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Does it Matter if We Get It Right? Impact of Appropriateness of Empiric Antimicrobial Therapy Among Surgical Patients

Stephen W. Davies, MD, MPH¹, Jimmy T. Efird, PhD, MSc², Christopher A. Guidry, MD, MSc¹, Tjasa Hranjec, MD, MSc³, Rosemarie Metzger, MD, MPH⁴, Brian R. Swenson, MD, MSc⁵, and Robert G. Sawyer, MD¹

¹University of Virginia School of Medicine, Department of General Surgery, Charlottesville, VA

²Biostatistics Unit, Center for Health Disparities, Brody School of Medicine, East Carolina University, Greenville, NC

³University of Texas Southwestern, Department of Surgery, Division of Burn/Trauma/Critical Care, Dallas, TX

⁴Cleveland Clinic, Department of Endocrine Surgery, Cleveland, OH

⁵Mercy Clinic General and Specialty Surgery, Colon and Rectal Surgery, Springfield, MO

Abstract

Background—Previous studies have shown conflicting evidence regarding the impact of inappropriate, initial antibiotic therapy. The purpose of this study was to evaluate the impact of inappropriate, empiric antimicrobial therapy for the treatment of infection among surgical patients.

Hypothesis—Inappropriate, empiric antimicrobial therapy predicts increased mortality risk compared with appropriate therapy.

Methods—This was a retrospective analysis of a prospectively maintained database of all surgical patients admitted to a tertiary care center from 1996-2007 and treated for sepsis. “Appropriate” empiric antibiotic treatment was determined by sensitivity testing. Demographics and comorbidities, infection sites, infection organisms, and outcomes were compared between inappropriately and appropriately treated groups. Multivariable, log-binomial regression was performed.

Results—There were 2,855 patients (7,158 infectious episodes) identified by culture analysis as either appropriately or inappropriately treated. Three hundred seventeen (15%) inappropriately treated infectious episodes resulted in death compared with 718 (14%) of the appropriately treated infectious episodes. After adjusting for statistically significant variables, inappropriately treated episodes of infection were not found to be associated with an increased risk for mortality compared with appropriately treated episodes of infection (RR=1.0, 95%CI=0.99-1.02; p=0.36).

CORRESPONDING AUTHOR: Stephen Davies **ADDRESS:** University of Virginia, School of Medicine Department of General Surgery PO Box 800679 Charlottesville, VA 22908-0679 **PHONE:** 919-414-6471 **FAX:** 434-243-5791 sd2wf@virginia.edu.

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Conclusion—Our study observed no difference in mortality between appropriately and inappropriately treated infections within a surgical population.

Keywords

Inappropriateness; Antibiotics; Mortality; Sepsis

Introduction

Sepsis is the presence of an infection followed by a systemic, inflammatory response(1, 2) and is responsible for over one million hospitalizations per year within the United States(3). Severe sepsis is sepsis followed by organ dysfunction(2). The incidence of severe sepsis has been estimated to range between 300-1,031 per 100,000 per year, depending upon ICD-9 coding(1, 4, 5). In 2007, severe sepsis was responsible for over two hundred thousand deaths within the United States(3).

The current guidelines for treatment of sepsis generated by the Surviving Sepsis Campaign include administration of intravenous, broad-spectrum antimicrobial therapy within the first hour of severe sepsis recognition(4). However, considerable differences of opinion exist as to which empiric therapies to start(6).

Previous studies have shown conflicting evidence regarding the impact of inappropriate, initial antibiotic therapy(7-15). The purpose of this study was to evaluate the impact of inappropriate, empiric antimicrobial therapy for the treatment of severe sepsis among a large cohort of surgical and trauma patients at a tertiary care center. We hypothesized that inappropriate, initial antimicrobial therapy among patients would predict greater mortality risk than appropriate, initial antimicrobial therapy.

