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Critical Analysis of Empiric Antibiotic Utilization: Establishing Benchmarks*

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Abstract

Aim: We critically evaluated empiric antibiotic practice in the surgical and trauma intensive care unit (STICU) with three specific objectives: (1) To characterize empiric antibiotics practice prospectively; (2) to determine how frequently STICU patients started on empiric antibiotics subsequently have a confirmed infection; and (3) to elucidate the complications associated with unnecessary empiric antibiotic therapy.
Methods: We collected data prospectively using the Surgical Intensive Care-Infection Registry (SIC-IR) including all 1,185 patients admitted to the STICU for >2 days from March 2007 through May 2008. Empiric antibiotics were defined as those initiated because of suspected infections.
Results: The mean patient age was 56 years and 62% were male. The mean STICU length of stay was eight days, and the mortality rate was 4.6%. Empiric antibiotics were started for 26.3% of the patients. The average length of antibiotic use was three days. Of the 312 patients started on empiric antibiotics, only 25.6% were found to have an infection. Factors associated with correctly starting empiric antibiotics were a longer STICU stay (5 vs. 3 days), prior antibiotics (29% vs. 17%), and mechanical ventilation (93% vs. 79%). Patients who were started on antibiotics without a subsequent confirmed infection were compared with patients not given empiric antibiotics. Incorrect use of empiric antibiotics was associated with younger age ($p < 0.001$), more STICU days (10.6 vs. 5.9 days; $p < 0.001$), more ventilator days ($p < 0.001$), more development of acute renal failure (24.1% vs. 12.1%; $p < 0.001$), and a significant difference in mortality rate (8.6% vs. 3.2%; $p < 0.001$).
Conclusions: After admission to the STICU, 26% of patients received at least one course of empiric antibiotics. Only 25.6% of these patients were confirmed to have an infection. These results provide key benchmark data for the critical care community to improve antibiotic stewardship.

The timely and correct identification of infection followed by appropriate treatment is crucial to the management of critically ill and injured patients. Accurate infection diagnosis in surgical and trauma intensive care units is confounded by the systemic inflammatory response syndrome (SIRS). Intensivists must use the same criteria (e.g., fever, leukocytosis, tachycardia, tachypnea) supplemented by clinical judgment to distinguish patients with infections from those with SIRS. Because of the devastating consequences of missing a true infection, empiric antibiotic therapy often is initiated when patients are critically ill and physicians are unable to distinguish SIRS from infection. The result is potential overuse of antibiotics [1, 2].

Incorrect use of broad-spectrum antibiotics has potentially serious consequences, including *Clostridium difficile* infection [3], renal toxicity [4, 5], and encouragement of multi-drug resistant organisms [6]. These events can lead to longer intensive care unit (ICU) stays, greater health care costs, and a higher mortality rate [7, 8]. The full extent of these effects in surgical and trauma intensive care unit (STICU) patients has not been well reported, and antibiotic overuse is inevitable. There currently is no consensus or benchmark for an acceptable rate of over-treatment or for utilizing empiric antibiotics in the STICU.

For this study, we had three primary objectives: (1) To characterize empiric antibiotic practice in a large STICU

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population prospectively; (2) to determine how frequently STICU patients started on empiric antibiotics have a later-confirmed infection; and (3) to elucidate the complications of unnecessary empiric antibiotic therapy.

Patients and Methods

This study was performed at the MetroHealth Medical Center (MHMC), a 748-bed tertiary-care facility and regional level I trauma center. The MHMC has two STICUs (27 total beds), which admit more than 1,700 patients a year, 50–65% of whom are trauma patients. As a collaborative STICU, each patient is cared for jointly by a dedicated critical care team and the primary admitting service (e.g., general surgery, trauma, orthopedics). Since March 1, 2007, all STICU patients have been registered in the Surgical Intensive Care–Infection Registry (SIC-IR), a novel research tool developed, implemented, and validated by our group [9-11]. The SIC-IR currently functions as the inpatient electronic medical record software for all STICU patients and collects more than 100 daily laboratory results and clinical variables at the point of care. The resulting information is organized into an accurate, validated, research-friendly, relational database that can be queried easily to allow analysis of a robust data set.

