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Improving Empiric Antibiotic Selection for Patients Hospitalized With Abdominal Infection

The INSPIRE 4 Cluster Randomized Clinical Trial

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IMPORTANCE Empiric extended-spectrum antibiotics are routinely prescribed for over a million patients hospitalized annually with abdominal infection despite low likelihoods of infection with multidrug-resistant organisms (MDROs).

OBJECTIVE To evaluate whether computerized provider order entry (CPOE) prompts providing patient- and pathogen-specific MDRO infection risk estimates can reduce empiric extended-spectrum antibiotics for non–critically ill patients admitted with abdominal infection.

DESIGN, SETTING, AND PARTICIPANTS This 92-hospital cluster randomized clinical trial assessed the effect of an antibiotic stewardship bundle with CPOE prompts vs routine stewardship on antibiotic selection during the first 3 hospital days (empiric period) in non–critically ill adults hospitalized with abdominal infection. The trial population included adults (≥18 years) treated with empiric antibiotics for abdominal infection in non–intensive care units (ICUs). The trial periods included a 12-month baseline from January to December 2019 and an intervention period from January to December 2023.

INTERVENTION CPOE prompts recommending standard-spectrum antibiotics in patients prescribed extended-spectrum antibiotics during the empiric period if the patient's estimated absolute risk of MDRO abdominal infection was less than 10%, coupled with feedback and education.

MAIN OUTCOMES AND MEASURES The primary outcome was empiric extended-spectrum antibiotic days of therapy. Safety outcomes: days to ICU transfer and hospital length of stay. Analyses compared differences between baseline and intervention periods across strategies.

RESULTS Among 92 hospitals with 198 480 patients, mean (SD) age was 60 (19) years and 118 723 (59.8%) were female. The trial included 93 476 and 105 004 patients hospitalized with abdominal infection during the baseline and intervention periods, respectively. Receipt of any empiric extended-spectrum antibiotics for the routine care group was 48.2% (22 519 of 46 725) during baseline and 50.5% (27 452 of 54 384) during intervention vs 47.8% (22 367 of 46 751) and 37.6% (19 010 of 50 620) for the CPOE bundle group. The group receiving CPOE prompts had a 35% relative reduction (rate ratio, 0.65; 95% CI, 0.60-0.71; $P < .001$) in empiric extended-spectrum antibiotic days of therapy vs routine care (raw absolute reduction between baseline and intervention periods was −169 for the CPOE bundle vs −20 for routine care). Hospital length of stay was noninferior to routine care (0.1 days longer during intervention; mean [SD], baseline, 5.4 [3.4] days vs intervention, 5.5 [3.5] days; hazard ratio [HR], 1.02; 90% CI, 0.99-1.06), and mean days to ICU transfer in the CPOE group was indeterminate (both groups 0.2 days longer during intervention; HR, 1.10; 90% CI, 0.99-1.23).

CONCLUSIONS AND RELEVANCE CPOE prompts recommending empiric standard-spectrum antibiotics (coupled with education and feedback) for patients admitted with abdominal infection who have low risk for MDRO infection significantly reduced extended-spectrum antibiotics without increasing ICU transfers or length of stay.

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Over 1 million US patients are hospitalized with abdominal infection annually.[1-5] Most are prescribed extended-spectrum antibiotics although few have antibiotic-resistant pathogens and can safely receive standard-spectrum antibiotics.[1,6-11] Several factors may contribute to extended-spectrum antibiotic overprescribing. First, the normal gut harbors many potential pathogens.[1,12,13] Second, not all pathogens are identified in clinical specimens, raising concerns that coverage for *Pseudomonas* or resistant gram-negative pathogens is necessary.[1,7,8,12,14,15] Third, clinical presentations can be complicated or nonspecific, heightening diagnostic uncertainty and necessitating imaging or procedures that cause delays, which further increase the tendency to prescribe extended-spectrum antibiotics while awaiting definitive diagnostic workup.[1,12] Finally, patients with abdominal infection can be severely and acutely ill, increasing the perceived penalty for failure to cover resistant pathogens.[6]

Conversely, exposure to broad-spectrum antibiotics increases patients' risk of adverse effects.[11,16,17] For abdominal infections in particular, antibiotics influence the gut microbiome and can select for antibiotic resistance.[18] Patients with abdominal infections are at increased risk of secondary abdominal infections due to multidrug resistant organisms (MDROs) and infections related to overgrowth of *Candida* and *Clostridioides difficile*.[11,12,14,19,20]

Antibiotic stewardship to minimize extended-spectrum antibiotic use has previously focused on pneumonia or urinary tract infections.[21-25] Despite global efforts to reduce antibiotic overuse in abdominal infections, few studies evaluate empiric antibiotic selection for abdominal infections.[8,26,27] Providing patient-specific risk estimates for MDRO infection at the time of antibiotic ordering reduces prescribing of empiric extended-spectrum antibiotics in patients hospitalized for pneumonia, urinary tract infection, and skin and soft tissue infection.[28-30] We evaluated the effectiveness and safety of similar interventions for patients hospitalized with abdominal infection.

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 antibiotics in patients hospitalized with abdominal infections?

Findings In a 92-hospital cluster randomized clinical trial including 105 004 non–critically ill adults, CPOE prompts (plus education and feedback) promoting standard-spectrum antibiotics in patients with low MDRO-infection risk had a 35% relative reduction in empiric extended-spectrum antibiotic days of therapy, without evidence of inferiority in intensive care unit transfers or length of stay.

Meaning Results suggest that CPOE-generated recommendations for standard-spectrum antibiotics using patient-specific risk for MDRO-associated abdominal infections substantially and safely reduced empiric extended-spectrum antibiotics in patients hospitalized for abdominal infection.

