ORIGINAL RESEARCH

Burden of methicillin-resistant *Staphylococcus aureus* pneumonia among hospitalized patients in Lebanon and Saudi Arabia

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Objectives: The objective of this study is to describe the real-world treatment patterns and burden of suspected or confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia in Saudi Arabia and Lebanon.

Methods: A retrospective chart review study evaluated 2011–2012 data from hospitals in Saudi Arabia and Lebanon. Patients were included if they had been discharged with a diagnosis of MRSA pneumonia, which was culture proven or suspected based on clinical criteria. Hospital data were abstracted for a random sample of patients to capture demographics (eg, age and comorbidities), treatment patterns (eg, timing and use of antimicrobials), hospital resource utilization (eg, length of stay), and clinical outcomes (eg, clinical status at discharge and mortality). Descriptive results were reported using frequencies or proportions for categorical variables and mean and standard deviation for continuous variables.

Results: Chart-level data were collected for 93 patients with MRSA pneumonia, 50 in Saudi Arabia and 43 in Lebanon. The average age of the patients was 56 years, and 60% were male. The most common comorbidities were diabetes (39%), congestive heart failure (30%), coronary artery disease (29%), and chronic obstructive pulmonary disease (28%). Patients most frequently had positive cultures from pulmonary (87%) and blood (27%) samples. All isolates were sensitive to vancomycin, teicoplanin, and linezolid, and only one-third of the isolates tested were sensitive to ciprofloxacin. Beta-lactams (inactive therapy for MRSA) were prescribed 21% of the time across all lines of therapy, with 42% of patients receiving first-line beta-lactams. Fifteen percent of patients did not receive any antibiotics that were considered to be MRSA active. The mean hospital length of stay was 32 days, and in-hospital mortality was 30%.

Conclusion: The treatment for MRSA pneumonia in Saudi Arabia and Lebanon may be suboptimal with inactive therapy prescribed a substantial proportion of the time. The information gathered from this Middle East sample provides important perspectives on the current treatment patterns.

Keywords: MRSA, resource use, mortality, length of stay, antibiotics, Middle East

Introduction

In recent years, morbidity and mortality of nosocomial infections have increased, at least partly due to the increased frequency of antibiotic resistance in both Gram-positive and Gram-negative organisms. In the past, Gram-negative aerobes were the most frequently reported pathogens, but *Staphylococcus aureus* has been increasing in frequency, particularly methicillin-resistant *S. aureus* (MRSA) in intensive care units.[1]

Over 70% of *S. aureus* isolates are resistant to methicillin in the Middle East and with >85% of *S. aureus* pneumonia cases being MRSA pneumonia in the Arabian

peninsula.[2] In Saudi Arabia, 76% of health-care workers have tested positive for MRSA colonization despite being asymptomatic.[3] On a separate note, a systematic review on the epidemiology of *S. aureus* in the Middle East indicates high incidence of community-acquired MRSA carried by healthy individuals, with positive MRSA samples obtained from random wound, throat, and nasal specimens.[4]

Glycopeptide antibiotics, vancomycin and teicoplanin, have been considered drugs of choice in treatment for infections due to suspected or documented MRSA.[5–8] Burgeoning glycopeptide prescribing is believed to have led to the emergence of vancomycin-resistant enterococci and, more recently, *S. aureus* with reduced glycopeptide susceptibility. Treatment resistance of clinical MRSA has also been shown in this region against both β-lactam and non-β-lactam antibiotics (erythromycin, clindamycin, ciprofloxacin, and tetracycline), chloramphenicol, gentamicin, and sulfamethoxazole–trimethoprim.[4]

Even though there is a recent debate surrounding the use of vancomycin,[9–11] it is still a common antibiotic for the treatment of nosocomial pneumonia and is recommended in the most recent guideline endorsed by the American Thoracic Society and the Infectious Disease Society of America.[1] Despite guidelines, real-world practice patterns are known to vary substantially from those recommended. Furthermore, little is known in low- and middle-income countries of the Middle East regarding practice patterns and resource associated with MRSA pneumonia.

