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Empirical Anti-MRSA vs Standard Antibiotic Therapy and Risk of 30-Day Mortality in Patients Hospitalized for Pneumonia

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IMPORTANCE Use of empirical broad-spectrum antibiotics for pneumonia has increased owing to concern for resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). The association of empirical anti-MRSA therapy with outcomes among patients with pneumonia is unknown, even for high-risk patients.

OBJECTIVE To compare 30-day mortality among patients hospitalized for pneumonia receiving empirical anti-MRSA therapy vs standard empirical antibiotic regimens.

DESIGN, SETTING, AND PARTICIPANTS Retrospective multicenter cohort study was conducted of all hospitalizations in which patients received either anti-MRSA or standard therapy for community-onset pneumonia in the Veterans Health Administration health care system from January 1, 2008, to December 31, 2013. Subgroups of patients analyzed were those with initial intensive care unit admission, MRSA risk factors, positive results of a MRSA surveillance test, and positive results of a MRSA admission culture. Primary analysis was an inverse probability of treatment–weighted propensity score analysis using generalized estimating equation regression; secondary analyses included an instrumental variable analysis. Statistical analysis was conducted from June 14 to November 20, 2019.

EXPOSURES Empirical anti-MRSA therapy plus standard pneumonia therapy vs standard therapy alone within the first day of hospitalization.

MAIN OUTCOMES AND MEASURES Risk of 30-day all-cause mortality after adjustment for patient comorbidities, vital signs, and laboratory results. Secondary outcomes included the development of kidney injury and secondary infections with *Clostridioides difficile*, vancomycin-resistant *Enterococcus* species, or gram-negative bacilli.

RESULTS Among 88 605 hospitalized patients (86 851 men; median age, 70 years [interquartile range, 62-81 years]), empirical anti-MRSA therapy was administered to 33 632 (38%); 8929 patients (10%) died within 30 days. Compared with standard therapy alone, in weighted propensity score analysis, empirical anti-MRSA therapy plus standard therapy was significantly associated with an increased adjusted risk of death (adjusted risk ratio [aRR], 1.4 [95% CI, 1.3-1.5]), kidney injury (aRR, 1.4 [95% CI, 1.3-1.5]), and secondary *C difficile* infections (aRR, 1.6 [95% CI, 1.3-1.9]), vancomycin-resistant *Enterococcus* spp infections (aRR, 1.6 [95% CI, 1.0-2.3]), and secondary gram-negative rod infections (aRR, 1.5 [95% CI, 1.2-1.8]). Similar associations between anti-MRSA therapy use and 30-day mortality were found by instrumental variable analysis (aRR, 1.6 [95% CI, 1.4-1.9]) and among patients admitted to the intensive care unit (aRR, 1.3 [95% CI, 1.2-1.5]), those with a high risk for MRSA (aRR, 1.2 [95% CI, 1.1-1.4]), and those with MRSA detected on surveillance testing (aRR, 1.6 [95% CI, 1.3-1.9]). No significant favorable association was found between empirical anti-MRSA therapy and death among patients with MRSA detected on culture (aRR, 1.1 [95% CI, 0.8-1.4]).

CONCLUSIONS AND RELEVANCE This study suggests that empirical anti-MRSA therapy was not associated with reduced mortality for any group of patients hospitalized for pneumonia. These results contribute to a growing body of evidence that questions the value of empirical use of anti-MRSA therapy using existing risk approaches.

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Editorial
Supplemental content

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Pneumonia is the leading cause of death from infection in the United States,[1] and timely empirical antibiotic therapy against the most likely pathogens is a cornerstone of care. However, causative pathogens are rarely identified,[2] leaving uncertainty in the choice of empirical antibiotic therapy. For patients hospitalized for community-onset pneumonia, this uncertainty has been magnified by the emergence of resistant organisms, chiefly methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. The concept of health care–associated pneumonia, intended to assist clinicians in risk assessment,[3] likely contributed to the overuse of broad-spectrum antibiotics.[4,5] Consequently, although fewer than 5% of hospitalized patients have resistant organisms detected, more than one-third receive broad-spectrum antibiotics.[6]

Efforts to enhance clinical prediction of resistant organisms have resulted in several new promising results.[7-10] For patients at risk of MRSA infection, the use of molecular diagnostic testing with the nasal polymerase chain reaction (PCR) surveillance test has also been proposed as a potential tool to stratify patients.[11-13] However, no single strategy has proved to substantially enhance decision accuracy,[7] and new clinical practice guidelines emphasize the need for validation of these approaches.[14] Some studies have suggested that empirical broad-spectrum therapy may be harmful.[15,16] It is thus unclear which patients benefit sufficiently from empirical treatment with broad-spectrum agents to warrant such therapy.

