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Improving Empiric Antibiotic Selection for Patients Hospitalized With Skin and Soft Tissue Infection

The INSPIRE 3 Skin and Soft Tissue Randomized Clinical Trial

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IMPORTANCE Empiric extended-spectrum antibiotics are routinely prescribed for patients hospitalized with skin and soft tissue infections (SSTIs) despite low likelihoods of infection with multidrug-resistant organisms (MDROs).

OBJECTIVE To evaluate whether computerized provider order entry (CPOE) prompts presenting patient-specific and pathogen-specific MDRO infection risk estimates could reduce empiric extended-spectrum antibiotics for noncritically ill patients admitted with SSTI.

DESIGN, SETTING, AND PARTICIPANTS This cluster randomized clinical trial included 92 hospitals and assessed the effect of an antibiotic stewardship bundle that included CPOE prompts vs routine stewardship on antibiotic selection during the first 3 hospital days (empiric period) in noncritically ill adults hospitalized with SSTI. The trial population included adults 18 years and older treated with empiric antibiotics for SSTI in non–intensive care unit (ICU) settings. Data were collected from January 2019 to December 2023.

INTERVENTIONS CPOE prompts recommending standard-spectrum antibiotics in patients prescribed extended-spectrum antibiotics during the empiric period when absolute risk of MDRO SSTI was estimated to be less than 10%, coupled with feedback and education.

MAIN OUTCOMES AND MEASURES The primary outcome was empiric extended-spectrum antibiotic days of therapy (summed number of different extended-spectrum antibiotics targeting *Pseudomonas* and/or MDR gram-negative bacteria received per patient each calendar day). The secondary outcome was antipseudomonal days of therapy. Safety outcomes included days to ICU transfer and hospital length of stay. Outcomes compared differences between baseline and intervention periods across strategies.

RESULTS Among 118 562 patients admitted with SSTI at 92 hospitals, 67 033 (56.7%) were male and the mean (SD) age was 58.0 (17.5) years. A total of 57 837 patients were included in the baseline period and 60 725 in the intervention period. Receipt of any empiric extended-spectrum antibiotic during the baseline and intervention periods was 57.0% (16 855 of 29 595) and 56.0% (17 534 of 31 337), respectively, for the routine stewardship group compared with 55.4% (15 650 of 28 242) and 43.0% (12 647 of 29 388), respectively, for the CPOE group. Empiric extended-spectrum days of therapy per 1000 empiric days targeting *Pseudomonas* and/or MDR gram-negative pathogens was 511.5 during the baseline period and 488.7 during the intervention period in the routine stewardship group and was 496.2 and 359.1, respectively, in the CPOE bundle group (rate ratio, 0.72; 95% CI, 0.67-0.79; $P < .001$). There was no evidence of inferiority in the CPOE bundle group for mean (SD) hospital length of stay (routine stewardship, 6.5 [3.8] days; CPOE bundle, 6.4 [3.8] days) and days to ICU transfer (routine stewardship, 6.3 [3.2] days; CPOE bundle, 6.3 [3.1] days).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, CPOE prompts recommending standard-spectrum empiric antibiotics for low-risk patients hospitalized with SSTI coupled with education and feedback significantly reduced use of extended-spectrum antibiotics without increasing admissions to ICUs or hospital length of stay.

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Community-acquired skin and soft tissue infections (SSTIs) account for nearly 900 000 adult hospitalizations annually in the US.[1-4] Although national guidelines support standard-spectrum antibiotics for nonpurulent and nonsurgical SSTIs, 30% to 50% of hospitalized patients receive extended-spectrum antibiotics.[1,5-8] A desire to cover methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa,* and/or other multidrug-resistant (MDR) gram-negative pathogens, especially in patients with diabetes or other comorbidities, leads physicians to initially select extended-spectrum antibiotics.[9-13] Among reasons for nonadherence to SSTI guidelines, physicians have cited insufficient data to discern the diagnosis or inciting pathogen and delays in hospital throughput from choosing the wrong antibiotic as important drivers.[11,14] However, extended-spectrum antibiotic overuse can cause harm, including *Clostridioides difficile* colitis, allergies, or kidney and liver adverse effects.[15-17]

We evaluated whether an antibiotic stewardship bundle consisting of computerized provider order entry (CPOE) prompts that identified patients at low risk of MDR organism (MDRO) infection and recommended standard-spectrum antibiotics, coupled with education and feedback, can reduce empiric extended-spectrum antibiotic prescribing for patients hospitalized with SSTI.

Key Points

Question Can computerized provider order entry (CPOE) prompts with patient-specific risk estimates for multidrug-resistant organisms (MDROs) safely reduce empiric extended-spectrum antibiotic overuse in patients admitted with skin and soft tissue infections (SSTIs)?

Findings In this cluster randomized clinical trial including 92 hospitals and 60 725 noncritically ill adults, CPOE prompts promoting standard-spectrum antibiotics for patients at low risk of MDRO-associated SSTI reduced empiric antibiotics targeting *Pseudomonas* and MDR gram-negative bacteria by 28%, without increasing intensive care unit transfers or length of stay.

Meaning Real-time CPOE recommendations for standard-spectrum antibiotics using patient-specific risk for MDRO-associated SSTIs substantially and safely decreased empiric extended-spectrum antibiotic overuse in patients hospitalized for SSTI.

