

# Antibiotic Shortages in Pediatrics

Ritu Banerjee, MD, PhD,<sup>a</sup> Cary W. Thurm, PhD,<sup>b</sup> Erin R. Fox, PharmD,<sup>c</sup> Adam L. Hersh, MD, PhD<sup>c</sup>

## MEDICATION SHORTAGES ARE INCREASING NATIONWIDE

Medication shortages are increasingly common and severe in the United States and are a serious health threat. Medication shortages occur when reduced supply of a drug influences how it is prepared, dispensed, or prescribed by pharmacies or providers.<sup>1</sup> According to the US Food and Drug Administration (FDA), most shortages are caused by quality and manufacturing problems.<sup>2</sup> Consequences of shortages include rationing limited supplies, delays in therapy, medication errors, use of less-efficacious alternatives, and death.<sup>3</sup> Recently, critical drugs like sodium chloride and amino acids have been on shortage, exacerbated by damage to manufacturing plants by natural disasters like Hurricane Maria. Although shortages have affected virtually all classes of medications, antimicrobial shortages are common and account for 15% of all drug shortages.<sup>1,4</sup>

## ANTIMICROBIAL SHORTAGES CAN CAUSE HARM TO PATIENTS, AND THEIR IMPACT ON CHILDREN IS NOT WELL STUDIED

Medication shortages can force clinicians to treat patients with suboptimal therapy, which, in turn, can lead to poor outcomes. Examples relating to antimicrobial agents are when a penicillin shortage led to use of second-line therapies for neurosyphilis, an intravenous trimethoprim-sulfamethoxazole shortage led to alternative therapies for *Pneumocystis jiroveci* infections, an acyclovir shortage led to use of alternative antiviral therapy for herpes encephalitis, and shortage of amikacin led to alternative antibiotic combinations for multidrug-resistant Gram-negative infections. Most infectious disease physicians surveyed through the Emerging Infections Network reported that antibiotic shortages had adversely affected patient outcomes in their practice because of use of inferior, more-toxic, or costly alternatives.<sup>1</sup> A recent shortage of piperacillin-tazobactam affected 88 of 107 hospitals in the MedMined Clinic Research Database and led many institutions to prescribe alternative antibiotics in place of piperacillin-tazobactam.<sup>5</sup> Hospitals that used more alternative antibiotics had higher rates of hospital-onset *Clostridium difficile* infection among adult patients.<sup>5</sup> Few evaluations of the impact of antimicrobial shortages on children have been performed. During a recent cefepime shortage, many pediatric institutions recommended the use of piperacillin-tazobactam in place of

<sup>a</sup>Vanderbilt University Medical Center, Nashville, Tennessee;

<sup>b</sup>Children's Hospital Association, Lenexa, Kansas; and <sup>c</sup>University of Utah, Salt Lake City, Utah

Drs Banerjee and Hersh conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Thurm collected the data, performed the initial analyses, and reviewed and revised the manuscript; Dr Fox critically reviewed the manuscript for important intellectual content and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**DOI:** <https://doi.org/10.1542/peds.2018-0858>

Accepted for publication Jul 30, 2018

Address correspondence to Ritu Banerjee, MD, PhD, Vanderbilt University Medical Center, 1161 21st Ave, Nashville, TN 37232. E-mail: [ritu.banerjee@vumc.org](mailto:ritu.banerjee@vumc.org)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2018 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** Vizient pays Dr Fox's affiliation, the University of Utah Drug Information Service, to provide them with drug shortage data; no funds are directly paid to Dr Fox; and Drs Banerjee, Thurm, and Hersh have indicated they have no potential conflicts of interest to disclose.

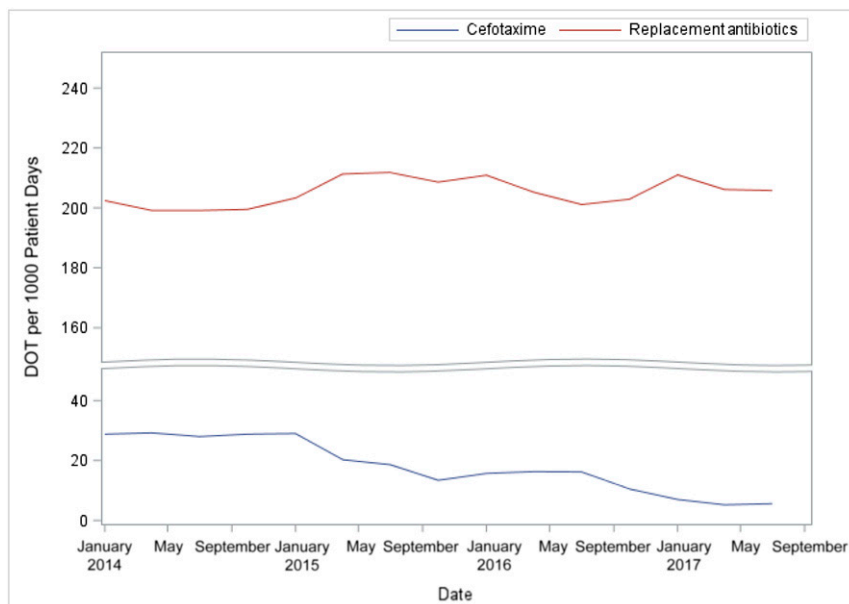
**To cite:** Banerjee R, Thurm CW, Fox ER, et al. Antibiotic Shortages in Pediatrics. *Pediatrics*. 2018;142(5):e20180858

