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Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: the INSPIRE Randomized Clinical Trial

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Key Points

Question: Can computerized provider order entry prompts that present patient-specific multidrug-resistant organism (MDRO) risk estimates reduce empiric extended-spectrum antibiotics in patients admitted with urinary tract infection (UTI)?

Findings: In a cluster-randomized trial of 59 hospitals (n = 55,412 adults in the intervention period), computerized provider order entry prompts promoting standard-spectrum antibiotics for patients at low risk of infection with MDROs significantly reduced empiric extended-spectrum antibiotic use in hospitalized patients with UTI by 17.4% without increasing intensive care unit transfers or length of stay.

Meaning: Real-time electronic health record–generated recommendations for standard-spectrum antibiotics using patient-specific risk for MDRO-associated infections can safely reduce empiric extended-spectrum antibiotic use in patients hospitalized for UTI

Abstract

Importance: Urinary tract infection (UTI) is the second most common infection leading to hospitalization and is often associated with gram-negative multidrug-resistant organisms (MDROs). Clinicians overuse extended-spectrum antibiotics although most patients are at low risk for MDRO infection. Safe strategies to limit overuse of empiric antibiotics are needed.

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Objective: To evaluate whether computerized provider order entry (CPOE) prompts providing patient- and pathogen-specific MDRO risk estimates could reduce use of empiric extended-spectrum antibiotics for treatment of UTI.

Design, Setting, and Participants: Cluster-randomized trial in 59 US community hospitals comparing the effect of a CPOE stewardship bundle (education, feedback, and real-time and risk-based CPOE prompts; 29 hospitals) vs routine stewardship (n = 30 hospitals) on antibiotic selection during the first 3 hospital days (empiric period) in noncritically ill adults (≥18 years) hospitalized with UTI with an 18-month baseline (April 1, 2017–September 30, 2018) and 15-month intervention period (April 1, 2019–June 30, 2020).

Intervention: CPOE prompts recommending empiric standard-spectrum antibiotics in patients ordered to receive extended-spectrum antibiotics who have low estimated absolute risk (<10%) of MDRO UTI, coupled with feedback and education.

Main Outcomes and Measures: The primary outcome was empiric (first 3 days of hospitalization) extended-spectrum antibiotic days of therapy. Secondary outcomes included empiric vancomycin and antipseudomonal days of therapy. Safety outcomes included days to intensive care unit (ICU) transfer and hospital length of stay. Outcomes were assessed using generalized linear mixed-effect models to assess differences between the baseline and intervention periods.

Results: Among 127,403 adult patients (71 991 baseline and 55,412 intervention period) admitted with UTI in 59 hospitals, the mean (SD) age was 69.4 (17.9) years, 30.5% were male, and the median Elixhauser Comorbidity Index count was 4 (IQR, 2-5). Compared with routine

stewardship, the group using CPOE prompts had a 17.4% (95% CI, 11.2%-23.2%) reduction in empiric extended-spectrum days of therapy (rate ratio, 0.83 [95% CI, 0.77-0.89]; *P* < .001). The safety outcomes of mean days to ICU transfer (6.6 vs 7.0 days) and hospital length of stay (6.3 vs 6.5 days) did not differ significantly between the routine and intervention groups, respectively.

Conclusions and Relevance: Compared with routine stewardship, CPOE prompts providing real-time recommendations for standard-spectrum antibiotics for patients with low MDRO risk coupled with feedback and education significantly reduced empiric extended-spectrum antibiotic use among noncritically ill adults admitted with UTI without changing hospital length of stay or days to ICU transfers.

Trial Registration ClinicalTrials.gov Identifier: NCT03697096

Introduction

Urinary tract infection (UTI) is the second most common infection requiring hospitalization, accounting for more than 480 000 hospitalizations in the US annually, with up to 40% of patients unnecessarily receiving extended-spectrum antibiotics.[1-3] The high propensity for UTI recurrence adds further to antibiotic use. Additionally, patients with urologic dysfunction and urinary stasis are predisposed to chronic bacterial colonization and asymptomatic bacteriuria, which also contribute to inappropriate antibiotic use.[4-7] Even brief antibiotic exposures can alter gut and urinary microbiomes, predisposing patients to UTI recurrence, future multidrug-resistant organism (MDRO) infections, *Clostridioides difficile* infection, and other adverse effects.[2,8-10] Effective and safe strategies are urgently needed to limit extended-spectrum antibiotics in patients with UTI.

Antibiotic stewardship efforts for UTI have largely focused on diagnostic stewardship (reducing unnecessary testing to limit inappropriate antibiotic use for asymptomatic bacteriuria), shortening duration of therapy, and deescalating extended-spectrum to standard-spectrum antibiotics.[11-15] Few studies have addressed reducing unnecessary extended-spectrum antibiotic use among hospitalized patients with UTI before culture results return.[11] Clinician concern for MDRO drives initial selection of extended-spectrum antibiotics, though the majority can be managed with standard-spectrum antibiotics.[11,16,17] Successfully identifying patients with low risk for MDRO UTI could reduce empiric extended-spectrum antibiotic exposure. This study evaluated the effect of the INSPIRE antibiotic stewardship bundle, consisting of education, feedback, and computerized provider order entry (CPOE) prompts recommending standard-spectrum antibiotics for patients with low MDRO UTI risk estimates, on empiric extended-spectrum antibiotic prescribing for patients hospitalized with UTI.

Methods

Study Design and Intervention

The INSPIRE (Intelligent Stewardship Prompts to Improve Real-time Empiric antibiotic selection) UTI Trial was a cluster-randomized trial comparing the effect of the INSPIRE stewardship bundle (CPOE bundle) vs routine antibiotic stewardship on empiric extended-spectrum antibiotic selection. The study population was noncritically ill adults (≥18 years) hospitalized with UTI at HCA Healthcare (hereafter referred to as *HCA*), the largest private community hospital system in the US. There was an 18-month baseline period (April 1, 2017–September 30, 2018), 6-month phase-in period (October 1, 2018–March 31, 2019), and 15-month intervention period (April 1, 2019–June 30, 2020). An analogous trial focusing on patients hospitalized with pneumonia was concurrently conducted in the same hospitals and is reported separately.[1]

Hospitals were randomized to the routine antibiotic stewardship group or CPOE bundle group. The routine antibiotic stewardship group received educational materials and quarterly coaching calls to maintain stewardship activities for UTI per national guidance (trial protocol in Supplement 1). Routine stewardship activities included providing hospital guidelines and protocols for antibiotic selection, requiring a documented indication (reason) for antibiotics, and prospectively evaluating antibiotic use with clinician feedback for deescalating antibiotics after microbiologic results returned.