The primary objective of this study was to evaluate 30-day risk of death in patients hospitalized for pneumonia who were receiving empirical anti-MRSA therapy plus guideline-concordant (ie, standard) antibiotics compared with those receiving standard therapy alone among groups of patients who may warrant therapy. The Veterans Health Administration comprises a large integrated health care system with a shared electronic health record and clinical data repository for more than 5 million veterans at 140 medical centers. Previous studies have reported substantial variation in the decision to use empirical anti-MRSA therapy across and within facilities[17] and year[6] that was unexplained by differences in patient characteristics. We leveraged this variation to examine risks of 30-day mortality among all patients as well as subgroups that may expect greater benefit from an empirical anti-MRSA strategy, including those initially admitted to the intensive care unit (ICU), those with a history of MRSA infection or colonization or other clinical risk factors, those with MRSA detected on results of nasal PCR, and those with MRSA detected by culture within 2 days of admission.

Key Points

Question What is the association of empirical anti–methicillin-resistant *Staphylococcus aureus* therapy with 30-day mortality for patients hospitalized with pneumonia?

Findings This national cohort study of 88 605 hospitalizations for pneumonia that used detailed clinical data to emulate a clinical trial did not find a mortality benefit of empirical anti–methicillin-resistant *S aureus* therapy vs standard antibiotics for any group of patients examined, even those with risk factors for methicillin-resistant *S aureus*.

Meaning This study contributes to a growing body of evidence suggesting that empirical anti–methicillin-resistant *S aureus* therapy using existing risk approaches may not be beneficial to most patients hospitalized with pneumonia.

Methods

Study Design, Setting, and Participation

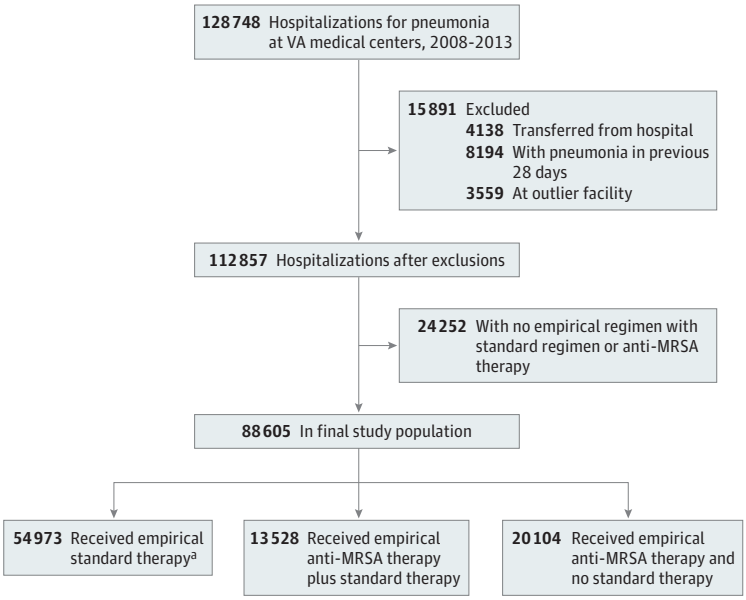
We conducted a retrospective cohort study of all hospitalizations for community-onset pneumonia in the Veterans Affairs (VA) health care system from January 1, 2008, to December 31, 2013 (**Figure 1**), using an existing data set that contained extensively validated clinical data[18] and demonstrated sufficient variation in treatment[17] to allow for comparative effectiveness research. We identified hospitalizations in acute inpatient wards with a principal *International Classification of Diseases, Ninth Revision (ICD-9)* code for pneumonia or secondary *ICD-9* code for pneumonia with a principal *ICD-9* code for sepsis and respiratory failure, a case-finding approach that has been found to be resilient to variation in diagnostic coding.[17,19] Patients were excluded if they were not administered an antimicrobial within the first calendar day of hospitalization, were hospitalized with pneumonia in the previous month, or were transferred from other acute care facilities. The study was reviewed and approved, and waivers of consent were granted on the basis of infeasibility and minimal risk of harm to participants, by the University of Utah Institutional Review Board and the Research and Development Committee of the VA Salt Lake City Health Care System.

Study Data and Measurements

The primary exposure of interest was treatment with anti-MRSA therapy (vancomycin hydrochloride or linezolid) plus guideline-recommended standard antibiotics (β-lactam and macrolide or tetracycline hydrochloride, or fluoroquinolone)[14,20] vs standard therapy alone. Because many patients received anti-MRSA therapy without standard antibiotics, we also evaluated this strategy as an additional treatment group. To conduct an analysis from observational data similar to an intention-to-treat clinical trial,[21,22] we classified all patients according to the treatment they received on the first calendar day of hospitalization. Medication administration was captured using the VA standardized barcode medication administration data, which was previously validated against manual medical record review to accurately represent empirical therapy.[18]

The primary outcome of interest was all-cause mortality within 30 days of hospitalization. Death data were obtained from the VA Vital Status file. Patient demographics, clinical risk factors for resistant organisms, and features associated with illness severity were extracted and curated for each hospitalization using a previously validated approach.[18] Comorbidities included age, sex, renal disease, liver disease, congestive heart failure, cerebrovascular disease, neoplastic disease, immunocompromise (including HIV, solid organ transplant, neutropenia, and immunosuppressive therapy), residence at a

Figure 1. Study Population



MRSA indicates methicillin-resistant *Staphylococcus aureus*; VA, Veterans Affairs.