Materials and Methods

Study Design

Institutional Review Board approval was obtained prior to data analysis. This was a retrospective analysis of a prospectively maintained database of all 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 sepsis (after 2007, study protocols dictating antibiotic timing and choice were enacted, such that the association between empiric therapy and outcome could no longer be independently determined). Data for each patient were prospectively collected every other day by chart review, patient interview/examination, and review of laboratory, microbiology, and pharmacy reports. Unique episodes of infection were identified for each patient, and classified as separate if more than 72 hours apart. Sites of infection, antibiotic therapy and duration, and organisms were recorded for each episode of infection. Patients were subsequently followed until death or hospital discharge. Initial antimicrobial therapy for each episode was compared with final culture results. Empiric therapy included all antibiotics started on the first day of treatment (administered shortly after blood cultures were taken), including those initiated for treatment of another simultaneous infection. Endpoints considered for antibiotic treatment duration

included culture-proven resistance or insensitivity, infection resolution, or death. Culture-specific antibiotics (definitive therapy) were subsequently initiated if resistance or insensitivity was determined.

Patients

Patient demographics and comorbidities evaluated at time of initial infectious episode included gender, age, race (patient-defined), solid organ transplant, trauma, diabetes (DM), hypertension (HTN), hyperlipidemia (HLD), obesity, cardiovascular disease, peripheral vascular disease (PVD), pulmonary disease, ventilator dependence, renal insufficiency (RI), hemodialysis dependence (HD), hepatic insufficiency, malignancy, chronic steroid use, human immunodeficiency virus (HIV), prior transfusion during same hospitalization, nosocomial infection, patient location at time of infection, acute physiology and chronic health evaluation II score (APACHE II), maximum temperature (Tmax), and white blood cell (WBC) count. Patient demographics and comorbidities measured at the time of each subsequent infectious episode included new onset or change in ventilator dependence, RI, HD, transfusion, patient location, APACHE II, Tmax, and WBC count. Similarly, sites of infection and organisms cultured were measured at time of each infectious episode.

Definitions

Infections were defined according to criteria specified by the Centers for Disease Control and Prevention(16). “Inappropriate” antimicrobial treatment was defined as empiric antibiotics initiated on day 1 of suspected sepsis that did not treat all organisms based on subsequent sensitivity testing, compared with “appropriate” treatment defined as initial coverage that met these criteria(15, 17). The microbiology lab at our institution limits the number of isolated microbial species to three and provides quantification of all isolates with the exception of blood cultures.

Fungal sensitivity testing was not performed during the study period due to availability reasons and thus *Candida* species were assumed sensitive to fluconazole, while *Candida kruzii* was considered resistant to fluconazole(18). Likewise, anaerobic sensitivity testing was not routinely performed and thus *Bacteroides fragilis* and *Bacteroides non-fragilis* were assumed sensitive to flagyl, clindamycin, piperacillin/tazobactam, ampicillin/sulbactam, and all carbapenems(18). Additionally, we assumed that all gram-positive cocci (GPC's) were sensitive to vancomycin excluding vancomycin resistant enterococci (VRE); we have no reported history of vancomycin-resistant *Staphylococcus aureus* (VRSA) or vancomycin-intermediate *Staphylococcus aureus* (VISA) at our institution(18). All GPC's (as part of mixed infections) were assumed adequately treated by penicillins, cephalosporins, carbapenems, and fluoroquinolones unless proven otherwise by sensitivity testing(18). Finally, we assumed that all gram-negative rods (GNR's) were adequately treated by penicillins, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and aztreonam unless proven otherwise by sensitivity testing(18).

Solid organ transplant was defined as kidney, liver, pancreas, heart, lung, kidney/pancreas, liver/pancreas, and small bowel. Patient location at time of infection episode was defined as home, hospital ward, intensive care unit (ICU), or other. Renal insufficiency was defined as

a serum creatinine of greater than or equal to 2.0 mg/dL at time of infection episode. Obesity was defined as body mass index (BMI) >30. Pulmonary disease was defined as active treatment for lung disease prior to hospital admission. Other comorbidities were defined by chart review or patient examination. Mortality was defined as any cause of death after infection diagnosis while hospitalized.

Statistical Analysis

Demographics and comorbidities, infection sites, infection organisms, and outcomes were compared between inappropriately and appropriately treated groups. Relative risk (RR) and 95% confidence intervals (CI), and P-values were computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber White “sandwich variance” estimates) to accommodate for a correlated data structure corresponding to multiple episodes of infection per individual. The Deddens-Petersen Replication Method was used to compute point estimates and confidence intervals when a convergence was not achieved with traditional GEE model(19). Variables deemed statistically significant among the demographics and comorbidities, infection sites, and infection-related organisms were included in the multivariable, log-binomial regression model. Analysis was performed using SAS Version 9.3© (Cary, NC) programming software. Statistical significance was defined as a P-value of less than 0.05.

