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Incremental clinical and economic burden of suspected respiratory infections due to multi-drug-resistant *Pseudomonas aeruginosa* in the United States☆

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SUMMARY

Background: Multi-drug resistant (MDR) *Pseudomonas aeruginosa* can negatively affect patients and hospitals.

Aim: To evaluate excess mortality and cost burden among patients hospitalized with suspected respiratory infections due to MDR *P. aeruginosa* vs patients with non-MDR *P. aeruginosa* in 78 United States (US) hospitals.

Methods: This study analyzed electronically captured microbiological and outcomes data of patients hospitalized with non-duplicate *P. aeruginosa* isolates from respiratory sources collected ≥3 days after admission to identify hospital-onset MDR or non-MDR *P. aeruginosa* per the Centers for Disease Control and Prevention definition. The risk of multi-drug resistance was estimated on mortality, length of stay (LOS), cost, operation gain/loss, and 30-day readmission. A sensitivity analysis was conducted utilizing a cohort with pharmacy data available.

Findings: Of 523 MDR and 1381 non-MDR *P. aeruginosa* cases, unadjusted mortality was 23.7% vs 18.0% and multi-variable-adjusted mortality was 20.0% (95% confidence interval (CI): 14.3–27.2%) vs 15.5% (95% CI: 11.2–20.9%; $P=0.026$), the average adjusted excess LOS was 6.7 days ($P<0.001$); excess cost per case was US$22,370 higher ($P=0.002$) and operational loss per case was US$10,661 ($P=0.024$) greater, and the multi-variable adjusted readmission rate was 16.2% (95% CI: 11.2–22.9%) vs 11.1% (95% CI: 7.8–15.6%; $P=0.006$). The sensitivity analysis yielded similar results.

Conclusions: Compared with suspected infections due to non-MDR *P. aeruginosa*, patients with MDR *P. aeruginosa* had higher risk of mortality, readmission, and longer LOS, as well as US$20,000 incremental cost and >US$10,000 incremental net loss per case after controlling for patient and hospital characteristics.

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Introduction

Antimicrobial resistance continues to have a profound impact on multiple aspects of healthcare, with an estimated two million people in the US developing resistant infections and 23,000 deaths attributed to antimicrobial resistance each year [1]. Resistance to antimicrobial drugs is associated with higher mortality, and has been found to add US$20 billion to direct healthcare costs and causes an additional US$35 billion in lost productivity annually [1]. Infections that are multi-drug resistant (MDR) pose a significant clinical challenge and therapeutic options are limited [1–3]. Hospital-associated infections with Gram-negative bacteria are more likely to be resistant compared with community-acquired infections [4–6]. In one study of 312,075 Gram-negative isolates obtained from intensive care unit patients, rates of carbapenem-non-susceptible, hospital-onset infections were 2.5-fold higher than rates of carbapenem-non-susceptible infection diagnosed at admission [5]. This same study found that 64% of *Pseudomonas aeruginosa* isolates that were carbapenem-non-susceptible were categorized as MDR. The Centers for Disease Control and Prevention identified MDR *P. aeruginosa* to be a major health threat [1]. In the acute-care setting, Gram-negative bacteria are involved in 80% of hospital-acquired bacterial pneumonia (HABP) [4], and *P. aeruginosa* is among the most common Gram-negative bacteria to cause HABP or ventilator-associated pneumonia [7,8].

A previous study showed high prevalence (23.6%) of MDR *P. aeruginosa* in hospitalized patients with pneumonia [9], and a separate study of 1449 *P. aeruginosa* isolates from patients with ventilator-associated bacterial pneumonia found that approximately 20% of these isolates were MDR [8]. However, there are very few multi-center studies that directly compare the clinical and financial outcomes of patients who are infected with MDR vs non-MDR *P. aeruginosa* pathogens in the hospital-onset setting. Existing estimates of the clinical and economic burden of MDR *P. aeruginosa* infections are distinct in that they are either: (i) from a single center, analyzed pooled data for multiple infection types; (ii) study-only clinical outcomes (mortality) and length of stay (LOS) as a marker of operational burden; (iii) assess differences in onset setting; (iv) or focus on the comparison of MDR *P. aeruginosa* with non-infection controls, which may inflate the impact of MDR *P. aeruginosa* due to inadequate controlling for potential confounders [10–14]. Historic mortality rates due to hospital-onset *P. aeruginosa* infection vary widely and range from 13% to 73% [13–19]. The objective of this multi-center study was to investigate the incremental mortality and cost burden among patients hospitalized with suspected respiratory infections due to MDR *P. aeruginosa* compared with patients with non-MDR *P. aeruginosa*.