[a] Standard antibiotics were defined as either a β-lactam plus macrolide or tetracycline, or a respiratory fluoroquinolone (moxifloxacin or levofloxacin). β-Lactams included nonpseudomonals (ampicillin, amoxicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime, cefotaxime, ceftriaxone, ceftizoxime, cefixime, cefpodoxime, ceftibuten, cefdinir, or ertapenem) or antipseudomonals (piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, cefepime, meropenem, doripenem, or imipenem).

nursing home, wound care, number of hospitalization days in the past 60 days, antibiotic therapy in the past 60 days, history of MRSA colonization or infection in the past year, and receipt of tube feeding. Acute illness severity features included vital signs and laboratory test results routinely collected from patients with pneumonia. We extracted the first laboratory test results (blood urea nitrogen, creatinine, glucose, potassium, sodium, white blood cell count, hematocrit, platelet count, albumin, bilirubin, arterial pH, arterial PaO_2, lactate, and troponin) between 12 hours before and 24 hours after admission. Because the patient's initial trajectory, best reflected by changing vital signs, can influence both the initial treatment decision and final outcome, we extracted the worst vital signs (minimum and maximum heart rate, minimum systolic blood pressure, maximum respiratory rate, and minimum oxygen saturation) within 12 hours prior to the time of treatment assignment (antibiotic administration). Missing vital signs, which occurred in less than 5% of all cases, were treated as missing at random and imputed with median values. All missing laboratory test values were imputed with normal values; we also created indicator variables when laboratory test values were missing that had more than 5% prevalence of missingness in the population (albumin, bilirubin, lactate, arterial pH, and troponin). We extracted MRSA culture and PCR surveillance data occurring within the first 2 calendar days and year prior to the admission. We defined a clinically relevant positive MRSA culture as one occurring within the first 2 calendar days from the day of admission from blood or a respiratory source (sputum, endotracheal aspirate, bronchoalveolar lavage, or pleura), as previously described.[17]