A secondary analysis was conducted on all patients admitted for >48 h to the STICUs between March 1, 2007, and May 30, 2008. The patient data collected were age, sex, trauma/non-trauma status, primary service, STICU length of stay (LOS), and STICU disposition. Baseline data regarding renal function (renal dysfunction as noted either in the patient's medical history or by serum creatinine concentration (Cr) > 2.2 mg/dL on admission) also were gathered.

In order to determine administration and de-escalation practices, patients were divided into two groups: Those who received empiric antibiotics during their STICU stay and those who did not. For this study, "empiric" antibiotics were defined as antibiotics intended to treat a suspected bacterial infection. To achieve this goal, we utilized a unique feature in SIC-IR in which the physician must enter every antibiotic agent, designate a reason for the drug, and enter the stop date to complete a daily note. This function is required daily, and designations are chosen from a defined list of choices. Empiric designation may have been given in one of two cases: (1) An infection is suspected, but the infection type is unknown, and treatment is therefore "empiric"; or (2) a certain type of infection is suspected, but the organism(s) remains unknown (e.g., "empiric–pneumonia"). Variations in recording were expected where people might have chosen either "empiric" or "empiric–pneumonia" if they suspected pneumonia. Consequently, both cases were used. When a patient was found to have an infection, the indication would change to denote the confirmed infection. In addition to empiric antibiotic data, the length of the antibiotic course, antibiotic days prior to empiric therapy, subsequent antibiotic days, and any infections documented prior to empiric therapy were collected.

A patient was considered to have received "clinically correct" empiric antibiotic therapy if a confirmed infection was diagnosed within six days of the start of antibiotics. The practice was considered "clinically incorrect" if an infection was not confirmed within six days. The six-day window was chosen as a conservative measure given that cultures may require five days to be finalized. Confirmed infections were diagnosed according to U.S. Centers for Disease Control and Prevention criteria [12]. These criteria require either a positive culture or a clinical diagnosis. For every patient who was given empiric therapy, the information about drug quantity, dates of administration, and types of cultures obtained for the infectious workup was evaluated. An "infectious workup" was defined as any culture taken between one day before and two days after initiation of empiric therapy.

In order to evaluate the costs of being "clinically wrong" in treating patients with empiric antibiotics, we compared the outcomes in patients who received empiric therapy without confirmed infections and those who never received empiric therapy. Drug-resistant organisms were defined by two criteria: Organism and antibiotic resistance pattern. The following organisms were categorized as drug-resistant without regard to the in vitro sensitivities: *C. difficile, Acinetobacter* spp., *Stenotrophomonas spp., Candida glabrata,* and *Bacterioides thetaiotaomicron*. Additionally, all organisms exhibiting resistance to two or more antimicrobial drugs beyond natural resistance patterns were included: Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and extended-spectrum beta-lactamase (ESBL)-producing gram-negative organisms. The other outcome variables were the development of renal dysfunction (an increase in serum Cr > 1 mg/dL over the course of the ICU stay), subsequent infections (any infection confirmed >24 h after an empiric course was initiated), presence of drug-resistant organisms, ventilator days, STICU LOS, disposition, and STICU death.

Statistical analysis was performed using SPSS 16.0 (SPSS, Inc., Chicago, IL). Numeric data are expressed as mean ± standard error of the mean (SEM), and comparisons were made with Student *t*-tests. Categorical data are expressed as percentages, with comparisons made using the χ^2 or the Fisher exact test where appropriate. Variables with a p value $\leq$0.1 after bivariable analysis were then analyzed using backwards stepwise logistic regression to determine the risk factors associated with being "clinically correct." A receiver operating characteristic (ROC) curve was created from the logistic regression analysis, and the area under the curve (AUC) was calculated. A p value of <0.05 was required for statistical significance. The study protocol was approved by our Institutional Review Board. Data were collected from the SIC-IR and from our hospital-wide electronic medical record system (Epic Systems Corporation, Madison, WI).

Results

General characteristics

Our study evaluated 1,185 patients with an STICU stay >48 h. Sixty-two percent were male, and the mean age was 56 years (range 17–99 years). The general characteristics and admitting service of the study population are shown in Table 1. On admission, 2.9% of patients had history of renal failure or renal insufficiency, and 5.9% of patients had a serum Cr > 2.2 mg/dL. Sixty-five percent of the patients required ventilator support, with an average of 6.3 ± 0.3 ventilator days per patient. The majority of patients (72.5%) were discharged to a regular surgical floor, and there was a 4.6% STICU mortality rate.

