An Evaluation of Selected Indications and Appropriateness of Ampicillin/Sulbactam, an Unrestricted Antimicrobial, at a Single Center

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ABSTRACT

Background: With antimicrobial resistance on the rise and few new agents in development, it is important to exercise prudent judgment when utilizing antimicrobials. The Antimicrobial Stewardship Program (ASP) is responsible for facilitating the appropriate use of antimicrobials at the institution. Restricted antimicrobials and select additional antimicrobials are monitored by the ASP team to determine if the indications chosen by the ordering prescribers correspond to and are appropriate for the patients’ infections. The purpose of this study was to review ampicillin/sulbactam, an unrestricted antimicrobial, due to its declining effectiveness against Escherichia coli.

Methods: A retrospective chart review was conducted with adult inpatients receiving ampicillin/sulbactam. One hundred consecutive orders for ampicillin/sulbactam were reviewed.

Results: The greatest number of orders for ampicillin/sulbactam came from the Emergency Trauma, Medicine, and Surgery services. The indications selected by the ordering providers were: skin and soft tissue infection (33 orders), community-acquired respiratory infection (22 orders), other (14 orders), intra-abdominal infection due to susceptible organism (13 orders), urinary tract infection (nine orders), head/neck infection (five orders), infection due to human or animal bite (three orders), and diabetic foot infection (one order).

Conclusions: The correct indication was selected in 78% of orders that were reviewed for correctness. Empiric ampicillin/sulbactam was appropriate in 51% of orders, with the majority of inappropriate empiric usage being intra-abdominal and urinary tract infections.

Keywords: ampicillin/sulbactam, antimicrobials, resistance, stewardship, appropriateness

INTRODUCTION

The emergence of antimicrobial resistance is a growing problem, and with few antibiotics in development, efforts to promote appropriate antibiotic usage to curtail the development of resistant organisms are important initiatives for health care institutions. Unnecessary drug interactions and adverse effects, including infection with Clostridium difficile, from the use of antibiotics are also a concern. The Antimicrobial Stewardship Program (ASP) is responsible for monitoring the use of antimicrobials at the institution, a 775-bed nonprofit research and teaching hospital that provides inpatient and outpatient services in a metropolitan area. Although antimicrobial monitoring has been ongoing at the medical center since January 1986, the official ASP was implemented in 2005. The ASP team consists of an infectious diseases physician and two infectious diseases pharmacists. The ASP team utilizes the Epic system to run daily reports on restricted and other monitored antimicrobials. From these reports, the team monitors for appropriate antimicrobial indications and approvals and intervenes when necessary. The ASP team also provides approval for restricted antimicrobials, develops and distributes clinical guidelines for the most common infections, maintains an ASP webpage on the hospital’s intranet, and educates health care professionals.

The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines for implementing an antibiotic stewardship program discuss multiple interventions and processes to improve antibiotic use within institutions. One such mechanism is to develop criteria for appropriate use and to incorporate these criteria into the medication ordering process. Historically, the ASP provided a guidance document containing appropriate indications for 26 antibiotics on the ASP intranet webpage as a resource for clinicians. With the activation of the Epic system, the ASP identified a unique opportunity to integrate the appropriate indications into the medication ordering process for all systemic antimicrobials on formulary (restricted and unrestricted). The ASP team created a living document listing the indications for more than 100 systemic antimicrobials (antibiotics, antivirals, antifungals, and antiprotozoals). The Epic building team utilizes this document to create the antimicrobial-specific indications as drop-down lists for clinicians to choose from during the medication ordering process. To complete an antimicrobial order, the prescriber must select an indication from the drop-down list or type an indication from scratch. For example, the following is the list of indications, in the order that they appear, that the clinicians pick from a drop-down menu when ordering ampicillin/sulbactam:

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1. Skin and soft tissue infection
2. Community-acquired respiratory infections
3. Infection due to a human/animal bite
4. Pelvic infection
5. Head/neck infection
6. Urinary tract infection
7. Bacteremia due to susceptible organisms
8. Diabetic foot infection
9. Musculoskeletal infections
10. Intra-abdominal infection due to susceptible organisms
11. Specify indication if not listed above.

