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The Impact of an Inpatient Nurse-Triggered Sepsis Alert on Antimicrobial Utilization

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Introduction: A nurse-triggered sepsis alert called "Code Sepsis" was implemented for early recognition and management of sepsis. The researchers analyzed its impact on antimicrobial use and identified factors associated with infection as source of Code Sepsis.

Methods: The medical records of hospitalized patients with Code Sepsis between January 1 and June 30, 2018, were reviewed. Patients were classified as "*Infection*" when probable or definitive infection was identified or "*No Infection*" when a probable or definitive noninfectious source was identified. Patients were categorized as "*Escalation*" with addition or change to broader-spectrum antimicrobials or "*No Escalation*" with no change or change to narrower-spectrum antimicrobials. *Escalation* was classified as "*Indicated*" with appropriate escalation or "*Not Indicated*" with inappropriate escalation. Logistic regression model was used to identify factors associated with *Infection* as Code Sepsis trigger.

Results: Code Sepsis was activated in 529 patients, with *Escalation* in 246 (46.5%) and *No Escalation* in 283 (53.5%) patients. Escalation was *Indicated* in 157 (63.8%) and *Not Indicated* in 89 (36.2%) patients. *Infection* was identified in 356 (67.3%) and *No Infection* in 173 (32.7%) patients. History of HIV (odds ratio [OR] = 2.75, $p = 0.03$), temperature > 38.3°C or < 36°C (OR = 2.63, $p < 0.01$), and respiratory rate > 20/minute (OR = 1.56, $p = 0.02$) were associated with *Infection*, while surgery within 3 days (OR = 0.30, $p < 0.01$) was associated with *No Infection*.

Conclusion: One hospital system's Code Sepsis inadvertently identified patients without infections and led to antimicrobial overuse. By refocusing Code Sepsis on early recognition of severe sepsis and septic shock only, the organization hopes to optimize resource utilization and improve patient outcomes.

Balancing antimicrobial stewardship with sepsis management based on national sepsis quality measures can result in conflicting goals toward optimal medical care. Prompt administration of broad-spectrum antimicrobial therapy has been the cornerstone of sepsis management.[1,2] In 2015 the Centers for Medicare & Medicaid Services (CMS) released the SEP-1 quality process measure for sepsis, which requires antimicrobial administration within three hours of identification of suspected or confirmed severe sepsis or septic shock.[3] Similarly, the Surviving Sepsis Campaign (SSC) also recommends the initiation of empiric broad-spectrum antimicrobial therapy within one hour of meeting sepsis criteria.[4] However, there are concerns over the lack of clear diagnostics for sepsis and the rigid time frame to initiate broad-spectrum antimicrobial therapy. In fact, the Infectious Diseases Society of America did not endorse the SSC guidelines due to the "one-size-fits-all" recommendation on antimicrobial use, given the potential for its overuse in uninfected patients.[5]

