SUPPLEMENT ARTICLE

Pneumonia Caused by Methicillin-Resistant *Staphylococcus aureus*

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A recent increase in staphylococcal infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), combined with frequent, prolonged ventilatory support of an aging, often chronically ill population, has resulted in a large increase in cases of MRSA pneumonia in the health care setting. In addition, community-acquired MRSA pneumonia has become more prevalent. This type of pneumonia historically affects younger patients, follows infection with influenza virus, and is often severe, requiring hospitalization and causing the death of a significant proportion of those affected. Ultimately, hospital-acquired MRSA and community-acquired MRSA are important causes of pneumonia and present diagnostic and therapeutic challenges. Rapid institution of appropriate antibiotic therapy, including linezolid as an alternative to vancomycin, is crucial. Respiratory infection–control measures and de-escalation of initial broad-spectrum antibiotic regimens to avoid emergence of resistant organisms are also important. This article reviews the clinical features of, diagnosis of, and therapies for MRSA pneumonia.

Until recently, staphylococcal pneumonia was considered an uncommon community-acquired pneumonia (CAP), accounting for 1%–5% of all CAP cases and occurring primarily in patients with influenza [1]. In addition, *Staphylococcus aureus* was recognized as an important but infrequent cause of nosocomial pneumonia, occurring especially in elderly persons [2, 3]. However, in the past 2 decades, there have been important changes in *S. aureus* pulmonary infection. First, most large medical centers in the United States have seen a dramatic increase in the percentage of staphylococcal infections caused by methicillin-resistant *S. aureus* (MRSA). At the same time, frequent and prolonged ventilatory support of an aging, often chronically ill population has become commonplace. The intersection of these developments has fueled a dramatic increase in cases of MRSA pneumonia. Indeed, MRSA now accounts for 20%–40% of all hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Until recently, most of the MRSA strains causing health care–associated pneumonia (HCAP), HAP, and VAP were labeled hospital-acquired MRSA (HA-MRSA) and contained the staphylococcal cassette chromosome (SCC) *mec* types I–III [4, 5]. Recently, however, a new variant of MRSA has emerged as a pulmonary pathogen. This new variant of *S. aureus* that causes pneumonia is community-acquired MRSA (CA-MRSA), containing SCC*mec* type IV.

CA-MRSA, although primarily a cause of skin and soft-tissue infection, has proved to be a formidable cause of pneumonia. In France in 2002, Gillet et al. [6] described 16 cases of CAP caused by CA-MRSA containing SCC*mec* type IV, as well as the gene encoding Panton-Valentine leukocidin (PVL), a toxin that destroys polymorphonuclear leukocytes. The patients were young (median age, 14.8 years), the pneumonia was frequently preceded by an influenza-like illness, the disease course was stormy, and the 48-h survival rate was 63% (figure 1). The lethal potential of this postinfluenza pneumonia was confirmed in the United States [7].

Recently, CA-MRSA has moved into the health care setting. This migration has been quite variable among

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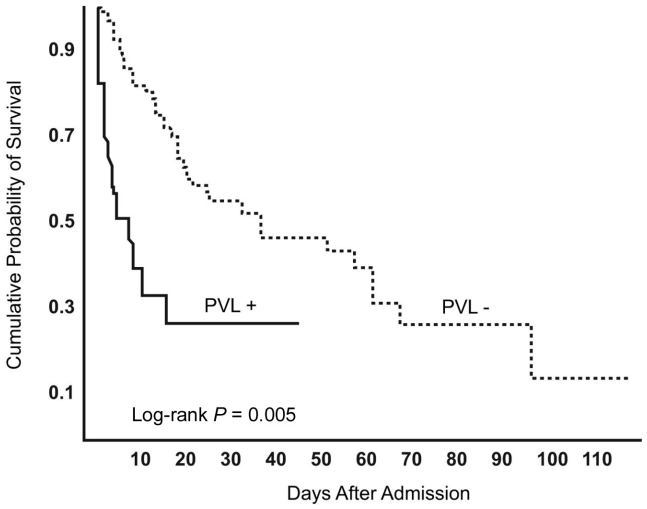

Figure 1. Probability of survival of patients with staphylococcal pneumonia, according to whether the pathogenic strain was positive or negative for the Panton-Valentine leukocidin (PVL) gene. Reprinted from [6], with permission from Elsevier.

hospitals, regions, and countries and has made the epidemiologic differentiation of CA-MRSA and HA-MRSA genotypes particularly difficult. The significance of this epidemiologic shift remains unknown. Although the point has been debated, PVL, commonly associated with CA-MRSA, has been considered a virulence factor associated with severe pneumonia. There may be other factors that increase the virulence of CA-MRSA and HA-MRSA strains, causing the morbidity and mortality of staphylococcal pneumonia to increase dramatically.

