Real-World Implications of Updated Surviving Sepsis Campaign Antibiotic Timing Recommendations*

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OBJECTIVE: To evaluate real-world implications of updated Surviving Sepsis Campaign (SSC) recommendations for antibiotic timing.

DESIGN: Retrospective cohort study.

SETTING: Twelve hospitals in the Southeastern United States between 2017 and 2021.

PATIENTS: One hundred sixty-six thousand five hundred fifty-nine adult hospitalized patients treated in the emergency department for suspected serious infection.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We determined the number and characteristics of patients affected by updated SSC recommendations for initiation of antibiotics that incorporate a risk- and probability-stratified approach. Using an infection prediction model with a cutoff of 0.5 to classify possible vs. probable infection, we found that 30% of the suspected infection cohort would be classified as shock absent, possible infection and thus eligible for the new 3-hour antibiotic recommendation. In real-world practice, this group had a conservative time to antibiotics (median, 5.5 hr; interquartile range [IQR], 3.2–9.8 hr) and low mortality (2%). Patients categorized as shock absent, probable infection had a median time to antibiotics of 3.2 hours (IQR, 2.1–5.1 hr) and mortality of 3%. Patients categorized as shock present, the probable infection had a median time to antibiotics 2.7 hours (IQR, 1.7–4.6 hr) and mortality of 17%, and patients categorized as shock present, the possible infection had a median time to antibiotics 6.9 hours (IQR, 3.5–16.3 hr) and mortality of 12%.

CONCLUSIONS: These data support recently updated SSC recommendations to align antibiotic timing targets with risk and probability stratifications. Our results provide empirical support that clinicians and hospitals should not be held to 1-hour targets for patients without shock and with only possible sepsis.

KEYWORDS: antibiotics; mortality; probability; sepsis; septic; shock

The 2021 Surviving Sepsis Campaign (SSC) Guidelines for Management of Sepsis and Septic Shock includes updated recommendations for initiation of antibiotics that incorporate a risk- (shock present vs. shock absent) and probability- (high, intermediate, or low likelihood of sepsis) stratified approach to decision making (1). Specifically, the SSC recommends 1-hour antibiotic timing targets for patients with shock regardless of infection probability and for patients without shock who have high likelihood of sepsis. A more lenient 3-hour timing target is suggested for patients without shock who have only possible infection (i.e., intermediate likelihood), and it is recommended to defer antibiotics while continuing close monitoring of patients without shock who have low likelihood of infection. An important emphasis of this new recommendation is the goal of preventing antibiotic overuse in patients with low

*See also p. 1138.

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KEY POINTS

Question: What are the anticipated real-world implications of applying updated Surviving Sepsis Campaign recommendations for antibiotic timing?

Findings: Thirty percent of patients with suspected infection were eligible for the new 3-hour antibiotic recommendation (i.e., classified as shock absent, possible infection). This group had a conservative time to antibiotics (median 5.5 hr) and low mortality (2%).

Meaning: Applying a 3-hour antibiotic target to suspected infection patients without shock and with an intermediate likelihood of infection appears to be a safe approach that would impact a substantial number of patients.

prevalence of sepsis and few adverse events, a major concern given reports of false positive sepsis treatments range from 20% to 42% (2–4). However, the impact of the changes in real-world practice is unknown.

METHODS

Identification of Cohort and Treatment Recommendation Categories

To evaluate the implications of these new recommendations, we applied them to a retrospective cohort of adult patients (≥ 18 yr) who presented to the emergency department (ED) of one of 12 hospitals between 2017 and 2021. Included patients had suspected infection, defined as: oral or parenteral antibiotic or bacterial culture order within 24 hours of ED presentation with: 1) culture drawn first, antibiotics ordered within 48 hours or 2) antibiotics ordered first, culture ordered within 48 hours. Following the SSC guidance, we intentionally selected a broad cohort to represent patients "at-risk" for sepsis for whom antibiotic decisions would be made, not those who already met the criteria for sepsis.

