RESEARCH ARTICLE

National Trends of Acute Osteomyelitis and Peripherally Inserted Central Catheters in Children

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ABSTRACT

OBJECTIVES: Although a growing body of evidence suggests that early transition to oral antimicrobial therapy is equally efficacious to prolonged intravenous antibiotics for treatment of acute pediatric osteomyelitis, little is known about the pediatric trends in peripherally inserted central catheter (PICC) placements. Using a national database, we examined incidence rates of pediatric hospitalizations for acute osteomyelitis in the United States from 2007 through 2016, as well as the trends in PICC placement, length of stay (LOS), and cost associated with these hospitalizations.

METHODS: This was a retrospective, serial cross-sectional study of the National Inpatient Sample database from 2007 through 2016. Patients ≤18 years of age with acute osteomyelitis were identified by using appropriate diagnostic codes. Outcomes measured included PICC placement rate, LOS, and inflation-adjusted hospitalization costs. Weighted analysis was reported, and a hierarchical regression model was used to analyze predictors.

RESULTS: The annual incidence of acute osteomyelitis increased from 1.0 to 1.8 per 100 000 children from 2007 to 08 to 2015 to 16 ($P < .0001$), whereas PICC placement rates decreased from 58.8% to 5.9% ($P < .0001$). Overall, changes in LOS and inflation-adjusted hospital costs were not statistically significant. PICC placements and sepsis were important predictors of increased LOS and hospital costs.

CONCLUSIONS: Although PICC placement rates for acute osteomyelitis significantly decreased in the face of increased incidence of acute osteomyelitis in children, LOS and hospital costs for all hospitalizations remained stable. However, patients receiving PICC placements had longer LOS. Further studies are needed to explore the long-term outcomes of reduced PICC use.

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The incidence of acute osteomyelitis is often underestimated given its varying clinical presentations. Despite that, it has shown a consistent rise and is a source of high morbidity and resource use in children and adults.[1–4] Substantial variability exists in the management of acute osteomyelitis in terms of the duration and route of antimicrobial therapy, which impacts the overall length of treatment.[5]

Children often receive long-term parenteral antibiotics, although some are switched to oral therapy after a short course of intravenous therapy.[6–13] Pediatric trends in peripherally inserted central catheter (PICC) placement for long-term treatment may lead to a prolonged length of stay (LOS) within the hospital and an increased cost of hospitalization.[3,13–15] PICC placements are also associated with high rates of return to emergency departments, medical complications, and infections. They are also a source of parental anxiety and poor quality of life due to disrupted school and sleep schedules.

Although nationally representative data for the incidence of pediatric osteomyelitis exists, little focus has been given to PICC placements and their impact on health care use in the treatment of acute osteomyelitis. With the evolution in the long-term management of acute osteomyelitis and early transition to oral antimicrobial therapy, we hypothesize a decline in PICC placements for the treatment of acute osteomyelitis. For this reason, our objectives were to (1) study the incidence of acute osteomyelitis hospitalizations using the National Inpatient Sample (NIS) database from 2007 through 2016, (2) explore the rate of PICC placements for osteomyelitis over time, and (3) analyze outcomes in terms of LOS and cost of hospitalization.

METHODS

Data Source

Our study cohort was derived from the NIS database, which is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality.[16] The NIS database is the largest, publicly available, all-payer inpatient care database derived from billing data submitted by hospitals to statewide data organizations across the United States. This inpatient data includes clinical and resource use information typically available from discharge abstracts. The NIS database approximates a ≤20% stratified sample of discharges from United States community hospitals, excluding rehabilitation and long-term acute care hospitals, and contains records for >7 million annual hospitalizations. Each individual hospitalization is deidentified and maintained in the NIS database as a unique entry with 1 primary discharge diagnosis and ≤24 secondary diagnoses during that hospitalization. Sampling weights are provided by the NIS database, and, when applied, the resultant sample is representative of all inpatient discharges in the United States. The NIS database underwent changes in its sampling strategy starting in 2012; therefore, to account for these changes, trend weights provided by HCUP were used for trend analysis.[17]

Estimates are weighted, unless otherwise noted. The NIS data has been used previously to study trends and predictors of health care usage, patterns of major procedures, access and disparity of care, procedural adverse effects, hospitalization trends, cost, quality, and outcomes.[18–20]

This study included publicly available deidentified data and thus was exempt from review by the institutional review board.