Overall, MRSA is an important cause of pneumonia. A survey of 59 US hospitals, involving 4543 patients with culture-positive pneumonia, between January 2002 and January 2004 [5] identified MRSA as a potential pathogen in 8.9% of CAP cases, 26.5% of HCAP cases, 22.9% of HAP cases, and 14.6% of VAP cases. Indeed, in this study, *S. aureus* was identified by logistic regression analysis as the only pathogen independently associated with mortality.

CLINICAL FEATURES

HCAP, HAP, and VAP. Patients who develop staphylococcal pneumonia while in nursing homes or extended-care facilities (i.e., HCAP) or in hospitals (i.e., HAP and VAP) are often infected with HA-MRSA. These patients are frequently elderly and have significant underlying diseases. Staphylococcal pneumonia in these patients is clinically similar to HCAP, HAP, and VAP secondary to gram-negative organisms. Bacteremia in patients with staphylococcal pneumonia occurs late (mean onset, 9 days after the onset of pneumonia symptoms) during the course of HAP or VAP [8]. These pneumonia cases are associated with an all-cause mortality of 55.5%, despite early and appropriate therapy.

CAP. Pneumonia in young, previously healthy adults with a preceding influenza-like illness characterized by severe respiratory symptoms, hemoptysis, high fever, leukopenia, very high C-reactive protein level (>400 g/L), hypotension, and a chest x-ray showing multilobular cavitating alveolar infiltrates should lead one to suspect CA-MRSA infection [6, 7, 9–13] (figure 2). Young age has been a remarkable feature of CA-MRSA pneumonia in both European and US series [6, 7, 14]. Importantly, preceding influenza or influenza-like illness has been described in 75% of cases [6, 7]. The severity of these pneumonia cases is demonstrated by the fact that, in one series, 81% of hospitalized patients needed to be admitted to the intensive care unit, 62% required intubation, 46% had chest tube placement, and 29% died [7].

From December 2006 through January 2007, 10 additional cases of MRSA CAP were reported from the southern United States in young, healthy, patients with preceding influenza or influenza-like illness (table 1) [15]. Six of the 10 patients died a mean of 3.5 days after the onset of symptoms. All tested isolates (isolates from 5 of the 10 patients) were positive for PVL and carried SCC*mec* type IVa. All isolates had an indistinguishable PFGE pattern, and all belonged to the USA300-0114 clone group. All isolates were resistant to β-lactams and erythromycin, 2 strains had inducible resistance to clindamycin, and 2 strains were not susceptible to levofloxacin [15].

DIAGNOSIS

HCAP, HAP, and VAP. There are many hurdles to accurate diagnosis of the etiology of nosocomial pneumonia, and all apply to the diagnosis of MRSA pneumonia. First, chest x-rays miss 26% of VAP cases, and, compared with autopsy, x-ray has shown a diagnostic accuracy of only 68% [14–18]. Second, positive blood cultures accompany only 5%–15% of HAP cases and 24%–36% of VAP cases [17, 18]. Third, endotracheal microbiological sampling has shown only 40% agreement with lung biopsy [19], and only 15% of the samples met adequacy criteria for having originated from the lower respiratory tract ($\geqslant$25 WBCs per field and $\leqslant$10 epithelial cells per field) [14–19]. More-invasive diagnostic procedures also have their problems. The diagnostic threshold of bacterial concentration based on semiquantitative results of culture of lower respiratory tract secretions, set at $\geqslant 10^3$ cfu/mL for protected brush specimens and $>10^4$/mL for bronchoalveolar lavage (BAL) specimens, is compromised by previous antibiotic use, and samples must be refrigerated overnight when they cannot be processed immediately. A recent randomized trial with a comparison of the diagnostic utility of BAL with quantitative culture results versus endotracheal aspiration with nonquantitative culture results found similar clinical outcomes among patients in both diag-

