

Community-associated methicillin-resistant *Staphylococcus aureus* necrotizing pneumonia without evidence of antecedent viral upper respiratory infection

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BACKGROUND: USA300 community-associated (CA) methicillin-resistant *Staphylococcus aureus* (MRSA) strains causing necrotizing pneumonia have been reported in association with antecedent viral upper respiratory tract infections (URI).

METHODS: A case series of necrotizing pneumonia presenting as a primary or coprimary infection, secondary to CA-MRSA without evidence of antecedent viral URI, is presented. Cases were identified through the infectious diseases consultation service records. Clinical and radiographic data were collected by chart review and electronic records. MRSA strains were isolated from sputum, bronchoalveolar lavage, pleural fluid or blood cultures and confirmed using standard laboratory procedures. MRSA strains were characterized by susceptibility testing, pulsed-field gel electrophoresis, *spa* typing, *agr* typing and multilocus sequence typing. Testing for respiratory viruses was performed by appropriate serological testing of banked sera, or nucleic acid testing of nasopharyngeal or bronchoalveolar lavage specimens.

RESULTS: Ten patients who presented or copresented with CA necrotizing pneumonia secondary to CA-MRSA from April 2004 to October 2011 were identified. The median length of stay was 22.5 days. Mortality was 20.0%. Classical risk factors for CA-MRSA were identified in seven of 10 (70.0%) cases. Chest tube placement occurred in seven of 10 patients with empyema. None of the patients had historical evidence of antecedent URI. In eight of 10 patients, serological or nucleic acid testing revealed no evidence of acute viral coinfection. Eight strains were CMRSA-10 (USA300). The remaining two strains were a USA300 genetically related strain and a USA1100 strain.

CONCLUSION: Pneumonia secondary to CA-MRSA can occur in the absence of an antecedent URI. Infections due to CA-MRSA are associated with significant morbidity and mortality. Clinicians need to have an awareness of this clinical entity, particularly in patients who are in risk groups that predispose to exposure to this bacterium.

Key Words: Community-associated methicillin-resistant *Staphylococcus aureus*; Necrosis; Pneumonia; Viral infection

La pneumonie nécrosante à *Staphylococcus aureus* résistant à la méthicilline d'origine non nosocomiale sans manifestation d'infection virale préalable des voies respiratoires supérieures

HISTORIQUE : Des souches USA300 de *Staphylococcus aureus* résistant à la méthicilline (SARM) d'origine non nosocomiale (ONN) responsables d'une pneumonie nécrosante ont été signalées après des infections des voies respiratoires supérieures.

MÉTHODOLOGIE : Les chercheurs présentent une série de cas de pneumonie nécrosante se manifestant sous forme d'infection ou de coinfection primaire découlant du SARM-ONN, sans manifestation d'IVRS virale antérieure. Ils ont dépisté les cas en dépouillant les dossiers des services de consultation en infectiologie. Ils ont colligé les données cliniques et radiographiques en analysant les dossiers papier et électroniques. Les souches de SARM avaient été isolées dans les expectorations, le lavage broncho-alvéolaire, le liquide pleural ou les hémocultures et confirmées au moyen d'analyses de laboratoire standards. Les souches de SARM étaient caractérisées par les tests de susceptibilité, l'électrophorèse sur gel en champ pulsé, le typage du gène *spa* ou du gène *agr* ou le typage génomique multilocus. Les tests de dépistage des virus respiratoires ont été faits au moyen du test sérologique pertinent du sérum en réserve ou du test d'amplification des acides nucléiques des échantillons de lavage nasopharyngé ou broncho-alvéolaire.

