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Improved Survival with Initial MRSA Therapy in High-Risk Community-Onset Pneumonia Patients: Application of a MRSA Risk Score

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Improved Survival with Initial MRSA Therapy in High-Risk Community-Onset Pneumonia Patients: Application of a MRSA Risk Score

by

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Dedication

To my family- I will forever be grateful for your love, sacrifices, and never-ending belief in me. I am incredibly blessed for having each and every one of you in my life.

To my friends- you were there for me at my worst to lift my spirits and at my best to celebrate with me. This would not be possible if you were not there for me every step of the way.

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Abstract

Improved Survival with Initial MRSA Therapy in High-Risk Community-Onset Pneumonia Patients: Application of a MRSA Risk Score

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The University of Texas at Austin, 2014

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Community-onset (CO) methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia is an evolving problem, and there is a great need for a reliable method to assess MRSA risk at hospital admission. A new MRSA prediction score classifies CO-pneumonia patients into low, medium, and high-risk groups based on objective criteria available at baseline. Our objective was to assess the effect of initial MRSA therapy on mortality in these three risk groups.

We conducted a retrospective cohort study using data from the Veterans Health Administration. Patients were included if they were hospitalized with pneumonia and received antibiotics within the first 48 hours of admission. They were stratified into MRSA therapy and no MRSA therapy treatment arms based

on antibiotics received in the first 48 hours. MRSA risk groups were analyzed separately. The primary outcome was 30-day patient mortality. Multivariable logistic regression was used to adjust for potential confounders.

A total of 80,330 patients met inclusion criteria, of which 36% received MRSA therapy and 64% did not receive MRSA therapy. The majority of patients were classified as either low (51%) or medium (47%) risk, with only 2% classified as high-risk. In the high-risk group, unadjusted 30-day mortality was lower among patients who received initial MRSA therapy (40% versus 58%; $p<0.0001$). Likewise, multivariable logistic regression analysis also demonstrated that initial MRSA therapy was associated with a lower 30-day mortality in the high-risk group (adjusted odds ratio 0.57; 95% confidence interval 0.42-0.77). There was no benefit of initial MRSA therapy in the low or medium-risk groups.

This study demonstrated improved survival with initial MRSA therapy in high-risk CO-pneumonia patients. The MRSA risk score should not replace clinical judgment, but it might be a useful tool to spare MRSA therapy for only those patients who are most likely to benefit.

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CHAPTER ONE

Introduction

CO-MRSA Pneumonia

Pneumonia is a major cause of mortality in the United States, with a reported 49,597 deaths in 2010.[1] Community-onset (CO) pneumonia is defined as pneumonia that occurs in the community and up to 48 hours into hospital admission. It encompasses both community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP). HCAP patients are defined as those CO-pneumonia patients with one or more of the following risk factors: hospitalization for ≥2 days in the past 90 days, residence in a nursing home or long-term care facility, recent home infusion or wound care, chronic dialysis, or family member with a multidrug-resistant (MDR) pathogen. Importantly, HCAP patients are at increased risk of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia.[2,3] Lastly, MRSA pneumonia is associated with greater morbidity and mortality than pneumonia caused by other etiologies, possibly due to the virulent and resistant nature of the MRSA pathogen.[3] MRSA accounts for 20% to 40% of pneumonia cases that occur after 48 hours into hospital admission and 2% to 25% of CO cases overall.[3-7]

HCAP Criteria Guiding Empiric MRSA Therapy

Previous studies have demonstrated that rapid initiation of appropriate antibiotic therapy is associated with improved survival in hospitalized patients with infections;[8,9] therefore, there is a great need for a reliable method to assess CO-MRSA pneumonia risk at hospital admission. Guidelines recommend use of the HCAP criteria to determine need for empiric MRSA therapy, but this definition lacks specificity for CO-MRSA pneumonia and may lead to overuse of broad-spectrum antibiotic therapy.[2,10] Furthermore, prior studies have demonstrated that when HCAP patients received guideline-recommended, broad-spectrum therapy (including MRSA therapy), outcomes were no better than when similar patients received alternative antibiotics.[11,12]

HCAP Inappropriate for CO-MRSA Pneumonia

HCAP criteria assume that the risk factors for MRSA and gram-negative MDR pathogens are identical, and therefore recommend broad-spectrum antibiotics, including MRSA therapy, for all HCAP patients. This approach lacks specificity for CO-MRSA. CO-MRSA pneumonia has its own distinct risk factors that differ from gram-negative MDR risk factors; therefore, the HCAP criteria might be inadequate to determine which patients should receive empiric MRSA therapy.[13-15] Furthermore, there are several reports of severe CO-MRSA pneumonia from strains arising solely from the community and causing infection in patients without HCAP risk factors.[16-20] In this case, the HCAP criteria might

lack sensitivity for CO-MRSA. Guidelines have since been published regarding empiric therapy for CO-MRSA pneumonia in certain patients; however, these recommendations are mostly based on case studies and expert opinion.[21,22]

MRSA Risk Score

Guidance is needed for clinicians to identify those CO-pneumonia patients that might benefit from empiric MRSA therapy. Recently, Shorr et al. derived a clinical prediction score that stratified patients with CO-pneumonia by their MRSA risk.[23] The total score ranged from 0 to 10, and patients were stratified into low (0-1), medium (2-5), and high (6-10) risk groups. The CO-MRSA pneumonia prevalence increased from <10% in the low-risk group to >30% in the high-risk group. The authors concluded that this risk score could help identify those patients at low risk of MRSA, for which MRSA therapy could be spared. They postulated that patients in the high-risk group might benefit from MRSA therapy;[23] however, this has yet to be proven. A similar claim was made for the HCAP criteria;[2,4] yet, follow-up studies have failed to show a survival benefit with the broad-spectrum therapies recommended by the HCAP guidelines as compared to alternative therapies.[11,12]

MRSA Risk Score Requires Application

The new MRSA risk score could help guide empiric MRSA therapy; however, studies are needed to determine which, if any, of the MRSA risk groups

benefit from such therapy. Our primary objective was to compare the effect of MRSA therapy on 30-day patient mortality among CO-pneumonia patients in the three MRSA risk groups (low, medium, and high-risk).

CHAPTER TWO

Methods

Study Design

This study used administrative data from the Veterans Health Administration (VHA) database. Description of the methods used to build this database have been previously reported.[11,24,25] In brief, we performed a retrospective, population-based cohort study using administrative data from the VHA system between fiscal years 2002 and 2007. These data are from over 150 VHA hospitals and 850 VHA outpatient clinics. Data for this study were obtained from the VHA electronic medical record system that includes administrative, clinical, laboratory, and pharmacy data.

Patient Eligibility

Patients were included if they were ≥65 years of age and had either a primary discharge diagnosis of pneumonia/influenza (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 480.0–483.99 or 485–487) (Table 1) or a secondary discharge diagnosis of pneumonia/influenza plus a primary diagnosis of respiratory failure (ICD-9-CM code 518.81), or sepsis (ICD-9-CM code 038.xx) in fiscal years 2002 to 2007. If a patient was admitted more than once during the study period, only the first

hospitalization was included. Patients were excluded if they did not receive antimicrobial therapy within the first 48 hours of admission.

