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MAJOR ARTICLE

Infectious Diseases Consultation Reduces 30-Day and 1-Year All-Cause Mortality for Multidrug-Resistant Organism Infections

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Background. Multidrug-resistant organism (MDRO) infections are associated with high mortality and readmission rates. Infectious diseases (ID) consultation improves clinical outcomes for drug-resistant *Staphylococcus aureus* bloodstream infections. Our goal was to determine the association between ID consultation and mortality following various MDRO infections.

Methods. This study was conducted with a retrospective cohort (January 1, 2006–October 1, 2015) at an academic tertiary referral center. We identified patients with MDROs in a sterile site or bronchoalveolar lavage/bronchial wash culture. Mortality and readmissions within 1 year of index culture were identified, and the association of ID consultation with these outcomes was determined using Cox proportional hazards models with inverse weighting by the propensity score for ID consultation.

Results. A total of 4214 patients with MDRO infections were identified. ID consultation was significantly associated with reductions in 30-day and 1-year mortality for resistant *S. aureus* (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.36–0.63; and HR, 0.73, 95% CI, 0.61–0.86) and *Enterobacteriaceae* (HR, 0.41; 95% CI, 0.27–0.64; and HR, 0.74; 95% CI, 0.59–0.94), and 30-day mortality for polymicrobial infections (HR, 0.51; 95% CI, 0.31–0.86) but not *Acinetobacter* or *Pseudomonas*. For resistant *Enterococcus*, ID consultation was marginally associated with decreased 30-day mortality (HR, 0.81; 95% CI, 0.62–1.06). ID consultation was associated with reduced 30-day readmission for resistant *Enterobacteriaceae*.

Conclusions. ID consultation was associated with significant reductions in 30-day and 1-year mortality for resistant *S. aureus* and *Enterobacteriaceae*, and 30-day mortality for polymicrobial infections. There was no association between ID consultation and mortality for patients with resistant *Pseudomonas*, *Acinetobacter*, or *Enterococcus*, possibly due to small sample sizes. Our results suggest that ID consultation may be beneficial for patients with some MDRO infections.

Keywords. infectious diseases consultation; multidrug-resistant organisms.

Multidrug-resistant organisms (MDROs) are an urgent public health threat, with increasing global incidence, progressively fewer treatment options, an association with significant health care costs, and high rates of morbidity, mortality, and readmissions [1–7]. With such a significant burden of disease due to MDROs, strategies are needed to reduce the morbidity, mortality, and societal cost of MDRO infections. One potential intervention to improve outcomes in patients with MDRO infections is infectious diseases (ID) consultation.

Previous research has shown that ID consultation is associated with up to 67% reductions in mortality, decreased rates of infection relapse, increased adherence to national treatment guidelines, reduced rates of readmission, and up to 58% lower rates of treatment failure in patients with various infections [8–15]. However, there is limited research regarding the association of ID consultation with clinical outcomes among patients with MDRO infections. Currently available research on ID consultation and MDROs centers on methicillin-resistant *Staphylococcus aureus* bacteremia, for which ID consultation is associated with improved patient outcomes [8, 12–14].

We studied hospitalized patients with MDRO infections, confirmed by positive bloodstream, bronchoalveolar lavage (BAL)/bronchial wash, or other sterile site cultures to determine whether ID consultation was associated with reductions in mortality and readmissions for various MDRO pathogens. Understanding the association of ID consultation with clinical outcomes will help guide the decisions of physicians caring for patients with MDRO infections.

METHODS

Study Location and Patient Population

This study was conducted at Barnes-Jewish Hospital (BJH), a 1250-bed academic medical center located in St. Louis, Missouri. The study period was January 1, 2006, to October 1, 2015. Hospitalized patients with a positive sterile site or BAL/bronchial wash culture for *Enterobacteriaceae*, *Enterococcus*

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spp., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Acinetobacter* spp. were analyzed for eligibility. Antimicrobial susceptibilities for all pathogens were determined using disc diffusion methodology. Sterile sites were defined as bloodstream; pleural, intra-abdominal, pericardial, cerebrospinal, and synovial fluids; bone marrow; and surgical specimens collected from lymph nodes, central nervous system (CNS), liver, spleen, kidney, pancreas, ovary, or vascular tissue. Patients were excluded if they died or were discharged 48 hours after the first positive culture was collected, as these patients' outcomes were unlikely to be affected by ID consultation. This study was approved by the Washington University School of Medicine Institutional Review Board with a waiver of informed consent.

