

# Leveraging stewardship to promote ceftriaxone use in severe infections with low- and no-risk AmpC Enterobacterales

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**ABSTRACT** AmpC  $\beta$ -lactamases are associated with development of ceftriaxone resistance despite initial *in vitro* susceptibility, but the risk of AmpC derepression is not equal among Enterobacterales. The purpose of this study was to evaluate the impact of an AmpC stewardship intervention on the definitive treatment of low- and no-risk Enterobacterales. This was an IRB-approved, single pre-test, post-test quasi-experiment at a 5-hospital system. An AmpC stewardship intervention was implemented in July 2022 and included prescriber education, the removal of microbiology comments indicating potential for ceftriaxone resistance on therapy, and the modification of a blood PCR comment for *Serratia marcescens* to recommend ceftriaxone. Adults  $\geq 18$  years pre-intervention (July 2021 to December 2021) and post-intervention (July 2022 to December 2022) who received  $\geq 72$  hours of inpatient definitive therapy and had non-urine cultures growing low- and no-risk organisms (*S. marcescens*, *Providencia* spp., *Citrobacter koseri*, *Citrobacter amalonaticus*, or *Morganella morganii*) were included. The primary endpoint was definitive treatment with ceftriaxone. A total of 224 patients were included; 115 (51%) in pre-intervention and 109 (49%) in post-intervention. Definitive ceftriaxone therapy was prescribed more frequently after intervention [6 (5%) vs 72 (66%),  $P < 0.001$ ]. After adjustment for critical illness, patients in the post-group were more likely to receive definitive ceftriaxone (adjOR, 34.7; 95% CI, 13.9–86.6). The proportion of patients requiring retreatment was 18 (15%) and 11 (10%) for pre- and post-intervention patients ( $P = 0.22$ ), and ceftriaxone resistance within 30 days occurred in 5 (4%) and 2 (2%) patients in the pre- and post-group ( $P = 0.45$ ). An antimicrobial stewardship intervention was associated with increased ceftriaxone prescribing and similar patient outcomes for low- and no-risk AmpC Enterobacterales.

**KEYWORDS** antimicrobial stewardship, AmpC, Enterobacterales, *Serratia marcescens*

AmpC  $\beta$ -lactamases are clinically significant enzymes associated with the development of ceftriaxone resistance on therapy, but the risk of AmpC derepression is not equal among all Enterobacterales species (1). Previously, organisms at high risk of AmpC derepression were denoted by mnemonics SPACE, SPICE, or ESCPM, which included all *Citrobacter* spp., *Serratia marcescens*, *Morganella* spp., and *Providencia* spp. (2, 3). These organisms were grouped together by their ability to harbor the *ampC* gene and also by the hallmark phenotypic pattern of appearing susceptible to third-generation cephalosporins if AmpC production is not derepressed (1, 3). However, the risk of AmpC derepression is significantly lower for some of these organisms (1, 4), which represents an opportunity to promote the use of ceftriaxone as an optimal therapy.

*Enterobacter cloacae*, *Klebsiella aerogenes* (formally *Enterobacter aerogenes*), *Citrobacter freundii*, and *Hafnia alvei* pose a moderate to high risk of AmpC derepression with a  $3 \times 10^{-8}$  mean mutation rate (1, 2, 4). As such, these organisms are more prone to AmpC derepression and corresponding resistance to third-generation cephalosporins; clinical reports suggest the emergence of resistance after exposure to these agents in

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approximately 8% to 40% of infections (1). In comparison, the mean mutation rates observed in *Providencia* spp., *Serratia* spp., and *Morganella morganii* are reported to be significantly lower (1, 2, 4, 5). As such, these species present with a significantly decreased risk than previously believed and demonstrate a ~10-fold lower risk of AmpC expression when compared to *E. cloacae* or *C. freundii* (4, 5). These data suggest that “low risk” species can be treated according to susceptibility patterns with third-generation cephalosporins (5).