Table 1. ICD-9-CM Codes for Patient Variables and Bacterial Pathogens

Variable	**ICD-9-CM Codes**
Hemodialysis	403.01, 403.11, 403.91, 404.02, 404.12, 404.92, 404.93, 584, 585, 586
Invasive mechanical ventilation	96.7
Non-invasive mechanical ventilation	93.90, 93.91
Comorbid conditions	
Dementia	290
Myocardial infarction	410, 412
Congestive heart failure	428
Cerebrovascular disease	430-438
COPD	490-496, 500-505, 506.4
Liver disease	571.2, 571.4, 571.5, 571.6, 572.2-572.8, 456.0-456.21
Diabetes	250.0-250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9
Renal disease	582, 583, 585, 586, 588
Neoplastic disease	140-172, 174-208
HIV/AIDS	42-44, V08
Organ failure	
Respiratory	518.81, 518.82, 518.85, 518.89, 786.09, 799.1, 96.7
Cardiovascular	458.0, 458.8, 458.9, 785.5, 796.3
Neurologic	293, 348, 348.3, 780.01, 780.09, 89.14
Renal	580, 584, 585, 039.95
Hematologic	286.2, 286.6, 286.9, 287.3, 287.4, 287.5
Hepatic	570, 572.2, 573.3
Bacterial Pneumonia Pathogens	
Streptococcus pneumoniae	481
Streptococcus, other	482.30, 482.31, 482.32, 482.40
Staphylococcus, unspecified	482.40
Staphylococcus aureus	482.41
MRSA	V09.0
Klebsiella pneumoniae	482.0
Pseudomonas spp.	482.1
Haemophilus influenzae	482.2
Escherichia coli	482.82
Other gram-negative bacteria	482.83
Legionella spp.	482.84
Mycoplasma pneumoniae	483.0
Chlamydia spp.	483.1
Anaerobes	482.81

COPD: chronic obstructive pulmonary disease; HIV/AIDS: human immunodeficiency virus /acquired immunodeficiency syndrome; MRSA: methicillin-resistant *Staphylococcus aureus*

Baseline Characteristics

Baseline demographics and comorbid conditions were recorded at the time of admission. Antibiotic use was recorded for the first 48 hours of admission. Race was recorded for “white” or “black” patients. Native Americans, Hawaiians, and those with missing race information were stratified into an “other” category. Ethnicity was reported for patients who identified themselves as Hispanic. Comorbid conditions were determined using ICD-9-CM codes from outpatient and inpatient care in accordance with the Charlson comorbidity scoring system.[26,27] Medication use within 90 days of admission was identified for cardiovascular medications, anti-diabetic medications, inhaled and systemic corticosteroids, and pulmonary medications using electronic inpatient and outpatient medical records (Table 2). Finally, patients with hemodialysis, organ failure, and those requiring mechanical ventilation (invasive or non-invasive) were also identified using ICD-9-CM codes.

Table 2. List Of Medications Used Within 90 Days Of Admission, By Class

Drug Class	Medications
Cardiovascular medications	Aliskiren, ambrisentan, amiloride, amlodipine, atenolol, atorvastatin, benazepril, bendroflumethizide, bepridil, betaxolol, bisoprolol, bretylium, bumetanide, carteolol, carvedilol, chlorothiazide, chlorthalidone, clevidipine, clonidine, diazoxide, digoxin, diltiazem, disopyramide, dofetilide, doxazosin, eplerenone, epoprostenol, esmolol, ethacrynic acid, felodipine, fenoldopam, flecainide, furosemide, guanabenz, guanadrel, guanethidine, guanfacine, hydralazine, hydrochlorothiazide, ibutilide, iloprost, inamrinone, indapamide, isosorbide, isoxsuprine, isradipine, labetalol, mannitol, mecamylamine, methyclothiazide, methyldopa, metolazone, metoprolol, metyrosine, mexiletine, milrinone, minoxidil, moricizine, nadolol, nebivolol, nesiritide, nicardipine, nifedipine, nimodipine, nisoldipine, nitroglycerin, papaverine, penbutolol, perindopril, phentolamine, pindolol, polythiazide, prazosin, procainamide, propafenone, propranolol, quinidine, reserpine, sotalol, spironolactone, terazosin, timolol, tocainidine, tolazoline, torsemide, treprostinil, triamterene, trimethaphan, verapamil
Antidiabetic medications	Acarbose, chlorpropamide, exenatide, glimepiride, glipizide, glyburide, insulin, metformin, miglitol, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, sitagliptin, tolazamide, tolbutamide
Inhaled corticosteroids	Flunisolide, fluticasone, mometasone, triamcinolone
Systemic corticosteroids	Betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone
Pulmonary medications	Acetylcysteine, albuterol, aminophylline, arformoterol, beractant, bitolterol, caffeine, calfactant, cetyl alcohol, ciclesonide, colfosceril, cromolyn, dornase alfa, doxapram, formoterol, ipratropium, levalbuterol, metaproterenol, montelukast, nedocromil, nitric oxide, omalizumab, pirbuterol, poractant alfa, salmeterol, terbutaline, theophylline, tobramycin, tyloxapol, zafirlukast, zileuton

MRSA Risk Score

The MRSA risk score variables were defined as: patient age >79 years, hospitalization in the past 90 days, intensive care unit (ICU) admission, outpatient intravenous (IV) antibiotic therapy within the past 90 days, nursing home resident in the last 90 days, cerebrovascular disease, dementia, and female with diabetes mellitus. These were based on the MRSA risk score developed by Shorr et al. and modified for our database. All of our patients were ≥65 years of age, so the criteria related to age <30 years did not apply. Also, recent hospitalization was not limited to stays of ≥2 days, prior IV antibiotic therapy was extended from 30 to 90 days, and ICU admission was not limited to on or before index culture.[23] Each variable contributed one point to the risk score, except for hospitalization in the past 90 days and ICU admission, for which each contributed two points. Patients were stratified into three risk groups based on their risk score: low (0-1), medium (2-5), and high (6-10).[23]

Antibiotic Therapy and Pathogens

Patients who met study criteria were divided into two groups: the “MRSA therapy” group and the “no MRSA therapy” group. Initial MRSA therapy was defined as the receipt of either vancomycin or linezolid within the first 48 hours of admission. Patients were also categorized based on the receipt of guideline-concordant community-acquired pneumonia (GC-CAP) therapy,[21] pseudomonal therapy, and atypical therapy (Table 3). Pneumonia pathogens were identified

using ICD-9-CM codes: *Streptococcus pneumoniae, Streptococcus* other, *Staphylococcus aureus*, MRSA, *Klebsiella pneumoniae, Pseudomonas* spp.*, Escherichia coli, Haemophilus influenzae,* other Gram-negative pathogens, *Mycoplasma pneumoniae, Legionella* spp.*, Chlamydia* spp.*,* and anaerobes (Table 1).