Methods

Study Design and Intervention

The INSPIRE 3 (Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotic Selection) Skin and Soft Tissue trial was a cluster-randomized trial comparing the effect of routine antibiotic stewardship vs a CPOE stewardship bundle on empiric extended-spectrum antibiotic selection. The study population was noncritically ill adults 18 years and older hospitalized with SSTI at HCA Healthcare, the largest private community hospital system in the US. There was a 12-month baseline period (January 1, 2019, to December 31, 2019, selected to avoid COVID-19–associated disruptions), 5-month phase-in (August 2, 2022, to December 31, 2022), and 12-month intervention (January 1, 2023, to December 31, 2023). The trial protocol can be found in Supplement 1. The Harvard Pilgrim Health Care Institute Institutional Review Board provided centralized oversight, with reliance agreements and committee approvals from participating hospitals (eAppendix in Supplement 2), and granted a waiver of informed consent as the study met criteria for minimal risk. This trial was registered with ClinicalTrials.gov (NCT05423756). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Hospitals were randomly assigned to either the routine stewardship group or the CPOE bundle group. Hospitals in the routine stewardship group received educational materials and quarterly coaching calls to maintain stewardship activities per national guidance. Routine activities included providing hospital guidelines for antibiotic selection, requiring documented antibiotics indications, and prospective clinician feedback to deescalate antibiotics. Coaching calls emphasized avoiding competing interventions. Educational content was developed by the investigative team and disseminated through existing hospital channels. Hospitals in the CPOE bundle group received all education and activities described for the routine stewardship group plus monthly coaching calls as well as (1) CPOE prompts recommending standard-spectrum antibiotics instead of extended-spectrum antibiotics during the first 3 hospital days (empiric period) for patients with an absolute risk less than 10% of *Pseudomonas* or MDRO SSTI; (2) clinician education on risk estimate calculations and local *Pseudomonas* or MDRO SSTI prevalence, investigator site visits to each facility during the phase-in period, and webinars; and (3) clinician SSTI antibiotic prescribing reports.

The CPOE algorithm was activated when extended-spectrum antibiotics (eTable 1 in Supplement 2) were ordered in a non–intensive care unit (ICU) location or emergency department for an SSTI indication within 72 hours of admission. Documentation of indication was required for all antibiotic orders. If the patient's estimated *Pseudomonas* or MDRO risk was low (less than 10%), a prompt was triggered recommending standard-spectrum antibiotics.

The CPOE algorithm and prompt were antibiotic specific. For example, if cefepime was ordered, the evaluation was for less than 10% risk for *Pseudomonas* SSTI infection; for carbapenem, the combined risk of extended-spectrum β-lactamase–producing *Enterobacterales* (ESBLs) or resistant-*Pseudomonas*; and for vancomycin, risk of MRSA.

Risk estimates were obtained from recursive partitioning models that estimated absolute *Pseudomonas* or MDRO risk using a dataset of 195 040 patients admitted with SSTI in 151 HCA Healthcare hospitals between January 1, 2017, and December 31, 2019 (eTables 2 and 3 in Supplement 2). Models assessed more than 60 variables: demographic characteristics, health care and antibiotic exposures, history or microbiologic evidence of MDROs from any body site, comorbidities, and admission laboratory values. They also included each hospital's *Pseudomonas* or MDRO prevalence (frequency of positive blood or skin/wound culture results among patients with SSTI) calculated once for each hospital and categorized

as high or low prevalence. Evaluation of hospital prevalence over 3 years showed no change over time.

Clinical workflow and prompts are shown in the eFigure in Supplement 2. Prompts provided a single-click option to substitute cefazolin (standard-spectrum antibiotics) or to override and proceed with ordering extended-spectrum antibiotics.

Hospital Recruitment and Study Cohort Definition

Hospitals were eligible to participate if they used the MEDITECH electronic health record (EHR) system and agreed to avoid new initiatives that directly affect empiric antibiotic selection in noncritically ill patients with SSTI. Hospitals sharing a single antibiotic stewardship program were randomized as a single unit. A contemporaneous trial focusing on patients hospitalized with abdominal infection in the same hospitals is reported separately, as are prior trials evaluating prompt-based stewardship in patients hospitalized with pneumonia and urinary tract infection.[18-20]

The analytic cohort was defined as patients with discharge claims codes for SSTI with a present-on-admission indicator (eTable 4 in Supplement 2). This definition substantially overlaps with patients assigned an SSTI indication during ordering and allows identification of the analogous population in the control hospitals; it ensures inclusion of patients for whom the prompt was not displayed because clinicians chose other indications, either because of initial diagnostic uncertainty or because of deliberate circumvention of the prompt. The cohort excluded patients transferred to the ICU within 2 calendar days of admission.

Randomization

Hospitals were randomized in a 1:1 ratio to routine stewardship or the CPOE bundle intervention. Data from January 1 to December 31, 2019, were used to establish pairs of similar hospitals based on (1) extended-spectrum antibiotic days of therapy for SSTI (primary and secondary outcomes), (2) percentage of patients with skin or soft tissue cultures or blood cultures sent, and (3) case mix, including annual SSTI admissions, length of stay, ICU transfers, hospital baseline percentage of patients with blood or skin cultures positive for MRSA, Elixhauser Comorbidity Index count, and percentage of patients calculated to have 10% or greater absolute risk for MRSA, *Pseudomonas*, or ESBLs. Pairing was done by calculating the Mahalanobis distance between facilities across values of weighted variables and choosing pairings with the minimum mean within-pair distance.[21,22] Randomization was performed within these pairs.

Data Collection

Data obtained from HCA Healthcare's centralized data warehouse included patient demographic characteristics, hospital unit, prior hospital or nursing home admissions, inpatient antibiotic exposures at the same hospital, comorbidities, and in-hospital mortality. Race and ethnicity data were included as collected in the EHR to address generalizability.

Extended-spectrum antibiotics are shown in eTable 1 in Supplement 2. History of *Pseudomonas* or MDRO was obtained from microbiologic results from any body site. MDROs included MRSA, vancomycin-resistant *Enterococci*, ESBL, MDR *Pseudomonas*, MDR *Acinetobacter*, and carbapenem-resistant *Enterobacterales* (eTable 5 in Supplement 2). SSTIs due to *Pseudomonas* or MDRO were based on culture-positive blood, skin, or wound from any site collected during the first 3 hospital days and the associated emergency department stay.

