Consecutive antibiotic shortages highlight discrepancies between microbiology and prescribing practices for intra-abdominal infections

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Piperacillin-tazobactam (TZP) is frequently used for intra-abdominal infection (IAI). Our institution experienced consecutive shortages of TZP and cefepime, providing an opportunity to review prescribing patterns and microbiology for IAI. Hospitalized adult patients treated for IAI, based on provider selection of IAI as the indication within the antibiotic order, between March 2014 and February 2018 were identified from the University of Virginia Clinical Data Repository and Infection Prevention and Control Database. Antimicrobial utilization, microbiologic data, and clinical outcomes were compared across four year-long periods: pre-shortage, TZP shortage, cefepime shortage, and post-shortage. There were 7,668 episodes of antimicrobial prescribing for an indication of IAI during the study period. Cefepime use for IAI increased 190% during the TZP shortage; meanwhile ceftriaxone use increased by only 57%. There was no increase in in-house mortality, colonization with resistant organisms, or *Clostridiodes difficile* infection among patients treated with IAI during the shortage periods. Among a subset of cases randomly selected for review, *Pseudomonas* sp. was a rare cause of IAI, but anti-pseudomonal antibiotics were commonly prescribed empirically. We observed a large increase in cefepime utilization for IAI during a TZP shortage that was not warranted based on the observed frequency of identification of *Pseudomonas* sp. as the causative organism in IAI, suggesting a need to revisit national guideline recommendations.
BACKGROUND

Drug shortages, and particularly antibiotic shortages, are an increasingly common problem faced by medical centers worldwide (1, 2). As exact therapeutic equivalents do not usually exist, substitutions made in the setting of shortages may increase use of agents that are less effective, more toxic, or unnecessarily broad in antibacterial spectrum compared to first-line therapy (3–5). A 2016 study of a piperacillin-tazobactam (TZP) shortage showed an 111% increase in meropenem use at one institution (5). The impact of antibiotic shortages on antimicrobial resistance and rates of Clostridioides difficile infection are also concerns. A 2017 study showed a near doubling of the frequency of vancomycin-resistant Enterococci (VRE) and carbapenem-resistant Enterobacterales during a TZP shortage (6); and a multicenter study of hospitals that experienced TZP shortages showed an increase in hospital onset C. difficile infection among those that responded by shifting antibiotic usage toward “high-risk” antibiotics (7).

Beginning in March 2015, supplies of TZP at our institution entered a period of shortage lasting approximately one year. Members of the stewardship team at our institution noted an apparent surge in cefepime utilization during this period. This was followed almost immediately by a year-long shortage of cefepime. As TZP is commonly prescribed for the indication of IAI, we sought to characterize changes in antimicrobial prescribing and microbiology in patients with IAI during these shortages, with the hypothesis that Pseudomonas sp. is frequently covered empirically and infrequently isolated in IAI. We also assessed whether there were changes in rates of colonization with resistant organisms (MRSA and VRE) or C. difficile infection, as this has been noted by others in shortage scenarios (6, 7). Finally, we also examined length of stay,
intensive care unit (ICU) transfer, and in-hospital mortality as outcomes that could potentially be
affected by disruption to prescribing patterns (and potentially suboptimal substitutions).

METHODS

Data

Antimicrobial usage, infection rate and culture data, and patient demographics were
extracted from the University of Virginia Clinical Data Repository and Infection Prevention and
Control Database. Adult patients admitted to the University of Virginia Health System in
Charlottesville, Virginia between March 2014 and February 2018 who received an antimicrobial
with “intra-abdominal infection” as the indication in the electronic medical record (EPIC
Verona, Wisconsin) during their admission were included. Indication selection was required to
sign intravenous antibiotic orders throughout the study period; providers could select one of
twenty provided indications or enter a free text indication. These patients were subdivided in to
one of four year-long time periods: pre-shortage (March 2014 – February 2015), TZP shortage
(March 2015 – February 2016), cefepime shortage (March 2016 – February 2017), or post-
shortage (March 2017 – February 2018). Patients less than 18 years of age and duplicate patients
re-admitted within 30 days of the initial admission were excluded. Antimicrobial utilization was
assessed using days of therapy (DOT) per 1000 patient-days. Antimicrobials on the inpatient
hospital formulary that are commonly prescribed for IAI at our institution were specifically
measured, including TZP, cefepime, ceftriaxone, ciprofloxacin, metronidazole, meropenem, and
vancomycin. Usage of other antimicrobials for IAI was also measured in one composite
category. Positivity for VRE or MRSA on surveillance screening, or positive C. difficile PCR
(GeneXpert, Cepheid, Sunnyvale, CA) were also assessed during these four periods, as well as
length of admission, admission to an ICU, and in-hospital mortality. There were no significant
changes to infection control practice regarding contact precautions or surveillance screening criteria for MRSA or VRE during the study period. In 2017, a previously described diagnostic stewardship initiative including a computerized clinical decision support tool for *C. difficile* testing was introduced (8), which was associated with reductions in overall testing but not a change in the percentage of positive tests across all hospitalized patients.