RÉSULTATS : Entre avril 2004 et octobre 2011, les chercheurs ont dépisté dix patients qui présentaient, seule ou conjointement, une pneumonie nécrosante d'ONN secondaire à une infection par le SARM-ONN. Ils ont été hospitalisés pendant une période médiane de 22,5 jours. Le taux de mortalité s'élevait à 20,0 %. Les chercheurs ont constaté des facteurs de risque classiques de SARM-ONN dans sept des dix cas (70,0 %). Sept des dix patients faisant de l'empyème avaient eu un drain thoracique. Aucun des patients n'avait d'antécédents démontrés d'IVRS. Chez huit des dix patients, le test sérologique et le test d'amplification des acides nucléiques n'ont révélé aucune manifestation de co-infection virale aiguë. Huit souches étaient des SARMC-10 (USA300). Les deux autres étaient une souche liée génétiquement au USA300 et une souche USA1100.

CONCLUSION : La pneumonie secondaire au SARM-ONN peut se manifester en l'absence d'IVRS antérieure. Les infections causées par le SARM-ONN s'associent à une morbidité et une mortalité importantes. Les cliniciens doivent connaître cette entité clinique, notamment chez les patients qui font partie de groupes vulnérables qui les prédisposent à être exposés à cette bactérie.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is recognized as an important human pathogen associated with a spectrum of clinical diseases including complicated pneumonia. (1). MRSA has

traditionally been considered a health care-associated infection (2). However, there is a growing concern for the emergence of MRSA in the community, occurring in otherwise healthy individuals (3,4). In Canada,

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a prevalence of 5.5% has been observed in a marginalized population (5), and a prevalence of 27% in wound cultures from a community-based sample of intravenous drug users (6). Outbreaks of community-associated MRSA (CA-MRSA) have been described in the United States (7,8), Australia (9), France (10), Japan (11), Canada (5) and Chile (12). In the United States, the most prominent strain is CA-MRSA USA300, which possesses the staphylococcal cassette chromosome *mec* (SCC*mec*) type IVa and the Panton-Valentine leukocidin (PVL) gene. In Canada, USA300 is known as CMRSA-10 and has been the dominant strain since it was first reported in 2004 (13).

Epidemiological studies have revealed that CA-MRSA strains differ from health care-associated MRSA strains (14,15) by causing significant morbidity and mortality in healthy individuals (7). Several studies have demonstrated a link between identified risk factors and CA-MRSA (2,5,14,16-19). In Canada, CA-MRSA was first described in 1990 by Taylor et al (20), who reported increasing numbers of MRSA infections in an Aboriginal community in Alberta, with evidence that multiple strains were involved. The first outbreak was published in 2006 and involved individuals experiencing homelessness, incarceration and drug use (21). Since then, several other reports have described cases of CA-MRSA infections in Canada (22,23).

Of the many clinical syndromes associated with CA-MRSA, pneumonia is frequently severe and rapidly progressive, often leading to septic shock and resulting in a high mortality rate (24,25). These cases are often complicated and consist of extensive lung necrosis, lung abscesses and empyema (7). CA-MRSA pneumonia is often preceded by skin or soft tissue infections (SSTI). An association with influenza-like illness preceding CA-MRSA pneumonia has been described in several reports (8,26-31). In a pediatric case series involving 159 patients, CA-MRSA infections occurred more frequently with abscesses and complicated pneumonias (50.3% and 70.6%, respectively). In this study, only two cases with documented viral respiratory tract illnesses preceded the *S aureus* pneumonia (32).

We describe our experience with a case series of adult patients who presented or copresented with community-associated MRSA necrotizing pneumonia without a preceding viral infection, determined clinically or by microbiological testing.

METHODS

Case definition and data collection

Patients with necrotizing pneumonia secondary to MRSA infection were identified within the Alberta Health Services (previously Calgary Health Region) from May 2004 to October 2011 through the infectious diseases consultation service case records at the three Calgary (Alberta) hospitals that provide adult care (Foothills Medical Centre, Peter Lougheed Centre and Rockyview General Hospital). All cases involved adult patients presenting with severe pneumonia and positive cultures (blood, sputum, bronchoalveolar lavage or pleural fluid) for MRSA, with a typical community-associated susceptibility profile on the antibiogram (defined as susceptibility to tetracycline and trimethoprim/sulfamethoxazole, and variable susceptibility to clindamycin) (33,34).

