Characteristics of surgical patients receiving inappropriate empiric antimicrobial therapy

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BACKGROUND: Inappropriate antibiotics have been observed to result in an increased duration of antibiotic treatment and hospital length of stay, development of multidrug-resistant organisms, and mortality rate compared with appropriate antibiotic treatment. Few studies have evaluated independent risk factors associated with inappropriateness. The purpose of this study was to identify independent predictors of inappropriate, empiric antimicrobial therapy for the treatment of severe sepsis.

METHODS: This was a retrospective analysis of a prospectively maintained database of all surgical/trauma patients admitted to a tertiary care center from 1996 to 2007 and treated for sepsis. "Appropriate" empiric antibiotic treatment was determined by sensitivity testing. Demographics and comorbidities, infection sites, infection organisms, and outcomes between strata were compared. Differences in outcome were estimated using relative risk and 95% confidence intervals for correlated data.

RESULTS: A total of 2,855 patients (7,158 infections) were identified. Independent predictors of inappropriate, empiric antimicrobial therapy for the treatment of severe sepsis included site of infection and organism type. Severity of illness, age, medical conditions, and community versus health care–associated infections were not associated with inappropriate therapy. Although inappropriate empiric therapy was associated with a longer length of stay and duration of antimicrobial use, it did not result in higher mortality.

CONCLUSION: Our study observed that inappropriate empiric antibiotic selection is related to site of infection and pathogen. Other clinical variables do not appear to predict inappropriateness of antibiotic treatment. Efforts should be focused on early broad-spectrum therapy and more rapid microbiologic methods. (*J Trauma Acute Care Surg*. 2014;77: 546–554. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic/care management study, level II.

KEY WORDS: Inappropriateness; appropriateness; empiric antimicrobial therapy; predictors.

Antibiotic initiation must often begin before the infecting organism or sensitivities are known. Thus, current guidelines for the treatment of sepsis include empiric broad-spectrum antibiotics within the first hour of recognized signs and symptoms; however, differences of opinion exist as to which antibiotics to start.[1,2]

Recent literature suggests that the incidence of inappropriate initial antibiotic selection for the treatment of sepsis varies between 9% and 56%.[3–10] Inappropriate antibiotic selection has been observed to result in an increased duration of antibiotic treatment, development of multidrug-resistant (MDR) organisms, duration of hospital length of stay (LOS), and mortality rate as compared with appropriate antibiotic selection.[4–21] However, few studies have evaluated independent risk factors associated with inappropriateness.

The purpose of this study was to identify independent predictors of inappropriate, empiric antimicrobial therapy for the treatment of severe sepsis among a large cohort of surgical and trauma patients at a large tertiary care center. We hypothesized that specific clinical characteristics would help identify patients at highest risk for inadequate empiric antimicrobial therapy and help guide antimicrobial choices.

PATIENTS AND METHODS

Study Design

Institutional review board approval was obtained before data analysis. This was a retrospective analysis of a prospectively maintained database of all infectious episodes affecting surgical patients (e.g., general, abdominal organ transplant, and trauma) admitted to the University of Virginia Health System from 1996 to 2007 and treated for infection. After 2007, study protocols dictating antibiotic timing and choice were enacted, making the analysis of the relationship between empiric therapy and outcome significantly more difficult. Data were collected by chart review every other day, as well as by patient examination, physician interview, review of pharmacy data, and review of laboratory/microbiologic data. Episodes of infection were classified separately for a single patient if more than 72 hours apart. Empiric broad-spectrum antibiotics were initiated and continued until antibiotic appropriateness was determined by in vitro resistance or sensitivity. Patients were followed until death or hospital discharge. This study is a comparison of patients stratified by appropriateness of empiric antibiotic therapy.

