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Predictors of Clinical Success Among a National Veterans Affairs Cohort with Methicillin-Resistant *Staphylococcus aureus* Pneumonia

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Running head: Predictors of MRSA Pneumonia Treatment Success

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ABSTRACT

Background: The treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia is exceedingly complicated, which is concerning because of the high mortality rate associated with the infection. Identification of independent predictors of clinical success can optimize patient care by assisting clinicians in treatment decisions.

Objectives: We sought to identify independent predictors of clinical success in a national Veterans Affairs (VA) cohort of MRSA pneumonia patients.

Methods: A nested case-control study was conducted among a cohort of VA patients with MRSA pneumonia receiving linezolid or vancomycin between January 2002 and September 2010. Cases included those demonstrating clinical success, defined as discharge from the hospital or intensive care unit (ICU) by day 14 after treatment initiation, in the absence of death, therapy change, or intubation by day 14. Controls represented non-success, defined as therapy change, intubation, ICU admission, re-admission, or death between treatment initiation and day 14. The potential predictors assessed included treatment, patient demographics and admission characteristics, previous healthcare and medication exposures, comorbidities, and medical history. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression.

Results: Our study included 2442 cases of clinical success and 1290 controls. Demographics varied between the clinical success and non-success groups, including age, race, and region of facility. A current diagnosis of chronic respiratory disease (46% vs 42%) and diagnosis of pneumonia in the year prior to the MRSA pneumonia admission (37% vs 32%) were both more common in the clinical success group. Despite these significant differences, only two predictors of clinical success were identified in our study: previous complication of an implant or graft, including mechanical complications and infections, in the year prior to the MRSA pneumonia admission (OR, 1.55; 95% CI, 1.17–2.06) and treatment with linezolid (1.53; 1.12–2.10). Predictors of non-success included concomitant urinary tract infection diagnosis

(OR, 0.82; 95% CI, 0.70–0.96), intravenous line (0.76; 0.66–0.89), previous coagulopathy (0.74; 0.56–0.96), previous amputation procedure (0.72; 0.53–0.98), current coagulopathy diagnosis (0.71; 0.53–0.96), dialysis (0.54; 0.38–0.76), multiple inpatient procedures (0.53; 0.45–0.62), inpatient surgery (0.48; 0.41–0.57), and previous endocarditis (0.24; 0.07–0.81).

Discussion: MRSA pneumonia tends to affect complex patients, and identification of the predictors of clinical success is useful when considering different therapeutic approaches.

Conclusions: In a national cohort of VA patients with MRSA pneumonia, treatment was the only modifiable variable predicting clinical success.

Key words: predictors of clinical success, linezolid, vancomycin, methicillin-resistant *Staphylococcus aureus*, pneumonia.

INTRODUCTION

Pneumonia is the leading cause of infectious disease-related deaths in the United States.¹ A prominent pathogen causing pneumonia in both healthcare and community settings is methicillin-resistant *Staphylococcus aureus* (MRSA).² In recent years, rates of community-associated MRSA pneumonia have been steadily increasing, while MRSA was also becoming a leading cause of healthcare-associated pneumonia, including ventilator-associated pneumonia (VAP).^{3,4}

Limited options exist for the treatment of MRSA pneumonia. Vancomycin has been the mainstay of treatment for MRSA infections for years, however rates of treatment failure for pneumonia as high as 40% have been reported.⁵ Linezolid is a well-studied alternative to vancomycin that has been available for more than 10 years. Several studies have demonstrated clinical equivalence between the 2 drugs,⁶⁻⁹ but some data suggest a significant benefit for linezolid compared with vancomycin for the treatment of pneumonia.¹⁰⁻¹² Currently, both drugs are recommended as first-line options for the treatment of MRSA pneumonia.²

In addition to treatment-related factors, host and pathogen characteristics can affect clinical outcomes for patients with MRSA pneumonia. For example, age, underlying comorbidities, severity of illness, multiple lobe involvement, and need for intensive care unit (ICU) admission have been associated with poor clinical outcomes.^{9-11,13,14} There are multiple differences among MRSA strains on a molecular level, including staphylococcal cassette chromosome *mec* (SCC*mec*) type, presence of the toxin Panton-Valentine leukocidin, and minimum inhibitory concentration, which can affect clinical outcomes.¹⁴⁻¹⁶