These indications are potential reasons for using ampicillin/sulbactam in the proper clinical context. For instance, intra-abdominal infection contains the added caveat “due to susceptible organisms” to stress that this may not be an appropriate empiric choice. Further, this appears at the bottom of the list because it is not a first-line empiric choice for these infections based the latest guidelines.

Restricted antimicrobials are monitored by the ASP team regularly to determine if the indications selected in Epic correspond to and are appropriate for the patients’ infections. Examples of some of the restricted antimicrobials at the institution are piperacillin/tazobactam, cefepime, and meropenem. However, the team currently does not routinely monitor the use of unrestricted antimicrobials.

The purpose of this study was for the ASP team to review the usage of ampicillin/sulbactam, an unrestricted antimicrobial, and assess the prescribing habits at the institution. In addition, the ASP team recognized the poor susceptibility of Escherichia coli to ampicillin/sulbactam at the institution. For example, in 2013 the E. coli susceptibility to this agent was 56% (hospital-wide inpatient and emergency department isolates from any source). Due to this issue worldwide, the Surgical Infection Society and the IDSA no longer recommend this agent for the empiric treatment of mild-to-moderate community-acquired intra-abdominal infections in adults. However, historically it has been widely used for this exact indication, commonly for empiric coverage of E. coli.

METHODS

Study Setting
This study took place at a 775-bed nonprofit research and teaching hospital that provides inpatient and outpatient services in a metropolitan area. The study was approved by the institutional review board.

Study Design
A retrospective chart review was conducted on individual adult inpatients (at least 18 years of age) receiving intravenous ampicillin/sulbactam. Patients receiving ampicillin/sulbactam as outpatients, patients less than 18 years old, and patients who did not receive at least one dose of ampicillin/sulbactam were excluded. One hundred consecutive, individual adult orders for ampicillin/sulbactam prescribed between January 1 and January 23, 2013, were reviewed. Repeat orders for the same patient during the same admission were evaluated as one order. The sample size of 100 orders was selected to obtain a convenient sample for this exploratory analysis. Data were retrospectively collected from the patients’ medical records using a standardized data collection tool. Collected data included patient-specific information (age, race, gender, weight, height, allergies, date of admission, date of discharge, service, hospital location, use of other antimicrobials during the admission, infection and colonization history, current infection for this admission), ampicillin/sulbactam information (dose, duration, indication), laboratory values (highest daily temperature, white blood cell count, serum creatinine, urine analysis, chest x-ray, computerized tomography scan, magnetic resonance imaging, or additional diagnostic tests), and culture data (types of cultures drawn, date of collection, culture site, date of final report, pathogens isolated, pathogen susceptibility, minimum inhibitory concentration for antibiotics).

Study Outcomes
The selected indication in the drug order entered by the providers from the drop-down menu was defined as correct if it matched the infection-related diagnosis documented in the medical record. It was designated as incorrect if the infection-related diagnosis per the medical record did not match the provider-selected indication. Selected indications were categorized in this manner if the provider selected an indication. If “other” was selected and the provider typed an indication, then a category of correct or incorrect was not assigned. Appropriateness of empiric ampicillin/sulbactam was defined as ampicillin/sulbactam having in vitro activity against the pathogen (or highly suspected pathogen) based on culture and susceptibility reports available at the time the ampicillin/sulbactam was initiated or by review of the infection-related diagnosis by the investigators (if culture/susceptibility results were not available). The three investigators reviewed the infection-related diagnoses and utilized disease-specific guidelines to assess appropriateness of ampicillin/sulbactam as an empiric

| Table 1 Baseline Patient Demographics And Ampicillin/Sulbactam Information |
|-----------------------------|----------------|
| Mean age (range), years     | 59 (19–94)    |
| Gender (N = 100)            |               |
| Male, n                     | 49            |
| Female, n                   | 51            |
| Mean weight, kg             | 80.7          |
| Mean serum creatinine on first day of ampicillin/sulbactam (range), mg/dL | 1 (0.4–7.2) |
| Mean length of stay (range), days | 8 (1–122) |
| Mean duration of ampicillin/sulbactam (range), days | 3 (1–13) |
| Ampicillin/sulbactam starting dose |
| 3 g, n                      | 93            |
| 1.5 g, n                    | 7             |
| Ampicillin/sulbactam starting frequency |
| Every 6 hours, n            | 57            |
| Every 8 hours, n            | 8             |
| Every 12 hours, n           | 1             |
| Every 24 hours, n           | 2             |
| Once, n                     | 32            |
antibiotic (including one-time doses) for all orders.8–15 Empiric use of ampicillin/sulbactam was considered inappropriate if it was not specified as an option in disease-specific guideline recommendations. Appropriateness of definitive ampicillin/sulbactam was assessed only if culture and susceptibility data were obtained during the admission in which the ampicillin/sulbactam was administered.