**Institutional Antimicrobial Stewardship Practices**

During the TZP shortage, a 24/7 formulary restriction and preauthorization strategy was used with a physician leader primarily holding the pager during that time, while during the cefepime shortage, a prospective audit with feedback approach was used and was largely led by an Infectious Diseases trained pharmacist. Guidance regarding preferred substitutions for various indications, including community-acquired and nosocomial IAI, was distributed via email during the TZP shortage. Cefepime plus metronidazole was recommended for nosocomial sepsis of abdominal origin, and ceftriaxone plus metronidazole was recommended for community-acquired IAI (CA-IAI) (Figure 1). Guidance was not provided during the cefepime shortage for IAI, as cefepime was not considered a typical first-line choice for this infection. Meropenem was a restricted agent requiring antimicrobial stewardship prior authorization throughout all time periods.

**In-depth review of cases**

A subset of cases (approximately 5%) were electronically randomly selected for in-depth chart review. Each case was categorized as CA-IAI, HA-IAI, possible IAI, or erroneous indication selection. HA-IAI was defined using the Surgical Infection Society Guidelines on IAI.
(9), with the exception that use of broad-spectrum antimicrobial therapy during the preceding 90 days was defined as intravenous antimicrobials exposure. Possible IAI included cases in which IAI was one of multiple possible diagnoses or there was potential for IAI (e.g. antibiotics were administered in the setting of esophageal perforation, however a clinically evident infection did not subsequently develop). Cases in which the provider inappropriately chose IAI as the indication were categorized as erroneous (e.g. for peri-operative prophylaxis after abdominal surgery or prophylaxis for spontaneous bacterial peritonitis in patients with cirrhosis and variceal bleeding). Additional information extracted from the chart during in-depth review included the initial antibiotic chosen, culture data, *Clostridium difficile* testing data, infectious disease consult presence, and narrative summary of the hospital course. Culture results considered attributable to IAI included blood cultures in the setting of clinically diagnosed IAI (excluding those consistent with blood culture contamination) or culture specimens obtained via surgical or percutaneous drainage (e.g. drained abscesses).

### Analysis

Data analysis was performed with R using the package (R, version 3.5.1). The Kruskal-Wallis test was used for continuous variables and Chi square test was performed for categorical variables. Antimicrobial usage data was reported as days of therapy per 1000 hospitalized patient-days for each period. For binary outcomes, logistic regression was performed to compare rates across time periods when the Chi square test indicated a significant difference between time periods. Descriptive statistics were used for analysis of data from the in-depth review of a subset of cases.

### Ethics Statement
Database and chart review were approved under University of Virginia Institutional Review Board (IRB #18393, #20562) with a waiver of consent.

RESULTS

There were 7,668 episodes of antimicrobial prescribing for an indication of IAI across all four time periods (Table 1). During the TZP shortage, there was a 93% reduction in TZP usage for an indication of IAI (measured in days of therapy per 1000 hospitalized patient-days), a 190% increase in cefepime usage, a 57% increase in ceftriaxone usage, a 13% increase in ciprofloxacin usage, and a 74% increase in metronidazole usage compared to the pre-shortage period (Figure 1). During the cefepime shortage, there was a 69% reduction in cefepime usage relative to the preceding (TZP shortage) period, however only a 9% reduction compared to the pre-shortage period; and cefepime usage was lowest in the post-shortage period. Meropenem was a restricted agent requiring antimicrobial stewardship approval throughout the time periods; usage was stable throughout the shortage periods. Vancomycin usage decreased across all four periods: there was a 40% reduction in the post-shortage relative to the pre-shortage period. Rates of VRE colonization declined over time (TZP shortage OR=0.73[0.59-0.89], cefepime shortage 0.56[0.45-0.69], post-shortage 0.43[0.33-0.54]; referent = baseline period), as did MRSA colonization (TZP shortage 0.72[0.53-0.97], cefepime shortage 1.13[0.87-1.48], post-shortage 0.31 [0.20-0.45]). The number of positive C. difficile PCR tests was similar across all time periods (p = 0.20) (Table 2). Length of stay and number of ICU admissions were similar across all time periods (p=0.71 and p=0.213, respectively); and in-house mortality was significantly higher in the baseline period compared to all other periods (TZP shortage 0.77[0.62-0.95], cefepime shortage 0.71[0.57-0.88], post-shortage 0.77[0.62-0.95]).

