Brief Report

Piperacillin-Tazobactam Usage at a Tertiary Pediatric Hospital: An Antimicrobial Stewardship Review

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In this review of 200 charts, piperacillin-tazobactam usage was analyzed at a pediatric tertiary hospital, with an assessment of the indications for initiation, and continuation at day 3 of usage. Significant cost savings could be obtained with antibiotic stewardship audit on day 3 of antibiotic administration.

Key words. antimicrobial stewardship; de-escalation; piperacillin/tazobactam.

Hospitals are increasingly implementing antimicrobial stewardship programs, and central to these programs is the combination of drug restriction and auditing of selected antibiotics [1]. The process by which individual antimicrobials are evaluated for restriction or subsequent auditing has not been fully described in the literature. Piperacillin is a semisynthetic ureidopenicillin used in combination with a β-lactamase inhibitor, tazobactam, marketed under the trade names Zosyn and Tazocin (Pfizer) [2, 3]. Piperacillin-tazobactam has a broad spectrum of activity against Gram-positive, Gram-negative (including *Pseudomonas aeruginosa*), and anaerobic bacteria. Because of this broad activity, piperacillin-tazobactam has been used in various clinical infections [2–6], and at the Children's Hospital of Pittsburgh of UPMC (CHP), piperacillin-tazobactam is used widely but its usage has not been audited nor restricted.

METHODS

Study Hospital

The medical records at CHP, a 296-bed tertiary care, university-based pediatric hospital, were reviewed. All work was carried out after approval of the UPMC Health System Quality Improvement Committee.

Chart Review

A list of all of the prescribed courses of piperacillin-tazobactam between September 2011 and August 2012 was provided by the CHP pharmacy department. The 1-year period was broken down into 4 consecutive 3-month blocks, with 50 courses of piperacillin-tazobactam within each block randomly selected for review. This was done to reduce seasonal or other biases that might exist. All medical records were deidentified, with demographic and medical data collected by a standardized data sheet for each of the selected 200 antibiotic courses.

Indications for initiation of piperacillin-tazobactam were developed by the investigators on the basis of hospital practice guidelines, primary literature, US Food and Drug Administration-approved indications, Infectious Disease Society of America recommendations, and a 50-chart pilot review study (by M. D. G.) [2-6]. All authors agreed on the predefined list of indications (Table 1). Three board certified pediatric infectious disease physicians (J. M. M., M. G. M., and M. D. G.) reviewed the patient summaries to determine whether the initiation of piperacillin-tazobactam met any of the predefined criteria. In addition, they determined whether piperacillin-tazobactam should have been continued beyond 72 hours, because this is a common evaluation point for reassessment of therapy in other studies [7]. Majority vote, at least 2 of 3, determined the appropriateness for initiation or for continuation beyond 72 hours.

Statistical Analysis

After random selection of 50 patients from each 3-month period, a χ^2 analysis was completed to establish the generalizability of the data to the entire 1554-course data set. For patient data, analysis included generation of mean, median, and range of various data sets. For the cost analysis

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Table 1. Predefined Indications for Initiation of Piperacillin-Tazobactam

Central venous catheter with fever, with at least 1 of the following criteria: history of intestinal insufficiency, fever/neutropenia, recent abdominal surgery, tracheostomy, or endotracheal tube
Cystic fibrosis (history of) for directed anti-*Pseudomonas* coverage
Intra-abdominal infections (suspected or proven) including cholangitis, appendicitis with rupture, abscess formation, or concerns of peritonitis*
Inta-abdominal perioperative prophylaxis, including liver or biliary tree surgery
Neonate with fever after thoracic surgery
Neutropenic fever
Pneumonia, aspiration
Pneumonia, moderate-to-severe, not community-acquired in an otherwise healthy child*
Pneumonia, ventilator-associated*
Pseudomonas, directed coverage (nonmeningitis)
Sepsis, suspected intra-abdominal or urinary source, or hospital-acquired (not community-acquired sepsis, or in concerns of meningitis)
Skin and soft tissue complicated infections*
Tracheitis, presence of a tracheostomy or an endotracheal tube
Targeted therapy towards pathogen(s) with known sensitivities
Urinary tract infection, complicated

*US Food and Drug Association indications.

for inappropriate continuation of piperacillin-tazobactam, the CHP formulary provides the average local acquisition cost for a 20 kg patient receiving the antibiotic at common dosing regimen over a 24-hour period.

RESULTS

The 1554 courses of piperacillin-tazobactam were initiated during the study time period. A total of 200 charts were selected for review, representing 149 individual patients; 23 patients had more than 1 course reviewed, including 20 patients who had 2 courses, 1 patient who had 3 courses, and 2 patients who had 4 courses. A statistical analysis was completed, demonstrating that there was homogeneity of the patients from all of the 3-month periods. The median age was 4.9 years (range of 28 days to 28 years), and 53% were male.