Various medical centers have implemented the SSC guidelines as a sepsis intervention bundle, which has been associated with decreased mortality and increased cost savings.[6–8] L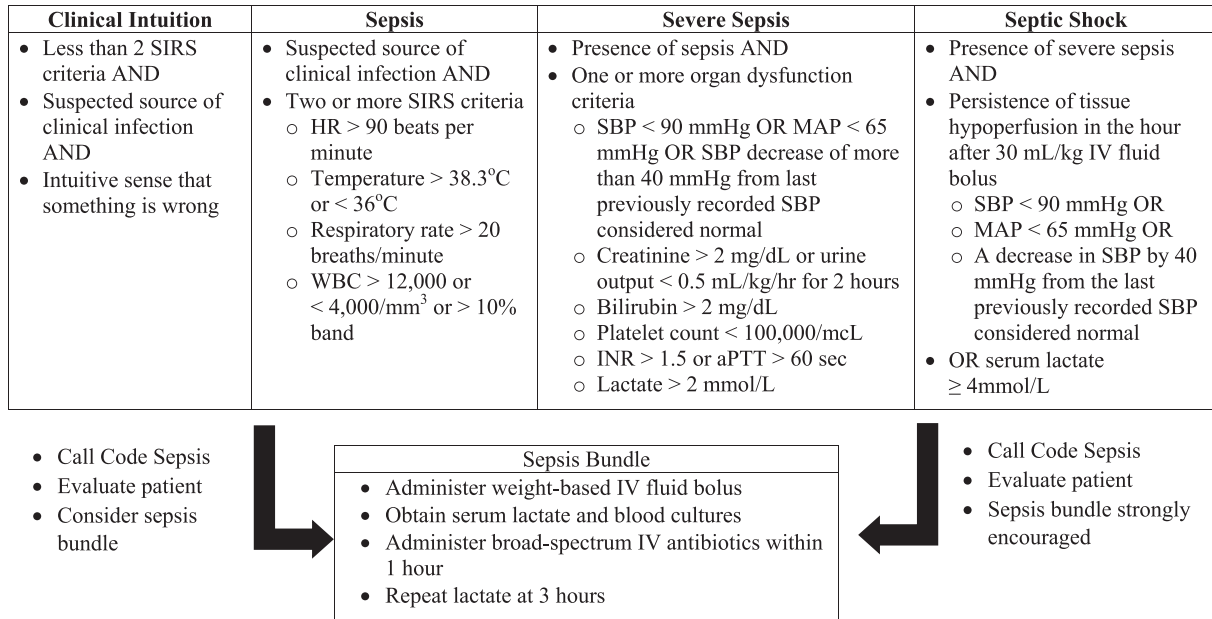ikewise, institutions have developed protocols to help improve compliance with the publicly reportable SEP-1 bundle. At our academic medical center, an inpatient, nurse-driven "Code Sepsis" protocol was implemented in 2016 to facilitate the early recognition of sepsis and the rapid delivery of the recommended bundle based on the SEP-1 approach. However, there is minimal literature on the accuracy of "Code Sepsis" in identifying severe sepsis or septic shock and on the appropriateness of administration of antimicrobial agents. Thus, the goal of this study was to determine the impact of Code Sepsis on antimicrobial use and to identify comorbidities, vital signs, or laboratory values predictive of infection as source of Code Sepsis activation.

METHODS

Study Setting and Population

We conducted a retrospective cohort study of hospitalized patients with Code Sepsis activation at University of California, San Diego Health (UCSDH). UCSDH consists of two campuses within the same health care system with a combined capacity of 799 beds. Patients ≥ 18 years of age who had Code Sepsis activation during an inpatient hospitalization from January 1, 2018, to June 30, 2018, were included in the study. Code Sepsis events that were canceled by the primary provider or activated in the emergency

Key Aspects of Code Sepsis

Clinical Intuition	Sepsis	Severe Sepsis	Septic Shock

• Less than 2 SIRS criteria AND
• Suspected source of clinical infection AND
• Intuitive sense that something is wrong
	• Suspected source of clinical infection AND
	• Two or more SIRS criteria
	  ○ HR > 90 beats per minute
	  ○ Temperature > 38.3°C or < 36°C
	  ○ Respiratory rate > 20 breaths/minute
	  ○ WBC > 12,000 or < 4,000/mm³ or > 10% band
		• Presence of sepsis AND
		• One or more organ dysfunction criteria
		  ○ SBP < 90 mmHg OR MAP < 65 mmHg OR SBP decrease of more than 40 mmHg from last previously recorded SBP considered normal
		  ○ Creatinine > 2 mg/dL or urine output < 0.5 mL/kg/hr for 2 hours
		  ○ Bilirubin > 2 mg/dL
		  ○ Platelet count < 100,000/mcL
		  ○ INR > 1.5 or aPTT > 60 sec
		  ○ Lactate > 2 mmol/L
			• Presence of severe sepsis AND
			• Persistence of tissue hypoperfusion in the hour after 30 mL/kg IV fluid bolus
			  ○ SBP < 90 mmHg OR
			  ○ MAP < 65 mmHg OR
			  ○ A decrease in SBP by 40 mmHg from the last previously recorded SBP considered normal
			• OR serum lactate ≥ 4mmol/L

| Call Code Sepsis
• Evaluate patient
• Consider sepsis bundle | Sepsis Bundle
• Administer weight-based IV fluid bolus
• Obtain serum lactate and blood cultures
• Administer broad-spectrum IV antibiotics within 1 hour
• Repeat lactate at 3 hours | • Call Code Sepsis
• Evaluate patient
• Sepsis bundle strongly encouraged |