The CPOE bundle group included routine stewardship activities, monthly coaching calls, and the same educational material for maintaining national antibiotic stewardship guidance, plus (1) CPOE prompts recommending standard-spectrum instead of extended-spectrum antibiotics for patients with a low absolute risk (<10%) for MDRO UTI for orders placed during the first 3 days (empiric period) and (2) clinician education and feedback reports.

The CPOE algorithm and prompt were activated when extended-spectrum antibiotics (eTable 1

in Supplement 2) were ordered in a non-ICU location for an indication of UTI within 72 hours of admission (including antibiotics administered in the emergency department). The hospitals' order-entry system required documentation of an indication for all antibiotic orders. If the patient's estimated absolute MDRO risk was below 10%, then a prompt was triggered that recommended standard-spectrum antibiotics. The 10% threshold was recommended by an expert panel. Patient-specific estimates were recorded within the electronic health record in both study groups, but prompts were displayed only in the CPOE bundle group.

The CPOE algorithm and prompt were tailored to the specific extended-spectrum antibiotic ordered. For example, if cefepime was ordered, the evaluation was for a less than 10% risk for *Pseudomonas* UTI; if a carbapenem was ordered, a less than 10% combined risk of extended-spectrum β-lactamase–producing Enterobacterales (ESBLs) or resistant *Pseudomonas* was evaluated. Although UTI with gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus*, are uncommon clinically and usually associated with instrumentation if present, prompts estimating the risk of UTI due to these pathogens were included to address overuse of vancomycin for UTI. These risks were obtained from recursive partitioning models that estimated absolute MDRO risk based on a retrospective data set of patients admitted with UTI in 140 HCA hospitals (304 584 patients). Models assessed more than 50 variables including each hospital's frequency of positive MDRO urine/blood cultures among patients with UTI, as well as factors previously associated with risk of MDRO-associated UTI such as demographics, health care exposures, antibiotic exposure, history or microbiologic evidence of MDROs (any body site), comorbidities, and admission laboratory values. Data were limited to information within HCA's health system. The modeling approach and factors associated with high risk of MDRO-associated UTI are provided in eTable 2 in Supplement 2.

The clinical workflow and prompts are shown in the eFigure in Supplement 2. The prompt provided a 1-click option to substitute ceftriaxone (standard-spectrum antibiotic) for the

extended-spectrum antibiotic. Clinicians could override (not accept) the recommendation and proceed with ordering extended-spectrum antibiotics.

Education for Both Study Groups. Clinician education emphasized national standards for empiric antibiotic treatment for cystitis and pyelonephritis, including treatment of ESBLs and avoiding antibiotics for asymptomatic bacteriuria in both study groups.[19-22] Coaching calls emphasized the importance of avoiding competing interventions and polling questions monitored any new interventions. All educational materials were developed by the investigative team, including presentations, handouts, and emails disseminated through existing hospital channels (Supplement 1).

Education and feedback in the CPOE Bundle group. In addition to education provided to the routine stewardship group, the CPOE bundle group received education on how MDRO UTI risk estimates were calculated and local frequency of positive MDRO cultures among patients with UTI. Additionally, lead investigators conducted 1-time site visits and additional webinars as requested. Investigators held coaching calls to support local education efforts. Feedback reports allowed local stewardship teams to monitor and provide feedback on extended-spectrum antibiotic prescribing for UTI at the hospital, department, and clinician levels, as well as prompt response.

Hospital Recruitment and Study Cohort Definition

Hospitals were eligible if they used the MEDITECH electronic health record system and agreed to avoid new initiatives that could directly affect empiric antibiotic selection in noncritically ill patients with UTI. Hospitals sharing clinicians under a single antibiotic stewardship program were randomized as a single unit.

The analytic cohort was defined in advance as patients with discharge claims codes for UTI that were accompanied by a “present on admission” indicator (eTable 3 in Supplement 2). This definition substantially overlaps with patients assigned an indication of UTI during antibiotic order entry and was selected to ensure full inclusion of patients with UTI independent of

clinician orders placed for a different indication. The cohort also excluded individuals in prison and patients transferred to the ICU within 2 calendar days of admission. The Harvard Pilgrim Health Care Institute Institutional Review Board provided centralized oversight, with reliance agreements and operational committee approvals from all participating hospitals. Individual informed consent was waived. This trial was registered with ClinicalTrials.gov, NCT03697096. Results are reported according to CONSORT guidelines.

Randomization

Hospitals were randomized in a 1:1 ratio to routine care or the intervention group for both the INSPIRE UTI Trial and the concurrent INSPIRE Pneumonia Trial, which is reported separately.[18] Aggregated baseline hospital data from May 1, 2014, to March 31, 2017, were used to establish pairs of similar hospitals based on the following variables: (1) baseline extended-spectrum antibiotic days of therapy for UTI (primary and secondary outcomes), (2) baseline clinical practice (percentage of cohort with cultures sent and time to first antibiotic dose), and (3) hospital patient case mix (annual UTI admissions, length of stay, ICU transfers, hospital baseline percentage of patients with UTI with cultures positive for MRSA and *Pseudomonas*, sex, Elixhauser Comorbidity Index count [mean], percentage of admitted patients with selected comorbidities, and percentage vancomycin and antipseudomonal antibiotic given to patients calculated to have <10% absolute risk for MRSA or *Pseudomonas* pneumonia, respectively). Pairing was done by calculating the Mahalanobis distance between facilities across baseline values of weighted variables, choosing pairings with the minimum average within-pair distance.[23,24] Randomization was performed within these pairs.

Data Collection

Data obtained from the HCA centralized data warehouse included patient demographics, hospital unit location, any prior hospital/nursing home admissions and inpatient antibiotic exposures at the same hospital, and comorbid conditions for patients within HCA's health system. Race and ethnicity were included as collected in the HCA electronic health record to address population diversity and generalizability. Extended-spectrum antibiotics are shown in eTable 1 in Supplement 2. History of MDROs was obtained from any microbiology laboratory result from a body site yielding MRSA, vancomycin-resistant *Enterococci*, ESBLs, multidrug-resistant *Pseudomonas*, multidrug-resistant *Acinetobacter*, and carbapenem-resistant Enterobacterales (CRE) (eTable 4 in Supplement 2). Designation of UTI due to an MDRO was based on positive cultures from blood or urinary source: bladder (including catheter), ureter, kidney (drain, nephrostomy, aspirate), and urostomy, regardless of colony or leukocyte count in cultures sent during the first 3 days of hospitalization and the associated emergency department stay.