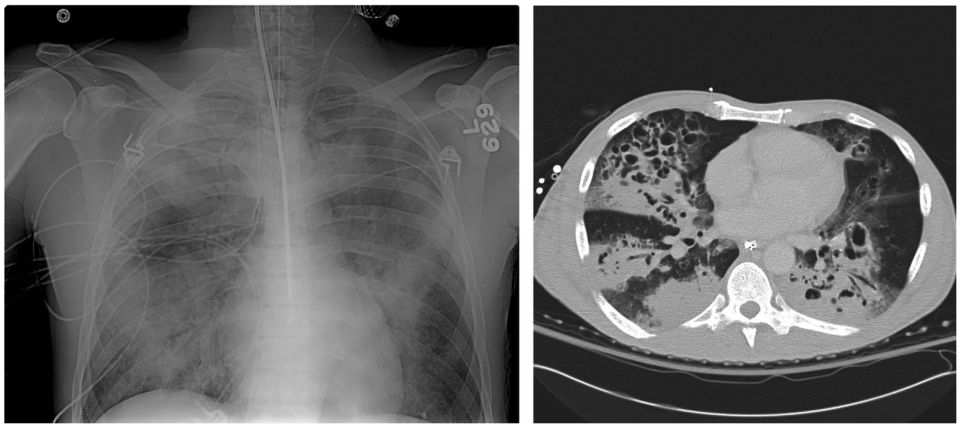

Figure 2. Chest x-ray and CT scan of the chest of a young patient with community-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Reprinted from [13], with permission from the American College of Chest Physicians.

nostic groups [20]. However, the authors of that study excluded patients known to be infected or colonized with *Pseudomonas* species and MRSA, thereby greatly limiting the generalizability of the results.

In the future, several new tests may help improve the diagnosis of VAP. A soluble triggering receptor expressed on myeloid cells has recently emerged as a possible candidate for diagnostic testing for VAP [21]. This test has an acceptable specificity, but its value still has to be confirmed in larger studies. A microarray-based technique for the detection of PVL components and possibly staphylococcal enterotoxins and superantigens may also prove to be useful in the diagnosis of CA-MRSA pneumonia [22]. Recently, Bouza et al. [23] applied E-test strips directly onto agar streaked with sputum and were able to predict the pathogen's susceptibility and MIC in 75.4% of patients within 24 h. Molecular-technique–based rapid tests for the detection of PVL, *mec*A, and SCC*mec* type IV are under development. It is conceivable that, in the not-too-distant future, rapid diagnostic methods will become available for a more timely diagnosis of MRSA pneumonia. The contribution of these diagnostic methods toward decreasing the mortality rates among patients with MRSA pneumonia remains to be determined.

CAP. The clinical diagnosis of CAP is frequently difficult. A high level of suspicion is probably the most important factor in obtaining an early rapid diagnosis. CA-MRSA should be suspected as the cause of CAP if the following key features are present: influenza-like prodrome, hemoptysis [24], severe respiratory symptoms, high fever, leukopenia, hypotension, and a chest x-ray showing multilobular infiltrates, which may have cavitated [15]. In addition, CA-MRSA as the causative agent of CAP should be suspected when pneumonia develops in a person known to be colonized with CA-MRSA or who belongs to a group associated with increased rates of colonization with CA-MRSA (e.g., men who have sex with men or prisoners).

THERAPY

The first, and perhaps the most important, aspect of treatment is the need for rapid institution of appropriate antibiotic therapy. This has been repeatedly recognized for HA-MRSA infection [25–27]. For example, Kollef and Ward [25] found that, when adequate therapy was instituted initially, the hospitalwide mortality from VAP decreased from 60.8% to 33.3%. In addition, Kumar et al. [26] demonstrated that, among patients with septic shock, each hour delay in therapy was associated with an increase in mortality of 6.3%. Similarly, Kim et al. [27] demonstrated that the delay of effective therapy in patients with MRSA bacteremia and noneradicable foci of infection, which included pneumonia, was associated with increased mortality.

For years, vancomycin was the only antibiotic available for the treatment of MRSA pneumonia. Unfortunately, the cure rate has been disappointing [28–30]. MRSA pneumonia (mostly cases caused by HA-MRSA) and methicillin-susceptible *S. aureus* (MSSA) pneumonia treated with vancomycin have been associated with mortality rates of 50% and 47%, respectively [28], whereas MSSA pneumonia treated with β-lactams has been associated with only 5% mortality [28–34]. The reasons for the unsatisfactory results of treatment with vancomycin are multifactorial. First, the vancomycin molecule is relatively large and penetrates poorly into the alveolar lining fluid (ALF) and into alveolar macrophages. As a result, levels attained in ALF are only one-sixth of the plasma concentration [35]. In a clinical trial, 36% of patients had ALF levels of $\leqslant$4 mg/mL [35–37], the breakpoint of vancomycin resistance for *S. aureus.*

Opinions differ as to whether higher vancomycin trough serum concentrations of 15–20 μg/mL would result in better therapeutic outcomes than do conventional trough levels of 5–15 μg/mL. Present experience suggests that patients with high vancomycin trough serum levels and high serum vancomycin areas under the curve (AUCs) have outcomes similar to those

Table 1. Factors associated with 10 cases of community-acquired pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) reported to the Centers for Disease Control and Prevention (CDC), 2006–2007.