To help guide optimal antibiotic selection for infections caused by Enterobacterales at varying levels of risk for clinically significant AmpC production, our institution implemented an AmpC stewardship intervention to help guide antibiotic prescribing for low- and no-risk AmpC organisms to ceftriaxone and away from previously recommended broad-spectrum therapies, such as cefepime, ertapenem, or meropenem. The purpose of this study was to evaluate the impact of a multi-modal AmpC stewardship intervention on the selection of optimal definitive therapy (i.e., ceftriaxone) for infections caused by Enterobacterales with low- and no-risk of clinically significant AmpC derepression.

## MATERIALS AND METHODS

This was an IRB-approved, single pre-test, post-test quasi-experiment with a non-equivalent dependent variable conducted at Henry Ford Health (Detroit, MI, USA), a five-hospital health system located in southeast Michigan. The study evaluated the impact of a stewardship intervention on the definitive antibiotic selection and outcomes of patients infected with low- and no-risk AmpC organisms. The study was conducted over two periods: a pre-AmpC stewardship intervention period (July 2021 to December 2021) and a post-AmpC stewardship intervention period (July 2022 to December 2022). Patients were included if they were adults  $\geq 18$  years of age; hospitalized with an infection caused by *Citrobacter koseri*, *Citrobacter amalonaticus* (no AmpC), *S. marcescens*, *M. morganii*, or *Providencia* spp. (low risk); and received definitive inpatient antimicrobial therapy with ceftriaxone, cefepime, or a carbapenem for  $\geq 72$  hours. Infections of a sterile site (i.e., blood, bone, central nervous system, pleural, peritoneal, organ, or organ space) or infections that met criteria for clinical infection for non-sterile sites (i.e., acute bacterial skin and skin structure, lower respiratory tract) were included. Patients were excluded if they had non-bacteremic urine isolates, received inactive empiric therapy, and were infected with a ceftriaxone-resistant organism or an organism with moderate to high risk of AmpC derepression, Enterobacterales-resistant to cefepime or carbapenems, or other organisms out of scope of the included organisms above. The primary outcome of this study was the proportion of patients who received definitive ceftriaxone therapy for low- and no-risk AmpC-harboring Enterobacterales.

### Study intervention

In 2022, a multi-modal AmpC stewardship intervention was performed at Henry Ford Health that consisted of three components: (i) elimination of an existing AmpC microbiology comment for the following organisms: *C. koseri*, *C. amalonaticus*, *S. marcescens*, *M. morganii*, or *Providencia* spp., which stated, “This organism is known to harbor an inducible AmpC  $\beta$ -lactamase and may develop resistance during prolonged therapy with third-generation cephalosporins such as cefoxitin [sic], ceftriaxone, cefotaxime. Therefore, isolates that are susceptible in vitro may develop resistance following 3 to 4 days of therapy...” (22 March 2022) (Fig. S1); (ii) modification of a blood PCR comment for *S. marcescens* recommending ceftriaxone as the treatment of choice (29 June 2022) (Fig. S2); and (iii) education that was provided in person and electronically for pharmacists and prescribers throughout quarter 2 of 2022 and utilized a one-page guidance document (Fig. S3).

## Key definitions

AmpC stable  $\beta$ -lactam was defined as cefepime or carbapenem (i.e., meropenem, ertapenem). Pneumonia was defined as having radiographic evidence with at least two or more of the following criteria (6): new/increased cough, shortness of breath, sputum production, chills, rales/crackles/rhonchi, tachypnea, leukocytosis or leukopenia, temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , or hypoxemia. Acute bacterial skin and skin structure infections (ABSSSI) were defined as bacterial infection of skin and associated tissues (7). Infective endocarditis was defined as a positive blood culture in addition to infectious diseases consultant physician diagnosis within the electronic medical record. Bone and joint infection was defined as a positive bone culture or biopsy in addition to infectious diseases consultation diagnosis within the electronic medical record.