Figure 1: This chart summarizes the key aspects of Code Sepsis. The diagnostic criteria for sepsis, severe sepsis, and septic shock were adapted from the Centers for Medicare & Medicaid Services criteria and the 2012 Surviving Sepsis Campaign guidelines (see references 3 and 9 on page 7). SIRS, systemic inflammatory response syndrome; HR, heart rate; WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time; IV, intravenous.

department (ED) prior to an inpatient admission were excluded. Repeat Code Sepsis events in the same patient were excluded, and only the first Code Sepsis in each patient was included in the analysis. This study was approved by the Institutional Review Board with waiver of informed consent at UCSDH.

Code Sepsis

Our inpatient Code Sepsis protocol was implemented across our hospital system, including hospital wards and ICUs. Code Sepsis was activated by the primary nurse for hospitalized patients admitted to any floor or ICU who met criteria for possible sepsis, severe sepsis, or septic shock, or in whom health care providers had clinical intuition that "something is wrong." Key aspects of Code Sepsis are summarized in Figure 1. Diagnostic criteria for sepsis, severe sepsis, and septic shock as outlined in Figure 1 were adapted from the 2012 SSC guidelines[9] and CMS criteria.[3]

Activation of Code Sepsis by the primary nurse notified physicians, pharmacists, respiratory therapists, and nursing manager. The implementation of the SEP-1 bundle was strongly encouraged for presumed or confirmed severe sepsis or septic shock. If deemed to be not indicated, physicians may decline to initiate broad-spectrum antimicrobials as well as other aspects of the SEP-1 bundle with appropriate documentation. The implementation of the SEP-1 bundle can be considered for sepsis if deemed to be indicated. The Code Sepsis response nurse obtained laboratory testing as necessary and encouraged compliance with the SEP-1

bundle when indicated by assisting with the administration of intravenous fluid bolus, broad-spectrum antibiotics, and vasoactive agents within the recommended time frame.

Definitions

We analyzed the impact of Code Sepsis on antimicrobial prescription. Code Sepsis events were categorized as "*Escalation*" or "*No Escalation*" according to the definitions provided below. We further categorized antimicrobial *Escalation* as "*Indicated*" or "*Not Indicated*" as per the criteria described below.

We also determined if infection was identified as source of Code Sepsis activation. Code Sepsis events were categorized as "*Infection*" or "*No Infection*" according to the criteria provided below.

The primary outcome was the proportion of patients with antimicrobial escalation that was indicated and the proportion of patients in whom an infection was identified as source of Code Sepsis activation.

Escalation vs. No Escalation. Code Sepsis events with changes in antimicrobial prescription were categorized as *Escalation* if one or more antimicrobial agents were prescribed within one hour after Code Sepsis in a patient who was previously not on antimicrobials, if one or more antimicrobial agents were added within one hour after Code Sepsis in a patient who was already on one or more antimicrobials, or if antimicrobials prescribed within one hour after Code Sepsis were broader spectrum compared to those

Table 1. Spectrum of Antimicrobials Used to Evaluate for Antimicrobial Escalation

Narrow Spectrum		→	Broad Spectrum
1	2	3	4
Penicillin Amoxicillin Ampicillin Nafcillin/Oxacillin 1st & 2nd generation cephalosporins Trimethoprim/sulfamethoxazole Doxycycline Nitrofurantoin Azithromycin Clindamycin	Amoxicillin/clavulanate Ampicillin/sulbactam Ceftriaxone	Piperacillin/tazobactam Cefepime, Ceftazidime Ertapenem Aztreonam Fluoroquinolones Vancomycin Aminoglycosides	Ceftazidime/avibactam Ceftolozane/tazobactam Meropenem Imipenem Daptomycin Ceftaroline Linezolid Tigecycline Colistin

prior to Code Sepsis as categorized in Table 1. Antimicrobial changes were categorized as *No Escalation* if no antimicrobials were prescribed within one hour after Code Sepsis in a patient who was previously not on antimicrobials or if antimicrobials prescribed within one hour after Code Sepsis were same or narrower spectrum compared to those prior to Code Sepsis as in Table 1.