Table 3. Antibiotic Therapy Definitions

MRSA therapy	
• Vancomycin • Linezolid	
Guideline-Concordant CAP therapy	
Ward patients • Beta-lactam[1] *plus* (macrolide or doxycycline) • Respiratory fluoroquinolone[2]	ICU patients • Beta-lactam[1] *plus* (macrolide or doxycycline) • Beta-lactam[1] *plus* respiratory fluoroquinolone[2]
Pseudomonal therapy	
• Antipseudomonal beta-lactam[3] *plus* antipseudomonal fluoroquinolone[4] • Antipseudomonal beta-lactam[3] *plus* aminoglycoside[5]	
Atypical therapy	
• Macrolide • Doxycycline • Any fluoroquinolone	

CAP: community-acquired pneumonia; ICU: intensive care unit
Macrolide includes azithromycin, clarithromycin, or erythromycin
[1]Beta-lactam includes cefotaxime, ceftriaxone, ampicillin-sulbactam, ertapenem, or aztreonam
[2]Respiratory fluoroquinolone includes moxifloxacin, levofloxacin, or gatifloxacin
[3]Antipseudomonal beta-lactam includes cefepime, ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanate, aztreonam
[4]Antipseudomonal fluoroquinolone includes ciprofloxacin or levofloxacin
[5]Aminoglycoside includes gentamicin, tobramycin, or amikacin

Primary Study Outcome

All-cause 30-day patient mortality was the primary study outcome. Previous research has demonstrated that 30-day mortality is more closely associated with pneumonia-related mortality, as compared to 60-day or 90-day mortality.[28] Mortality was assessed using the VHA vital status file, which has been demonstrated to have 98% exact agreement with the National Death Index, the "gold standard" to determine mortality.[29]

Statistical Analyses

All statistical analyses were conducted using JMP 10.0® (SAS Corp, Cary, NC). Chi-square or Fisher's exact test were used to compare categorical variables between patients who received MRSA therapy and did not receive MRSA therapy (Table 4). Continuous variables were compared using the Wilcoxon Rank Sum test (Table 4). For bivariate statistical tests, we defined significance as a two-tailed alpha ≤0.0001 to avoid spurious associations in this large patient cohort.

Separate multivariable logistic regression models were constructed to examine if MRSA therapy was associated with 30-day mortality in the overall population and each of the three MRSA risk groups. The dependent variable was 30-day patient mortality, and the independent variable was MRSA therapy versus no MRSA therapy. Covariates included all unbalanced characteristics from table 4. Because the dependent variable in the multivariable model was 30-day

mortality, baseline characteristics that were significant in the bivariate analysis comparing 30-day mortality versus no 30-day mortality were also included as covariates in the multivariable models (Table 5). Finally, MRSA culture-positivity was also entered into the model.

A few of the variables were then excluded from the model because of collinearity. For instance, most patients on hemodialysis also had renal failure; therefore, renal failure was chosen for the model. Likewise, most patients who had diabetes mellitus also received anti-diabetic medications; therefore, anti-diabetic medications was chosen for the model. The Charlson score and the "any organ failure" variables were excluded from the model because individual comorbidities and organ failures were already included in the model. Individual MRSA risk score variables were also excluded from the model because we ran separate multivariable models for the three risk groups, and these individual characteristics were used to define those risk groups.

The final list of 25 covariates included: patient age, race, Hispanic ethnicity, myocardial infarction, heart failure, chronic obstructive pulmonary disease (COPD), liver disease, renal disease, neoplastic disease, cardiovascular medications, anti-diabetic medications, inhaled corticosteroids, pulmonary medications, vasopressors, invasive and non-invasive mechanical ventilation, respiratory failure, cardiovascular failure, neurological failure, renal failure, hematological failure, hepatic failure, GC-CAP therapy, pseudomonal therapy, atypical therapy, and MRSA culture-positivity.

Adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) were calculated; those 95% CI that did not cross one were considered to be statistically significant. This was done for the overall population and each of the three risk groups.

Table 4. Baseline Characteristics Grouped by MRSA Therapy

	Overall (n=80,330)	**MRSA therapy (n=29,254)**	**No MRSA therapy (n=51,076)**	**P-value**
Patient age (years), median (IQR)	78 (72-83)	78 (73-83)	77 (72-83)	0.1016
Male, %	98.3	98.3	98.3	0.6847
Race, %				
White	81.1	79.1	82.3	<0.0001
Black	13.1	15.4	11.7	<0.0001
Other	5.8	5.5	6.0	<0.0001
Hispanic ethnicity, %	7.0	8.0	6.4	<0.0001
MRSA risk score variables, % (1 point, unless noted)				
Age >79	43.8	44.0	43.7	0.3867
Hospitalization in the past 90 days (2 points)	27.8	33.7	24.5	<0.0001
Intensive care unit admission (2 points)	21.1	29.3	16.4	<0.0001
Outpatient IV antibiotic therapy in past 90 days	4.9	5.3	4.7	0.0001
Nursing home resident in last 90 days	1.0	1.1	0.9	0.0028
Cerebrovascular disease	18.1	19.6	17.3	<0.0001
Dementia	5.2	5.8	4.9	<0.0001
Female with diabetes mellitus	0.4	0.4	0.4	0.8129
MRSA risk score, median (IQR)	1 (0-3)	2 (1-3)	1 (0-2)	<0.0001
Low (0-1), %	51.4	41.6	57.0	<0.0001
Medium (2-5), %	47.3	56.4	42.1	<0.0001
High (6-10), %	1.3	2.1	0.9	<0.0001
Charlson comorbidity score, median (IQR)	2 (1-4)	3 (1-4)	2 (1-4)	<0.0001
Comorbid conditions, %				
Myocardial infarction	7.2	7.6	7.0	0.0020
Heart failure	25.9	27.0	25.3	<0.0001
Chronic obstructive pulmonary disease	48.7	45.5	50.5	<0.0001
Liver disease	1.3	1.5	1.2	0.0035

Table 4, cont.