Definitive therapy was defined as antibiotics prescribed after organism identification. *Clostridioides difficile* infection was defined as a positive *C. difficile* toxin test or a positive *C. difficile* PCR test accompanied by three or more loose stools within a 24-hour period for up to 30 days after definitive therapy (8). All-cause, 30-day mortality was defined as mortality from any cause resulting up to 30 days from hospital discharge. Retreatment was defined as treatment for the same organism at any culture site within 30 days of initial definitive therapy. Immunocompromised status was defined as an active solid tumor or hematologic malignancy; HIV with a CD4 cell count  $<200$ , active treatment with prednisone 20 mg for more than 14 days, and/or active treatment with transplant immunosuppressant medications or biologics. Hospital length of stay was defined as the duration, in days, from draw time of positive culture for low- and no-risk Enterobacterales to discharge or death. A non-equivalent dependent variable of switch to oral antibiotics was utilized and defined as oral, step-down therapy after initial definitive therapy to ciprofloxacin or moxifloxacin, or trimethoprim/sulfamethoxazole.

## Data collection

Patients were identified for screening using Microsoft SQL Server (Microsoft, Redmond, WA, USA) queries based on organism type and culture location site. After patients were screened for inclusion, patient data were extracted from the electronic health record through manual chart review and collected using a standardized electronic case report form. The data collected included patient demographics, comorbid conditions, infection characteristics (i.e., bacterial isolates, severity of illness, infection type, and site of infection), and treatment characteristics (i.e., empiric and definitive antibiotic selection, dose, and duration).

## Statistical analysis

The study was powered to detect an increase in ceftriaxone definitive therapy, assuming that 5% of patients received ceftriaxone definitive therapy in the pre-intervention group and 30% in the post-intervention group. This assumption was made based on historical treatment practices of high-risk AmpC organisms and an expected difference of at least 25% in practice change (1–3). Using a two-sided alpha of 0.05 and a power of 80%, a total of 35 patients were required for the pre-intervention group, and 35 patients were required for the post-intervention group. The population was enriched to a total of 240 patients to evaluate any potential meaningful differences in clinical outcomes among patients who received definitive ceftriaxone or cefepime/carbapenem therapy. An *a priori* subgroup analysis was planned for patients with bloodstream infections.

Continuous data were reported as the median and interquartile range (IQR). Categorical data were described as a frequency and percentage and compared using the Chi-square or Fisher's exact test. A multivariable logistic regression model was constructed to identify variables independently associated with definitive ceftriaxone therapy. Variables from bivariate analysis with a *P*-value of  $<0.2$  or with clinical rationale were included in a backward, step-wise regression model. A Hosmer-Lemeshow test was used to assess goodness-of-fit. The non-equivalent dependent variable of oral switch therapy was assessed using bivariate statistics to assess maturation.

## RESULTS

### Patient and infection characteristics

A total of 224 patients were included; 115 (51%) patients in the pre-intervention group and 109 (49%) patients in the post-intervention group. Baseline characteristics of the pre- and post-group patients are described in Table 1. The population was primarily white/Caucasian (148, 66%) and men (148, 66%), with a median (IQR) age of 66 (58–73) years. The most common comorbidities were congestive heart failure (72, 32%) and moderate-to-severe chronic kidney disease (71, 32%); there was a higher proportion of patients with COVID-19 infection in the pre-intervention group when compared to the post-intervention group [21 (18%) vs 5 (5%),  $P < 0.001$ ]. Of the entire cohort, the proportion of patients infected with low-risk and no-risk AmpC was 190 (85%) and 33 (15%), respectively; one patient was co-infected with a low-risk and no-risk organism.

Infection and treatment characteristics comparing the pre- and post-group are reported in Table 2. The most common organism identified in either group was *S. marcescens* (129, 57%), followed by *M. morgani* (40, 18%), and other organisms (53, 24%). The three most common sources of infection were pneumonia (90, 40%), bone and joint (39, 17%), and ABSSSI (38, 17%). There were 79 (35%) patients with concurrent bacteremia.

### Primary outcome

Definitive ceftriaxone therapy was prescribed in 6 (5%) patients in the pre-intervention group and 72 (66%) patients in the post-intervention group ( $P < 0.001$ ). The median (IQR) total duration of therapy for pre- and post-intervention groups were 9 (7–17) days vs 10 (7–18) days,  $P = 0.46$  (Table 2). The results of the bivariate analysis and clinical rationale dictated which variables were included into a multivariable regression model: intensive care unit admission and patients in the post-intervention group. Other variables were excluded from the model due to unmet statistical criteria or due to co-variability. In the final model, patients in the post-intervention group were more likely to receive definitive ceftriaxone therapy (adjOR, 34.7; 95% CI, 13.9–86.6) (Table 3).

