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# Prevalence of Polypharmacy Exposure Among Hospitalized Children in the United States

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**Objective:** To assess the prevalence and patterns of exposure to drugs and therapeutic agents among hospitalized pediatric patients.

**Design:** Retrospective cohort study.

**Setting:** A total of 411 general hospitals and 52 children's hospitals throughout the United States.

**Patients:** A total of 587 427 patients younger than 18 years, excluding healthy newborns, hospitalized in 2006, representing one-fifth of all pediatric admissions in the United States.

**Main Outcome Measures:** Daily and cumulative exposure to drugs and therapeutic agents.

**Results:** The most common exposures varied by patient age and by hospital type, with acetaminophen, albuterol, various antibiotics, fentanyl, heparin, ibuprofen, morphine, ondansetron, propofol, and ranitidine being among the most prevalent exposures. A considerable fraction of patients were exposed to numerous medications: in children's hospitals, on the first day of hospitalization, patients younger than 1 year at the 90th percentile of daily exposure to distinct medications received 11 drugs, and patients 1 year or older received 13 drugs; in general hospitals, 8 and 12 drugs, respectively. By hospital day 7, in children's hospitals, patients younger than 1 year at the 90th percentile of cumulative exposure to distinct distinct medications had received 29 drugs, and patients 1 year or older had received 35; in general hospitals, 22 and 28 drugs, respectively. Patients with less common conditions were more likely to be exposed to more drugs ($P=.001$).

**Conclusion:** A large fraction of hospitalized pediatric patients are exposed to substantial polypharmacy, especially patients with rare conditions.

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IN THE UNITED STATES, FOR PERsons young and old, exposure to medications is essentially universal.[1] Over the past decade, the relatively neglected area of pediatric drug effectiveness and safety has received increasing attention. The 2002 Best Pharmaceuticals for Children Act (BPCA),[2] building on the 1997 US Food and Drug Administration Modernization Act,[3,4] set forth the goal of reducing pharmaceutical errors in the dispensing of drugs to hospitalized children. In the hospital setting, the efficacy and safety of many pediatric medications have not been well established[5]; much of the use of medications is for off-label indications[6]; and medication errors occur.[5,7-10] Both the BPCA and the complementary Pediatric Research Equity Act of 2003[11] have underscored the need for pediatric studies regarding both on- and off-label drug treatments[12-14] and for improvements in pediatric drug labeling.[15,16]

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To advance this agenda, we need to refine our knowledge of the overall patterns of pediatric inpatient drug and therapeutic agent use, including what drugs and therapeutic agents are used most commonly, the number of different drugs and therapeutic agents that hospitalized children receive, and potential differences in drug and therapeutic agent exposures across different types of hospitals. This



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knowledge, especially if based on population-level data, would enhance efforts to prioritize and design research studies regarding the effectiveness and safety of pediatric inpatient medications.[17-19]

To address these objectives, we combined hospital medication use data from 2 large databases, the first of which comprises data exclusively from children's hospitals while the second data set comprises data from mostly general hospitals; together these data sets represent approximately 19.9% of all pediatric inpatient hospitalizations in the United States. In this report, we examine drug and therapeutic agent use patterns among hospitalized pediatric patients (excluding healthy newborns) evident in the combined data, focusing on exposure to polypharmacy, which has been shown to be associated with an increased risk of adverse drug reactions in adult patients in intensive care units and other settings.[20,21]

## METHODS

### HUMAN RESEARCH SUBJECTS PROTECTIONS

The institutional review board of The Children's Hospital of Philadelphia reviewed the study and determined exempted status.

### DATA SOURCES

We used 2 primary data sources. First, the Pediatric Health Information System (PHIS) comprises administrative discharge data from children's hospitals for most of the major metropolitan areas across the United States and is maintained by Child Health Corporation of America (Kansas City, Kansas). Second, the Perspective Data Warehouse (PDW), maintained by Premier Inc (San Diego, California), comprises data from a broad array of academic medical centers, community-based hospitals, and large systems of multiple hospitals distributed throughout the United States in both urban and rural settings. For this study, 40 hospitals in PHIS and 423 hospitals in the PDW in 2006 contained detailed information on pharmacy activity for each day of hospital stay, including codes for each generic entity dispensed. Patient characteristics used in this study were available in all but 0.01% of records, with the exception of race, which was missing in 3.82% of records in the PHIS data source.