Trial Outcomes

The primary outcome was extended-spectrum days of therapy in the first 3 calendar days of hospitalization calculated as the summed number of different extended-spectrum antibiotics received per patient each calendar day in a non-ICU location, beginning at the time of admission. For convenience, this period was called the *empiric period* and *empiric days* were calculated. For example, 2 different extended-spectrum antibiotics administered at least once during each of the first 3 days would yield an extended-spectrum days of therapy of 6. The study had 97% power (95% CI, 91%-99%) to detect a 12.5% difference in extended-spectrum days of therapy between the intervention and routine stewardship groups during the first 3 days (statistical analysis plan in Supplement 1). The 2 secondary outcomes were extended-spectrum

subsets: (1) vancomycin and (2) antipseudomonal days of therapy. Antibiotics given in the emergency department were counted toward antibiotic days of therapy if administered on the first hospital day. Because patients initially admitted to a non-ICU location who were subsequently transferred to an ICU on hospital day 1 or 2 were excluded, their antibiotic days were not included. However, patients transferred to the ICU on hospital day 3 had all empiric antibiotics counted, including those given in the ICU.

Three prespecified safety outcomes were assessed for the duration of the hospital stay: (1) days to antibiotic escalation defined as hospital days from standard-spectrum antibiotic start until switch to extended-spectrum antibiotic (including antibiotics received after ICU transfer); (2) days to ICU transfer defined as days from admission until ICU transfer; and (3) hospital length of stay in days.

Statistical Analysis

Unadjusted, as-randomized outcomes were assessed using generalized linear mixed-effects models assessing differences in empiric extended-spectrum days of therapy between the intervention vs baseline periods across groups (difference-in-differences). Random effects accounted for clustering within hospital and period. Data from the phase-in period were excluded from all analyses. The unit of analysis was the patient. Patients with multiple admissions contributed 1 randomly selected admission. 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.

Each safety outcome was assessed using as-randomized, unadjusted proportional hazards models with random effects to account for clustering by hospital and period. To maximize detection of safety risks, each safety outcome was assessed with 1-tailed significance at $\alpha = .05$.

Adjusted analyses accounted for age, sex, race and ethnicity, Medicaid insurance, prior antibiotic or nursing home exposure within the last year, mean Elixhauser Comorbidity Index count,[25] and history of MDRO. Race and ethnicity information was included given prior evidence of association with risk for MDRO UTIs and predisposing urologic conditions.[26-29] All analyses were performed using SAS (version 9.4; SAS Institute) or R (version 4.0.0; R Project for Statistical Computing). The a priori statistical analytic plan is provided in Supplement 1.

Three sets of sensitivity analyses were completed, none prespecified. First, all outcomes were reevaluated after including patients transferred to the ICU after the first admission day (the original analysis evaluated these after the second admission day). Second, to account for the competing risk of death for safety outcomes, patients who died were counted as having transferred to the ICU and having had an antibiotic escalation on the day of death; for length of stay, each patient who died was assigned a length of stay of 30 days (99th percentile of hospitalization length in the baseline period). Third, to provide a clinically relatable metric for primary and secondary outcomes, these outcomes were reevaluated after redefining them as extended-spectrum doses per patient during the empiric period.

Results

Patient Characteristics

We randomly assigned 59 hospitals to either the routine antibiotic stewardship group (30 hospitals, 64,244 patients) or the CPOE bundle intervention (29 hospitals, 63,159 patients) (Figure 1). Patient characteristics by group and period are provided in Table 1. The routine stewardship group had 36,739 patients during the baseline period and 27,505 during the intervention period; the CPOE bundle group had 35,252 patients during the baseline period and 27 907 during the intervention period. Study groups were well-balanced overall. Compared with

the routine stewardship group, the CPOE bundle group had a higher proportion of White patients (76.5% vs 70.8%), Medicaid insurance (9.7% vs 8.2%), nursing home stay (15.1% vs 14.4%), and neurological disorders (41.7% vs 40.0%)

The percentage of patients with urinary or blood cultures sent within the empiric period (first 3 days of hospitalization) and associated emergency department stay during baseline was 89.9% (33,018/36,739) for routine stewardship and 89.8% (31,655/35,252) for the CPOE bundle group; for the intervention period, it was 86.9% (23,896/27,505) and 85.1% (23,761/27,907), respectively. Among patients with urinary or blood cultures sent, the percentage with cultures positive for *Pseudomonas* during baseline was 2.9% (974/33,018) for the routine stewardship group and 3.2% (1,014/31,655) for the CPOE bundle group; during the intervention period, it was 3.3% (788/23,896) and 3.4% (806/23,761), respectively (eTable 5 in Supplement 2). Culture positivity for ESBL during the baseline period was 7.3% (2419/33,018) and 7.2% (2,286/31,655) for the routine and CPOE bundle groups, respectively; during the intervention period, it was 8.0% (1,906/23,896) and 7.6% (1,794/23,761), respectively. MDRO UTI for all 59 hospitals is provided in eTable 6 in Supplement 2.

Antibiotic Prescribing and MDRO Risk Estimation

Receipt of any empiric extended-spectrum antibiotics was 40.9% (15,011/36,738) during the baseline period and 42.6% (11,720/27,505) during the intervention period for the routine stewardship group and 37.3% (13,132/35,251) and 33.5% (9,346/27,909), respectively, in the baseline and intervention periods for the CPOE bundle group. Reductions in monthly extended-spectrum days of therapy in the CPOE bundle group were evident by 3 months into the phase-in period (Figure 2A and B; eTable 7 in Supplement 2). These reductions continued during the COVID-19 pandemic, with a COVID-19 positivity rate of 23 per 1000 admissions in the routine stewardship group and 34 per 1000 admissions in the CPOE bundle group.

The study algorithm classified more than 94% of patients with UTI in both stewardship groups as low risk; fewer than 6% subsequently had an MDRO-positive culture (eTable 8 in Supplement 2).

Primary and Secondary Trial Outcomes.

For the primary outcome, the empiric extended-spectrum days of therapy per 1000 empiric days was 431.1 and 446.0 during the baseline and intervention periods, respectively, for the routine stewardship group. For the CPOE bundle group, extended-spectrum days of therapy decreased from 392.2 during the baseline period to 326.0 during the intervention period. The overall rate ratio (RR) when clustering by hospital and period was 0.83 (95% CI, 0.77-0.89; $P < .001$) for the primary outcome (Table 2, Figure 3A), indicating a 17.4% (95% CI, 11.2%-23.2%) significantly lower rate of empiric extended-spectrum days of therapy in the CPOE bundle group compared with the routine stewardship group. Secondary outcomes of vancomycin and antipseudomonal days of therapy showed similar reductions (Table 2, Figure 3A).