Statistical Analyses
Descriptive statistics were utilized to analyze the data. The continuous variables are summarized using the mean and range. The categorical responses are presented in frequency (percentage) terms.

RESULTS
One hundred consecutive orders for ampicillin/sulbactam were reviewed. The baseline patient demographics and ampicillin/sulbactam information are listed in Table 1. The Emergency Trauma service had the most orders (25) for ampicillin/sulbactam, followed by the Medicine (21), Surgery (13), Diabetes (eight), and Urology (five) services. All other services had between one and three orders for ampicillin/sulbactam. The indications selected by the providers from the drop-down menu for the ampicillin/sulbactam orders are illustrated in Figure 1. The most common indications selected by providers were skin and soft tissue infections (33 orders), community-acquired respiratory infections (22 orders), and other (14 orders). Other refers to the selection of “Specify indication if not listed above” whereby providers must type an indication from scratch.

Table 2 demonstrates the indications selected by the provider and whether the selected indication was deemed correct, meaning that it matched the infection-related diagnosis documented in the medical record, or incorrect, meaning that the infection-related diagnosis per the medical record did not match the provider-selected indication. Of 86 orders that had a provider-selected indication from the drop-down menu, 67 (78%) were deemed correct and mirrored the infection-related diagnosis in the medical record. For 19 of the 86 orders, the selection did not match the infection-related diagnosis. For instance,

<table>
<thead>
<tr>
<th>Provider-Selected Indication, n</th>
<th>Correct Provider-Selected Indication, n</th>
<th>Incorrect Provider-Selected Indication, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and soft tissue infection, 33</td>
<td>23/33 orders (69.7%): Cellulitis, 8, Facial cellulitis, 2, Wound, 6, Abscess, 5, Mastitis, 1, Chronic hidradenitis, 1</td>
<td>10/33 orders (30.3%): Animal bite, 4, Pneumonia, 2, Parotitis, 2, Sinusitis, 1, Diabetic foot infection, 1</td>
</tr>
<tr>
<td>Community-acquired respiratory infection, 22</td>
<td>16/22 orders (72.7%): Community-acquired pneumonia, 5, Aspiration, 6, Sinusitis/bronchitis, 5</td>
<td>6/22 orders (27.3%): Health care-associated pneumonia, 3, Appendicitis, 1, Meningitis/brain abscess, 1, Bleeding esophageal varices, 1</td>
</tr>
<tr>
<td>Intra-abdominal infection, 13</td>
<td>12/13 orders (92.3%): Acute cholecystitis, 6, Acute appendicitis, 1, ERCP without complete drainage, 1, Collitis/diverticulitis, 1, Ovarian cyst, 1, Cholangitis, 1, Cholelithiasis, 1</td>
<td>1/13 orders (77%): Prostate abscess, 1</td>
</tr>
<tr>
<td>Urinary tract infection, 9</td>
<td>8/9 orders (88.9%): Urinary tract infection, 7, Pyelonephritis, 1</td>
<td>1/9 orders (11%): Ventriculoperitoneal shunt, 1</td>
</tr>
<tr>
<td>Head/neck infection, 5</td>
<td>4/5 orders (80%): Tonsillar abscess, 1, Mastoiditis/otitis, 1, Pharyngitis/tonsillitis, 1, Cranial facial fractures, 1</td>
<td>1/5 orders (20%): Endocarditis, 1</td>
</tr>
<tr>
<td>Infection due to human or animal bite, 3</td>
<td>3/3 orders (100%): Dog bite, 3</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetic foot infection, 1</td>
<td>1/1 orders (100%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ERCP = endoscopic retrograde cholangiopancreatography; N/A = not applicable
community-acquired respiratory infection was selected, but the patient had health care-associated pneumonia based on the diagnosis in the medical record. In another example, head/neck infection was the selection, but the patient had endocarditis upon review of the chart. In addition, some providers did not select the best option from the drop-down list. In one illustration of this, the provider selected skin and soft tissue infection, which is at the top of the list, but the patient had an animal bite per the medical record. The provider should have selected infection due to human or animal bite from the drop-down list rather than skin and soft tissue infection. Finally, there were 14 orders for “other” in which clinicians typed the indication. These free-texted indications were as follows: seven not specified, one aspiration pneumonia, one sinusitis, one positive blood culture, one perioperative, one intra-abdominal, one fever, and one prior to endoscopic retrograde cholangiopancreatography pancreatic cancer-obstructed common bile duct.