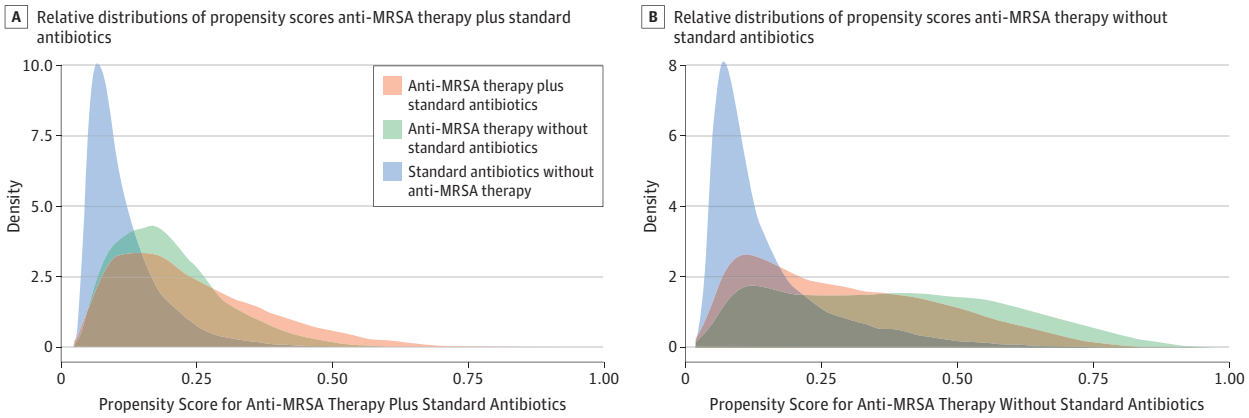
Statistical Analysis

Statistical analysis was conducted from June 14 to November 20, 2019. Our primary analysis was an inverse probability of treatment propensity score–weighted analysis that estimated the mean treatment effect for the entire population of the 3 defined empirical treatments—standard therapy, anti-MRSA therapy plus standard therapy, and anti-MRSA therapy without standard therapy—on 30-day mortality after controlling for patient characteristics potentially associated with both the propensity of treatment and the risk of 30-day mortality. To implement this approach, we first computed propensity scores for the 2 anti-MRSA treatments based on 41 patient characteristics as covariates, including all extracted comorbidities, vital signs, and laboratory test values mentioned above. The propensity scores were estimated by applying generalized boosted machine-learning models as described by McCaffrey et al[23] to minimize the maximum standardized mean differences in the covariates between the 3 treatment groups using the twang package in the *R* statistical computing environment.[24] The distributions of propensity scores in the 3 treatment groups were visually inspected for the degree of common support between patients prior to weighting (**Figure 2**). The balance of characteristics between treatment groups after weighting was considered adequate if standardized differences were less than 0.2 (**Figure 3**). We then fit an inverse propensity score–weighted regression with generalized estimating equation that accounted for clustering of patients within facility using independent working covariance matrices under modified Poisson regression models[25] to estimate population-average adjusted risk ratios (aRRs) of 30-day mortality for the 2 anti-MRSA treatment groups compared with standard therapy as the control group. We hereafter use *weighted propensity score analysis* to refer to this full sequence of analyses.

Subgroup Analyses

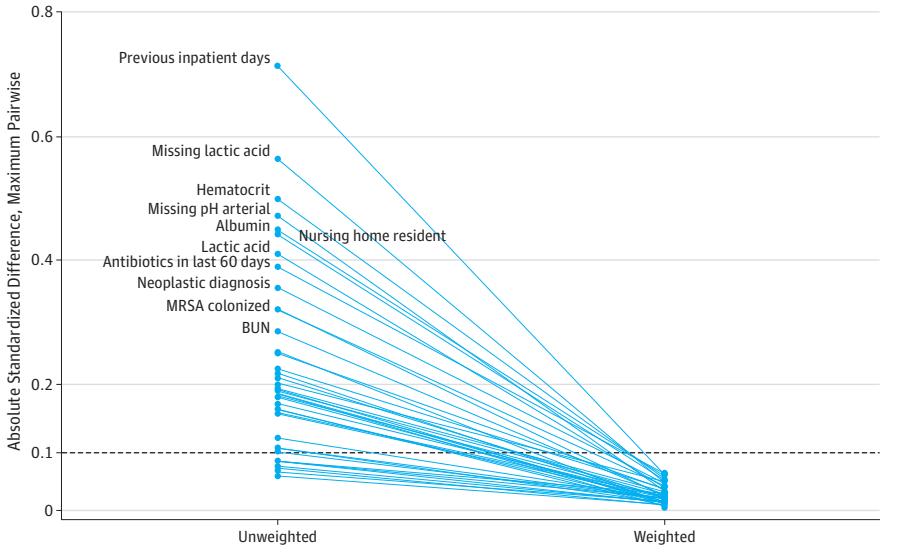
To explore associations between treatment and death for different patient groups, we applied the same weighted propen-

Figure 2. Relative Distribution of Propensity Scores for Treatment With Anti–Methicillin-Resistant *Staphylococcus aureus* (MRSA) Therapy



Conditional density curves demonstrating relative distributions of propensity scores for treatment with anti-MRSA therapy with and without standard antibiotics.

Figure 3. Patient Characteristics Before and After Inverse Probability of Treatment Weighting



Balance plot of patient characteristics for primary analysis before and after inverse probability of treatment weighting using 41 patient characteristics. Dots represent the maximum of pairwise absolute standardized mean difference between 3 treatment groups for each of the covariates. For each variable, lines connect dots for the same variable with and without weighting. BUN indicates blood urea nitrogen.

sity score analysis to 4 subgroups of patients who might warrant empirical anti-MRSA treatment owing to (1) initial admission to the ICU, (2) clinical risk for MRSA detection, (3) positive initial results of MRSA PCR surveillance screening, and (4) positive results of a clinical culture for MRSA (detected on results of blood or respiratory culture within 48 hours). We defined clinical risk for MRSA as a history of MRSA infection or colonization in the past year or at least 2 of the following: previous hospitalization, nursing home residence, and previous intravenous antibiotic therapy, which was based on a previous examination of these risk factors in the VA population[17] as well as a revalidation in the study cohort (eAppendix 4 in the Supplement).

Secondary Analyses

Even after controlling for measured patient characteristics in the weighted propensity score analysis, it is possible that residual confounding owing to unmeasured patient characteristics (ie, mental status or radiographic findings) may bias our estimates of the association of anti-MRSA therapy with mortality. In particular, physicians may have disproportionately assigned anti-MRSA therapy to patients whom they perceived to be at greater risk for infection and death; this perception may have been influenced by factors unavailable in the electronic health record. In view of this risk, we capitalized on the variation in practice patterns for use of anti-MRSA therapy across facilities and over different years that was unexplained by patient characteristics or prevalence[6,17,26] to perform an instrumental variable analysis. The proportion of hospitalizations with empirical anti-MRSA therapy for each facility and year was treated as an instrument to evaluate the association of empirical anti-MRSA therapy with 30-day mortality. We implemented the instrumental variable analysis using a 2-stage residual inclusion approach.[27,28] We also adjusted for

patient characteristics as covariates to control for confounding at the facility and year level. Although residual confounding is also possible for instrumental variable analysis, the instrumental variable analysis should avoid the type of confounding that results from use of anti-MRSA therapy for individual patients who are perceived to be at greater risk. A full description of this analysis, including assessments of its underlying assumptions,[28,29] is available in eAppendix 2, eTable 2, eFigure 6, and eAppendix 3 in the Supplement.