### DATA MANAGEMENT

We reassigned records in PHIS and PWD into 2 categories consisting of children's hospitals and general hospitals. All PHIS records were assigned to the children's hospital category. From PWD, records from 2 hospitals included in PHIS were omitted; records from 12 hospitals identified as children's hospitals and exhibiting distributions of patient age and rates of mortality consistent with distributions and rates observed in children's hospitals were classified as children's hospitals; the remaining hospitals were classified as general hospitals. We implemented a standardized drug and therapeutic agent dictionary building up from generic drugs and therapeutic agents that were specified by 1227 distinct codes in PHIS and 1564 in PWD. After cleaning and harmonizing terminology, we found that PHIS had 1144 distinct codes and PWD, 1337, which specified either specific generic drugs or unspecified drug entities within a narrow therapeutic category. Using principally the American Hospital Formulary System Pharmacologic-Therapeutic Classification hierarchy of drug and therapeutic agent classes and prevalent subclasses,[22] the generic entities were grouped into major categories, 27 in PHIS and 29 in PWD.

### STATISTICAL ANALYSIS

We first described the demographic and clinical characteristics of the sample of patients and hospitalizations by calculating percentages. Differences between patients in children's and general hospitals were assessed using Wilcoxon rank sum (for length of stay) and $\chi^2$ tests (for all other patient characteristics).

To describe the patterns of exposures, we calculated percentages of exposure to specific generic drugs and therapeutic agents and exposure to major drug and therapeutic agent categories by patient (across potentially several hospitalizations), by each hospitalization, and by each hospital day. We calculated hospitalization-level percentiles of (1) the number of exposures to discrete generic drugs and therapeutic agents on each day of hospitalization (reflecting concurrent exposure to medications that might interact) and (2) the cumulative number of exposures to discrete generic drugs and therapeutic agents on each successive day of hospitalization (reflecting the total exposure to different drugs and therapeutic agents that each pose some hazard of adverse drug reactions).

To assess the relationship of cumulative total drug and therapeutic agent exposure to the prevalence of the patients' conditions, we calculated the mean cumulative number of exposures to discrete generic drugs and therapeutic agents across each entire hospitalization for patients in each All Patient Refined Diagnostic Related Group (APR-DRG) category, and we regressed this mean number for each APR-DRG against the volume for each APR-DRG as a percentage of all patients using linear regression.

To assess the relationship of cumulative total drug and therapeutic agent exposure (which is a count of the number of distinct entity exposures for each patient during each hospitalization) by hospital type and the impact of different patient populations, we fitted a base case negative binomial model (which is suitable for modeling counts and comparing rates of exposure) with hospital type (children's vs general hospital) as the only covariate (unadjusted), the added covariates of patient age in years, sex, length of stay (LOS) in days, and whether the patient had surgery (partially adjusted), and then each patient's APR-DRGs assignment using 311 indicator variables for each APR-DRGs (fully adjusted); we focused on the change in the estimate for the hospital type covariate across the models. All data management and analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina) and Stata 11.1 (StataCorp, College Station Texas).

## RESULTS

In our 2006 sample, a total of 365 868 pediatric patients younger than 18 years experienced 491 451 hospitalizations in 52 children's hospitals, and a total of 221 559 pediatric patients experienced 260 740 hospitalizations in 411 general hospitals (**Table 1**). Compared with patients in general hospitals, patients in children's hospitals were older and slightly more likely to be male and to die during the hospitalization.

**Figure 1** shows an alphabetical list of 20 common medication categories, stratified by patient age, and the prevalence of exposures to intravenous fluids; analgesics (including drugs such as acetaminophen and ibuprofen, which are also used as antipyretics); antiinfective agents; gastrointestinal, hematologic, and



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**Table 1. Characteristics of Patients in Children's and General Hospitals[a]**

| Characteristic | Children's Hospitals (n=52) (491 451 Hospitalizations) | General Hospitals (n=411) (260 740 Hospitalizations) |
|---|---|---|
| Age, y | | |
| <1 | 29.6 | 40.0 |
| 1-4 | 25.2 | 18.5 |
| 5-9 | 16.8 | 9.9 |
| 10-14 | 17.0 | 11.2 |
| 15-17 | 11.4 | 20.4 |
| Sex | | |
| Male | 54.9 | 50.0 |
| Female | 45.1 | 50.0 |
| Race | | |
| White | 49.8 | 49.1 |
| Hispanic | 17.9 | 11.8 |
| Black | 21.9 | 18.2 |
| Asian/Pacific Islander | 2.2 | 1.5 |
| American Indian | 0.5 | 1.3 |
| Other | 7.7 | 18.1 |
| Geographic region | | |
| Midwest | 27.9 | 16.2 |
| Northeast | 16.2 | 10.7 |
| South | 37.3 | 57.3 |
| West | 18.6 | 15.8 |
| Urban/rural | | |
| Urban | 99.4 | 87.1 |
| Rural | 0.6 | 12.9 |
| Teaching status | | |
| Teaching | 98.2 | 39.8 |
| Nonteaching | 1.8 | 60.2 |
| Length of stay, mean (range), d | 3 (2-5) | 2 (2-5) |
| Payers | | |
| Medicaid | 43.9 | 46.5 |
| Other government payers | 3.5 | 2.1 |
| Nongovernment insurance | 32.9 | 45.0 |
| Self-pay | 2.7 | 4.0 |
| No charge | 0.1 | 0.1 |
| Other | 17.0 | 2.3 |
| Disposition | | |
| Home | 93.4 | 88.7 |
| Short-term hospital | 1.3 | 4.5 |
| Home health care | 2.8 | 4.2 |
| Died in hospital | 1.1 | 0.9 |
| Other | 1.4 | 1.7 |