Methods

Study Design and Intervention

The Harvard Pilgrim Health Care Institute institutional review board provided centralized oversight, with reliance agreements and operational committee approvals from participating hospitals. Waiver of informed consent was granted because the study met criteria for minimal risk. The INSPIRE (Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotic Selection) Abdominal Infection Trial was a cluster randomized clinical trial comparing the effect of routine antibiotic stewardship to a computerized provider order entry (CPOE) stewardship bundle on empiric extended-spectrum antibiotic selection in non-critically ill adults (≥18 years) hospitalized with abdominal infection at HCA Healthcare (HCA), the largest US private community hospital system. There was a 12-month baseline period (January 1, 2019-December 31, 2019), 5-month phase-in period (August 2, 2022-December 31, 2022), and a 12-month intervention period (January 1, 2023-December 31, 2023). A contemporaneous trial for patients hospitalized with skin and soft tissue infection is reported separately.[30] This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

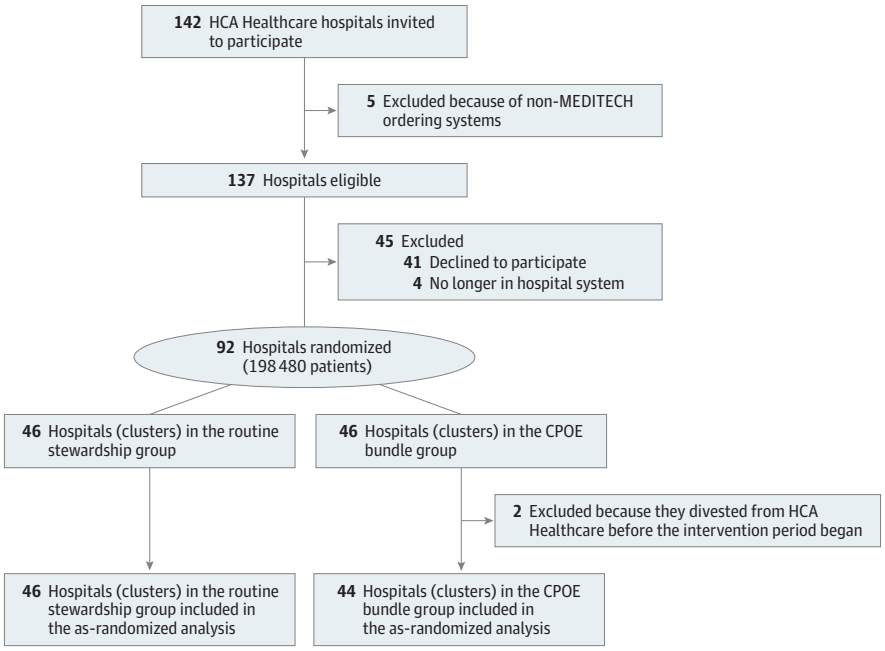
Hospitals were randomly assigned to either of the following:

1. Routine antibiotic stewardship group: received educational materials and quarterly coaching calls to maintain stewardship activities per national guidance (Supplement 1).[1] Routine activities included providing hospital guidelines for antibiotic selection, requiring documented antibiotic indications, and prospective clinician feedback to de-escalate antibiotics. Education emphasized national standards for empiric abdominal infection treatment.[1] Coaching calls also emphasized avoiding competing interventions.
2. CPOE bundle group: received the same educational activities as the routine stewardship group plus monthly coaching calls and (1) CPOE prompts recommending standard-spectrum vs extended-spectrum antibiotics during the first 3 hospital days (empiric period) for patients with an absolute risk less than 10% of MDRO abdominal infection; (2) clinician education on prompt workflow, risk estimate calculations, and local MDRO prevalence among patients with abdominal infection, (3) site visits and webinars during the phase-in period, and (4) clinician-specific prescribing reports from local stewardship teams for monitoring and feedback.

Educational content was developed by the investigative team, including presentations, handouts, and emails disseminated through existing hospital channels by local study champions and/or leadership (Supplement 1). Education targeted physicians, physicians-in-training, pharmacists, and nurses.

The clinical workflow and prompts are shown in the eFigure in Supplement 2. 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 abdominal infection indication within 72 hours of admission. Documentation of indication was required for all antibiotic orders. If the patient's estimated absolute MDRO risk was low (≤10%), a prompt was triggered recommending standard-spectrum antibiotics with a single-click option to substitute ceftriaxone (standard spectrum) and

Figure 1. Hospital Recruitment and Randomization in the Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotic Selection (INSPIRE) Abdominal Infection Trial



All analyses are as-randomized because all hospitals remained in the trial until end of intervention (no hospital withdrawals after enrollment). There was a median (IQR) of 2055 (1289-2,739) patients per hospital in the routine stewardship group and 1876 (1157-2702) patients in the Computerized Provider Order Entry (CPOE) bundle group. MEDITECH is a hospital electronic health record system.

language reminding clinicians to order metronidazole if indicated. Clinicians could override (not accept) the recommendation and proceed with ordering extended-spectrum antibiotics. Education emphasized that prompts relied on available electronic health record (EHR) data and that clinicians should consider any externally available information to inform their antibiotic selection.

The CPOE algorithm and prompt were antibiotic specific. For example, if cefepime was ordered, the evaluation was for less than 10% risk for *Pseudomonas* abdominal infection, carbapenems triggered a risk estimate of extended-spectrum β-lactamase-producing *Enterobacterales* (ESBLs) or resistant *Pseudomonas*, and vancomycin triggered a risk estimate for methicillin-resistant *Staphylococcus aureus* (MRSA).