Sensitivity Analyses. Point estimates remained nearly identical for all outcomes after adjusted analyses and sensitivity analyses (eTables 9 and 10 in Supplement 2). There was a 19% reduction in empiric extended-spectrum antibiotic doses per patient, from 2.3 (83,317/36,739) during the baseline period and 2.4 (66,089/27,505) during the intervention period vs 2.1 (73,041/35,252) for the routine stewardship group and 1.7 (48,621/27,907) for the CPOE bundle group during the baseline and intervention periods, respectively (eTable 10 in Supplement 2).

Safety Outcomes

The percentage of patients transferred to the ICU was 4.0% vs 3.7% and the percentage requiring antibiotic escalation was 10.2% and 10.0% in the routine vs CPOE bundle groups, respectively (eTable 11 in Supplement 2). There were no significant differences between the groups for the safety outcomes of hospital length of stay, ICU transfer, or time to antibiotic escalation (from standard-spectrum to extended-spectrum antibiotics) (Table 2, Figure 2B). Hazard ratios for all safety outcomes remained nearly identical during sensitivity analyses (eTable 12 in Supplement 2).

Monitoring of CPOE Prompt and Competing Interventions

Auditing of the CPOE algorithm showed that the automated system was working as intended when extended-spectrum antibiotics were ordered for a UTI indication, with prompt activation if the relevant MDRO(s) risk was less than 10% in the CPOE bundle group. The reduction in prescribing of extended-spectrum antibiotics in the CPOE bundle group consisted largely of (1) a reduction in clinicians' initial choice of extended-spectrum antibiotics (13.3% [3,707/27,907] in the CPOE bundle hospitals vs 18.8% [5,180/27,505] in the routine stewardship hospitals during the intervention period) and (2) a change from extended- to standard-spectrum therapy in 10.3% (267/2,592) among those who encountered the real-time prompt. The percentage of patients for whom UTI was chosen as the indication for antibiotic among those with UTI as a discharge diagnosis was similar in the routine stewardship (65.4% [18,002/27,505]) and CPOE bundle (64.1% [17,880/27,907]) groups.

Of the 39 proposed changes in antibiotic stewardship practices reported by hospitals in both study groups, 2 conflicted with the trial protocol and were not implemented.

Discussion

The antibiotic stewardship intervention used in this study resulted in a 17.4% reduction in empiric extended-spectrum antibiotic use for noncritically ill patients hospitalized for UTI. In this trial, approximately 40% of patients hospitalized for UTI in the baseline period received empiric extended-spectrum antibiotics, suggesting that this intervention could be a viable strategy to reduce extended-spectrum antibiotics in up to 200 000 adults hospitalized in the US who receive unnecessarily broad antibiotics for UTI annually.[1,2,30] Antipseudomonal antibiotics are the most commonly overused antibiotics in hospitalized patients with UTI and its use was reduced by one-fifth.[19] These reductions were accompanied by an increase in initial prescribing of standard-spectrum antibiotics, suggesting increased clinician comfort to avoid empiric extended-spectrum antibiotics. Notably, the reductions occurred without a change in the safety outcomes of ICU transfer and hospital length of stay and persisted despite COVID-19 pandemic disruptions in the last quarter of the trial.

Excessive antibiotic use for community-onset UTI and the high propensity for recurrent UTI have likely contributed to a national rise in the prevalence of gram-negative MDROs.[2] This in turn raises clinical concern for MDRO UTI in hospitalized patients. In this trial, the overall frequency of patients with UTI who had urine cultures positive for *Pseudomonas* was 3.4% or less and for ESBL was 8.0% or less (eTable 5 in Supplement 2), confirming that most patients do not require empiric extended-spectrum antibiotics. These are likely overestimates because culture positivity cannot distinguish colonization (including asymptomatic bacteriuria) from infection. Notably, among those estimated to be at low risk for MDRO by the study algorithm, less than 6% grew an MDRO. These risk estimates accounted for sex, insurance status, each hospital's UTI MDRO prevalence, and MDRO history to successfully identify low-risk patients. Providing a tailored approach likely increased clinician confidence in selecting standard-spectrum antibiotics in low-risk patients.

Influencing empiric antibiotic selection can be time and resource intensive and requires convincing data, generally relying on culture results as a rationale to deescalate extended-spectrum antibiotics.[2,11,12] In this trial, a prompt-based approach (1) shifted initial prescriptions from extended- to standard-spectrum antibiotics and (2) guided clinicians toward standard-spectrum antibiotics through guidance driven by patient-, pathogen-, and infection-specific MDRO risk when extended-spectrum antibiotics were still the initial choice. Notably, this automated approach included each hospital's prevalence of syndrome-specific MDROs, which is nationally recommended but rarely operationalized. Further, the automated approach offers a pragmatic and efficient solution to influence prescribing at order entry, reaching clinicians in the emergency department and non-ICU wards at all hours. Importantly, the automated approach allowed documentation of each patient's estimated MDRO risk within the electronic health record, which helped mitigate potential medicolegal concerns by recording what was known to clinicians at the time of prescribing. Finally, the conservative definition of less than 10% as a "low-risk" threshold for MDRO infection addressed the issue of variability in clinician-defined "risk tolerance" for warranting extended-spectrum antibiotic use.

Limitations

There are several limitations to this study. First, because the prompts were designed to conservatively identify low-risk patients who could be spared extended-spectrum antibiotics, positive urine cultures were included regardless of colony count and asymptomatic bacteriuria could not be distinguished from true UTI. Second, the trial's threshold of prompting use of standard-spectrum antibiotics for MDRO risks less than 10% may be overly conservative. A higher threshold could have improved reductions in unnecessary antibiotic use. Given the precedence of national guidance to use trimethoprim/sulfamethoxazole when local antibiotic resistance is less than 20%, a higher threshold of MDRO risk could have safely served as a more effective stewardship intervention.[19,31] Nevertheless, the majority (nearly 95%) had less

than a 10% absolute risk of MDRO UTI, suggesting that raising the threshold would have had marginal effects. Third, this trial was performed in private community hospitals; applicability to other settings is unknown. Fourth, the CPOE prompts for UTI were implemented simultaneously with pneumonia prompts; while this could have improved prompt adoption through increased attention and normalization of the prompt, it is also possible that concurrent pneumonia prompts could have decreased adoption through alert fatigue.32 Fifth, the effects of each component of the multifactorial intervention could not be estimated, although it is believed that the CPOE prompt played the dominant role because education and feedback were tied to the prompt and generally require more time to effect change.[33-35]

Conclusions

Compared with routine stewardship, CPOE prompts providing real-time recommendations for standard-spectrum antibiotics for patients with low MDRO risk coupled with feedback and education significantly reduced empiric extended-spectrum antibiotic use in noncritically ill adults admitted with UTI without changing hospital length of stay or days to ICU transfers.

