

Opioid-Related Critical Care Resource Use in US Children's Hospitals

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abstract

BACKGROUND AND OBJECTIVES: There has been a rapid increase in the rate of pediatric opioid-related hospitalizations. It is unknown how this increase has impacted the use of pediatric critical care. Our objective in this study was to assess the trends in pediatric hospitalization for opioid ingestions in a cohort of US children's hospitals and, specifically, to evaluate the impact on pediatric critical care resource use.

METHODS: A retrospective cohort study of the Pediatric Health Information System was performed to identify hospitalizations for opioid ingestions from 2004 to 2015. Admission to the PICU and the use of naloxone, vasopressors, and ventilation were assessed by using billing data. The primary outcome measure was the trend in the rate of PICU admission for opioid-related ingestion over time, assessed by using Poisson regression.

RESULTS: There were 3647 opioid-related hospitalizations in 31 hospitals; 42.9% required PICU care. The overall mortality was 1.6%, with annual deaths decreasing from 2.8% to 1.3% ($P < .001$). The number of opioid-related hospitalizations requiring PICU care doubled between 2004 and 2015. The rate of PICU admission for opioid-related hospitalization increased significantly, from 24.9 to 35.9 per 10 000 PICU admissions ($P < .001$). Among PICU admissions, 37.0% required mechanical ventilator support, and 20.3% required vasopressors.

CONCLUSIONS: The US opioid crisis is negatively impacting children, and the rate of hospitalization and PICU admission for pediatric opioid ingestions is increasing. Current efforts to reduce adult opioid use have not curtailed the incidence of pediatric opioid ingestions, and additional efforts are needed to reduce preventable opioid exposure in children.

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Dr Kane conceptualized and designed the study and drafted the initial manuscript; Dr Hall collected data, conducted the initial analyses, and provided interpretation of data; Dr Bartlett provided substantial input to the study design and provided interpretation of data; Dr Colvin provided substantial interpretation of data; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Currently, there is an opioid epidemic in the United States. Pediatric exposure to these drugs has been associated with a rapid increase in the annual rate of pediatric opioid-related hospitalizations.

WHAT THIS STUDY ADDS: This is the first study to assess PICU resource use because of opioid ingestion. Between 2004 and 2015, PICU admissions for opioid ingestion increased by 35%, with a concomitant increase in mechanical ventilation and vasopressors but reduced costs per PICU admission.

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The number of deaths in the United States that are attributable to opioid medications has doubled since 2000.^{1,2} Poisonings that are attributed to prescription drugs are now the leading cause of injury-related mortality in the United States.^{3,4} Despite a number of high-profile prevention strategies, poisonings from prescription medications continue to be a major cause of morbidity among children.⁵ Emergency department (ED) visits for opioid-related indications have risen substantially in both children and adults during the past 2 decades; ED visits for prescription-opioid overdose, abuse, and misuse now rival those of illicit drugs, including heroin and cocaine.^{6,7} Even in children <6 years old, opioids now account for the majority of drug poisonings.⁸

The incidence of hospitalization for prescription-opioid poisonings among children and adolescents 1 to 19 years of age increased nearly twofold from 1997 to 2012, with the largest percentage increase occurring among the youngest children, aged 1 to 4 years.⁹ Additionally, there has been a worrisome increase in the adult intensive care mortality from opioid overdose.¹⁰ It is unknown whether this trend, either in-hospital mortality or the need for critical care, is also occurring in the pediatric population. Understanding these trends is essential for appropriate planning within the pediatric critical care community. It is also essential to understand the financial contribution of complex and expensive multiorgan care provided in the PICU relative to overall hospital-associated costs of opioid-related hospitalization so that cost-reduction strategies can be implemented.

Little is known about the epidemiology of opioid ingestions among admissions to PICUs in the United States. Thus, our purpose in this study was to assess the trends in pediatric hospitalization from opioid

ingestion in a cohort of US children's hospitals and, specifically, to evaluate the impact on pediatric critical care resource use. We hypothesized that opioid-related admissions to the PICU have increased significantly over time as has critical care resource use.