Patients

Patient demographics and comorbidities evaluated at time of each infectious episode included sex, age, patient-defined race, solid organ transplant (e.g., kidney, liver, pancreas, kidney/pancreas, liver/kidney, heart, lung, or small bowel), trauma, diabetes mellitus, hypertension, hyperlipidemia, obesity, cardiovascular disease, peripheral vascular disease, cerebrovascular disease, pulmonary disease, ventilator dependence, renal insufficiency (RI), hemodialysis dependence, hepatic insufficiency, malignancy, long-term steroid use, human immunodeficiency virus (HIV), prior blood cell product transfusion during same hospitalization period, nosocomial infection, patient location at time of infection (e.g., home, hospital ward, intensive care unit [ICU], other), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, maximum temperature, white blood cell count, site of infection, and cultured organism. Patient outcomes evaluated included mortality, hospital LOS, and antibiotic duration.

Definitions

"Inappropriate" antimicrobial treatment was defined as empiric antibiotics initiated on Day 1 of therapy that did not treat all organisms based on subsequent sensitivity testing as opposed to "appropriate" treatment, defined as initial coverage that met these criteria. RI was defined as a prehospital, baseline serum creatinine of greater than or equal to 2.0 mg/dL. Obesity was defined as a body mass index of greater than 30. Pulmonary disease was defined as the active treatment of lung disease before hospital admission. Other comorbidities were defined by chart review or patient examination. The following assumptions were made regarding bacterial and fungal sensitivities: (1) fungal

TABLE 1. Demographics and Comorbidities Stratified by Appropriateness in Empiric Antimicrobial Therapy and Unadjusted Log-Binomial Regression Analysis of Inappropriateness*

Characteristics	Inappropriate, n (%)	Appropriate, n (%)	*p***	RR (95%CI)**
No. patients	597 (21)	2,258 (79)	—	—
No. infectious episodes	2,085 (29)	5,073 (71)	—	—
Sex				
Female	929 (45)	2,243 (44)	—	1.0 Referent
Male	1,156 (55)	2,830 (56)	0.63	0.98 (0.90–1.07)
Age, y				
Mean ± SD	54 ± 16	53 ± 16	0.067	—
Median (IQR)	55 (24)	53 (24)		
Q1 (≤41)	498 (24)	1,328 (26)	—	1.0 Referent
Q2 (42–54)	540 (26)	1,330 (26)	0.36	1.1 (0.94–1.2)
Q3 (55–65)	516 (25)	1,217 (24)	0.044	1.1 (1.004–1.3)
Q4 (≥66)	531 (25)	1,198 (24)	0.042	1.1 (1.005–1.3)
Race				
White	1,716 (82)	4,107 (81)	—	1.0 Referent
Black	321 (15)	810 (16)	0.20	0.92 (0.82–1.04)
Other	21 (1)	91 (2)	0.078	0.64 (0.38–1.05)
Hispanic	27 (1)	65 (1)	0.95	0.99 (0.69–1.4)
Transplant†				
No	1,628 (78)	3,992 (79)	—	1.0 Referent
Yes	457 (22)	1,081 (21)	0.71	1.0 (0.92–1.1)
Trauma				
No	1,654 (79)	3,910 (77)	—	1.0 Referent
Yes	431 (21)	1,163 (23)	0.058	0.91 (0.82–1.003)
Diabetes mellitus				
No	1,609 (77)	4,019 (79)	—	1.0 Referent
Yes	476 (23)	1,054 (21)	0.29	0.95 (0.86–1.05)
Hypertension				
No	1,367 (66)	3,323 (66)	—	1.0 Referent
Yes	718 (34)	1,750 (35)	0.80	1.0 (0.93–1.1)
Hyperlipidemia				
No	1,964 (94)	4,780 (94)	—	1.0 Referent
Yes	121 (6)	293 (6)	0.98	1.0 (0.85–1.2)
Obesity				
No	1,940 (93)	4,728 (93)	—	1.0 Referent
Yes	145 (7)	345 (7)	0.96	1.0 (0.84–1.2)
Cardiovascular disease				
No	1,661 (80)	4,124 (81)	—	1.0 Referent
Yes	424 (20)	949 (19)	0.25	1.1 (0.96–1.2)
PVD				
No	1,985 (95)	4,878 (96)	—	1.0 Referent
Yes	100 (5)	195 (4)	0.18	1.1 (0.94–1.4)
Pulmonary disease				
No	1,826 (88)	4,505 (89)	—	1.0 Referent
Yes	259 (12)	568 (11)	0.13	1.1 (0.97–1.3)
Ventilator dependence				
No	1,512 (73)	3,671 (72)	—	1.0 Referent
Yes	573 (27)	1,402 (28)	0.69	0.98 (0.88–1.08)
RI				
No	1,523 (73)	3,671 (72)	—	1.0 Referent
Yes	573 (27)	1,402 (28)	0.78	1.0 (0.87–1.2)
Hemodialysis				
No	1,823 (87)	4,492 (89)	—	1.0 Referent
Yes	262 (13)	581 (11)	0.40	1.1 (0.93–1.2)