Review of Selected Cases
Among the 416 (~5%) cases randomly selected for in-depth chart review, categorization of cases and positive C. difficile tests were similar across all time periods (Table 3), with the exception that there were fewer erroneous indication selections in the post-shortage period. The proportion of cases with an infectious disease consult doubled in the TZP shortage period relative to the pre-shortage period and remained stable in subsequent periods, including the post-shortage period.

**Microbiology**

Among the 416 cases, 92 (22.1%) had at least one organism isolated that was attributed to an intra-abdominal source. In the pre-shortage period, fewer cases (16/108, 15%) had an associated organism identified relative to subsequent time periods (Table 3). The most commonly isolated organism was *Escherichia coli* followed by *Bacteroides fragilis*. For CA-IAI cases, 27/91 (30%) had positive microbiologic data, none of which were *Pseudomonas* sp.; however, 39/91 (43%) reviewed cases of CA-IAI received initial empiric therapy that included anti-pseudomonal spectrum. For HA-IAI cases, 58/125 (46%) had positive microbiologic data, 3 of which were *P. aeruginosa*; 82/125 (66%) received initial empiric therapy that included anti-pseudomonal spectrum. Among cases with positive culture data (n = 92), only 3 (3%) were *P. aeruginosa* and 6 organisms (7%) were ceftriaxone non-susceptible *Enterobacterales*, and all were HA-IAI (Table 4). Cases of IAI due to *P. aeruginosa* included a patient with recurrent peritoneal dialysis catheter-associated peritonitis (with prior isolation of *P. aeruginosa*), one with an indwelling biliary drain complicated by cholangitis, and one patient with inflammatory bowel disease complicated by *C. difficile* colitis who underwent fecal microbiota transplantation and subsequently developed polymicrobial bacteremia.
Enterococcus sp. was isolated in 13 cases, 11 of which were HA-IAI. One community-acquired case was a patient with metastatic gallbladder carcinoma admitted for cholangitis, and the other was a patient on peritoneal dialysis who presented with septic shock due to VRE bacteremia, potentially due to peritonitis versus endocarditis. Staphylococcus aureus was rarely identified as the causative organism (n=4, 2 of which were MRSA) and was exclusively found in patients following procedures (3 patients were post-operative from abdominal surgery and 1 following endoscopic retrograde cholangiopancreatography with common bile duct stent placement).