The objectives of this study were to describe the microbiologic profile of MRSA pneumonia in Lebanon and Saudi Arabia and assess the treatment received by these patients, in terms of drug selection, dosing, timing, and sensitivity of the infection pathogen, and to document hospital resource utilization and clinical outcomes among patients with this infection.

Methods
Study design
This study is a retrospective, observational medical chart review that took place at a total of five study sites in Saudi Arabia (two sites) and Lebanon (three sites). Per the study protocol, the study investigator (local physician responsible for data collection) assessed the need for ethics/IRB application at each site, IRB waiver or approval was completed at all sites based on local requirements. Specifically, approval was obtained from National Guard Health Affairs, King Abdalaziz Medical City- Jeddah and Riyadh, Kingdom of Saudi Arabia; Ain Wazein Hospital IRB; and Makassed General Hospital, Riad El-Solh Beirut, Lebanon.

Inclusion and exclusion criteria
In order to be included, patients had to have suspected or culture-proven MRSA pneumonia with appropriate respiratory symptoms. In the absence of culture results, suspected cases needed to have at least two of the following symptoms for inclusion: fever (body temperature ≥38.5°C), hypothermia (body temperature ≤35.5°C), respiratory rate (>30 breaths/min), systolic hypotension (<90 mmHg), heart rate (>120 beats/min), elevated peripheral white blood cell count (>10,000/mm³), leukopenia with total white blood cell count (<4,500 cells/mm³), and elevated inflammatory markers (eg, procalcitonin or C-reactive protein). Patients were excluded if they had inadequate data on the treatments and outcomes of interest or hospital resource utilization for the study, as judged by the investigators.

Data collection
Data were collected from patient medical records by hospital-based infectious disease specialists, medical microbiologists, internal medicine specialists, surgeons, and intensivists. All data collection instruments were translated into local language and, prior to roll out, pilot tested to ensure relevance and clarity of data points to be collected.

Extracted chart data included demographics and comorbid conditions; antibiotic treatment patterns, including initial and subsequent inpatient antibiotic regimens prescribed and antibiotic therapy prescribed at discharge; health-care resource utilization, including diagnostic procedures, laboratory tests, and length of hospital stay; and clinical outcomes, including clinical response at discharge and rehospitalization. Pneumonia was classified into one of the four categories by the abstracting physician as follows:

- Community-acquired pneumonia: Symptom onset prior to hospital admission but with no known patient history of 1) another hospital visit, 2) visit to another health-care institution, or 3) residence in a nursing home within 90 days prior to the present hospital admission
- Health-care-associated pneumonia (HCAP): Symptom onset during 1) another hospital visit, 2) visit to another health-care institution, or 3) residence in a nursing home within 90 days prior to the present hospital admission
- Nosocomial pneumonia: Symptom onset at least 48 hours after hospital admission
- Unknown

Antibiotics received during hospitalization were categorized as MRSA active and not MRSA active. MRSA-active antibiotics as defined by guidelines included vancomycin (intravenous

only), teicoplanin (intravenous only), clindamycin, doxycycline, trimethoprim/sulfamethoxazole, linezolid, fusidic acid, rifampin, and tigecycline.[12] Antibiotics categorized as not MRSA active included beta-lactams (by definition), and in the

absence of institution-specific antibiograms, fluoroquinolones and carbapenems were only categorized as MRSA active if culture results indicated sensitivity to the respective antibiotic.

Statistical analysis

Unless otherwise listed, binary and categorical end points were summarized in terms of percentages in each category, and continuous variables were presented using number of observations (when less than the entire sample), arithmetic mean, and standard deviation (SD).