cefepime. At 1 children's hospital, this resulted in higher rates of acute kidney injury, which is associated with piperacillin-tazobactam and vancomycin combination therapy.<sup>6</sup>

### THE CEFOTAXIME SHORTAGE IS AN EXAMPLE OF A DRUG SHORTAGE THAT HAS NOT IMPACTED ALL INSTITUTIONS EQUALLY

The number of companies supplying the third-generation cephalosporin, cefotaxime, has dwindled in recent years until only 1 company was supplying cefotaxime by 2016, as reported by the American Society of Health System Pharmacists drug shortage Web site.<sup>7</sup> Other companies that previously supplied cefotaxime made a business decision to discontinue production because of an increase in the price of the raw materials. The single-remaining supplier was unable to keep up with the demand for cefotaxime, leading to a national shortage.

The cefotaxime shortage has disproportionately affected infants, compared with older patients. This is because a comparable cephalosporin, ceftriaxone, that can be used in older children, is generally not used in infants <2 months of age because of increased risk of kernicterus and calcium-ceftriaxone vascular deposits. Because of limited supply, the American Academy of Pediatrics recommended in February 2015 that clinicians use ceftazidime in place of cefotaxime in infants <2 months of age with proven or suspected infections because of Gram-negative bacilli, particularly meningitis.<sup>8</sup> Use of broad-spectrum therapies in place of cefotaxime may select for drug-resistant bacteria and have adverse consequences on patients' microbiomes. At each of our institutions, the cefotaxime shortage has led to restricted indications for its use and review of alternative regimens.



**FIGURE 1**

Trends in use of cefotaxime and replacement antibiotics (ampicillin, ceftriaxone, ceftazidime, cefepime, gentamicin, meropenem) among children hospitalized at 45 Pediatric Hospital Information System (PHIS) hospitals, 2014 through 2017. DOT, days of therapy (unpublished data).

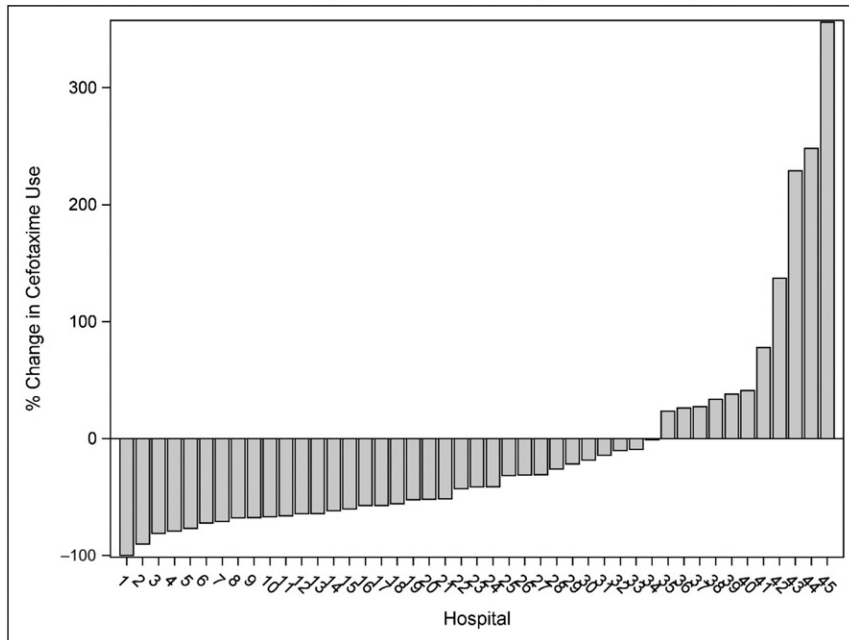
To examine the impact of the cefotaxime shortage on hospitalized children nationwide, we evaluated cefotaxime use, a surrogate for drug availability, among children's hospitals within the Pediatric Hospital Information System network. The change in cefotaxime use was quantified for each hospital between 2014 and 2015 and 2016 through quarter 2, 2017. Cefotaxime use declined by 81%, from 28.8 to 5.6 days of therapy per 1000 patient days between 2014 and 2017, while replacement antibiotic use increased (Fig 1). However, the shortage was not experienced equally among hospitals. There was great variation in the extent to which cefotaxime use declined, for all hospitalized children and for infants <60 days of age with a diagnosis of meningitis (Fig 2).