Sensitivity Analysis Incorporating Antipseudomonal Antibiotics

Because receipt of empirical anti-MRSA therapy often coincides with receipt of antipseudomonal therapy, which may also have an association with outcomes, we estimated the association of anti-MRSA therapy and antipseudomonal therapy separately with 30-day mortality by applying a weighted propensity score analysis to compare patients receiving anti-MRSA therapy alone, antipseudomonal therapy alone, and no anti-MRSA or antipseudomonal therapy as 3 treatment groups. The analysis is similar to the primary analysis except that we added receipt of standard therapy as a covariate in the outcome model. Statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc), Stata, version 16.0 (StataCorp LLC), and R (R Foundation for Statistical Computing; http://cran.r-project.org) software.

Examination of Secondary Outcomes

The weighted propensity score analysis was applied to the following secondary events occurring between 48 hours and 30 days after hospitalization: kidney injury (defined as an increase in creatinine of 0.3 mg/dL [to convert to micromoles per liter, multiply by 88.4] or 50% from initial creatinine level), incident or recurrent *Clostridioides difficile* infection (detection of toxin without previous positive test results for toxin in the past 14 days), and detection of vancomycin-resistant *Enterococcus* spp and gram-negative rods in blood or urine cultures.

Results

A total of 88 605 hospitalizations for pneumonia were studied (Figure 1), with a 30-day all-cause mortality of 10% (n = 8929). Empirical anti-MRSA therapy was administered to 33 632 patients (38%). Of these, 13 528 received empirical anti-MRSA therapy plus standard antibiotics, 20 104 received empirical anti-MRSA therapy without standard antibiotics, and 54 973 received empirical standard guideline-recommended therapy alone (**Table 1**).[20]

Patients receiving empirical anti-MRSA therapy demonstrated a greater comorbidity burden (renal disease, 29% vs 25%; congestive heart failure, 35% vs 30%; neoplastic disease, 34% vs 3%; and nursing home residents, 9% vs 3%), more risk factors for MRSA (7% vs 2% with history of MRSA infection, 36% vs 12% with previous hospitalization, and 42% vs 29% with previous antibiotics), and greater illness severity (median Pneumonia Severity Index, 124 [interquartile range, 95-156] vs 103 [interquartile range, 81-131]) as well as worse outcomes (16% vs 6% for 30-day all-cause mortality) compared with patients receiving standard therapy alone (Table 1).[20] However, the distribution of propensity for treatment demonstrated sufficient overlap between the treatment groups (Figure 2A), and weighting resulted in sufficient balance in patient characteristics for all 3 pairwise comparisons (Figure 2B).

Empirical anti-MRSA treatment was significantly associated with greater 30-day mortality compared with standard therapy alone, with a propensity score-weighted aRR of 1.4 (95% CI, 1.3-1.5) for empirical anti-MRSA treatment plus standard therapy and 1.5 (1.4-1.6) for empirical anti-MRSA treatment with nonstandard therapy (**Table 2**). The corresponding propensity score-weighted marginal probabilities of 30-day mortality were 11.6% for empirical anti-MRSA treatment plus standard therapy and 12.7% for empirical anti-MRSA treatment with nonstandard therapy compared with 8.6% for standard therapy alone.

Subgroup Analyses

Among all hospitalizations, 14 370 patients (16%) were initially admitted to the ICU, 19 045 (22%) had clinical risk factors for MRSA, 2775 (3%) had positive PCR results, and 2154 (2%) had MRSA detected by clinical culture. Sufficient common support resulted in adequate balance in patient characteristics after weighting for all subgroups (eAppendix 1; eTable 1; and eFigures 1, 2, 3, 4, and 5 in the Supplement).

We found a significant increase in 30-day mortality associated with empirical anti-MRSA therapy plus standard therapy compared with standard therapy alone among patients admitted to the ICU (aRR, 1.3; 95% CI, 1.2-1.5), with a high clinical risk for MRSA (aRR, 1.2; 95% CI, 1.1-1.4), and with positive results of surveillance PCR (aRR, 1.6; 95% CI, 1.3-1.9) but no significant difference in risk of 30-day mortality for patients with positive results of clinical culture (aRR, 1.1; 95% CI, 0.8-1.4 [Table 2]). Similar associations were found for the group receiving anti-MRSA therapy without standard therapy (Table 2).