MRSA pneumonia is a complex disease associated with significant morbidity and mortality. Despite the large public health impact of MRSA pneumonia, there are limited published data examining clinical predictors of success or failure. Identification of independent predictors of clinical success could optimize patient care by assisting clinicians in treatment

decisions. It was therefore the aim of this study to identify independent predictors of clinical success among a national Veterans Affairs (VA) cohort of MRSA pneumonia patients.

METHODS

The study design and methods were defined *a priori* in the study protocol, which was reviewed and approved by the Institutional Review Board and Research and Development Committee of the Providence Veterans Affairs Medical Center.

Data Sources

The Veterans Health Administration has utilized an electronic medical record system since 1999. Our study included national standardized databases capturing patient care: International Classification of Diseases, 9th Revision (ICD-9) diagnostic and procedure codes, pharmacy records for prescriptions, laboratory tests, select laboratory results, mortality, and patient vital signs.^{17,18}

Patient Population and Study Design

Our nested case-control study was conducted among an original cohort of patients admitted to VA hospitals between January 1, 2002, and September 30, 2010, with an ICD-9 code for MRSA (038.12, 041.12, 482.42, V09.0) and pneumonia (482.40-482.42, 482.49, 482.89, 482.9, 484.8, 485-486, 510.0, 510.9, 513.0-513.1).¹⁹ Patients aged 18 years or older were selected for inclusion if they were initiated on linezolid or vancomycin during the admission, in the absence of linezolid or vancomycin therapy in the 7 days prior to the hospitalization, with at least 3 days of therapy dosed per hospital protocol. Patients were excluded if they died or were discharged within 3 days of treatment initiation, were initiated on vancomycin or linezolid in the nursing home before their hospital admission, or were exposed to

more than 2 consecutive days of anti-MRSA antibiotics in the 3 days before treatment initiation or during treatment with linezolid or vancomycin. Only the first admission within the study period meeting all inclusion and exclusion criteria was included.

To identify independent predictors of clinical success among our MRSA pneumonia cohort, we identified cases of clinical success and a non-success control group. Clinical success was defined as discharge from the hospital and/or from the ICU by day 14 after treatment initiation, in the absence of therapy change, intubation, admission to the ICU, re-admission, and/or death by day 14.¹⁹ Non-success was defined as therapy change, intubation, ICU admission, discharge and readmission, or death between treatment initiation and day 14.¹⁹ Day 14 was chosen to replicate the average end-of-treatment time frame from existing linezolid and vancomycin clinical trials.^{6,7,12} Our definition of clinical success was defined a priori based on recently published clinical trials utilizing clinical outcomes available from our data source.^{6,7,12}

Independent Predictors

The potential predictors assessed included treatment (linezolid or vancomycin), patient demographics and admission characteristics, comorbidities and medical history, vital signs and laboratory results, previous surgeries and procedures, previous healthcare exposures, and previous medication exposures.¹⁹ To identify comorbidities and medical history, including site-specific and organism-specific infections in the year before admission, ICD-9 diagnosis and procedure codes from inpatient and outpatient records were utilized.¹⁸ Surgeries, procedures, and radiologic examinations during the admission were identified using ICD-9 diagnosis and procedure codes. Hospital admissions, surgeries, and nursing home or extended-care stays were evaluated from 5 non-mutually exclusive time periods (30 days, 60 days, 90 days, 180 days, 365 days) to identify previous healthcare exposures. Previous antibiotic and immunosuppressant exposures during the 90 days before admission were identified from inpatient and outpatient prescription records.