Study Population

We evaluated the NIS database between 2007 through 2016 and identified all pediatric hospitalizations (age ≤18 years). Furthermore, we excluded neonatal (≤28 days) hospitalizations because neonatal acute osteomyelitis differs from older children in terms of presentation, severity, location, causative organisms, and, therefore, management.[21] To eliminate double counting and improve completeness of data, transfers to a skilled nursing facility, intermediate care facility, or short-term facility were excluded by using the "DISPUNIFORM" variable.[22]

Pediatric hospitalizations with acute osteomyelitis were identified by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *10th Revision, Clinical Modification* (ICD-10-CM) diagnosis codes "730.0x" and "M860x, M861x" in the first-listed diagnosis or secondary diagnosis fields. This was done because the primary diagnosis could be sepsis and then diagnosed as osteomyelitis later. Chronic osteomyelitis, septic arthritis, sickle cell disease, and cancer-related hospitalizations were excluded in all diagnostic fields by using ICD-9-CM/ICD-10-CM diagnosis codes (Supplemental Table 4). PICC placement was defined by using ICD-9-CM/ICD-10-CM diagnosis codes. The population derivation for this study is described in detail in Fig 1.

Definition of Variables

Demographics were studied, such as age in years (categorized as ≤1 year, 2–4 years, 5–9 years, 10–14 years, and 15–18 years), sex, and race (white, Black, Hispanic, and others). Additional clinical variables were identified on the basis of relevant ICD-9-CM/ICD-10-CM codes as mentioned in Supplemental Table 4. The NIS database contains data on cost stored as total charges for each hospitalization. We used HCUP cost-to-charge files to estimate the cost of inpatient resource use. Costs reflect the actual expenses incurred in the production of hospital services, such as wages, supplies, and utility costs; charges represent the amount a hospital billed for the case.[23] Adjusted cost for each year was calculated in terms of 2016 cost after adjusting for inflation as per the consumer price index data released by the US government. This enabled us to standardize cost over the study period.[24]

Statistical Analysis

Descriptive statistics were used to present baseline differences in sociodemographic and hospital characteristics. Continuous variables were reported as medians and

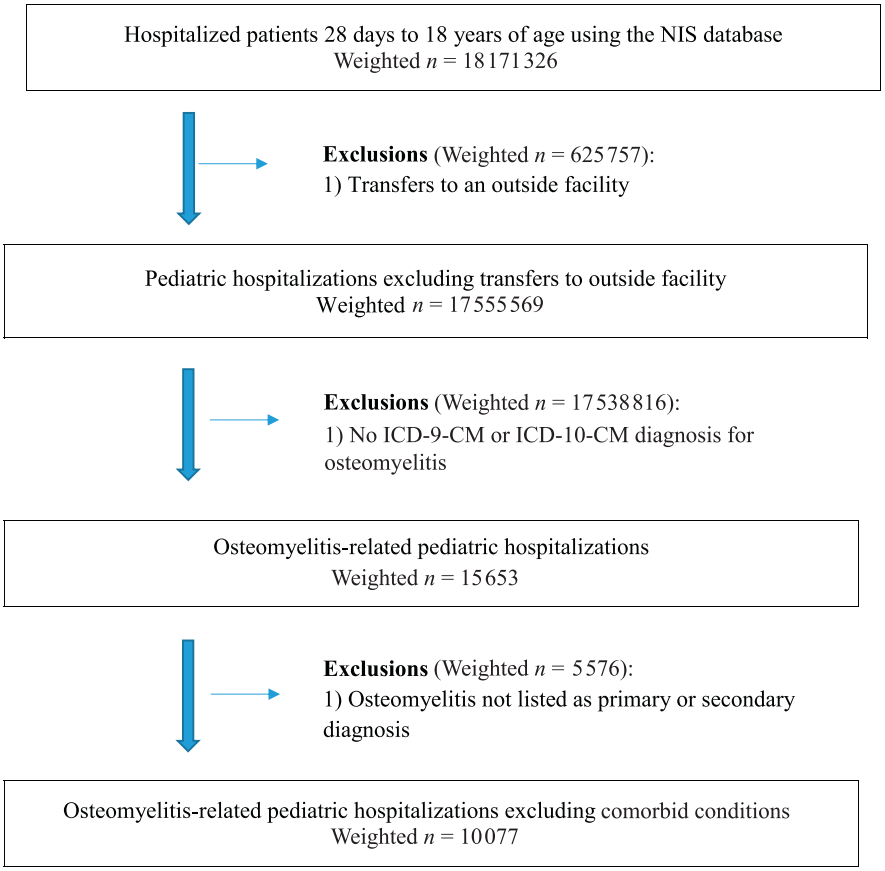

FIGURE 1 Population derivation. This flowchart displays steps applied to the original pediatric population identified in the NIS database (2007–2016). Acute osteomyelitis cases were identified by using ICD-9-CM/ICD-10-CM codes. Transfers of hospitalization, patients with comorbid conditions and chronic osteomyelitis were excluded, leaving the final population of patients with osteomyelitis as primary or secondary diagnosis.

