Prescription Drug Shortages: Implications for Ambulatory Pediatrics

Katie A. Donnelly, MD[1], Mark S. Zocchi, MPH[2], Tamara A. Katy, MD[3], Erin R. Fox, PharmD[4], John N. van den Anker, MD, PhD[5], and Maryann E. Mazer-Amirshahi, PharmD, MD, MPH[6]

Objective To describe contemporary drug shortages affecting general ambulatory pediatrics.

Study design Data from January 2001 to December 2015 were obtained from the University of Utah Drug Information Service. Two pediatricians reviewed drug shortages and identified agents used in ambulatory pediatrics. Shortage data were analyzed by the type of drug, formulation, reason for shortage, duration, marketing status, if a pediatric friendly-formulation was available, or if it was a single-source product. The availability of an alternative, and whether that alternative was affected by a shortage, also was noted.

Results Of 1883 products in shortage during the study period, 314 were determined to be used in ambulatory pediatrics. The annual number of new pediatric shortages decreased initially but then increased to a high of 38 in 2011. Of the 314 pediatric shortages, 3.8% were unresolved at the end of the study. The median duration of resolved shortages was 7.6 months. The longest shortage was for ciprofloxacin 500-mg tablets. The most common class involved was infectious disease drugs. Pediatric-friendly dosage forms were affected in 19.1% of shortages. An alternative agent was available for 86% drugs; however, 29% of these also were affected. The most common reason for shortage was manufacturing problems.

Conclusions Drug shortages affected a substantial number of agents used in general ambulatory pediatrics. Shortages for single-source products are a concern if a suitable alternative is unavailable. Providers working in the ambulatory setting must be aware of current shortages and implement mitigation strategies to optimize patient care. *(J Pediatr 2018;■■:■■-■■).*

Drug shortages are a significant issue facing pediatric health professionals. A drug shortage is defined as a time when the projected demand for a drug is expected to overwhelm the supply of the drug.[1] These shortages remain a consistent threat to optimal patient care and safety.[2] The driving forces behind these shortages include supply issues, quality concerns, and economic forces.[3] Despite recent interventions from the federal government and the Food and Drug Administration (FDA), drug shortages remain a critical issue that can negatively affect patient care.[4]

Drug shortages disproportionately affect pediatric patients.[5] The recent shortages of clindamycin suspension and intramuscular penicillin are just a few examples of medications used in the pediatric ambulatory setting that are affected by shortages. These shortages force healthcare providers to use medications that may be less familiar, less efficacious, less evidenced-based, or with more adverse effects. Even seemingly unrelated shortages can have devastating consequences for pediatric patients, such as when a shortage of sodium bicarbonate lead to an incorrect compounding of baclofen suspension.[6] This led to an invasive workup and intensive care unit admission for the patient. Fifty-six percent of children in the US use at least 1 prescription or over-the-counter medication at home per week, yet there are limited data describing shortages of medications used in the pediatric ambulatory setting.[7] Therefore, we describe trends in drug shortages for medications commonly used in ambulatory pediatrics.

Methods

Drug shortage data from January 2001 to December 2015 were obtained from the University of Utah Drug Information Services (UUDIS). UUDIS has clinical pharmacists who receive voluntary reports on drug shortages from clinicians and hospitals, confirm the shortage with the manufacturer, and compile data on the specific formulations of drug on shortage. They rely on the manufacturer to determine the reason for the shortage. They also confirm the end of a shortage with the manufacturer and the FDA. This drug-shortage information is published online on the

ASHP	American Society of Health-Systems Pharmacists
FDA	Food and Drug Administration
UUDIS	University of Utah Drug Information Service

From the [1]Emergency Medicine and Trauma Center, Children's National Health System, Washington, DC; [2]The Center for Healthcare Innovation and Policy Research, George Washington University, Washington, DC; [3]Department of Pediatrics and Emergency Medicine, MedStar Georgetown University Hospital, Washington, DC; [4]Drug Information Service, University of Utah Health, Salt Lake City, UT; [5]Department of Pediatrics, Integrative Systems Biology, Pharmacology & Physiology, George Washington University School of Medicine and Health Sciences/Children's National Health System; and [6]Department of Emergency Medicine, MedStar Washington Hospital Center, Washington, DC

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Web site of the American Society of Health-Systems Pharmacists (ASHP). UUDIS started this data compilation in January 2001.

A pediatrician practicing in emergency medicine and a specialist in pediatric emergency medicine reviewed pharmaceutical products affected by shortages in the UUDIS database and identified agents that are used in ambulatory pediatrics (n = 314). Identification was based on the practitioners' clinical experience in their respective fields. Pharmaceuticals primarily prescribed by subspecialties were excluded. An additional member of the study team, an emergency medicine physician who is also a registered pharmacist and board-certified clinical pharmacologist and practices at a pediatric hospital, reviewed discrepancies until a consensus was reached.