***Indicated* vs. *Not Indicated*.** Code Sepsis events with antimicrobial *Escalation* were further categorized as *Indicated* or *Not Indicated*. Anti-infective changes were considered *Indicated* when (1) empiric broad-spectrum antimicrobial therapy was initiated in the setting of a change in clinical status due to a suspected infection. Changes in clinical status were defined as the presence of two or more systemic inflammatory response syndrome (SIRS) criteria that were previously absent; new hypoxia requiring high-flow nasal oxygen, noninvasive ventilation, or invasive ventilation; or ICU transfer due to shock or mental status or vital sign changes. In addition, anti-infective changes were considered *Indicated* with (2) initiation of targeted antimicrobial therapy directed at a suspected or confirmed source. Examples include the initiation of ceftriaxone for a suspected urinary tract infection or gentamicin and ampicillin for chorioamnionitis. Finally, antimicrobial *Escalation* was considered *Indicated* with (3) initiation of antimicrobial therapy in patients with less than two SIRS criteria but with a confirmed infection. Examples include the initiation of vancomycin, ceftazidime, and metronidazole in a patient with symptoms and findings consistent with cholangitis but with less than two SIRS criteria (Figure 2).

Antimicrobial *Escalations* were categorized as *Not Indicated* when (1) a noninfectious source was suspected. Examples of noninfectious sources documented include medication side effects, autoimmune disorders, alcohol and drug withdrawal, and pancreatitis. Antimicrobial changes were also categorized as *Not Indicated* when (2) less than two SIRS criteria were present at the time of Code Sepsis, and

the providers did not have suspicion for a specific infection. In addition, antimicrobials that were escalated despite (3) an ongoing appropriate treatment of a known infection were categorized as *Not Indicated*. Examples include initiation of broad-spectrum antibiotics in a patient undergoing therapy for known *Mycobacterium tuberculosis* (MTB) infection without suspicion for a new infectious process, or the addition of gram-negative coverage in a patient with known methicillin-resistant *Staphylococcus aureus* (MRSA) infection who did not have source control. Finally, changes to antimicrobial therapy were categorized as *Not Indicated* when (4) the providers prescribed antibiotics for an infection despite diagnostics available at the time of the Code Sepsis event supporting an absence of the infection. Examples include initiation of antimicrobials for urinary tract infection despite a normal urinalysis, or for a pneumonia despite a normal computed tomography of the chest (Figure 2).

***Infection* vs. *No Infection*.** Patients were classified as *Infection* when consistent results of microbiology, molecular, or serology tests were present to suggest a definitive infection. Patients with probable or possible infection in which consistent microbiology, molecular, or serology results were absent but imaging and/or physical exam findings consistent with an infection were present were classified as *Infection*. Examples include suspected pneumonia in a patient without sputum culture but with chest radiograph with new infiltrates. Patients with neutropenic fevers with or without identified infectious sources were classified as having *Infection*, as neutropenic fever warrants antimicrobial therapy regardless of the source.[10] Patients were classified as *No Infection* when a noninfectious source was suspected or confirmed with no laboratory, microbiology, or imaging results suggesting an infection.

Data Collection
Code Sepsis events were identified through an internal quality variance reporting data collection system. Data were