Creating Risk Stratification Categories

Shock Vs. No Shock. We categorized patients as a shock present if mean arterial pressure was less than 65 mm Hg and lactate was greater than 2 mmol/L or vasopressors were administered within 6 hours following Centers for Medicare and Medicaid Services Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) guidance.

Probable/Definite Vs. Possible Infection. Although the SSC recommendations stratify antibiotic decisions by likelihood of infection, there are no existing validated risk models to distinguish these categories. To explore the application of infection risk assessment to antibiotic recommendations, we first developed an infection probability model to enable the categorization of patients as "probable" vs. "possible" sepsis. The model was developed from data obtained from our health system's Enterprise Data Warehouse, using a cohort of 561,023 adult patients (≥ 18 yr) with encounters via the ED. We defined the outcome of infection as receiving four Qualifying Antimicrobial Days based on the Centers for Disease Control and Prevention (CDC) Adult Sepsis Event (ASE) criteria (5). This criterion has been shown to be a valid measure of infection (6, 7). Consistent with ASE definitions, if a patient dies or transitions to comfort measures or is discharged to another hospital or hospice before four qualifying antimicrobial days (QADs) have elapsed, then the presumed infection criteria are met if they have consecutive QADs until day of, or 1 day before, death, or discharge.

Variables included sociodemographic and clinical characteristics (e.g., age, gender, race, laboratory values, vital signs in 6 hr from ED arrival, and past health condition). We transformed most vital signs and laboratory values variables to categorical variables if the missingness greater than 2% due to their longitudinal characteristics, that is, multiple values recorded or ordered over time and missing value phenomenon. We evaluated nine different models including Logistic regression, Naïve Bayes, Random Forest, Least Absolute Shrinkage and Selection Operator Regression, Ridge Regression, Elastic Net, Gradient Boosting Machine, eXtreme Gradient Boosting (XGBoost), and the Deep Learning (multiple perception model) via H_2O R package (R Core Team, Vienna, Austria) (8). We used 80/20 splitting training and testing dataset to compare these nine models' performance in terms of the area under the receiver operating characteristic curve (AUROC) (**e-Table 1**, http://links.lww.com/CCM/H509). We selected the model with highest AUROC, that is, XGBoost, and calculated its sensitivity, specificity, positive predictive value (PPV), and negative predictive

value (NPV) with the cutoff point of 0.5. The selected model had AUROC of 0.84 (95% CI, 0.839–0.844), PPV of 0.73, and NPV of 0.80. The variables used in the model are shown in **e-Table 2** (http://links.lww.com/CCM/H509). The median hour to the first antibiotics administration of the 12 AH hospitals can be found in **e-Table 3** (http://links.lww.com/CCM/H509).

Evaluating Patients in Each Risk Category

For each of the four groups delineated by the 2 × 2 shock/no shock and sepsis probable/possible matrix, we calculated the number and proportion of patients in the group, median time to antibiotic administration (calculated from ED arrival), and hospital mortality.

The study was approved by the Atrium Health institutional review board (08-17-03E) approved June 29, 2020, under the title "Non-Interventional Studies Using Retrospective Healthcare Data or Residual Clinical Specimens/Isolates to Evaluate Outcomes Related to Delivery of care for Patients Related to Sepsis and/or Infection Related Diseases," and procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

RESULTS

A flow diagram depicting patient selection and categorization is shown in **Figure 1**. We identified 166,556 patients treated in the ED for suspected infection during the study period. Application of the updated 2021 SSC guidelines shock and infection probability criteria resulted in classification of patients as shown in **Table 1** along with demographic, treatment, and outcome results. Using this schema, 50,486 patients (30%) with suspected infection were categorized as shock absent and possible infection—the group with updated recommendations allowing a more conservative antibiotic target of 3 hours. In real-world practice, patients in this shock absent, possible infection group had median time to antibiotics of 5.5 hours (interquartile range [IQR], 3.2–9.8 hr) and low mortality (2%).