Instrumental Variable Analysis, Analysis of Antipseudomonal Antibiotics, and Secondary Outcomes

Results of secondary analyses suggested similar associations. In the instrumental variable analysis, we found a significant association between use of anti-MRSA therapy and 30-day mortality (aRR, 1.6; 95% CI, 1.4-1.9). In the weighted propensity score analysis examining separate associations of empirical antipseudomonal therapy from anti-MRSA antibiotics, we found both therapies to be separately associated with higher risk of 30-day mortality after controlling for standard therapy (anti-MRSA therapy: aRR, 1.2; 95% CI, 1.1-1.3; antipseudomonal therapy: aRR, 1.3; 95% CI, 1.2-1.4). Use of empirical anti-MRSA therapy was associated with a higher risk of kidney injury (aRR, 1.4; 95% CI, 1.3-1.5), *C difficile* infection (aRR, 1.6; 95% CI, 1.3-1.9), vancomycin-resistant *Enterococcus* spp (aRR, 1.6; 95% CI, 1.0-2.3), and secondary gram-negative rod detection (aRR, 1.5; 95% CI, 1.2-1.8).

Table 1. Patient Characteristics and Outcomes by Treatment Group

Characteristic	Value[a]			
			Anti-MRSA Therapy	
	All Patients (N = 88 605)	Standard Antibiotics Alone (n = 54 973)[b]	Plus Standard Antibiotics (n = 13 528)	Without Standard Antibiotics (n = 20 104)
Age, median (IQR), y	70 (62-81)	70 (62-81)	68 (61-80)	70 (62-81)
Female sex	1754 (2)	1711 (3)	279 (2)	354 (2)
Renal disease	23 924 (27)	13 594 (25)	3912 (29)	6418 (32)
Liver disease	2810 (3)	1393 (3)	548 (4)	869 (4)
Cerebrovascular disease	17 048 (19)	9477 (17)	2767 (20)	4804 (24)
Congestive heart failure	28 679 (32)	16 654 (30)	4721 (35)	7304 (36)
Neoplastic disease	25 772 (29)	1393 (3)	4569 (34)	7602 (38)
Nursing home resident	5879 (7)	1829 (3)	1179 (9)	2871 (14)
Wound care	3914 (4)	1407 (3)	959 (7)	1548 (8)
Immunocompromised	1628 (2)	595 (1)	440 (3)	593 (3)
History of MRSA				
Infection	4168 (5)	1226 (2)	679 (7)	1408 (9)
Colonization	6060 (7)	2317 (4)	884 (9)	1847 (12)
Previous hospitalization in 90 d	21 082 (24)	6794 (12)	4804 (36)	9484 (47)
Previous antibiotics in 60 d	31 365 (35)	16 067 (29)	5679 (42)	9619 (48)
Tube feeding	1108 (1)	375 (1)	218 (2)	515 (3)
Pneumonia Severity Index, median (IQR)[c]	111 (86-142)	103 (81-131)	124 (95-156)	128 (100-162)
Heart rate, median (IQR), beats per min	100 (86-113)	98 (85-110)	104 (90-118)	102 (88-116)
Respiratory rate, median (IQR), breaths per min	22 (20-24)	22 (20-24)	22 (20-28)	22 (20-26)
Systolic blood pressure, median (IQR), mm Hg	113 (100-128)	115 (103-130)	108 (95-124)	109 (95-124)
Maximum temperature, median (IQR), °C	37.3 (36.8-38.2)	37.3 (36.9-38.4)	37.4 (38.9-38.4)	37.4 (36.8-38.3)
Pulse oximetry <90% or arterial Pao_2<60 mm Hg	22 201 (25)	9889 (18)	3908 (29)	3250 (24)
Albumin, median (IQR), g/dL	3.2 (3.0-3.6)	3.7 (3.2-4.5)	3.3 (2.7-4.1)	3.4 (2.8-4.0)
Bilirubin, median (IQR), mg/dL	0.7 (0.5-0.9)	0.9 (0.6-1.0)	0.8 (0.5-1.0)	0.8 (0.5-1.0)
Blood urea nitrogen, median (IQR), mg/dL	20 (14-29)	19.9 (14-27)	22 (15-34)	22 (15-33)
Serum bicarbonate, median (IQR), mEq/L	26 (23-28)	26 (23-28)	26 (23-28)	25 (22.9-28.0)
Creatinine, median (IQR), mg/dL	1.1 (0.9-1.5)	1.1 (0.9-1.5)	1.2 (0.9-1.7)	1.2 (0.9-1.7)
Glucose, median (IQR), mg/dL	122 (103-156)	121 (102-154)	123 (103-160)	123 (103-159)
Hematocrit, median (IQR), %	37.1 (33.0-41.1)	38.4 (34.4-41.8)	35.1 (30.7-39.3)	36 (31.7-40.1)
Lactate, median (IQR), mEq/L	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.1)	1 (1-1.3)
Arterial pH	7.4 (7.4-7.4)	7.4 (7.4-7.4)	7.4 (7.4-7.4)	7.4 (7.4-7.4)
Platelet count, median (IQR), $\times 10^3/\mu L$	216 (164-281)	219 (168-275)	223 (159-296)	214 (156-285)
Potassium, median (IQR), mEq/L	4.1 (3.7-4.4)	4.0 (3.7-4.4)	4.1 (3.8-4.5)	4.1 (3.7-4.5)
Sodium, median (IQR), mEq/L	137 (134-139)	137 (134-139)	137 (133-140)	136 (133-139)
Troponin, median (IQR), ng/mL	0.03 (0.03-0.04)	0 (0-0)	0 (0-0)	0 (0-0)
White blood cell count, median (IQR), $\times 10^3/\mu L$	11 800 (8500-16 000)	11 500 (8500-15 400)	12 300 (8400-17 000)	12 300 (8500-17 200)
Patient subgroups, No. (%)				
ICU admission	14 320 (16)	4774 (9)	4332 (32)	5214 (26)
MRSA risk factors (history or previous hospitalization)	19 045 (22)	6331 (12)	4804 (36)	9484 (47)
MRSA surveillance PCR positive	2775 (3)	1682 (3)	389 (3)	704 (4)
MRSA detected on clinical culture	2154 (2)	592 (1)	600 (4)	962 (5)
Treatment patterns				
Total antibiotic days, median (IQR), d	10 (7-13)	10 (7-13)	11 (7-14)	10 (7-14)
Total days of anti-MRSA therapy, median (IQR), d	0 (0-3)	0 (0-0)	3 (2-5)	4 (2-6)