Methods

Data source

We used the BD Insights Research Database, which is an electronically captured and structured database that contains de-identified microbiological, general laboratory, pharmacy orders, and administrative data (Becton, Dickinson & Company, Franklin Lakes, NJ, USA (formerly the CareFusion Clinical Research Database)) [20–22]. The dataset used for the current study was collected from 78 US acute-care hospitals beginning 1st January 2013, through 30th September 2015, prior to the transition of ICD-9 to ICD-10 in the USA, and included microbiological data (i.e. specimen collection date, source, and culture and susceptibility results), general laboratory test results, hospital data, and postdischarge administrative data (i.e. principal diagnosis, discharge disposition, payer, hospital LOS, hospital cost, and payment received) collected from adult inpatients. The study dataset was a deidentified limited retrospective dataset exempted from patient consent by the New England Institutional Review Board (Wellesley, MA, USA).

Patients

Consecutive adult patients ≥18 years of age who were admitted as inpatients with culture-confirmed non-duplicate *P. aeruginosa* infections from a lower, upper, or abscess respiratory source were included. The *P. aeruginosa* isolates were further classified based on MDR or non-MDR status. Laboratory data included in the database were obtained through the microbiological reporting of the local hospital. Hospital-onset infections were defined as *P. aeruginosa* respiratory specimens that were collected ≥3 days postadmission.

Definition of MDR P. aeruginosa

Based on the Centers for Disease Control and Prevention National Healthcare Safety Network definition, MDR *P. aeruginosa* was defined as non-duplicate *P. aeruginosa* isolates from the lower, upper, or abscess respiratory source that were tested as 'resistant' or 'intermediate', to at least one drug in three of the five antibiotic classes: (i) extended-spectrum cephalosporins; (ii) fluoroquinolones; (iii) aminoglycosides; (iv) carbapenems; (v) piperacillin or piperacillin/tazobactam [8].

Outcomes

In-hospital mortality, LOS, hospital total cost, and operating gain/loss (payment received minus total cost, with a negative value being designated as a 'net loss'), and 30-day readmission data were retrieved from administrative and hospital financial databases.

Statistical analysis

We first conducted a univariate analysis to examine the associations between each candidate covariate and outcome variable. The candidate covariate variables included age, gender, payer, intensive care unit admission status, underlying clinical conditions as assessed by the principal diagnosis-based disease category (Clinical Classification System) [23], and hospital characteristics (teaching status, number of beds, and geographic location). We also included an aggregated measure of clinical severity using a published Acute Laboratory Risk of Mortality Score (ALaRMS) [24]. The ALaRMS uses patient demographics and 23 numeric laboratory test results to score the probability of in-hospital mortality (an aggregated measure of disease severity). The laboratory results included: serum chemistry (alphabetically ordered albumin, alkaline

phosphatase, aspartate transaminase, blood urea nitrogen, calcium, creatinine, glucose, potassium, sodium, and total bilirubin); hematology and coagulation parameters (bands, hemoglobin, partial thromboplastin time, prothrombin time international normalized ratio, platelets, and white blood cell count); arterial blood gas (partial pressure of carbon dioxide, partial pressure of oxygen, and pH value); cardiac markers (brain natriuretic peptide, creatine phosphokinase-MB, pro-brain natriuretic peptide, and troponin I or troponin T).

We estimated the incremental burden of MDR *P. aeruginosa* using a generalized linear mixed model (GLMM) to control for disease severity, underlying clinical conditions, exposure time, and other potential confounding factors. In GLMM mode, the SAS procedure assumes that the model contains random effects or possibly correlated errors, or that the data have a clustered structure. We used a GLMM approach because it accounts for skewed distributions and variations among hospitals. Specifically, categorical outcomes (mortality, readmission) were modeled using a random intercept logistic regression model and continuous outcomes (LOS, cost, gain/loss) were modeled using GLMM with the gamma distribution and a log-link function in the Statistical Analysis Software (SAS Institute, Cary, NC, USA) V9.4 "GLIMMIX" procedure.

Sensitivity analysis

We analyzed a subset of patients from 48 sites that provided pharmacy data to determine the antibiotic treatment rate and used the analysis to support the likelihood of the presence of infections. We conducted univariate analyses and refit all five models to reestimate the effect of MDR compared to non-MDR.