Study Design and Data Collection

Utilizing a retrospective cohort study design, the first hospitalization between January 2006 and October 2015 of all patients age ≥18 years with MDR *Enterobacteriaceae*, *Enterococcus* spp., *S. aureus*, *P. aeruginosa*, or *Acinetobacter* spp. isolated from the bloodstream, other sterile sites, or BAL/bronchial wash culture was identified. The primary end points were death and readmission after MDRO infection. Baseline characteristics, including age, gender, race, Acute Physiology and Chronic Health Evaluation (APACHE) II [22] scores (calculated based on clinical data from the 24 hours before and after positive cultures were obtained), and medical comorbidities (based on ICD-9-CM diagnosis codes), were obtained. Patients who died during the index hospitalization or were discharged on hospice were considered to be expired at the time of hospital discharge and excluded from the readmission analyses.

Definitions and Data Sources

Time to death was calculated from the day that a culture positive for an MDRO was obtained. All data were obtained from the BJC Healthcare Informatics database, maintained by the Center for Clinical Excellence, BJC Healthcare. BJH is the largest adult teaching institution for BJC Healthcare, a large integrated health care system of both inpatient and outpatient care. The system includes 13 hospitals in a geographic region surrounding and including St. Louis, Missouri. BJH has >50 000 admissions annually, and the BJC system >140 000. All index hospitalizations used to define the cohort occurred at BJH. Readmissions to BJH or any other BJC acute care facility were captured. Expiration dates from stays in any BJC facility are included in the Informatics database. For patients with less than 1 year of follow-up after index hospitalization, the Social Security Death Index (SSDI) was used to identify patient deaths. Patients without follow-up in the BJC system and not in the SSDI were considered lost to follow-up on their last date of care in a BJC facility.

Defining MDROs

We utilized multiple definitions of drug resistance as outlined by the US Centers for Disease Control and Prevention (CDC) and European CDC (Supplementary Table 1) [16–18]. Any *Enterobacteriaceae* was presumed to be an extended-spectrum beta lactamase (ESBL) producer if ceftriaxone or ceftazidime was intermediate or resistant. Patients were considered to have a vancomycin intermediate *S. aureus* (VISA) infection if *S. aureus* isolated in culture was determined to have a vancomycin minimum inhibitory concentration of 4 or 8 μg/mL, in accordance with Clinical and Laboratory Standards Institute recommendations [19].

Statistical Analysis

Mortality and readmissions by index hospitalization pathogen group were analyzed using Kaplan-Meier curves. Univariate analysis was performed by chi-square or the Fisher exact test where appropriate for categorical values. The Student *t* test or Mann-Whitney *U* test was used where appropriate for continuous variables. Continuous variables were reported as means with standard deviations or medians and interquartile ranges (IQRs). Categorical data were expressed as frequencies. For univariate analysis of variables associated with mortality or readmission, Kaplan-Meier analysis with comparison by the log-rank test was used for categorical values, and univariate Cox regression for continuous variables.

Descriptive statistics were performed using the chi-square and Mann-Whitney *U* tests. To create the propensity score for ID consultation, we used multivariable logistic regression, with ID consult as the dependent variable and a wide range of independent variables (Supplementary Table 2). The independent variables chosen for inclusion in the propensity score model included all variables with $P < .20$ in univariate analysis or clinical/biological plausibility for association with mortality or ID consultation. Balance diagnostics using standardized differences were used to assess the performance of the propensity score model, with an SD >0.10 considered evidence of imbalance [20]. Standard differences of the factors in the propensity score are shown in Supplementary Table 4.

For analysis of 30-day and 1-year mortality and 30-day readmissions, Cox proportional hazards models with backward selection were performed with inverse weighting by the propensity score. Before model development, the top 5% and bottom 5% of the population based on the propensity score were trimmed from the population [21]. To determine the impact of ID consultation on mortality and readmission depending on pathogen type, interaction terms were created. All variables included in the final Cox proportional hazards model are reported. A *P* value of <.05 was considered significant in all analyses. All analyses were done using SAS v9.4.