Renal disease	14.1	17.2	12.3	<0.0001
Diabetes	30.5	31.8	29.8	<0.0001
Neoplastic disease	25.2	26.2	24.7	<0.0001
HIV/AIDS	0.2	0.3	0.2	0.0961
Medication use within 90 days, %				
Cardiovascular medications	66.5	64.9	67.3	<0.0001
Anti-diabetic medications	22.2	22.6	22.1	0.0852
Inhaled corticosteroids	21.1	18.9	22.4	<0.0001
Systemic corticosteroids γ	22.2	21.8	22.5	0.0217
Pulmonary medications	34.8	31.4	36.8	<0.0001
Vasopressors, %	10.2	15.2	7.2	<0.0001
Invasive mechanical ventilation, %	11.1	16.3	8.2	<0.0001
Noninvasive mechanical ventilation, %	4.0	5.7	3.1	<0.0001
Hemodialysis, %	18.3	22.7	15.7	<0.0001
Organ failure, %				
Any organ failure, %	32.2	41.8	26.7	<0.0001
Respiratory	14.4	19.4	11.5	<0.0001
Cardiovascular	9.7	13.0	7.8	<0.0001
Neurological	2.5	3.3	2.0	<0.0001
Renal	20.1	26.8	16.2	<0.0001
Hematologic	4.1	5.5	3.3	<0.0001
Hepatic	0.7	0.9	0.6	<0.0001
Antibiotic therapy, %				
Guideline-concordant CAP therapy	64.1	64.9	63.6	0.0001
Pseudomonal therapy	17.5	31.1	9.7	<0.0001
Atypical therapy	75.2	83.6	70.5	<0.0001

MRSA: methicillin-resistant *Staphylococcus aureus;* IQR: interquartile range; IV: intravenous; HIV/AIDS: human immunodeficiency virus / acquired immunodeficiency syndrome:

γ Includes oral and/or injectable corticosteroids; CAP: community-acquired pneumonia

Table 5. Baseline Characteristics Grouped by 30-Day Patient Mortality

	Overall (n=80,330)	30-day mortality (n=15,909)	No 30-day mortality (n=64,421)	P-value
Patient age (years), median (IQR)	78 (72-83)	79 (74-84)	77 (72-82)	<0.0001
Male, %	98.3	98.5	98.2	0.0100
Race, %				
White	81.1	77.3	82.0	<0.0001
Black	13.1	14.9	12.6	<0.0001
Other	5.8	7.8	5.3	<0.0001
Hispanic ethnicity, %	7.0	7.9	6.8	<0.0001
MRSA risk score variables, % (1 point, unless noted)				
Age >79	43.8	51.0	42.0	<0.0001
Hospitalization in the past 90 days (2 points)	27.8	40.7	24.7	<0.0001
Intensive care unit admission (2 points)	21.1	42.0	16.0	<0.0001
Outpatient IV antibiotic therapy in past 90 days	4.9	6.0	4.7	<0.0001
Nursing home resident in last 90 days	1.0	0.8	1.0	0.0292
Cerebrovascular disease	18.1	20.0	17.7	<0.0001
Dementia	5.2	6.7	4.9	<0.0001
Female with diabetes mellitus	0.4	0.4	0.4	0.8881
MRSA risk score, median (IQR)	1 (0-3)	2 (1-2)	1 (0-2)	<0.0001
Low (0-1), %	51.4	28.4	57.1	<0.0001
Medium (2-5), %	47.3	68.4	42.1	<0.0001
High (6-10), %	1.3	3.25	0.9	<0.0001
Charlson comorbidity score, median (IQR)	2 (1-4)	3 (1-5)	2 (1-4)	<0.0001
Comorbid conditions, %				
Myocardial infarction	7.3	8.7	6.9	<0.0001
Heart failure	25.9	28.2	25.4	<0.0001
Chronic obstructive pulmonary disease	48.7	41.7	50.4	<0.0001
Liver disease	1.3	2.3	1.1	<0.0001

Table 5, cont.

Renal disease	14.1	16.7	13.4	<0.0001
Diabetes	30.5	30.3	30.5	0.5493
Neoplastic disease	25.2	31.1	23.8	<0.0001
HIV/AIDS	0.2	0.2	0.2	0.2145
Medication use within 90 days, %				
Cardiovascular medications	66.5	60.0	68.0	<0.0001
Anti-diabetic medications	22.2	20.0	22.8	<0.0001
Inhaled corticosteroids	21.1	14.8	22.7	<0.0001
Systemic corticosteroids γ	22.2	21.1	22.5	0.0002
Pulmonary medications	34.8	27.8	36.6	<0.0001
Vasopressors, %	10.2	26.9	6.0	<0.0001
Invasive mechanical ventilation, %	11.1	26.8	7.3	<0.0001
Noninvasive mechanical ventilation, %	4.0	7.1	3.3	<0.0001
Hemodialysis, %	18.3	23.5	17.0	<0.0001
Organ failure, %				
Any organ failure, %	32.2	57.8	25.9	<0.0001
Respiratory	14.4	32.6	9.9	<0.0001
Cardiovascular	9.7	22.1	6.7	<0.0001
Neurological	2.5	4.2	2.0	<0.0001
Renal	20.1	35.3	16.3	<0.0001
Hematologic	4.1	8.3	3.0	<0.0001
Hepatic	0.7	2.0	0.3	<0.0001
Antibiotic therapy, %				
MRSA therapy	36.4	42.9	34.8	<0.0001
Guideline-concordant CAP therapy	64.1	38.6	70.4	<0.0001
Pseudomonal therapy	17.5	23.8	15.9	<0.0001
Atypical therapy	75.2	54.3	80.4	<0.0001

MRSA: methicillin-resistant *Staphylococcus aureus;* IQR: interquartile range; IV: intravenous; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome

γ Includes oral and/or injectable corticosteroids; CAP: community-acquired pneumonia

CHAPTER THREE

Results

Overall Population

Baseline patient characteristics are shown in table 4. A total of 80,330 patients met inclusion criteria, with 36% in the MRSA therapy group and 64% in the no MRSA therapy group. Patients were predominately elderly (median age 78 years), white (81%) men (98%). Age >79 was the most common MRSA risk factor (44%), followed by hospitalization in the past 90 days (28%) and ICU admission (21%). There were very few women with diabetes mellitus (0.4%) in this population. The median MRSA risk score was 1 (interquartile range [IQR] 0–3). The majority of patients were classified as either low (51%) or medium (47%) risk, with only 2% classified as high-risk. None of the patients scored above an 8 on the MRSA risk score.

The median (IQR) Charlson score was 2 (1-4), and common comorbidities included COPD (49%), diabetes (31%), heart failure (26%), and neoplastic disease (25%). The most commonly used medications within 90 days prior to admission included cardiovascular medications (67%) and pulmonary medications (35%). Organ failure occurred in 32% of patients. Finally, most patients received atypical (75%) and GC-CAP (64%) therapy.

Baseline Characteristics: MRSA Therapy vs. No MRSA Therapy

Patient age and sex were similar between MRSA therapy and no MRSA therapy groups. A lower proportion of white patients received MRSA therapy (79% versus 82%), while higher proportions of black (15% versus 12%) and Hispanic (8% versus 6%) patients received MRSA therapy (all $p<0.0001$).

Among the MRSA risk factors, patients who received MRSA therapy had higher rates of hospitalization in the past 90 days (34% versus 25%), ICU admission (29% versus 16%), outpatient IV antibiotic therapy in the past 90 days (5.3% versus 4.7%), cerebrovascular disease (20% versus 17%), and dementia (6% versus 5%) (all $p\leq0.0001$). The proportions of patients with age >79 years, nursing home residence in the last 90 days, and women with diabetes mellitus were similar between groups.