Statistical Analysis

Between-group differences were assessed using a χ^2 or Fisher's exact test for categorical covariates and the *t*-test or Wilcoxon rank-sum test for continuous variables, as appropriate. An unconditional logistic regression model was developed to identify independent predictors associated with clinical success using a manual backward, non-computer-generated, elimination approach.²⁰ We report unadjusted and multivariable adjusted odds ratios (ORs) for each predictor, including their respective 95% confidence intervals (CIs). All analyses were performed using SAS (SAS Institute Inc., Cary, NC, Version 9.1.3).

RESULTS

Our study included 2442 cases of clinical success and 1290 non-success controls. There were significant differences in demographics between the clinical success and non-success groups, including age and race (**Table I**). Patients in the clinical success group were older than patients in the non-success group (mean age 69.5 ± 12.6 years vs 68.5 ± 12.0 years, $P < 0.05$). White patients made up a larger proportion of the clinical success group than the non-success group (81.7% vs 79.1%, $P < 0.05$). Several significant differences in comorbidities were also observed between groups, including less frequent peripheral vascular disease, coagulopathy, and dialysis and more frequent chronic respiratory disease among patients experiencing clinical success. In addition, patients with clinical success were less likely to have an intravenous line or current complication of an implant or graft and were less likely to be in a surgical unit at treatment initiation.

Treatment with linezolid was more common in the clinical success group (6.8% vs 5.0%, $P < 0.05$), as shown in **Table II**. Other differences between cases and controls included shorter length of therapy and a larger proportion of subjects with pneumonia infections or previous implant or graft in the last year among those with clinical success.

Statistically significant predictors of clinical success, as compared with non-success, are shown in **Table III**. In the adjusted logistic regression model, 2 independent predictors of clinical success were identified: previous complication of an implant or graft, including mechanical complications and infections, in the year prior to the MRSA pneumonia-related admission (adjusted OR, 1.55; 95% CI, 1.17–2.06) and treatment with linezolid (1.53; 1.12–2.10). Predictors with Odds Ratios <1, and as such associated with non-success, included concomitant urinary tract infection diagnosis (adjusted OR, 0.82; 95% CI, 0.70–0.96), intravenous line during the current MRSA pneumonia admission (0.76; 0.66–0.89), coagulopathy in the year prior to the MRSA pneumonia admission (0.74; 0.56–0.96), previous amputation procedure (0.72; 0.53–0.98), current coagulopathy diagnosis (0.71; 0.53–0.96), current dialysis (0.54; 0.38–0.76), 3 or more inpatient procedures (0.53; 0.45–0.62) or inpatient surgery (0.48; 0.41–0.57) during the current MRSA pneumonia admission, and previous endocarditis (0.24; 0.07–0.81).

DISCUSSION

In our study, the only modifiable variable predicting clinical success among patients with MRSA pneumonia was linezolid treatment. Clinical success was 1.53 times more likely among patients treated with linezolid compared with those treated with vancomycin. Two earlier retrospective post hoc studies demonstrated, in subgroup analyses, that treatment with linezolid (vs vancomycin) was an independent predictor of clinical cure for MRSA pneumonia (OR, 3.3; 95% CI, 1.3–8.3, $P = 0.01$) and MRSA VAP (OR, 20.0; 95% CI, 4.3–92.0, $P < 0.001$).^{10,11} Limitations of these studies include their post hoc design, subgroup analyses, and lack of vancomycin dose optimization.

Several studies have evaluated the comparative clinical efficacy of linezolid and vancomycin with conflicting results. In contrast to our findings, numerous randomized trials have demonstrated no difference in clinical cure rates for the treatment of nosocomial pneumonia

when comparing linezolid and vancomycin.^{6-9,21} Moreover, in 2 meta-analyses, linezolid treatment for nosocomial pneumonia was not associated with clinical superiority over glycopeptides (vancomycin or teicoplanin).^{22,23}

The few trials that support our finding of more frequent clinical success associated with linezolid treatment have been criticized for methodological and statistical flaws.^{11,12,24-31} One of these studies, a recent randomized controlled trial, demonstrated higher clinical success associated with linezolid versus vancomycin in the treatment of MRSA pneumonia.¹² In this study, 57.6% (95/165) of linezolid patients and 46.6% (81/174) of vancomycin patients achieved clinical success (95% CI for the difference, 0.5%–21.6%, $P = 0.042$). However, questions regarding vancomycin dose optimization remain, since median trough levels of vancomycin fell below the Infectious Diseases Society of America's recommendations in that trial.² Several retrospective studies have developed algorithms to evaluate clinical success or failure related to MRSA pneumonia.³²⁻³⁴ Our study further adds to this developing literature by assessing a large national cohort of patient with MRSA pneumonia using objective clinical outcomes.