Results

Patient characteristics

A total of 1904 admissions with laboratory-confirmed non-duplicate *P. aeruginosa* isolates from a respiratory source were identified (Table I). Among them, 27.5% (523/1904) were MDR. Patients with MDR *P. aeruginosa* were younger than patients with non-MDR *P. aeruginosa* infections with an average age of 58.2 years (standard deviation (SD): 16.9) vs 64.0 (15.9) years ($P<0.001$). Although the patients were younger, MDR cases had a more severe clinical presentation as measured by the mean ALaRMS compared with non-MDR cases (60.4 (25.9) vs 58.0 (22.5); $P=0.037$). MDR status was positively associated with previous hospital admissions within the 90 days prior to the index hospital admission ($P<0.001$), as well as longer hospital stay exposure time prior to the onset of respiratory infections ($P<0.001$). However, intensive care unit admission status was not significantly different between the MDR and non-MDR group ($P=0.306$). For the underlying clinical conditions, the MDR group had a higher proportion of patients with septicemia or infectious diseases as the primary reason for hospital admission compared with the non-MDR group (22.8% vs 12.7%). In contrast, the non-MDR group had a higher proportion of patients with diseases of the circulatory system as the primary reason for hospital admission (19.1% vs 9.0%). The majority of MDR cases (82.6%) were identified in large hospitals with number of beds >300 and there was no significant difference between MDR and non-MDR groups according to hospital teaching status ($P=0.132$).

Crude (unadjusted) and adjusted outcomes

The MDR group had a higher in-hospital mortality for both unadjusted and multi-variable adjusted rates compared with patients in the non-MDR group (Figure 1). The unadjusted mortality rate was 23.7% and 18.0% for MDR vs non-MDR cases, respectively ($P=0.005$). The multi-variable adjusted mortality rate and 95% confidence interval (CI) was 20.0% (95% CI: 14.3–27.2%) vs 15.5% (95% CI: 11.2–20.9%; $P=0.026$).

The MDR group had a significantly longer LOS for both unadjusted and multi-variable- adjusted LOS compared with the non-MDR group (Figure 2). The unadjusted average LOS (SD) for MDR vs non-MDR cases was 39.7 days (39.4) vs 25.3 days (21.7; $P<0.001$). The multi-variable-adjusted LOS was 29.1 days (95% CI: 25.8–32.9) vs 22.4 days (95% CI: 20.7–24.3; $P<0.001$).

The MDR group incurred significantly higher costs for both unadjusted and multi-variable adjusted total cost per case (Figure 3a). The unadjusted average total cost (SD) per case for MDR vs non-MDR was US$124,335 ($170,947) vs $68,404 ($77,258; $P<0.001$). The multi-variable adjusted total cost was US$81,515 (95% CI: $64,912–102,364) vs $59,145 (95% CI: $49,532–70,623; $P=0.002$) for cases of MDR and non-MDR, respectively.

The MDR group incurred a significantly larger net loss for hospitals compared with the non-MDR group for both unadjusted and multi-variable adjusted net loss per case (Figure 3b). The unadjusted average net loss per case for MDR vs non-MDR cases was −US$21,404 (SD $129,556) vs −$9092 (SD $63,722; $P=0.008$). The multi-variable adjusted net loss was −US$36,797 (95% CI: −$49,264 to −$24,331) vs −$26,136 (95% CI: −$37,032 to −$15,240); $P=0.024$).

For patients who survived until discharge, the MDR group had a higher 30-day readmission rate for both unadjusted and multi-variable adjusted rates compared with the non-MDR group (Figure 4). The unadjusted readmission rate was significantly higher for MDR vs non-MDR cases (20.8% vs 14.8%; $P=0.006$). The multi-variable adjusted readmission rate was 16.2% (95% CI: 11.2–22.9%) vs 11.1% (95% CI: 7.8–15.6%; $P=0.006$).

Sensitivity analysis

Of the 1904 patients in the full study population from 78 sites, 48 sites provided pharmacy data accounting for 77.9% (1483/1904) of total admissions. Among the 1483 patients, 1458 (98.3%) had both a positive culture and evidence of antibiotic treatment, which suggested a high likelihood of the presence of an infection. The sensitivity analyses for all five outcomes for those 1458 patients were very similar to our original findings for the full study population (Supplementary Table S1).