Results

Demographic and clinical characteristics

Chart-level data were collected for 93 patients with MRSA pneumonia, 50 in Saudi Arabia and 43 in Lebanon. Of the 93 patients in the sample, 20% of the MRSA infections were community acquired, 32% health-care associated, 35% nosocomial, and 12% of unknown origin. Underlying chronic pulmonary disease was present in 28% of patients (Table 1). However, the most common comorbidities among these patients were diabetes (39%) and congestive heart failure (30%).

Antibiotic treatment patterns

Ninety of the 93 patients in the sample (97%) had at least one culture taken, and 82 of these (91%) had at least one culture positive for MRSA. As would be expected, only one-third of the isolates tested were sensitive to ciprofloxacin and only 15% were sensitive to beta-lactams. Patients most frequently had positive cultures from pulmonary (87%) and blood (27%) samples; nasal sites were also culture positive in 16% of patients. Table 2 shows the susceptibility profile for MRSA isolates from patients with pneumonia. All isolates tested were

Table 1 Patient profile – MRSA pneumonia

	Overall, N=93	Saudi Arabia, N=50	Lebanon, N=43
Male, %	60	64	56
Age at hospital admission, mean ± SD	56.0±26.8	56.1±26.0	55.9±28.0
Weight at hospital admission, kg			
Patients with information, n	67	38	29
Mean ± SD	63.5±25.4	61.9±24.1	65.6±27.2
Body mass index, mg/m²			
Patients with information, n	44	29	15
Mean ± SD	26.0±5.8	25.8±6.3	26.4±4.8
Number of reported comorbidities, mean ± SD	2.5±2.0	2.5±2.0	2.4±1.9
Diabetes, %	39	38	40
Congestive heart failure, %	30	26	35
Coronary artery disease, %	29	22	37
Chronic pulmonary disease, %	28	20	37
Cerebrovascular disease, %	18	22	14
Peripheral vascular disease, %	9	10	7
Dementia, %	8	12	2
Moderate-to-severe renal disease, %	8	4	12
MRSA pneumonia symptoms, %			
Fever	65	52	79
Hypothermia	12	16	7
Respiratory rate >30 breaths/min	47	66	26
Systolic hypotension	29	28	30
Heart rate >120 beats/min	46	54	37
Elevated peripheral WBC >10,000/mm³	76	74	79
Leukopenia with total WBC <4,500 cells/mm³	6	2	12
Elevated appropriate inflammatory markers (eg, PCT or CRP)	59	34	88
Cultures taken to confirm MRSA, %	97	100	93
Any positive MRSA culture, %[a]	91	100	80
1 positive culture	57	66	45
2 positive cultures	19	12	28
3+ positive cultures	16	22	8
Site of culture, %[a,b]			
Pulmonary	79	90	65
Blood	24	18	33
Nasal	14	20	8
Other (pus, urine, catheter tip)	5	8	3
Timing of MRSA infection,%			
Community-acquired pneumonia	20	14	28
Health-care-associated pneumonia	32	30	35
Nosocomial pneumonia	35	44	26
Unknown	12	12	12

Notes: [a]Denominator is patients with a culture taken to confirm MRSA. [b]Patients may have had MRSA confirmed by more than one type of culture. Groups not mutually exclusive.
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; WBC, white blood cell; PCT, procalcitonin; CRP, C-reactive protein.

Table 2 MRSA pneumonia susceptibility profile

Antibiotics	N tested	% sensitive
Vancomycin	80	100
Teicoplanin	32	100
Linezolid	10	100
Rifampin	29	76
Erythromycin	12	75
Gentamicin	8	75
Fusidic acid	9	67
Moxifloxacin	3	67
Levofloxacin	16	63
Trimethoprim/sulfamethoxazole	53	66
Clindamycin	73	53
Tetracycline	4	50
Tigecycline	4	50
Ciprofloxacin	18	33
Beta-lactam antibiotic	54	15

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

sensitive to vancomycin (n=80) and teicoplanin (n=32). Only ten isolates were tested for linezolid sensitivity, and all were found to be sensitive. Only one-third of the isolates tested were sensitive to ciprofloxacin.

