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BRIEF REPORT

Evaluating the Impact of Source-specific Order Sets for Sepsis on Empiric Antibiotic Selection in the Emergency Department

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This retrospective cohort study found that implementing source-specific antibiotic order sets for sepsis in the emergency department increased appropriate empiric antibiotic selection from 51% to 74% ($P = .01$).

Keywords. antibiotics; order sets; sepsis; stewardship.

BACKGROUND

Sepsis is a medical emergency that can progress to septic shock and death [1]. In October 2015, the Centers for Medicare and Medicaid Services (CMS) implemented core quality measures for severe sepsis and septic shock. Recent verbiage updates requiring administration of "broad-spectrum or other antibiotics" from CMS provide increased flexibility for empiric antibiotic selection [2]. Because delays in antimicrobial administration can increase mortality, it is important to establish processes that facilitate prompt and optimal antibiotic decisions [3].

Order sets can be a promising tool to assist with standardizing evidence-specific best practices and meeting the CMS sepsis core measures [3]. There are data to support the use of order sets for sepsis, mainly focusing on patient outcomes, ordering time, and time to antibiotic administration [4–6]. Some studies have also shown that implementation of syndrome-specific interventions can significantly reduce antipseudomonal β-lactam use [7]. The purpose of this study was to assess the impact of source-specific antibiotic order sets for sepsis on appropriate empiric antibiotic selection.

METHODS

Source-specific order sets for sepsis were implemented in April 2022 at a not-for-profit community hospital with approximately 200 licensed beds. The new order sets provided a standardized hierarchy of orderable antimicrobials by infection source. Relevant diagnostic tests (eg, methicillin-resistant *Staphylococcus aureus* [MRSA] nares swabs) were also strategically included within order sets. The source-specific antibiotic order sets replaced a general sepsis order set that had been in place for years and included broad-spectrum antibiotics. Across the entire study period, order set use was not mandated but was encouraged. This study was approved by the local institutional review board.

A retrospective cohort study of patients receiving antibiotics for an indication of sepsis was conducted. The definition for time zero in the emergency department (ED) was adopted from the CMS guidelines as time of sepsis documentation by a provider, or clinical criteria including meeting 2 or more systemic inflammatory response syndrome (SIRS) criteria that are not attributed to a documented chronic condition, or by new-onset organ dysfunction [2]. Regardless of whether the patients met SIRS criteria, documentation of severe sepsis alone by a physician, physician assistant or nurse practitioner qualified as "time zero" from the time the note was posted. Subjects were included if at least 18 years of age and treated for sepsis or septic shock with time zero for antibiotic administration in the ED between October 2021 and March 2022 (preimplementation) or from May to October 2022 (postimplementation). A washout period (April 2022) was used to allow for implementation. Exclusion criteria consisted of preexisting antibiotics on admission, pregnancy, or documented refusal of antibiotics.

The primary endpoint was the appropriate choice of empiric antibiotic therapy. Inappropriate selection was defined as coverage that was too broad (eg, unnecessary MRSA or antipseudomonal coverage) or too narrow (eg, not administering anti–extended-spectrum β-lactamase [ESBL] therapy when indicated) based on culture results and patient-specific factors available on admission and at the time of retrospective evaluation. Determination of appropriateness of MRSA and antipseudomonal coverage for bacterial pneumonia, urinary, intra-abdominal, and intravascular catheter sources was based

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on risk factors outlined in previously published guidelines [8–11]. ESBL coverage was considered appropriate if the patient had known colonization or infection within the past year or received broad-spectrum antibiotics within the past 90 days [12].

Secondary endpoints included antibiotic selection, use of MRSA nasal swabs to modify antibiotic therapy, order set utilization by suspected sepsis source, assessment of timing of antibiotic ordering, processing, administration and discontinuation, intensive care unit admission, and hospital length of stay. Because of CMS developing a community-onset sepsis 30-day mortality electronic clinical quality measure, 30-day all-cause in-hospital mortality from time of diagnosis was selected as the last secondary outcome [13]. Regulatory fallouts were monitored. The definition of sepsis fallout was not meeting 1 of the measures, including selection of antibiotics, blood cultures, fluids, initial lactate, repeat lactate, or vasopressor use.

A population size of 73 patients in each group was estimated to achieve 80% power. This was calculated using a 2-tailed hypothesis and z-score of 1.96. Standard deviation was estimated at 0.5, α at 0.05, and effect size difference at 10%. Evaluations used a P value set at .05 to evaluate statistically significant differences. Mann-Whitney U test was used to compare differences between independent groups with continuous data. Chi-squared test was used to assess statistically significant differences for nominal data.