Discussion

Antibacterial-resistant infections substantially add to clinical and economic burdens compared with non-resistant infections, and this is consistent with reports in the literature [25,26]. Our multi-center study specifically examined the

Table I
Patient characteristics

Variable	Non-MDR ($N = 1381$)	MDR ($N = 523$)	P
Age, years			
Mean (standard deviation)	64.0 (15.9)	58.2 (16.9)	<0.001
Median (1st, 3rd quartile)	66 (55, 75)	61 (49, 70)	
Sex, *N* (%)			
Female	519 (37.6)	204 (39.0)	0.568
Male	862 (62.4)	319 (61.0)	
Payer, *N* (%)			
Medicare	773 (56.0)	241 (46.1)	<0.001
Medicaid	122 (8.8)	61 (11.7)	
Private/other	486 (35.2)	221 (42.3)	
ALaRMS value (aggregated measure of clinical severity)			
Mean (standard deviation)	58.0 (22.5)	60.4 (25.9)	0.037
Median (1st, 3rd quartile)	55 (42, 72)	59 (42, 75)	
Intensive care unit admission status, *N* (%)			
No	593 (42.9)	211 (40.3)	0.306
Yes	788 (57.1)	312 (59.7)	
Hospital admissions 90 days prior to index hospital admission, *N* (%)			
0	1028 (74.4)	344 (65.8)	<0.001
1	239 (17.3)	110 (21.0)	
>1	114 (8.3)	69 (13.2)	
Exposure time (days from admission to onset of infections), *N* (%)			
3–4 (1st quartile)	391 (28.3)	108 (20.7)	<0.001
4–7 (2nd quartile)	396 (28.7)	128 (24.5)	
8–15 (3rd quartile)	297 (21.5)	105 (20.1)	
15+ (4th quartile)	297 (21.5)	182 (34.8)	
Underlying diseases (Clinical Classification System), *N* (%)			
Diseases of the respiratory system	361 (26.1)	130 (24.9)	<0.001
Septicemia/infectious diseases	176 (12.7)	119 (22.8)	
Injury/trauma/poisoning	228 (16.5)	93 (17.8)	
Diseases of the circulatory system	264 (19.1)	47 (9.0)	
Endocrine/nutritional/metabolic/immunity disorders	34 (2.5)	33 (6.3)	
Diseases of the digestive system	84 (6.1)	35 (6.7)	
Neoplasms	84 (6.1)	14 (2.7)	
Other principal diagnoses	150 (10.9)	52 (9.9)	
Teaching status, *N* (%)			
Non-teaching	847 (61.3)	301 (57.6)	0.132
Teaching	534 (38.7)	222 (42.5)	
Hospital size (beds), *N* (%)			
≤300	363 (26.3)	91 (17.4)	<0.001
>300	1018 (73.7)	432 (82.6)	
Geographic region, *N* (%)			
Midwest	234 (16.9)	83 (15.9)	0.013
Northeast	33 (2.4)	15 (2.9)	
South	1013 (73.4)	407 (77.8)	
West	101 (7.3)	18 (3.4)	
All, *N* (%)	1381 (100.0)	523 (100.0)	—

ALaRMS, Acute Laboratory Risk of Mortality Score; MDR, multi-drug resistant; —, not applicable.

effect of MDR *P. aeruginosa* on patients with suspected respiratory infections compared with those with non-MDR *P. aeruginosa* in order to more rigorously estimate the attributable effect specific to MDR. The large sample size allowed for a more precise estimation of attributable clinical and economic burden, as supported by the relatively narrow CIs.

In this analysis, based on a large number of patients across the US, patients in the MDR group presented with significantly higher severity of illness, as measured using the ALaRMS, despite the significantly younger average age compared with the non-MDR group. MDR *P. aeruginosa* status was associated with hospitalization within the 90 days prior to the index infection and had a longer LOS that has been shown to increase the likelihood of developing MDR respiratory infections [27,28]. In addition, the majority of MDR cases were from larger hospitals (>300 beds).