Drug selection for MRSA pneumonia, expressed as the percentage of patients receiving each antibiotic (with potential for multiple antibiotics per line of therapy), is summarized in Figure 1. Overall, 79 patients (85%) received at least one antibiotic considered to be MRSA active. The 93 MRSA pneumonia patients received a total of 140 antibiotic orders designated by study investigators

to be first-line therapy (as some regimens consisted of multiple antibiotics). Of these, 28% were beta-lactams (thus representing inactive therapy), and the most frequently prescribed MRSA-active antibiotic was vancomycin (22% of orders). Among the 48 patients (52%) who were prescribed a total of 66 second-line antibiotic orders, vancomycin remained the most commonly prescribed antibiotic (39% of orders), followed by teicoplanin (12%) and linezolid (9%). Of the eleven third-line drugs received by eight patients, linezolid was the most commonly used (36% of orders), followed by vancomycin (27%) and ciprofloxacin (18%).
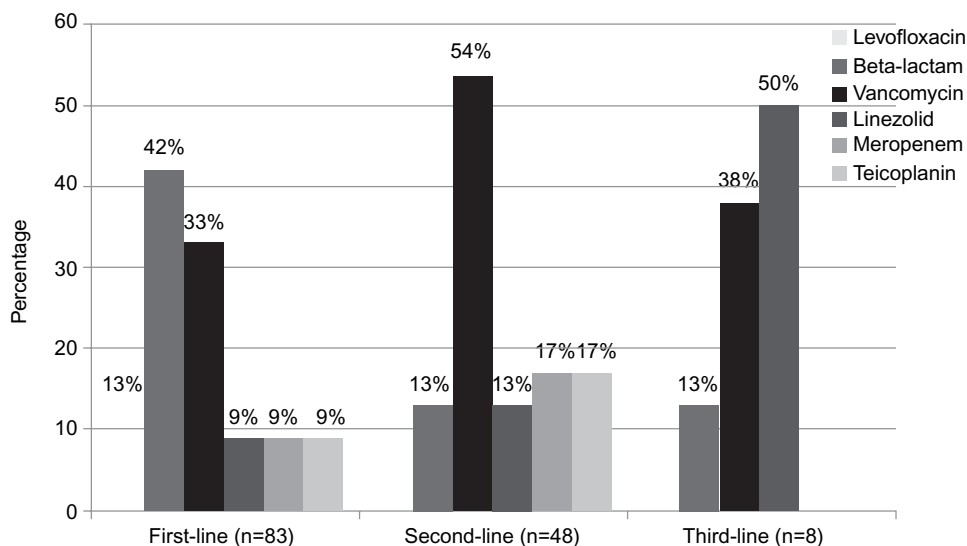
Figure 1 Medications utilized for MRSA pneumonia treatment.
Notes: Medications are not mutually exclusive. Patients could have received multiple antibiotics during a single-line therapy.
Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.
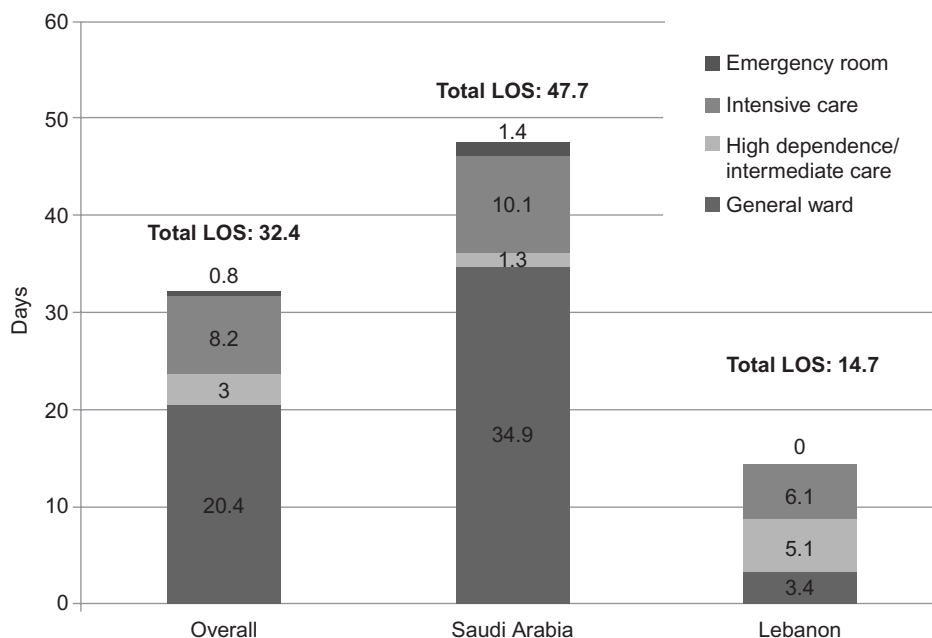
Figure 2 Length of stay (LOS) among patients with MRSA pneumonia.
Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Other health-care resource utilization