RESULTS

A total of 4429 patients with MDROs from sterile sites or BAL/bronchial wash cultures were identified, 202 of which were excluded due to death or discharge in the 48 hours after positive

culture. An additional 13 patients who had left-ventricular assist devices were excluded, as all but 1 had an ID consult. Of the remaining 4214 patients, 840 (19.9%) died or were discharged on hospice within 30 days of the first positive culture, and 1832 (43.5%) died within 1 year. Among survivors of the index MDRO hospitalization, 1076 (31.9%) were readmitted within 30 days and 2049 (60.7%) were readmitted within 1 year. Table 1 shows 30-day and 1-year mortality and readmission rates by pathogen group and ID consultation status. Among patients without an ID consult, 578 (24.4%) died within 30 days of positive culture and 1115 (47.0%) within 1 year. For patients who had ID consults, 262 (14.2%) died within 30 days and 717 (38.9%) within 1 year.

In univariate analyses for each drug-resistant pathogen group, nonsurvivors tended to be older, have more comorbidities, and higher APACHE-II scores than survivors (Supplementary Table 3).

Mortality

After adjustment using a multivariate Cox proportional hazards model with inverse weighting by the propensity score, ID consultation was significantly associated with reduced all-cause mortality for several pathogen groups at different time points. The median time from positive MDRO culture to ID consultation was 2.1 days, with an interquartile range of 0.4 to 4.5. The time to ID consultation was not significantly different between survivors and nonsurvivors (2.08 vs 2.43 days, respectively; $P = .12$). At 30 days after positive culture, ID consultation was associated with a reduced risk of all-cause mortality for drug-resistant *S. aureus* (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.36–0.63; $P < .0001$), drug-resistant *Enterobacteriaceae* (HR, 0.41; 95% CI, 0.27–0.64; $P < .0001$), and polymicrobial MDRO infections (HR, 0.51; 95% CI, 0.31–0.86; $P = .011$) (Table 2). At 30 days, ID consultation was associated with marginally reduced risk of mortality for drug-resistant *Enterococcus* (HR, 0.81; 95% CI, 0.62–1.06; $P = .12$).

At 1 year, ID consultation remained associated with reduced risk of all-cause mortality for drug-resistant *S. aureus* (HR, 0.73; 95% CI, 0.61–0.86; $P < .001$) and drug-resistant *Enterobacteriaceae* (HR, 0.74; 95% CI, 0.59–0.94; $P < .012$). ID consultation was not associated with reduced mortality for patients with drug-resistant *Pseudomonas* or *Acinetobacter* at 30 days or 1 year.

Other risk factors for 30-day mortality in the multivariate Cox proportional hazards model with inverse weighting by the propensity score included patient and infection characteristics, as well as admitting service (Table 2). Patients with positive blood cultures and those in an ICU at the time a positive culture was drawn had increased hazard ratios for 30-day mortality (Table 2). In addition, bone marrow transplant, cardiovascular disease, cirrhosis, leukemia, lymphoma, metastatic cancer, human immunodeficiency virus, and presence of an automated implantable cardioverter defibrillator were all associated with increased risk of 30-day mortality (Table 2).

Readmissions

In propensity score–weighted multivariable Cox proportional hazards models, ID consultation was associated with decreased risk of 30-day readmission for drug-resistant *Enterobacteriaceae* infections (HR, 0.74; 95% CI, 0.56–0.97; $P = .028$) only. ID consultation was not associated with decreased risk of 30-day or 1-year readmissions for other pathogens. In patients receiving

Table 1. 30-Day and 1-Year Mortality and Readmission Rates by Drug-Resistant Pathogen Group and ID Consultation Status