RESULTS

A total of 286 patients were screened to allot 73 patients for inclusion in each group. The most common reasons for exclusion were time-zero outside of the ED (n = 106) and preexisting antibiotics on admission (n = 32). Most of the patients excluded because of a diagnosis outside of the ED were either transferred from a different facility or had hospital-onset sepsis. Demographics for the study population are displayed in Table 1. The predominant source-specific order sets for sepsis used in the postgroup were bacterial pneumonia source (22 patients, 30%), unknown source (19 patients, 26%), and urinary source (8 patients, 11%). The least used order set was intra-abdominal source (7 patients, 10%). Antibiotics were ordered outside of the order sets for 56 patients (77%) in the pregroup compared with 17 patients (23%) in the postgroup ($P < .05$). Antibiotic selection was labeled as appropriate in 37 of 73 cases (51%) in the pregroup versus 54 of 73 cases (74%) in the postgroup ($P = .01$). In the postgroup, coverage was sometimes classified as too narrow regardless of the order set; this was mainly from growth of ESBL producers in the setting of ceftriaxone administration. Coverage was often classified as too broad when the unknown sources order set was used instead of a source-specific order set. Reasons for being labeled as inappropriate and additional secondary endpoints are provided in Table 2. There was no difference in coverage that was too broad or too narrow based on patient's allergy status (5 patients in the pregroup compared with 4 patients in the postgroup, $P = .83$).

Table 1. Comparison of Baseline Characteristics of Preimplementation and Postimplementation Groups

Baseline Characteristic	Preimplementation (n = 73)	Postimplementation (n = 73)	*P* value
Median age—y (IQR)	78 (68–88)	73 (53–81)	.01
Median weight—kg (IQR)	73 (57–86)	78 (61–95)	.02
Male sex, n (%)	33 (45)	32 (44)	.87
COVID-19 positive, n (%)	9 (12)	7 (10)	.60
Any antibiotic allergy, n (%)	20 (27)	23 (32)	.61
Febrile upon arrival, n (%)	14 (19)	11 (15)	.51
Median white blood cell count on admission—K/μL (IQR)	14.3 (9.5–18.6)	13.2 (9.7–16.9)	.86
Median creatinine clearance on admission—mL/min (IQR)	44 (29–65)	53 (40.0–90.0)	<.01
Median lactic acid on admission—mmol/L (IQR)	1.9 (1.3–2.8)	2.1 (1.4–3.0)	.33

Abbreviation: IQR, interquartile range.

One regulatory fallout was identified in the pregroup, which was due to untimely antibiotic administration. Two regulatory fallouts were identified in the postgroup, both from untimely blood culture ordering that, on evaluation, were not found to be associated with the new order sets.

DISCUSSION

Implementation of source-specific empiric antibiotic order sets for sepsis in the ED significantly increased appropriate empiric antibiotic selection and enhanced antimicrobial stewardship. This was driven by a combination of factors including increased order set utilization and avoidance of regimens that were excessively broad-spectrum or lacked sufficient coverage.

Antimicrobial stewardship programs seeking to improve antibiotic decision making for sepsis in the ED may consider this initiative. Diagnosis of sepsis is by nature tied to broad-spectrum antibiotic prescribing such as vancomycin and piperacillin-tazobactam. In this analysis, meaningful reductions in both workhorse antibiotics were detected, whereas a numerical increase in ceftriaxone prescribing was observed, and there was no change in meropenem utilization. The shift from less piperacillin-tazobactam to more ceftriaxone was largely influenced by changes in prescribing patterns when the suspected source of sepsis was bacterial pneumonia or urinary tract for which agents with antipseudomonal activity are not routinely necessary [14–16]. Although this trend was not statistically significant, a larger impact could be observed with more provider education and increased use of the order sets. Impacting prescribing patterns in the ED is highly influential for curbing antibiotic use downstream during hospitalization. Although this study did not explore downstream use,