Overall, the mean total length of stay (LOS) was 32.4 days, with the majority (20.4 days) spent in general wards (Figure 2). Thirty-six patients (39%) required mechanical ventilation, for a mean ± SD of duration of 18.7±24.4 days per patient. Four patients (4%) required hemodialysis, for a mean of 9.8 ± 11.9 days per patient. Of these patients, two patients were reported to have moderate-to-severe renal disease on admission, but whether these patients were receiving dialysis prior to admission is unknown.

Other interventions required among patients with MRSA pneumonia included peripheral catheters (52%), central venous catheters (52%), and peripherally inserted central catheters (6%).

Clinical outcomes

Over one-fourth of the patients were considered treatment failures at the time of discharge (Table 3). The overall in-hospital mortality rate was 30%, with nearly one-third of

Table 3 MRSA pneumonia clinical outcomes

Outcome	Overall, N=87, %	Saudi Arabia, N=49, %	Lebanon, N=38, %
Clinical response at discharge			
Cure (resolution of all signs and symptoms/improvement to such an extent that further antimicrobial therapy was not necessary)	41	54	26
Improvement (improvement in signs and symptoms)	24	10	40
Failure (persistence, incomplete clinical resolution, or worsening in signs and symptoms)	27	28	26
Indeterminate (inability to determine an outcome)	9	8	9
In-hospital mortality	30	34	26
Cause of death[a]			
Underlying disease-related complication	54	71	27
MRSA related	32	18	55
Cardiac arrest	7	12	0
Another hospital-acquired pneumonia	4	6	0
Other	18	29	0
Unknown	11	6	18
Outcomes 30 days post-discharge[b]			
Relapse of MRSA pneumonia	3	3	3
Rehospitalization for MRSA pneumonia	2	3	0
Rehospitalization, any reason	20	21	19

Notes: [a]Multiple causes of death could be listed. [b]only measured in patients who survived to discharge (n=65; Saudi Arabia =33 and Lebanon =32).
Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

deaths being MRSA related. Of the 28 patients who died, treatment response at discharge was failure in 24 (86%) cases, improved in one (3.5%), cure in two (7%), and indeterminate in one (3.5%). Relapse of MRSA pneumonia (3%) and rehospitalization for MRSA pneumonia (2%) were rare; however, all-cause rehospitalization occurred in 20% of patients.