Index Hospitalization Drug-Resistant Pathogen	30-d Mortality, %	1-y Mortality, %	Hospital Discharge Survivors, %	30-d Readmission, %	1-y Readmission, %
Staphylococcus aureus (n = 1674)	284 (17.0)	633 (37.8)	1412 (84.3)	428 (30.3)	840 (59.5)
ID consultation (n = 832)	87 (10.5)	259 (31.1)	753 (90.5)	240 (31.9)	457 (60.7)
No ID consultation (n = 842)	197 (23.4)	374 (44.4)	659 (78.3)	188 (28.5)	383 (58.1)
Enterococcus spp. (n = 807)	235 (29.1)	479 (59.4)	561 (69.5)	225 (40.1)	384 (68.4)
ID consultation (n = 359)	90 (25.1)	194 (54.0)	251 (69.9)	98 (39.0)	168 (66.9)
No ID consultation (n = 448)	145 (32.4)	285 (63.6)	310 (69.2)	127 (41.0)	216 (69.7)
Enterobacteriaceae (n = 1168)	185 (15.8)	434 (37.2)	975 (83.5)	298 (30.6)	585 (60.0)
ID consultation (n = 375)	31 (8.3)	116 (30.9)	329 (87.7)	85 (25.8)	202 (61.4)
No ID consultation (n = 793)	154 (19.4)	318 (40.1)	646 (81.5)	213 (33.0)	383 (59.3)
Acinetobacter spp. (n = 96)	35 (36.5)	53 (55.2)	61 (63.5)	13 (21.3)	33 (54.1)
ID consultation (n = 54)	16 (29.6)	27 (50)	37 (68.5)	7 (18.9)	21 (56.8)
No ID consultation (n = 42)	19 (45.2)	26 (61.9)	24 (57.1)	6 (25.0)	12 (50.0)
Pseudomonas aeruginosa (n = 190)	36 (18.9)	82 (43.2)	145 (76.3)	49 (33.8)	92 (63.4)
ID consultation (n = 77)	13 (16.9)	36 (46.8)	59 (75.3)	23 (39.0)	41 (69.5)
No ID consultation (n = 113)	23 (20.4)	46 (40.7)	86 (76.1)	26 (30.2)	51 (59.3)
Polymicrobial (n = 279)	65 (23.3)	151 (54.1)	185 (66.3)	63 (34.1)	115 (62.2)
ID consultation (n = 146)	25 (17.1)	85 (58.2)	93 (63.7)	31 (33.3)	57 (61.3)
No ID consultation (n = 133)	40 (30.1)	66 (49.6)	92 (69.2)	32 (34.8)	58 (63.0)

Abbreviation: ID, infectious diseases.

Table 2. Adjusted Hazard Ratios of Risk Factors for 30-Day Mortality in Propensity Score–Weighted Cox Proportional Hazards Model

Risk Factor	HR for 30-d Mortality (95% CI)	*P* Value
ID consult*Drug-resistant pathogen group[a]		
Staphylococcus aureus	0.48 (0.36–0.63)	<.0001
Enterococcus	0.81 (0.62–1.06)	.12
Enterobacteriaceae	0.41 (0.27–0.64)	<.0001
Acinetobacter	0.64 (0.32–1.25)	.19
Pseudomonas	0.82 (0.39–1.69)	.58
Polymicrobial	0.51 (0.31–0.86)	.01
Positive blood culture	1.51 (1.22–1.86)	.0002
Comorbidities		
BMT	1.92 (1.42–2.58)	<.0001
CHF	1.18 (0.99–1.41)	.062
CKD	0.85 (0.70–1.03)	.093
Cardiovascular disease	1.46 (1.21–1.76)	<.0001
Cirrhosis	2.73 (2.21–3.37)	<.0001
ESRD	0.77 (0.59–1.01)	.059
Leukemia	1.35 (1.07–1.70)	.012
Lymphoma	1.35 (1.03–1.77)	.030
Solid organ malignancy	1.22 (0.99–1.50)	.060
Presence of an AICD	1.61 (1.10–2.34)	.014
History of HIV/AIDS	3.01 (1.58–5.75)	.0009
Metastatic cancer	2.31 (1.77–3.02)	<.0001
Admitting service		
Medicine	1.58 (1.30–1.93)	<.0001
Neurology	1.89 (1.11–3.19)	.018
In ICU at time of positive culture	1.96 (1.67–2.30)	<.0001

[a]Modeled as an interaction term between ID consult and drug-resistant pathogen group. Age and APACHE-II scores were also included in the model as categorical variables.

Abbreviations: AICD, automated implantable cardioverter defibrillator; AIDS, acquired immunodeficiency syndrome; BMT, bone marrow transplant; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HR, hazard ratio; ICU, intensive care unit; ID, infectious diseases.

ID consultation, there was an increased risk of 30-day readmission for patients with drug-resistant *S. aureus* infections (HR, 1.27; 95% CI, 1.03–1.57; $P = .023$).

