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Major Article

Impact of an electronic sepsis initiative on antibiotic use and health care facility–onset *Clostridium difficile* infection rates

Robert Hiensch MD [a,*], Jashvant Poeran MD, PhD [b], Patricia Saunders-Hao PharmD [c], Victoria Adams PharmD [c], Charles A. Powell MD [a], Allison Glasser BSPT, MBA [d], Madhu Mazumdar PhD [b], Gopi Patel MD, MS [e]

[a] *Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY*
[b] *Institute for Healthcare Delivery Science, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY*
[c] *Department of Pharmacy, The Mount Sinai Hospital, New York, NY*
[d] *Office for Excellence in Patient Care, Icahn School of Medicine at Mount Sinai, New York, NY*
[e] *Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY*

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Background: Although integrated, electronic sepsis screening and treatment protocols are thought to improve patient outcomes, less is known about their unintended consequences. We aimed to determine if the introduction of a sepsis initiative coincided with increases in broad-spectrum antibiotic use and health care facility–onset (HCFO) *Clostridium difficile* infection (CDI) rates.

Methods: We used interrupted time series data from a large, tertiary, urban academic medical center including all adult inpatients on 4 medicine wards (June 2011-July 2014). The main exposure was implementation of the sepsis screening program; the main outcomes were the use of broad-spectrum antibiotics (including 3 that were part of an order set designed for the sepsis initiative) and HCFO CDI rates. Segmented regression analyses compared outcomes in 3 time segments: before (11 months), during (14 months), and after (12 months) implementation of a sepsis initiative.

Results: Antibiotic use and HFCO CDI rates increased during the period of implementation and the period after implementation compared with baseline; these increases were highest in the period after implementation (level change, 50.4 days of therapy per 1,000 patient days for overall antibiotic use and 10.8 HCFO CDIs per 10,000 patient days; $P < .05$). Remarkably, the main drivers of overall antibiotic use were not those included in the sepsis order set.

Conclusions: The implementation of an electronic sepsis screening and treatment protocol coincided with increased broad-spectrum antibiotic use and HCFO CDIs. Because these protocols are increasingly used, further study of their unintended consequences is warranted.

Sepsis is a common cause of in-hospital morbidity and mortality. Although case fatality rates are declining, the overall incidence of sepsis and sepsis-related deaths appears to be increasing.[1-3] The Surviving Sepsis Campaign (SSC) was launched by a multinational consensus committee of experts and international organizations to increase clinician and public awareness of sepsis and to develop and implement guidelines to improve the overall care of septic patients.[4] The SSC recommends routine screening for sepsis because interventions essential in improving outcomes are time-sensitive, and delayed recognition leads to worse outcomes. These interventions have been grouped into bundles that are expected to be completed within specific time windows.[5,6] Although many studies have demonstrated positive impacts of sepsis programs on patient outcomes, less information is available on unintended consequences, such as nonspecific increases in broad-spectrum antibiotic use and related outcomes, including health care facility–onset (HCFO) *Clostridium difficile* infection (CDI).[7-10] This an important issue because the prevalence of HCFO CDI has increased substantially in recent years with the principal, modifiable risk factor being broad-spectrum antibiotic use.[11,12]

In 2012, our hospital introduced a sepsis performance improvement program called Strengthening Treatment and Outcomes for

* Address correspondence to Robert Hiensch, MD, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave L Levy Place, Box 1232, New York, NY 10029.
E-mail address: robert.hiensch@mountsinai.org (R. Hiensch).
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Patients (STOP) Sepsis based on guidelines developed by the Greater New York Hospital Association and SSC. STOP Sepsis includes a sepsis screening tool integrated in the electronic health record (EHR) system and an electronic sepsis treatment bundle that facilitates antibiotic administration to patients with suspected sepsis. We aimed (1) to determine antibiotic prescription patterns before, during, and after implementation of STOP Sepsis; and (2) to identify any concurrent changes in incidence of HCFO CDIs. We hypothesized that the implementation of STOP Sepsis would led to increased use of broad-spectrum antibiotics that would coincide with an increased rate of HCFO CDI.

METHODS

Data source and study design

This single institutional study using retrospective time series data was conducted at an urban 1,171-bed, tertiary care teaching hospital. All patients >18 years of age admitted to 4 medicine wards from June 1, 2011-June 30, 2014, who were prescribed selected broad-spectrum antibiotics, were included for analysis. The 4 wards were selected because (1) they were the pilot wards that implemented the sepsis program, and (2) they have the highest incidence of sepsis, antibiotic use, and HCFO CDIs. Study approval was obtained from the Icahn School of Medicine at Mount Sinai Institutional Review Board.