The mortality rate observed in this study for patients in the MDR *P. aeruginosa* group was 23.7%, and was slightly higher

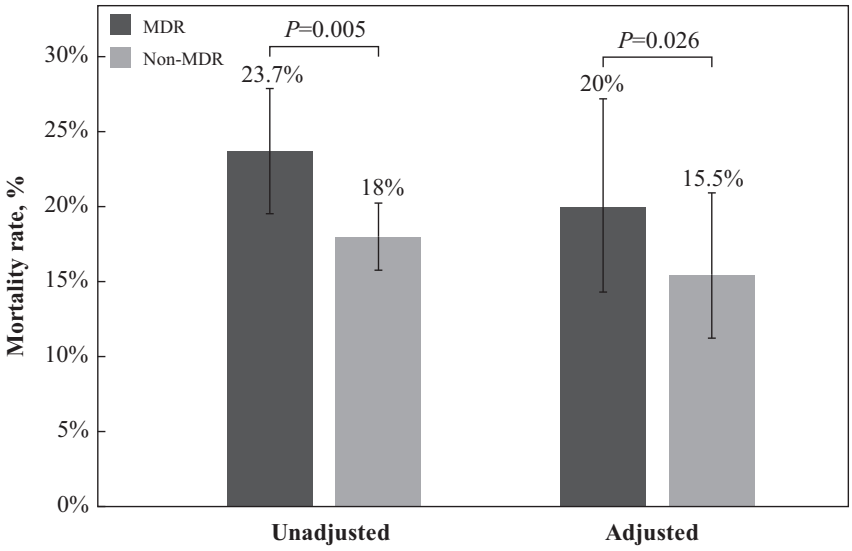

Figure 1. Unadjusted and multi-variable-adjusted mortality rates (multi-drug resistant (MDR) vs non-MDR).

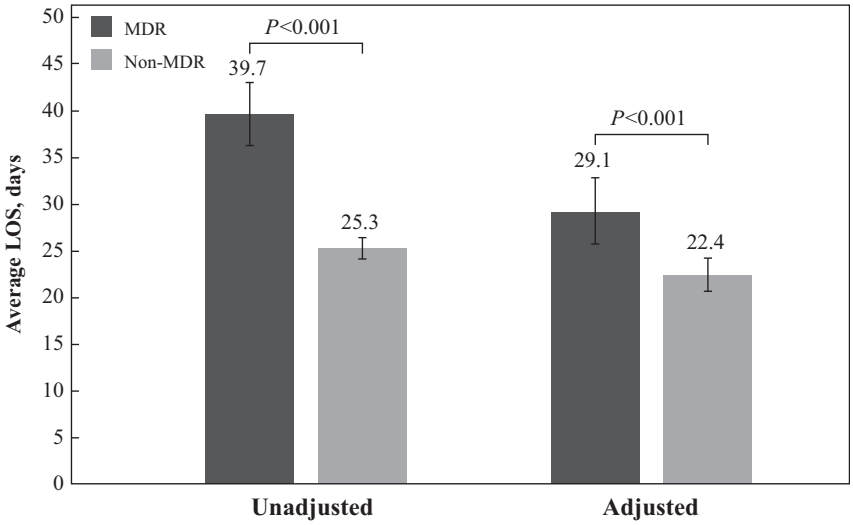

Figure 2. Unadjusted and multi-variable-adjusted LOS (multi-drug resistant (MDR) vs non-MDR). LOS, length of stay.

than US mortality rates found in previous studies of various infections due to MDR *P. aeruginosa* (17–19%) [14,16], and aligned with the 22.5% mortality rate reported from the US stratum in an international study of patients with nosocomial *P. aeruginosa* respiratory infections [29].

In a previous study, a subgroup analysis of patients with antibacterial-susceptible ($N = 73$) and antibacterial-resistant ($N = 47$) *Pseudomonas* spp. infections evaluated mortality rates and did not find a significant difference between the groups (21% vs 15%; $P=0.43$) [25], perhaps due to a small sample size. In contrast, our study, which was restricted to suspected respiratory infections with *P. aeruginosa* and included a larger study population (non-MDR, $N = 1381$; and MDR, $N = 523$), was sufficiently powered to find a significant difference in mortality between non-MDR and MDR groups, even after adjusting for both patient-level and hospital-level confounders. For those patients who survived until discharge, the rates of readmission were significantly higher for the MDR group vs the non-MDR group.