A total of 18 (15%) patients in the pre-intervention group and 11 (10%) patients in the post-intervention group required retreatment for infection with the same organism ( $P = 0.22$ ). Ceftriaxone resistance within 30 days after initial treatment was observed in 5 (4%) and 2 (2%) patients in the pre- and post-intervention groups, respectively ( $P = 0.45$ ). The

**TABLE 1** Baseline characteristics of patients infected with low- and no-risk AmpC organisms<sup>a</sup>

| N (%) or median (IQR)                                    | Pre-intervention (N = 115) | Post-intervention (N = 109) | P-value |
|--|----------------------------|-----------------------------|---------|
| Age, years   | 66 (58–74)                 | 67 (57–73)                  | 0.66    |
| Male   | 78 (68%)                   | 70 (64%)                    | 0.57    |
| Race   |                            |                             |         |
| White/Caucasian  | 70 (61%)                   | 56 (51%)                    | 0.15    |
| Black/African American                                   | 33 (29%)                   | 42 (39%)                    | 0.12    |
| Other Race   | 12 (10%)                   | 11 (10%)                    | 0.93    |
| Comorbidities  |                            |                             |         |
| CHF  | 39 (34%)                   | 33 (30%)                    | 0.56    |
| CKD (moderate–severe)                                    | 33 (29%)                   | 38 (35%)                    | 0.32    |
| Diabetes mellitus  | 54 (46%)                   | 45 (41%)                    | 0.47    |
| COPD   | 27 (24%)                   | 30 (28%)                    | 0.49    |
| PVD  | 22 (19%)                   | 35 (32%)                    | 0.026   |
| Charlson Comorbidity Index score                         | 5 (3–7)                    | 5 (3–8)                     | 0.20    |
| Any immunosuppression                                    | 26 (23%)                   | 19 (17%)                    | 0.33    |
| Intensive care unit admission at time of hospitalization | 66 (57%)                   | 51 (47%)                    | 0.11    |
| COVID-19 infection                                       | 21 (18%)                   | 5 (5%)                      | 0.001   |

<sup>a</sup>CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; COVID-19, coronavirus disease of 2019.

**TABLE 2** Infection and treatment characteristics of patients infected with low- and no-risk AmpC organisms<sup>b</sup>

| N (%) or median (IQR)   | Pre-intervention (N = 115) | Post-intervention (N = 109) | P-value |
|---|----------------------------|-----------------------------|---------|
| Bacterial isolate <sup>a</sup>  |                            |                             |         |
| <i>Serratia marcescens</i>  | 67 (58%)                   | 64 (59%)                    | 0.95    |
| <i>Morganella morganii</i>  | 19 (17%)                   | 24 (22%)                    | 0.30    |
| <i>Citrobacter koseri</i>   | 21 (18%)                   | 12 (11%)                    | 0.13    |
| <i>Providencia</i> spp.   | 9 (8%)                     | 11 (10%)                    | 0.55    |
| <i>Citrobacter amalonaticus</i>   | 0 (0%)                     | 1 (1%)                      | 1.0     |
| Infection source  |                            |                             |         |
| Pneumonia   | 51 (44%)                   | 39 (36%)                    | 0.19    |
| Bone and joint  | 18 (16%)                   | 21 (19%)                    | 0.48    |
| ABSSSI  | 19 (17%)                   | 19 (17%)                    | 0.86    |
| Intra-abdominal   | 14 (12%)                   | 11 (10%)                    | 0.62    |
| UTI with bacteremia   | 8 (7%)                     | 12 (11%)                    | 0.29    |
| Infective endocarditis  | 2 (2%)                     | 2 (2%)                      | 1.0     |
| Bacteremia (unclear source)   | 0                          | 2 (2%)                      | 0.24    |
| Other   | 3 (3%)                     | 3 (2%)                      | 1.0     |
| Any bloodstream infection   | 45 (39%)                   | 34 (31%)                    | 0.21    |
| Definitive intravenous antibiotic                                       |                            |                             |         |
| Ceftriaxone   | 6 (5%)                     | 72 (66%)                    | <0.001  |
| Cefepime  | 71 (62%)                   | 27 (25%)                    | <0.001  |
| Ertapenem   | 30 (26%)                   | 8 (7%)                      | <0.001  |
| Meropenem   | 8 (7%)                     | 2 (2%)                      | 0.10    |
| Switch to oral antibiotics  | 33 (29%)                   | 33 (30%)                    |         |
| Ciprofloxacin   | 18 (55%)                   | 10 (30%)                    | 0.14    |
| TMP/SMX   | 14 (42%)                   | 17 (52%)                    | 0.46    |
| Other   | 1 (3%)                     | 6 (18%)                     | 0.060   |
| Duration of therapy, days   | 9 (7–17)                   | 10 (7–18)                   | 0.46    |
| <i>C. difficile</i> infection within 30 days after antibiotic treatment | 3 (3%)                     | 3 (3%)                      | 1.0     |
| Document ceftriaxone resistance within 30 days of treatment             | 5 (4%)                     | 2 (2%)                      | 0.45    |
| Required antibiotic retreatment   | 18 (15%)                   | 11 (10%)                    | 0.22    |