Results

A total of 2,855 patients with 7,158 separately identified episodes of infection were identified from our prospectively maintained database between 1996 and 2007. Infections were treated with empiric, antimicrobial therapy when sepsis was initially suspected. Empiric antimicrobial therapy was determined to be “inappropriate” for 597 patients (2,085 infectious episodes) and “appropriate” for 2,258 patients (5,073 infectious episodes) by culture results. There were 2.2 ± 2.4 episodes of infection per patient (inappropriate= 1.6 ± 1.3 vs. appropriate= 1.9 ± 1.7 ; $p<0.0001$). Time from sepsis recognition to antibiotic initiation for each episode of infection was 0.59 ± 2.4 (inappropriate) vs. 0.67 ± 2.1 (appropriate) hours ($p=0.66$). Two hundred forty-one patients (1035 infectious episodes) died during their hospitalization, while 2,614 patients (6,123 infectious episodes) lived.

Demographics and comorbidities stratified by appropriateness in empiric antimicrobial therapy are listed in Table 1. Age (>55), prior transfusion, nosocomial infection, APACHE II score (16-20), and WBC (13.4-18.8) were more commonly associated with inappropriately treated episodes of infection compared with appropriately treated episodes of infection.

Sites of infection stratified by appropriateness in empiric antimicrobial therapy are listed in Table 2. Infections of the peritoneum, pleura, wound, and line were more commonly associated with inappropriately treated episodes of infection compared with appropriately treated episodes of infection.

Culture-proven organisms stratified by appropriateness in empiric antimicrobial therapy are listed in Table 3. *Candida albicans*, *Candida glabrata*, *Enterobacter cloacae*, MRSA,

Coagulase Negative Staphylococcus, *Enterococcus faecalis*, *Enterococcus faecium*, and VRE were more prevalent among inappropriately treated episodes of infection compared with appropriately treated episodes of infection.

Patient outcomes stratified by appropriateness in empiric antimicrobial therapy are listed in Table 4. Inappropriately treated patients received more antibiotics per episode of infection ($p<0.0001$) for a longer duration ($p<0.0032$), and experienced longer HLOS ($p=0.0027$) than appropriately treated patients. Additionally, more inappropriately treated patients underwent surgical and or procedural source control compared to appropriately treated patients ($p=0.0008$). However, a difference between groups was not observed regarding time from sepsis recognition to surgical/procedural source control ($p=0.23$) or mortality ($p=0.19$). After adjusting for statistically significant variables in Tables 1-3, inappropriate, empiric antibiotic selection for treatment of suspected sepsis was not found to be associated with an increased risk for mortality compared with appropriate, empiric antibiotic selection (RR=1.0, 95% CI=0.99-1.02; $p=0.36$) (Not included in Table).

Discussion

Of the 7,158 infections treated empirically for sepsis at our hospital during the study period, 29% were determined to be inappropriate. This incidence is similar to that reported within the literature, varying between 9 and 56% (9, 10, 12-14). Of the inappropriately treated infections, approximately 317 (15%) resulted in death (51 patients). Our mortality incidence among inappropriately treated infections is similar to that reported within the literature, varying between 1.7 and 61.9% (12, 14, 20-22).

In contrast to previous studies citing a negative impact on survival (10-15) our study found that inappropriate, empiric antibiotic therapy for treatment of suspected sepsis did not independently predict an increased risk for mortality among patients. Based on our sample size, the difference between our 95% upper and lower confidence interval for our multivariable result was less than 0.03. This indicates that our study was sufficiently powered and that the variance associated with the point estimate was extremely small and well within an equivalence region showing no difference from the null. Our results may be explained by the fact that a significantly greater number of infection episodes were present within the appropriately treated group, but were also localized to the upper gastrointestinal tract and colon compared with the inappropriately treated group. Previous studies have observed an increased risk of mortality associated with intra-abdominal infections (12, 20-22). Turnbull, et. al, evaluated genetically identical mice and their response to antibiotic therapy after receiving double-puncture cecal ligation (23). They observed an improvement in outcome with the incorporation of antibiotic use. However, there was a critical IL-6 threshold, above which, mortality was assured regardless of antibiotic treatment. In our group of appropriately treated patients, a significantly fewer number of infectious episodes were managed surgically; walled-off abscesses or unresolved enteric leaks may be recalcitrant to antibiotics no matter how appropriate. Alternatively, inappropriately treated infections may have experienced improved survival regardless of inappropriateness due to surgical management and source control (10, 13, 14).

