

DUKE ANTIMICROBIAL STEWARDSHIP OUTREACH NETWORK (DASON)

Antimicrobial Stewardship News

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Drug Shortages: Focus on Piperacillin/Tazobactam (Zosyn™)

Background

Unfortunately, drug shortages are common and unavoidable in modern healthcare. Current drug shortages in the United States include over 200 medications as of 4/21/2015.¹ These drug shortages create significant obstacles for clinicians and have a profound impact on the quality of healthcare.²

The American Society of Health-System Pharmacists (ASHP) provides guidelines on how to manage drug shortages.² An effective plan to deal with drug shortages requires analysis at an individual hospital level and depends upon a number of factors: current drug inventory, purchasing history, frequency of use, and formulary costs of alternative agents (figure). Thus, each DASON member hospital must be responsible for creating a personalized drug shortage plan.

Piperacillin/tazobactam has officially been on shortage since 4/2/2014.³ The shortage has been critical over the past few months. As a result, we have heard that several DASON hospitals have already been impacted by this shortage. Thus, this month's newsletter has two main objectives. First, we will discuss up-to-date details regarding the current piperacillin/tazobactam shortage. Second, we will discuss specific recommendations for how to manage the current piperacillin/tazobactam shortage.

1. Piperacillin/tazobactam drug shortage news

The piperacillin/tazobactam shortage is due to several reasons. Of the eight current pharmaceutical manufacturers, two companies are experiencing manufacturing delays; one has regulatory delays; one has not disclosed a reason; and the remaining four cite increased demand.

Estimated resupply dates vary based on medication dosage, formulation, and manufacturer. For example, Fresenius currently expects to resupply hospitals by early May, whereas some other manufacturers have yet to provide a resupply date.

Regularly updated news on the piperacillin/tazobactam drug shortage can be found online through the ASHP website.⁴

2. Specific piperacillin/tazobactam shortage recommendations

Piperacillin/tazobactam substitutes

The following factors should be taken into consideration when determining a substitute for piperacillin/tazobactam: antibiotic spectrum of activity, formulary cost, and local bacterial susceptibility patterns.

Piperacillin/tazobactam is a potent workhorse agent with broad spectrum activity against many Gram-positive and most Gram-negative and anaerobic pathogens – including many healthcare-associated pathogens such as *Pseudomonas aeruginosa*. An ideal antibiotic substitute should, alone or in combination with other agents, provide similar antimicrobial coverage to piperacillin/tazobactam – at least until bacterial susceptibilities can help direct therapy. As a result, many hospitals are currently substituting piperacillin/tazobactam with cefepime (+/- metronidazole) or a formulary carbapenem.

Cefepime, a fourth-generation cephalosporin, offers similar broad spectrum Gram-positive and Gram-negative activity (including *Pseudomonas aeruginosa*). However, cefepime lacks anaerobic activity; thus metronidazole should be co-administered when an anaerobic infection is possible. In our experience, however, anaerobic coverage is often not needed even when piperacillin/tazobactam is used. Cephalosporin alternatives to cefepime also exist, but these have significant limitations. Ceftriaxone offers good Gram-positive and Gram-negative activity, but it does not cover *P. aeruginosa*. Ceftazidime offers good Gram-negative activity, including *Pseudomonas spp.* However, ceftazidime has poor Gram-positive activity and also lacks anaerobic activity. In addition, many hospitals report a higher incidence of ceftazidime-resistant *Pseudomonas spp.*

Carbapenems can provide a similar spectrum of activity to piperacillin/tazobactam. Meropenem, doripenem, and imipenem/cilastatin provide excellent Gram-positive, Gram-negative, and anaerobic activity; these agents retain activity against important organisms such as *Pseudomonas aeruginosa*. However, the practice of substituting piperacillin/tazobactam for carbapenems has 2 major limitations. First, carbapenems promote the development of the most multi-drug resistant organisms: carbapenem-resistant Enterobacteriaceae (CRE).^{5,6} CRE infections are associated with high mortality, nosocomial-outbreaks, and poor patient outcomes.⁷ Second, these antibiotics are generally more costly than piperacillin/tazobactam. Thus, in general, we do not favor the substitution of piperacillin/tazobactam with a carbapenem.

Infectious Diseases Society of America (IDSA) guidelines provide a reasonable list of other disease-specific antibiotics which can be utilized as piperacillin/tazobactam alternatives. These recommendations are freely available through the IDSA website.⁸

Piperacillin/tazobactam conservation strategies

Current stocks of piperacillin/tazobactam should be conserved. Numerous antibiotic conservation strategies exist. Piperacillin/tazobactam should be restricted to pharmacy or infectious diseases approval; extended-infusion piperacillin/tazobactam should allow stocks to last longer; and piperacillin/tazobactam should be temporarily removed from electronic order sets when possible.