<sup>a</sup>Four patients had polymicrobial BSI with a low-risk AmpC-producing Enterobacterales.<sup>b</sup>ABSSSI, acute bacterial skin and skin structure infections; UTI, urinary tract infection; TMP/SMX, trimethoprim/sulfamethoxazole.

median (IQR) length of stay was 10 (5–15) days in the pre-group and 10 (6–16) days in the post-group ( $P = 0.4$ ). All-cause, 30-day mortality was 29 (25%) in the pre-group and 15 (14%) in the post-group ( $P = 0.031$ ). Three (3%) patients in the pre-intervention group and 3 (3%) in the post-intervention group developed *C. difficile* within 30 days of initial antibiotic treatment ( $P = 1.0$ ).

**TABLE 3** Variables associated with definitive ceftriaxone therapy<sup>a</sup>

| Variable, N (%)                  | Definitive ceftriaxone (N = 78) | Definitive AmpC stable (N = 146) | UnAdjOR (95% CI) | P-value | AdjOR (95% CI)   | P-value |
|----------------------------------|---------------------------------|----------------------------------|------------------|---------|------------------|---------|
| Post-intervention group          | 72 (92%)                        | 37 (25%)                         | 35.4 (14.2–88.0) | <0.001  | 34.7 (13.9–86.6) | <0.001  |
| Intensive care unit admission    | 35 (45%)                        | 82 (56%)                         | 0.64 (0.4–1.1)   | 0.12    | 0.75 (0.37–1.5)  | 0.44    |
| Stroke/Transient Ischemic Attack | 16 (21%)                        | 14 (10%)                         | 2.4 (1.1–5.3)    | 0.02    | Not tested       | –       |
| Peripheral vascular disease      | 26 (33%)                        | 31 (21%)                         | 1.9 (1.0–3.4)    | 0.048   | Not tested       | –       |
| Charlson Score $\geq 5$          | 51 (65%)                        | 77 (53%)                         | 1.7 (0.96–2.9)   | 0.068   | Not tested       | –       |
| Bloodstream infection            | 30 (39%)                        | 49 (34%)                         | 1.24 (0.70–2.2)  | 0.47    | Not tested       | –       |
| Infectious diseases consult      | 51 (65%)                        | 113 (77%)                        | 0.55 (0.30–1.0)  | 0.053   | Not tested       | –       |
| COVID-19 infection               | 5 (6%)                          | 21 (14%)                         | 0.41 (0.15–1.1)  | 0.08    | Not tested       | –       |

<sup>a</sup>Hosmer-Lemeshow test result (method used: backward, likelihood ratio),  $P = 0.999$ . COVID-19, coronavirus disease of 2019.