Patients categorized as shock absent, probable infection (n = 83,070, 50%) had median time to antibiotics of 3.2 hours (IQR, 2.1–5.1 hr); those categorized as shock present, probable infection (n = 25,705, 15%) had median time to antibiotics 2.7 hours (IQR, 1.7–4.6 hr); and those categorized as shock present, possible infection (n = 7,296, 4%) had median time to antibiotics 6.9 hours (IQR, 3.5–16.3 hr). Hospital mortality was high for both groups of patients with shock (12–17%) and low for both groups of patients without shock (2–3%), regardless of infection probability.

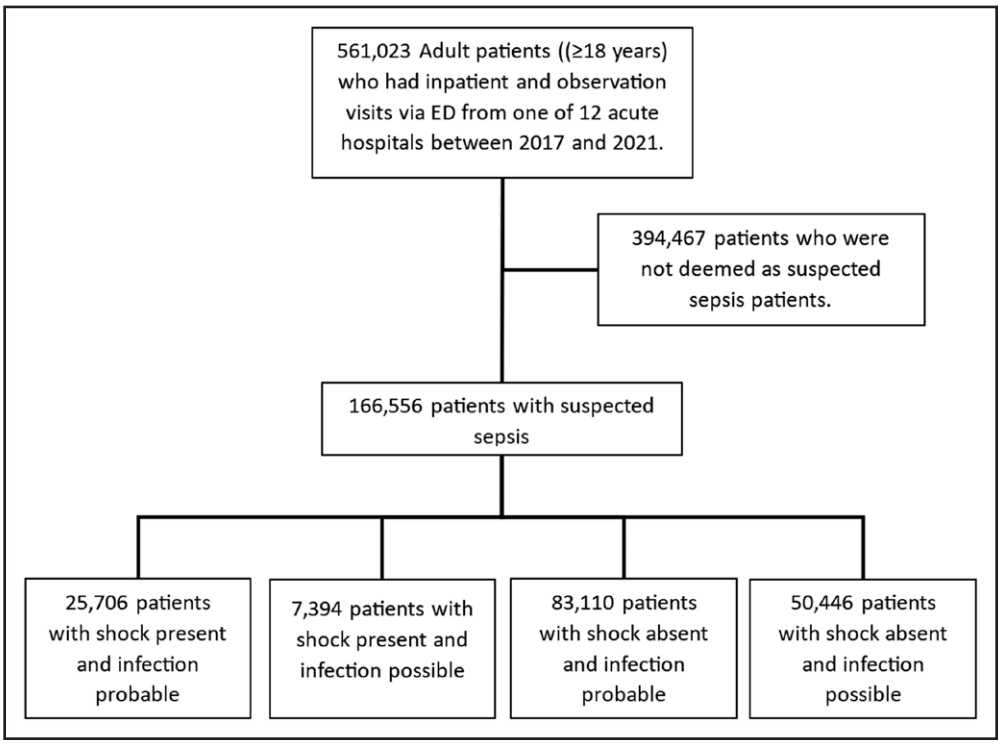

Figure 1. Flow diagram showing patient inclusion and categorization. ED = emergency department.

DISCUSSION

Our exploratory study generates several important real-world observations and implications related to the 2021 SSC recommendations for risk- and probability-stratified antibiotic timing in sepsis. First, the recommendations suggest stratification by likelihood of infection, but no validated models currently exist to predict infection likelihood separate from illness severity. We developed a model using

TABLE 1.
Proportion, Antibiotic Timing, and Mortality Among Patients Treated in the Emergency Department for Suspected Infection in 12 Hospitals Between 2017 and 2021