Clinical data were collected via chart review of medical records from hospitalized patients and/or electronic databases (laboratory results, diagnostic imaging). Patients were excluded if they did not undergo chest imaging (chest radiograph or enhanced computed tomography scan) within the first 48 h of admission, did not have clinical, laboratory or radiological signs of pneumonia (fever/chills, cough, sputum production, dyspnea, tachypnea, pleuritic chest pain, hypoxia, leukocytosis/leukopenia or consolidation on radiological imaging) or were not diagnosed with pneumonia within the first 48 h based on review of the clinician's admission notes. The diagnosis of necrotizing pneumonia was determined as indicated below. This required the presence of new radiographic findings (Table 1) and positive cultures of MRSA of either blood or respiratory source. Acceptable positive culture specimens included sputum, tracheal aspirate, bronchoalveolar lavage fluid or blood. Patients were excluded from consideration as

having community-acquired pneumonia for the present study if one of the following health care-related risk factors were present: hospitalizations to a health care facility in the preceding 12 months; residence in a nursing home; or dialysis patient. Patients with infective endocarditis were excluded. The present case series focused on patients with CA-MRSA pneumonia who had no documentation of antecedent viral illness according to history and/or appropriate diagnostic testing to suggest viral infection.

Definitions

CA-MRSA pneumonia was defined as a pulmonary infection with an onset <48 h after hospital admission, no other hospitalizations in the previous 12 months and with no other health care-related exposures, as noted above in the exclusion criteria (35). Clinical and radiographic correlation was present and MRSA was isolated from culture (blood, sputum, pleural fluid, bronchoalveolar lavage). The CA-MRSA pneumonia may have occurred alone or have been copresenting with another concomitant site of infection.

Severe CA-MRSA pneumonia was identified according to standard practice guidelines published by the Infectious Diseases Society of America (36). The guidelines define severe pneumonia as having any one of the following: requiring an intensive care unit (ICU) admission, necrotizing or cavitary infiltrates, or empyema.

Necrotizing pneumonia was determined to be present based on an adaptation of the criteria described by Tsai and Ku (37): typical radiographic features detected on a contrast-enhanced chest computed tomography scan, and pneumonic consolidation plus the presence of a cavity or multiple areas of low attenuation.

Phenotypic and genotypic characterization of MRSA isolates

Screening for methicillin and other antibiotic-resistant phenotypes was performed using VITEK 1 (bioMérieux Inc, USA) and the Clinical and Laboratory Standards Institute oxacillin agar screen, or Kirby Bauer methods, plus a D-test for clindamycin susceptibility (38), whereas confirmation of methicillin resistance was performed using an in-house polymerase chain reaction (PCR) assay for *nuc*, *femA* and *mecA* genes, as previously described (39). All isolates were typed by pulsed-field gel electrophoresis (PFGE) according to the Canadian standardized protocol (40). The strains were tested for the presence of the PVL gene and the arginine deiminase (*arcA*) gene using a multiplex PCR assay (41). The isolates were characterized by SCC*mec* typing (42,43), staphylococcal protein A (*spa*) typing (44) and multilocus sequence typing (MLST) (45). Identification of strains matching the MRSA USA300 strain was based on the following: SCC*mec* type IVa, *spa* type t008, MLST type ST8 and identical PFGE patterns with standard USA300 control strain CMRSA-10.

Nucleic acid testing and serological testing for respiratory viruses

Nasopharyngeal specimens were tested using nucleic acid testing (NAT) for influenza virus, parainfluenza viruses, adenovirus and respiratory syncytial virus at the Provincial Laboratory of Alberta, and serological testing for influenza virus (46) was performed by appropriate testing of banked sera at the National Microbiology Laboratory in Winnipeg, Manitoba. Nasopharyngeal swabs were collected in Universal Transport medium (Copan Diagnostics, USA) to maintain the integrity and viability of the respiratory viruses during transport to the laboratory. Influenza A and B viruses were individually detected using a singleplex real-time reverse-transcriptase PCR to each of these agents. The primers, probes and cycling conditions have been previously described (47). Testing for the respiratory viruses, ie, respiratory syncytial virus, parainfluenza types 1 to 4 and adenovirus, was performed using the Respiratory Viral Panel assay from Luminex Molecular Diagnostics (Abbott Laboratories, Canada). For patients for whom no NAT was performed and banked paired serum samples were available, stored serum samples were forwarded to the National Medical Laboratory for testing of antibodies to influenza A and B using a hemagglutination inhibition assay performed according to standard