Piperacillin-Tazobactam Course Data

The median duration of piperacillin-tazobactam administration was 3 days. Most patients were medically complex with underlying diagnoses including the following: solid organ transplantation (including heart, liver, kidney, small bowel, or pancreas), 39 of 200 (19.5%); intestinal failure, 21 of 200 (10.5%); and cystic fibrosis, 8 of 200 (4%). In addition, 25 of 200 (12.5%) were oncology patients, including 12 of 200 (6%) courses associated with a history of autologous or allogenic stem cell transplants. For 126 of 200 (63%) of the courses, the evaluated patient had a central venous catheter, an endotracheal tube was inserted in 35 of 200 (17.5%), a tracheostomy tube was in place for 36 of 200 (18%), or 87 of 200 (43.5%) were admitted to an intensive care unit (general pediatric, neonatal, or cardiac) in the courses. Piperacillin-tazobactam was the only antibiotic started in 54 of 200 (27%) of courses, and vancomycin was coadministered in 124 of 200 (62%) of the courses. The infectious diseases service was formally consulted in 35 of 200 (17.5%) of the courses. Blood cultures were obtained in 100 of 126 (79.4%) of courses in which the patient had a central venous catheter compared with 37 of 74 (50%) of courses without a central catheter. Pathogens were recovered from 39 of 137 (28.5%) of courses with a blood culture, with 35 of 39 (89.7%) of positive cultures obtained from patients with a central venous catheter. Isolated organisms included coagulase-negative *Staphylococcus* species 8 of 39 (20.5%), *Enterococcus faecalis* 6 of 39 (15.4%), *Klebsiella pneumoniae* 3 of 39 (7.7%), *Clostridium species* 2 of 39 (5.1%), *Escherichia coli* 2 of 39 (5.1%), *Pseudomonas aeruginosa* 2 of 39 (5.1%), polymicrobial infections 11 of 39 (28.2%), and single cases of bacteremia with organisms including methicillin-resistant *Staphylococcus aureus*, *Alpha hemolytic streptococcus*, *Flavimonas* species, *Enterobacter cloacae*, and *Morganella morganii*.

Table 2. Panel Assessment of the Utilization of Piperacillin-Tazobactam at Initiation and at 72-Hour Review Mark

Piperacillin-Tazobactam Initiated	200, N (%)
• Agreed with initiation	186 (93)
• Disagreed with initiation	14 (7)
Piperacillin-tazobactam discontinued before or at 72 hours	110 (55)
• Agreed with discontinuation	104 (94.5)
• Disagreed with discontinuation	6 (5.5)
Piperacillin-tazobactam continued beyond 72 hours	90 (45)
• Agreed with continuation	67 (74.4)
• Disagreed with continuation	23 (25.6)

Review for Initiation and Continuation of Piperacillin-Tazobactam

There were 186 courses (93%) in which the majority of the reviewers agreed with the initiation of piperacillin-tazobactam (Table 2); unanimous agreement occurred in 171 of 186 courses (91.9%).

In 110 of 200 (55%) of the courses, piperacillin-tazobactam was stopped before the 72-hour mark, with 3 of these courses being in patients who died within that time period (Table 2). The panel's agreement with the continuation and discontinuation of piperacillin-tazobactam at 72 hours is summarized in Table 2. In the 23 courses in which piperacillin-tazobactam was continued but the panel disagreed, a cost analysis was performed. For those courses, piperacillin-tazobactam was continued a total of 88 antibiotic-days beyond 72 hours. After we extrapolated this value across the total of 1554 courses of piperacillin-

tazobactam over 1 year, this result yielded a total of 684 antibiotic days that could have been eliminated. For a 20 kg child, the daily acquisition cost of piperacillin-tazobactam at CHP is of $27.49. Applied to the 684 antibiotic days, this would translate into an excessive cost of $18,796.56.

DISCUSSION

This medical record review describes the indications and usage of piperacillin-tazobactam at a tertiary care pediatric hospital using 15 established criteria for initiation. In reviewing whether piperacillin-tazobactam's initiation was appropriate, 93% of the courses met a predefined criterion for starting. The current results are similar to the study by Raveh et al [8] in evaluating meropenem, cefepime, and piperacillin-tazobactam use in an adult population, which found appropriate initiation in 90% of courses even before an educational intervention. In contrast, results of the current study differ from 3 other studies in which piperacillin-tazobactam was appropriately initiated in only 71%–71.5% of a primarily adult patient population [9–11]. The differences from those 3 studies may denote different indications for initiation of piperacillin-tazobactam in the pediatric versus adult setting or possible differences in provider education. This study's list of indications was also set broadly and may have overestimated the number of appropriate courses of initiation of the antibiotic.

A unique aspect of the current study was the assessment of the need for continuation of piperacillin-tazobactam at 72 hours after initiation. The panel disagreed with continuing piperacillin-tazobactam beyond 72 hours in 25.6% of the courses, supporting the potential role of day 3 auditing, rather than the introduction of a requirement for preapproval at initiation. Given the frequency of piperacillin-tazobactam prescriptions, implementation of day 3 auditing could lead to a reduction of prescriptions, reduction of antimicrobial pressure on the bacterial organisms, and the hospital bacterial resistance patterns could be used as a marker of future improvement of this intervention [12]. A conservative savings analysis was conducted on the subgroup of patients in which piperacillin-tazobactam was continued beyond 72 hours, but the panel would have stopped or switched to an alternative antibiotic. These calculations identify a potential annual savings of $18,796.56, but this amount does not include the costs of alternative antibiotics and administration costs, and it was based on the dosing of a 20 kg patient.

The potential limitations of this study include evaluating piperacillin-tazobactam in only a 1-year period. In addition, the abstraction of the patient chart may have missed potentially important pieces of information that could have altered conclusions by the panelists, including the day-to-day changes in a patient's exam or vitals. In addition, the prescribed dose and interval of piperacillin-tazobactam or the associated adverse effects were not reviewed. The chart review could not identify the reasons for initiation of the antibiotic on every patient, because a comparison between the primary team and the panel of reviewers could reveal potential areas of education for initiation. Finally, the need for alternate antibiotics was not analyzed in courses where the panel recommended discontinuation of piperacillin-tazobactam after 72 hours.

CONCLUSIONS

In summary, this systematic chart review provides insight into the indications for piperacillin-tazobactam initiation and continuation at 72 hours. Our results suggest that a review at 72 hours could reduce usage and provide cost savings. This study may serve as a guide for determination of which antibiotics require formal approval at initiation or should be audited at 72 hours for reassessment.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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