Patients in the MRSA therapy group had higher MRSA risk scores compared to those in the no MRSA therapy group (median [IQR] 2 [1–3] versus 1 [0–2]; $p<0.0001$). Those in the MRSA therapy group were also more likely to be assigned to the medium (56% versus 42%) and high-risk (2% versus 1%) groups, whereas they were less likely to be assigned to the low-risk group (42% versus 57%) (all $p<0.0001$).

Charlson scores were higher in the MRSA therapy group (median [IQR] 3 [1–4] versus 2 [1–4]; $p<0.0001$) and these patients had a higher prevalence of heart failure, renal disease, diabetes, and neoplastic disease (all $p<0.0001$). In

addition, the MRSA therapy group had a higher prevalence of vasopressor use, mechanical ventilation, hemodialysis, organ failure, GC-CAP therapy, pseudomonal therapy, and atypical therapy (all $p \leq 0.0001$). In contrast, the no MRSA therapy group had a higher prevalence of COPD and were more likely to receive cardiovascular medications, inhaled corticosteroids, and pulmonary medications in the last 90 days (all $p < 0.0001$)

Bacterial Pathogens

The prevalence of bacterial pathogens is shown in table 6. *Staphylococcus aureus* was the most commonly isolated pathogen and the majority of those isolates were MRSA. *Streptococcus pneumoniae* was the second most common pathogen. The MRSA therapy group had more patients who were culture-positive and had higher rates of *Staphylococcus aureus*, MRSA, *Pseudomonas* spp., and most other gram-negative pathogens except for *Haemophilus influenzae.*

Table 6. Bacterial Pathogen Distribution Grouped by MRSA Therapy

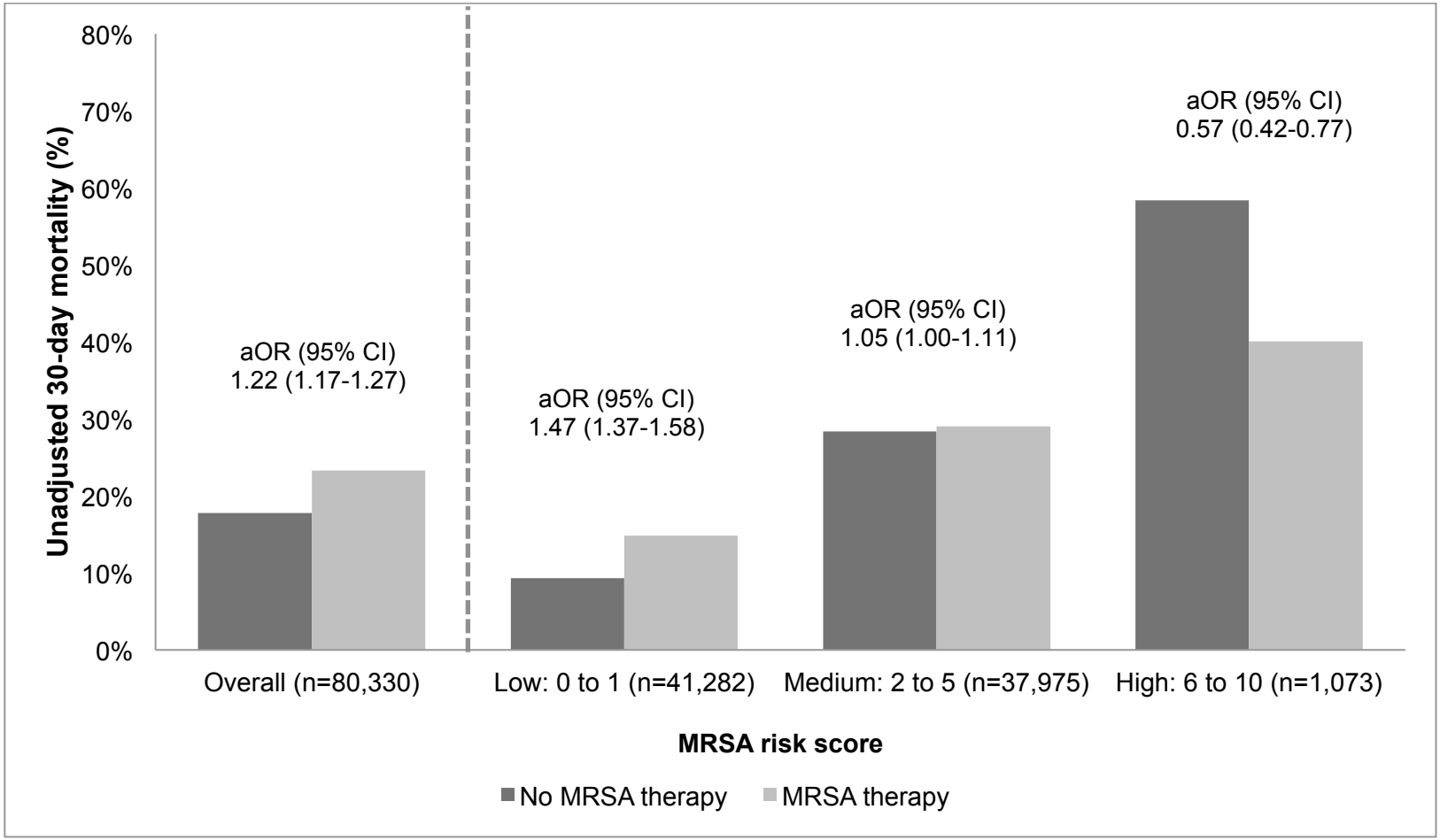
	Overall (n=80,330)	**MRSA therapy (n=29,254)**	**No MRSA therapy (n=51,076)**	**P-value**
Organism identified, %	10.3	13.9	8.2	<0.0001
Single organism identified	9.3	12.1	7.7	<0.0001
Multiple organisms identified	1.0	1.9	0.5	<0.0001
Gram-positive pathogens, %				
Streptococcus pneumoniae	2.8	2.7	2.9	0.0571
Streptococcus, other	0.4	0.5	0.4	0.0270
Staphylococcus aureus	5.1	8.7	3.1	<0.0001
MRSA	3.3	5.1	2.3	<0.0001
Gram-negative pathogens, %				
Klebsiella pneumoniae	0.7	1.0	0.6	<0.0001
Pseudomonas spp.	1.5	1.9	1.2	<0.0001
Haemophilus influenzae	0.8	0.5	0.9	<0.0001
Escherichia coli	0.2	0.4	0.2	<0.0001
Other gram-negatives	0.5	0.6	0.4	0.0007
Atypical pathogens, %				
Mycoplasma pneumoniae	< 0.1	< 0.1	0.1	0.0839
Legionella spp.	0.1	0.2	0.1	0.2029
Chlamydia spp.	< 0.1	< 0.1	< 0.1	0.7561
Anaerobes, %	0.1	0.1	0.1	0.0139