interquartile ranges, and categorical variables were reported as percentages. A χ^2 test, *t* test, or Wilcox-rank sum test, depending on the data and distribution, was used for unadjusted analysis. In keeping with previous studies, the annual incidence of acute osteomyelitis was estimated by using the number of acute osteomyelitis hospitalizations as the numerator and the US Census population between 28 days and 18 years as the denominator.[25,26]

We reported the rate per hospitalization because it is possible for the same patient to have >1 encounter reported. This represented the rate of acute osteomyelitis hospitalizations to all pediatric hospitalizations. Because of a change in sampling and weighting strategies after 2012, HCUP has provided trend weights for years 1993 to 2011 to make estimates comparable to the new design.[17]

For trend analysis, χ^2 tests of trend for proportions were used by using the Cochrane Armitage test.[27] The NIS database contains a complex survey design wherein discharges are clustered within the hospitals. Survey regression was used for continuous variables such as LOS.[28] Two-level hierarchical models (smaller unit factors [encounters] nested within larger unit factors [hospital]) were created, with the unique hospital identification number incorporated as a random effect within the model. Hospital identification was incorporated as a random effect in the model to account for the impact of hospital clustering, allowing for similar outcomes in patients being treated at the same hospital due to certain processes of care received.[29] Hierarchical regression was used to analyze predictors for LOS and cost. Because >10% of the data were missing for race, it was excluded from the adjusted analysis. We checked variables for multicollinearity using tolerance and the variance inflation factor. No collinearity was noted among variables.[30] SAS software 9.4 (SAS Institute, Inc, Cary, NC) was used for all analyses. We considered 2-sided *P* value of <.05 as significant.

RESULTS

The NIS database included 18 171 326 weighted pediatric hospitalizations from 2007 through 2016. After excluding children who were transferred to outside facilities and those with comorbid conditions including chronic osteomyelitis, septic arthritis, sickle cell disease, and cancer-related hospitalization, a final cohort of 10 077 pediatric hospitalizations was derived and assigned an ICD-9-CM/ICD-10-CM diagnosis of acute osteomyelitis as the primary or secondary diagnosis (Fig 1).

Children assigned a diagnosis of acute osteomyelitis were more likely to be boys (64.6%) in the age range of 10 to 14 years (33.2%) or 5 to 9 years (29.2%) and were classified as white race (49.1%) (Table 1). Common comorbidities included sepsis (17.2%) and bone surgery (12.5%). The most common sites of infection were lower leg (25.3%), ankle or foot (24.5%), and the pelvic region or thigh (20.3%) (Supplemental Table 5).

The overall rate of acute osteomyelitis among hospitalized children was 57.4 per 100 000 hospitalizations. The rate of acute osteomyelitis hospitalizations significantly increased from 42.9 to 81.5 per 100 000 hospitalizations from 2007 to 08 to 2015 to 16 ($P < .0001$). During the study period, the rate of PICC placement among acute osteomyelitis hospitalization decreased

TABLE 1 Baseline Characteristics of Pediatric Patients Hospitalized With Osteomyelitis

	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	Total	P^a
Osteomyelitis hospitalizations: unweighted (*N*)	330	392	376	422	539	2059	—
Osteomyelitis hospitalizations: weighted (*n*)	1553	1901	1818	2110	2695	10 077	—
Age, y, %							<.001
0–1	5.2	3.1	6.6	12.1	11.7	8.2	
2–4	17.7	15.3	18.6	16.8	13.2	16.0	
5–9	27.0	32.3	28.7	27.5	30.1	29.2	
10–14	29.3	35.0	32.6	34.6	33.4	33.2	
15–18	20.8	14.3	13.5	9.0	11.7	13.3	
Sex, %							<.001
Male	69.5	66.4	59.6	62.1	66.1	64.6	
Female	29.2	32.6	40.2	37.7	33.8	34.8	
Missing	1.3	1.0	0.3	0.2	0.2	0.5	
Race and ethnicity, %							<.001
White	41.9	51.8	48.9	51.2	49.7	49.1	
Black	14.8	15.7	12.6	14.7	13.7	14.3	
Hispanic	11.2	16.3	19.1	15.9	16.5	16.0	
Other	6.0	5.6	7.3	8.8	7.4	7.1	
Missing	26.1	10.6	12.1	9.5	12.6	13.6	

—, not applicable.

significantly from 58.8% in 2007% to 08% to 5.9% in 2015 to 16 ($P < .0001$) (Fig 2).