<table>
<thead>
<tr>
<th>Provider-Selected Indication</th>
<th>Appropriate for Empiric Therapy</th>
<th>Inappropriate for Empiric Therapy</th>
</tr>
</thead>
</table>
| Skin and soft tissue infection | 21/33 orders (63.6%) | 12/33 orders (36.4%):  
  • Developed infection during or soon after receiving antibiotics and/or history of recurrent infection, 6  
  • History of ESBL, 1  
  • More broad-spectrum than necessary, 3  
  • More broad-spectrum needed, 2 |
| Community-acquired respiratory infection | 16/22 orders (72.7%) | 6/22 orders (27.3%):  
  • HCAP, 3  
  • Brain abscess/meningitis, 1  
  • Esophageal varices with bleeding, 1  
  • Intra-abdominal infection, 1 |
| Other | 5/14 orders (35.7%) | 9/14 orders (64.3%):  
  • HCAP, 1  
  • Developed infection during or soon after receiving antibiotics, 1  
  • Inappropriate empiric choice for Escherichia coli coverage, 7 |
| Intra-abdominal infection | 0 orders | 13/13 orders (100%):  
  • Inappropriate empiric choice for E. coli coverage |
| Urinary tract infection | 0 orders | 9/9 orders (100%):  
  • Inappropriate empiric choice for E. coli coverage |
| Head/neck infection | 5/5 orders (100%) | N/A |
| Infection due to human or animal bite | 3/3 orders (100%) | N/A |
| Diabetic foot infection | 1/1 orders (100%) | N/A |

ESBL = extended-spectrum beta-lactamases; HCAP = health-care associated pneumonia; N/A = not applicable
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All orders were reviewed for appropriateness of empiric ampicillin/sulbactam. Fifty-one of 100 orders were deemed appropriate for empiric therapy. The number of orders determined to be appropriate for empiric therapy for each indication is displayed in Table 3. All of the orders for intra-abdominal infections and urinary tract infections were inappropriate for empiric therapy based on poor susceptibility rates for *E. coli*. In contrast, all of the orders for head/neck infections, infections due to human or animal bites, and the diabetic foot infection were appropriate for empiric therapy. For skin and soft tissue infections, community-acquired respiratory infections, and “other,” there was a mix of appropriate and inappropriate empiric ampicillin/sulbactam (Table 3).

Definitive therapy with ampicillin/sulbactam was determined to be appropriate for 12 orders. The descriptions of these cases appear in Table 4. For example, for the indication of intra-abdominal infection, only one order for ampicillin/sulbactam was deemed appropriate for definitive therapy based on the cultures. However, this was for a case in which the infection-related diagnosis was actually a urinary tract infection. In this case, the patient had a prostate abscess with urine and prostate fluid cultures positive for *Klebsiella pneumoniae* and *Enterococcus faecalis* susceptible to ampicillin/sulbactam.

DISCUSSION

Requiring providers to select an indication each time they order an antibiotic is a powerful tool for ASPs. It is a means of having a checkpoint for providers to evaluate their rationale for initiating an antibiotic. It may also be utilized to streamline certain treatment algorithms within the institution. For instance, if a provider selects neutropenic fever for cefepime, a restricted antibiotic, the provider does not have to call the ASP for approval. However, if the provider wants to use cefepime for an alternative indication, then a call for approval must be made. The ASP monitors this on a daily basis for all restricted and monitored antibiotics and intervenes as necessary.