MRSA: methicillin-resistant *Staphylococcus aureus*

Patient Mortality

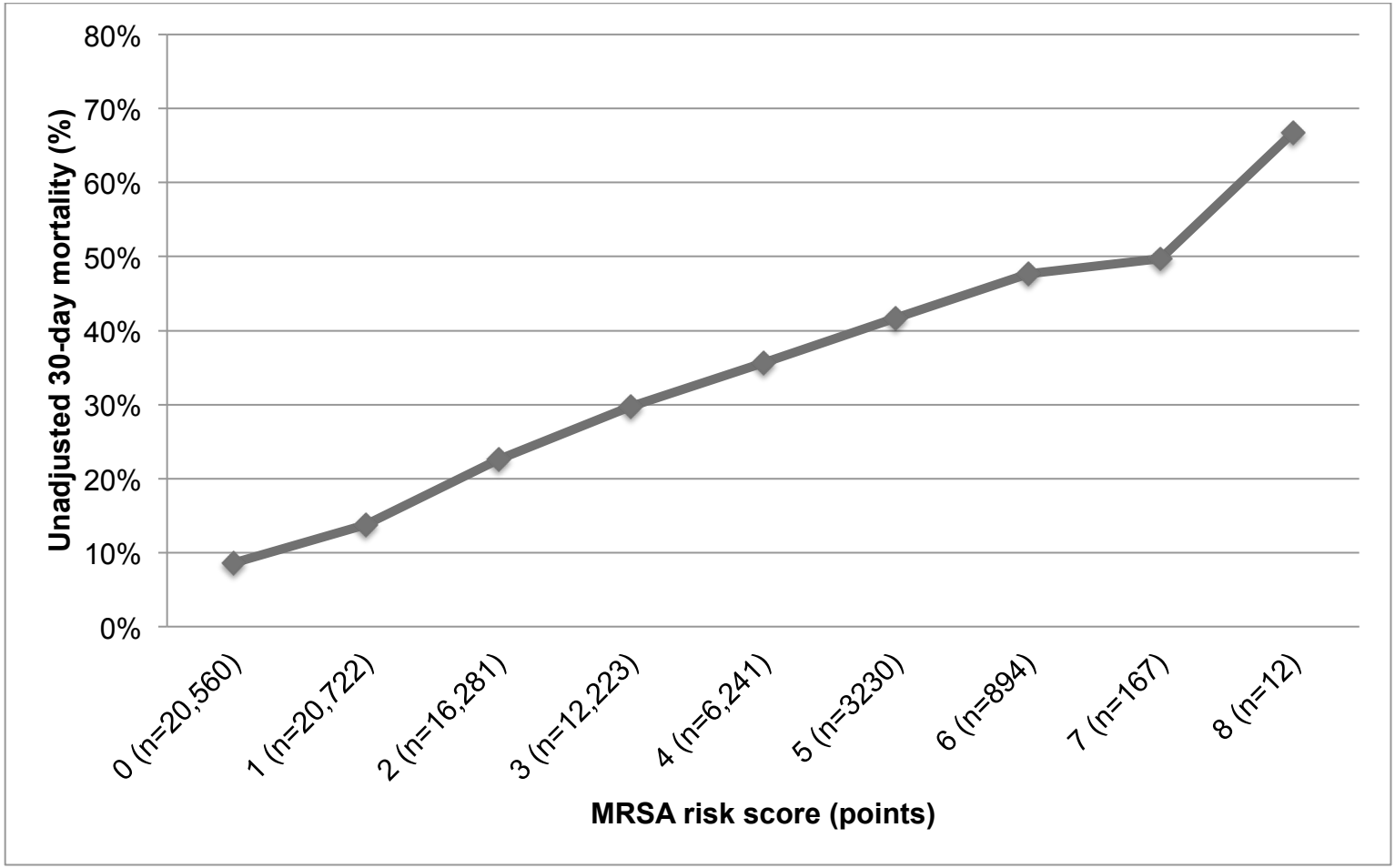
The overall 30-day patient mortality rate was 20%, and the unadjusted 30-day mortality increased from the low (11%), medium (27%), and high (48%) risk groups ($p<0.0001$). In the overall population, MRSA therapy was associated with a higher unadjusted 30-day mortality compared to the no MRSA therapy group (23% versus 18%; $p<0.0001$). Unadjusted 30-day mortality was higher among patients who received MRSA therapy in the low-risk group (15% versus 9%; $p<0.0001$), but lower in the high-risk group (40% versus 58%; $p<0.0001$), as compared to those who did not receive MRSA therapy (Figure 1). In addition, an increase in unadjusted 30-day mortality was observed with each additional point of the MRSA risk score (Figure 2). After adjustment for potential confounders, MRSA therapy was associated with higher 30-day mortality in the low-risk group (aOR 1.47; 95% CI 1.37-1.58) and lower 30-day mortality in the high-risk group (aOR 0.57; 95% CI 0.42-0.77) (Figure 1)

Figure 1. 30-Day Patient Mortality by MRSA Risk Group and MRSA Therapy



aOR: Adjusted Odds Ratio; 95% CI: 95% Confidence Interval; MRSA: methicillin-resistant *Staphylococcus aureus*

Figure 2. Unadjusted 30-Day Patient Mortality by MRSA Risk Score



MRSA: methicillin-resistant *Staphylococcus aureus*

Mortality Risk Factors

The multivariable regression analysis revealed several variables that were independently associated with 30-day mortality (Table 7). The strongest independent predictors of 30-day mortality in the overall population were hepatic failure (aOR 2.54; 95% CI 2.08-3.11) and respiratory failure (aOR 2.48; 95% CI 2.34-2.63). Other independent risk factors for 30-day mortality included increasing patient age, myocardial infarction, heart failure, liver disease, use of vasopressors, mechanical ventilation, any type of organ failure, and pseudomonal therapy. Cardiovascular medications, anti-diabetic medications, inhaled corticosteroids, GC-CAP therapy, and atypical therapy were associated with greater 30-day survival. Risk factors varied for low, medium, and high-risk groups (Table 7).