Schematic Diagram of Inpatient Code Sepsis and Analysis
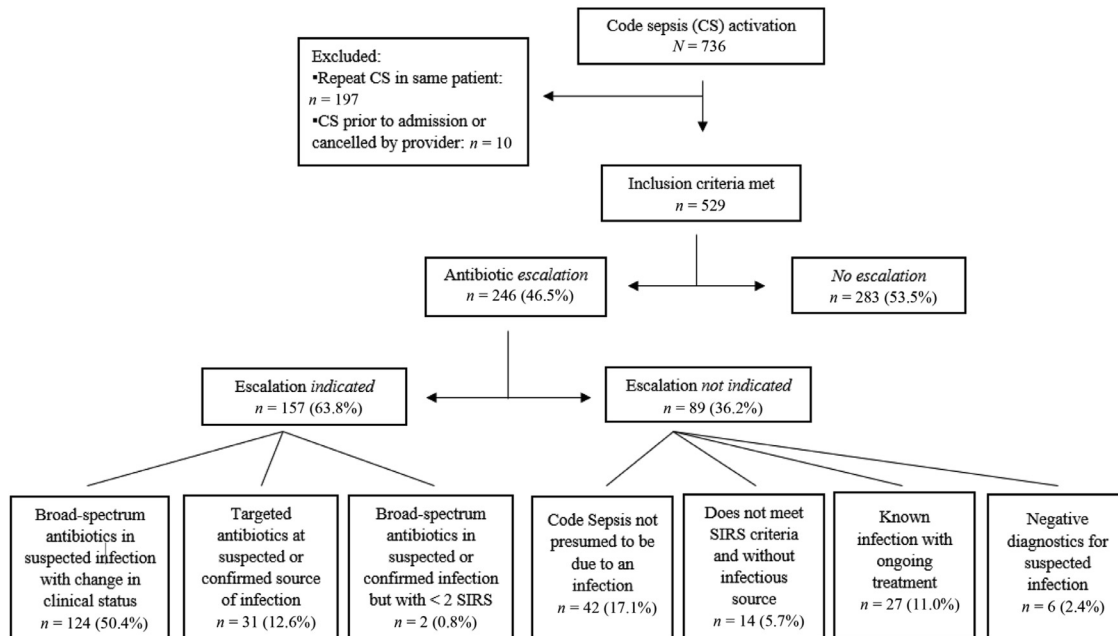
Figure 2: Shown here is a diagram of the nurse-triggered inpatient sepsis alert called "Code Sepsis" and analysis.

collected retrospectively by an infectious disease specialist [M.K.] from manual chart review of the patients' electronic medical record. Cases in which categorization of "*Indicated*" and "*Not Indicated*" or "*Infection*" and "*No Infection*" were ambiguous were adjudicated by additional infectious disease specialists [F.J.T. or S.R.A.]. The following baseline demographics and comorbidities were collected: age, gender, HIV infection, active solid organ malignancy, active hematologic malignancy, hematopoietic stem cell transplantation, solid organ transplantation, congestive heart failure, end-stage renal disease requiring renal replacement therapy, diabetes mellitus (DM), cirrhosis, and recent surgery within 3 days of Code Sepsis activation. Suspected source of Code Sepsis was collected based on provider documentation at time of Code Sepsis or daily progress note. Vital signs at the time of Code Sepsis and laboratory values within 24 hours of Code Sepsis activation, including creatinine, bilirubin, platelet, International Normalized Ratio (INR), and lactate, were collected. Antimicrobial agents prescribed before and within 1 hour after Code Sepsis were abstracted from the Medication Administration Record in the electronic chart.

Statistical Analysis

Data were analyzed using SPSS Statistics 25 (IBM Corp., SPSS, Armonk, New York). Continuous variables were reported as means with standard deviations (SDs). Differences between means were tested with Student's *t*-test. Categorical data were reported as proportions. Chi-square test or Fischer's exact test were used to analyze categorical data.

We developed a logistic regression model to identify comorbidities, vital signs, or laboratory values associated with *Infection* as source of Code Sepsis event. All factors significant at $p \leq 0.20$ with univariable analyses were used in the multivariable regression model. Backward manual elimination method was used to derive the most parsimonious model. All tests were two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Patient Characteristics

Code Sepsis was activated 736 times during the study period. Of these events, 197 were repeat episodes in the same patient and were therefore excluded, and an additional 10 were canceled by the provider; thus, 529 patients were included in the study (Figure 2).

A total of 507 (95.8%) patients were hospitalized in floor units, while 22 (4.2%) were in the ICU. Two hundred ninety patients (54.8%) were under general medicine service, 107 (20.2%) were under surgical services, and 66 (12.5%) were under the oncology service; the remainder of patients were on obstetrics/gynecology, neurology, cardiology, psychiatry, and pulmonary services.