[a] Unless otherwise noted, all data are reported as percentage of patients; $P<.001$ for all comparisons between children's and general hospitals for all characteristics.

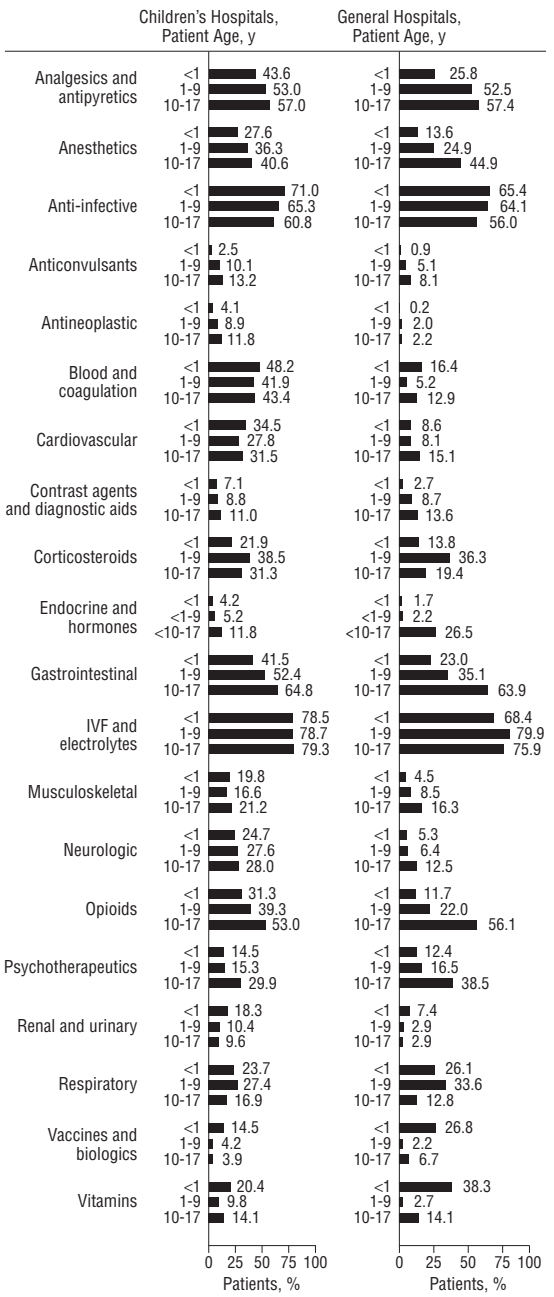


**Figure 1.** Percentage of patients exposed to major drug and therapeutic agent classes by age group and hospital type.

anesthetic drugs; and, among patients aged 10 to 17 years, psychopharmacologic drugs.

**Table 2** lists the 15 most common generic medication exposures (excluding intravenous fluids, hyperalimentation, multivitamins, heparin flushes, glycerin suppositories, dextrose water, and sterile water) in rank order for both the children's and general hospitals, stratified by age, and reveals the prevalence of exposure to acetaminophen, albuterol, various antibiotics, fentanyl, heparin, ibuprofen, morphine, ondansetron, propofol, and ranitidine (as well as oxytocin among adolescent female patients hospitalized for the delivery of newborn infants). A complete table of the number and percentage of patient hospitalizations exposed to all drugs and therapeutic agents, likewise stratified by patient age and hospital type, is available from the corresponding author.