(continued on next page)

TABLE 1. *(Continued)*

Characteristics	Inappropriate, n (%)	Appropriate, n (%)	*p***	RR (95%CI)**
Hepatic insufficiency				
No	1,903 (91)	4,659 (92)	—	1.0 Referent
Yes	182 (9)	414 (8)	0.13	1.1 (0.97–1.3)
Malignancy				
No	1,844 (88)	4,476 (88)	—	1.0 Referent
Yes	241 (12)	597 (12)	0.91	1.0 (0.89–1.1)
Long-term steroid use				
No	1,495 (72)	3,710 (73)	—	1.0 Referent
Yes	590 (28)	1,363 (27)	0.37	1.0 (0.95–1.1)
HIV				
No	2,079 (100)	5,062 (100)	—	1.0 Referent
Yes	6 (0)	11 (0)	0.49	1.3 (0.62–2.8)
Prior transfusion				
No	1,056 (51)	2,749 (54)	—	1.0 Referent
Yes	1,029 (49)	2,324 (46)	0.019	1.1 (1.02–1.2)
Nosocomial infection				
No	322 (15)	976 (19)	—	1.0 Referent
Yes	1,763 (85)	4,097 (81)	0.0014	1.2 (1.1–1.4)
Patient location				
Home	592 (28)	1,499 (30)	—	1.0 Referent
Hospital ward	677 (32)	1,647 (32)	0.65	1.0 (0.92–1.1)
ICU	727 (35)	1,755 (35)	0.82	1.0 (0.91–1.1)
Other	89 (4)	172 (3)	0.087	1.2 (0.97–1.5)
APACHE II score during infection				
Mean ± SD	15 ± 7.3	15 ± 7.8	0.48	—
Median (IQR)	15 (9)	14 (11)		
Q1 (≤9)	502 (24)	1,357 (27)	—	1.0 Referent
Q2 (10–15)	631 (30)	1,479 (29)	0.058	1.1 (0.996–1.2)
Q3 (16–20)	524 (25)	1,128 (22)	0.011	1.2 (1.04–1.3)
Q4 (≥21)	428 (21)	1,109 (22)	0.61	1.0 (0.91–1.2)
Tmax during infection‡				
Mean ± SD	38 ± 1.2	38 ± 1.7	0.37	—
Median (IQR)	38 (1.1)	38 (1.7)		
Q1 (≤37.2)	595 (29)	1,376 (27)	—	1.0 Referent
Q2 (37.3–38.2)	500 (24)	1,196 (24)	0.95	1.0 (0.89–1.1)
Q3 (38.3–38.9)	533 (26)	1,295 (26)	0.62	0.97 (0.86–1.1)
Q4 (≥39.0)	456 (22)	1,201 (24)	0.25	0.93 (0.81–1.1)
WBC during infection				
Mean ± SD	15 ± 8.9	15 ± 8.6	0.089	—
Median (IQR)	14 (10)	13 (10)		
Q1 (≤8.7)	497 (24)	1,306 (26)	—	1.0 Referent
Q2 (8.8–13.3)	499 (24)	1,300 (26)	0.75	1.0 (0.91–1.1)
Q3 (13.4–18.8)	549 (26)	1,224 (24)	0.031	1.1 (1.01–1.3)
Q4 (≥18.9)	540 (26)	1,243 (25)	0.11	1.1 (0.98–1.2)

*Characteristics analyzed per infectious episode.

**To accommodate for a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of inappropriateness among episodes of infection was computed using a GEE approach with robust SEs (i.e., Huber-White sandwich variance estimates).