Factor	No. (%) of cases examined
Patient age <30 years	8 (80)[a]
Preceding or concurrent influenza-like illness	10 (100)
Concurrent SSTI due to MRSA or living with a person infected with MRSA	4 (40)
Multilobar (lung) involvement	7 (70)
MRSA isolate contains SCC*mec* IV and PVL	5 (100)[b]
USA300-0114 clone	5 (100)[b]
Strain resistant to β-lactams and erythromycin	5 (100)[b]
Strain with inducible resistance to clindamycin	2 (40)[b]
Strain not susceptible to levofloxacin	2 (40)[b]
Pneumonia caused death	6 (60)

NOTE. PVL, Panton-Valentine leukocidin; SCC, staphylococcal cassette chromosome; SSTI, skin and soft-tissue infection. Data from [15].

[a] Median age of patients, 17.5 years; range, 4 months to 48 years.

[b] Only 5 of 10 isolates were tested for microbiological evaluation by the CDC.

of patients with lower vancomycin serum levels [38, 39]. Limited vancomycin efficacy may also be associated with the drug's diminished bactericidal activity against MRSA strains with higher, although still susceptible, vancomycin MICs (≥1.0 mg/mL) [39, 40]. Furthermore, vancomycin given at dosages to achieve higher trough serum concentrations may be associated with renal dysfunction when given concomitantly with known nephrotoxic agents [39].

Another US Food and Drug Administration–approved therapeutic option for the treatment of MRSA pneumonia is linezolid. Linezolid, unlike vancomycin, has favorable lung pharmacokinetics, with AUC/MIC in the ALF of ~120, C_{max}/MIC in the ALF of 16.1, and concentrations in the ALF that exceed the linezolid MIC for MRSA during the entire dose-to-dose interval [41].

Two large, prospective, randomized clinical trials that used identical protocols to compare vancomycin with linezolid for the treatment of staphylococcal VAP and HAP have been completed. In one trial [42], patients were randomized to receive either linezolid (600 mg iv every 12 h) plus aztreonam (1–2 g iv every 8 h) or vancomycin (1 g iv every 12 h) plus aztreonam (1–2 g every 8 h). Of the 396 patients included in the intention-to-treat analyses, 203 received linezolid and aztreonam, and 193 received vancomycin and aztreonam. Only 32 patients received a diagnosis of MRSA pneumonia. Among clinically evaluable patients, cure rates were 66% for patients who received linezolid and 68% for patients who received vancomycin. In the second trial [43], which enrolled 623 patients, the clinical cure rate in the clinically evaluable population was 68% for patients who received linezolid ($n = 168$) and 65% for patients who received vancomycin ($n = 171$). The eradication rate for the microbiologically evaluable population with MRSA was 63% for the 19 patients who received linezolid and 43% for the 23 patients who received vancomycin (P value was nonsignificant).

In an analysis of the pooled results of these 2 trials [43] that compared linezolid with vancomycin for the treatment of HAP and VAP due to MRSA, clinical outcomes with linezolid therapy were found to be significantly better than those with vancomycin therapy. This analysis, however, was criticized on methodological grounds, specifically because of a non-prespecified subgroup analysis, the heterogeneity of results in the separate studies, and the small numbers of patients infected with MRSA (7.3% of the combined microbiologically evaluable population) [44]. An additional study is under way to clarify whether linezolid is superior to vancomycin for the treatment of MRSA pneumonia.

Therapeutic decisions are required while we await new studies or new antimicrobial agents. Available data suggest that linezolid is not likely to be inferior to optimally dosed vancomycin and may be superior. Some investigators recommend vancomycin (with a loading dose of 15 mg/kg and trough levels of 15–20 mg/mL—a target that, in younger patients with normal renal function, may require larger doses per kilogram or dosing intervals of <12 h) for pneumonia caused by MRSA strains with vancomycin MICs ≤0.5 mg/mL. For patients with pneumonia caused by MRSA strains with vancomycin MICs ≥1.0 mg/mL, who require concomitant nephrotoxic therapy or who have preexisting renal failure, linezolid at 600 mg every 12 h is advised [45, 46]. Although there may be concerns regarding the increased acquisition cost of linezolid in the application of this approach, one study [47] suggests that the total hospitalization cost per patient given linezolid treatment exceeds that for vancomycin treatment by only $612.