Author Contributions:

Dr Gohil had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures

Dr Platt reported contracts to his academic department from GlaxoSmithKline, Pfizer, Janssen, and the US Food and Drug Administration and grants from the National Institutes of Health. Dr Huang reported conducting clinical studies in which participating nursing homes and hospital patients received contributed antiseptic product from Xttrium Laboratories and Medline Industries. No other disclosures were reported.

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The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of CDC nor HCA nor any affiliated entities.

Data Sharing Statement: See Supplement 3.

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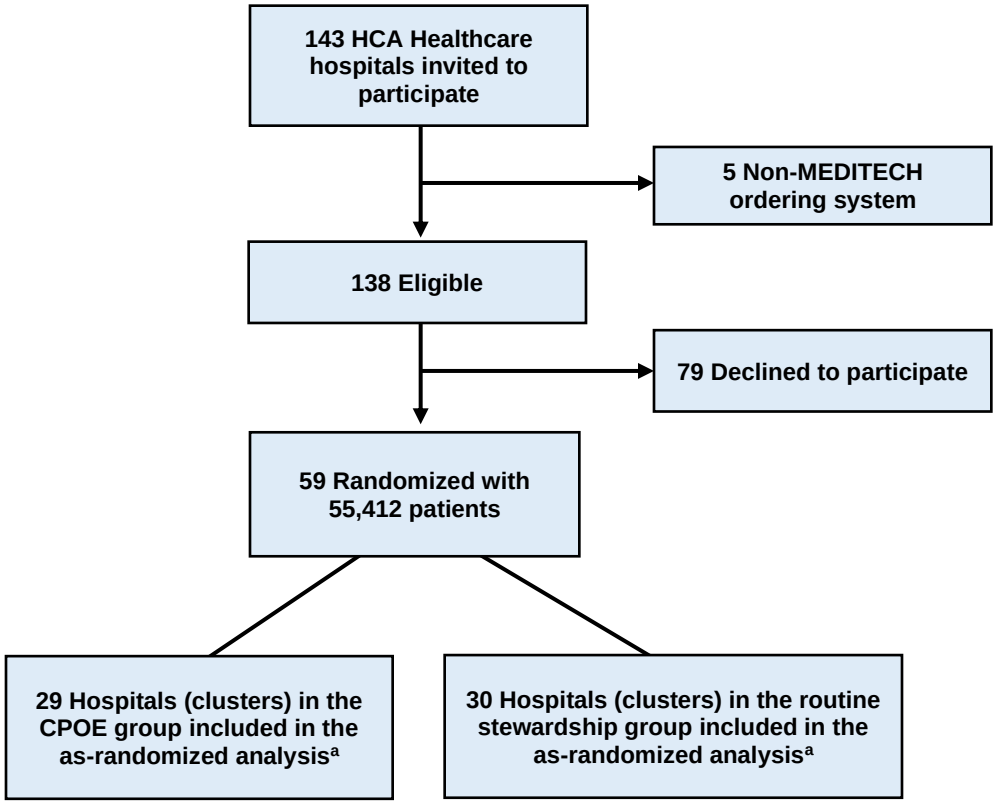
Figure 1. Hospital Recruitment and Randomization in the INSPIRE Urinary Tract Infection Trial



MEDITECH is a hospital electronic health record system. CPOE indicates computerized provider order entry and INSPIRE, Intelligent Stewardship Prompts to Improve Real-time Empiric antibiotic selection.

[a]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 2,364 (1,277-2,963) patients per hospital in the CPOE bundle group and 2,008 (1,365-3,064) in the routine stewardship group.

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 19, 2024. doi:10.1001/jama.2024.6259

Table 1: Characteristics of Patients with Urinary Tract Infection (UTI) During Baseline and Intervention Periods

	BASELINE (18 months)		INTERVENTION (15 months)	
	CPOE Bundle N (%)	Routine Stewardship N (%)	CPOE Bundle N (%)	Routine Stewardship N (%)
Patients	35,252	36,739	27,907	27,505
Mean Age (SD)	69.5 (17.9)	69.2 (18.2)	69.5 (17.8)	69.5 (17.7)
Age Category				
18-44	3,900 (11.1)	4,288 (11.7)	3,144 (11.3)	2,979 (10.8)
45-54	2,750 (7.8)	2,965 (8.1)	2,043 (7.3)	2,143 (7.8)
55-64	4,874 (13.8)	4,906 (13.4)	3,982 (14.3)	3,798 (13.8)
65-74	7,334 (20.8)	7,653 (20.8)	5,841 (20.9)	5,875 (21.4)
75-84	8,714 (24.7)	9,028 (24.6)	7,041 (25.2)	7,050 (25.6)
≥85	7,680 (21.8)	7,899 (21.5)	5,856 (21.0)	5,660 (20.6)
Male	10,739 (30.5)	10,799 (29.5)	8,793 (31.5)	8,398 (30.6)
Female	24,382 (69.2)	25,814 (70.3)	19,040 (68.2)	19,013 (69.1)
Race				
Black	4,538 (12.9)	4,123 (11.2)	3,455 (12.4)	3,314 (12.0)
White	26,891 (76.3)	26,497 (72.1)	21,352 (76.5)	19,477 (70.8)
Other[a]	1,891 (5.4)	1,193 (3.3)	1,357 (4.9)	901 (3.3)
Unknown	1,932 (5.4)	4,926 (13.4)	1,743 (6.2)	3,813 (13.9)
Hispanic/Latino Ethnicity	6,881 (19.5)	6,929 (18.9)	5,399 (19.3)	5,116 (18.6)
Insurance Type				
Medicare	25,726 (73.0)	26,611 (72.4)	20,335 (72.9)	19,985 (72.7)
Medicaid	3,463 (9.8)	3,111 (8.5)	2,703 (9.7)	2,257 (8.2)
Commercial	3,147 (8.9)	3,543 (9.6)	2,417 (8.7)	2,543 (9.2)
Other (e.g. Self-pay, Free care)	2,916 (8.3)	3,474 (9.4)	2,452 (8.8)	2,720 (9.9)
Antibiotic & Healthcare Exposures in Year Prior to Admission[b]				
Emergency Department Visit	18,157 (51.5)	17,808 (48.5)	13,997 (50.2)	13,222 (48.1)
Hospitalization	12,786 (36.3)	12,872 (35.0)	10,021 (35.9)	9,673 (35.2)
Antibiotics	10,078 (28.6)	10,186 (27.7)	7,830 (28.1)	7,705 (28.0)
Nursing Home Stay	5,721 (16.2)	5,468 (14.9)	4,221 (15.1)	3,973 (14.4)
Hours to First Antibiotics (Current Admission)[c]				
Median (IQR)	3.5 (1.5-7.5)	3.5 (1.5-7.5)	2.5 (1.0-6.0)	2.5 (1.0-6.5)
History of Pathogen Requiring Extended-Spectrum Antibiotics – Any[d]	4,364 (12.4)	4,340 (11.8)	3,592 (12.9)	3,398 (12.4)
MRSA	2,294 (6.5)	2,218 (6.0)	1,871 (6.7)	1,715 (6.2)
Pseudomonas	1,301 (3.7)	1,307 (3.6)	1,152 (4.1)	1,053 (3.8)
ESBL	1,844 (5.2)	1,826 (5.0)	1,520 (5.4)	1,480 (5.4)
VRE	333 (0.9)	400 (1.1)	281 (1.0)	235 (0.9)
CRE	314 (0.9)	327 (0.9)	214 (0.8)	224 (0.8)