Many of the patients in our study experienced protracted hospital lengths of stay and were treated with multiple antibiotics for prolonged periods of time and for multiple concomitant infections; risk factors known to be associated with multidrug-resistant pathogens(24). Many of these organisms (e.g., MRSA and VRE) were more prevalent within the inappropriately treated group compared to the appropriately treated group. Additionally, fungal infections (e.g., *Candida albicans* and *Candida glabrata*) were more prevalent within the inappropriately treated group compared to the appropriately treated group. This may be attributable to immunosuppression brought about by patient comorbidity or septic state, or superinfection secondary to antibiotic use and thought to be caused by a disruption of the normal microflora, allowing opportunistic pathogens to proliferate(25). Both multidrug resistant (MDR) organisms and invasive fungal infections have previously been associated with poor outcomes including death in critically ill patients(26-29). Recent attention has been devoted towards biomarker identification, metabolomic profiling, and/or rapid microbiologic microarrays to be used for the early diagnosis and prognosis of sepsis(29, 30). Further refinement, verification and validation, and incorporation of this technology may serve to expedite appropriate antibiotic selection prior to the onset of drug resistance.

While the number of antibiotics and source control operations/procedures were significantly greater in the inappropriately treated group than the appropriately treated group, the time to antimicrobial therapy (inappropriate= 0.59 ± 2.4 vs. appropriate= 0.67 ± 2.1 hours; $p=0.66$) and source control intervention (inappropriate= 19 ± 30 vs. appropriate= 21 ± 30 hours; $p=0.23$) were similar between groups. As previously mentioned, current recommendations for the management of sepsis include broad-spectrum antimicrobial therapy within the first hour of recognition(4). A recent prospective study comparing an aggressive antimicrobial treatment protocol (i.e., initiation of empiric antibiotics for the suspicion of infection after blood cultures were drawn) to a conservative antimicrobial protocol (i.e., antimicrobial initiation was withheld until objective, culture proven data was obtained) among a critically ill surgical population observed that the aggressive treatment protocol resulted in reduced appropriateness of initial antimicrobial therapy, prolonged duration of antimicrobial therapy, and a significant reduction in survival compared with the conservative treatment protocol(17).

As previously mentioned, 1,498 of the 2,085 inappropriately treated infections were ultimately changed to appropriate antimicrobial therapy once culture results were obtained. Patient survival would be expected to improve with appropriate therapy and this may have resulted in the observed findings of our study. Additionally, some studies have shown that early adequate antibiotic therapy may only improve survival in patients with minimal illness severity whereas in other patients the baseline severity is so great that no benefit is appreciated(9). Among the appropriately treated infections in our study, an increased prevalence of younger, trauma patients with greater APACHE II scores were observed compared with inappropriately treated infections. Some studies have shown that APACHE II scores may underestimate the true mortality risk in many trauma patients secondary to an increased prevalence of younger patients who lack chronic health problems commonly observed in the older population(31, 32).

Strengths and Limitations

Our study is strengthened by its large sample size and multivariable analysis; however, may be limited by its retrospective design (e.g., selection bias and confounding). This was a single center study, and thus external validity may be limited in generalizing results to other areas as the demographics and comorbidities of our patient population may differ. Cause of death was not captured by our database. Thus, it is possible that mortality was caused by factors unrelated to sepsis and/or antibiotic inappropriateness. Furthermore, only 12.4% of inpatient deaths at our institution, during the study period, received post-mortem autopsies. Previous studies have observed a wide discrepancy between clinical and postmortem findings attributable to cause of death, especially within surgical ICU, trauma, and transplant patients(33-35). While time from sepsis recognition to antibiotics (appropriate and inappropriate) was captured by our database, time to ultimate appropriate antibiotic treatment was not. Previous studies have observed a significant association between delay in treatment with appropriate antibiotics and mortality(15). Additionally, while our database captured APACHE II scores at time of each infectious episode, it is not explicitly clear at what point during the episode this occurred. Previous studies recommend that the optimal time to record severity of illness be just before the true onset of bacteremia (i.e., 48 hours prior to collection of the initial blood sample obtained for culture)(15).