(continued)

Table 1. Patient Characteristics and Outcomes by Treatment Group (continued)

Characteristic	Value[a]			
			Anti-MRSA Therapy	
	All Patients (N = 88 605)	Standard Antibiotics Alone (n = 54 973)[b]	Plus Standard Antibiotics (n = 13 528)	Without Standard Antibiotics (n = 20 104)
Empirical treatment, No. (%)				
β-Lactam	63 437 (72)	34 412 (63)	11 345 (84)	17 679 (88)
Fluoroquinolone	33 304 (38)	25 738 (47)	7566 (56)	0
Macrolide	35 753 (40)	29 414 (54)	5951 (44)	388 (2)
Antipseudomonal therapy	30 243 (34)	3127 (6)	9877 (73)	17 238 (86)
Outcomes				
30-d Mortality, No. (%)	8929 (10)	3261 (6)	2126 (16)	3542 (18)
Length of stay, median (IQR), d	4 (3-7)	4 (2-6)	6 (3-10)	6 (4-10)
Readmission in 28 d, No. (%)	17 682 (20)	9276 (17)	3099 (23)	5307 (26)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction.

SI conversion factors: To convert albumin to grams per liter, multiply by 10.0; bilirubin to micromoles per liter, multiply by 17.104; blood urea nitrogen to millimoles per liter, multiply by 0.357; bicarbonate to millimoles per liter, multiply by 1.0; creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555; hematocrit to proportion of 1.0, multiply by 0.01; lactate to millimoles per liter, multiply by 0.111; platelets to 10^9 per liter, multiply by 1.0; potassium to millimoles per liter, multiply by 1.0; sodium to millimoles per liter, multiply by 1.0; troponin to micrograms per liter, multiply by 1.0; and white blood cells to 10^9 per liter, multiply by 0.001.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Standard antibiotics were defined as either a β-lactam plus macrolide or tetracycline, or a respiratory fluoroquinolone (moxifloxacin or levofloxacin). β-Lactams included nonpseudomonals (ampicillin, amoxicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime, cefotaxime, ceftriaxone, ceftizoxime, cefixime, cefpodoxime, ceftibuten, cefdinir, or ertapenem) or antipseudomonals (piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, cefepime, meropenem, doripenem, or imipenem).

[c] Pneumonia Severity Index was estimated for each patient using all features extractable from the electronic health record, which included all elements except for mental status and presence of pleural effusion on results of chest imaging.[20]

Table 2. Adjusted Risk Ratios for 30-Day Mortality Among Primary and Subgroup Inverse Probability–Weighted Analyses

Group	Adjusted Risk Ratio (95% CI)	
	Anti-MRSA Therapy Plus Standard Antibiotics	Anti-MRSA Therapy Without Standard Antibiotics
All patients	1.4 (1.3-1.5)	1.5 (1.4-1.6)
Patients admitted to ICU	1.3 (1.2-1.5)	1.4 (1.2-1.5)
High clinical risk for MRSA	1.2 (1.1-1.4)	1.3 (1.1-1.4)
MRSA surveillance PCR positive	1.6 (1.3-1.9)	1.8 (1.4-2.3)
MRSA culture positive	1.1 (0.8-1.4)	1.2 (0.9-1.6)

Abbreviations: ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction.