Estimated MDRO risk was obtained from recursive partitioning models that estimated absolute MDRO risk using a retrospective dataset of 227 481 patients admitted with abdominal infection in 151 HCA hospitals. Model methods and risk estimates are provided in eMethods 1 and eTables 2 and 3 in Supplement 2. This modeling approach was chosen to provide clinicians with the absolute risks of MDRO infection, counteracting the tendency toward exaggerated risk perception associated with relative risk. Models assessed over 60 variables, including demographics, health care utilization, antibiotic exposures, history or microbiologic evidence of MDROs (any body site), comorbidities, admission laboratory values, and each hospital's frequency of positive MDRO abdominal/blood cultures in this population.

Hospital Recruitment and Study Cohort Definition

HCA hospitals were eligible to participate if they used MEDITECH, a hospital EHR system, and agreed to avoid new initiatives that directly affected empiric antibiotic selection in the target population (eAppendix in Supplement 2). Hospitals sharing an antibiotic stewardship program were randomized as a single unit.

The analytic cohort included patients who were prescribed antibiotics during the empiric period (hospital days 1-3) and had claims codes for abdominal infection with a present on admission indicator (eTable 4 in Supplement 2) using Agency for Healthcare Research and Quality infection diagnosis codes.[31] Codes included some conditions that may not require antibiotics but patients were included if clinicians decided to prescribe empiric antibiotic therapy. This cohort definition substantially overlapped with patients assigned an abdominal infection indication during ordering and allowed identification of the analogous population in control hospitals; it also ensured inclusion of patients for whom the prompt was not displayed because clinicians chose other indications, either because of initial diagnostic uncertainty or deliberate efforts to circumvent 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) baseline extended-spectrum antibiotic days of therapy for abdominal infection (primary and secondary outcomes), (2) percentage of patients with abdominal/blood cultures sent, and (3) hospitals' case mix; annual admissions for abdominal infection; length of stay; Elixhauser comorbidity count (mean), ICU transfers, and percentage of patients calculated to have greater than or equal to 10% absolute risk for

Table 1. Characteristics of Patients With Abdominal Infection During Baseline and Intervention Periods

Patient characteristics	No. (%)			
	Baseline (12 mo)		Intervention (12 mo)	
	CPOE bundle	Routine stewardship	CPOE bundle	Routine stewardship
Patients	46 751	46 725	50 620	54 384
Age, mean (SD), y	59 (19)	61 (19)	59 (19)	61 (19)
Age categorized, y				
18-44	11 613 (24.8)	10 609 (22.7)	12 962 (25.6)	12 672 (23.3)
45-54	6237 (13.3)	6089 (13.0)	6732 (13.3)	7013 (12.9)
55-64	8268 (17.7)	7983 (17.1)	8733 (17.3)	8871 (16.3)
65-74	8997 (19.2)	9045 (19.4)	9639 (19.0)	10 691 (19.7)
75-84	7321 (15.7)	7814 (16.7)	8394 (16.6)	9753 (17.9)
≥85	4315 (9.2)	5185 (11.1)	4160 (8.2)	5384 (9.9)
Sex				
Female	28 249 (60.4)	28 375 (60.7)	29 985 (59.2)	32 114 (59.1)
Male	18 349 (39.2)	18 185 (38.9)	20 635 (40.8)	22 268 (40.9)
Unknown	153 (0.3)	165 (0.4)	0 (0)	2 (<0.1)
Race				
Black	5754 (12.3)	4591 (9.8)	6033 (11.9)	5730 (10.5)
White	33 004 (70.6)	35 197 (75.3)	35 429 (70.0)	39 497 (72.6)
Other[a]	1702 (3.6)	2915 (6.2)	1066 (2.1)	1981 (3.6)
Unknown	6291 (13.5)	4022 (8.6)	8092 (16.0)	7176 (13.2)
Hispanic or Latino ethnicity	10 565 (22.6)	10 227 (21.9)	12 688 (25.1)	13 086 (24.1)
Non-Hispanic or non-Latino ethnicity	36 186 (77.4)	36 498 (78.1)	37 932 (74.9)	41 298 (75.9)
Insurance type				
Medicare	23 748 (50.8)	24 497 (52.4)	24 318 (48.0)	27 183 (50.0)
Commercial	10 018 (21.4)	10 179 (21.8)	10 958 (21.6)	11 255 (20.7)
Other (eg, self-pay, free care)	7431 (15.9)	6792 (14.5)	9341 (18.4)	9544 (17.6)
Medicaid	5554 (11.9)	5257 (11.3)	6003 (11.9)	6402 (11.8)
Antibiotic and health care exposures in year before admission[b]				
Emergency department visit	21 496 (46.0)	20 999 (44.9)	21 957 (43.4)	23 172 (42.6)
Hospitalization	15 131 (32.4)	14 678 (31.4)	15 234 (30.1)	16 323 (30.0)
>1 Hospitalization	7032 (15.0)	6812 (15.6)	6880 (13.6)	7399 (13.6)
Antibiotics	12 247 (26.2)	11 828 (25.3)	12 321 (24.3)	13 222 (24.3)
Nursing home stay	3827 (8.2)	3919 (8.4)	3393 (6.7)	3654 (6.7)
Abdominal surgery in year before admission	2229 (4.8)	2053 (4.4)	2196 (4.3)	2379 (4.4)
Time to first antibiotics (current admission), median (IQR), h[c]	3 (1.5-5.5)	3 (1.0-5.5)	3 (1.5-6.5)	3 (1.0-6.5)
History of pathogen requiring extended-spectrum antibiotics, (any MDRO)[d]	4984 (10.7)	4729 (10.1)	4977 (9.8)	5127 (9.4)
MRSA	2768 (5.9)	2521 (5.4)	2488 (4.9)	2592 (4.8)
VRE	507 (1.1)	364 (0.8)	375 (0.7)	399 (0.7)
Pseudomonas	1231 (2.6)	1156 (2.5)	1345 (2.7)	1336 (2.5)
ESBL	2213 (4.7)	2158 (4.6)	2432 (4.8)	2447 (4.5)
Carbapenem-resistant gram negative bacteria[e]	315 (0.7)	276 (0.6)	280 (0.5)	266 (0.5)

(continued)

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.[32,33] Randomization was performed within these pairs.