†Transplants included kidney, 212 (45%); liver, 211 (45%); pancreas, 4 (1%); heart, 5 (1%); lung, 1 (0%); kidney/pancreas, 34 (7%); liver/kidney, 1 (0%); and small bowel, 1 (0%).

‡Missing category not shown.

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; ICU, intensive care unit; HIV, human immunodeficiency virus; IQR, interquartile range; PVD, peripheral vascular disease; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; RI, renal insufficiency; RR, relative risk; SD, standard deviation; Tmax, maximum temperature; WBC, white blood cell count.

TABLE 2. Sites of Infection Stratified by Appropriateness in Empiric Antimicrobial Therapy and Unadjusted Log-Binomial Regression Analysis of Inappropriateness*

Sites	Inappropriate, n (%)	Appropriate, n (%)	p**	RR (95%CI)**
No. patients	597 (21)	2,258 (79)	—	—
No. infectious episodes	2,085 (29)	5,073 (71)	—	—
CNS				
No	2,080 (100)	5,069 (100)	0.051	1.0 Referent
Yes	5 (0)	4 (0)		1.9 (0.996–3.5)
Peritoneum				
No	1,690 (81)	4,326 (85)	<0.0001	1.0 Referent
Yes	395 (19)	747 (15)		1.3 (1.1–1.4)
Upper GI				
No	2,064 (99)	4,958 (98)	0.0022	1.0 Referent
Yes	21 (1)	115 (2)		0.52 (0.34–0.79)
Colon				
No	2067 (99)	4,808 (95)	<0.0001	1.0 Referent
Yes	18 (1)	265 (5)		0.18 (0.11–0.30)
Lung				
No	1,766 (85)	4,059 (80)	<0.0001	1.0 Referent
Yes	319 (15)	1,014 (20)		0.79 (0.71–0.87)
Pleura				
No	2,056 (99)	5,035 (99)	0.017	1.0 Referent
Yes	29 (1)	38 (1)		1.5 (1.1–2.0)
Skin/soft tissue				
No	2,016 (97)	4,788 (94)	0.0004	1.0 Referent
Yes	69 (3)	285 (6)		0.66 (0.52–0.83)
Wound				
No	1,859 (89)	4,692 (92)	<0.0001	1.0 Referent
Yes	226 (11)	381 (8)		1.3 (1.2–1.5)
Line				
No	1,923 (92)	4,781 (94)	0.0010	1.0 Referent
Yes	162 (8)	292 (6)		1.2 (1.1–1.4)
Blood				
No	1,695 (81)	4,211 (83)	0.099	1.0 Referent
Yes	390 (19)	862 (17)		1.1 (0.99–1.2)
Urine				
No	1,652 (79)	4,104 (81)	0.068	1.0 Referent
Yes	433 (21)	969 (19)		1.1 (0.99–1.2)
Other				
No	2,075 (100)	5,056 (100)	0.75	1.0 Referent
Yes	10 (0)	17 (0)		1.2 (0.71–2.2)

*Characteristics analyzed per infectious episode.

**To accommodate for a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of inappropriateness among infectious episodes was computed using a GEE approach with robust SEs (i.e., Huber-White sandwich variance estimates).

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; RR, relative risk.

sensitivity testing was not available during the study period, and thus, we assumed that *Candida* species were always sensitive to fluconazole, except for *Candida kruzii*, which was considered resistant to fluconazole; (2) we did not routinely perform anaerobic sensitivity testing, and thus, we assumed that *Bacteroides fragilis* and Bacteroides non-fragilis were sensitive to flagyl, clindamycin, piperacillin/tazobactam, ampicillin/sulbactam, and all carbapenems; (3) we assumed all gram-positive (GP) cocci to be sensitive to vancomycin with the exception of vancomycin-resistant enterococci (VRE) (we have had no history of vancomycin-resistant *Staphylococcus aureus* or vancomycin-intermediate *S. aureus* at our institution); (4) we assumed all GP cocci as part of mixed infections to be adequately treated with penicillins, cephalosporins, carbapenems, and fluoroquinolones unless proven otherwise by sensitivity testing; and (5) we assumed all gram-negative rods to be adequately treated with penicillins, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and aztreonam unless proven otherwise by sensitivity testing.