TABLE 1
Clinical characteristics of patients with severe community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia

Variable	Patients in case series									
	1	2	3	4	5	6	7	8	9	10
Age, years	34	38	68	36	48	37	41	71	44	34
Sex	Female	Male	Male	Male	Female	Male	Female	Female	Male	Male
Hospital stay, days	6	66	26	3	17	25	95	179	20	15
Comorbidities										
Cardiac			+							
Chronic pulmonary disease										
Diabetes mellitus			+							
Hypertension			+					+		
Hepatitis C*				+	+	+				+
HIV infection						+				
MRSA risk factors	+	+	+	+	+		+			+
Complications										
MRSA bacteremia	+	-	+	-	+	-	+	+	+	+
Transthoracic echicardiogram performed	-	-	+	-	+	-	+	+	+	+
MRSA from respiratory source	-	+	+	+	+	+	-	+	+	-
Skin and soft tissue infection	+	+	-	-	+	-	+	+	+	-
Admission to intensive care unit	+	-	-	+	+	-	-	+	+	-
Chest tube placement	+	+	+	+	+	-	-	-	+	+
Empyema/oculations	+	+	+	+	+	-	-	-	+	+
Pulmonary nodules	+	+	-	-	+	-	+	-	+	+
Cavitary lesion on computed tomography	+	+	-	+	+	+	-	+	+	+
Lung abscess on computed tomography	-	-	-	+	+	-	-	+	-	-
Multiorgan failure	+	-	-	+	-	-	-	-	-	-
Outcome	D	R	R	D	R	R	R	R	R	R

*Hepatitis C positivity indicated by hepatitis C antibody; D Death; R Recovery

techniques (48). All sera were pretreated with receptor-destroying enzyme (Accurate Chemical & Scientific Corporation, USA) to reduce nonspecific agglutination. The highest serum dilution to show an absence of agglutination was the titre recorded.

RESULTS

Clinical results

Between May 2004 to October 2011, screening of the consultation records revealed 21 potential cases, of which 10 patients with severe CA-MRSA pneumonia who met the case definition were identified. Demographic and clinical characteristics of the 10 cases are presented in Table 1. These 10 patients comprised four women (40.0%) and six men (60.0%). The median age was 39.5 years. The median length of stay was 22.5 days. Seven (70.0%) of the patients required chest tube placement. Two (20.0%) of the patients presented with rapidly progressive necrotizing pneumonia and died from this infection. Seven of 10 cases (70.0%) had a history of illicit drug use, Aboriginal ethnicity, homelessness and/or incarceration (Table 1), which are acknowledged risk factors (17,21). Overall, the patients with risk factors for CA-MRSA were associated with worse clinical outcomes as observed by the presence of empyema in six of 10 (five had risk factors), chest tube placement in seven (six of seven had risk factors) and ICU admission in five of 10 (three of five had risk factors); both patients that died also had risk factors.

Among these high-risk patients, four (57%) also tested positive for hepatitis C antibody (Table 1). Six (60%) of 10 patients had SSTIs copresenting with pneumonia at the time of admission (Table 1). Additional characteristics and risk factors of the 10 cases are summarized in Table 1. Empirical antibiotic therapy was initiated in all patients including vancomycin in nine (90%) of 10 cases and linezolid in seven (70%) of 10 cases (Table 2).

Laboratory results

Eight (80.0%) of 10 of the isolates were found to be USA300 (CMRSA-10) (PVL+, *arcA*+, *spa* t008 SCCmec IVa and MLST ST8) (Figure 1).