METHODS

Data Source

This was a retrospective cohort study of the Pediatric Health Information System (PHIS) database. The PHIS contains administrative and billing data from 49 tertiary-care children's hospitals located in 27 states and the District of Columbia. Admissions to children's hospitals with data provided to the PHIS account for ~20% of all pediatric hospitalizations in the United States.¹¹ The database contains encounter-level data, including demographics, up to 41 *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, 10th Revision* (ICD-10) diagnoses, and up to 41 ICD-9 and ICD-10 procedure codes.¹² Daily billing data and daily indicators of PICU use are also present. Data are deidentified before inclusion in the database; however, encrypted medical record numbers allow for tracking individual patients across hospital visits and admissions. The Children's Hospital Association (Lenexa, KS) and participating hospitals jointly ensure the quality and integrity of the data, as previously described.¹³ The University of Chicago Institutional Review Board determined this study to be exempt from review.

Population and Selection Criteria

All inpatient and observation encounters of children aged 1 to 17 years that were included in the PHIS from January 1, 2004, to September 30, 2015, were included from the 31 hospitals that provided

continuous data during this period. We identified hospitalizations that were attributed to opioid toxicity, either via prescription or illicit drugs, by means of a previously validated case-identification schema by using specific *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes (or their *International Classification of Diseases, 10th Revision, Clinical Modification* equivalents using available crosswalks): E850.0 (accidental poisoning by heroin), E850.1 (accidental poisoning by methadone), E850.2 (accidental poisoning by another opioid), 965.00 (poisoning by opium), 965.01 (poisoning by heroin), 965.02 (poisoning by methadone), or 965.09 (poisoning by other opiates).^{10,14} Hospital costs were estimated from charges by using hospital- and year-specific cost-to-charge ratios and inflated to 2015 dollars by using the medical component of the consumer price index. Admission to the PICU and the use of naloxone, vasopressors, and mechanical ventilation (invasive and noninvasive) were assessed by using billing data.

Outcome Measures

The primary outcome measure was the rate of PICU admission for opioid ingestion per 10 000 PICU admissions over the study period. Secondary outcomes included in-hospital mortality, total and PICU-associated costs and length of stay, and the use of vasopressors, naloxone, and mechanical ventilation.

Statistics

To aid in bivariate analyses, years were grouped into epochs of 2004 to 2007, 2008 to 2011, and 2012 to 2015. Categorical variables were summarized with frequencies and percentages and compared across epochs by using χ^2 statistics. Continuous variables were summarized with medians

TABLE 1 Demographics of Opioid-Related Hospitalizations

	Total	2004–2007	2008–2011	2012–2015 ^a	<i>P</i>
No. cases of opioid ingestion	3647	797	1346	1504	—
Age group, y					
1–5	1249 (34.2)	274 (34.4)	481 (35.7)	494 (32.8)	.529
6–11	175 (4.8)	42 (5.3)	61 (4.5)	72 (4.8)	—
12–17	2223 (61)	481 (60.4)	804 (59.7)	938 (62.4)	—
Sex					
Male	1735 (47.6)	412 (51.7)	686 (51)	637 (42.4)	<.001
Female	1909 (52.3)	385 (48.3)	659 (49)	865 (57.5)	—
Race or ethnicity					
Non-Hispanic white	2278 (62.5)	514 (64.5)	873 (64.9)	891 (59.2)	.020
Non-Hispanic African American	707 (19.4)	148 (18.6)	249 (18.5)	310 (20.6)	—
Hispanic	326 (8.9)	65 (8.2)	101 (7.5)	160 (10.6)	—
Other	336 (9.2)	70 (8.8)	123 (9.1)	143 (9.5)	—
Insurance or primary payer					
Government	1921 (52.7)	371 (46.5)	705 (52.4)	845 (56.2)	<.001
Private	1411 (38.7)	266 (33.4)	546 (40.6)	599 (39.8)	—
Other	315 (8.6)	160 (20.1)	95 (7.1)	60 (4)	—
Hospital region					
Midwest	1380 (37.8)	322 (40.4)	502 (37.3)	556 (37)	.340
Northeast	391 (10.7)	85 (10.7)	154 (11.4)	152 (10.1)	—
South	1379 (37.8)	286 (35.9)	520 (38.6)	573 (38.1)	—
West	497 (13.6)	104 (13)	170 (12.6)	223 (14.8)	—
Season of admission					
Spring	942 (25.8)	189 (23.7)	318 (23.6)	435 (28.9)	.015
Summer	949 (26)	211 (26.5)	349 (25.9)	389 (25.9)	—
Fall	874 (24)	199 (25)	349 (25.9)	326 (21.7)	—
Winter	882 (24.2)	198 (24.8)	330 (24.5)	354 (23.5)	—
Diagnosis					
E850.0 (accidental poisoning by heroin)	43 (1.2)	5 (0.6)	15 (1.1)	23 (1.5)	<.001
E850.1 (accidental poisoning by methadone)	288 (7.9)	74 (9.3)	119 (8.8)	95 (6.3)	—
E850.2 (accidental poisoning by other opioids)	1327 (36.4)	278 (34.9)	531 (39.5)	518 (34.4)	—
965.00 (poisoning by opium)	519 (14.2)	80 (10)	195 (14.5)	244 (16.2)	—
965.01 (poisoning by heroin)	62 (1.7)	10 (1.3)	12 (0.9)	40 (2.7)	—
965.02 (poisoning by methadone)	203 (5.6)	73 (9.2)	62 (4.6)	68 (4.5)	—
965.09 (poisoning by other opiates)	1205 (33)	277 (34.8)	412 (30.6)	516 (34.3)	—