Statistical Analysis

Categorical data were analyzed using either χ^2 or Fisher's exact test depending upon the size of data for each respective category. Continuous data were analyzed using either Student's *t* test or Deuchler-Wilcoxon test depending upon the normalcy of distribution. Variables not previously categorized were divided into quartiles before statistical analysis. Quartile categorization is advantageous because it limits the influence of outliers and allows for the assessment of trend across categories. Demographics and comorbidities, infection sites, infection organisms, and outcomes between strata were compared. To accommodate for a correlated data structure corresponding to multiple episodes of infection per individual, univariable and multivariable analyses of inappropriateness among infectious episodes were computed using a generalized estimating equation (GEE) approach with robust SEs (i.e., Huber-White "sandwich variance" estimates). Variables deemed statistically significant among the demographics and comorbidities, infection sites, and infection-related organisms were included in the multivariable, log-binomial regression model. A second, more parsimonious model was then generated in a similar fashion using statistically significant results from the first model. The quasi-likelihood under the independence model criterion (QIC) statistic was used as a measure of model goodness of fit and to assess the working correlation structure of the model.[22,23] Analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC) programming software. Statistical significance was defined as a p value of less than 0.05.

RESULTS

A total of 7,158 separately identified infectious episodes among 2,855 surgical patients admitted to our hospital between 1996 and 2007 were identified. Empiric antimicrobial therapy was determined to be appropriate for 5,073 infections (2,258 patients) and inappropriate for 2,085 infections (597 patients).

Demographics and comorbidities of the study population at time of infection are listed in Table 1. Estimated relative risk (RR) and 95% confidence intervals (CIs) represent each respective demographic or comorbidity's unadjusted association with inappropriateness. Older patients (i.e., >54 years), patients who received blood product transfusions during their hospitalization but before infection, patients with nosocomial infections, patients with APACHE II scores between 16 and 20, and patients with WBC counts between 13.4 and 18.8 were more likely to be associated with inappropriate, compared with appropriate, empiric antimicrobial therapy. Infection site is listed in Table 2. RR

TABLE 3. Culture-Proven Organisms Stratified by Appropriateness in Empiric Antimicrobial Therapy and Unadjusted Log-Binomial Regression Analysis of Inappropriateness*

Organism	Inappropriate, n (%)	Appropriate, n (%)	p**	RR (95%CI)**†
No. patients	597 (21)	2,258 (79)	—	—
No. infectious episodes	2,085 (29)	5,073 (71)	—	—
Fungal	600 (29)	649 (13)	<0.0001	1.9 (1.7–2.1)
C. albicans	301 (14)	298 (6)	<0.0001	1.9 (1.7–2.0)
C. glabrata	125 (6)	125 (2)	<0.0001	1.7 (1.5–2.0)
Gram-negative bacteria	831 (40)	1,968 (39)	0.36	1.0 (0.96–1.1)
Escherichia coli	133 (6)	462 (9)	0.0011	0.76 (0.65–0.90)
Klebsiella pneumoniae	82 (4)	257 (5)	0.11	0.84 (0.69–1.04)
Serratia species	50 (2)	133 (3)	0.41	0.91 (0.71–1.1)
Pseudomonas aeruginosa	184 (9)	377 (7)	0.14	1.1 (0.97–1.3)
E. cloacae	122 (6)	164 (3)	<0.0001	1.5 (1.3–1.7)
GP bacteria	1,129 (54)	1,833 (36)	<0.0001	1.7 (1.6–1.9)
MSSA	63 (3)	345 (7)	<0.0001	0.54 (0.43–0.69)
MRSA	187 (9)	249 (5)	<0.0001	1.6 (1.4–1.8)
Coagulase-negative *Staphylococcus*	77 (4)	98 (2)	<0.0001	1.6 (1.3–1.9)
E. faecalis	171 (8)	291 (6)	0.0001	1.3 (1.1–1.5)
E. faecium	66 (3)	54 (1)	<0.0001	1.9 (1.6–2.3)
VRE	148 (7)	85 (2)	<0.0001	2.2 (2.0–2.5)
Streptococcus species	115 (6)	259 (5)	0.35	1.1 (0.92–1.3)
Anaerobic bacteria	142 (7)	505 (10)	<0.0001	0.72 (0.61–0.84)
Clostridium difficile	15 (1)	234 (5)	<0.0001	0.17 (0.10–0.30)
Other	174 (8)	963 (19)	<0.0001	0.48 (0.42–0.56)

*Characteristics analyzed per infectious episode.