Trial Outcomes

The primary outcome was extended-spectrum antibiotics days of therapy in the first 3 calendar days of hospitalization (termed the *empiric period*) calculated as the summed number of different extended-spectrum antibiotics targeting *Pseudomonas* and/or MDR gram-negative bacteria received per patient each calendar day, beginning at admission. For example, 2 different extended-spectrum antibiotics administered at least once during each of the first 3 days would yield 6 days of extended-spectrum antibiotic therapy. The study design had more than 95% power to detect a 12.5% difference in the primary outcome with 60 hospitals. Because 92 hospitals volunteered, the study period was able to be reduced from 18 to 12 months (Supplement 1).

The prespecified secondary outcome was unadjusted, as-randomized antipseudomonal days of therapy. We evaluated vancomycin days of therapy as a post hoc outcome rather than prespecified outcome because only 34% of patients were estimated to exceed the less than 10% risk alerting threshold (eTable 3 in Supplement 2).

Antibiotics administered in the emergency department counted toward antibiotic days of therapy if given on the first hospital day. Patients transferred to the ICU on hospital day 3 had all empiric antibiotics counted, including those given in the ICU.

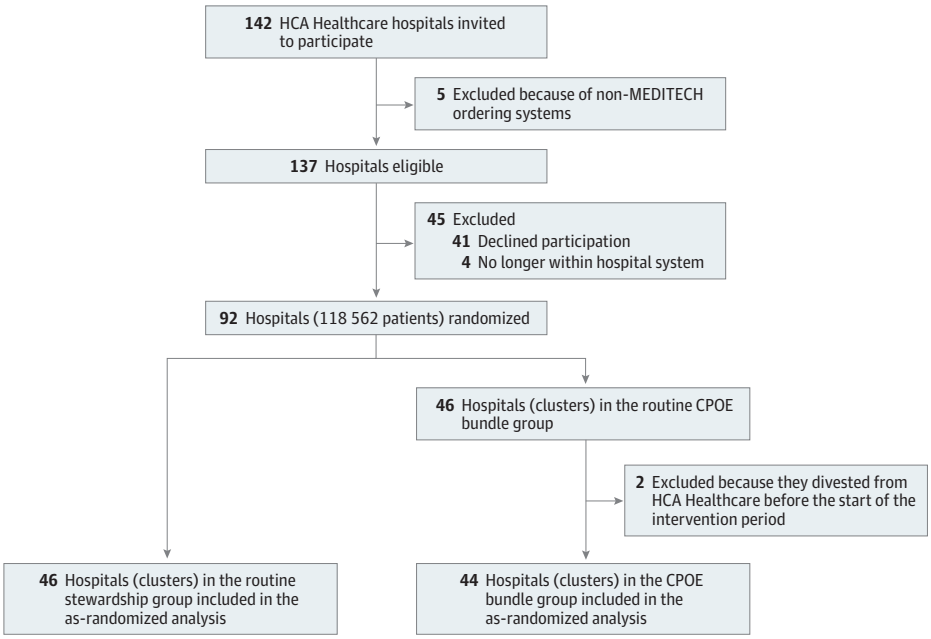
Two prespecified safety outcomes were assessed during the hospital stay: (1) length of stay in days and (2) days to ICU transfer, defined as days from admission until ICU transfer (eMethods 1 in Supplement 2). The prespecified noninferiority margins for length of stay and days to ICU transfer were hazard ratios of 0.98 and 1.1, respectively.

Statistical Analysis

Unadjusted as-randomized outcomes were assessed using generalized linear mixed-effects models assessing differences in empiric extended-spectrum antibiotics days of therapy between intervention and baseline periods across the groups (difference-in-differences). Random effects accounted for clustering within patient, hospital, and period-within-hospital. Data from the phase-in period were excluded from all analyses. The unit of analysis was patient admission (patients with multiple admissions contributed all admissions). The primary and secondary outcomes were each assessed with 2-tailed significance at $\alpha < .05$. Post hoc analysis of vancomycin days of therapy was evaluated using the same methods described for the prespecified effectiveness outcomes.

For vancomycin days of therapy, only 1 randomly selected admission per patient was assessed because admission-level models did not converge. These models assessed random effects clustered by hospital and period-within-hospital.

Figure 1. Hospital Recruitment and Randomization



All analyses are as randomized because all hospitals remained in the trial until end of intervention (no hospital withdrawals after intervention period began). There was a median (IQR) of 1332 (652-1675) patients per hospital in the routine stewardship group and 1097 (671-1528) patients in the CPOE bundle group. MEDITECH is a hospital electronic health record system. CPOE indicates computerized provider order entry.

Safety outcomes were assessed using unadjusted as-randomized proportional hazards models. For days to ICU transfer, random effects accounted for clustering by patient, hospital, and period-within-hospital. Length of stay used 1 admission per patient, clustering by hospital and period-within-hospital.

Adjusted analyses accounted for age, sex, race, ethnicity, Medicaid insurance, antibiotic or nursing home exposure in the last year, mean Elixhauser Comorbidity Index count, and MDRO history.[23] Race and ethnicity data were included given evidence of higher risk for SSTI, morbidity, mortality, and underdiagnosis due to dark skin pigmentation.[24-28] All analyses were performed using SAS version 9.4 (SAS Institute) or R version 4.2.3 (The R Foundation). The a priori statistical analytic plan is provided in Supplement 1.

Three post hoc sensitivity analyses were performed: (1) one for all outcomes that included patients transferring to an ICU after the first rather than second admission day; (2) one for safety outcomes that accounted for competing risk of death (eMethods 2 in Supplement 2); and (3) one for effectiveness outcomes that assessed extended-spectrum antibiotic doses per patient rather than patient days.