Overall median LOS among acute osteomyelitis hospitalizations was 4.6 days (2.9–7.1). On univariate trend analysis, overall median LOS decreased from 4.9 days in 2007 to 08 to 4.3 days in 2015 to 16 ($P = .0065$). Of the acute osteomyelitis hospitalizations who underwent PICC placement, the overall median LOS was 5.3 days (3.5–8.3), and there was an insignificant downward trend from 5.0 days in 2007 to 08 to 4.9 days in 2015 to 16 ($P = .7549$). Overall, median cost of hospitalization among acute osteomyelitis hospitalizations was $11 065 (7105–17 830). During the study period, cost of hospitalization among acute osteomyelitis hospitalizations remained stable, from $10 137 in 2007 to 08 to $10 842 in 2015 to 16 ($P = .0671$). Median cost of hospitalization among acute osteomyelitis who underwent PICC placements significantly increased from $11 295 in 2007 to 08 to $12 213 in 2015 to 16 ($P = .0075$) (Table 2).

On multivariate analysis of LOS after adjusting for potential confounders, LOS among acute osteomyelitis hospitalizations decreased by 0.3 days per year, but this was not significant ($P = .4475$). PICC placement and presence of sepsis were noted to lengthen hospital stay by 1.2 days and 1.9 days, respectively. Similarly, on multivariate analysis for cost of hospitalization, inflation-adjusted cost increased by $345 per year, but again, this was not significant ($P = .608$). PICC placement, bone debridement, and occurrence of sepsis during hospitalization were associated with additional increase in cost of hospitalization by $1890, $4958, and $1183, respectively (Table 3).

DISCUSSION

In this population-based study, using a national health care database, we observed an increase in the incidence of acute osteomyelitis hospitalization in children from 2007 to 2016. We identified a substantial decline in the use of PICC placements in these patients during the study period. Hospitalizations with acute osteomyelitis were higher in boys, more common in white children, and highest in children aged 10 to 14 years. Overall, LOS and inflation-adjusted cost of hospitalization remained stable during the study period for all acute osteomyelitis hospitalizations. Hospitalizations with PICC placements had stable LOS but increased cost.

Overall, the incidence of acute osteomyelitis hospitalizations in children nearly doubled during the study period. Our findings mirror previous reports.[2] Okubo et al[2] reported similar incidence rates of acute osteomyelitis ranging from 1.34 to 1.66 cases per 100 000 children using the Kids' Inpatient Database. One possible reason for this increase may be easier availability and higher use of MRI leading to increased diagnosis of osteomyelitis.[31,32]

We observed that school-aged boys between 10 and 14 years were predominantly affected, and the incidence rate was highest among white patients, followed by African Americans, which differed from previous reports.[2] In an attempt to build on previous reports, we focused predominantly on healthy hospitalized children, thereby excluding those with major immunocompromised conditions, chronic osteomyelitis, and sickle cell disease and neonates, which could have attributed to these racial