CAP CAUSED BY CA-MRSA

Despite the growing importance of CA-MRSA as a causative agent of CAP, the recent Canadian guidelines are the only ones that address this infection [24]. This systematic review suggests that the management of CA-MRSA pneumonia should include culture of blood, sputum, and pleural specimens; admission to the intensive care unit; drainage of empyema, if present; and a combination of parenteral antibiotic treatment including vancomycin (1 g iv every 12 h) or linezolid (600 mg every 12 h). These guidelines consider linezolid to be superior to vancomycin. Treatment should be guided by an infectious diseases consultant, since other options, such as the addition of rifampicin, may also be considered. Finally, respiratory infection–control measures are important for prevention of the nosocomial spread of MRSA infection among patients in the intensive care unit.

The choice of antibiotics must be made on the basis of experiential and theoretical grounds, since there are no treatment trials for CA-MRSA pneumonia. A recent in vitro study evaluating the effect of vancomycin, nafcillin, clindamycin, and linezolid on clinical isolates of MSSA and MRSA has shown that antibiotics have differing effects on the expression of toxins by staphylococci [48]. Clindamycin and linezolid markedly suppressed the formation of PVL, α-hemolysin, and toxic shock syndrome toxin 1 by suppressing translation but not transcription. Nafcillin, on the other hand, stimulated toxin production, whereas toxin levels with use of vancomycin were comparable to those in control samples not exposed to antibiotics. Since suppression of toxin production may correlate with improved outcome, these data suggest that vancomycin alone may not be the optimal treatment for pneumonia caused by toxin-producing CA-MRSA. Although it has not been established that the combination of a bactericidal agent with a toxin-suppressing agent, such as clindamycin or linezolid, is associated with improved outcome, it is the general impression of experienced clinicians that vancomycin should not be used as a single agent for the treatment of CA-MRSA pneumonia.

Intravenous immunoglobulin has recently been shown to neutralize the damaging pore-forming effect of PVL on polymorphonuclear neutrophils [49]. The mechanism of this action is not entirely clear, and the role of intravenous immunoglobulin in the treatment of CA-MRSA pneumonia still awaits clinical confirmation.

DURATION AND MODIFICATION OF THERAPY

Because unnecessarily broad-spectrum antibiotic therapy promotes the emergence of resistant organisms in individual patients and the environment, modification of the initial broad-spectrum antibiotic regimen administered empirically to patients with HCAP, HAP, or VAP, by use of a de-escalation strategy, should occur whenever possible. De-escalation should be based on the patient's clinical response, as well as on results of microbiological testing (especially quantitative culture results of lower respiratory tract specimens) and the change in the clinical pulmonary infection score (CPIS). Modification should include decreasing the number and/or spectrum of antibiotics, shortening the duration of therapy in patients who have uncomplicated infections and who demonstrate signs of clinical improvement, and discontinuing antibiotics altogether in patients who have a noninfectious etiology identified for their clinical event (figure 3). Kollef and Kollef [50] found that patients for whom VAP was suspected and BAL culture results were negative for a major pathogen or who had a CPIS of $\leqslant 6$ on day 3 could have antimicrobial therapy safely discontinued [51, 52]. Similarly, several clinical trials have found that 7–8 days of antibiotic treatment is acceptable for most patients with VAP without bacteremia [53]. However, the duration of therapy for HAP or VAP due to MRSA needs additional evaluation, since the studies that evaluated treatment duration included insufficient numbers of MRSA-infected patients [53, 54]. As a result, the duration of therapy for nonbacteremic MRSA should be based on clinical judgment; most investigators would provide a minimum of 14 days of therapy. For patients with bacteremic MRSA pneumonia, the duration of therapy must consider the potential for complicated bacteremia and the need for more-prolonged antibiotic therapy. On the basis of the available evidence, the suggested clinical management for a patient with suspected staphylococcal pneumonia is depicted in figure 3.