Data Collection

Data obtained from the HCA centralized data warehouse included patient demographics, unit location, prior hospital/nursing home admissions, including prior antibiotic exposures at the same hospital, comorbidities, and in-hospital mortality. Race and ethnicity were included as collected in the EHR to address generalizability. Racial groups included Black, White, other (ie, Asian Hawaiian, multiracial, and Native American), and unknown; ethnic groups included Hispanic or Latino.

MDRO history was obtained from microbiology laboratory results from any body site. MDROs included MRSA, vancomycin-resistant *Enterococci*, ESBL, multidrug-resistant (MDR) *Pseudomonas*, MDR *Acinetobacter*, or carbapenem-resistant *Enterobacterales* (eTable 5 in Supplement 2). Abdominal infections due to MDROs were based on culture-positive blood or abdominal sources (stool, wounds, fluid/abscess or tissue cultures from any intraperitoneal and non-urinary retroperitoneal organ or cavity) collected during the

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

Patient characteristics	No. (%)			
	Baseline (12 mo)		Intervention (12 mo)	
	CPOE bundle	Routine stewardship	CPOE bundle	Routine stewardship
Selected Elixhauser comorbidities[f]				
Hypertension	27 911 (59.7)	28 155 (60.3)	31 415 (62.1)	33 905 (62.3)
Diabetes	11 927 (25.5)	11 329 (24.2)	13 023 (25.7)	13 824 (25.4)
Chronic pulmonary disease	9777 (20.9)	9334 (20.0)	9849 (19.5)	10 323 (19.0)
Neurological disorders	8800 (18.8)	8718 (18.7)	10 025 (19.8)	11 004 (20.2)
Obesity	9700 (20.7)	8665 (18.5)	10 993 (21.7)	9787 (18.0)
Anemias	8213 (17.6)	8429 (18.0)	8772 (17.3)	10 500 (19.3)
Kidney disease	8364 (17.9)	7741 (16.6)	8273 (16.3)	8748 (16.1)
Heart failure	6124 (13.1)	5796 (12.4)	6929 (13.7)	7305 (13.4)
Liver disease	5084 (10.9)	4839 (10.4)	7800 (15.4)	8543 (15.7)
Thyroid disorders	5615 (12.0)	5767 (12.3)	5727 (11.3)	6873 (12.6)
Alcohol and drug abuse	3961 (8.5)	3659 (7.8)	4103 (8.1)	4359 (8.0)
Coagulopathy	3359 (7.2)	3329 (7.1)	3993 (7.9)	4809 (8.8)
Solid tumor	2344 (5.0)	2501 (5.4)	2822 (5.6)	3276 (6.0)
Hematologic malignancy	476 (1.0)	535 (1.1)	393 (0.8)	628 (1.2)
Elixhauser count, median (IQR)[g]	3 (1.0-4.0)	2 (1.0-4.0)	3 (1.0-4.0)	3 (1.0-4.0)

Abbreviations: ESBL, extended-spectrum β-lactamase producer; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

[a] Other race category included: Asian, Hawaiian, multiracial, and Native American.

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

[c] Hours to first antibiotics includes first dose of any antibiotics administered in the emergency department or inpatient wards from 2 days before the 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, carbapenem-resistant gram negative pathogen, or VRE; also includes any MRSA or VRE PCR positivity, *ICD-10* coding, or any infection prevention isolation flag placed on the patient's medical record for with any of these organisms.

[e] Carbapenem-resistant *Enterobacterales*, *Acinetobacter*, and *Pseudomonas*.

[f] Selected from Elixhauser comorbidity conditions; 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 count is the sum of each comorbid condition (among 38) as available in the electronic health record for each patient.

first 3 hospital days and the associated emergency department stay.

Trial Outcomes

The primary outcome was extended-spectrum antibiotic days of therapy in the empiric period (first 3 calendar days of hospitalization), calculated as the summed number of different extended-spectrum antibiotics 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 therapy. The study design had greater 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 (statistical analysis plan available in Supplement 1).

Secondary outcomes included days of therapy of the subsets of vancomycin and antipseudomonals. 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.