Discussion

In this national observational study of patients hospitalized for pneumonia using detailed clinical data, we were unable to establish benefit of empirical anti-MRSA therapy, even when risk factors for MRSA were present or clinical severity warranted admission to the ICU. These findings, which were robust to multiple methods of analysis, contribute to a growing body of evidence that raises questions surrounding widespread empirical use of extended-spectrum antibiotics in patients with community-acquired pneumonia.[15,16,30]

These findings should be interpreted carefully. Estimates of treatment effects, whether generated from randomized trials or observational studies, are population means. Individual members of a population may vary widely in outcomes from different treatments. In the patient cohort that we analyzed, it is plausible that there were individuals who would have experienced a net clinical benefit from empirical receipt of an anti-MRSA regimen and others who would have experienced net harm. Potential sources of harm from vancomycin, which accounted for 98% of the anti-MRSA therapy in our study, include renal toxic effects, allergy, and superinfection.[16,31-33] In our secondary analyses, anti-MRSA therapy was associated with increased risk of kidney injury and secondary infections. The influence of the decision to treat with anti-MRSA therapy on other antibiotic choices was another pathway that likely had an association with outcomes.

Our evaluation of patients whose admission cultures grew MRSA was not a test of whether MRSA should be treated when it is isolated. Rather, our analysis addressed only the question of whether empirical therapy against MRSA was beneficial compared with standard empirical treatment. The strategy of adding anti-MRSA therapy once results of cultures were positive was not specifically examined. However, MRSA was most commonly isolated from sputum. A recognized limitation of respiratory cultures is that they often reflect oropharyngeal colonization.[34] Thus, a contributing explanation for our results is that respiratory cultures may have poor positive predictive value for MRSA pneumonia. This finding calls into question whether respiratory cultures should be used as a criterion standard for infection in pneumonia and adds urgency to the need for better diagnostic tools to more precisely identify bacterial and viral causes of pneumonia and other infections.

Future studies should extend the work presented here to examine treatment decisions during the postempirical

treatment phase, such as deescalation,[3,35] as well as dosing and therapeutic drug monitoring, which were not examined in our study. Valid approaches can draw causal inferences about sequential decisions that use time-varying information, such as sequential multiple assignment randomized trials[36] and observational studies of dynamic treatment regimens.[37] Identifying optimal antibiotic decision-making strategies for patients—including how best to integrate information from results of cultures and molecular diagnostic tests to make subsequent decisions about antibiotics after empirical therapy—merits further research.

Limitations

This observational study has limitations. While our large population size, variation, and detailed clinical data allowed us to compare outcomes for patients with similar measured illness severity, and while the instrumental analysis should provide some protection against bias by unmeasured severity, residual confounding is still possible. In our secondary analysis, antipseudomonal therapy was found to be associated with 30-day mortality. This finding warrants further investigation as may be suggested by the added association of concomitant therapy. Our case-finding approach is widely used but relied on diagnosis codes assigned at the end of the hospitalization; while adequate precision has been found in this approach,[38] we may have included some patients who did not initially receive a diagnosis of pneumonia. We captured all antibiotics administered in the hospital, but an estimated 2% of patients in our population received a different antibiotic in the emergency department.[18] Our population is disproportionately male, and although no differences in antibiotic effects have been reported, women have different outcome patterns from men in pneumonia.[39] Similarly, our population had an insufficient number of patients receiving linezolid to compare its separate effects.

Conclusions

Clinicians are constantly seeking innovations that might promise better outcomes for our patients. However, our eagerness to improve outcomes, particularly for critically ill patients, makes us susceptible to adopt practices that may have plausibility and promise but lack significant evidence or validation.[40-43] Once adopted, these practices become norms that persist despite cautionary studies. With a mortality rate that has not substantially improved in decades, the threat of resistant organisms, and the emphasis on timely antibiotics in sepsis, it is not surprising that the strategy of early broad-spectrum antibiotics for pneumonia has become the norm. The underlying assumption of this approach is that the benefit of more potent antibiotics during the empirical phase exceeds the harms. Our study questions this assumption. We hope that newer diagnostic approaches[44-46] and more evidence informing antimicrobial decisions will enhance our ability to accurately treat our patients. In the meantime, administration of empirical anti-MRSA therapy for pneumonia using current approaches should be reconsidered, even in high-risk patients.

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