Data are presented as *n* (%). —, not applicable.

^a Data for 2015 include quarter 1 through quarter 3 only because of the ICD-10 conversion.

and interquartile ranges and then compared with Kruskal–Wallis tests. Trends in the annual rates of opioid-related hospitalizations were assessed with generalized estimating equations to account for patient clustering within a hospital, assuming an underlying Poisson distribution. All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Inc, Cary, NC), and *P* values of <.05 were considered statistically significant.

RESULTS

Of 4 175 624 hospital admissions to 31 different children's hospitals during the study period, 3647 (0.09%) patients were admitted

for opioid-related conditions. The number of opioid-related hospitalizations increased across the epochs from 797 to 1504 (Table 1). When combining all the years, there were 8.7 opioid-related admissions per 10 000 hospital admissions, with the rate of hospitalization increasing significantly from 6.7 per 10 000 admissions in 2004 to 10.9 per 10 000 admissions in 2015 (*P* < .001). Although the majority of opioid-related hospitalizations were of children between 12 and 17 years of age in all time periods, one-third of the hospitalizations were of children <6 years old. The subtype of opioid ingested differed by age group, with 19.5% (243 of 1249) of patients 1 to 5 years old ingesting methadone,

whereas methadone only accounted for 9.8% (218 of 2223) of ingestions in the 12- to 17-year-old group. Heroin accounted for 4.4% (99 of 2223) of patient hospitalizations for the 12- to 17-year-old age group.

A total of 501 831 patients (12%) required admission to the PICU during the study period, and 1564 patients with opioid-related hospitalizations (43%) required PICU care (Table 2). Opioid ingestions accounted for 31.2 per 10 000 PICU admissions. The rate of PICU admission for opioid-related hospitalization increased significantly, from 24.9 to 35.9 per 10 000 PICU admissions (*P* < .001), with a peak of 36.6 per 10 000 PICU admissions in 2014 (Fig 1). The number of patients requiring PICU care nearly doubled