Variables	Overall	Shock Present and Infection Probable	Shock Present and Infection Possible	Shock Absent and Infection Probable	Shock Absent and Infection Possible[a]
n (%)	166,556	25,704 (15)	7,296 (4)	83,070 (50)	50,486 (30)
Age, median (IQR)	65 (50–76)	66 (54–76)	67 (55–78)	63 (48–75)	65 (51–77)
Female, *n* (%)	91,490 (55)	13,326 (52)	3,894 (53)	44,243 (53)	30,027 (60)
Non-White race, *n* (%)	50,591 (30)	6,669 (26)	2,360 (32)	23,418 (28)	18,144 (36)
Charlson Comorbidity Index score, median (IQR)	3 (1–6)	4 (2–7)	4 (1–6)	3 (1–6)	3 (1–6)
Hospital mortality, *n* (%)	8,471 (5)	4,321 (17)	869 (12)	2,326 (3)	955 (2)
Hours to IV antibiotics, median (IQR)	3.6 (2.2–6.4)	2.7 (1.7–4.6)	6.9 (3.5–16.3)	3.2 (2.1–5.1)	5.5 (3.2–9.8)

IQR = interquartile range.
[a]Category with updated recommendations to allow 3-hr antibiotic target instead of 1-hr target.

routine clinical data to predict likelihood of infection that demonstrated good accuracy to serve as a proof-of-concept model for this work. Future work is needed to validate this model in external data or to develop new, high-performing infection probability models to advance the science and practice of risk-stratified sepsis treatment strategies.

Second, we demonstrated that applying the updated recommendation for a 3-hour target for patients without shock and with only possible infection impacts a sizeable proportion of patients treated in the ED with suspected sepsis. Nearly one-third of patients in our large sample would be eligible for this more lenient antibiotic target that allows additional time for diagnostic testing and potentially reduce unnecessary antibiotic use or allow tailoring to narrow spectrum therapy. Our real-world data suggest that clinicians may have already been triaging these patients because median time to antibiotics was over 5 hours in this group. The reassuringly low mortality in this group supports the safety of longer targets for antibiotic initiation for this group. These data provide empirical support alongside strong theoretical arguments that clinicians and hospitals should not be held to 1-hour targets for patients without shock and with only possible infection.

Third, our results draw attention to another potential opportunity to apply more conservative antibiotic timing targets—patients with probable sepsis but without shock comprised nearly 50% of the suspected sepsis cohort. These patients received antibiotics at a more conservative target (median, 3.2 hr) with a low hospital mortality rate similar to that of patients without shock and only possible sepsis. Our data suggest that a 3-hour target may be safe for this group as well, which would have significant population impact due to the large proportion of patients in this category. However, timely antibiotics may have contributed to low mortality in this group and prospective studies are needed. The strategy suggested by our real-world data—implementing a 1-hour antibiotic target for patients with shock only—is consistent with other data (9–11) and current propositions of some stakeholders including the Infectious Disease Society of America (12).

Limitations of this study include data acquired from a single health system and inclusion of data from the early surges of COVID-19 pandemic, which may impact generalizability. Given the lack of existing valid models to predict risk of infection, we applied an internally derived infection probability model to categorize probable vs. possible infection that represents only one of multiple acceptable approaches. We used the infection criterion of the CDC ASE definition as the outcome definition for infection because of its demonstrated validity and widespread use, but acknowledge even this measure is not a perfect surrogate for true infection. We also chose a broad cohort definition of patients to represent the population for whom antibiotics are considered, narrowing the cohort to patients

at higher risk for sepsis may lead to different conclusions. Finally, we recognize the limitations of evaluating observational data and suggest that changes to sepsis treatment strategies be guided by randomized controlled trial data where possible.

In summary, the application of the updated SSC stratified approach to antibiotic timing targets to a large dataset of patients with suspected sepsis resulted in nearly one-third of the cohort eligible for 3-hour vs. 1-hour antibiotic targets. In support of this recommendation, these real-world patients had longer antibiotic times and low mortality. Additionally, the group of patients without shock with probable sepsis made up nearly one-half of the overall cohort. This large group also had longer time to antibiotics with low mortality and may represent another high-impact opportunity to apply stewardship principles.

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