DISCUSSION

TZP is commonly prescribed for IAI in hospitalized patients and has anti-pseudomonal activity as well as providing coverage of increasingly resistant E. coli; however the actual antimicrobial coverage intent may not be well understood by all prescribers (10). The microbiologic data from the subset of cases we reviewed demonstrates the relative rarity of Pseudomonas sp. as the causative organism, even for hospital-associated cases, in IAI. P. aeruginosa is infrequently carried in the human gut of healthy individuals and thus would not be generally expected to play a large role in IAI, especially from the community (11, 12). Even in ICU patients without specific perturbations in their gut flora, P. aeruginosa was infrequently identified compared to Enterobacterales (13). Here, ceftriaxone non-susceptible Enterobacterales were more common than Pseudomonas sp., and all had elevated MICs to cefepime, TZP, or both. Despite this, antipseudomonal antibiotics were commonly used for IAI, and the increased cefepime usage in the setting of a TZP shortage particularly highlights the discrepancy between prescribing practices and the microbiology of IAI.
The most recent IDSA guidelines for IAI recommend that empiric therapy for healthcare-associated IAI (HA-IAI) be driven by local microbiologic results, but also state: “to achieve empiric coverage of likely pathogens, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ceftazidime, or cefepime plus metronidazole…” (14). The empiric use of antimicrobial regimens with broad-spectrum gram-negative organisms is also recommend for CA-IAI (14). Revised 2017 guidelines provided by the Surgical Infection Society highlight the need for individual risk assessment for various resistant pathogens, however also recommend the use of antimicrobials with broad-spectrum gram-negative coverage for “high risk” patients with CA-IAI and patients with HA-IAI [9]. Other guidelines focus more on severity of illness as the indication for the empiric use of agents with broader spectrum (15, 16). However, our data suggest that considering all patients in these groups as high-risk for IAI due to resistant gram-negative organisms results in significant overutilization of agents with expanded gram-negative spectrum, and this recommendation may need to be revisited in the next edition. Furthermore, when resistant gram-negative organisms were isolated from an abdominal source, extended spectrum beta-lactamase (ESBL)-producing Enterobacterales were more common than P. aeruginosa, thus a carbapenem may be the superior agent over anti-pseudomonal beta-lactams, such as cefepime, when more broad-spectrum gram-negative coverage is deemed appropriate (17, 18). This highlights the importance of institutional guidelines and the need for better ways to identify the minority of patients with IAI due to resistant gram-negative organisms.

Existing guidelines additionally recommend considering empiric antimicrobial coverage directed against MRSA for patients with HA-IAI “who are known to be colonized with the
organism or who are at risk of having an infection due to this organism because of prior
treatment failure and significant antibiotic exposure”(14). Among the cases reviewed in our
study, *Staphylococcus aureus* was rarely isolated and was exclusively found in patients with a
history of recent surgery or procedure. Recommendations for empiric coverage of *Enterococcus*
spp. generally include consideration based on individual patient risk given clinical characteristics
and/or severity of illness, though risk factors are variably and vaguely defined (9, 14–16).
Interestingly, the marked increase in cefepime use during the TZP shortage in this study was not
accompanied by a concomitant surge in vancomycin use, suggesting that coverage of
*Enterococcus* spp. may not play a large role in prescribers’ antibiotic decision-making for IAI at
our institution.

The antimicrobial prescribing data from this study also highlight important points
pertinent to antibiotic stewardship efforts in the setting of shortages. We observed a far more
dramatic decrease in utilization of the shortage antibiotic during the TZP shortage. This may be
due in part to the greater severity of the TZP shortage at our institution relative to the cefepime
shortage, however it is also likely that the restriction and preauthorization approach had more
impact on prescribing practices than the prospective audit and feedback approach (19). Since the
challenge in antibiotic shortage situations is helping providers to choose the most appropriate
alternative antibiotic (not reducing utilization of a target antibiotic), those strategies that
maximize interaction with stewardship teams or otherwise provide more tailored guidance may
be more advisable (20). At our institution, providers seemingly learned that there was a shortage
of TZP and preferentially chose another antibiotic rather than calling the antibiotic stewardship
team for prior authorization, which is known to be a potentially frustrating process for clinicians
(21). This likely contributed to the large surge in cefepime utilization, when discussion with the
antibiotic stewardship team may have led to more ceftriaxone use, consistent with the institutional guidance.

Our study was not designed to evaluate the reasons that prescribing practices were inconsistent with the provided guidance, however possible explanations include low read rates for the email that was circulated or selective retention of information from the email (of note, recommendations for nosocomial infections were listed first, and the recommendations for CA-IAI were listed last). We also recognize that passive information has not been shown to frequently change practice (22). Other possible contributing factors include limited understanding of antimicrobial spectrum or misconceptions about the frequency of *Pseudomonas* sp. involvement in IAI (23, 24), and the availability of different sets of guidelines that providers may reference (9, 14–16).