One isolate (Patient 1) was a USA300 genetically related strain, which had a similar PFGE pattern to USA300 and carried PVL, *arcA* and SCCmec IVa and shared the same MLST ST8 profile but with a slightly different *spa* type t818 (*spa* repeats YHGFMB instead of YHGFMBQLQ in a typical USA300 strain) (Figure 1). The remaining isolate (patient 9) was a PVL+, ST30-*spa* t019-SCCmec-IVa strain belonging to USA1100, a commonly encountered community-associated strain in South America (49). Interestingly, all of these 10 isolates were PVL positive and carried CA-MRSA-associated SCCmec type IVa (Figure 1). The majority (90.0%) of the strains were resistant to beta-lactams, ciprofloxacin and erythromycin but susceptible to clindamycin, trimethoprim-sulfamethoxazole, rifampin, tetracycline, gentamicin and vancomycin (Table 2). Vancomycin minimum inhibitory concentrations were determined for all clinical isolates of MRSA using the Vitek II AST-GP67 susceptibility card (bioMerieux Canada). All isolates had minimum inhibitory concentrations <1.0 µg/mL. Eight patients were tested for viral infection with either NAT or serology. For the other two patients, testing was not performed due to the absence of obtaining a nasopharyngeal specimen or the lack of stored serum samples. Viral testing results are summarized in Table 3. In eight of 10 patients, documentation supporting the presence of any concomitant viral infection at the time of admission could not be found. At the time of admission, none of the 10 cases had a nasopharyngeal swab for respiratory viruses performed. In all cases, a comprehensive review of the patient charts revealed no clinical history or records to support the presence of a viral-like illness preceding the CA-MRSA pneumonia.

DISCUSSION

CA-MRSA is increasingly recognized as an emerging pathogen in the community (50). Severe cases of CA-MRSA necrotizing pneumonia have been reported worldwide in adult and pediatric series (25,32). Although previous studies have suggested a relationship between CA-MRSA pneumonia and preceding influenza or other viral respiratory illness (25-27,51), a viral etiology for community-acquired