Conclusion

In contrast to our hypothesis, our study observed no difference in mortality between infections initially treated with either appropriate or inappropriate antimicrobial therapy. The difference in our data and those previously reported might lie in the fact that all of our patients were treated on a surgical service, where a large percentage of infections are treated primarily by mechanical source control procedures rather than antimicrobials alone. Perhaps, “appropriateness” in empiric antimicrobial therapy is less critical in surgical patients compared with timing of antimicrobial therapy and/or source control. Until biomarker identification, metabolomic profiling, and/or rapid microbiologic microarrays become mainstream, an awareness of hospital microbial flora/fauna and patient acuity, combined with rapid intervention (i.e., source control), close attention to culture results with subsequent de-escalation, and infectious disease involvement should remain paramount regarding standard of care in this surgical patient population.

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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 (%)	RR 95%(CI) ^{*†}	P-Value [‡]
Number of Patients	597 (21)	2258 (79)	---	---
Number of Infectious Episodes	2085 (29)	5073 (71)	---	---
Gender				
Female	929 (45)	2243 (44)	1.0 Referent	---
Male	1156 (55)	2830 (56)	0.98 (0.90-1.07)	0.63
Age (years)				
Q1 (41)	498 (24)	1328 (26)	1.0 Referent	---
Q2 (42-54)	540 (26)	1330 (26)	1.1 (0.94-1.2)	0.36
Q3 (55-65)	516 (25)	1217 (24)	1.1 (1.004-1.3)	0.044
Q4 (66)	531 (25)	1198 (24)	1.1 (1.005-1.3)	0.042
Race				
White	1716 (82)	4107 (81)	1.0 Referent	---
Black	321 (15)	810 (16)	0.92 (0.82-1.04)	0.20
Other	21 (1)	91 (2)	0.64 (0.38-1.05)	0.078
Hispanic	27 (1)	65 (1)	0.99 (0.69-1.4)	0.95
Transplant [‡]	457 (22)	1081 (21)	1.0 (0.92-1.1)	0.71
Trauma	431 (21)	1163 (23)	0.91 (0.82-1.003)	0.058
Diabetes	476 (23)	1054 (21)	0.95 (0.86-1.05)	0.29
Hypertension	718 (34)	1750 (35)	1.0 (0.93-1.1)	0.80
Hyperlipidemia	121 (6)	293 (6)	1.0 (0.85-1.2)	0.98
Obesity	145 (7)	345 (7)	1.0 (0.84-1.2)	0.96
Cardiovascular Disease	424 (20)	949 (19)	1.1 (0.96-1.2)	0.25
PVD	100 (5)	195 (4)	1.1 (0.94-1.4)	0.18
Pulmonary Disease	259 (12)	568 (11)	1.1 (0.97-1.3)	0.13
Ventilator Dependence	573 (27)	1402 (28)	0.98 (0.88-1.08)	0.69
Renal Insufficiency	573 (27)	1402 (28)	1.0 (0.87-1.2)	0.78
Hemodialysis	262 (13)	581 (11)	1.1 (0.93-1.2)	0.40
Hepatic Insufficiency	182 (9)	414 (8)	1.1 (0.97-1.3)	0.13
Malignancy	241 (12)	597 (12)	1.0 (0.89-1.1)	0.91