TABLE 2 Resource Use of Opioid-Related Hospitalizations

	Total	2004–2007	2008–2011	2012–2015 ^a	<i>P</i>
Total No. cases	3647	797	1346	1504	—
Length of stay, d	1 [1–3]	2 [1–3]	1 [1–2]	1 [1–3]	<.001
Total cost (inflated to 2015 dollars)	4931 [2875–9555]	6254 [3438–12 835]	4799 [2778–9049]	4552 [2665–8449]	<.001
Pharmaceutical cost (inflated to 2015 dollars)	201 [53–743]	324 [84–1206]	204 [54–711]	163 [39–606]	<.001
Naloxone used during hospitalization	1047 (28.7)	250 (31.4)	382 (28.4)	415 (27.6)	.154
PICU admission	1564 (42.9)	367 (46)	554 (41.2)	643 (42.8)	.086
Patients requiring PICU					
Total No. cases	1564	367	554	643	—
Total length of stay, d	2 [1–4]	2 [1–4]	2 [1–3]	2 [1–3]	<.001
PICU length of stay, d	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–2]	.248
Mechanical ventilation	578 (37)	168 (45.8)	207 (37.4)	203 (31.6)	<.001
Mechanical ventilator or those who required it, d	2 [1–3]	2 [1–3]	2 [1–3]	2 [1–4]	.510
Noninvasive ventilation	61 (3.9)	12 (3.3)	16 (2.9)	33 (5.1)	.105
Vasopressors	318 (20.3)	99 (27)	105 (19)	114 (17.7)	.001

Data are presented as the median [interquartile range] or *n* (%) of case patients. —, not applicable.

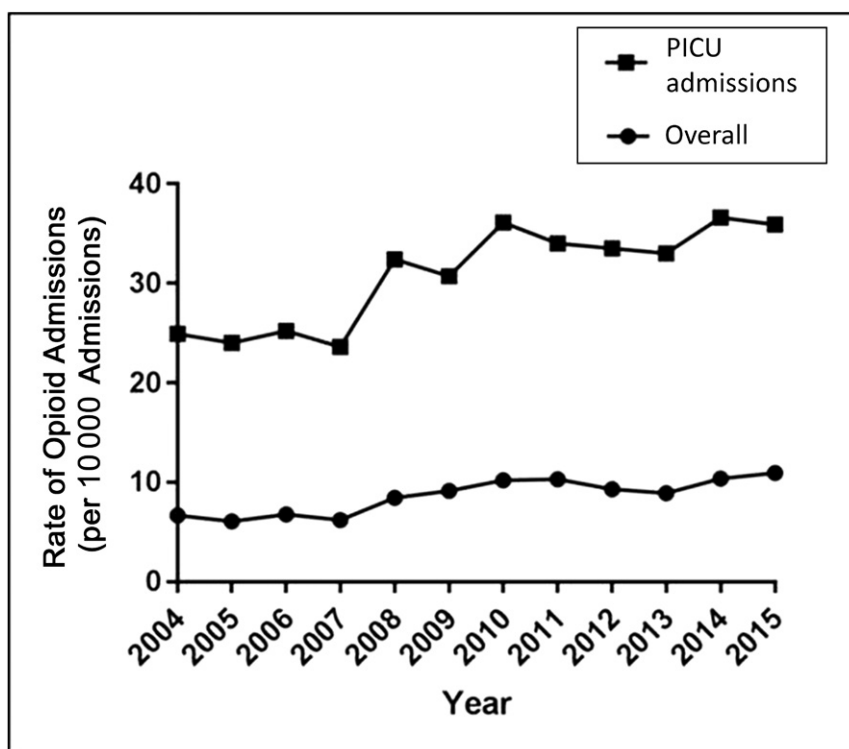
^a Data for 2015 include quarter 1 through quarter 3 only because of the ICD-10 conversion.

between 2004 and 2015, but the relative percentage of children with opioid-related hospitalizations requiring PICU care was similar across all years. The median cost per PICU admission was \$4931, with a significant decrease from \$6253 in the 2004–2007 epoch to \$4552 in the 2012–2015 epoch ($P < .001$). Overall, 37% of PICU admissions required mechanical ventilator support, and this decreased over time ($P < .001$). Of the PICU admissions, 20% required vasopressors, and this also decreased over time ($P < .001$).

The overall mortality was 1.6%, with deaths decreasing from 2.8% in the 2004–2007 epoch to 1.3% in the 2012–2015 epoch (Table 3). In the 1- to 5-year-old age group, the average mortality was 1.4%, with a significant decrease over time ($P < .001$). There was a significant decrease in the number of patients who were discharged directly home from the hospital, with an increase in the number of patients who were sent to other care facilities, including skilled nursing, long-term care, and inpatient psychiatric facilities ($P < .001$; Table 4).