Table 7. Risk Factors for 30-Day Patient Mortality Grouped by MRSA Risk Score

	Adjusted Odds ratio (95% confidence interval)			
Risk score	**All (n= 80,330)**	**0-1 (n=41,282)**	**2-5 (n=37,975)**	**6-10 (n=1,073)**
MRSA therapy	**1.22 (1.17-1.27)**	**1.47 (1.37-1.58)**	1.05 (1.00-1.11)	**0.57 (0.42-0.77)**
Age (1-year increments)	**1.05 (1.04-1.05)**	**1.05 (1.05-1.06)**	**1.04 (1.03-1.04)**	**1.05 (1.02-1.08)**
Race	0.99 (0.94-1.05)	0.95 (0.86-1.06)	0.98 (0.91-1.05)	1.18 (0.85-1.64)
Hispanic ethnicity	**0.85 (0.79-0.92)**	**0.84 (0.73-0.96)**	**0.86 (0.79-0.95)**	0.79 (0.47-1.32)
Comorbid conditions				
Myocardial infarction	**1.14 (1.06-1.23)**	1.11 (0.94-1.30)	1.05 (0.97-1.14)	1.06 (0.74-1.51)
Heart failure	**1.16 (1.11-1.21)**	1.07 (0.97-1.17)	**1.11 (1.05-1.18)**	1.16 (0.88-1.53)
COPD	0.96 (0.91-1.00)	0.92 (0.85-1.00)	0.95 (0.89-1.01)	1.30 (0.96-1.77)
Liver disease	**1.79 (1.54-2.08)**	1.34 (0.97-1.87)	**1.80 (1.50-2.14)**	**3.46 (1.08-13.51)**
Renal disease	0.98 (0.93-1.04)	0.91 (0.81-1.02)	0.96 (0.90-1.03)	1.12 (0.83-1.53)
Neoplastic disease	**1.54 (1.47-1.60)**	**1.57 (1.46-1.69)**	**1.48 (1.40-1.56)**	1.18 (0.87-1.59)
Medication use, by class				
Cardiovascular medications	**0.72 (0.69-0.75)**	**0.60 (0.56-0.64)**	**0.78 (0.73-0.82)**	0.91 (0.66-1.24)
Anti-diabetic medications	**0.92 (0.87-0.96)**	**0.78 (0.71-0.86)**	0.95 (0.90-1.01)	0.95 (0.70-1.29)
Inhaled corticosteroids	**0.76 (0.72-0.81)**	**0.73 (0.65-0.81)**	**0.80 (0.74-0.86)**	1.13 (0.77-1.65)
Pulmonary medications	1.00 (0.94-1.05)	0.93 (0.85-1.03)	1.03 (0.97-1.11)	**0.68 (0.48-0.97)**
Vasopressors	**1.81 (1.70-1.93)**	**3.00 (2.49-3.61)**	**1.66 (1.55-1.79)**	**1.52 (1.12-2.04)**
Mechanical ventilation				
Invasive	**1.08 (1.01-1.16)**	**2.48 (1.98-3.10)**	1.02 (0.95-1.10)	0.92 (0.65-1.29)
Noninvasive	**1.16 (1.06-1.27)**	**2.03 (1.60-2.57)**	1.03 (0.94-1.13)	1.22 (0.80-1.86)
Organ failure				
Respiratory	**2.48 (2.34-2.63)**	**3.84 (3.45-4.29)**	**2.03 (1.90-2.18)**	**1.47 (1.06-2.04)**
Cardiovascular	**1.91 (1.80-2.02)**	**1.90 (1.68-2.15)**	**1.81 (1.69-1.94)**	**1.36 (1.02-1.82)**
Neurological	**1.53 (1.38-1.71)**	**1.64 (1.33-2.02)**	**1.40 (1.23-1.58)**	**1.92 (1.03-3.65)**
Renal	**1.58 (1.51-1.66)**	**1.77 (1.62-1.94)**	**1.46 (1.38-1.55)**	1.15 (0.87-1.51)
Hematologic	**1.65 (1.52-1.80)**	**1.97 (1.67-2.32)**	**1.53 (1.39-1.69)**	1.18 (0.73-1.90)

Table 7, cont.

Hepatic	**2.54 (2.08-3.11)**	**3.21 (2.05-5.00)**	**2.38 (1.90-2.99)**	0.66 (0.20-2.16)
Antibiotic therapy				
GC-CAP therapy	**0.67 (0.63-0.70)**	**0.60 (0.54-0.67)**	**0.73 (0.69-0.79)**	0.73 (0.50-1.08)
Pseudomonal therapy	**1.25 (1.19-1.32)**	**1.68 (1.53-1.85)**	1.05 (0.99-1.12)	0.76 (0.54-1.06)
Atypical therapy	**0.45 (0.43-0.48)**	**0.59 (0.53-0.66)**	**0.46 (0.43-0.49)**	0.75 (0.52-1.08)
MRSA	**0.66 (0.59-0.74)**	**0.58 (0.45-0.73)**	**0.66 (0.58-0.75)**	**0.56 (0.31-0.99)**

Bold indicates statistical significance; MRSA: methicillin-resistant *Staphylococcus aureus*; Race was ordered as black versus nonblack; COPD: Chronic obstructive pulmonary disease; GC-CAP: guideline-concordant community-acquired pneumonia

CHAPTER FOUR

Discussion

Summary

CO-MRSA pneumonia is an evolving problem, and clinicians need strategies to determine appropriate candidates for empiric MRSA therapy. Shorr et al. developed a risk score to specifically identify CO-pneumonia patients at risk for MRSA infection.[23] Using a MRSA risk score similar to Shorr et al., our study demonstrates a survival advantage for CO-pneumonia among high-risk patients who received initial MRSA therapy. This survival advantage was not present for patients in the low and medium-risk groups.

Clinical Implications

Our study supports the notion that the MRSA risk score might be a better alternative to guide empiric MRSA therapy in patients with CO-pneumonia as compared to the HCAP criteria. Several studies have demonstrated that the HCAP criteria have low specificity for MRSA pneumonia, and that grouping risk factors for MRSA with other gram-negative MDR pathogens may lead to inappropriate treatment.[10,13,30-32] Recently, Chalmers et al. conducted a meta-analysis of 24 studies that compared HCAP and CAP cohorts. The study concluded that the ability for the HCAP criteria to appropriately identify patients with MDR pathogens (including MRSA) was low and did not meet the threshold

for clinical use.[33] In addition, most studies evaluating the utility of HCAP criteria to guide broad-spectrum therapy, including MRSA therapy, have not demonstrated improved mortality with guideline-concordant therapy.[11,12]

One advantage of the MRSA risk score is weighting of important risk factors. The MRSA risk score assigns more weight (2 points each) to patients with recent hospitalization and severe pneumonia requiring ICU admission compared to the other risk factors (1 point each). In a recent study stratifying risk factors for MDR pathogens in CO-pneumonia patients, recent hospitalization and severe pneumonia were found to be independent predictors of mortality.[34] This highlights a key feature of the MRSA risk score, because patients with either of those two risk factors cannot be classified into the low-risk group. Recently, Minejima et al. compared a smaller cohort of CO-pneumonia patients with culture-proven MRSA pneumonia and non-MRSA pneumonia. They found 37% of patients with non-MRSA pneumonia met HCAP criteria and 28% received unnecessary MRSA therapy. Had the MRSA risk score been applied, unwarranted MRSA therapy could have been decreased by 20% in low-risk patients without MRSA pneumonia.[35] Our findings further support the idea that the new MRSA risk score can help identify low-risk CO-pneumonia patients who are unlikely to benefit from empiric MRSA therapy.

Our data also demonstrate the utility of the MRSA risk score to identify high-risk patients that are likely to benefit from initial MRSA therapy. CO-MRSA pneumonia has been associated with mortality rates of 22% to 51% among

inpatients.[3,19,36] In our study, patients stratified to the low-risk group had an overall 30-day mortality of 11%, which is similar to mortality rates in CAP patients from previous studies.[4-6] In contrast, patients in the high-risk group had the highest overall 30-day mortality at 48%, which is within the range of mortality rates previously reported for CO-MRSA pneumonia.[3,19,36] Importantly, 30-day mortality was decreased by 18% in our high-risk patients who received initial MRSA therapy as compared to those who did not receive initial MRSA therapy. The number needed to treat with initial MRSA therapy to save one life in the high-risk group was 5.