Results

Patient Characteristics

A total of 92 HCA Healthcare hospitals participated and were distributed across 15 states serving rural and urban communities, with a median (IQR) size of 286 (163.5-396.0) acute care beds (**Figure 1**). Among 118 562 patients admitted with SSTI at 92 hospitals, 67 033 (56.7%) were male, the mean (SD) age was 58.0 (17.5) years, and the median (IQR) Elixhauser Comorbidity Index count was 3 (2-5). A total of 14 351 patients (12.1%) were Black, 88 153 patients (74.4%) were White, and 2951 patients (2.5%) were another race (including American Indian of Alaska Native, Asian, and Native Hawaiian and Other Pacific Islander). A total of 57 837 patients were included during the baseline period and 60 725 during the intervention period. The routine stewardship group included 46 hospitals with 29 595 and 31 337 patients during the baseline and intervention periods, respectively, and the CPOE group included 44 hospitals with 28 242 and 29 388 patients during the baseline and intervention periods, respectively. The groups were well balanced overall (**Table 1**), including similar percentages of patients with peripheral vascular disease and *Pseudomonas* and MDRO history. Compared with the routine stewardship group, the CPOE group had higher percentages of patients of Black race (3638 [12.9%] vs 3052[10.3%]), without insurance (5790 [20.4%] vs 5548 [18.8%]), and with diabetes (11 717 [41.5%] vs 11 485 [38.7%]) during the baseline period.

At baseline, the percentage of patients with skin or blood cultures sent during the first 3 days of hospitalization and associated emergency department stay was 89% or more across both study groups and study periods (eTable 6 in Supplement 2). Of these, the percentage with cultures positive for pathogens requiring an extended-spectrum antibiotic targeting *Pseudomonas* or MDR gram-negative bacteria during baseline was 5.6% (1352 of 24 068) for the routine stewardship group and 5.7% (1345 of 23 760) for the CPOE group; during the intervention period, the percentages were 5.6% (1421 of 25 621) for the routine stewardship group and 6.3% (1499 of 23 900) for the CPOE group (eTable 6 in Supplement 2). Cultures were positive for *Pseudomonas* and ESBL in less than 4.4% and 2.3%, respectively, among patients across study groups and periods combined; hospital

Table 1. Characteristics of Patients With Skin and Soft Tissue Infection During Baseline and Intervention Periods

Characteristic	No. (%)			
	Baseline (12 mo)		Intervention (12 mo)	
	CPOE bundle	Routine stewardship	CPOE bundle	Routine stewardship
Total, No.	28 242	29 595	29 388	31 337
Age, y				
Mean (SD)	58 (18)	58 (18)	58 (17)	59 (18)
18-44	7107 (25.2)	7347 (24.8)	7040 (24.0)	7365 (23.5)
45-54	4798 (17.0)	4975 (16.8)	4915 (16.7)	5175 (16.5)
55-64	6085 (21.5)	6102 (20.6)	6468 (22.0)	6637 (21.2)
65-74	5026 (17.8)	5318 (18.0)	5625 (19.1)	5867 (18.7)
75-84	3356 (11.9)	3735 (12.6)	3625 (12.3)	4154 (13.3)
≥85	1870 (6.6)	2118 (7.2)	1715 (5.8)	2139 (6.8)
Sex				
Male	15 719 (55.7)	16 320 (55.1)	17 015 (57.9)	17 979 (57.4)
Female	12 377 (43.8)	13 087 (44.2)	12 373 (42.1)	13 356 (42.6)
Unknown	146 (0.5)	188 (0.6)	0	2 (<0.1)
Race[a]				
Black	3638 (12.9)	3052 (10.3)	3989 (13.6)	3672 (11.7)
White	20 730 (73.4)	23 153 (78.2)	20 885 (71.1)	23 385 (74.6)
Other race	687 (2.4)	1246 (4.2)	333 (1.1)	685 (2.2)
Unknown	3187 (11.3)	2144 (7.2)	4181 (14.2)	3595 (11.5)
Ethnicity[a]				
Hispanic	5246 (18.6)	5335 (18.0)	6435 (21.9)	6118 (19.5)
Non-Hispanic	22 996 (81.4)	24 260 (82.0)	22 953 (78.1)	25 219 (80.5)
Insurance type				
Medicare	13 730 (48.6)	14 548 (49.2)	13 640 (46.4)	14 588 (46.6)
Commercial	4512 (16.0)	4842 (16.4)	4503 (15.3)	4865 (15.5)
Other (eg, self-pay, free care)	5790 (20.4)	5548 (18.8)	6581 (22.4)	6779 (21.6)
Medicaid	4210 (14.9)	4657 (15.7)	4664 (15.9)	5105 (16.3)
Antibiotic and health care exposures in year prior to admission[b]				
Emergency department visit	14 488 (51.3)	14 553 (49.2)	14 311 (48.7)	14 795 (47.2)
Hospitalization	10 821 (38.3)	11 063 (37.4)	10 737 (36.5)	11 076 (35.3)
>1 Hospitalization	5341 (18.9)	5467 (18.5)	5044 (17.2)	5231 (16.7)
Antibiotics	9313 (33.0)	9537 (32.2)	9264 (31.5)	9559 (30.5)
Nursing home stay	2830 (10.0)	2976 (10.1)	2552 (8.7)	2606 (8.3)
Time to first antibiotics (current admission), median (IQR), h[c]	2 (1.0-3.0)	2 (1.0-3.0)	2 (1.0-4.0)	2 (1.0-3.5)
History of pathogen requiring any extended-spectrum antibiotics[d]	5879 (20.8)	6100 (20.6)	5663 (19.3)	5804 (18.5)
MRSA	4650 (16.5)	4775 (16.1)	4213 (14.3)	4379 (14.0)
Pseudomonas	1435 (5.1)	1459 (4.9)	1574 (5.4)	1572 (5.0)
ESBL	1217 (4.3)	1145 (3.9)	1421 (4.8)	1374 (4.4)
VRE	359 (1.3)	343 (1.2)	315 (1.1)	336 (1.1)
CRE[e]	273 (1.0)	251 (0.8)	321 (1.1)	290 (0.9)

(continued)

MDRO prevalence among patients with SSTI is provided in eTable 7 in Supplement 2.