There were 236 patients (19.9%) who developed a total of 324 infections, 120 (38.0%) of which were associated with antibiotic-resistant organisms. The infections for the entire

Table 1. Characteristics of 1,185 Patients

Mean age (years)[a]	55.6 ± 0.54
Percent (n) male	62.2 (737)
Mean STICU LOS (days)	7.7 ± 0.22
Percent (n) intubated	65.2 (773)
Mean ventilator days	6.3 ± 0.26
Percent (n) of patients by disposition	
Regular floor	72.5 (859)
Stepdown unit	6.7 (79)
Cardiac care unit	5.7 (67)
Long-term acute care facility	4.8 (57)
Death	4.6 (55)
Transfer	2.0 (24)
Home	1.4 (16)
Other	2.3 (27)
Percent (n) of patients by admitting service	
Trauma	48.3 (572)
Cardiothoracic/vascular	18.7 (222)
Neurosurgery	9.5 (113)
General	15.4 (182)
Ear, nose, and throat	2.6 (31)
Orthopedics	2.2 (25)
Gynecology	1.4 (17)
Urology	1.0 (12)
Oral and maxillofacial surgery	0.6 (7)
Plastic surgery	0.3 (4)

[a]Means ± standard deviation.
STICU LOS = surgical and trauma intensive care unit length of stay.

Table 2. Types of Confirmed Infections (n = 324)

	Number	*Percent*
Ventilator-associated pneumonia	62	19.1
Bacteremia–non-catheter-related	46	14.2
Nosocomial urinary tract	46	14.2
Intra-abdominal	45	13.9
Sinusitis	13	4.0
Nosocomial pneumonia	12	3.7
C. difficile	10	3.1
Meningitis	10	3.1
Community-acquired urinary tract	9	2.8
Necrotizing soft tissue	8	2.5
Osteomyelitis	8	2.5
Community-acquired pneumonia	8	2.5
Surgical site infection–deep incisional	7	2.2
Surgical site infection–superficial incisional	5	1.5
Empyema	4	1.2
Bacteremia–catheter-related	3	0.9
Endocarditis	3	0.9
Oral/pharyngeal	3	0.9
Epidural abscess	2	0.6
Skin–cellulitis	2	0.6
Other (single occurrence)	18	5.6

study population are listed in Table 2. Ventilator-associated pneumonia, non-catheter-related bacteremia, nosocomial urinary tract infection (UTI), and intra-abdominal infection accounted for 72% of the confirmed infections.

Characterization of empiric administration practices

There were 312 patients (26.3% of the series) who were given at least one course of empiric antimicrobial therapy. A comparison of patients who received empiric antibiotics and those who did not is provided in Table 3. Younger, ventilated patients with a longer STICU LOS were more likely to receive empiric therapy. Patients who received empiric antibiotics also had more baseline renal dysfunction (Cr > 2.2 mg/dL) and were more likely to develop renal dysfunction during their STICU stays. The two groups had similar rates of infection on admission, but the empiric antibiotic group had a greater number of total antibiotic days, was more likely to develop a confirmed infection, had more resistant organisms, and ultimately had a higher STICU mortality rate. General surgery patients were more likely to receive empiric antibiotics, whereas cardiothoracic and vascular surgery patients were less likely to. Trauma surgery, the largest admitting service, did not demonstrate a difference in empiric antibiotic use. Trauma patients did not have a greater or lesser tendency to receive empiric antibiotics than patients on the other surgery services.

Effectiveness of empiric antibiotic use

Only 80 patients (25.6%) developed a confirmed infection (n = 98) within six days of initiating empiric therapy, the majority of whom (83.8%) developed an infection within three days. Resistant infections were found in 31 patients. The most common infections are shown in Table 4. Empiric antibiotic courses ranged from 1 to 20 days with an average of 3.1 ± 0.2 days (median two days). Seventy-one percent of patients had a course of three days or less. Table 5 compares patients who were subsequently found to have an infection with patients who were not (i.e., "clinically right" vs. "clinically wrong"). Empiric antibiotic use was more likely to be correct in patients who were infected on admission, had received prior antibiotics, had empiric therapy initiated later in their STICU course, or who were ventilated. Patients who were treated appropriately had more total infections, more total antibiotic days, a greater number of subsequent infections, and a greater likelihood of developing any infection during their STICU stay. These patients also had more ventilator days and longer STICU stays.