As illustrated in **Figure 2**, on the first day of hospitalization, the typical (median) exposure of an infant patient in a children's hospital was 4 distinct generic drugs and therapeutic agents, and this number dipped to 3 on hospital day 2 and then rose to 4 by hospital days 3 through 30 (for patients who remained hospitalized for that LOS); the infant patient at the 90th percentile of daily drug and therapeutic agent exposures was exposed to 11 drugs and therapeutic agents on hospital day 1, and this



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**Table 2. Top Dozen Generic Drug Entity Exposures by Patient Age and Hospital Type[a]**

| | Children's Hospitals | | General Hospitals | |
|---|---|---|---|---|
| Age, y | Drug Entity | Patients, % | Drug Entity | Patients, % |
| <1 | Heparin | 42.9 | Ampicillin | 38.9 |
| | Acetaminophen | 40.6 | Vitamin K | 31.0 |
| | Ampicillin | 31.0 | Erythromycin | 29.8 |
| | Gentamicin | 23.6 | Gentamicin | 29.7 |
| | Fentanyl | 23.0 | Acetaminophen | 24.1 |
| | Potassium chloride | 21.6 | Hepatitis B vaccine | 21.4 |
| | Morphine | 20.3 | Potassium chloride | 15.6 |
| | Ranitidine | 19.7 | Calcium gluconate | 15.5 |
| | Albuterol | 17.7 | Ceftriaxone | 14.0 |
| | Cefotaxime | 17.3 | Albuterol | 12.2 |
| | Furosemide | 16.5 | Cefotaxime | 12.0 |
| | Midazolam | 15.7 | Heparin | 10.2 |
| | Lidocaine | 14.6 | Ranitidine | 8.5 |
| | Epinephrine | 14.3 | Fentanyl | 7.9 |
| | Cefazolin | 13.6 | Lidocaine | 7.5 |
| 1-9 | Acetaminophen | 42.0 | Acetaminophen | 42.5 |
| | Heparin | 36.6 | Ceftriaxone | 32.1 |
| | Ondansetron | 28.1 | Albuterol | 23.8 |
| | Morphine | 27.3 | Ibuprofen | 22.8 |
| | Albuterol | 23.2 | Methylprednisolone | 14.6 |
| | Fentanyl | 22.2 | Potassium chloride | 14.0 |
| | Midazolam | 22.0 | Morphine | 13.8 |
| | Ibuprofen | 18.2 | Prednisolone | 13.4 |
| | Propofol | 17.3 | Fentanyl | 12.3 |
| | Lidocaine | 15.7 | Ipratropium | 12.0 |
| | Diphenhydramine | 15.5 | Ondansetron | 11.9 |
| | Narcotic combination | 15.1 | Midazolam | 11.3 |
| | Ranitidine | 15.0 | Azithromycin | 11.3 |
| | Cefazolin | 14.7 | Propofol | 11.0 |
| | Ceftriaxone | 14.2 | Levalbuterol | 10.1 |
| 10-17 | Ondansetron | 40.4 | Fentanyl | 31.6 |
| | Acetaminophen | 39.4 | Morphine | 30.0 |
| | Morphine | 38.2 | Acetaminophen | 29.4 |
| | Heparin | 36.7 | Ibuprofen | 25.8 |
| | Fentanyl | 28.1 | Ondansetron | 22.7 |
| | Narcotic combination | 23.9 | Oxytocin | 20.7 |
| | Propofol | 23.4 | Midazolam | 20.4 |
| | Diphenhydramine | 22.8 | Propofol | 19.8 |
| | Midazolam | 22.4 | Promethazine | 19.7 |
| | Lidocaine | 20.8 | Lidocaine | 19.3 |
| | Ibuprofen | 18.9 | Cefazolin | 16.5 |
| | Ketorolac | 18.8 | Hydrocodone/acetaminophen | 14.3 |
| | Cefazolin | 18.4 | Ketorolac | 14.2 |
| | Ranitidine | 16.7 | Docusate | 13.1 |
| | Potassium chloride | 13.8 | Oxycodone/aspirin | 12.5 |

[a] Percentage of patients exposed to the named drug at any point during the hospitalization; rank ordering omits intravenous fluids, sterile water, dextrose water, heparin intravenous flushes, hyperalimentation, multivitamins, and glycerin suppository.

number increased to 13 drugs and therapeutic agents after the first week of hospitalization. For patients 1 year or older, in children's hospitals, the median (90th percentile) level of exposure was 5 (13) distinct drugs and therapeutic agents on day 1 and rose to 9 (20) by day 30. For infant patients in general hospitals, the typical patient on hospital day 1 was exposed to 3 drugs and therapeutic agents, and this number did not exceed 3 drugs and therapeutic agents through 30 days of hospitalization; infant patients at the 90th percentile of daily drug and therapeutic agent exposure received 8 drugs and therapeutic agents on day 1 and between 8 and 11 drugs and therapeutic agents after hospital day 5. For patients 1 year or older in general hospitals, the median (90th percentile) level of exposure on day 1 was 5 (12), and by day 30 it was 6 (15).