DISCUSSION

We present the first study of the impact of the current US opioid

**FIGURE 1**

Rate of hospital admissions for opioid ingestion per 10 000 hospitalizations and the rate of PICU admissions for opioid ingestion per 10 000 PICU hospitalizations from 2004 through quarter 3 of 2015. Trends in the rate change over time were significant ($P < .001$).

crisis on the pediatric critical care community using a national sample of patients who were admitted to major pediatric hospitals. In this study, we demonstrate a significant and steady increase in the diagnosis of opioid ingestion and poisoning across all age groups in US children's

hospitals from 2004 to 2015. Not only did the absolute number of opioid-related admissions increase but the rate of both hospital and PICU admissions increased as well. The opioid-related hospital admission rate increase of 39% is substantial as is the 35% increase in the rate of

TABLE 3 Outcomes and Disposition for All Cases

	Total	2004–2007	2008–2011	2012–2015 ^a	<i>P</i>
Total No. cases	3647	797	1346	1504	—
Disposition, <i>n</i> (%)					
Home	2591 (71)	618 (77.5)	970 (72.1)	1003 (66.7)	<.001
Died	58 (1.6)	22 (2.8)	17 (1.3)	19 (1.3)	—
Home health	16 (0.4)	3 (0.4)	7 (0.5)	6 (0.4)	—
Short-term care	104 (2.9)	24 (3)	45 (3.3)	35 (2.3)	—
Other care	790 (21.7)	124 (15.6)	282 (21)	384 (25.5)	—
Other	88 (2.4)	6 (0.8)	25 (1.9)	57 (3.8)	—

—, not applicable.

^a Data for 2015 include quarter 1 through quarter 3 only because of the ICD-10 conversion.

TABLE 4 Outcomes and Disposition for Patients 1–5 Years of Age

	Total	2004–2007	2008–2011	2012–2015 ^a	<i>P</i>
Total No. cases	1249	274	481	494	—
Disposition, <i>n</i> (%)					
Home	1195 (95.7)	260 (94.9)	455 (94.6)	480 (97.2)	<.001
Died	18 (1.4)	11 (4)	3 (0.6)	4 (0.8)	—
Home health	9 (0.7)	2 (0.7)	5 (1)	2 (0.4)	—
Short-term care	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Other care	12 (1)	1 (0.4)	8 (1.7)	3 (0.6)	—
Other	15 (1.2)	0 (0.0)	10 (2.1)	5 (1)	—

—, not applicable.

^a Data for 2015 include quarter 1 through quarter 3 only because of the ICD-10 conversion.

PICU admissions for opioid-ingestion. This increase in PICU use parallels the increase in hospital admissions and is consistent with previously published data that reveal an increase in the annual incidence of hospitalizations and ED encounters for opioid poisoning in children.^{7,9}

The percentage of PICU patients requiring mechanical ventilation decreased over time, from nearly half of PICU admissions to only one-third. The percentage of PICU admissions for opioid ingestion requiring vasopressors also fell by nearly half. However, because of the increase in the number of patients with opioid-related hospitalizations requiring PICU care across the study period, the absolute number of patients with opioid ingestion requiring mechanical ventilation and vasopressors increased over time. The median cost of care decreased significantly during the study period, likely because of a shorter overall hospital length of stay. However, because of the increases in all hospitalizations and those hospitalizations requiring critical

care for opioid ingestion, the actual overall financial burden on the health system increased. Additionally, the total number of hospital days that were attributed to patients with opioid ingestion and the total number of patients requiring mechanical ventilators and/or vasopressors continue to increase over time at an alarming rate.

The only other data that reveal the impact of the US opioid crisis on critical care resource use are from the adult population.¹⁰ Stevens et al¹⁰ found that there was a marked increase in critically ill adult patients who were admitted to the ICU with overdoses from opioids between 2009 and 2015, with an increase in mortality and a near doubling of ICU deaths. In addition, the total cost of care increased by 58% in the adult ICUs over that same period. In contrast, although the total number of pediatric patients admitted to the PICU has also increased significantly, the pediatric health care system has become more efficient, with lower lengths of stay per hospitalization, less mechanical ventilation per

hospitalization, less vasopressor use per hospitalization, and reduced mortality over time. The underlying cause of the difference between adult and pediatric critical care outcomes is likely due to the difference in the opioid class leading to hospitalization. In this study, methadone and other opioids were the major contributors to pediatric hospitalization, whereas in the adult study, heroin was shown to be the key driver to adult ICU hospitalization and mortality. Adult heroin users are likely to have a number of clinical comorbidities that may contribute to their increased cost of care. Additionally, illicit heroin can be contaminated with other opioid and nonopioid substances that may make its use more lethal compared with regulated prescription drugs, such as methadone.