The mean age ± SD was 54.5 ± 18.1 years, and 57.8% were men. Common comorbidities included DM in 18.7% of the patients and solid organ malignancy in 16.6%. Patients met mean ± SD of 2.60 ± 0.92 SIRS criteria and 1.02 ±1.05 organ dysfunction criteria. Prior to Code Sep-

Table 2. Baseline Characteristics of Patients with Code Sepsis

		Total N = 529 (%)	Infection n = 356 (%)	No Infection n = 173 (%)	p Value
Gender	Male	306 (57.8)	207 (58.1)	99 (57.2)	NS
Age	Mean ± SD	54.5 ± 18.1	54.2 ± 18.5	55.2 ± 17.2	NS
Underlying Diagnosis	HIV	41 (7.8)	35 (9.8)	6 (3.5)	< 0.01
	Solid organ malignancy	88 (16.6)	54 (15.2)	34 (19.7)	NS
	Hematologic malignancy	42 (7.9)	30 (8.4)	12 (6.9)	NS
	Hematopoietic stem cell transplantation	30 (5.7)	24 (6.7)	6 (3.5)	NS
	Solid organ transplantation	26 (4.9)	19 (5.3)	7 (4.0)	NS
	Congestive heart failure	44 (8.3)	31 (8.7)	13 (7.5)	NS
	End stage-renal disease	16 (3.0)	9 (2.5)	7 (4.0)	NS
	Diabetes mellitus	99 (18.7)	73 (20.5)	26 (15.0)	NS
	Cirrhosis	15 (2.8)	12 (3.4)	3 (1.7)	NS
	Recent surgery within 3 days	46 (8.7)	19 (5.3)	27 (15.6)	< 0.01
SIRS Criteria	Number of criteria (mean ± SD)	2.60 ± 0.92	2.72 ± 0.90	2.33 ± 0.91	< 0.01
	Heart rate > 90 beats/min	468 (88.5)	316 (88.8)	152 (87.9)	NS
	Temperature > 38.3 or < 36°C	294 (55.6)	225 (63.2)	69 (39.9)	< 0.01
	Respiratory rate > 20/min	319 (60.3)	228 (64.0)	91 (52.6)	0.01
	WBC > 12,000 or < 4,000/mm^3	291 (55.0)	200 (56.2)	91 (52.6)	NS
Organ Dysfunction	Number of criteria (mean ± SD)	1.02 ± 1.05	1.03 ± 1.07	0.99 ± 1.01	NS
	SBP < 90 or MAP < 65 mmHg	107 (20.2)	70 (19.7)	37 (21.4)	NS
	Creatinine > 2 mg/dL	53 (10.0)	36 (10.1)	17 (9.8)	NS
	Bilirubin > 2 mg/dL	45 (8.5)	34 (9.6)	11 (6.4)	NS
	Platelet count < 100,000/mm^3	107 (20.2)	77 (21.6)	30 (17.3)	NS
	INR > 1.5 OR aPTT > 60 sec	41 (7.8)	29 (8.1)	12 (6.9)	NS
	Lactate > 2 mmol/L	186 (35.2)	121 (34.0)	65 (37.6)	NS
Antibiotics Prior to Code Sepsis	None	186 (35.2)	85 (23.9)	101 (58.4)	< 0.01
	Broad-spectrum	139 (26.3)	118 (33.1)	21 (12.1)	
	Miscellaneous	204 (38.6)	153 (43.0)	51 (29.5)	
Antibiotic Escalation	Escalation	246 (46.5)	162 (45.5)	84 (48.6)	NS
	No escalation	283 (53.5)	194 (54.5)	89 (51.4)	

NS, not significant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial pressure; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time.

sis events, 35.2% of the patients were not on antimicrobial agents, while 26.3% were already receiving broad-spectrum antibiotics (Table 2).

Indicated Antimicrobial Escalation in Code Sepsis

Escalation occurred in 246 (46.5%) patients, and *No Escalation* occurred in 283 (53.5%) patients (Figure 2). *Escalation* in 157 (63.8%) patients was deemed *Indicated*. *Indicated* antimicrobial escalations included initiation of (1) broad-spectrum antibiotics due to worsening clinical status in 124 (50.4%) patients, (2) targeted antimicrobials directed at a suspected or confirmed infectious source in 31 (12.6%) patients, and (3) antimicrobials in confirmed infection despite < 2 SIRS criteria in 2 (0.8%) patients (Figure 2). Antimicrobial *Escalation* was identified as *Not Indicated* in 89 (36.2%) patients due to (1) suspicion for a noninfectious source as documented in the electronic medical record in 42 (17.1%) patients, (2) lack of ≥ 2 SIRS criteria along with a lack of suspicion for an infectious source in 14 (5.7%) patients, (3) presence of a known infectious etiology in 27 (11.0%) patients, and (4) initiation of targeted antimicrobial therapy against suspected infection despite negative di-

agnostics indicating the absence of the suspected infection in 6 (2.4%) patients (Figure 2).