**To accommodate for a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of inappropriateness among infectious episodes was computed using a GEE approach with robust SEs (i.e., Huber-White sandwich variance estimates).

†The 1.0 referent for each type of organism is the absence of the organism.

CI, confidence interval; MRSA, methicillin resistant S. aureus; MSSA, methicillin-sensitive *S. aureus;* RR, relative risk; VRE, vancomycin-resistant enterococcus.

represents each respective site of infection's unadjusted association with inappropriateness. Infections of the peritoneum, pleura, wound, and line were more likely to be associated with inappropriate, compared with appropriate, empiric antimicrobial therapy. Infections of the central nervous system (CNS) approached a significant association with inappropriateness ($p = 0.051$).

Culture results are listed in Table 3. RR represents each respective culture-proven organism's unadjusted association with inappropriateness. Initially, fungal infections in general, *Candida albicans, Candida glabrata, Enterobacter cloacae*, GP infections in general, methicillin-resistant *S. aureus* (MRSA), coagulase-negative *S. aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, and VRE were more likely to be associated with inappropriate, compared with appropriate, empiric antimicrobial therapy. Outcomes are listed in Table 4. Inappropriately treated sepsis was associated with a longer hospital stay and longer antibiotic duration, as compared with appropriately treated sepsis, but not mortality.

After adjusting for statistically significant variables within Tables 1 to 3, independent variables associated with inappropriate, empiric antimicrobial therapy for the treatment of severe sepsis included peritoneal, pleural, and wound-related infections with *C. albicans*, *Candida glabratta*, *E. cloacae*, MRSA, coagulase-negative *S.*, *E. faecalis*, *E. faecium*, and VRE infections (Model 1, Table 5). Significant variables from Model 1 were then used to build a more parsimonious model predicting inappropriateness,

TABLE 4. Patient Outcomes Stratified by Appropriateness in Empiric Antimicrobial Therapy

Outcomes	Inappropriate, n (%)	Appropriate, n (%)	p
No. patients	597 (21)	2,258 (79)	—
No. infectious episodes	2,085 (29)	5,073 (71)	—
Mortality			0.93
No	546 (91)	2,068 (92)	
Yes	51 (9)	190 (8)	
Hospital LOS, d			0.0011
Mean ± SD	22 ± 22	20 ± 33	
Median (IQR)	15 (22)	13 (18)	
Antibiotic duration,* d			<0.0001**
Mean ± SD	15 ± 11	13 ± 12	
Median (IQR)	13 (11)	11 (9)	

*Analyzed by total number of episodes of infection (N = 7,158).

**To accommodate for a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of inappropriateness among episodes of infection was computed using a GEE approach with robust SEs (i.e., Huber-White sandwich variance estimates).

For categorical data, the Fisher's exact or the χ^2 was used depending upon the size of the data for each respective variable. For continuous data, the Deuchler-Wilcoxon or the independent *t* test was used depending upon the normalcy of distribution.

IQR, interquartile range; LOS, length of stay; SD, standard deviation.

TABLE 5. Multivariable, Log-Binomial Regression Analysis Modeling Inappropriateness of Empiric Antimicrobial Therapy for Each Episode of Infection