Notably, there are distinct differences between our study population and the study cohort used by Shorr et al. to derive the MRSA risk score. Our study included both culture-positive and culture-negative patients in the cohort, whereas the study by Shorr et al. was limited to culture-positive patients. We believe that our study population might be more generalizable because clinicians frequently do not know the pneumonia etiology at admission, if ever. CO-pneumonia studies using exclusively culture-positive cohorts tend to report higher MRSA prevalence (14% to 25%) compared to studies that include both culture-positive and culture negative-patients (2% to 3%).[4-7] This may help explain the difference in the overall MRSA prevalence between Shorr et al. and our study (14% versus 3%).[23] Culture-positive HCAP patients have been shown to have increased rates of ICU admission and mortality compared to culture-negative patients;[37] however, the majority of CO-pneumonia patients are culture-

negative, and clinicians often have to initiate antimicrobial therapy before obtaining culture data.[21] The inclusion of both culture-positive and culture-negative patients in our study allows for data that more closely resemble real-life situations. We used the MRSA risk score in a manner similar to widely accepted severity-of-illness scores (i.e., CURB-65), and we were able to demonstrate its utility for this purpose.

Limitations

While our study provides valuable data regarding the management of CO-MRSA pneumonia patients, it has some important limitations. First, several studies have identified risk factors associated with CO-MRSA pneumonia that were not included in the MRSA risk score. These include: MRSA infection in the past year, known MRSA colonization, necrotizing or cavitary pneumonia, severity-of-illness scores, and preceding or concurrent influenza.[15-22,35] Clinicians should utilize individual patient characteristics to help them in the decision to initiate MRSA therapy among all risk groups, especially those that fall into the medium-risk group where the benefit of initial MRSA therapy was inconclusive. Second, the data source included mostly males and only contained patients ≥65 years of age, limiting the generalizability of the results. This brings to light some inherent limitations of the risk score and its ability to be applied in various populations. Nevertheless, our results demonstrate the risk score still retains its clinical utility despite use of a population different from that which the risk score

was derived. We also attempted to account for potential confounders by using multivariable logistic regression models; however, this might not control for confounding by unmeasured variables. Lastly, the retrospective nature of our study and reliance on ICD-9-CM codes can possibly lead to confounding and misclassification bias.

CHAPTER FIVE

Conclusions

This study demonstrated the clinical utility of the MRSA risk score for CO-pneumonia patients by showing that 30-day mortality is lower in high-risk patients who receive initial MRSA therapy; however, this positive effect on mortality was not present in the low and medium-risk groups. The MRSA risk score should not replace clinical judgment, but it may be a useful tool to identify patients who do and do not warrant empiric MRSA therapy.

References

1. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. Natl Vital Stat Rep 2013;61:1-118.

2. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

3. Rubinstein E, Kollef MH, Nathwani D. Pneumonia caused by methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 2008;46:S378-S85.

4. Kollef MH, Shorr AF, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 2005;128:3854-62.

5. Micek ST, Kollef KE, Reichley RM, et al. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. Antimicrob Agents Chemother 2007;51:3568-73.

6. Chalmers JD, Taylor JK, Singanayagam A, et al. Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. Clin Infect Dis 2011;53:107-13.

7. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* as an etiology of community-acquired pneumonia. Clin Infect Dis 2012;54:1126-33.

8. Schramm GE, Johnson JA, Doherty JA, et al. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. Crit Care Med 2006;34:2069-74.

9. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237-48.

10. Schreiber M, Chan C, Shorr A. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia? Chest 2010;137:1283-8.

11. Attridge RT, Frei CR, Restrepo MI, et al. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. Eur Respir J 2011;38:878-87.

12. Grenier C, Pepin J, Nault V, et al. Impact of guideline-consistent therapy on outcome of patients with healthcare-associated and community-acquired pneumonia. J Antimicrob Chemother 2011;66:1617-24.

13. Shorr AF, Zilberberg MD, Micek ST, et al. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. Arch Intern Med 2008;168:2205-10.

14. Wooten DA, Winston LG. Risk factors for methicillin-resistant *Staphylococcus aureus* in patients with community-onset and hospital-onset pneumonia. Respir Med 2013;107:1266-70.

15. Jung WJ, Kang YA, Park MS, et al. Prediction of methicillin-resistant *Staphylococcus aureus* in patients with non-nosocomial pneumonia. BMC Infect Dis 2013;13:370.

16. Centers for Disease Control and Prevention. Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza--Louisiana and Georgia, December 2006-January 2007. MMWR Morb Mortal Wkly Rep 2007;56:325-9.

17. Francis JS, Doherty MC, Lopatin U, et al. Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. Clin Infect Dis 2005;40:100-7.

18. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003-04 influenza season. Emerg Infect Dis 2006;12:894-9.

19. Kallen AJ, Brunkard J, Moore Z, et al. *Staphylococcus aureus* community-acquired pneumonia during the 2006 to 2007 influenza season. Ann Emerg Med 2009;53:358-65.

20. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. Chest 2010;138:130-6.

21. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27-S72.

22. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:e18-e55.

23. Shorr AF, Myers DE, Huang DB, et al. A risk score for identifying methicillin-resistant *Staphylococcus aureus* in patients presenting to the hospital with pneumonia. BMC Infect Dis 2013;13:268.

24. Mortensen EM, Nakashima B, Cornell J, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. Clin Infect Dis 2012;55:1466-73.

25. Mortensen EM, Halm EA, Pugh MJ, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. JAMA 2014;311:2199-208.

26. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.

28. Mortensen EM, Coley CM, Singer DE, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 2002;162:1059-64.

29. Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006;4:2.

30. Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia. Curr Opin Infect Dis 2009;22:316-25.

31. Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? Curr Opin Infect Dis 2012;25:166-75.

32. Shorr AF, Zilberberg MD, Reichley R, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. Clin Infect Dis 2012;54:193-8.

33. Chalmers JD, Rother C, Salih W, et al. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clin Infect Dis 2014;58:330-9.

34. Aliberti S, Di Pasquale M, Zanaboni AM, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. Clin Infect Dis 2012;54:470-8.

35. Minejima E, Lou M, Nieberg P, et al. Patients presenting to the hospital with MRSA pneumonia: differentiating characteristics and outcomes with empiric treatment. BMC Infect Dis 2014;14:252.

36. Taneja C, Haque N, Oster G, et al. Clinical and economic outcomes in patients with community-acquired *Staphylococcus aureus* pneumonia. J Hosp Med 2010;5:528-34.

37. Labelle AJ, Arnold H, Reichley RM, et al. A comparison of culture-positive and culture-negative health-care-associated pneumonia. Chest 2010;137:1130-7.

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