Antibiotic Prescribing and MDRO Risk Estimation

Receipt of any empiric extended-spectrum antibiotic for the routine stewardship group was 57.0% (16 855 of 29 595) during baseline and 56.0% (17 534 of 31 337) during the intervention period; for the CPOE bundle group, receipt of extended-spectrum antibiotics was 55.4% (15 650 of 28 242) during baseline and 43.0% (12 647 of 29 388) during the intervention period. Reductions in monthly extended-spectrum days of therapy in the CPOE group were evident by 3 months into the phase-in period (**Figure 2**; eTable 8 in Supplement 2). Similarly, receipt of any vancomycin use decreased from 73%

Table 1. Characteristics of Patients With Skin and Soft Tissue Infection During Baseline and Intervention Periods (continued)

Characteristic	No. (%)			
	Baseline (12 mo)		Intervention (12 mo)	
	CPOE bundle	Routine stewardship	CPOE bundle	Routine stewardship
Elixhauser Comorbidity Index comorbidities[f]				
Hypertension	18 380 (65.1)	18 785 (63.5)	20 443 (69.6)	21 049 (67.2)
Diabetes	11 717 (41.5)	11 458 (38.7)	13 223 (45.0)	13 151 (42.0)
Obesity	8037 (28.5)	8111 (27.4)	8721 (29.7)	8309 (26.5)
Chronic pulmonary disease	6319 (22.4)	6488 (21.9)	6216 (21.2)	6328 (20.2)
Kidney disease	6356 (22.5)	6206 (21.0)	6201 (21.1)	6099 (19.5)
Heart failure	5409 (19.2)	5421 (18.3)	6197 (21.1)	5852 (18.7)
Anemias	4733 (16.8)	5171 (17.5)	5235 (17.8)	6404 (20.4)
Neurological disorders	4873 (17.3)	4920 (16.6)	5280 (18.0)	5541 (17.7)
Alcohol and drug abuse	3344 (11.8)	3718 (12.6)	3052 (10.4)	3589 (11.5)
Peripheral vascular disease	2741 (9.7)	2940 (9.9)	2977 (10.1)	3147 (10.0)
Liver disease	1690 (6.0)	1728 (5.8)	2284 (7.8)	2227 (7.1)
Solid tumor	720 (2.5)	810 (2.7)	800 (2.7)	992 (3.2)
Hematologic malignancy	256 (0.9)	273 (0.9)	197 (0.7)	258 (0.8)
Elixhauser Comorbidity Index count, median (IQR)[g]	3 (2.0-5.0)	3 (1.0-5.0)	3 (2.0-5.0)	3 (2.0-5.0)

Abbreviations: CPOE, computerized provider order entry; CRE, carbapenem-resistant *Enterobacterales*; ESBL, extended-spectrum β-lactamase–producing *Enterobacterales*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococci*.

[a] Race and ethnicity data were self-reported. The other race category included American Indian and Alaska Native, Asian, Native Hawaiian and Other Pacific Islander, and multiple races; these categories were combined due to low numbers.

[b] Health care exposures limited to those documented within a prior inpatient or emergency department visit in the HCA Healthcare electronic medical record.

[c] Time to first antibiotics includes first dose of any antibiotics administered in the emergency department or inpatient wards from 2 days prior to date of admission up to 3 days of hospitalization.

[d] History of multidrug-resistant pathogen included any prior growth of pathogen requiring extended-spectrum antibiotics, including *Pseudomonas* or multidrug-resistant organisms: MRSA, ESBL (includes multidrug-resistant *Acinetobacter* and multidrug-resistant *Pseudomonas*), VRE, CRE, carbapenem-resistant *Acinetobacter,* and carbapenem-resistant *Pseudomonas*; also included any MRSA or VRE positivity on polymerase chain reaction, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* coding, or any infection prevention isolation flag placed on the patient's medical record for with any of these organisms.

[e] CRE, carbapenem-resistant *Acinetobacter,* and carbapenem-resistant *Pseudomonas*.

[f] Chronic pulmonary disease includes pulmonary circulation disease; diabetes includes with and without chronic complications; anemias includes anemias due to nutritional and iron deficiencies; liver disease includes mild, moderate, and severe; kidney disease includes moderate and severe; neurologic disease includes dementia, cerebrovascular disease, paralysis, neurologic disorders affecting movement, seizures and epilepsy, and other neurological diseases; solid tumor includes with and without metastases; and hematologic malignancy includes lymphoma and leukemia.

[g] Elixhauser Comorbidity Index count is the sum of each comorbid condition (among 38) as available in the electronic health record for each patient.

(20 741 of 28 242) during baseline to 67% (19 752 of 29 388) during the intervention period for the CPOE bundle group.

The INSPIRE algorithm classified more than 95% of patients with SSTI in both groups as low risk for *Pseudomonas* and other MDR gram-negative pathogens (eTable 9 in Supplement 2). Among those estimated to be at low risk, less than 3% subsequently had a *Pseudomonas*-positive or MDRO-positive culture result. Similarly, the algorithm classified more than 76% of patients as being at low risk for MRSA infection, and of these, less than 6% subsequently had an MRSA-positive culture result.