Characteristics	Inappropriate n (%)	Appropriate n (%)	RR 95%(CI) ^{*†}	P-Value [‡]
Chronic Steroid Use	590 (28)	1363 (27)	1.0 (0.95-1.1)	0.37
HIV	6 (0)	11 (0)	1.3 (0.62-2.8)	0.49
Prior Transfusion	1029 (49)	2324 (46)	1.1 (1.02-1.2)	0.019
Nosocomial Infection	1763 (85)	4097 (81)	1.2 (1.1-1.4)	0.0014
Patient Location				
Home	592 (28)	1499 (30)	1.0 Referent	---
Hospital Ward	677 (32)	1647 (32)	1.0 (0.92-1.1)	0.65
ICU	727 (35)	1755 (35)	1.0 (0.91-1.1)	0.82
Other	89 (4)	172 (3)	1.2 (0.97-1.5)	0.087
APACHE II Score During Infection				
Q1 (9)	502 (24)	1357 (27)	1.0 Referent	---
Q2 (10-15)	631 (30)	1479 (29)	1.1 (0.996-1.2)	0.058
Q3 (16-20)	524 (25)	1128 (22)	1.2 (1.04-1.3)	0.011
Q4 (21)	428 (21)	1109 (22)	1.0 (0.91-1.2)	0.61
Tmax During Infection [¥]				
Q1 (37.2)	595 (29)	1376 (27)	1.0 Referent	---
Q2 (37.3-38.2)	500 (24)	1196 (24)	1.0 (0.89-1.1)	0.95
Q3 (38.3-38.9)	533 (26)	1295 (26)	0.97 (0.86-1.1)	0.62
Q4 (39.0)	456 (22)	1201 (24)	0.93 (0.81-1.1)	0.25
WBC During Infection				
Q1 (8.7)	497 (24)	1306 (26)	1.0 Referent	---
Q2 (8.8-13.3)	499 (24)	1300 (26)	1.0 (0.91-1.1)	0.75
Q3 (13.4-18.8)	549 (26)	1224 (24)	1.1 (1.01-1.3)	0.031
Q4 (18.9)	540 (26)	1243 (25)	1.1 (0.98-1.2)	0.11

[£]All variables analyzed per infectious episode.

[†]Relative risk and 95% confidence intervals, and P-values were computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates) to accommodate for a correlated data structure corresponding to multiple episodes of infection per individual.

[¥]Missing category not shown.

* Unless otherwise specified, 1.0 Referent is taken to be the absence of the variable being analyzed.

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

APACHE=acute physiology and chronic health evaluation. CI=confidence interval. HIV=human immunodeficiency virus. ICU=intensive care unit. IQR=interquartile range. LOS=length of stay. PVD=peripheral vascular disease. Q1=first quartile. Q2=second quartile. Q3=third quartile. Q4=fourth quartile. 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 (%)	RR 95%(CI) ^{*‡}	P-Value [‡]
Number of Patients	597 (21)	2258 (79)	---	---
Number of Infectious Episodes	2085 (29)	5073 (71)	---	---
CNS	5 (0)	4 (0)	1.9 (0.996-3.5)	0.051
Peritoneum	395 (19)	747 (15)	1.3 (1.1-1.4)	<0.0001
Upper GI	21 (1)	115 (2)	0.52 (0.34-0.79)	0.0022
Colon	18 (1)	265 (5)	0.18 (0.11-0.30)	<0.0001
Lung	319 (15)	1014 (20)	0.79 (0.71-0.87)	<0.0001
Pleura	29 (1)	38 (1)	1.5 (1.1-2.0)	0.017
Skin/Soft Tissue	69 (3)	285 (6)	0.66 (0.52-0.83)	0.0004
Wound	226 (11)	381 (8)	1.3 (1.2-1.5)	<0.0001
Line	162 (8)	292 (6)	1.2 (1.1-1.4)	0.0010
Blood	390 (19)	862 (17)	1.1 (0.99-1.2)	0.099
Urine	433 (21)	969 (19)	1.1 (0.99-1.2)	0.068

[‡]All variables analyzed per infectious episode.

[‡]Relative risk and 95% confidence intervals, and P-values were computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates) to accommodate for a correlated data structure corresponding to multiple episodes of infection per individual.

* 1.0 Referent is taken to be the absence of the variable being analyzed.