Infection vs. No Infection

Infection was identified in 356 (67.3%) patients, while *No Infection* was identified in 173 (32.7%) patients. There was no difference in demographics, but patients with *Infection* were more likely to be HIV positive (9.8% *Infection* vs. 3.5% *No Infection, p < 0.01*) and were less likely to have had surgery within 3 days (5.3% *Infection* vs. 15.6% *No Infection, p < 0.01*). Patients with *Infection* met significantly more SIRS criteria (2.72 ± 0.90 *Infection* vs. 2.33 ± 0.91 *No Infection, p < 0.01*); specifically temperature > 38.3°C or < 36 °C (63.2% *Infection* vs. 39.9% *No Infection, p < 0.01*) and respiratory rate > 20/min (64.0% *Infection* vs. 52.6% *No Infection, p = 0.01*). There was no significant difference in the proportion of patients with antimicrobial escalation between the two groups (Table 2).

Factors Associated with *Infection* as Source of Code Sepsis

In multivariable analysis, HIV was associated with *Infection* (odds ratio [OR] = 2.75, 95% confidence interval

Table 3. Factors Associated with *Infection* as Source of Code Sepsis*

Predictor	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
HIV	3.04 (1.25–7.36)	0.01	2.75 (1.09–6.90)	0.03
Solid organ malignancy	0.73 (0.46–1.17)	0.19		
Hematopoietic stem cell transplantation	2.01 (0.81–5.02)	0.13		
Diabetes mellitus	1.46 (0.89–2.38)	0.13		
Recent surgery within 3 days	0.31 (0.16–0.57)	< 0.01	0.30 (0.15–0.57)	< 0.01
Number of SIRS criteria	1.61 (1.31–1.98)	< 0.01		
Temperature > 38.3°C or < 36°C	2.59 (1.78–3.76)	< 0.01	2.63 (1.79–3.87)	< 0.01
Respiratory rate > 20 per minute	1.61 (1.11–2.32)	0.01	1.56 (1.06–2.31)	0.02

* Univariable analysis performed but not retained in the model as alpha > 0.20 include gender, age, ethnicity, hematologic malignancy, solid organ transplantation, congestive heart failure, end-stage renal disease, cirrhosis, heart rate > 90 beats/min, white blood cell > 12,000 or < 4,000/mm^3, number of organ dysfunction criteria met, systolic blood pressure < 90 or mean arterial pressure < 65mmHg, creatinine > 2 mg/dL, bilirubin > 2 mg/dL, platelet count < 100,000/mm^3, International Normalized Ratio (INR) > 1.5 or activated partial thromboplastin time (aPTT) > 60 sec.CI, confidence interval; SIRS, systemic inflammatory response syndrome.

[CI] = 1.09–6.90, p = 0.03), while recent surgery within 3 days was associated with *No Infection* (OR = 0.30, 95% CI = 0.15–0.57, p < 0.01). Temperature > 38.3°C or < 36°C (OR = 2.63, 95% CI = 1.79–3.87, p < 0.01) and respiratory rate > 20 per minute (OR = 1.56, 95% CI = 1.06–2.31, p = 0.02) were associated with *Infection* (Table 3).

DISCUSSION

Although the association with lower in-hospital mortality after the implementation of sepsis bundles cannot be ignored,[6–8] there are unintended consequences. At our institution the implementation of Code Sepsis based on SIRS criteria to improve early recognition and management of sepsis led to a significant number of activations in patients in whom infection was not present and antimicrobial escalation was not warranted. When antimicrobials were escalated during Code Sepsis, approximately one third were not indicated. Patient harm from inappropriate antimicrobial use has been previously well-described.[11–13] Provider time and resources may also be strained by unnecessary evaluations and result in higher health care costs. Our results may help inform development and revisions of sepsis protocols and highlight the current limitations of the SEP-1 quality bundle and international guidelines for the management of sepsis.