Selected Elixhauser Comorbidities[f]				
Hypertension	24, 697 (70.1)	25, 670 (69.9)	20,588 (73.8)	20,477 (74.4)
Neurological Disorders	13,814 (39.2)	13,865 (37.7)	11,632 (41.7)	10,992 (40.0)
Diabetes	12, 894 (36.6)	13, 709 (37.3)	10,673 (38.2)	10,763 (39.1)
Anemias	9,688 (27.5)	10,862 (29.6)	7,980 (28.6)	8,566 (31.1)
Chronic Pulmonary Disease	8,416 (23.9)	8,873 (24.2)	6,940 (24.9)	7,025 (25.5)
Kidney Disease	8,304 (23.6)	8,793 (23.9)	6,976 (25.0)	6,955 (25.3)
Heart Failure	6,960 (19.7)	7,528 (20.5)	6,009 (21.5)	5,976 (21.7)
Obesity	5,484 (15.6)	6,593 (17.9)	4,779 (17.1)	5,250 (19.1)
Alcohol and Drug Abuse	2,413 (6.8)	2,383 (6.5)	2,115 (7.6)	1,901 (6.9)
Solid Tumor with and without Metastasis	2,388 (6.8)	2,461 (6.7)	2,029 (7.3)	2,042 (7.4)
Liver Disease	1,946 (5.5)	2,088 (5.7)	2,110 (7.6)	2,034 (7.4)
Hematologic Malignancy	575 (1.6)	536 (1.5)	470 (1.7)	401 (1.5)
Elixhauser Count[g]				
Median (IQR)	4.0 (2.0-5.0)	4.0 (2.0-5.0)	4.0 (2.0-5.0)	4.0 (2.0-6.0)

Abbreviations: CRE = carbapenem-resistant Enterobacterales; ESBL = extended-spectrum β-lactamase-producing Enterobacterales; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococci*.

[a]The numbers for sex may not equal the group totals because some patients had missing or unknown sex.

[b]Other race category included: Asian, Hawaiian, Native American, or Multiracial.

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

[d]Hours 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.

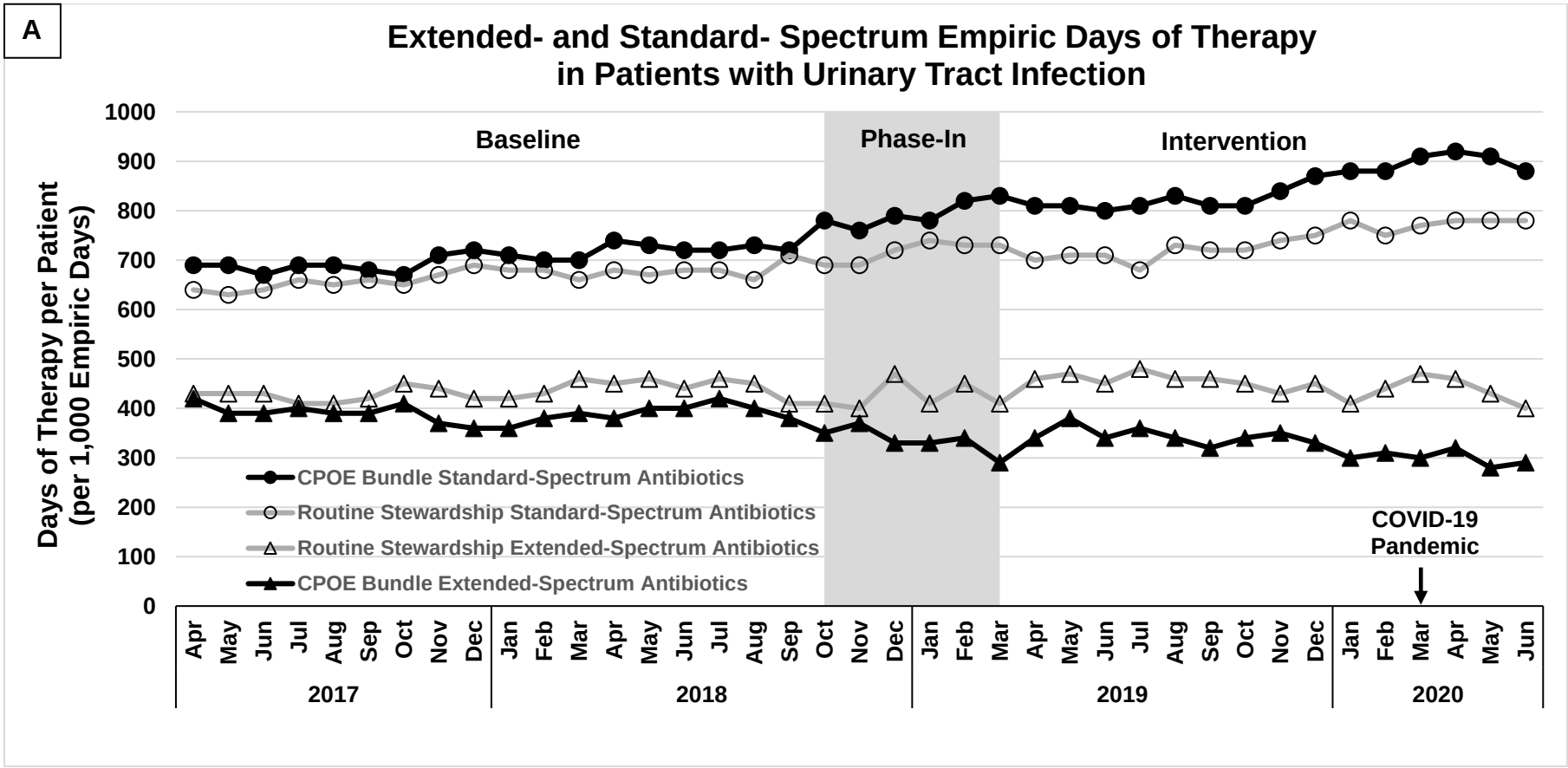
[e]History of multidrug-resistant pathogen included any prior growth of pathogen requiring extended-spectrum antibiotics, including *Pseudomonas* or multidrug-resistant organisms: MRSA, ESBL producer, and VRE. Includes MRSA polymerase chain reaction test positivity and MRSA *International Statistical Classification of Diseases and Related Health Problems, Tenth* Revision diagnosis codes.