## Subgroup analysis of bloodstream infections

A subgroup analysis of patients with bloodstream infections (79/224 patients, 35%) was performed to evaluate for any potential differences in primary analysis results: 45 patients pre-intervention and 34 patients post-intervention. The overall median (IQR) duration of antibiotic treatment for patients with bloodstream infections was 10 (7–18) days [11 (7–21) days pre-intervention vs 10 (7–14) post-intervention,  $P = 0.731$ ]. The most common organism identified from blood was *S. marcescens* [25 (56%) pre-intervention vs 19 (56%) post-intervention,  $P = 0.98$ ], followed by *M. morganii* [11 (24%) vs 7 (21%),  $P = 0.69$ ], and other organisms [9 (20%) pre-intervention vs 9 (27%) post-intervention,  $P = 0.50$ ]; one patient had bacteremia with *S. marcescens* and *Providencia* spp. Among the bloodstream infection subgroup, cefepime was the most frequently used definitive antibiotic in the pre-intervention group [25 (56%) pre-intervention vs 6 (18%) post-intervention,  $P < 0.001$ ], and ceftriaxone was most widely prescribed in the post-intervention group [4 (9%) pre-intervention vs 26 (77%) post-intervention,  $P < 0.001$ ]. In regard to patient outcomes, 6 (13%) patients in the pre-intervention group and 5 (15%) patients in the post-intervention group required 30 day-retreatment ( $P = 1.0$ ). The median (IQR) length of stay was 9 (6–18) days in the pre-intervention group vs 8 (4–13) days in the post-intervention group ( $P = 0.23$ ), respectively.

When comparing patients with bloodstream infections based on definitive therapy, retreatment was required in 4 (13%) patients who received ceftriaxone and 7 (14%) of patients who received cefepime/carbapenem definitive therapy ( $P = 1.0$ ). The median (IQR) length of stay was 9 (5–13) days for patients treated with ceftriaxone and 8 (5–19) days for the cefepime/carbapenem group ( $P = 0.71$ ).

## DISCUSSION

In this single pre-test, post-test quasi-experiment, an antimicrobial stewardship intervention that leveraged microbiology comments and prescriber education resulted in a significantly higher proportion of patients receiving definitive ceftriaxone for low- and no-risk AmpC Enterobacterales. The development of ceftriaxone resistance within 30 days of treatment was infrequent. After adjustment for intensive care unit admissions, patients in the post-intervention group were 35 times more likely to receive definitive ceftriaxone therapy. There were no meaningful outcome differences between the pre- and post-intervention groups when evaluating 30 days retreatment or length of stay within the overall study population or a subgroup of patients with bloodstream infections. With the shift to narrower spectrum treatment for these organisms consistent with the Infectious Diseases Society of America guidance on the treatment of AmpC-producing Enterobacterales (1), this study helped assess ceftriaxone prescribing after a stewardship nudge in the form of an interpretative microbiology comment for *S. marcescens*, removal of AmpC comments for low-risk organisms, and education. For low-risk AmpC-harboring Enterobacterales such as *S. marcescens*, *M. morganii*, and *Providencia* spp., the secondary outcomes of this study suggest that treatment with a third-generation cephalosporin is safe and effective, but future comparative studies are warranted.

There are few data that describe the treatment and outcomes of patients specifically with low-risk AmpC Enterobacterales. A retrospective cohort study conducted by Maillard et al. compared 30-day all-cause mortality in patients who received third-generation cephalosporins or piperacillin ± tazobactam, cefepime, or carbapenems as definitive therapy for pneumonia or bloodstream infections caused by wild-type AmpC-harboring Enterobacterales (9). A total of 575 patients were enrolled in the primary analysis: 302 (52%) patients with pneumonia and 273 (48%) patients with bloodstream infections. The most frequently isolated organisms were *E. cloacae* ( $n = 240$ , 42%), *S. marcescens* ( $n = 111$ , 19%), *K. aerogenes* ( $n = 106$ , 18%), and *M. morganii* ( $n = 46$ , 8%) (9). The study found similar 30-day, all-cause mortality between the third-generation cephalosporin group and the cefepime or carbapenem reference group (adjusted hazard

ratio, 0.86; 95% CI, 0.57–1.31) (9). Of note, these results study did not distinguish between high and low- and no-risk of AmpC derepression among Enterobacterales (9).