Algorithmic sepsis alert systems are known to result in high false-positive activation of sepsis bundles.[14,15] A prospective study that evaluated algorithmic sepsis alert in the ED revealed that 37.8% were false-positive activations.[14] Similarly, the use of Best Practice Alerts in the electronic medical record misclassified patients with SIRS as having sepsis.[15] At our institution, 197 (26.8%) Code Sepsis activations were repeat activations on patients with a prior Code Sepsis event. Although a rapid response inter-

vention may still be indicated, developing a mechanism to prevent recurrent activations of Code Sepsis may help decrease staff fatigue and unnecessary blood draws or therapies. In addition, Code Sepsis activation based on SIRS criteria may not have been indicated in more than half of patients with Code Sepsis activation in whom Code Sepsis resulted in no antimicrobial changes. These patients were not exposed to unnecessary antimicrobial therapy, but Code Sepsis activation resulted in patient anxiety and the use of unnecessary resources such as laboratory tests and health care personnel time.

We postulate that the unnecessary activation of Code Sepsis is in part due to the lack of specificity of SIRS criteria. Although SIRS criteria are present in many hospitalized patients without infections[16] and are no longer used by the SSC,[4] CMS continues to endorse SIRS as a screening tool for sepsis. In addition, although the clinical suspicion of an infection is a crucial aspect in diagnosing sepsis, the accuracy of diagnosing an infection has been limited.[17,18] In a prospective analysis, the accuracy of diagnosing an infection was poor, with up to 43% of ICU patients treated for presumed sepsis unlikely to have had an infection on post hoc assessment.[17] In our analysis, no infection was identified in one third of the Code Sepsis events. In our attempt to identify factors associated with infection as trigger for Code Sepsis, temperature > 38.3°C or < 36°C, respiratory rate > 20 per minute, and HIV were found to be significantly associated with infection as source of Code Sepsis, while recent surgery within 3 days was associated with no infection.

It is currently recommended that antimicrobial therapy be initiated within one hour of presentation of sepsis[4] due to data suggesting that every hour delay in antibiotics is associated with a 7.6% increase in mortality in patients with hypotension.[19] The CMS SEP-1 bundle recommends that this be accomplished within three hours.[3] The prompt ini-

tiation of antimicrobial therapy in critically ill patients with septic shock is crucial in improving mortality, but the time pressure to provide broad-spectrum antimicrobial therapy in clinically stable patients with presumed sepsis is over-stated. In fact, this time pressure may have unintended consequences, with uncertainty avoidance driving antimicrobial administration even when the certainty regarding an infection is minimal.[18,20] At our institution, close to a third of antimicrobial escalations were not indicated, and antimicrobials were escalated despite documented suspicion for a noninfectious etiology or the presence of a known infectious source that was appropriately being treated. With observational studies casting doubts on the correlation between timing of antimicrobials and mortality in sepsis,[21–23] relaxing the time pressure in less sick patients with uncertain presence of infections may allow for additional diagnostics and more judicious use of antimicrobial therapy.

Limitations to this study include the single academic medical center and the retrospective and observational study design. Given the heterogeneity in the management and decision-making process that are institution and provider based, this study may not be generalizable to other institutions. In addition, as the retrospective review of Code Sepsis cases regarding antimicrobial use was made without medical or legal risks associated with clinical medicine, this may lead to differences in decision-making process that may not be reflective of clinical medicine. Furthermore, data regarding de-escalation, duration of inappropriate antimicrobial therapy, and patient outcomes such as *Clostridioides difficile* infection or 30-day mortality were not collected, so we cannot determine the consequences of unindicated antimicrobial use. Finally, we cannot definitively state that Code Sepsis led to increased unindicated antimicrobial escalation, as we do not have data regarding antimicrobial use prior to the implementation of Code Sepsis.

CONCLUSION

Although sepsis bundles are associated with improved compliance and mortality, institutional efforts to improve early recognition and intervention of sepsis based on SIRS criteria led to the activation of Code Sepsis and antimicrobial escalation that may not have been indicated. Thus, at our institution, we have opted to raise the bar to activate Code Sepsis at the level of severe sepsis and/or septic shock rather than sepsis alone in order to remove the impetus of prescribing antimicrobial therapy in less severe disease while ensuring a mechanism for early recognition and management in severe disease. We expect that this change will lead to a decline in unindicated Code Sepsis activation and antimicrobial escalations. Further work is necessary to develop a consensus on the definition of sepsis and antimicrobial appropriateness to improve antimicrobial-related decision making in sepsis.

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