As illustrated in **Figure 3**, the cumulative number of distinct generic drug and therapeutic agent exposures for each successive day of hospitalization for the median (and 90th percentile) infant patient in a children's hospital increases from 4 (11) on the first hospital day to 25 (51) by hospital day 30; for patients 1 year or older, the increase is from 5 (13) to 42 (66). For patients in general hospitals, the increase for infant patients at the median (90th percentile) level of exposure is from 3 (8) to 21 (35), and for patients 1 year or older, over 5 (12) to 25 (57).



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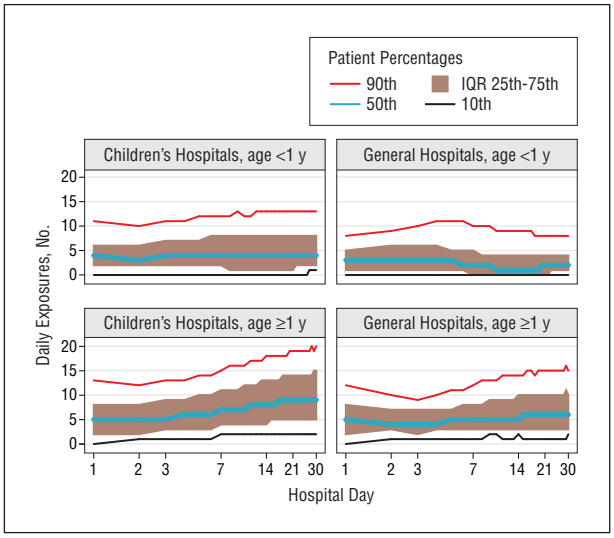


**Figure 2.** Number of daily distinct drug and therapeutic agent exposures over hospital course by hospital type and patient age. Shown are the levels of exposure to distinct drugs and therapeutic agents for each hospital day, from day 1 up to day 30 of hospitalization, for patients who remained hospitalized for those lengths of stay. For each hospital day, we determined the level of exposure for patients at various percentiles of exposure and the interquartile range (IQR). *Daily exposure* is defined as the number of distinct drugs and therapeutic agents that patients at each percentile were exposed to on that hospital day.

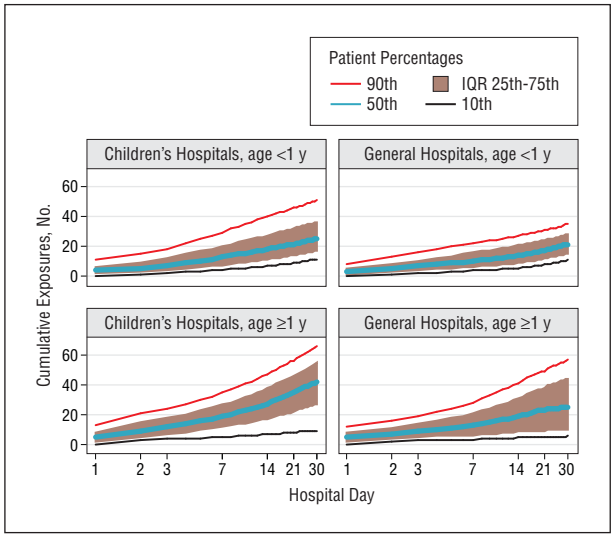


**Figure 3.** Cumulative number of distinct drug and therapeutic agent exposures per hospitalization by length of stay, hospital type, and patient age. Shown are the levels of cumulative exposure to distinct drugs and therapeutic agents that had occurred for patients up to each hospital day, including all preceding days; exposure to the same drug or therapeutic agent across days in this cumulative exposure assessment was counted only once. For each hospital day, we determined the level of cumulative exposure for patients at various percentiles of exposure and the interquartile range (IQR). *Cumulative exposure* is defined as the number of distinct drugs and therapeutic agents that patients at each percentile had been exposed to up to and including that hospital day.

The mean cumulative number of distinct generic drug and therapeutic agent exposures for the entire hospitalization for each APR-DRG in children's hospitals ranged from 1.0 to 74.4 (median of the individual APR-DRG means, 13.5), and for patients in general hospitals, it ranged from 0.7 to 59 (median of the means, 12.0). Plotting the mean number of cumulative drug and therapeutic agent exposures for patients in each APR-DRG against the percentage of all patients in each APR-DRG reveals that the highest levels of cumulative drug and therapeutic agent exposures are for the less common conditions (**Figure 4**) (linear trend, $P=.001$ for children's hospitals and $P<.001$ for general hospitals).

Hospitals varied substantially in the cumulative number of distinct generic drug and therapeutic agent exposures for patients in the common APR-DRGs of asthma, appendectomy, and seizure, even when accounting for differences in the mean LOSs across hospitals for these conditions, and with no discernable relationship to a hospital's volume of patients in each APR-DRG (**Figure 5**).