Our study was designed primarily to look at changes in antibiotic prescribing practices for IAI during specific β-lactam antibiotic shortages. Thus, our ability to detect overall changes in colonization rates of resistant organisms and rates of *C. difficile*, which have been previously associated with shortages (6, 7), was limited, and we cannot rule out contributions of temporal factors to the observed colonization rates. However, there was no increase in resistant organism colonization or *C. difficile* among patients with IAI (as identified by selection of IAI as the indication for antibiotic orders). There also was no increase in in-hospital mortality during shortage periods. In fact, in-house mortality was highest in the pre-shortage period and declined over time. Based on the reviewed subset of cases, the frequency of infectious diseases consultation and identification of pathogens was lowest in the pre-shortage period. However, the observational nature of this study precludes making conclusions about causality.
Another limitation of this study is the inclusion of patients based on a provider selecting IAI as the indication for an antibiotic order. Per our review of a subset of cases, approximately 12% of these indications were erroneous selections. However, the majority of erroneous selections were for patients receiving prophylaxis for spontaneous bacterial peritonitis in the setting of variceal bleeding (typically with ceftriaxone) or peri-operative prophylaxis for patients undergoing abdominal surgery, both instances in which providers would be targeting similar organisms and that would be more likely to inflate ceftriaxone usage. Inclusion based on this parameter allowed for the large number of patients, which is a strength, and allowed assessment at the point of prescribing for IAI, which is highly relevant for analysis of prescribing behavior from a stewardship standpoint. Furthermore, the erroneous selections did not impact the analysis of the microbiologic etiologies or rates of empiric use of anti-pseudomonal agents as these were analyzed based on classification within the reviewed subset of cases. However, this method of identification for inclusion likely did miss some cases of IAI wherein IAI was not selected as the indication by prescribers at the time of the order.

Antibiotic shortages are a barrier to best antimicrobial stewardship practices (5, 25). We found that the alternative selections providers made in the setting of TZP shortage were suboptimal, with cefepime being substituted at a rate that was not supported by the microbiologic epidemiology of IAI at our institution. Future research and guideline updates should seek to refine indications and recommendations for various resistant gram-negative organisms (e.g. Pseudomonas sp. and ESBL-producing Enterobacterales). Institutional guidelines may be critical, particularly in the setting of antibiotic shortages, however the best method for optimizing adherence to such guidance remains unclear.
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Table 1. Characteristics across time periods

| Time period                  | Pre-shortage | Piperacillin-tazobactam Shortage | Cefepime Shortage | Post-shortage |
|------------------------------|--------------|----------------------------------|-------------------|---------------|
| Total patients with IAI      | 2107         | 1896                             | 1888              | 1777          |
| Total patient-days           | 190,145      | 216,707                          | 194,919           | 198,008       |
| Age, median (IQR)            | 58 (47.0-68.5)| 58 (46.0-69.0)                   | 59 (45.0-70.0)    | 58 (46.0-70.0)|
| Charlson score, median (IQR) | 2 (0-4)      | 1 (0-4)                          | 0 (0-4)           | 1 (0-4)       |
Table 2. Outcomes among inpatients who received antibiotics for IAI by time period

| Outcome                              | Time period          | Pre- shortage | TZP Shortage | Cefepime Shortage | Post- Shortage | p value<sup>a</sup> |
|--------------------------------------|----------------------|---------------|--------------|-------------------|---------------|-------------------|
| Days of therapy per 1000 hospital patient-days<sup>b</sup> |                      |               |              |                   |               |                   |
| cefepime                             |                      | 4.85          | 14.08        | 4.41              | 2.66          | <0.001            |
| ceftriaxone                          |                      | 4.23          | 6.66         | 5.52              | 4.57          | <0.001            |
| ciprofloxacin                        |                      | 6.56          | 7.43         | 6.49              | 4.05          | <0.001            |
| meropenem                            |                      | 2.45          | 2.17         | 2.38              | 2.50          | 0.11              |
| metronidazole                        |                      | 15.34         | 26.66        | 16.90             | 10.60         | <0.001            |
| piperacillin-tazobactam              |                      | 22.34         | 1.60         | 16.35             | 16.64         | <0.001            |
| other                                |                      | 12.24         | 10.65        | 10.56             | 8.02          | <0.001            |
| vancomycin                           |                      | 8.03          | 6.36         | 6.14              | 4.79          | <0.001            |
| Median Length of Admission, days (IQR) | 5 (2-11)            | 5 (2-12)      | 5 (2-11.25)  | 5 (2-11)          | 0.71          |                   |
| ICU Admission (n, %)<sup>c</sup>     | 115 (5.46%)          | 86 (4.54%)    | 105 (5.56%)  | 108 (6.08%)       | 0.213         |                   |
| In-Hospital Mortality (n, %)         | 222 (10.54%)         | 157 (8.28%)   | 144 (7.63%)  | 136 (7.65%)       | 0.002         |                   |
| VRE Positive (n, %)                  | 258 (12.24%)         | 175 (9.23%)   | 136 (7.20%)  | 100 (5.63%)       | <0.001        |                   |
| MRSA Positive (n, %)                 | 112 (5.32%)          | 74 (3.90%)    | 113 (5.99%)  | 30 (1.69%)        | <0.001        |                   |
| C. diff Positive (n, %)              | 111 (5.27%)          | 109 (5.75%)   | 84 (4.45%)   | 80 (4.50%)        | 0.20          |                   |

<sup>a</sup>Based on Kruskal-Wallis test for continuous variables and Chi square test for categorical variables.