These results of the present study also support the use of microbiology nudges as an efficient antimicrobial stewardship strategy to promote appropriate prescribing. A 2019 review by Langford et al. demonstrated the utility of microbiology nudging to influence decision making in antimicrobial prescribing (10). By strategically reporting microbiology results while maintaining prescriber autonomy, nudging strategies within the electronic medical record can be effective in improving antimicrobial use (10). The majority of studies reviewed were performed in acute-care settings and utilized strategies to alter default antibiotic choices on microbiology reports. Eighty percent of studies reported an overall benefit in antimicrobial use outcomes associated with these nudges (10). The antimicrobial stewardship pharmacists in our institution do not perform routine prospective audit and feedback on non-bloodstream isolates, so we hypothesize that the microbiology nudge combined with education was essential to the success of this effort. The results of the present study support recent efforts of our antimicrobial stewardship program in leveraging microbiology nudges to “work smarter, not harder,” with positive and sustained impact (11–13). Interestingly, the median duration of therapy was greater than 7 days in the pre- and post-groups, as well as the subgroup of bloodstream infections, and may be reflective of a high acuity of illness within this population. This area is an additional focus of our antimicrobial stewardship program to promote shorter antibiotic durations.

Due to the quasi-experimental nature of this study and the anticipated extreme pre-intervention values of cefepime and carbapenem prescribing, regression to the mean was an expected limitation. Maturation may also pose a limitation, as the Infectious Diseases Society of America guidance on the treatment of AmpC-producing Enterobacterales may guide prescribers toward definitive ceftriaxone therapy in lieu of the study intervention. To mitigate maturation, a non-equivalent dependent variable of oral antibiotic switch was utilized. Pre- and post-intervention groups were statistically similar, both demonstrating ~30% oral switch, which strengthens the case for causality. Overall, the large magnitude of change in prescribing observed is unlikely to be due only to maturation and regression to the mean. This study used strict definitions for pneumonia and skin and structure infections; however, it is possible that some patients were colonized. This study was not powered to detect a difference in all-cause, 30-day mortality between groups, although no difference was observed. Clinical patient outcomes (i.e., mortality imbalance between groups) could have been confounded by COVID-19 infection, other severity of illness measures, and/or optimal antibiotic dosing; these components should be more properly accounted for in a subsequent study evaluating bloodstream infections. This study included *C. koseri* and *C. amalonaticus*, which do not possess AmpC; however, the previous standard of care at our institution was an oversimplified approach where all *Citrobacter* spp. had an AmpC microbiology comment appended that propagated unnecessary cefepime/carbapenem use. While study results suggest that this stewardship intervention is effective in promoting narrower spectrum antibiotic use, the value of de-escalation strategies is relatively unproven when compared to those targeting antibiotic discontinuation or optimal duration of therapy. Nonetheless, de-escalation or maintenance of narrower spectrum empiric therapy is a common sense antimicrobial stewardship strategy. Future efforts should evaluate an adequately powered population of bloodstream infection caused by only low-risk AmpC Enterobacterales to provide more robust outcome data.

An antimicrobial stewardship intervention was successful in influencing definitive ceftriaxone prescribing for infections due to low- and no-risk AmpC Enterobacterales. Significantly more patients received ceftriaxone definitive therapy post-intervention, and patient outcomes were comparable with ceftriaxone and AmpC-stable  $\beta$ -lactam therapy. Antibiotic stewardship nudges provided as microbiology interpretative comments are a valuable and efficient approach to influence prescribing.

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## ADDITIONAL FILES

The following material is available [online](#).

### Supplemental Material

**Supplemental Figures 1 - 3 (AAC00826-23-s0001.docx).** Supplemental figures describing a low- and no-risk AmpC stewardship intervention and education.

