated CA-MRSA strains present susceptibility to TMP/SMX *in vitro*.^{13,14} However, despite its good *in vitro* activity TMP/SMX has been associated with clinical failures when a high bacterial burden or small abscesses exist. For example, in the case of a lung abscess, TMP/SMX treatment was associated with a higher rate of failures compared to vancomycin.⁵⁶

Clindamycin can work in an environment with a high bacterial burden, has anti-PVL activity, and is cheap.⁵⁷ Clindamycin is lipophilic, has good intracellular penetration,⁵⁸ and in this respect its use offers advantages in the treatment of pneumonia and empyema.⁵⁷ However, it exhibits inducible resistance during therapy and therapeutic failures have been observed. This phenomenon can be easily diagnosed with the D-zone test that discriminates the fully sensitive strains from the ones that show inducible resistance. Thus, recent guidelines for UK practice¹⁵ recommended the use of high-dose clindamycin 1.2-1.8 g six hourly in the initial empiric treatment; as an alternative to add linezolid 600 mg 12 hourly. The duration of therapy is not defined.

Despite covering MRSA, daptomycin is inhibited by surfactant *in vitro* and is therefore not suitable for treating pneumonia.⁵⁹ The role of tigecycline, ceftobiprole (cephalosporin with anti-MRSA activity), novel glycopeptides (dalbavancin, telavancin, oritavancin), and iclaprim has not been defined for the treat-

ment of CA-MRSA pneumonia.⁵⁰

Adjunctive therapies

A hyperimmune polyclonal antibody preparation (Altastaph) derived from healthy volunteers immunized with StaphVAX was tested⁶⁰ in patients with *S. aureus* bacteremia and was ineffective.

Immunoglobulin infusion provides high concentrations of anti-PVL antibodies, and at least *in vitro*, neutralizes the toxin.⁶¹ Immunoglobulin should thus be considered in severe sepsis and necrotizing pneumonia known or suspected to be because of *S. aureus*. The recommended dose is 2 g/kg of body weight and is repeated at 48 hours if there is still evidence of sepsis or failure to respond.¹⁵ Activated protein C might be beneficial in very early sepsis in the setting of CAP-MRSA but once active hemorrhage has occurred the agent should not be used.¹⁵

Conclusions

CA-MRSA has emerged as a serious public health issue and is responsible for a severe form of community-acquired pneumonia. Despite the progress in our knowledge of the pathogen, more studies are needed to better clarify its pathogenesis and the role of its virulence factors, like PVL toxin. Wider public awareness of the problem and implementation of the basic principles of hygiene will help to prevent its spread. Finally, the rising microbial resistance and the fear of running out of antibiotics leads to research for effective anti-MRSA immunotherapy. The latter consists of antibody therapy and, hopefully, an effective vaccine might solve the problem in the long run.

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