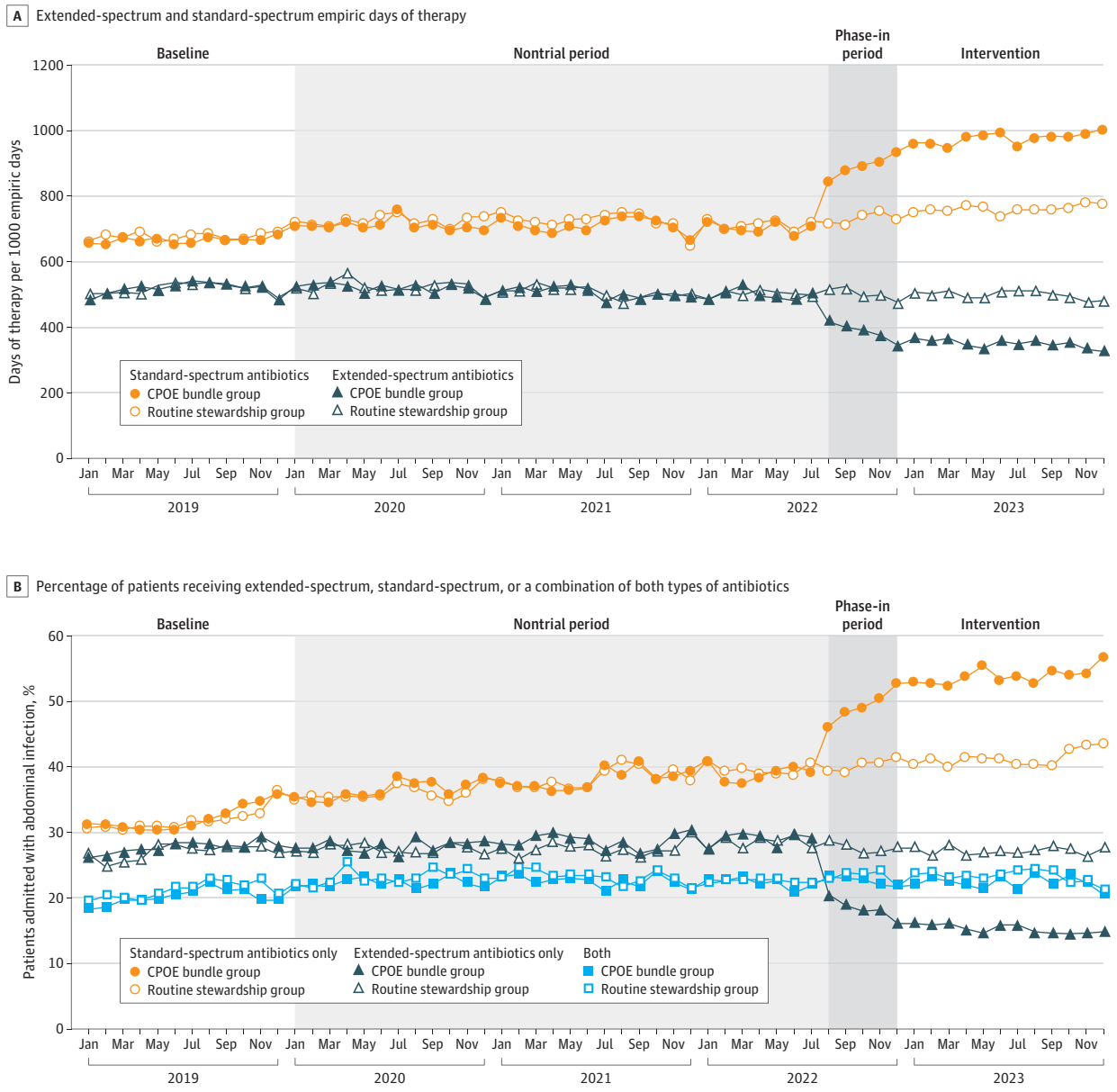
Two prespecified safety outcomes were assessed as follows: (1) days to ICU transfer, defined as days from admission until ICU transfer and (2) hospital length of stay in days (see Supplement 1 for details). The prespecified noninferiority margins (NIMs) for length of stay and days to ICU transfer were hazard ratios (HRs) 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 days of therapy between intervention and baseline periods across the groups (difference-in-differences analysis). 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 outcome was measured as the total number of extended-spectrum antibiotics received per patient from admission to hospital day 3 divided by the number of empiric days ×1000). The primary outcome was assessed with 2-tailed significance at $\alpha = .05$, and the 2 secondary outcomes were each assessed with 2-tailed significance at $\alpha = .025$ to account for multiple comparisons (statistical analysis plan in Supplement 1).

Safety outcomes were assessed using unadjusted as-randomized proportional hazards models (Supplement 1 and

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



A, Temporal trends in empiric (hospital days 1-3) extended- 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. Effects persisted despite arrival of the COVID-19 pandemic. B, Temporal trends in percentage of patients with abdominal infection who received either extended-spectrum antibiotics only, standard-spectrum antibiotics only, or a combination of both (mutually exclusive categories) during the empiric period. Percentage of patients receiving standard-spectrum antibiotics only in the intervention group increased, and the percentage receiving extended-spectrum antibiotics only or combination of both decreased.

eMethods 2 in Supplement 2). For days to ICU transfer, clustering by patient, hospital, and period within hospital. Length of stay used 1 admission per patient, and random effects accounted for clustering by hospital and period.

Adjusted analyses accounted for age, sex, race and ethnicity, Medicaid insurance, antibiotic or nursing home exposure in the last year, abdominal surgery in the last year, mean Elixhauser comorbidity count,[34] history of MDRO, and race and ethnicity (included given prior evidence of high risk for abdominal infection, MDRO, and chronic abdominal conditions).[35-38] All analyses were performed using SAS, version 9.4 (SAS Institute), or R, version 4.2.3 (R Foundation). The a priori statistical analytic plan is provided in Supplement 1.

In addition, 3 post hoc sensitivity analyses were performed: (1) all outcomes: inclusion of patients transferring to an ICU after the first rather than second admission day,

(2) safety outcomes: accounting for competing risk of death (eMethods 2 in Supplement 2), and (3) effectiveness outcomes: as assessment of extended-spectrum doses per patient rather than patient day).