Study intervention

As part of the Greater New York Hospital Association and the United Hospital Fund STOP Sepsis Collaborative, The Mount Sinai Hospital launched STOP Sepsis to improve sepsis outcomes through a multidisciplinary approach involving physicians, advanced practice clinicians, nurses, pharmacists, and laboratory personnel. It aims to increase early recognition of sepsis in the hospital and reduce delays in therapy, ultimately to improve sepsis outcomes. Paramount to the program is an automated, EHR-based sepsis screening program (Appendix 1; more details available on request from the authors). When ≥2 vital signs meeting certain criteria are entered into the EHR, a 3-part screening questionnaire is generated for the nurse to complete. If the patient then screens in by meeting ≥1 of the criteria, an automated trigger, a STOP Sepsis best-practice alert (BPA), is generated by the EHR, and the nurse escalates care to the patient's primary team. Physicians, once alerted, must evaluate the patient and document a plan of care. The use of a specifically designed STOP Sepsis order set is encouraged, which guides the physician through severity evaluation, provides education about sepsis guidelines, and facilitates rapid entry of sepsis management orders, including monitoring, laboratory tests, and fluid and antibiotic administration. The order set recommends select antibiotics that are immediately available on the floor without requiring preauthorization from the hospital's antibiotic stewardship team. Cefepime is the recommended antibiotic for gram-negative coverage in the STOP Sepsis order set based on the antimicrobial susceptibility profile at our hospital. Aztreonam and imipenem-cilastatin are also available in the order set, but their use is typically reserved for special considerations, such as β-lactam allergies, or specific resistance patterns. Providers, however, are not limited to ordering the antibiotics in the order set. Some antibiotics, such as ceftriaxone, clindamycin, ciprofloxacin, and levofloxacin, are also available without prior approval from the antibiotic stewardship team; however, they are not as readily available on the floor. Others, such as ertapenem, require approval at all times.

Other features of the order set include recommendations on fluid resuscitation, laboratory testing such as lactate levels, patient monitoring, and further escalation of care. Metrics are extensively tracked and analyzed, and individual cases are regularly reviewed to identify areas for improvement.

Time line

STOP Sepsis was introduced as a pilot program on 2 medicine wards in May 2012 and on another medicine and an oncology ward in July 2012. The program was subsequently expanded to most inpatient wards in July 2013. Data were analyzed in 3 time segments: prior to the STOP Sepsis pilot program (June 1, 2011-April 30, 2012), during the pilot and implementation phase (May 1, 2012-June 30, 2013), and after expansion (July 1, 2013-June 30, 2014). Prior to STOP Sepsis, there were no universal inpatient sepsis screening and treatment protocols.

Effects of interest

The main effects of interest were (1) administration of selected broad-spectrum antibiotics in days of therapy (DOT) per 1,000 patient days per month, and (2) HCFO CDI cases per 10,000 patient days per month. Antibiotic administration data were extracted retrospectively from the EHR for 9 antibiotics: cefepime, levofloxacin, imipenem-cilastatin, ceftriaxone, ciprofloxacin, piperacillin-tazobactam, ertapenem, aztreonam, and clindamycin. These antibiotics were chosen because they were either included in the STOP Sepsis order set, represented commonly prescribed broad-spectrum antibiotics, or are antibiotics strongly associated with CDI. A prespecified analysis of the STOP Sepsis order set antibiotics (cefepime, imipenem-cilastatin, and aztreonam) was planned. Intravenous, intramuscular, and enteral routes of administration were included. Administration was measured in patient days, with any dose(s) given on a day counting as 1 patient day.

In our hospital, patients with HCFO CDI are prospectively identified by the infection prevention and control department. CDI testing at our institution changed from testing by enzyme immunoassay to polymerase chain reaction in the baseline period. HCFO CDI was defined as a positive *C difficile* test >3 days after admission as prescribed by the National Healthcare Safety Network.[13] To assess if possible changes in HCFO CDI incidence reflect changes in CDI testing behavior, we similarly studied the number of CDI tests ordered per 1,000 discharges, aggregated by month. Although not directly related to the main study objectives, we additionally assessed HCFO CDI mortality to gain a better understanding of the potential hospital-wide effects of possible changes in HCFO CDI incidence.

Statistical analysis

We aggregated DOT per 1,000 patient days and HCFO CDIs per 10,000 patient days by monthly intervals for time series analysis to estimate the effect of STOP Sepsis on antibiotic utilization and HCFO CDIs, adjusting for trend before implementation of STOP Sepsis. We further investigated the existence of autocorrelation, including seasonal effects.

The effect of STOP Sepsis on antibiotic utilization and HCFO CDI was assessed using a segmented regression analysis to estimate (1) baseline characteristics pre-STOP Sepsis, (2) changes between pre-STOP Sepsis and during STOP Sepsis implementation, and (3) changes between pre-STOP Sepsis and after hospital expansion.[14] This analysis allows an assessment of the effects of STOP Sepsis on antibiotic utilization and HCFO CDI, immediately (changes in intercept or level) and over time (changes in trend or slope). We used the PROC AUTOREG procedure in SAS v9.4 statistical software (SAS Institute, Cary, NC). *P* values <.05 were considered to be statistically significant.