CONCLUSIONS

The frequency of pneumonia caused by HA-MRSA and CA-MRSA is increasing. CA-MRSA pneumonia is associated with an influenza-like illness, often occurs in young healthy individuals, and results in an acute infection with a stormy course, numerous complications, and high mortality rates. HA-MRSA pneumonia is a frequently fatal illness that occurs in older, debilitated patients, especially those who are receiving ventilatory support. A high level of suspicion, aggressive diagnostic measures, and rapid institution of effective therapy are essential to change the mortality rate for these diseases. Unfortunately, early diagnosis is often difficult and relies on a careful epidemiologic history as well as invasive techniques. Since the rapid determination of the etiology of severe pneumonia is possible only in a limited number of cases, broad-spectrum antibiotic therapy that will treat infection with MRSA as well as other potential pathogens should be instituted early. Therapy with vancomycin for MRSA (and MSSA) pneumonia has been disappointing. Linezolid may be a better choice for the treatment of MRSA pneumonia, although additional studies of its efficacy for both HA-MRSA pneumonia and CA-MRSA pneumonia are

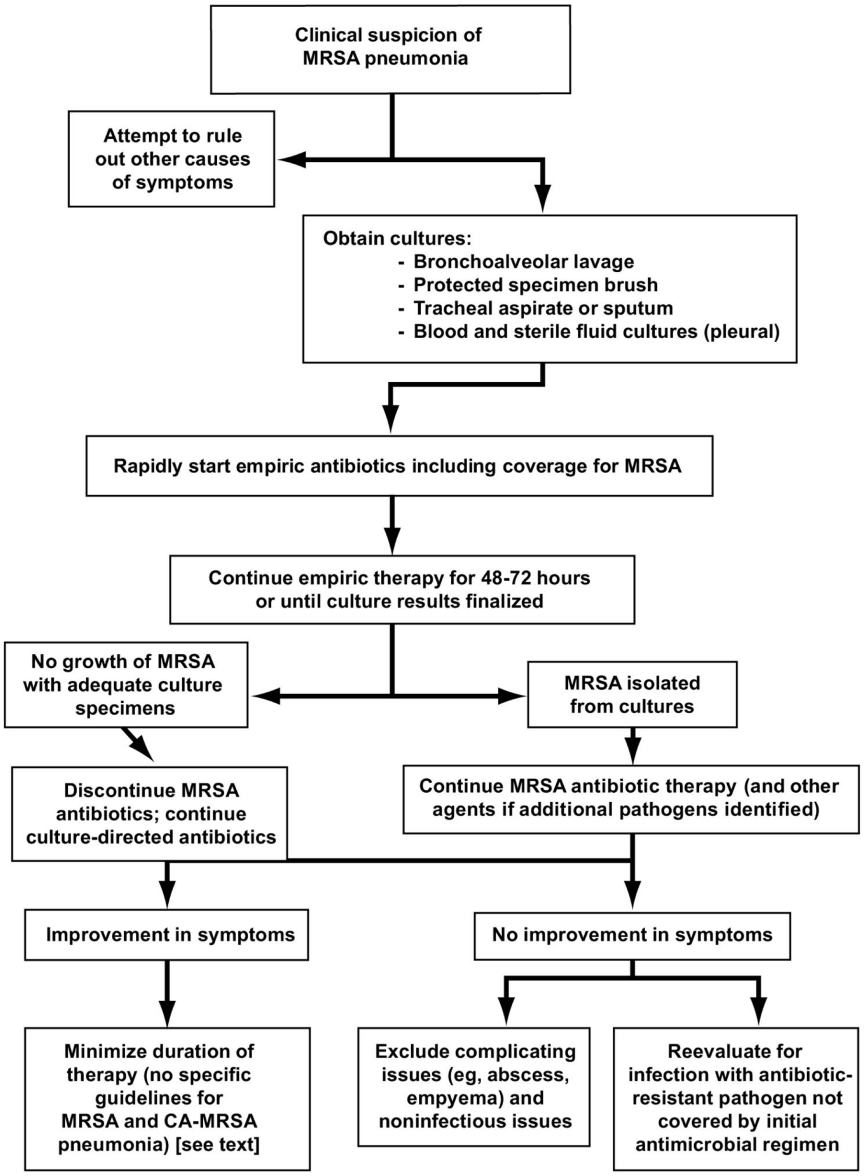

Figure 3. Schematic of clinical management for patients with suspected staphylococcal pneumonia. CA, community-associated; MRSA, methicillin-resistant *Staphylococcus aureus.*

essential. The role of combination antimicrobial therapy and adjuvant therapy remains unclear. Therapy to inhibit staphylococcal toxin production or its activity warrants testing.

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