Results

Patient Characteristics

A total of 92 hospitals with 198 480 patients (mean [SD] age, 60 [19] years; 118 723 female [59.8%]; 79 437 male [40.0%]; 320 unknown [0.2%]) were randomized to either the routine antibiotic stewardship group (46 hospitals; 101 109 patients) or the CPOE bundle group (44 hospitals; 97 371 patients) (**Figure 1**). Patients self-reported the following races: 22 108 Black (11.1%), 143 127 White (72.1%), 7664 other (3.9%), and 25 581 unknown (12.9%). Patients self-reported the following ethnicities: 46 566 Hispanic or Latino (23.5%). The routine stewardship group had 46 725 patients during the baseline period and 54 384 during the intervention period; the CPOE bundle intervention group had 46 751 patients and 50 620 during the baseline and intervention periods, respectively (93 476 [47.1%] total baseline; 105 004 [52.9%] total intervention). Study groups were well balanced overall (**Table 1**), including similar percentages of patients with abdominal surgery, liver disease, and alcohol or drug misuse. Compared with routine stewardship, the CPOE bundle group had a higher median (IQR) Elixhauser score (3.0 [1.0-4.0] vs 2.0 [1.0-4.0]) and higher baseline percentages of participants of Black race (12.3% [5754 of 46 751] vs 9.8% [4591 of 46 725]) and with obesity (20.7% [9700 of 46 751] vs 18.5% [8665 of 46 725]).

At baseline, the percentage of patients with abdominal or blood cultures sent during the first 3 days of hospitalization and associated emergency department stay was 74% or greater across both study groups and study periods (eTable 6 in Supplement 2). Of these, the percentage with cultures positive for pathogen requiring extended-spectrum antibiotics during baseline was 3.9% (1030 of 26 296) for the routine stewardship group and 3.6% (992 of 27 657) for the CPOE group; during the intervention period, the percentages were 3.6% (1097 of 30 523) for the routine stewardship group and 3.3% (966 of 29 159) for the CPOE bundle group (eTable 6 in Supplement 2). Cultures were positive for MRSA or *Pseudomonas* in 1% or less and ESBL in 2% or less among patients across study groups and periods combined; hospital prevalence of MDROs among patients with abdominal infection is provided in eTable 7 in Supplement 2 across all 92 hospitals.

Antibiotic Prescribing and MDRO Risk Estimation

Receipt of any empiric extended-spectrum antibiotic for the routine stewardship group was 48.2% (22 519 of 46 725) during baseline and 50.5% (27 452 of 54 384) during the intervention period; for the CPOE bundle group, it was 47.8% (22 367 of 46 751) during baseline and 37.6% (19 010 of 50 620) during the intervention period. Reductions in monthly extended-spectrum days of therapy in the CPOE bundle group were evident by 3 months into the phase-in period (**Figure 2** and eTable 8 in Supplement 2).

Although more than half of patients received extended-spectrum antibiotics during the baseline period, the CPOE algorithm classified more than 98% of patients with abdominal infection in both groups as low risk; of these, less than 2% subsequently had an MDRO-positive culture (eTable 9 in Supplement 2).

Primary and Secondary Trial Outcomes

For the primary outcome, the raw absolute reduction in empiric extended-spectrum days of therapy per 1000 empiric days in the routine stewardship group declined by 19.8 (baseline: 519.4, intervention: 499.6), whereas the CPOE bundle group declined by 169.3 (baseline: 518.9, intervention: 349.6, a raw absolute difference in extended-spectrum days of therapy rate of 149.5). The clustered rate ratio was 0.65 (95% CI, 0.60-0.71; $P < .001$), indicating a relative reduction of 35% in empiric extended-spectrum days of therapy with the CPOE bundle vs routine care (**Table 2** and **Figure 3**A). Secondary outcomes of vancomycin and antipseudomonal days of therapy showed similar reductions (Table 2 and Figure 3A). As-treated analyses after removing the 2 hospitals that divested from HCA during phase-in showed nearly identical results.

Sensitivity Analyses

Point estimates remained nearly identical for all outcomes after adjusted and sensitivity analyses (eTable 10 in Supplement 2). When evaluating antibiotics given per patient (vs days of therapy), there was a 45% reduction in empiric extended-spectrum antibiotic doses per patient, from 3.0 (140 137 of 46 725) during the baseline period to 2.9 (157 224 of 54 384) during the intervention period for the routine stewardship group vs 3.0 (138 747 of 46 751) during the baseline period and 2.0 (99 143 of 50 620) during the intervention period for the CPOE bundle group (eTable 11 in Supplement 2).

Safety Outcomes

Hospital length of stay in the CPOE bundle group was noninferior to routine care (mean [SD], baseline, 5.4 [3.4] days vs intervention, 5.5 [3.5] days; HR, 1.02; 90% CI, 0.98-1.08; NIM, 0.98). There were fewer transfers to the ICU in the CPOE bundle (3.4% [1473 of 42 897]) vs the routine group (3.6% [1664 of 45 818]) (eTable 12 in Supplement 2), with mean (SD) days to ICU transfer changing from 5.6 (2.9) days to 5.8 (3.0) days vs 5.5 (2.8) days to 5.7 (2.9) days, respectively. The HR was indeterminate—neither inferior nor noninferior (both groups 0.2 days longer during intervention; HR, 1.10; 90% CI, 0.99-1.23; NIM, 1.1) due to wide confidence limits (Table 2). HRs for all safety outcomes remained nearly identical in sensitivity analyses (eTable 13 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) a reduction in clinicians' initial choice of extended-spectrum antibiotics (37.6% [19 010 of 50 620] in the CPOE bundle hospitals vs 50.5% [27 452 of 54 384] in routine stewardship hospitals) and (2) a change from extended- to standard-spectrum antibiotic