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

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 (%)	RR 95%(CI) ^{*†}	P-Value [‡]
Number of Patients	597 (21)	2258 (79)	---	---
Number of Infectious Episodes	2085 (29)	5073 (71)	---	---
Fungal	600 (29)	649 (13)	1.9 (1.7-2.1)	<0.0001
<i>Candida albicans</i>	301 (14)	298 (6)	1.9 (1.7-2.0)	<0.0001
<i>Candida glabrata</i>	125 (6)	125 (2)	1.7 (1.5-2.0)	<0.0001
Gram Negative Bacteria	831 (40)	1968 (39)	1.0 (0.96-1.1)	0.36
<i>Escherichia coli</i>	133 (6)	462 (9)	0.76 (0.65-0.90)	0.0011
<i>Klebsiella pneumonia</i>	82 (4)	257 (5)	0.84 (0.69-1.04)	0.11
<i>Serratia spp.</i>	50 (2)	133 (3)	0.91 (0.71-1.1)	0.41
<i>Pseudomonas aeruginosa</i>	184 (9)	377 (7)	1.1 (0.97-1.3)	0.14
<i>Enterobacter cloacae</i>	122 (6)	164 (3)	1.5 (1.3-1.7)	<0.0001
Gram Positive Bacteria	1129 (54)	1833 (36)	1.7 (1.6-1.9)	<0.0001
MSSA	63 (3)	345 (7)	0.54 (0.43-0.69)	<0.0001
MRSA	187 (9)	249 (5)	1.6 (1.4-1.8)	<0.0001
Coagulase Negative Staphylococcus	77 (4)	98 (2)	1.6 (1.3-1.9)	<0.0001
<i>Enterococcus faecalis</i>	171 (8)	291 (6)	1.3 (1.1-1.5)	0.0001
<i>Enterococcus faecium</i>	66 (3)	54 (1)	1.9 (1.6-2.3)	<0.0001
Vancomycin-Resistant Enterococcus	148 (7)	85 (2)	2.2 (2.0-2.5)	<0.0001
<i>Streptococcus spp.</i>	115 (6)	259 (5)	1.1 (0.92-1.3)	0.35
Anaerobic Bacteria	142 (7)	505 (10)	0.72 (0.61-0.84)	<0.0001
<i>Clostridium difficile</i>	15 (1)	234 (5)	0.17 (0.10-0.30)	<0.0001

[‡]All variables analyzed per infectious episode.

[†]Relative risk and 95% confidence intervals, and P-values were computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates) to accommodate for a correlated data structure corresponding to multiple episodes of infection per individual.

* 1.0 Referent is taken to be the absence of the variable being analyzed.

CI=confidence interval. MSSA=methicillin sensitive *Staphylococcus aureus*. MRSA=methicillin resistant *Staphylococcus aureus*. RR=relative risk. Spp=species

Table 4Patient Outcomes^ξ stratified by Appropriateness in Empiric Antimicrobial Therapy.

Outcomes	Inappropriate n (%)	Appropriate n (%)	P-Value [‡]
Number of Patients	597 (21)	2258 (79)	---
Number of Infectious Episodes	2085 (29)	5073 (71)	---
Mortality			
No	1768 (85)	4355 (86)	1.0 Referent
Yes	317 (15)	718 (14)	0.19
Hospital LOS (days)			
Mean ± SD	39 ± 46	35 ± 45	0.0027
Median (IQR)	25 (36)	20 (35)	
Number of Antibiotics			
Mean ± SD	2.9 ± 1.5	2.3 ± 1.3	<0.0001
Median (IQR)	3 (2)	2 (2)	
Antibiotic Duration (days)			
Mean ± SD	15 ± 11	13 ± 12	<0.0032
Median (IQR)	13 (11)	11 (9)	
Surgery/Procedure Performed for Source Control			
No	1299 (62)	3400 (67)	1.0 Referent
Yes	786 (38)	1673 (33)	0.0008
Time from Sepsis Recognition to Source Control Intervention (hr)			
Mean ± SD	19 ± 30	21 ± 30	0.23
Median (IQR)	11 (20)	11 (20)	
Reoperation Performed for Source Control			
No	1955 (94)	4813 (95)	Referent
Yes	130 (6)	260 (5)	0.16

^ξAll variables analyzed per infectious episode.[‡]P-value computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates) to accommodate for a correlated data structure corresponding to multiple episodes of infection per individual. Abx=antibiotics. IQR=interquartile range. LOS=length of stay. Q1=first quartile. Q2=second quartile. Q3=third quartile. Q4=fourth quartile. SD=standard deviation.