[f]Includes carbapenem-resistant Enterobacterales, *Acinetobacter,* and *Pseudomonas*.

[g]Selected from Elixhauser comorbidity conditions (Elixhauser, Anne, et al. Medical Care, 36 (1):8-27, 1998); 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.

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

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



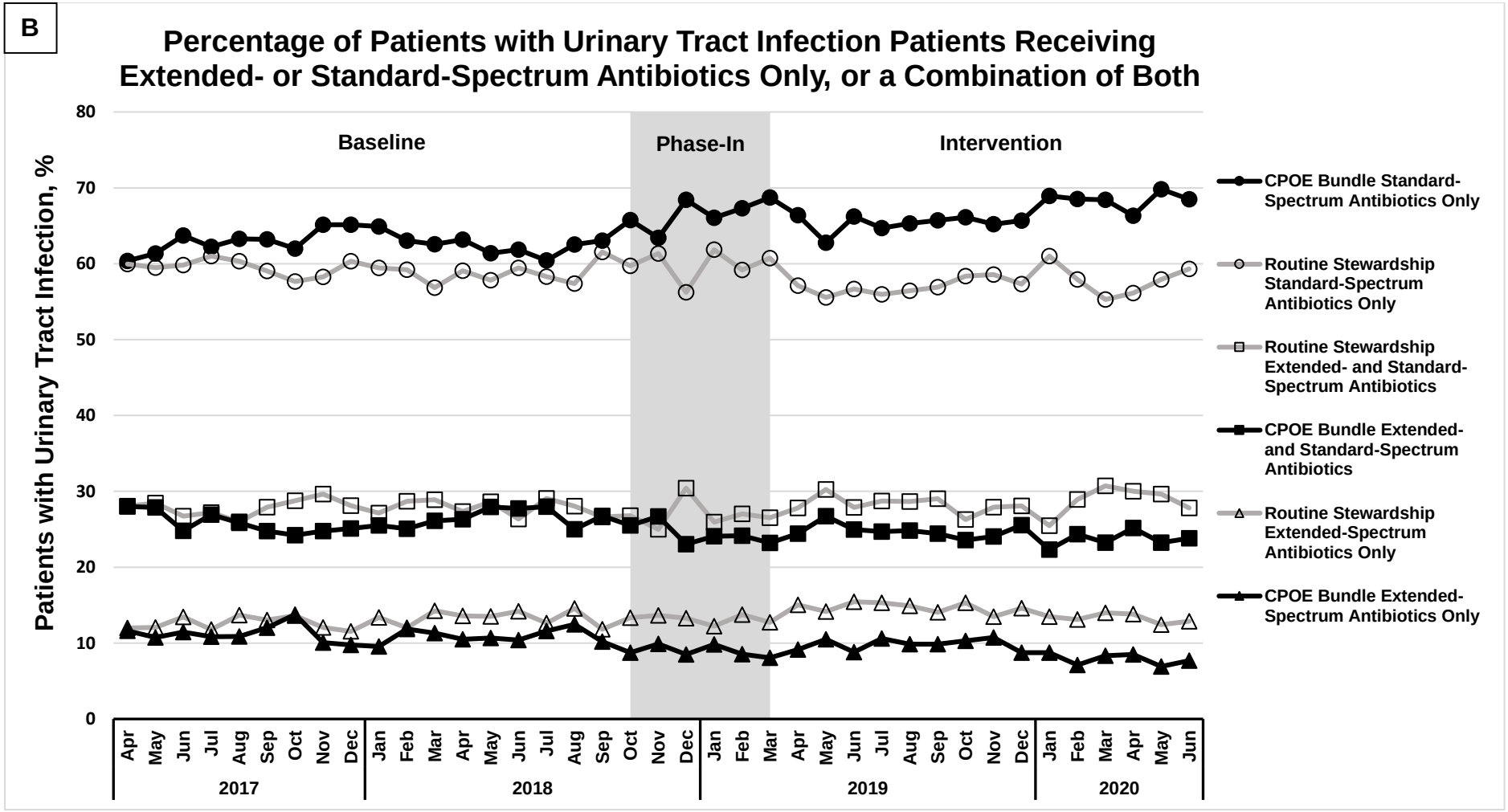


Figure 2: (A) Temporal trends in empiric (hospital days 1-3) extended- and standard-spectrum antibiotic days of therapy show sustained reductions in monthly extended-spectrum antibiotic and increases in standard-spectrum antibiotic days of therapy in the intervention group that was evident early in the phase-in period. Effects persisted despite arrival of the COVID-19 pandemic. **(B)** Temporal trends in the percentage of patients with urinary tract 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, while the percentage receiving extended-spectrum antibiotics only or combination of both decreased.

Table 2: INSPIRE Urinary Tract Infection Trial Primary, Secondary, & Safety Outcomes in the As-Randomized Analysis

Effectiveness Outcomes	CPOE Bundle			Routine Stewardship			Overall Rate Ratio Difference-in-Differences	P-value[c]
	Baseline Days-of-Therapy Raw Rate[a]	**Intervention** Days-of-Therapy Raw Rate[a]	**Rate Ratio (RR)** (95% CI)[b]	**Baseline** Days-of-Therapy Raw Rate[a]	**Intervention** Days-of-Therapy Raw Rate[a]	**Rate Ratio (RR)** (95% CI)[b]		
Primary Outcome								
Extended-spectrum days-of-therapy	392.2 (39,497/100,711)	326.0 (25,987/79,714)	0.84 (0.80-0.88)	431.1 (45,340/105,168)	446.0 (35,023/78,528)	1.02 (0.97-1.07)	0.83 (0.77-0.89)	<.001
Secondary Outcomes								
Vancomycin days-of-therapy	123.1 (12,393/100,711)	101.2 (8,071/79,714)	0.83 (0.78-0.87)	131.5 (13,829/105,168)	124.7 (9,795/78,528)	0.93 (0.88-0.98)	0.89 (0.82-0.96)	0.0021
Antipseudomonal days-of-therapy	213.0 (21,449/100,711)	178.0 (14,186/79,714)	0.83 (0.77-0.88)	248.8 (26,167/105,168)	264.8 (20,792/78,528)	1.05 (0.98-1.12)	0.79 (0.72-0.87)	<.001
Safety Outcomes	**CPOE Bundle**			**Routine Stewardship**			**Overall Rate Ratio Difference-in-Differences**	**P-value[f]**
	Baseline Mean (SD) Days-to-Event[d]	**Intervention** Mean (SD) Days-to-Event[d]	**Hazard Ratio (HR) (95% CI)[e]**	**Baseline** Mean (SD) Days-to-Event[d]	**Intervention** Mean (SD) Days-to-Event[d]	**Hazard Ratio (HR) (95% CI)[e]**		
Length-of-Stay	6.3 (6.0)	6.5 (6.6)	0.99 (0.95-1.02)	6.4 (5.8)	6.3 (5.8)	1.02 (0.98-1.05)	0.96 (0.91-1.01)	0.21
Days-to-ICU Transfers	6.6 (5.4)	7.0 (5.8)	0.96 (0.87-1.06)	6.8 (6.7)	6.6 (5.7)	0.98 (0.89-1.08)	0.98 (0.85-1.12)	0.77
Days-to-Antibiotic Escalations	5.0 (4.4)	5.4 (5.2)	1.04 (0.94-1.15)	5.1 (4.5)	5.0 (4.5)	1.01 (0.91-1.11)	1.03 (0.89-1.19)	0.66