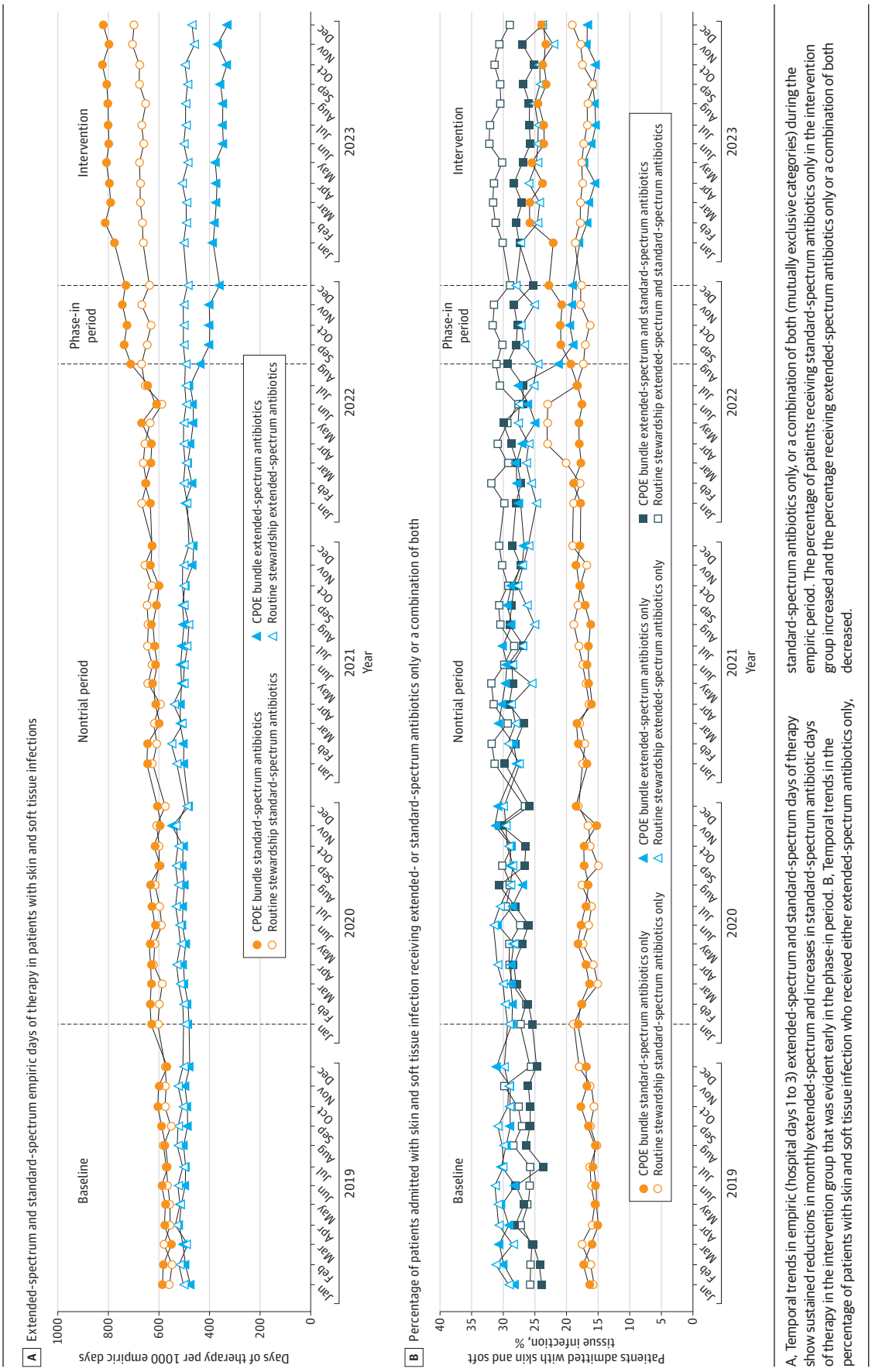
Primary and Secondary Trial Outcomes

For the primary outcome, empiric extended-spectrum days of therapy per 1000 empiric days targeting *Pseudomonas* and/or MDR gram-negative pathogens in the routine stewardship group was 511.5 during the baseline period and 488.7 during the intervention period. For the CPOE bundle group, this decreased from 496.2 during the baseline period to 359.1 during the intervention periods. The overall rate ratio was 0.72 (95% CI, 0.67-0.79; $P < .001$), indicating a 27.5% (95% CI, 21.2-33.3; $P < .001$) significantly lower rate of empiric extended-spectrum days of therapy in the CPOE bundle group compared with routine stewardship (**Table 2**; **Figure 3**A). The secondary outcome of antipseudomonal days of therapy showed similar reductions (Table 2; Figure 3A).

Sensitivity Analyses

Point estimates remained nearly identical for all effectiveness outcomes after adjusted and sensitivity analyses (eTable 10 in Supplement 2). When evaluating antibiotics given per patient (vs days of therapy), there was a 37% reduction in empiric extended-spectrum (ie, targeting *Pseudomonas* and/or MDR gram-negative pathogens) antibiotic doses per patient, from 3.2 (94 549 doses among 29 595 patients) to 3.1 (97 116 doses among 31 337 patients) during the baseline and intervention period, respectively, for the routine stewardship group vs 3.1 (86 488 doses among 28 242 patients) and 2.2 (64 116 doses among 29 388 patients) during the baseline and intervention periods, respectively, for the CPOE bundle group (eTable 11 in Supplement 2).

Figure 2. Monthly Empiric Extended-Spectrum and Standard-Spectrum Antibiotic Days of Therapy in the Computerized Provider Order Entry (CPOE) Bundle vs Routine Stewardship Groups Across the Baseline and Intervention Periods



A, Temporal trends in empiric (hospital days 1 to 3) extended-spectrum and standard-spectrum days of therapy show sustained reductions in monthly extended-spectrum and increases in standard-spectrum antibiotic days of therapy in the intervention group that was evident early in the phase-in period. B, Temporal trends in the percentage of patients with skin and soft tissue infection who received either extended-spectrum antibiotics only, standard-spectrum antibiotics only, or a combination of both (mutually exclusive categories) during the empiric period. The percentage of patients receiving standard-spectrum antibiotics only in the intervention group increased and the percentage receiving extended-spectrum antibiotics only or a combination of both decreased.