### CONCLUSIONS AND STRATEGIES TO MITIGATE THE IMPACT OF MEDICATION SHORTAGES

In the United States, medication shortages are common but may not affect all hospitals equally. An example of inequity is demonstrated

by the ongoing cefotaxime shortage, which has led to decreased use of cefotaxime in pediatric hospitals. However, when evaluated at the institutional level, there was significant variation in use (and by implication, uneven availability) of cefotaxime among individual hospitals.

Variation in supplies of critical medications may be due to differences in patient populations, drug use patterns, supply chain management, existence of antimicrobial stewardship programs, and restrictions on use of short-supply drugs. In 2011, the IMS Institute for Healthcare Informatics reported that some states are impacted more than others by drug shortages and attributed this to differences in per capita usage of short-supply products.<sup>4</sup> This variability in drug shortage impact seems unjust. More research is needed to identify optimal strategies for preventing and managing shortages of critical medications, which are likely to continue.



**FIGURE 2**  
Change in cefotaxime use for infants <60 days with a diagnosis of meningitis, between 2014 and 2015 and 2016 through second quarter 2017, among 45 Pediatric Hospital Information System (PHIS) hospitals (unpublished data).

The extent to which medication shortages have affected outcomes in children should be better evaluated. The shortages of antimicrobial agents are especially problematic given that fewer antimicrobial agents are FDA approved for use in neonates, infants, and children, compared with adults, and finding safe, alternative agents during shortages is therefore challenging. Antimicrobial stewardship champions frequently manage the rationing of short-supply drugs and are valuable resources during medication shortages, even for classes other than antimicrobial agents. Stewards have substantial experience in helping to prioritize patients who should receive agents with limited supply, identifying therapeutic alternatives, developing clinical guidelines that incorporate alternative therapies, and communicating with providers about shortages and judicious prescribing. Additionally, antimicrobial shortages may lead to unintended consequences that have benefits.

These include opportunities for more judicious antimicrobial use, wider stewardship efforts, and evaluation of replacement drug safety in pediatric populations (eg, ceftriaxone use in young infants).

There must be interventions to address the problem of critical medication shortages, including increased awareness of the problem and more advocacy and political will to increase FDA oversight of the manufacturing of critical medications. Manufacturers should be required to disclose to the medical community their manufacturing sites, products, and volume, and sole-source medications should not be produced in a single plant. Direct government involvement in the manufacturing of critical medications should be explored. Lastly, manufacturers should receive incentives to continue making products like antibiotics, for which there are small markets, because although these drugs may not be profitable, they are lifesaving.

## ABBREVIATION

FDA: US Food and Drug Administration

## REFERENCES

1. Quadri F, Mazer-Amirshahi M, Fox ER, et al. Antibacterial drug shortages from 2001 to 2013: implications for clinical practice [published correction appears in *Clin Infect Dis*. 2015;61(11):1769]. *Clin Infect Dis*. 2015;60(12):1737–1742
2. US Food and Drug Administration. *A Review of FDA's Approach to Medical Product Shortages*. Washington, DC: US Department of Health and Human Services; 2011
3. Institute for Safe Medical Practices. Medication safety alert. Special issue: Drug shortages: National survey reveals high level of frustration, low level of safety. September 23, 2010. Available at: <https://www.ismp.org/resources/special-issue-drug-shortages-national-survey-reveals-high-level-frustration-low-level>. Accessed September 21, 2018
4. IMS Institute for Healthcare Informatics. *Drug Shortages: A Closer Look at Products, Suppliers, and Volume Volatility*. Parsippany, NJ: IMS Institute for Healthcare Informatics; 2011
5. Gross AE, Johannes RS, Gupta V, Tabak YP, Srinivasan A, Bleasdale SC. The effect of a piperacillin/tazobactam shortage on antimicrobial prescribing and *Clostridium difficile* risk in 88 US medical centers. *Clin Infect Dis*. 2017;65(4):613–618
6. Cook KM, Gillon J, Grisso AG, et al. Incidence of nephrotoxicity among pediatric patients receiving vancomycin with either piperacillin-tazobactam or cefepime: a cohort study [published online ahead of print March 26, 2018]. *J Pediatric Infect Dis Soc*. doi:10.1093/jpids/piy030
7. American Society of Health-System Pharmacists. Cefotaxime sodium injection. Available at: <https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=51>. Accessed July 16, 2018
8. Bradley JS. Alternatives to consider during cefotaxime shortage. *AAP News*. February 25, 2015. Available at: <http://www.aappublications.org/content/early/2015/02/25/aapnews.20150225-1>. Accessed July 16, 2018