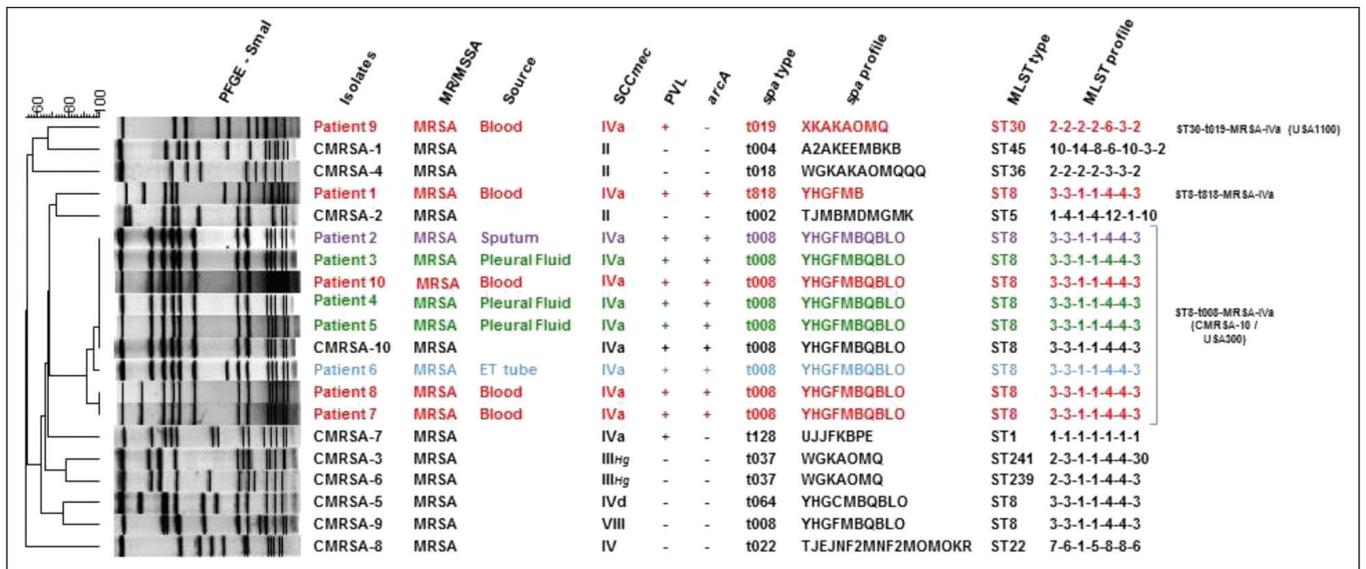


Figure 1) Pulsed-field gel electrophoresis and molecular characterization of methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolates. arcA Arginine deiminase; ET Endotracheal aspirate; MLST Multilocus sequence typing; MSSA Methicillin-sensitive *S. aureus*; PVL Panton-Valentine leukocidin; SCCmec *Staphylococcal cassette chromosome mec*; spa *Staphylococcal protein A*

TABLE 2
Characteristics of antibiotic therapy and antibacterial susceptibility of patients' community-associated methicillin-resistant *Staphylococcus aureus* isolates

Patient	Antibiotic therapy				Antibiotic susceptibility							
	Vm	Cm	TMP-SMX	Ld	Vm	Cm	Em	Tet	Gm	Rf	Cp	TMP-SMX
1	+	+		+	S	S	S	S	S	S	R	S
2	+			+	S	S	R	S	S	S	R	S
3	+			+	S	S	R	S	S	S	R	S
4	+				S	S	R	S	S	S	R	S
5	+			+	S	R	R	S	S	S	R	S
6			+		S	S	R	S	S	S	R	S
7	+		+		S	S	R	S	S	S	R	S
8	+			+	S	S	R	S	S	S	R	S
9	+			+	S	S	S	S	S	S	R	S
10	+	+		+	S	S	R	S	S	S	R	S

+ Indicates use of antibiotic; Cm Clindamycin; Cp Ciprofloxacin; Em Erythromycin; Gm Gentamicin; Ld Linezolid; R Resistant; Rf Rifampin; S Sensitive; Tet Tetracycline; TMP-SMX Trimethoprim-sulfamethoxazole; Vm Vancomycin

pneumonia cases is not always investigated (52,53). Few studies have considered the role of *S. aureus* in non-influenza-associated pneumonia as outlined by Kallen et al (31). The results of our case series suggest that severe CA-MRSA pneumonia may occur in the absence of antecedent influenza or other viral respiratory infection. Our findings are corroborated by another recent retrospective analysis, in which 15 cases of CA-MRSA pneumonia were described as having no relationship to a preceding influenza infection (54). In this study, viral testing was performed on all 15 patients using either the rapid influenza test or influenza viral culture, and only one was positive.

Infections due to CA-MRSA have been reported and are associated with significant morbidity and mortality (8,20,28,55). In our series, this was illustrated by the presence of empyema in seven of 10 patients and the death of two patients. The varying degrees of morbidity in our series included the development of empyema (70.0%), cavitory lesions (80.0%) and ICU admission (50.0%). Our findings showed that the majority of our patients required chest tube placement (70.0%), revealing the virulent capacity of MRSA. The mortality rate was 20.0%, which is comparable with a previously reported case series of CA-MRSA without previous viral infection (54). In all our cases, MRSA was the only bacterial pathogen identified that was associated with the initial

presentation. All 10 of the isolates harboured the PVL gene (Figure 1) and had the SCCmec type IVa element. Our results demonstrate that these isolates were consistent with previously described strains of CA-MRSA (7), of which 80.0% were the North American dominant strain USA300 strain.