To assess the impact of patient case mix on the level of drug and therapeutic agent exposure in children's hospitals compared with general hospitals, we examined the effect of sequentially adjusting for more patient characteristics (**Table 3**). In the unadjusted model, patients in children's hospitals were estimated to be exposed during the hospitalization to 1.34 times more drugs and therapeutic agents than those in general hospitals; adjusting for patient age, sex, LOS, and whether surgery was performed reduced this estimate to 1.19 times more medications; further adjustment for patients' APR-DRGs reduced the estimate to 1.09 times more medications, suggesting that the difference in the number of medications used by the hospitals is predominantly owing to underlying differences in their patient populations.

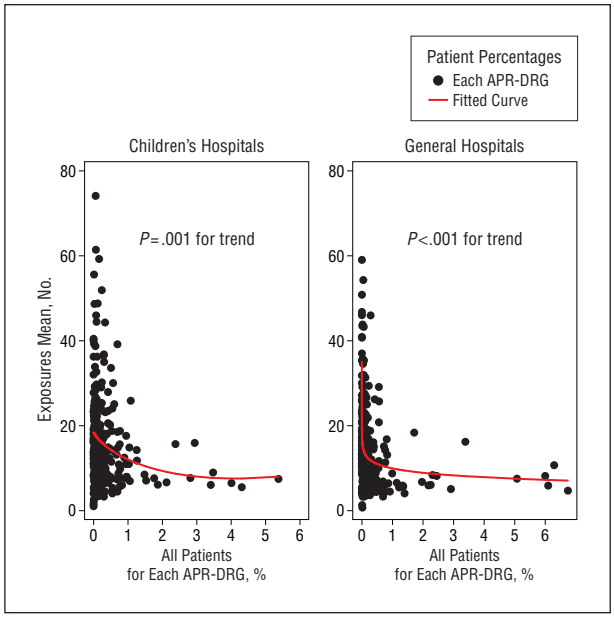


**Figure 4.** Levels of exposure to drugs and therapeutic agents were higher for patients with less prevalent medical conditions (All Patient Refined Diagnostic Related Groups [APR-DRGs]). Illustrated is the relationship between the prevalence of patients' conditions (as classified in 311 APR-DRGs) and the mean cumulative exposure to distinct drugs and therapeutic agents during hospitalizations for patients in each APR-DRG. For both children's hospitals and general hospitals, patients with less common conditions were exposed to a greater number of distinct drugs and therapeutic agents during their hospitalizations. No APR-DRG accounted for more than 6%.



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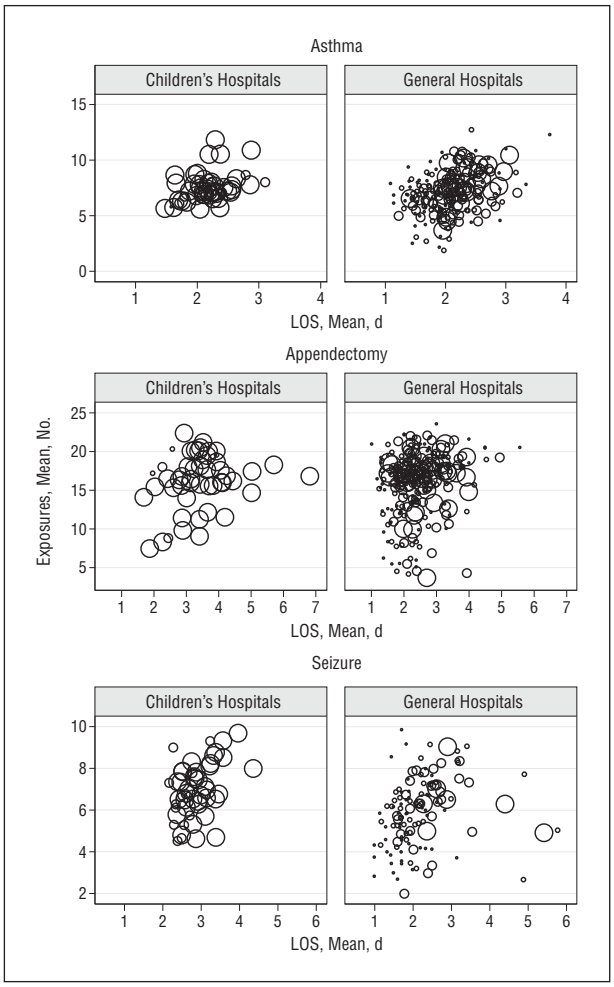


**Figure 5.** Cumulative exposure to distinct drugs and therapeutic agents during hospitalization for 3 common pediatric conditions. Illustrated is the variation among hospitals in mean cumulative number of exposures to distinct drugs and therapeutic agents for patients hospitalized for asthma, appendectomy, or seizure. Each hospital's circular symbol is proportional in size to its number of patients treated for the given condition. Since cumulative exposure increases with longer length of stay (LOS), measured in days, each hospital's circular symbol is located at that hospital's mean LOS.