<sup>b</sup>Total hospitalized patient-days per time period.

<sup>c</sup>Percent of admitted patients with IAI selected as the indication for an antibiotic.
Table 3. Characteristics of selected cases from different time periods

| Time Period                  | Pre-shortage (n=108) | TZP Shortage (n=100) | Cefepime Shortage (n=100) | Post-Shortage (n=108) |
|------------------------------|----------------------|----------------------|---------------------------|-----------------------|
| CA-IAI                       | 22 (20.4%)           | 23 (23%)             | 24 (24%)                  | 22 (20.4%)            |
| HA-IAI                       | 29 (26.9%)           | 27 (27%)             | 33 (33%)                  | 36 (33.3%)            |
| IAI Possible                 | 38 (35.2%)           | 32 (32%)             | 25 (25%)                  | 38 (35.2%)            |
| Erroneous                    | 19 (17.6%)           | 18 (18%)             | 18 (18%)                  | 12 (12%)              |
| Infectious Diseases consult  | 10 (9.3%)            | 22 (22%)             | 22 (22%)                  | 20 (18.5%)            |
| C. diff positive             | 3 (2.8%)             | 4 (4%)               | 4 (4%)                    | 3 (2.8%)              |
| Organism (s) isolated        | 16 (14.8%)           | 19 (19%)             | 27 (27%)                  | 30 (27.8%)            |
| Bacteremia                   | 4 (3.7%)             | 5 (5%)               | 7 (7%)                    | 10 (9.3%)             |
| Empiric anti-Pseudomonal regimen       |                      |                      |                           |                       |
| CA-IAI                       | 12 (54.5%)           | 5 (21.7%)            | 11 (45.8%)                | 11 (50%)              |
| HA-IAI                       | 20 (70%)             | 14 (51.9%)           | 22 (66.7%)                | 26 (72.2%)            |
| Neutropenia                  | 2 (1.9%)             | 4 (4%)               | 2 (2%)                    | 3 (2.8%)              |

*a* defined as piperacillin-tazobactam, cefepime, or meropenem
Table 4 Organisms isolated and attributed to IAI among subset of reviewed cases

| Organism                        | n = 92 (%) | Resistance of note                  |
|---------------------------------|------------|-------------------------------------|
| **Facultative and aerobic gram-negative** |            |                                     |
| *Escherichia coli*              | 18 (19.6)  |                                     |
| *Klebsiella sp.*                | 11 (12)    |                                     |
| *Enterobacter sp.*              | 10 (10.7)  | 2 ceftriaxone non-susceptible       |
| *Pseudomonas aeruginosa*        | 3 (3.3)    |                                     |
| *Raoultella sp.*                | 4 (4.3)    | 2 ceftriaxone non-susceptible       |
| *Aeromonas sp.*                 | 3 (3.3)    |                                     |
| *Citrobacter freundii*          | 2 (2.2)    | 2 ceftriaxone non-susceptible       |
| *Serratia marcescens*           | 2 (2.2)    |                                     |
| *Morganella morganii*           | 1 (1.1)    |                                     |
| *Moraxella sp.*                 | 1 (1.1)    |                                     |
| *Kluyvera intermedia*           | 1 (1.1)    |                                     |
| *Stenotrophomonas maltophilia*  | 1 (1.1)    |                                     |
| *Pantoea sp.*                   | 1 (1.1)    |                                     |
| **Anaerobic**                   |            |                                     |
| *Bacteroides fragilis*          | 13 (13.8)  |                                     |
| *Lactobacillus sp.*             | 1 (1.1)    |                                     |
| *Prevotella sp.*                | 2 (2.2)    |                                     |
| *Clostridium sp.*               | 1 (1.1)    |                                     |
| *Leuconostoc mesenteroides*     | 1 (1.1)    |                                     |
| **Gram-positive aerobic cocci** |            |                                     |
| *Enterococcus faecium*          | 10 (10.9)  | 5 VRE                               |
| *Enterococcus faecalis*         | 3 (3.3)    |                                     |
| *Streptococcus sp.*             | 6 (6.5)    |                                     |
| *Staphylococcus aureus*         | 4 (4.3)    | 2 MRSA                              |
| *Rothia mucilaginosa*           | 1 (1.1)    |                                     |
| **Fungi**                       |            |                                     |
| *Candida albicans*              | 6 (6.5)    |                                     |
| *Candida glabrata*              | 8 (8.7)    |                                     |
| *Candida dubliniensis*          | 2 (2.2)    |                                     |
| *Candida guilliermondii*        | 2 (2.2)    |                                     |
| *Candida lusitaniae*            | 1 (1.1)    |                                     |