Table 2. Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotic Selection (INSPIRE) Abdominal Infection Trial Primary, Secondary, and Safety Outcomes, As-Randomized Analysis

Outcome	CPOE bundle			Routine stewardship			Overall rate ratio difference in differences	*P* value[c]
	Days of therapy raw rate[a]		Rate ratio (95% CI)[b]	Days of therapy raw rate[a]		Rate ratio (95% CI)[b]		
	Baseline	Intervention		Baseline	Intervention			
Effectiveness outcomes								
Primary outcome								
Extended-spectrum days of therapy	518.9 (68 679/ 132 346)	349.6 (50 001/ 143 018)	0.62 (0.59-0.66)	519.4 (68 616/ 132 097)	499.6 (76 605/ 153 342)	0.95 (0.90-1.01)	0.65 (0.60-0.71)	<.001
Secondary outcomes								
Vancomycin days of therapy	99.7 (13 198/ 132 346)	70.0 (10 016/ 143 018)	0.67 (0.63-0.71)	96.7 (12 780/ 132 097)	84.9 (13 019/ 153 342)	0.84 (0.79-0.89)	0.80 (0.73-0.87)	<.001
Antipseudomonal days of therapy	372.1 (49 249/ 132 346)	240.3 (34 362/ 143 018)	0.60 (0.56-0.64)	373.8 (49 377/ 132 097)	368.2 (56 465/ 153 342)	0.97 (0.91-1.04)	0.61 (0.56-0.67)	<.001
	Days to event, mean (SD)[d]		HR (90% CI)[e]	Days to event, mean (SD)[d]		HR (90% CI)[e]	Overall HR difference in differences	*P* value[f]
Safety outcomes								
Length of stay	5.4 (3.4)	5.5 (3.5)	0.98 (0.95-1.00)	5.4 (3.4)	5.5 (3.5)	0.95 (0.93-0.98)	1.02 (0.99-1.06)	.27
Days to ICU transfers	5.6 (2.9)	5.8 (3.0)	0.98 (0.90-1.06)	5.5 (2.8)	5.7 (2.9)	0.89 (0.82-0.96)	1.10 (0.99-1.23)	.15

Abbreviations: CPOE, Computerized Provider Order Entry; HR, hazard ratio; ICU, intensive care unit.

[a] Days of therapy rate calculated per patient per empiric day (first 3 days of hospitalization) expressed with multiplier 1000 empiric days.

[b] Rate ratios represent group-specific comparisons of intervention to baseline.

[c] Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within patient, hospital, and period within hospital. *P* value assessed at 2-tailed significance set at α = .05 for null hypothesis that the relative rate ratio in each arm is not different for primary outcome; α = .025 for secondary outcomes to account for multiple comparisons.

[d] Days to event: mean days calculated within a single admission. Days to ICU transfer = days from admission to date of first ICU transfer among those requiring transfer on hospital day 3 through hospital day 14. Length of stay 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 intervention to baseline. 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.

[f] *P* value for the difference in HR between periods. Each safety outcome was evaluated for noninferiority using with a 1-tailed significance set at α = .05. For length of stay, the noninferiority margin is a HR of 0.98. For days to ICU transfer, the noninferiority margin is a HR of 1.1.

therapy by 12.2% (1255 of 10 256) when clinicians encountered the prompt during antibiotic ordering. The percentage of patients for whom abdominal infection was chosen as the indication for antibiotic use among those with abdominal infection as a discharge diagnosis was similar in the routine (52.0% [28 297 of 54 384]) and CPOE bundle (54.4% [27 532 of 50 620]) groups.