## REFERENCES

1. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. 2022. Infectious diseases society of America guidance on the treatment of AmpC  $\beta$ -lactamase-producing enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections. Clin Infect Dis 74:2089–2114. <https://doi.org/10.1093/cid/ciab1013>
2. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ, Antibacterial Resistance Leadership Group. 2019. A primer on AmpC  $\beta$ -lactamases: necessary knowledge for an increasingly multidrug-resistant world. Clin Infect Dis 69:1446–1455. <https://doi.org/10.1093/cid/ciz173>
3. Tamma PD, Girdwood SCT, Gopaul R, Tekle T, Roberts AA, Harris AD, Cosgrove SE, Carroll KC. 2013. The use of cefepime for treating AmpC  $\beta$ -lactamase-producing enterobacteriaceae. Clin Infect Dis 57:781–788. <https://doi.org/10.1093/cid/cit395>
4. Kohlmann R, Bähr T, Gatermann SG. 2018. Species-specific mutation rates for AmpC derepression in enterobacterales with chromosomally encoded inducible AmpC  $\beta$ -lactamase. J Antimicrob Chemother 73:1530–1536. <https://doi.org/10.1093/jac/dky084>
5. Mizrahi A, Delerue T, Morel H, Le Monnier A, Carbonnelle E, Pilimis B, Zahar JR, on behalf the Saint-Joseph/Avicenna Study Group. 2020. Infections caused by naturally AmpC-producing enterobacteriaceae: can we use third-generation cephalosporins? A narrative review. Int J Antimicrob Agents 55:105834. <https://doi.org/10.1016/j.ijantimicag.2019.10.015>
6. Michigan Hospital Medicine Safety Consortium. n.d. Inappropriate diagnosis of community-acquired pneumonia (CAP) in hospitalized medical patients. Available from: <https://mi-hms.org/inappropriate->

- diagnosis-community-acquired-pneumonia-cap-hospitalized-medical-patients
7. Shah M, Shah HD. 2011. Acute bacterial skin and skin structure infections: current perspective. *Indian J Dermatol* 56:510–512. <https://doi.org/10.4103/0019-5154.87134>
  8. Bagdasarian N, Rao K, Malani PN. 2015. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. *JAMA* 313:398–408. <https://doi.org/10.1001/jama.2014.17103>
  9. Maillard A, Delory T, Bernier J, Villa A, Chaibi K, Escout L, Contejean A, Bercot B, Robert J, El Alaoui F, Tankovic J, Poupet H, Cuzon G, Lafaurie M, Sargers L, Joseph A, Paccoud O, Molina JM, Bleibtreu A, Treatment of AmpC-producing Enterobacterales Study Group. 2023. Effectiveness of third-generation cephalosporins or piperacillin compared with cefepime or carbapenems for severe infections caused by wild-type AmpC  $\beta$ -lactamase-producing enterobacterales: a multi-centre retrospective propensity-weighted study. *Int J Antimicrob Agents* 62:106809. <https://doi.org/10.1016/j.ijantimicag.2023.106809>
  10. Langford BJ, Leung E, Haj R, McIntyre M, Taggart LR, Brown KA, Downing M, Matukas LM. 2019. Nudging in microbiology laboratory evaluation (NIMBLE): a scoping review. *Infect Control Hosp Epidemiol* 40:1400–1406. <https://doi.org/10.1017/ice.2019.293>
  11. Musgrove MA, Kenney RM, Kendall RE, Peters M, Tibbetts R, Samuel L, Davis SL. 2018. Microbiology comment nudge improves pneumonia prescribing. *Open Forum Infect Dis* 5:ofy162. <https://doi.org/10.1093/ofid/ofy162>
  12. Kaur S, Hutton M, Kenney RM, Weinmann A, Samuel L, Tibbetts R, Davis SL. 2022. The long-term Sustainability of a respiratory culture nudge. *Antimicrob Steward Healthc Epidemiol* 2:e15. <https://doi.org/10.1017/ash.2022.5>
  13. Arena CJ, Kenney RM, Kendall RE, Tibbetts RJ, Veve MP. 2023. Respiratory culture nudge improves antibiotic prescribing for *Moraxella catarrhalis* and *Haemophilus influenzae* lower respiratory tract infections. *Antimicrob Steward Healthc Epidemiol* 3:e23. <https://doi.org/10.1017/ash.2023.1>