**Table 3. Multivariable Adjusted Rate Ratios of Cumulative Total Number of Exposures to Distinct Drugs and Therapeutic Agents for Hospitalized Pediatric Patients**

| | Rate Ratio (95% CI) of Exposure to Additional Drug or Therapeutic Agent[a] | | |
|---|---|---|---|
| Characteristic | Unadjusted | Partial Adjustment | Full Adjustment |
| Children's hospitals vs general hospitals | 1.341 (1.338-1.343) | 1.185 (1.183-1.342) | 1.089 (1.088-1.091) |
| Age, y | | | |
| <1 | NA | [Referent] | [Referent] |
| 1-4 | NA | 0.943 (0.941-0.945) | 1.117 (1.115-1.119) |
| 5-9 | NA | 0.969 (0.967-0.972) | 1.158 (1.155-1.161) |
| 10-14 | NA | 1.032 (1.030-1.034) | 1.245 (1.242-1.248) |
| 15-17 | NA | 1.145 (1.143-1.148) | 1.313 (1.309-1.317) |
| Female vs male sex | NA | 0.982 (0.981-0.983) | 0.999 (0.998-0.999) |
| Each additional day of LOS | NA | 1.006 (1.006-1.006) | 1.005 (1.005-1.005) |
| Surgery vs no surgery | NA | 2.163 (2.160-2.166) | 1.558 (1.554-1.563) |
| Patient APR-DRG (311 indicator variables) | NA | NA | ✓ |

Abbreviation: APR-DRG, All Patient Refined Diagnostic Related Group; CI, confidence interval; LOS, length of stay; NA, not applicable; ✓, 311 indicator variables for each APR-DRG included in this full adjustment model.
[a] $P < .001$ for all parameters listed.

## COMMENT

In this study of nearly one-fifth of all pediatric hospitalizations across the United States, we found that the most common generic drugs and therapeutic agents to which children were exposed included intravenous fluids; analgesics such as the narcotics fentanyl and morphine or the antipyretics/analgesics acetaminophen and ibuprofen; anti-infective agents such as ampicillin, gentamicin, and cephalosporins; anesthetic agents such as lidocaine and propofol; gastrointestinal drugs such as ranitidine, ondansetron, and metoclopramide; and a bundle of drugs often provided to newborns as part of routine care, including vitamin K, erythromycin eye drops, immunization drugs, and application of triple dye anti-infective agents to the umbilicus. Exposures to certain classes of drugs, such as antineoplastic and cardiovascular agents, were much more likely to occur in children's hospitals. We also found that a large proportion of hospitalized children were exposed to 5 or more drugs and therapeutic agents during each day of their hospitalization. The total number of drug and therapeutic agent exposures over the course of the entire hospitalization equaled a dozen drugs and therapeutic agents for the typical patient admitted to a children's hospital (with a median LOS of 5 days) but was only 2 drugs and therapeutic agents for the typical patient admitted to a general hospital (with a median LOS of 2 days). The difference between children's and general hospitals in the total exposure of patients to drugs and therapeutic agents, though, was essentially nullified when patient clinical characteristics were taken into account. By contrast, variation among the children's hospitals and among the general hospitals of the number of medication exposures during admissions for 3 common medical conditions was substantial.

This study, based on data from 752 191 admissions among 587 427 patients to 463 hospitals, provides a broad overview of pediatric inpatient drug and therapeutic agent exposures, and complements the few existing reports regarding pediatric medication exposures in either hospital or community settings. An assessment of 32 484 patients admitted to a single US children's hospital[23] found that the most common drug exposures were to acetaminophen (40.5% of patients), midazolam (26.0%), morphine (24.4%), albuterol (22.4%), acetaminophen-codeine (22.4%), cefazolin (16.7%), ondansetron (15.7%), ranitidine (15.1%), and ibuprofen (10.1%), and noted apparent variation in the likelihood of exposure to medications based on patient age, sex, and race (statistical testing for variation was not performed). An analysis of the PDW 2008 database[24] found that the most common drug expo-