Shortage data were analyzed with a focus on the type of drug involved (eg, infectious disease, pulmonary), formulation, reason for shortage, shortage duration, marketing status (brand vs generic), and whether the drug was a pediatric-friendly formulation (liquid/chewable dosing form or having a pediatric concentration) or a single-source product (produced by one manufacturer). Drugs may have multiple uses, but they were included with the most common ambulatory care use, as determined by the authors. The availability of a substitute therapy and whether the alternative also was affected by a shortage at any time during the study period also was noted. Discontinued products were excluded. This study was not evaluated by an institutional review board because it does not involve human subjects.

The final dataset was analyzed for annual trends, shortage duration, and the reasons given for the shortages. To examine annual trends, counts of new shortages were aggregated by month and by year and were examined graphically. We then compared the number of shortages reported per month in the first half of the study period (2001-2008) with the last half of the study period (2009-2015) using the Wilcoxon rank-sum (Mann–Whitney) test. Shortage duration was defined as the number of days between the date of notification to the date of shortage resolution as reported by the UUDIS. Product discontinuations (shortages that lasted zero days) were excluded. A standard conversion factor of 30.4375 days = 1 month was used to convert shortage days to shortage months for ease of interpretation. Shortage duration was not normally distributed (long right tail) as evidenced by a histogram and confirmed by a Shapiro–Wilk W test for normal data. Therefore, shortage duration is presented as medians and IQRs. The nonparametric 2-sample Wilcoxon rank-sum (Mann–Whitney) test and the Kruskal–Wallis equality-of-populations rank tests were used to compare shortage durations.

To determine whether shortage length was changing over time, we used ordinary least-squares linear with month fixed-effects to estimate the annual (yearly) trend in shortage duration. We used the log of shortage duration as our outcome, so the coefficient of year can be approximately interpreted as the percent change in the dependent variable (shortage duration) per year. For all hypothesis tests, a P value of <.05 was considered statistically significant. For shortages still active as of December 31, 2015, data from the first quarter of 2016 were examined to determine whether the shortage had been resolved. If the shortage was still active as of March 31, 2016, shortage duration was calculated as the number of months between the shortage notification and March 31, 2016. Data were collected in Microsoft Excel (Microsoft, Seattle, Washington) and analyzed with Stata 14.1 (StataCorp LLC, College Station, Texas).

Results

After we excluded discontinued products (n = 221), a final dataset of 1883 drug shortages reported between January 2001 to December 2015 was examined. Of these, 314 (17%) were identified as being used in ambulatory pediatrics, 60 of which were identified as having a pediatric-friendly form (19.1%). Annual shortage totals by year are displayed graphically in **Figure 1**. There was a median of 22 ambulatory pediatric shortages reported each year from 2001 through 2015 (IQR = 11-28). Shortages became more frequent in the last half of the study period, where the median number of annual shortages increased to 28 between 2009 and 2015 ($P = .003$). For shortages of pediatric-specific drug forms, there was a median of 4.5 shortages per year (IQR = 1-7). Shortages of pediatric-specific forms became more frequent in the last half of the study period, averaging 7 new shortages per year (IQR = 4-8, $P = .026$).

Table I presents median duration of ambulatory pediatric drug shortages. Of the 314 shortages, 302 were resolved by the end of the study period (96.2%). The median duration of a resolved shortage was 7.6 months (IQR = 3.0-15.2). The 12 unresolved drug shortages had a median duration of 11.1 months (IQR = 5.1-41.9). Shortage duration experienced a continuous linear decline over the study period (2001-2015, $P = .004$), at a rate of approximately −4.8% per year (95% CI −7.9% to −1.5%). One in four drug shortages was administered parenterally, and the majority of these were vaccines. Parenterally administered drugs were on shortage longer than orally administered drugs (16.2 vs 6.2 months, $P < .001$). Drugs with no alternative available were on shortage longer compared with drugs with an alternative available (16.7 vs 6.8 months, $P = .002$), as were drugs produced by more than one manufacturer compared with single-sourced drugs (9.4 vs 6.0 months, $P = .035$).

A reason for the shortage was not reported for 159 of the pediatric ambulatory care drug shortages (50.6%). When a reason was reported, the most commonly cited was manufacturing problems (25.8%), followed by supply/demand issues (13.7%), raw material shortages (4.8%), regulatory issues (2.9%), and business decisions (1.6%). Shortage duration did not differ significantly based on the reason given for the shortage ($P = .082$).

Therapeutic classifications of the drug shortages are presented in **Table II**. The most common type of shortage for ambulatory pediatric drugs were used to treat infectious diseases (n = 60), with a median shortage of 8.9 months (IQR = 4.0-17.9). Vaccine shortages (n = 36) had a median length of 18.5

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