Discussion

This real-world burden and treatment patterns study of MRSA pneumonia in the Middle East indicates a resource-intensive disease with a high LOS and mortality, consistent with other studies in high-income countries. Inappropriate/inactive therapy for MRSA nosocomial pneumonia was prescribed more than a quarter of the time over the entire course of therapy, and in first-line treatment was prescribed 42% of the time. The relatively high mortality rate in this study may have been influenced by the high proportion receiving suboptimal therapy as first-line treatment. In a multinational observational study in Asia and a randomized clinical trial in Canada, the frequency of prescribing inadequate initial antibiotic therapy in pneumonia may be >50%, and this significantly increases mortality rates.[13,14] MRSA-targeted antibiotics were more frequently prescribed in second-line (vancomycin 54%) and third-line (linezolid 51%) treatments. Potential reasons for the administration of inappropriate antibiotics may be due to lack of physician knowledge, delay in receiving culture results, or availability of medications that cover MRSA. While the exact reason for prescribing inappropriate antibiotics cannot be determined from this study, a body of literature has focused on inadequate initial therapy as a driver of added morbidity and mortality.[14,15]

Administration of inappropriate empiric antibiotic therapy can increase mortality in patients with hospital-acquired pneumonia (defined in this study as occurring within 48 hours of admission) and ventilator-associated pneumonia (VAP, defined as occurring within 48 hours of endotracheal intubation). Results from a prospective surveillance study conducted through the Asian Network for Surveillance of Resistant Pathogens (ANSORP) found that of the 15.8% of patients with *S. aureus* hospital-acquired pneumonia or VAP, 50.4% received discordant therapy.[13] Patients receiving discordant therapy had higher all-cause (44% vs 35%) and pneumonia-related (32% vs 21%) mortality than patients who received concordant therapy. Multivariate analysis results showed that discordant therapy was a risk factor for pneumonia-related mortality (OR, 1.542; 95% CI, 1.127–2.110; P=0.007).

Administration of inappropriate empiric antibiotic therapy can also increase mortality in patients with HCAP, defined as pneumonia in a patient admitted from a nursing home or other long-term care setting, who was hospitalized within

the last 12 months, receiving dialysis or infusion therapy requiring regular visits to a hospital-based clinic, or who is immunocompromised. In a US-based study, patients with HCAP compared to community acquired pneumonia had higher mortality (24.6% vs 9.1%, *P*<0.001) and were more likely to receive inappropriate antimicrobial treatment (28.3% vs 13.0%, *P*<0.001).[16] Mortality was higher for patients who received inappropriate compared to appropriate antibiotic therapy (32.2% vs 15.7%, *P*<0.001). Inappropriate initial antimicrobial therapy was identified as an independent risk factor for hospital mortality (OR, 2.19; 95% CI, 1.27–3.78; *P*<0.005).

Results from separate studies conducted at the same institution found that treatment escalation did not decrease mortality in patients with HCAP treated with inappropriate empiric antibiotic therapy[17] and that initial therapy for HCAP should include an antibiotic that targets MRSA.[16]

The resource use findings were quite disparate between countries in this study where the mean LOS was 30 days longer in Saudi Arabia than in Lebanon. It is unclear whether this difference results from an underlying disparity in the severity of infection between groups, or a difference in health-care infrastructure. A surveillance study in Saudi Arabia looking at 2,800 patients admitted to the medical-surgical intensive care unit suggests that long LOS is not uncommon for patients that are severely ill. They found that patients with VAP had a longer mean LOS of 85 days versus 61 days in those without VAP.[18] This population had primarily Gram-negative pneumonias, but 20% were attributed to Gram-positive infection.

The study is naturally limited by its retrospective design and reliance on data that are documented in the medical chart. Since inclusion criteria required that the patients were diagnosed with MRSA pneumonia, we do not have details on other patients that may have been colonized and not developed active infection. However, the information gathered from the charts represents a snapshot of the real-world treatment patterns and supplements the limited data we have in this indication and region of the world.

Conclusion

MRSA pneumonia in Saudi Arabia and Lebanon may be treated with antibiotics that are inactive against MRSA in a majority of patients for first-line therapy, resulting in an added resource use burden and mortality. The information gathered in this Middle East population provides important real-world perspectives on the current treatment patterns and opportunities to improve care. Future studies should more closely examine the appropriateness of initial therapy in MRSA pneumonia patients.

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