Summary/Recommendations

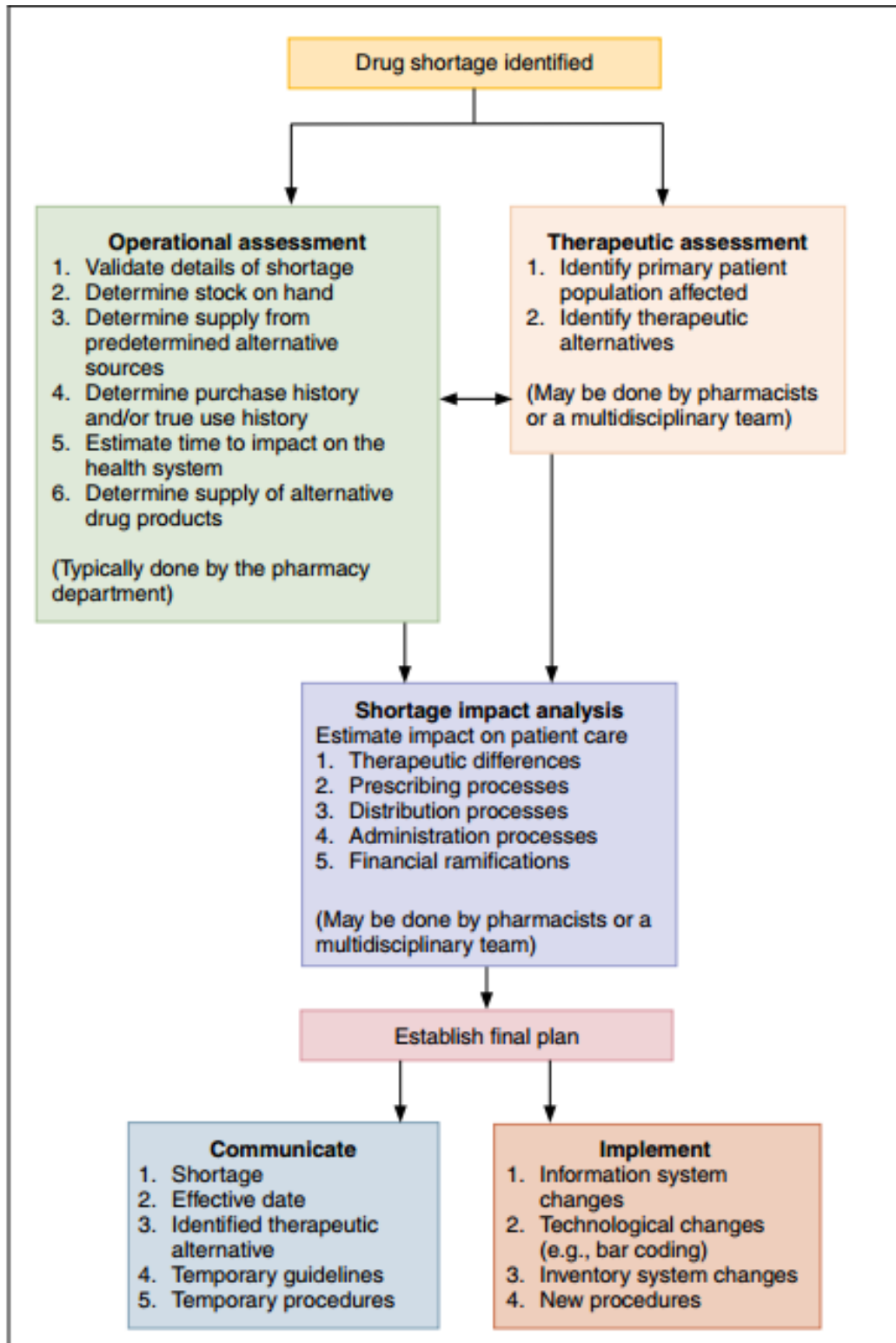
Drug shortages are a significant obstacle in providing excellent patient care, especially when shortages impact workhorse agents such as piperacillin/tazobactam. There is no single “correct” strategy for addressing the current shortage of piperacillin/tazobactam. In general, any strategy and formally designated piperacillin/tazobactam substitutes must be implemented by a local team that includes physicians, pharmacists, administrators, and the microbiology lab.

DASON recommends the following interventions to help reduce the impact of the current piperacillin/tazobactam shortage:

- Review ASHP drug shortage guidelines
- Utilize a multidisciplinary team to develop a drug shortage protocol
- Identify reasonable piperacillin/tazobactam substitutes with assistance from physicians, pharmacists, hospital administrators, and microbiology staff. Possible substitutions may include
 - Cefepime +/- metronidazole
 - Carbapenems
 - Others (via disease-specific IDSA guidelines)
- Conserve current piperacillin/tazobactam stocks
 - Restrict antibiotic use.
 - Use the opportunity to discuss the use of alternatives to piperacillin/tazobactam as an opportunity to discuss de-escalation of therapy
 - Utilize extended-infusions when feasible
 - Remove piperacillin/tazobactam from electronic order sets
- Order piperacillin/tazobactam in multiple doses and from multiple vendors to procure additional stock.

As a DASON member, we can help you develop a reasonable strategy to address the piperacillin/tazobactam shortage that is specific to your hospital.

Figure. American Society for Health-System Pharmacists (ASHP) recommended product shortage decision making algorithm.²



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