The increasing number of adult drug prescriptions is strongly associated with rising pediatric exposures and poisonings; young children are at the greatest risk for exposure, with substantial health care use and

morbidity specifically associated with opioid ingestions.⁶ The exploratory nature of young children makes them particularly vulnerable to harm from accidental medication ingestions as opposed to adolescents and teenagers, who are more likely to have intentional ingestions, including for recreational purposes or for self-harm.^{5,15} We identified methadone ingestions, in particular, as an important driver for hospital care, with nearly 20% of children <6 years of age being admitted with methadone ingestion. From 2000 to 2007, the US Drug Enforcement Administration data showed a 559% increase in prescriptions for methadone; these data help to inform the findings in this study.⁸ Additionally, data from the American Association of Poison Control Centers revealed that methadone was responsible for 24.9% of serious medical outcomes in all patients who are admitted to health care facilities, which is consistent with our finding of 20%.⁷

Insurance coverage for the majority of pediatric patients in this study who were hospitalized with opioid ingestion was provided by Medicaid. The percentage of patients with opioid ingestion who have Medicaid as the primary payer source has increased over time. Additionally, 66.5% of patients <6 years of age were covered by Medicaid. In the current health care climate, in which proposed changes to the funding of state-based Medicaid programs is under consideration, any reduction of Medicaid funding could have a profound impact on the ability to recuperate the cost of acute hospital care that is associated with pediatric opioid ingestions.

There are a number of limitations to this study. First, the PHIS database offers the unique advantage of detailed, national-level, pediatric data from the majority of US metropolitan areas. The PHIS provides up to 21 diagnosis codes per hospitalization and provides more diagnostic data per patient than most administrative data sets. However, the data provide an unweighted convenience sample because member hospitals change over time. To control for this, only those data from member hospitals that enrolled patients throughout the entire study period were included. Additionally, the data may not be generalizable to nontertiary-care, nonchildren's hospitals. For example, because of referral bias, the PHIS may overrepresent the true incidence of opioid ingestions requiring PICU care. Also, because the PHIS data represent ~20% of all pediatric hospitalizations in the United States, the total cost burden to the US health care system is clearly understated. Second, case identification is dependent on ICD-9-CM codes, which, like all administrative data, rely on accurate coding. Errors of both miscoding and the omission of key codes may occur. However, the search strategy used in this study has now been employed in a number of publications and has previously been validated in the literature. Additionally, validation studies involving other common medication poisonings support the use of ICD-9-CM codes for the identification of hospitalizations for medication toxicities in children.¹⁶ Because of the limitations of the ICD-9 and ICD-10 coding system, the identities of the specific opioids

ingested are unknown. It is possible that other data may better inform which specific agents are key drivers to pediatric hospitalization and PICU resource use, and they may provide targets for strategic public health initiatives.

The current US opioid crisis is negatively impacting pediatric patients as the rate of hospitalization and PICU care for the ingestion of opioids by children continues to increase over time. With higher volumes of patients being admitted to the PICU because of opioid ingestion, the overall use of pediatric critical care resources, including mechanical ventilation and vasopressors, has increased over time, although efficiencies in both life-sustaining interventions and the total cost of care per patient have improved. Current efforts to reduce prescription opioid use in adults have not curtailed the incidence of pediatric opioid ingestion, and additional efforts are needed to reduce preventable opioid exposure in children.

ABBREVIATIONS

ED: emergency department
ICD-9: *International Classification of Diseases, Ninth Revision*
ICD-10: *International Classification of Diseases, 10th Revision*
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
PHIS: Pediatric Health Information System

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Jason M. Kane, Jeffrey D. Colvin, Allison H. Bartlett and Matt Hall

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