In this study, the investigators evaluated an unrestricted antibiotic to review whether providers were selecting the correct indications. The correct indication for ampicillin/sulbactam from the drop-down menu was selected by providers for 67 of 86 orders (77.9%). This implies that most of the time providers will select the correct indication from a drop-down list for the use of an antibiotic that correlates to the infection-related diagnosis in the medical record. This is helpful information for the ASP as it reinforces that, even for unrestricted antibiotics, providers are being thoughtful about their antibiotic selection, but there is room for improvement in terms of the usage of this particular agent.

The use of empiric ampicillin/sulbactam was appropriate in 51 of 100 orders (51%). The proportion of appropriate use was low because providers were still utilizing ampicillin/sulbactam as empiric therapy for intra-abdominal and urinary tract infections, despite the poor *E. coli* susceptibility to this antibiotic and the updates to the guidelines on the management of these infections that removed or downgraded the recommendations for this agent. The *E. coli* susceptibility for this agent at this institution was 61% in 2007 and declined to 54% in 2015. In contrast, the *E. coli* susceptibility for ceftriaxone, also an unrestricted antibiotic at this institution, was 96% in 2007 and 89% in 2015, highlighting that there are potential alternatives to use to target therapy to this pathogen. This type of review is useful to identify specific providers or services within the institution that perhaps need re-education about the intention of this process and/or guidance on the use of specific antibiotics for certain infections. For instance, those that continue to utilize ampicillin/sulbactam for intra-abdominal and urinary tract infections may need to receive ongoing education about the treatment recommendations for these infections. This information prompted the ASP team to add ampicillin/sulbactam to the list of monitored antimicrobials and to re-educate via one-on-one interventions regarding the appropriate empiric use of this specific antibiotic. The use of this agent since this change has not yet been formally evaluated by the ASP team.

The other interesting finding in this study is that it is very difficult to characterize the appropriateness of definitive therapy for the common disease states for which ampicillin/sulbactam is used. Very few patients had cultures drawn (and very few, if drawn, were positive) that could then be used to “check”...
whether ampicillin/sulbactam would have been appropriate for definitive therapy. This makes it difficult to reinforce to clinicians the impact of selecting inappropriate empiric antibiotics for their patients. For instance, if a provider uses ampicillin/sulbactam to manage the majority of his or her intra-abdominal infections and no tangible consequences are observed, this may be a barrier to altering the antibiotic selection for future cases. This may occur in situations where no cultures are done, the patients have surgery, they recover, and they are discharged without any complications as inpatients. This makes it challenging to make recommendations for empiric therapy for these and other types of infections.

There were several limitations to our study. This was a single-center retrospective study of a small sample size based on medical record reviews. The information may not be applicable to other institutions or patient populations with different resistance patterns for *E. coli* and other organisms. The cases were reviewed only for inpatient stays, and the investigators were unable to evaluate patient outcomes after discharge. The investigators were not able to characterize the evolution of the infection-related diagnosis across the admission. It is difficult to discern retrospectively the thought process for the antibiotic selection based on the working infection diagnosis at the start of empiric therapy compared with the final diagnosis at 48 to 72 hours based on a more complete evaluation of the patient and history, clinical response, and/or culture and susceptibility data if it is not wholly documented in the medical record. Thus, the investigators only reviewed cases for ampicillin/sulbactam definitive therapy based on cultures and susceptibility data when they were available.

**CONCLUSION**

This study highlights that there is still a niche for empiric ampicillin/sulbactam, but it must be used in the context of careful consideration of the patients’ disease states, histories, allergies, risk factors for resistance, and local resistance patterns. This type of scrutiny is needed to select the best empiric antibiotic for individual patients in light of the more global perspective of upholding the overall balance between using broad-spectrum versus narrow-spectrum agents, weighing the risks versus benefits of overtreating or undertreating, and the collateral damage from antibiotic use.

This study also implies that ASP initiatives may have to be expanded beyond select antibiotics to all antibiotics in order to continue to improve antibiotic usage within institutions and globally. ASP targets may need to evolve over time based on the changing antibiotic resistance rates and clinical practices within certain services and patient populations. Rather than using a one-size-fits-all approach, ASPs must continuously strategize different methods to improve antibiotic use within various parts of the institution.

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**REFERENCES**