Table 2. Sepsis Order Set Impact on Outcome Characteristics

	Preimplementation (n = 73)	Postimplementation (n = 73)	*P* value
Coverage too broad or too narrow	36 (49)	19 (26)	<.01
Coverage too broad, n (%)	28 (38)	15 (21)	.53
Antipseudomonal coverage not warranted, n/n evaluable (%)	19/28 (68)	14/15 (93)	
MRSA coverage not warranted, n/n evaluable (%)	4/28 (14)	0/15 (0)	
Antipseudomonal and MRSA coverage not warranted, n/n evaluable (%)	5/28 (18)	1/15 (7)	
Other, n/n evaluable (%)	0/28 (0)	0/15 (0)	
Coverage too narrow, n (%)	8 (11)	4 (5)	
Antipseudomonal coverage warranted, n/n evaluable (%)	1/8 (13)	1/4 (25)	
MRSA coverage warranted, n/n evaluable (%)	1/8 (13)	0/4 (0)	.37
Anaerobic coverage indicated, n/n evaluable (%)	1/8 (13)	0/4 (0)	
Multidrug-resistant organism, n/n evaluable (%)	4/8 (50)	3/4 (75)	
Other, n/n evaluable (%)	1/8 (13)	0/4 (0)	
Sources of infection when coverage was too broad or too narrow, n (%)	32 (44)	15 (21)	.24
Urinary, n/n evaluable (%)	16/32 (50)	5/15 (33)	
Pulmonary, n/n evaluable (%)	9/32 (28)	5/15 (33)	
Intra-abdominal, n/n evaluable (%)	3/32 (10)	0/15 (0)	
Unknown, n/n evaluable (%)	2/32 (6)	4/15 (27)	
Other, n/n evaluable (%)	2/32 (6)	1/15 (7)	
Antibiotic and MRSA nares orders			
Piperacillin-tazobactam, n (%)	49 (67)	39 (53)	.13
Cefepime, n (%)	8 (11)	11 (16)	.74
Ceftriaxone, n (%)	9 (12)	18 (25)	.09
Aztreonam, n (%)	6 (8)	4 (5)	.74
Meropenem, n (%)	6 (8)	6 (8)	1
Vancomycin, n (%)	42 (58)	30 (41)	.01
MRSA nares swab orders for patient on vancomycin, n/n (%)	22/42 (52)	25/30 (83)	.72
Vancomycin orders discontinued within 24 h of vancomycin nares results, n/n (%)	22/22 (100)	25/25 (100)	1
Antibiotic and blood culture timing			
Median time to antibiotic order, min	106 (56–183)	119 (72–232)	.10
Median time to antibiotic order in critically ill patients, min	107 (86–228)	89 (60–169)	.11
Median time from antibiotic order to pharmacist verification, min	18 (7–43)	12 (4–28)	.73
Median time to administration, min	158 (112–254)	176 (116–366)	.17
Median time to blood culture order, min	57 (39–109)	56 (23–145)	.32
Intensive care unit admission at time of finalized culture report, n (%)	23 (32)	23 (32)	.50
Vasopressor use, n (%)	6 (8)	4 (5)	.26
Median intensive care unit length of stay, d (IQR)	2.5 (1.0–6.0)	3 (2.0–7.5)	.53
Median hospital length of stay, d (IQR)	5 (4.0–8.0)	5 (2.0–8.0)	.37
30-day all-cause in-hospital mortality, n (%)	7 (10)	5 (7)	.55

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.

antibiotics were considered appropriate if they had activity against the organism(s) isolated from cultures, if any. With sepsis as a common reason for antibiotic initiation in the ED, this initiative is anticipated to be of interest to many antimicrobial stewardship programs. Pulia et al. identified that acute infectious diseases are frequently encountered in the ED setting, making this a critical setting for antimicrobial stewardship efforts because this is the place where the first medical contact for septic patients is likely to occur [17].

The new order sets were not found to impact use of negative MRSA nares results to stop vancomycin for patients with suspected pneumonia (which was already frequent); however, there was an increase in MRSA nasal swab ordering for patients that received vancomycin in the postgroup. Although not statistically significant, it is suggestive that building this screening into the workflow for treating sepsis in the ED can improve laboratory stewardship.

Antibiotic ordering in the pregroup was more rapid than in the postgroup; however, the opposite was found for antibiotic ordering in critically ill patients. Although neither data point was statistically significant, antibiotic timing for sepsis is critical. Increased provider familiarity and order set use could lead to the potentially clinically significant reduced time to antibiotic ordering that has been observed in other studies [18]. When the new order sets were implemented, clinicians were educated on the order set contents and workflows, which likely contributed to enhanced utilization. Assurance that the order sets did not negatively impact antibiotic timing is supported by the lack of

any regulatory fallouts related to antibiotic timing during the postperiod. These findings are consistent with literature reporting no statistically significant differences in time to antibiotic ordering during pre- and postorder set implementation [18, 19].

Limitations of this study include inherent challenges of retrospective analysis and assessing time zero for sepsis. In addition, acute severity of illness scores and specifications as to the SIRS criteria met were not collected. Inappropriate stratification of patient risks could have occurred periodically as only the documented electronic health record information could be used. Additionally, there was a notably low mortality rate in the cohort that is reflective of a population with sepsis rather than severe sepsis, which should be a consideration in the context of external validity. Also, not requiring order set use in either group allowed for a pragmatic study design, but some institutions may be able to ensure universal use, which may alter potential outcomes of a project of this type.

As a result of this project, source-specific order sets for sepsis were expanded to 11 other hospitals within the healthcare system. The willingness of the health system to adopt the order sets is an indication of their success locally, with widespread support from ED leadership. In the future, a larger study spanning a wider time frame could be considered to evaluate sustainability or the impact of source-specific sepsis order sets on additional endpoints such as antibiotic resistance and long-term antimicrobial drug consumption.

CONCLUSION

Implementing source-specific antibiotic order sets for sepsis in the ED can increase appropriate empiric antibiotic selection.

Notes

Potential conflicts of interest. T. P. G. is the owner of www.LearnAntibiotics.com and www.IDstewardship.com. He reports consulting for Pattern Biosciences (formerly Klaris Diagnostics), Tabula Rasa (DoseMeRx), GoodRx Inc, ProCE, Antimicrobial Therapy, Inc. (Sanford Guide), Kaleio Brands, Firstline (formerly Spectrum) Mobile Health Inc, VinPin, GSK (not drug-specific engagement), Pfizer (not drug-specific engagement), Melinta Therapeutics, Ferring Pharmaceuticals, and Gilead. All other authors report no potential conflicts.

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