Similar to previous reports of costs relating to antibacterial-resistant infections [11,13,14,25,26], patients in the MDR group incurred significantly greater costs than those in the non-MDR group. In a previous study of hospital-associated infections due to various pathogens, MDR infections cost US$178,359 (SD $198,247) compared with $106,293 (SD $128,447) in 2008 ($P<0.001$) [26], whereas our study found substantially lower costs associated with suspected respiratory infections due to *P. aeruginosa*, but similarly showed higher costs for MDR infections compared with non-MDR infections ($124,335, SD $170,947 vs $68,404, SD $77,258; $P<0.001$). As far as we are aware, our analysis is one of the first studies showing that overall, hospitals lost money treating patients with suspected respiratory infection due to *P. aeruginosa* and for those cases in the MDR group, the average loss increased by over US$10,000 compared with patients in the non-MDR group. Significant covariates associated with MDR in this study include patients who were severely ill, have had previous hospitalizations, and patients with septicemia, consistent with previous studies

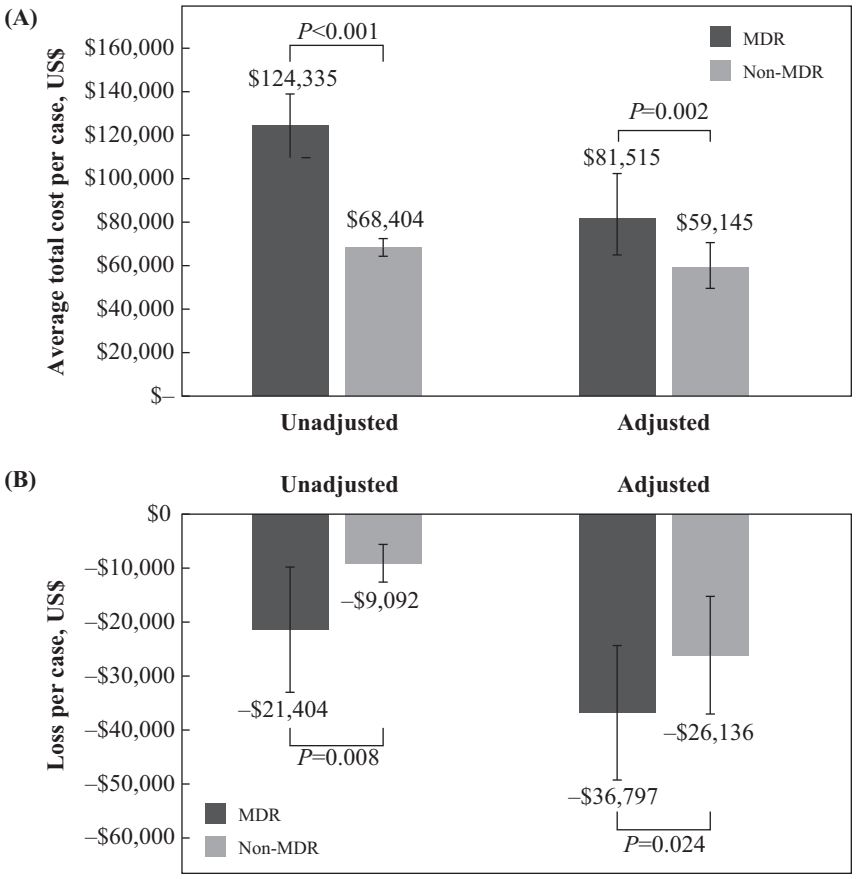

Figure 3. Unadjusted and multi-variable adjusted costs (multi-drug resistant (MDR) vs non-MDR). (a) Average total cost per case. (b) Loss per case. US$, United States dollar.

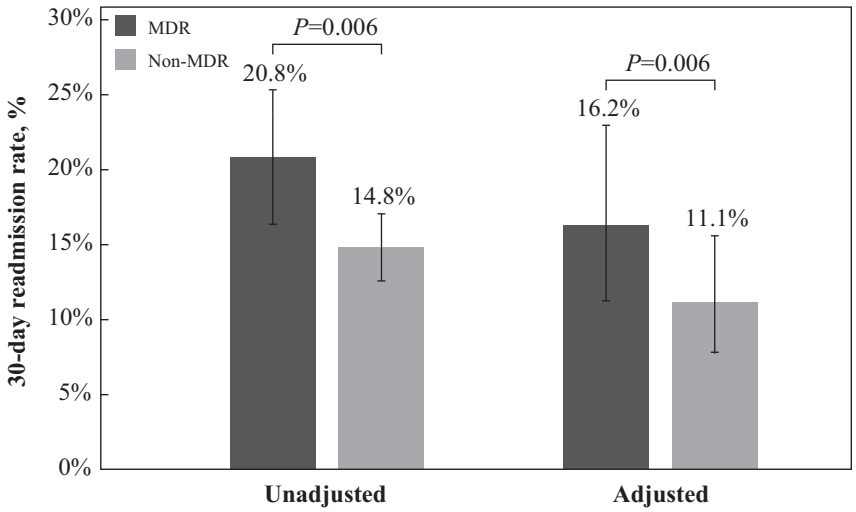

Figure 4. Unadjusted and multi-variable-adjusted readmission rates (multi-drug resistant (MDR) vs non-MDR).