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sures were acetaminophen (14.7% of patients), lidocaine (11.0%), ampicillin (8.0%), gentamicin (6.6%), fentanyl (6.6%), ibuprofen (6.3%), morphine (6.2%), ondansetron (6.2%), ceftriaxone (5.6%), and albuterol (5.1%). A European study of outpatient pediatric drug use[25] documented prevalent exposures to anti-infective agents (such as amoxicillin, amoxicillin/clavulanic acid, clarithromycin, or azithromycin, with 48% of the population exposed to an anti-infective agent during the course of a year); dermatologic drugs (such as fusidic acid, hydrocortisone, or miconazole, with 30% annual exposure); and respiratory drugs (such as albuterol, fluticasone, or desloratadine, with 30% annual exposure). This study also found substantial variation in likelihood of exposure by patient age and sex (especially for adolescent girls).[25]

While the present study has considerable breadth and depth and represents a wide spectrum of pediatric inpatient drug and therapeutic agent exposures, 5 primary limitations of the study warrant consideration. First, as is also the case for outpatient drug exposure studies,[26] the fact that a patient in our data was prescribed and billed for a particular medication does not necessarily assure that the patient received the medication; the patient may have refused the medication, or clinical events affecting the patient may have altered the course of therapy from what had been prescribed. While the degree to which such events occur is currently unknown, and should be assessed, we believe that nonreceipt of prescribed medications in the hospital setting does not occur frequently.

Second, while patients should not be billed for medications that are ordered to be received on a *pro re nata* (PRN) basis, or as needed, and in fact are not received, we cannot assess whether the billing data are entirely accurate in this regard, and overbilling would increase (likely to a small degree) the levels of drug and therapeutic agent exposures that we report. Third, some prescribed entities were recorded in the data as being simply an unspecified entity within a therapeutic class of drugs or therapeutic agents (such as an unspecified respiratory or analgesic drug); if a patient received more than 1 distinct entity that shared a common "unspecified" code, then we would have undercounted that patient's exposure to distinct entities and underestimated the level of polypharmacy exposure. Fourth, we do not report drug doses in terms of either the amount of medications or the number of doses because these aspects of the pharmacy data files were of uncertain consistency across all the hospitals in this study.

Fifth, the data do not contain any information on the indication or purpose for which the medications were prescribed. This is an inherent limitation regarding the certainty with which investigators can study drugs used for a particular purpose, and it underscores a sixth limitation regarding drug classification schemes, which tend to categorize drugs according to a single major therapeutic intention, anatomic location of activity, or physiologic mechanism. A drug such as caffeine, for example, used primarily in the neonatal setting to stimulate respiratory drive, is classified as a psychotherapeutic agent due to its stimulation of the nervous system. Patients' exposure to various classes of drugs and therapeutic agents must be interpreted with this important caveat in mind.

These limitations notwithstanding, the findings and the data of this study offer at least 3 important means to improve pediatric inpatient medication efficacy, effectiveness, and safety. First, ranking of drug and therapeutic agents based on the prevalence of hospitalized children's exposure can guide prioritization of further research. For example, research should focus on (1) drugs and therapeutic agents that lack sufficient pediatric data to support therapeutic efficacy or (2) drugs that are used principally for off-label indications. Other research should develop methods to detect adverse events for pediatric inpatients[27] or to teach parents how to administer medications for those patients who are discharged while taking multiple medications.[28] Furthermore, one can contemplate methods to extrapolate the prevalence of drug and therapeutic agent exposure observed in these data to the entire US population of pediatric inpatients to provide an estimated denominator for reports from inpatient settings of adverse events associated with exposure to a particular drug and therapeutic agent; the actual techniques and validity of such extrapolations would need to be developed and assessed.

Second, the level of polypharmacy exposure found in this study raises patient safety concerns, given the relationship between polypharmacy and adverse drug events that has been documented for adults in both hospital and nursing home settings.[20,21] The common exposure to polypharmacy among hospitalized children motivates investigation of combinations of drugs and therapeutic agents to which patients are exposed and studies to detect potentially adverse drug-drug interactions, especially for patients in intensive care unit settings and patients with complex chronic conditions, who are at higher risk of polypharmacy.[29] In addition, the substantial variation in the number of total medication exposures observed across hospitals for common medical conditions suggests that systems of care may enable the degree of polypharmacy to be diminished while maintaining (or even improving) outcomes.

Third, these databases offer the potential to conduct rigorous comparative effectiveness and safety studies. Their data are sufficiently detailed regarding the timing and patterns of medication exposures during the course of a hospitalization episode and present a well-ordered temporal sequence of the health conditions or complications that precede drug and therapeutic agent exposure and the health outcomes or adverse events that follow drug exposure.[30] Research in this area is already under way.[31-33] For pediatric patients with rare conditions, who are likely to be exposed to higher levels of polypharmacy, observational studies of treatment effects based on data sources large enough to amass a sufficient number of patients with varying exposure status may prove to be a vital adjunct to controlled clinical trials.

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