After analyzing our use of empiric antibiotics, we performed backward logistic regression analysis to determine the factors for beginning empiric antibiotics correctly and constructed a ROC curve. Included in our analysis were intubation status, STICU day of initiation of empiric antibiotics, admission to a surgery service other than cardiothoracic and vascular, and infection on admission. The C-statistic was 0.82, and the strongest independent predictor of beginning empiric antibiotics correctly was infection on admission, with an odds ration (OR) of 29.1 (95% confidence interval [CI] 7.9–108). Additional independent predictors were STICU day of empiric antibiotic initiation (OR 1.13; 95% CI 1.06–1.20) and intubation (OR 2.8; 95% CI 1.1–8.0).

Incorrect administration of empiric antibiotics and consequences

In order to understand better the factors associated with being clinically wrong, patients who received empiric antibiotics without an infection being confirmed were compared with those who never received empiric antibiotics (Table 6).

Table 3. Characteristics of Patients Who Did and Did Not Receive Empiric Antibiotics

	Antibiotics (n = 312)	*No antibiotics (n = 873)*	*P value*
Mean age (years)[a]	53.4 ± 1.06	56.4 ± .62	<0.05
Percent (n) male	66.7 (208)	60.6 (529)	NS
Percent (n) intubated	82.4 (257)	59.1 (516)	<0.001
Percent (n) with history of renal failure[b]	2.2 (7)	1.9 (17)	NS
Percent (n) with renal failure at baseline	9.3 (29)	4.7 (41)	<0.05
Percent (n) by admitting surgery service			
Trauma	48.4 (151)	44.7 (390)	NS
General	26.0 (81)	19.0 (166)	<0.05
Cardiothoracic/vascular	10.3 (32)	21.8 (190)	<0.001
Percent (n) with antibiotic use and infections			
Infection at admission	6.4 (20)	6.1 (53)	NS
Developed infection	30.4 (95)	7.8 (68)	<0.001
Any infection	36.9 (115)	13.9 (121)	<0.001
Any resistant infection	18.9 (59)	5.7 (50)	<0.001
Mean total antibiotic days	6.9 ± 0.35	2 ± 0.11	<0.001
Outcomes			
Mean STICU LOS (days)	12.7 ± 0.56	5.9 ± 0.19	<0.001
Mean ventilator days	8.8 ± 0.53	2.4 ± 0.13	<0.001
Percent (n) developing renal failure	22.4 (70)	11.9 (104)	<0.001
Percent (n) dying	8.7 (27)	3.2 (28)	<0.001

[a]Means ± standard deviation.
[b]Serum creatinine concentration >2.2 mg/dL.
NS = not significant; STICU LOS = surgical and trauma intensive care unit length of stay.

Empiric antibiotic use was significantly associated with younger age ($p < 0.001$), more STICU days (10.6 vs. 5.9; $p < 0.001$), more ventilator days ($p < 0.001$), more development of renal dysfunction (24.1% vs. 12.1%; $p < 0.001$), and a higher mortality rate (8.6% vs. 3.2%; $p < 0.001$).

Discussion

In this study, we had three specific aims with the overall goal of providing benchmark information for improving antibiotic stewardship. Our first aim was to evaluate our empiric antibiotic use. Our second aim was to determine the accuracy of empiric antibiotic administration. Our final aim was to investigate the consequences of unnecessary empiric antibiotic therapy.

Empiric antibiotics were initiated for 26.3% percent of our patients. Of those patients, only 25.6% developed confirmed infections ("clinically right"). Thus, 74% of patients receiving empiric antibiotics did not have an infection ("clinically wrong"). Factors associated with being "clinically right" included infection on admission, receiving prior antibiotics, and being intubated. "Clinically incorrect" antibiotic administration was associated with a longer STICU LOS, more ventilator days, development of renal dysfunction, and STICU death.