[27,28]. This highlights the need for early identification of high-risk patients and appropriate intervention [19].

As this is a retrospective, electronic-database study, one limitation is the potential for residual confounding due to unmeasured variables. The multi-variable models included patient demographics, clinical severity, comorbidities, underlying clinical conditions, and time prior to the onset of infection to control for the measurable potential confounders in the outcome measures. It is also important to note that the laboratory data included in the database came from multiple hospitals with locally applied microbiological assessments; therefore, there may be differences in interpretation between sites, which could be considered a limitation of this study. Another limitation is that differences in testing methodology at

centers, as well as variances in interpretation of susceptibility at individual centers and treatment information were not available for all study sites. For 48 sites that provided pharmacy data, we were able to confirm that 98.3% of the study population had evidence of antibiotic treatment. This additional evidence supports a high likelihood of infections for the full study population. Our sensitivity analysis of all five outcomes yielded results consistent with those from the full study population, which lends support to the validity of this study. To more rigorously define infections, other clinical metrics, including chest X-rays, signs, and symptoms would be needed. With the rapid automation of electronic medical records, these more complex data may become available in the future for epidemiology studies.

Although beyond the scope of this study, analysis of appropriate vs inappropriate initial antibacterial therapy (IIAT) is an area that warrants future study. Currently the literature shows inconsistent results. An earlier study found that IIAT occurred more often in antibacterial-resistant infections in that 5% of patients needed a different antibacterial agent for appropriate coverage after reviewing culture results compared with <1% patients with susceptible infections ($P<0.001$) [25]. Data from a study of patients with bacteremia due to *P. aeruginosa* showed that appropriate treatment that was delayed by >52 h significantly increased the 30-day mortality compared with patients who received appropriate therapy in a timely fashion (43.8% vs 19.2%; $P=0.008$) [16]. However, these results were in contrast to a study of a similar patient population that found no increased risk of mortality in patients who received IIAT, but did find a 7% reduction in mean LOS for patients who received appropriate empiric therapy [30]. Finally, the adjusted estimate of incremental burden of MDR compared with non-MDR *P. aeruginosa* in our study is more conservative than previous studies that compared MDR with non-infection cases, a comparison which may generate an inflated estimate.

Patients with suspected respiratory infections due to laboratory-confirmed MDR *P. aeruginosa* had a higher in-hospital mortality for both unadjusted and multivariable adjusted rates compared with patients in the non-MDR group. In addition, hospitals lost money while treating patients with suspected respiratory infections due to *P. aeruginosa* and the average loss increased by over US$10,000 for patients in the MDR group compared with the non-MDR group.

MDR infections present a substantial clinical challenge in that there are limited therapeutic options, and MDR infections often occur in patients who are additionally compromised with severe illness. Rapid identification of the infecting pathogen, pathogen resistance type, selection of an antibacterial agent with appropriate coverage, and resolution of the infection is of utmost importance. There is a clear need to identify patients at high risk of MDR and aggressively treat and manage these patients to minimize the clinical and economic burden.

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Author contributions

Study concept and design: Y.T., S.M., G.Y., L.V., V.G., L.P. Data analysis and interpretation: Y.T., S.M., G.Y., L.V., V.G., S.K., L.P. Drafting manuscript: Y.T., L.P. Critical revision of manuscript: Y.T., S.M., G.Y., L.V., V.G., S.K., L.P. Final approval of manuscript: Y.T., S.M., G.Y., L.V., V.G., S.K., L.P. The authors Y.T., L.V., S.K., and G.Y. have access to all the data used for the current study. Y.T. takes responsibility for data accuracy and integrity.

Conflict of interest statement

Y.T., G.Y., L.V., S.K., and V.G. are employees of Becton, Dickinson & Company, Franklin Lakes, New Jersey, USA. S.M. and L.P. are employees of MSD, and may own stock and/or hold stock options in the Company.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.06.005.

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