It is unclear why a previous complication of an implant or graft was associated with clinical success in our study. Complications included a range of conditions, such as mechanical complications, infections, or other non-specified complications of medical devices, implants, or grafts.¹⁸ One possible explanation is that this specific medical history could have prompted more aggressive measures to improve the likelihood of clinical success. If this were the case, our findings suggest that MRSA pneumonia patients with previous endocarditis, coagulopathy, and amputation procedures in the year prior to admission may also benefit from additional efforts to improve clinical success.

There are multiple limitations to our study. First, it should be noted that our definition of clinical success varies from those of the aforementioned clinical trials, which affects our ability to make direct comparisons. However, our definition was determined by objective criteria of clinical outcomes rather than clinical judgment as used in those trials. Other limitations include our

retrospective design and use of diagnosis codes to identify MRSA pneumonia. There may be variations in coding practices across institutions, and the MRSA coding can be discordant with culture-confirmed MRSA.³⁵ Furthermore, we were unable to molecularly classify the MRSA isolates; molecular differences in MRSA strains have been shown to affect clinical results.¹⁴⁻¹⁶ Susceptibility data and trough data were not available, and therefore it is not known if subjects reached therapeutic levels of the treatment agent.

In summary, clinical success in our study was 53% higher among MRSA pneumonia patients treated with linezolid compared with those treated with vancomycin. Previous complication of an implant or graft in the year prior to the MRSA pneumonia-related admission was also a predictor of clinical success. In addition, concomitant urinary tract infection, intravenous line, previous coagulopathy, previous amputation procedure, current coagulopathy, dialysis, 3 or more inpatient procedures, inpatient surgery, and previous endocarditis were associated with lower odds of clinical success. This study helps to identify patients who may have additional complexities owing to comorbid conditions or medical history and who may benefit from alterations in treatment regimen or require additional attention. Treatment was the only modifiable predictor of clinical success in our study. These findings, based on existing national health data, support the results of previous studies and can assist clinicians in managing patients with MRSA pneumonia.

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CONFLICTS OF INTEREST

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Table I. Demographics, hospitalization-related characteristics, and comorbidities by clinical success.

Potential Predictors	Clinical Success (n = 2442)	Clinical Non-success (n = 1290)
Age (years), mean (SD)*	69.5 (12.6)	68.5 (12.0)
Male gender, n (%)	2401 (98.3)	1263 (97.9)
Race, n (%)*		
White	1996 (81.7)	1021 (79.1)
Other/unknown	446 (18.3)	269 (20.9)
Admission source		
Home	919 (37.6)	462 (35.8)
Emergency room	1071 (43.9)	588 (45.6)
Hospital	150 (6.1)	83 (6.4)
Nursing home	302 (12.4)	157 (12.2)
Unit at treatment initiation*		
Intensive care	1042 (42.7)	544 (42.2)
Surgery	121 (5.0)	91 (7.1)
General medicine	1279 (52.4)	655 (50.8)
Treating specialty		
Intensive care	953 (39.0)	519 (40.2)
Surgery	78 (3.2)	54 (4.2)
General medicine	1411 (57.8)	717 (55.6)
Region of facility*		
North	320 (13.1)	169 (13.1)
South	1056 (43.2)	620 (48.1)
Midwest	512 (21.0)	243 (18.8)
West	554 (22.7)	258 (20.0)
Charlson comorbidity index, median (IQR)*	2 (1-4)	2 (1-4)
Comorbid conditions, n (%)		
Chronic respiratory disease*	1123 (46.0)	536 (41.6)
Renal disease	364 (14.9)	219 (17.0)
Dialysis*	68 (2.8)	87 (6.7)
Diabetes	778 (31.9)	419 (32.5)
Heart failure	608 (24.9)	334 (25.9)
Coronary heart disease	596 (24.4)	296 (22.9)
Cancer	430 (17.6)	247 (19.1)
Amputation*	59 (2.4)	51 (4.0)
Cerebrovascular disease	215 (8.8)	123 (9.5)
Peripheral vascular disease*	148 (6.1)	111 (8.6)
Moderate or severe liver disease	43 (1.8)	30 (2.3)
HIV/AIDS	25 (1.0)	16 (1.2)
Coagulopathy*	109 (4.5)	93 (7.2)
Peripheral line*	804 (32.9)	622 (48.2)
Complication of implant or graft*	153 (6.3)	127 (9.8)
Urinary tract infection*	616 (25.2)	377 (29.2)
Bacteremia	475 (19.5)	263 (20.4)
Skin infection	560 (22.9)	323 (25.0)