Table 4. Percent (n) of Confirmed Infections in 98 Patients Receiving Empiric Antibiotics ("Clinically Right")

Ventilator-associated pneumonia	27.6 (27)
Intra-abdominal	15.3 (15)
Bacteremia– non-catheter-related	14.3 (14)
Urinary tract–nosocomial	11.2 (11)
Meningitis	6.1 (6)
Necrotizing soft tissue	4.1 (4)
Surgical site	3.1 (3)
Bacteremia–catheter-related	2.0 (2)
Empyema	2.0 (2)
Nosocomial pneumonia	2.0 (2)
Sinusitis	2.0 (2)
C. difficile	1.0 (1)
Other single occurrence	9.0 (9)

Because there are a limited number of studies directly addressing broad-based empiric antibiotic treatment rates, comparison of our findings with those of similar studies was difficult. The closest approximation to our study was the Survey of Surgical Infections Currently Known (SOSICK) study, a multi-center examination of antimicrobial use conducted by the Surgical Infection Society. The investigators reported that 27% of the administered antibiotics were designated as empiric, which is similar to our experience [13].

There are a few papers describing the rate of empiric antibiotic over-treatment, but these are diagnosis specific; i.e. ventilator-associated pneumonia [14]. There is no literature that addresses a benchmark for a broad-based, acceptable over-treatment rate for empiric antibiotics in an STICU. A 2007 study of 195 patients in a combined medical and surgical ICU showed that 70% of those with suspected nosocomial infections were given antimicrobial therapy, but only 20% had adjudicated infections [15].

The association of unnecessary empiric antibiotics with more ventilator days, greater renal dysfunction, longer STICU LOS, and death is multifaceted. One of the implications may be that unnecessary antibiotics are causing more ventilator days, increasing the STICU LOS, and worsening the mortality rate. It is more plausible that there are other factors contributing to worse outcomes. This implies that patients are started on empiric antibiotics because they are deteriorating clinically for unknown reasons. One 2009 study from Spain discovered

Table 5. Characteristics of Clinically Right (Confirmed Infection) vs. "Clinically Wrong" (No Confirmed Infection) Cases

	Clinically right (n = 80)	*Clinically wrong (n = 232)*	*P value*
General characteristics			
Mean age (years)[a]	54.1 ± 2.15	53.1 ± 1.2	NS
Percent (n) male	66.2 (53)	66.8 (155)	NS
Percent (n) intubated	92.5 (74)	78.9 (183)	<0.05
Percent (n) with history of renal failure[b]	1.2 (1)	2.6 (6)	NS
Percent (n) in renal failure at baseline	11.2 (9)	8.6 (20)	NS
Percent (n) having trauma surgery	53.8 (43)	46.6 (108)	NS
Percent (n) having general surgery	27.5 (22)	25.4 (59)	NS
Percent (n) having cardiothoracic/vascular surgery	5.0 (4)	12.1 (28)	NS
Infections and organisms			
Percent (n) with infection on admission	21.2 (17)	1.3 (3)	<0.001
Percent (n) with any resistant infection	47.5 (38)	9.1 (21)	<0.001
Percent (n) who developed infection	78.8 (63)	13.8 (32)	<0.001
Mean total infections	1.5 ± 0.08	0.2 ± 0.04	<0.001
Antibiotic use			
Percent (n) with prior antibiotics	28.8 (23)	17.2 (40)	<0.05
Mean number of prior antibiotic days	0.9 ± 0.23	0.7 ± 0.15	NS
Mean duration of empiric antibiotics (days)	2.9 ± 0.23	3.1 ± 0.19	NS
Mean STICU day antibiotic initiated	5.1 ± 0.49	3.0 ± 0.26	<0.001
Percent (n) having empiric course >3 days	26.2 (21)	30.6 (71)	NS
Mean number of post-course days	7.0 ± 0.66	1.8 ± 0.26	<0.001
Mean total antibiotic days	10.7 ± 0.70	5.6 ± 0.36	<0.001
Outcomes			
Mean STICU LOS (days)	18.4 ± 1.18	10.7 ± 0.58	<0.05
Ventilator days	14.1 ± 1.15	6.9 ± 0.54	<0.05
Percent (n) who developed renal failure	17.5 (14)	24.1 (56)	NS
Percent (n) who died	8.8 (7)	8.6 (20)	NS

[a]Means ± standard deviation.
[b]Serum creatinine concentration >2.2 mg/dL.
NS = not significant; STICU = surgery and trauma intensive care unit; LOS = length of stay.