Abbreviations: CPOE = computerized provider order entry, INSPIRE = Intelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection

[a] Days-of-therapy rate calculated per patient per empiric day (first 3 days of hospitalization) expressed with multiplier 1,000 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 hospitals and period. *P*-value assessed at 2-tailed significance set at α = 0.05 for null hypothesis that the relative rate ratio in each arm is not different for primary outcome; α=0.025 for secondary outcomes to account for multiple comparisons. [d]Days-to-event is defined as mean days calculated within a single admission. Days to intensive care unit (ICU) transfer is the days from admission to date of first ICU transfer among those requiring transfer on hospital day 3 through discharge. Days-to-antibiotic escalation is the days from admission to date of first change in antibiotics from standard-spectrum to extended-spectrum among those who were started on standard-spectrum in the empiric period (first 3 days of hospitalization). Length of stay is calculated as days from admission to date of hospital discharge among those discharged alive. [e]Hazard ratios represent group-specific comparisons of intervention to baseline. [f]Results are based on unadjusted proportional hazards models that accounted for clustering within hospitals and period. *P*-value for the difference in hazard ratio between periods.

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

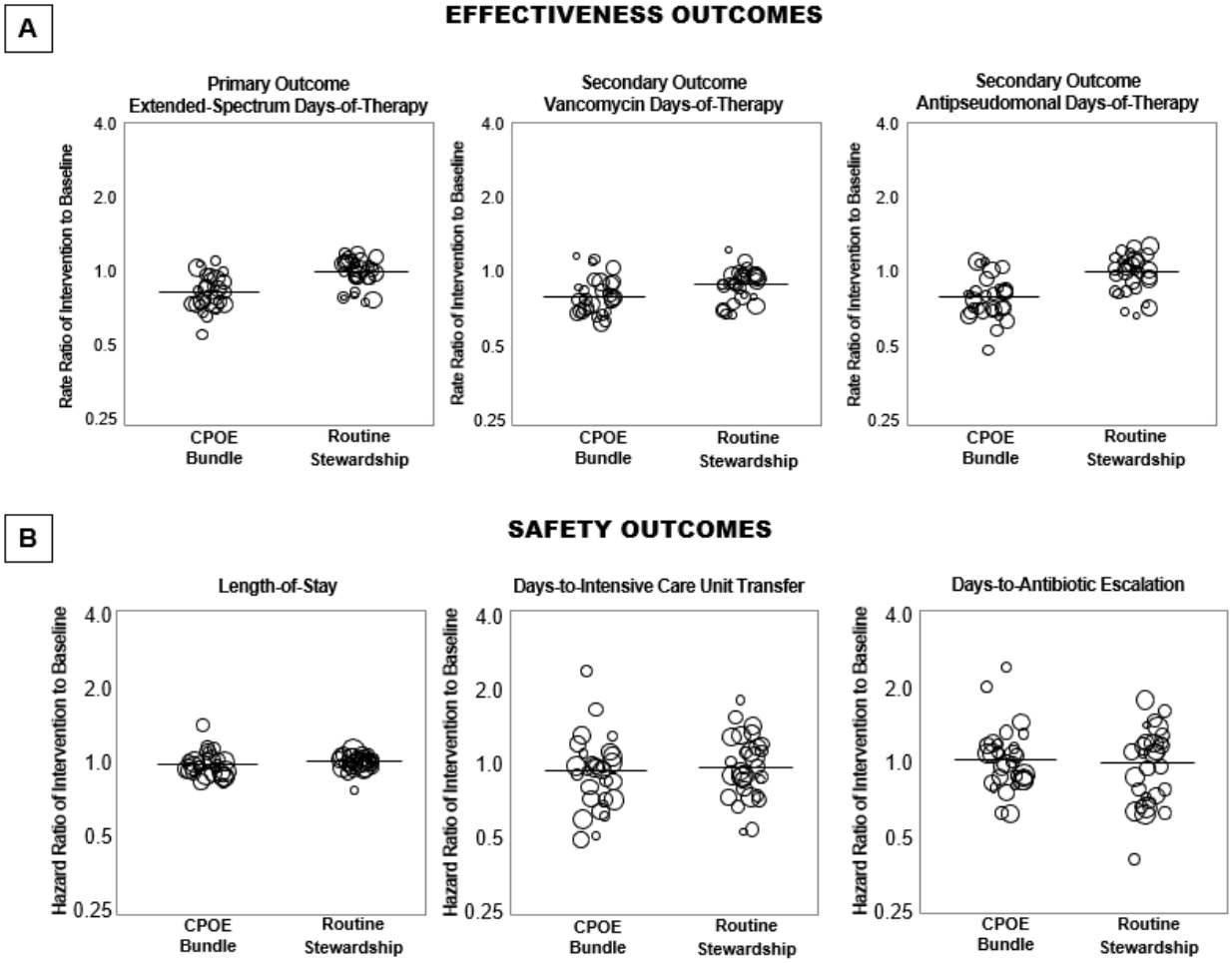

Figure 3: (A) Shown are group-specific relative rate ratios of intervention to baseline periods (indicated by horizontal lines) for the primary and secondary outcomes. Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within hospitals and period. Bubble plots of raw rate ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown. The area of the bubble indicates the relative number of patients contributing data to the trial. **(B)** Shown are group-specific hazard ratios of intervention to baseline periods (indicated by horizontal lines) for safety outcomes. Results are based on proportional hazards models that accounted for clustering within hospitals and period. Bubble plots of raw hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown. The area of the bubble indicates the relative number of patients contributing data to the trial.