SD = standard deviation; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*.
* $P < 0.05$.

Table II. Previous infections, healthcare and medication exposures by clinical success.

Potential Predictors	Clinical Success (n = 2442), n (%)	Clinical Non-success (n = 1290), n (%)
Treatment*		
Linezolid	167 (6.8)	64 (5.0)
Vancomycin	2275 (93.2)	1226 (95.0)
Length of therapy, days, median (IQR)*	7 (5-10)	6 (4-12)
Previous hospitalization last year	1682 (68.9)	866 (67.1)
Previous hospitalization last 90 days	1256 (51.4)	655 (50.8)
Previous hospitalization last 30 days	929 (38.0)	497 (38.5)
Previous surgery last year	496 (20.3)	277 (21.5)
Previous surgery last 90 days	256 (10.5)	146 (11.3)
Previous surgery last 30 days	117 (4.8)	72 (5.6)
Previous procedure last year	1468 (60.1)	778 (60.3)
Previous procedure last 90 days	983 (40.3)	539 (41.8)
Previous procedure last 30 days	608 (24.9)	350 (27.1)
Previous anti-MRSA antibiotics last 90 days	1108 (45.4)	563 (43.6)
Previous immunosuppressants last 90 days	60 (2.5)	39 (3.0)
Previous corticosteroids last 90 days	631 (25.8)	311 (24.1)
Previous infections last year		
Pneumonia [†]	910 (37.3)	418 (32.4)
Skin or subcutaneous tissue infection [†]	720 (29.5)	403 (31.2)
Bacteremia [†]	159 (6.5)	77 (6.0)
Urinary tract infection [†]	592 (24.2)	302 (23.4)
Osteomyelitis [†]	86 (3.5)	58 (4.5)
MRSA	290 (11.9)	160 (12.4)
<i>Pseudomonas aeruginosa</i>	120 (4.9)	58 (4.5)
Previous complication of implant or graft last year*	205 (8.4)	81 (6.3)

IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*.

* $P < 0.05$.

[†]Attributed to any organism.

Table III. Independent predictors of clinical success.

Predictors	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Previous complication of an implant or graft Treatment (linezolid vs vancomycin)	1.37 (1.05–1.79)	1.55 (1.17–2.06)
Urinary tract infection	0.82 (0.70–0.95)	0.82 (0.70–0.96)
Peripheral line	0.53 (0.46–0.61)	0.76 (0.66–0.89)
Previous coagulopathy	0.72 (0.56–0.92)	0.74 (0.56–0.96)
Previous amputation procedure	0.71 (0.53–0.94)	0.72 (0.53–0.98)
Coagulopathy	0.60 (0.45–0.80)	0.71 (0.53–0.96)
Dialysis	0.40 (0.29–0.55)	0.54 (0.38–0.76)
Inpatient procedures, 3 or more	0.40 (0.35–0.46)	0.53 (0.45–0.62)
Inpatient surgery	0.38 (0.33–0.45)	0.48 (0.41–0.57)
Previous endocarditis	0.23 (0.07–0.76)	0.24 (0.07–0.81)