Table 2. Primary, Secondary, and Safety Outcomes in the As-Randomized Analysis

Effectiveness outcome	CPOE bundle			Routine stewardship				
	Days of therapy (raw rate)[a]			Days of therapy (raw rate)[a]			Overall rate ratio difference-in-differences (95% CI)	*P* value[c]
	Baseline	Intervention	Rate ratio (95% CI)[b]	Baseline	Intervention	Rate ratio (95% CI)[b]		
Primary outcome								
Extended-spectrum antibiotics days of therapy	496.2 (40 156/80 929)	359.1 (30 287/84 344)	0.69 (0.65-0.73)	511.5 (43 305/84 666)	488.7 (43 927/89 879)	0.95 (0.89-1.00)	0.72 (0.67-0.79)	<.001
Secondary outcome								
Antipseudomonal days of therapy	470.3 (38 059/80 929)	337.7 (28 482/84 344)	0.68 (0.64-0.72)	484.7 (41 034/84 666)	459.1 (41 261/89 879)	0.94 (0.88-1.00)	0.72 (0.66-0.79)	NA
	Days to event, mean (SD)[d]			Days to event, mean (SD)[d]				
	Baseline	Intervention	Hazard ratio (90% CI)[e]	Baseline	Intervention	Hazard ratio (90% CI)[e]	Overall hazard ratio difference-in-differences (90% CI)[f]	*P* value
Safety outcomes								
Length of stay	6.1 (3.6)	6.4 (3.8)	0.92 (0.89-0.94)	6.2 (3.7)	6.5 (3.8)	0.92 (0.90-0.95)	0.99 (0.95-1.04)	NA
Days to ICU transfers	6.1 (2.9)	6.3 (3.1)	0.96 (0.87-1.06)	5.9 (2.8)	6.3 (3.2)	0.84 (0.77-0.93)	1.14 (1.00-1.31)	NA

Abbreviations: CPOE, computerized provider order entry; HR, hazard ratio; ICU, intensive care unit; NA, not applicable; RR, rate ratio.

[a] Days of therapy rate calculated as total extended-spectrum antibiotics targeting *Pseudomonas* or multidrug-resistant gram-negative bacteria received per patient during the first 3 days of admission / number of empiric days × 1000.

[b] RRs represent group-specific comparisons of intervention with baseline.

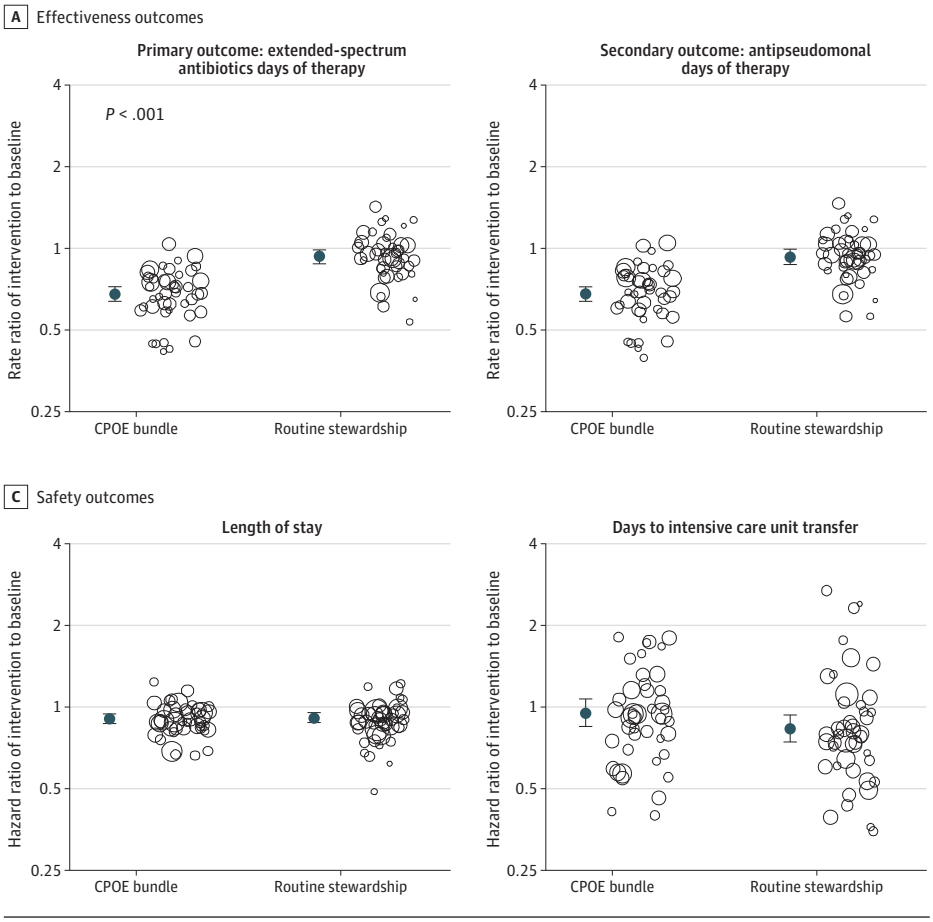
[c] Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within hospitals and period-within-hospital. *P* values were assessed at a 2-tailed significance set at α < .05 for null hypothesis that the relative RR in each arm is not different for the primary outcome.

[d] Days to event calculated within a single admission. Days to ICU transfer indicates days from admission to date of first ICU transfer among those requiring transfer on hospital day 3 through discharge up to hospital day 14. Length of stay was calculated as days from admission to date of hospital discharge among those discharged alive up to hospital day 14.

[e] HRs represent group-specific comparisons of the intervention period with the baseline period. Results are based on unadjusted proportional hazards models that accounted for clustering by patient, hospital, and period-within-hospital for ICU transfers; length of stay was assessed at the patient level, and models accounted for clustering by hospital and period-within-hospital. Each safety outcome was evaluated for noninferiority.

[f] For length of stay, the noninferiority margin is an HR of 0.98. For days to ICU transfer, the noninferiority margin is an HR of 1.1.