Includes only organisms identified that were attributed to intra-abdominal source (e.g. microbiology for erroneous selections not included). More than 1 organism was isolated in 20 cases. Mixed flora was isolated in 26 cases.
There is currently a national shortage of piperacillin/tazobactam and the supply on hand is extremely limited and must be reserved for known resistant pathogens. In order to conserve supply of piperacillin/tazobactam vials for injection, the following restrictions, approved by the Antimicrobial Utilization Committee (AUC), will be implemented beginning on Friday, February 13th, 2015.

With very few exceptions piperacillin/tazobactam has multiple equivalent alternatives. Frequently, piperacillin/tazobactam use may be better directed to alternative therapies with a careful assessment to cause/source of infection. In a recent internal quality project assessing selected antibiotic indications of adult ICU patients and concordance with ongoing clinical documentation, piperacillin/tazobactam orders were significantly more discordant than those for cefepime or vancomycin. In addition, 2014 antibiogram data illustrates that piperacillin/tazobactam appears to have the lowest percentage chance of covering important clinical pathogens such as *Pseudomonas aeruginosa* (82%, 90%, 86% and 83% for piperacillin/tazobactam, cefepime, meropenem and ciprofloxacin respectively) and *Enterobacter cloacae* (68%, 94%, and 94% susceptible for piperacillin/tazobactam, cefepime and ciprofloxacin respectively).

Piperacillin/tazobactam will be temporarily removed from all sepsis order sets. Alternatives recommended by AUC for common indications are as follows, and will be reflected in the options within the order sets:

- **Sepsis of Pulmonary Origin - Nosocomial (ICU):** Preferred therapy remains Cefepime + Vancomycin
- **Sepsis of Abdominal Origin - Nosocomial:** Cefepime + Metronidazole
- **Sepsis of Skin/Soft Tissue Origin - Necrotizing Fasciitis:** Meropenem + Vancomycin + Clindamycin
- **Sepsis of Unknown Origin:** Cefepime + Vancomycin + Metronidazole
- **Diabetic Foot Infections:** Ceftriaxone + Metronidazole due to low rates of *Pseudomonas aeruginosa* involvement reported in the literature for these infections
- **Community-acquired Intraabdominal Infections (i.e. appendicitis, biliary obstruction):** Ceftriaxone + Metronidazole where isolation of resistant Gram-negative pathogens is infrequent

There will be a hard stop put in place when piperacillin/tazobactam is ordered. The regimens above would be appropriate alternatives for both pediatric and adult patients. If you still feel that this is the most appropriate drug for your patient without an equivalent alternative please call your clinical pharmacist, the antimicrobial stewardship team (PIC 1337), the ID fellow on-call (PIC 1369) or the pediatric ID consult service (1825) for assistance.
Figure 2. Antimicrobial utilization for IAI before, during, and after consecutive piperacillin-tazobactam and cefepime shortages.
There is currently a national shortage of piperacillin/tazobactam and the supply on hand is extremely limited and must be reserved for known resistant pathogens. In order to conserve supply of piperacillin/tazobactam vials for injection, the following restrictions, approved by the Antimicrobial Utilization Committee (AUC), will be implemented beginning on Friday, February 13th, 2015.

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- **Sepsis of Unknown Origin:** Cefepime + Vancomycin + Metronidazole
- **Diabetic Foot Infections:** Ceftriaxone + Metronidazole due to low rates of *Pseudomonas aeruginosa* involvement reported in the literature for these infections

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