	Model 1*		Model 2**	
Variables	**RR (95%CI)†‡**	***p*‡**	**RR (95%CI)†‡**	***p*‡**
Age, y				
Q2 (42–54)	1.0 (0.93–1.2)	0.50		
Q3 (55–65)	1.1 (0.94–1.2)	0.33		
Q4 (≥66)	1.1 (0.99–1.2)	0.085		
Prior transfusion	0.99 (0.90–1.1)	0.79		
Nosocomial	1.0 (0.88–1.1)	0.96		
APACHE II score during infection				
Q2 (10–15)	1.0 (0.93–1.2)	0.50		
Q3 (16–20)	1.1 (0.94–1.2)	0.39		
Q4 (≥21)	0.91 (0.80–1.04)	0.16		
WBC during infection				
Q2 (8.8–13.3)	0.98 (0.88–1.09)	0.71		
Q3 (13.4–18.8)	1.1 (0.94–1.2)	0.35		
Q4 (≥18.9)	1.0 (0.92–1.2)	0.58		
Peritoneum	1.1 (1.005–1.2)	0.040	1.2 (1.1–1.3)	0.0013
Upper GI	0.62 (0.46–1.03)	0.071		
Colon	0.45 (0.15–1.3)	0.15		
Lung	0.88 (0.79–0.99)	0.027	0.93 (0.84–1.04)	0.19
Pleura	1.4 (1.008–1.8)	0.044	1.4 (1.08–1.9)	0.014
Skin/soft tissue	0.82 (0.65–1.03)	0.087		
Wound	1.3 (1.1–1.4)	0.0002	1.3 (1.2–1.5)	<0.0001
Line	1.1 (0.98–1.2)	0.11		
Fungal infections				
C. albicans	1.6 (1.4–1.8)	<0.0001	1.7 (1.5–1.8)	<0.0001
C. glabrata	1.4 (1.2–1.6)	<0.0001	1.5 (1.3–1.7)	<0.0001
Gram-negative bacteria				
E. coli	0.73 (0.62–0.86)	0.0001	0.77 (0.65–0.90)	0.0011
E. cloacae	1.4 (1.2–1.6)	<0.0001	1.5 (1.3–1.7)	<0.0001
GP bacteria				
MSSA	0.57 (0.45–0.72)	<0.0001	0.58 (0.56–0.73)	<0.0001
MRSA	1.5 (1.3–1.7)	<0.0001	1.5 (1.4–1.8)	<0.0001
Coagulase-negative *Staphylococcus*	1.4 (1.2–1.7)	0.0002	1.5 (1.2–1.8)	<0.0001
E. faecalis	1.2 (1.02–1.3)	0.028	1.2 (1.08–1.4)	0.0025
E. faecium	1.5 (1.3–1.8)	<0.0001	1.6 (1.3–1.9)	<0.0001
VRE	1.9 (1.7–2.2)	<0.0001	2.0 (1.8–2.2)	<0.0001
Anaerobic bacteria				
C. difficile	0.42 (0.12–1.4)	0.17		
Other organism	0.53 (0.46–0.62)	<0.0001	0.34 (0.46–0.62)	<0.0001

*Model 1 includes all variables in Tables 1 to 3 that were significantly predictive of inappropriateness (QIC goodness-of-fit statistic = 12442.95).

**Model 2 includes all variables in Model 1 that were significantly predictive of inappropriateness (QIC = 12602.46).

†The 1.0 referent is taken to be the absence of the variable being analyzed or the lowest quartile (Q1).

‡To accommodate for a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of inappropriateness among infectious episodes was computed using a GEE approach with robust SEs (i.e., Huber-White sandwich variance estimates).

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; GI, gastrointestinal; MRSA, methicillin-resistant S. Aureus; MSSA, methicillin-sensitive *S. aureus*; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; RR, relative risk; VRE, vancomycin-resistant enterococcus; WBC, white blood cell count.

and all remained significant, excluding lung infections (Model 2, Table 5).

DISCUSSION

Of the 7,158 infections treated during this study period, approximately 29% were done so with inappropriate, empiric therapy. This incidence is well within the reported range of 9% to 56% found in the literature.[3–10]

Previous studies have observed an increased association between inappropriate antibiotic selection and peritoneal,[24,25] urinary tract,[7] catheter-associated,[7] and bloodstream infections.[7] While our study did not observe an association between inappropriateness and urinary tract or bloodstream infections, we did

observe an independent association between inappropriateness and pleura, wound, and CNS in addition to peritoneal and catheter-associated infections. This may be explained by the emergence of MDR organisms within the health care setting. Our patients were hospitalized for approximately 20 to 22 days on average and received multiple antibiotics for multiple nosocomial-related infectious episodes, both risk factors known to be associated with MDR pathogens.[16] Second, peripheral edema and avascular, necrotic tissue (known complications of surgery, trauma, and resuscitation) have been observed to reduce antimicrobial distribution to target areas (e.g., wound).[17] Furthermore, antibiotic concentrations within CNS and pleural tissue are not well equilibrated with serum, possibly because of poor transport across multiple membrane barriers and lymphatic clearance, potentially resulting in poor antimicrobial penetrance.[17,19,26,27] Finally, many of the infectious agents evaluated by this study and independently associated with inappropriate empiric selection involved MDR pathogens (e.g., MRSA and VRE).