Although the point has been debated, PVL, commonly associated with CA-MRSA, has been considered to be a virulence factor associated with severe pneumonia (11,24,26,37). PVL is a cytotoxin that appears to be associated with *S. aureus* causing SSTIs (6) and necrotizing pneumonia (24). In contrast, a study by Sharma-Kuinkel et al (56) provide evidence that clinical outcome may be more significantly influenced by several bacterial virulence factors and that PVL is not the primary determinant of outcome. Investigators have shown that other factors need to be considered in the pathogenesis of serious infections due to MRSA (57).

In our series, nine of 10 patients received vancomycin and seven of this group received concomitant linezolid. Clinically, linezolid and vancomycin have shown no significant difference in outcomes (58) while a post hoc analysis in a multicentre study suggested increased survival and cure rates with linezolid (59). Guidelines by the Canadian Thoracic Society and Canadian Infectious Diseases Society

TABLE 3
Viral screening of respiratory samples of patients' community-associated methicillin-resistant *Staphylococcus aureus* isolates

Patient	Adenovirus	Influenza A*	Influenza B*	Parainfluenza 1-3	RSV
1	ND	ND	ND	ND	ND
2	Negative	1:16/negative	Negative	Negative	Negative
3	Negative	Negative	Negative	Negative	Negative
4	Negative	Negative	1:16	Negative	Negative
5	ND	ND	ND	ND	ND
6	Negative	Negative	Negative	Negative	Negative
7	ND	Negative	Negative	ND	ND
8	Negative	Negative	Negative	Negative	Negative
9	ND	1:160	1:80	ND	ND
10	Negative	1:32/1:16	1:16/1:16	Negative	Negative

Patient samples that show two titres reveal viral testing performed at different intervals. Difference in titres is not significant. Patients 7 and 9 had hemagglutination inhibition assays (serology) testing. All others had nucleic acid testing. *Titres show results of paired serum samples at different intervals. ND No data available; RSV Respiratory syncytial virus

recommend the use of vancomycin or linezolid in the case of hospitalized patients with severe community-acquired pneumonia (60).

With regard to demographic factors, 70.0% of our patients had known risk factors for CA-MRSA and were at a higher risk for a complicated evolution of pneumonia. Among our designated high-risk patients, 85.7% required chest tube placement and 42.9% required ICU admission. Both patients who died were in the high-risk group.

We recognize that our study had several limitations. Selection of patients was limited to those seen by the infectious diseases consultation group and, therefore, not all patients with CA-MRSA may have been identified. It is possible that less severe cases were managed without asking for an infectious diseases consultation. Generally, more severe cases of CA-MRSA are managed in consultation with the infectious disease service; however, we recognize that some cases may not have been reported. In addition, as is local practice in our centres, linezolid is not available unless approved by the infectious diseases service. We do acknowledge that this may represent a selection bias. Our results may be limited due to chart accuracy for documented influenza-like symptoms. We based our selection on the available description of onset of symptoms as detailed in the admission notes. We acknowledge that in some cases there may have been incomplete charting or that only positive findings were noted and that no record of a previous viral-like prodrome or investigations for viral illness does not preclude their presence. The lack of any viral testing for two of our patients did not allow us to fully assess the role of a possible viral infection in these cases. In addition, we

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acknowledge that we did not test for additional respiratory viruses, including human metapneumovirus, coronaviruses and rhinocoronaviruses, but they were not routinely available at our centre. Nonetheless, in 80% of the patients, viral testing demonstrated no evidence of viral infection based on the available testing.

SUMMARY

Our study revealed that CA-MRSA pneumonia can occur in the absence of a preceding viral-like illness. Nevertheless, the potential role of preceding influenza or other viral illnesses in the pathogenesis of CA-MRSA pneumonia has been previously described (26,27,48) and should always be considered in the historical data of patients presenting with rapidly progressive pneumonic illnesses with known risk factors for CA-MRSA. Given the severity, rapid progression, frequency of empyema and other complications, and high mortality of pulmonary infections associated with CA-MRSA, an awareness of this clinical entity for CA-MRSA, especially in patient groups with known risk factors, is crucial for prompt initiation of empirical antimicrobial therapy.

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