Figure 3. Effect of Computerized Provider Order Entry (CPOE) Bundle Intervention vs Routine Stewardship on Trial Effectiveness and Safety Outcomes Across Hospitals



Bubble position represents the hospital relative rate ratio of days of therapy (summed across individuals within each individual hospital) per empiric day dividing the intervention period by the baseline period. Bubble area is proportional to the number of admissions that the hospital contributed to the trial. Also shown are the estimated relative rate ratio and 95% CIs comparing intervention with baseline periods for each study group, based on unadjusted generalized linear mixed-effects models that accounted for clustering within patient, hospital, and period-within-hospital. For length of stay, only 1 admission per patient was used, and clustering accounted for hospital and period-within-hospital. Error bars indicate 95% CIs.

Vancomycin Days of Therapy

Vancomycin days of therapy per 1000 empiric days for the routine stewardship group were 582.0 and 566.0 during the baseline and intervention periods, respectively. For the CPOE group, this decreased from 596.3 to 524.7 during the baseline and intervention periods, respectively. The overall rate ratio when clustering by hospital and period was 0.90 (95% CI, 0.86-0.95) (eTable 12 in Supplement 2), indicating a 9.6% (95% CI, 5.4-13.5) lower rate of vancomycin days of therapy in the CPOE bundle group compared with the routine stewardship group.

Safety Outcomes

The percentage of patients transferred to the ICU was 3.0% (835 of 27 837) in the routine stewardship group and 3.0% (784 of 26 174) for the CPOE bundle group (eTable 13 in Supplement 2). There was no evidence of inferiority for the CPOE bundle group for the safety outcomes of days to ICU (hazard ratio, 1.14; 90% CI, 1.00-1.31) or hospital length of stay (hazard ratio, 0.99; 90% CI, 0.95-1.04) (Figure 3B; Table 2). Hazard ratios for all safety outcomes remained nearly identical in sensitivity analyses (eTable 14 in Supplement 2).

Monitoring of CPOE Prompt and Competing Interventions

Auditing of the CPOE algorithm and prompt showed that the automated system was working as intended. Reductions in extended-spectrum antibiotic prescribing in the CPOE bundle group during the intervention period consisted largely of (1) lower initial extended-spectrum antibiotic selection (31.4% [4832 of 29 388] in the CPOE bundle hospitals vs 40.9% [12 823 of 31 337] in routine stewardship hospitals) and (2) a change from extended-spectrum to standard-spectrum antibiotic therapy by 9.5% (657 of 6886) when clinicians encountered the prompt. The percentage of patients for whom SSTI was chosen as the indication for antibiotic use among those with SSTI as a discharge diagnosis was similar in the routine stewardship group (76.9% [24 107 of 31 337]) and CPOE bundle group (76.8% [22 573 of 29 388]).

Discussion

Among 118 562 patients admitted with SSTI, we demonstrated that a CPOE bundle intervention with patient-specific and pathogen-specific risk estimates for MDROs reduced

antipseudomonal and MDR gram-negative extended-spectrum antibiotic use by 28%, without evidence of a change in safety outcomes of days to ICU transfer or length of stay. In the usual care arm, 58% of patients received treatment for antibiotic-resistant gram-negative bacteria, suggesting that this intervention could be useful for hundreds of thousands of patients hospitalized annually for SSTI in the US.[2,3]

Successful reduction of antibiotics targeting *Pseudomonas* and other MDR gram-negative pathogens is important since overuse persists despite national guidance to limit use to severe SSTI (eg, necrotizing fasciitis). Numerous studies confirm empiric coverage is unnecessary for most patients, including patients with diabetes.[1,5,7,8,25,29,30] In this trial, *Pseudomonas* and ESBLs were isolated from cultures in only a small percentage of patients hospitalized with SSTI (4% and 2%, respectively), supporting empiric standard-spectrum antibiotics in the vast majority of cases.

Although this trial was not designed to assess CPOE bundle effects on vancomycin, post hoc analyses found a 10% decrease in its empiric use. This is notable because vancomycin ranks highest among antibiotics associated with serious drug effects and costs, and yet stewardship of vancomycin has been mostly limited to deescalation strategies.[1,9,31,32] Overall, 12.5% of patients with SSTI grew MRSA-positive cultures, but among those predicted to be low risk, only 6% grew MRSA, suggesting that the risk-based prompt provided clinically meaningful information to limit unnecessary empiric vancomycin use.

In this trial, initial standard-spectrum antibiotic prescribing increased, suggesting growing acceptance of national guidance; for those who continued to order extended-spectrum for low-risk patients, prompt recommendations encouraged switch to standard-spectrum antibiotics. Possible reasons for the intervention's success include (1) clinician buy-in due to the patient-specific approach; (2) use of hospital-specific MDRO prevalence in patients with SSTI, allowing compliance with nationally recommended practice that is infrequently adopted; (3) flagging those at low MDRO risk countered presumptions that extended-spectrum antibiotics are needed; (4) EHR documentation of risk mitigated clinician medicolegal concerns; and (5) determination of patients' risk required real-time access to only a few variables, all of which are routinely available in EHRs. Importantly, the prompt provided an efficient means of influencing prescribing in the emergency department and non-ICU wards day or night.

Limitations

There were several limitations. First, positive skin cultures were included regardless of specimen quality; colonization was indistinguishable from infection. Second, a threshold of MDRO risk greater than 10% might have been equally safe and more effective. Third, the trial was performed in community hospitals. Fourth, SSTI prompts implemented alongside abdominal infection prompts could have increased familiarity with prompt processes, but concurrent prompts could also have negatively affected adoption through alert fatigue. Fifth, we were unable to account for physician-level effects. Sixth, separation of the prompt's effect from education and feedback is not possible, although rapid reductions in extended-spectrum antibiotics suggest the prompt played a prominent role because education and feedback generally require more time to effect change.

Conclusions

In this randomized clinical trial, empiric extended-spectrum antibiotic use was significantly and safely lowered among adults admitted with SSTI to non-ICU settings in hospitals using education, feedback, and real-time CPOE prompts recommending standard-spectrum antibiotics for patients at low risk of MDRO infection compared with routine stewardship practices. Hospital length of stay and days to ICU transfer were unchanged.

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