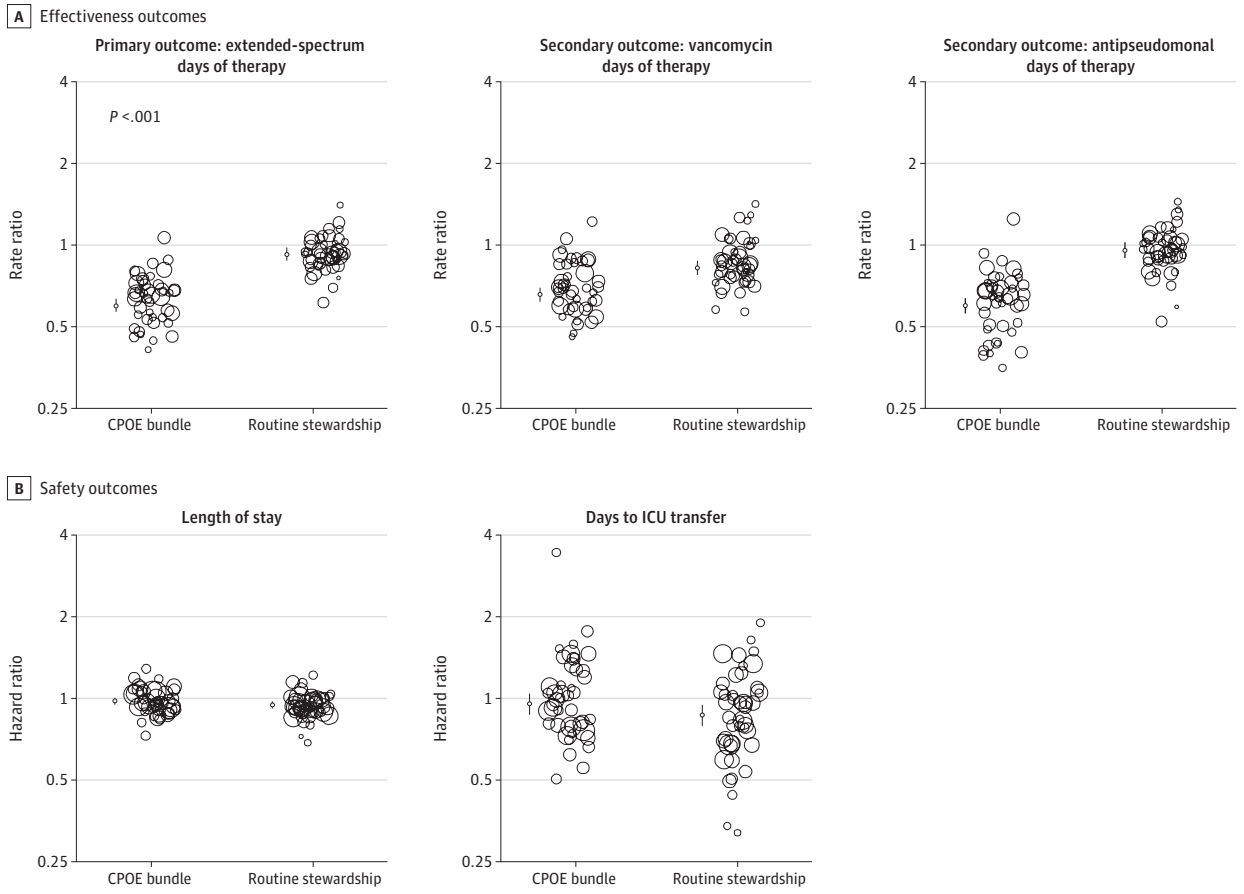
Discussion

In this embedded, pragmatic, cluster randomized clinical trial to evaluate the impact of a CPOE-based antibiotic stewardship strategy on empiric antibiotic selection for noncritically ill patients with abdominal infection, we found a 35% relative reduction in empiric extended-spectrum antibiotic use. This rapid and sustained reduction occurred without evidence of inferiority in days to ICU transfer or length of stay. Inclusion of a wide variety of abdominal infections diagnoses suggests the intervention's broad applicability to hundreds of thousands of patients who receive extended-spectrum antibiotics for abdominal infection in US hospitals annually.[2,3,5,6,8,12,19]

The finding that *Pseudomonas*, ESBL, and MRSA each was recovered from less than 2% of inpatients with abdominal infection provides much needed reassurance that the vast majority of patients with abdominal infections can be safely treated initially with standard-spectrum antibiotics. In fact, the risk models developed for this study suggest that anti-MRSA and antipseudomonal antibiotics are needed in the empiric period only if a patient has previously had these pathogens and had abdominal surgery in the past year.

Patient- and pathogen-specific CPOE prompts may have changed empiric antibiotic prescribing in several ways. First, initial selection of standard-spectrum antibiotics increased with time, a behavior that eliminated the indication for the prompt. We believe that this reflected growing recognition among prescribers of the low risk of resistance in these patients. Second, for low-risk patients in whom extended-spectrum antibiotics remained as the prescriber's initial choice, the prompts offered standardized guidance and reassurance to switch to standard-spectrum antibiotics. Third, pathogen-specific risk estimates for abdominal infections may have been particularly valuable because timely identification of pathogens is often delayed in abdominal infections. Fourth, because antibiotics started in the emergency department are commonly continued during the hospital stay, initial selection of standard-spectrum antibiotics likely influenced prescribing by admitting physicians. Fifth, EHR documentation of each patient's estimated MDRO risk may have mitigated medicolegal concerns.

Figure 3. Effect of Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotic Selection (INSPIRE) for Abdominal Infection Routine Stewardship vs Computerized Provider Order Entry (CPOE) Bundle on Trial Effectiveness and Safety Outcomes



A, Bubble position represents the hospital relative rate ratio of days of therapy (summed across individuals within each individual hospital) per empiric day dividing intervention by baseline. Bubble area is proportional to the number of admissions that the hospital contributed to the trial. Also shown are the estimated relative rate ratio (RR) and 95% CI comparing intervention to baseline period for each study group, based on unadjusted generalized linear mixed-effects models that accounted for clustering within patient, hospital, and period within hospital. B, Bubble position represents hazard ratio (HR) for each hospital comparing intervention to baseline from a model with only that hospital. Bubble area is proportional to the number of admissions that the hospital contributed to the trial. Also shown are the estimated HR and 90% CI comparing intervention to baseline period for each study group, based on a proportional hazards model that accounted for clustering within patient (for days to intensive care unit only), 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.

Limitations

This study has some limitations. First, the trial was performed in community hospitals where MDRO prevalence may be low; applicability to other settings is unknown. Second, it is not possible to separate the effect of the prompt from education and feedback. However, the rapid reduction in extended-spectrum antibiotic use suggests that the prompt played a prominent role because education and feedback campaigns generally require more time to effect change.[39-41] Third, hospital variation in education and feedback efforts was not measured. Fourth, a predicted resistance threshold greater than 10% might have been more effective and equally safe. Fifth, inclusion of all clinical specimens, including those from sites such as indwelling drains, may have overestimated the role of MDROs as pathogens. These were included because clinicians may interpret any recovery of an MDRO as an indication for empiric extended-spectrum therapy. Sixth, similar prompts were implemented simultaneously with skin and soft tissue infection prompts, which may have generally improved standard-spectrum antibiotic prescribing among clinicians in intervention hospitals but may also have negatively affected adoption through alert fatigue. Seventh, our study population was limited to those assigned a diagnosis code of abdominal infection.

Conclusions

CPOE prompts recommending empiric standard-spectrum antibiotics (coupled with education and feedback) for patients admitted with abdominal infection who have low risk for MDRO infection significantly reduced extended-spectrum antibiotics without increasing ICU transfers or length of stay.

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