Table 6. Characteristics and Outcomes of Patients without Confirmed Infection

	Empiric antibiotics (n = 232)	*No empiric antibiotics (n = 873)*	*P value*
General characteristics			
Mean age (years)[a]	53.1 ± 1.21	56.4 ± 0.62	<0.05
Percent (n) male	66.8 (155)	60.6 (529)	NS
Percent (n) intubated	78.9 (183)	59.1 (516)	<0.001
Percent (n) with history of renal failure[b]	2.6 (6)	1.9 (17)	NS
Percent (n) with renal failure at baseline	8.6 (20)	4.7 (41)	<0.05
Percent (n) having trauma surgery	46.6 (108)	44.7 (390)	NS
Percent (n) having general surgery	25.45 (59)	19.0 (166)	<0.05
Percent (n) having cardiothoracic/vascular surgery	12.1 (28)	21.8 (190)	<0.05
Infections			
Percent (n) with infection on admission	2.6 (6)	7.1 (62)	<0.05
Percent (n) with any infection	15.1 (35)	13.9 (121)	NS
Mean total infections per patient	0.2 ± 0.04	0.17 ± 0.02	NS
Antibiotic use			
Mean total antibiotic days	5.6 ± 0.36	2.04 ± 0.11	<0.05
Drug resistance			
Percent (n) with any resistant organism	9.1 (21)	5.7 (50)	0.051
Mean total resistant organisms/patient	0.7 ± 0.11	0.4 ± 0.05	<0.05
Outcomes			
Mean STICU LOS	10.7 ± 0.58	5.9 ± 0.19	<0.05
Mean ventilator days	6.9 ± 0.54	2.4 ± 0.13	<0.05
Percent (n) who developed renal failure	24.1 (56)	11.9 (104)	<0.001
Percent (n) dying in STICU	8.6 (20)	3.2 (28)	<0.001

[a]Mean ± standard deviation.
[b]Serum creatinine concentration >2.2 mg/dL.
NS = not significant; STICU = surgery and trauma intensive care unit.

a high mortality rate among immunocompetent patients who received appropriate therapy for pneumonia but still developed shock and renal failure and had an Acute Physiology and Chronic Health Evaluation (APACHE) II score >24 [16]. This result suggests that in their ICU population, there were factors contributing to death beyond inadequate treatment of infections.

There are several limitations of our study. Although we describe our empiric antibiotic practices, we do not specifically describe the regimen or address whether all patients received appropriate initial empiric therapy. Furthermore, we used only a limited number of variables to determine factors associated with administering empiric antibiotics correctly. For example, we did not calculate the APACHE II score or evaluate vital signs, which other studies addressing antibiotic use and outcomes have done. However, this was not a primary study objective. We also grouped cardiothoracic and vascular surgery patients. This grouping could skew the results, as these populations embody different disease processes. Another limitation is that we relied on correct documentation within SIC-IR, our research database. We have previously validated the accuracy of the data [9, 10]; however, we did discover some errors in the indication for antibiotic use. This has led us to improve our educational process in the STICU. Moreover, there is no clear definition of or consensus on the definition of empiric antibiotics.

Our overall goal was to improve antibiotic stewardship. There is literature discussing the use of empiric antibiotic cycling [17, 18], adherence to guidelines on length of empiric antibiotic treatment, antibiotic streamlining [19], inadequate empiric treatment [20], and discontinuation of empiric antibiotics after shorter courses [7, 21] and multiple articles discussing antibiotic stewardship [22].

We established a baseline from which we can improve antibiotic utilization. Our results support the view that unnecessary empiric antibiotics are associated with worse outcomes and more antibiotic days. Roughly 26% of patients in the STICU will receive at least one course of empiric antibiotics, but only 25% of these will show evidence that these empiric antibiotics were necessary. Our study appears to be unique; however, our results are consistent with the limited literature. Thus, we have room for improvement with regard to empiric antibiotic use. We intend to use these data to implement clinical decision-support tools in our existing system, SIC-IR, and to continue to educate healthcare providers. Lastly, we trust that these results provide key benchmark data for the critical care community to strive to improve antibiotic stewardship.

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Author Disclosure Statement

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