Additional organisms observed to be independently associated with inappropriateness included *E. cloacae*, *C. albicans*, and *C. glabrata*. An increasing incidence of plasmid-encoded extended-spectrum β-lactamases and carbapenemases has also been reported among Enterobacteriaceae.[28–30] Other studies have observed a significant, independent association between inappropriate antibiotic selection and fungal infections.[6,16,19,31,32] This may be explained by superinfection, a known complication of antibiotic use thought to be caused by a disruption of the normal microflora, allowing opportunistic pathogens to proliferate.[33] As previously mentioned, many of our patients were treated with polymicrobial therapy, for prolonged periods and for multiple infectious episodes.

A difference in immunosuppression (e.g., transplant, steroid use, malignancy, and HIV) was not observed between appropriately and inappropriately treated groups. Other studies have observed similar results and may be explained by the use of broad, empiric therapy for these high-risk patient populations.[6,7,34] An unexpected finding from our analysis was the lack of association of clinical factors with inadequate empiric antimicrobial therapy. Age, severity of illness, hospital-acquired infection, and other characteristics plausibly would have been overrepresented in the inadequate groups, but after controlling for site and pathogen, these were not. This observation suggests that increased efforts to understand the resident flora of a given patient may be more fruitful than tailoring empiric therapy on the basis of these clinical characteristics. For example, surveillance cultures of hospitalized patients before infection could improve empiric therapy if the patient became infected. In addition, faster microbiologic diagnosis, doubtlessly based on molecular techniques, should be a major focus for innovation.

In contrast to previous studies citing a negative impact on survival,[4–10,12,21,35] our study found that inappropriate, empiric antibiotic therapy for treatment of suspected sepsis did not result in a higher prevalence of mortality. Our results may be explained by the fact that a significantly greater number of infections within the appropriately treated group were localized to the lung or the skin/soft tissue compared with the inappropriately treated group. Ventilator-associated pneumonia is one of the most common ICU-associated infections and is responsible for prolonged ventilatory support, prolonged hospital LOS, and high mortality rates.[36–38] Skin/soft tissue infections have also been observed to be independently associated with increased risk for mortality.[3,15] Alternatively, a significantly greater number of wound and catheter-related infections were prevalent among the inappropriately treated group within our study, which has been shown to be associated with lower mortality rates.[3,34,39] However, there was a greater prevalence of peritoneal infections among patients treated inappropriately, which has previously been shown to be associated with higher mortality rates.[3,15,40]

Our study is strengthened by its large sample size and multivariable analysis; however, it may be limited by its nonrandomized, retrospective cohort design. This may result in selection bias and potential confounding in the interpretation of outcomes between study groups. In addition, this was a single-center study, and thus, external validity may be limited in generalizing results to other areas because the demographics and comorbidities of our patient population may differ.

Our study observed that inappropriate empiric antibiotic selection is still common and is dependent on individual pathogens and site of infection rather than clinical characteristics of the patient. This may be attributable to the introduction of foreign bacterial flora from the hospital and ICU environment into anatomic sites previously vacant of bacteria and not easily predicted in advance. Optimizing empiric antimicrobial choice will depend on broadening coverage against resistant GP organisms and fungi, as well as developing rapid microbiologic assays with improved sensitivity and specificity.

AUTHORSHIP

R.G.S. designed this study, for which S.W.D. conducted the literature search. R.G.S. collected the data. S.W.D., J.T.E., and R.G.S. contributed to data analysis. All authors performed data collection. S.W.D., C.A.G., T.H., R.M., B.R.S., and R.G.S. wrote the manuscript. All authors participated in critical revision.

DISCLOSURE

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