DISCUSSION

We found that ID consultation was associated with reductions in 30-day and 1-year all-cause mortality for several MDRO pathogens. Previous studies have shown a mortality benefit to ID consultation for patients with bloodstream infections due to drug-resistant *S. aureus* [8, 12]. In addition, ID consultation has been shown to result in reductions in mortality and improvements in a variety of other quality-of-care metrics [9–11]. For the other MDROs characterized in the present study, we are unaware of any literature that examines an association between ID consultation and mortality. To our knowledge, this is the first study to report an association between ID consultation and reductions in mortality for drug-resistant *Enterobacteriaceae* and polymicrobial MDRO infections.

We did not find an association with ID consultation and reduced mortality for drug-resistant *Acinetobacter* and *Pseudomonas*. However, these were the 2 smallest groups in our study, and we were underpowered to detect a mortality difference. ID consultation has been associated with higher rates of appropriate empiric antimicrobial therapy in other studies [8], and delays in appropriate therapy are known determinants of mortality in patients with *Pseudomonas* and *Acinetobacter* infections [22–26]. Therefore, it is possible that ID consultation would reduce mortality for infections with these organisms if studied in larger cohorts. Future studies should address this question.

For patients with drug-resistant *Enterococcus* infections, ID consultation was marginally associated with a reduction in 30-day mortality. It is possible that with a larger sample size, this finding would reach statistical significance.

ID consultation was associated with a significant reduction in 30-day readmission rates for patients with drug-resistant *Enterobacteriaceae*, a novel finding. Increasing the use of ID consultation for drug-resistant *Enterobacteriaceae* infections could potentially help hospitals reduce financial penalties for readmissions. On the other hand, ID consultation was associated with increased risk of 30-day readmission in patients with drug-resistant *S. aureus* infections. This may be due to high rates of vancomycin use for *S. aureus* at our institution [27] and associated adverse drug events, although we do not have treatment data for this cohort to confirm this possibility. Even with this increased readmission rate, ID consultation was associated with a significant reduction in mortality after drug-resistant *S. aureus* infection, pointing to an overall benefit. The lack of an association between ID consultation and readmissions for the other pathogen groups could be due to small sample size or underlying medical comorbidities associated with high morbidity and mortality such as diabetes, heart failure, leukemia, and solid organ malignancies.

Our study has several limitations. The retrospective nature of the study makes it difficult to elucidate possible confounders that could have biased the outcome measures. It is possible that due to the retrospective study design, we were unable to account for unrecognized confounding variables that linked ID consultation and mortality. Without drug administration data, we are unable to determine if the higher rate of appropriate therapy in the ID consultation group was the reason for reduced mortality. This was a single-center study, and results may not be generalizable to other centers. Even in a large center, numbers were small for some pathogen groups. However, the strength of the association between ID consultation and mortality in the largest pathogen groups is robust and likely applicable to other tertiary care referral centers with similar patient case mixes.

We are also limited by a lack of data on non-MDRO pathogens with which to compare benefit of ID consultation, but previous work has shown that patients acquiring MDRO infections are fundamentally different than patients with non-MDRO infections [28, 29]. Therefore, we felt it was more useful to compare patients with different types of MDROs rather than

comparing patients with non-MDRO infections with those with MDRO infections of the same type of organism.

Another limitation of our study is loss to follow-up. It is possible that some patients went to a facility outside of the BJC Healthcare network and that we were unable to capture their mortality and readmission status. However, we cross-checked all patients in the Social Security Death Index if they did not have follow-up within the BJC Healthcare network within 1 year in an attempt to reduce the number of uncaptured deaths.

In conclusion, ID consultation is significantly associated with reductions in all-cause mortality for drug-resistant *S. aureus*, *Enterobacteriaceae*, and polymicrobial MDRO infections as well as reductions in 30-day readmissions after *Enterobacteriaceae* infection. Comorbidities and severity of acute and chronic illnesses also were risk factors for mortality and readmissions. By analyzing outcomes after ID consultation, we hope to encourage ID involvement and collaboration with teams caring for patients with MDRO infections to improve patient outcomes. Our research further emphasizes the crucial role of ID physicians in the face of ever-increasing antimicrobial resistance.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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