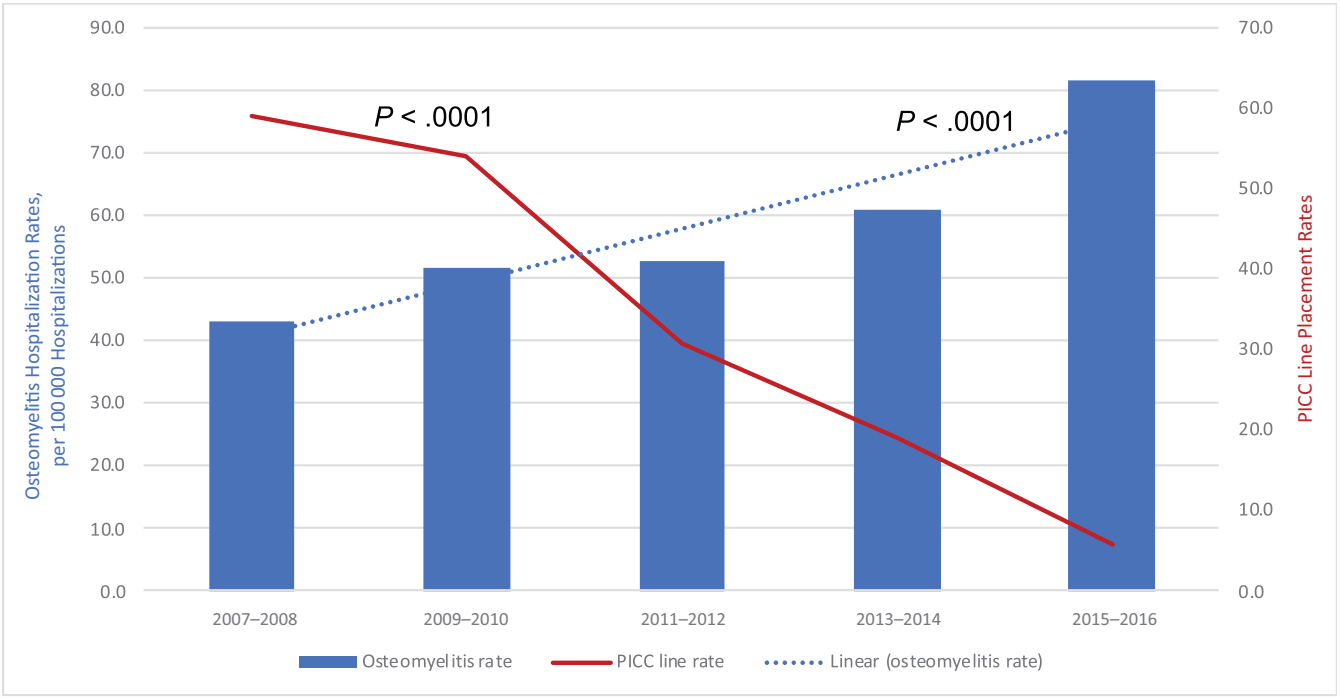

FIGURE 2 Trends of osteomyelitis hospitalization rates and PICC line rates. This chart represents distribution of acute osteomyelitis hospitalization rates per 100 000 hospitalizations per year and PICC line placement as a percentage per year during the study period. A statistically significant increase in hospitalization rate is seen ($P < .001$). Also, a statistically significant decrease in PICC line placement rate is observed ($P < .001$).

TABLE 2 Osteomyelitis Hospitalization Rates and Trends of LOS and Costs per 100 000 Hospitalizations

	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	Total	*P*
Overall rate of osteomyelitis (rate per 100 000 hospitalizations)	42.9	51.5	52.6	60.8	81.5	57.4	<.001
Overall incidence of osteomyelitis (incidence per 100 000 children)	1.0	1.3	1.2	1.4	1.8	1.4	<.001
PICC placement, %	58.8	54.0	30.8	19.2	5.9	30.4	<.001
LOS, median (IQR), d							
All osteomyelitis hospitalization	4.9 (3.2–7.7)	4.9 (3.0–7.8)	4.4 (2.7–7.1)	4.5 (2.9–7.1)	4.3 (2.8–6.5)	4.6 (2.9–7.1)	.007
PICC	5.0 (3.5–8.0)	5.6 (3.5–8.7)	5.2 (3.3–7.9)	5.6 (4.0–8.6)	4.9 (3.5–8.7)	5.3 (3.5–8.3)	.76
No PICC	4.6 (2.6–7.4)	4.1 (2.5–7.0)	4.0 (2.5–6.5)	4.3 (2.7–6.8)	4.3 (2.7–6.4)	4.3 (2.7–6.6)	.80
Cost of hospitalization, median (IQR), US $							
All osteomyelitis hospitalization	10 137 (6526–16 892)	11 618 (7650–19 625)	11 472 (7356–17 942)	11 082 (7354–17 615)	10 842 (6946–16 911)	11 065 (7105–17 830)	.07
PICC	11 295 (7309–18 395)	12 284 (8747–20 667)	13 316 (8653–22 431)	14 209 (9610–23 407)	12 213 (7086–16 074)	12 461 (8204–20 360)	.008
No PICC	8494 (4891–13 302)	9987 (6390–16 937)	10 816 (6758–15 474)	10 380 (6776–16 476)	10 788 (6884–16 911)	10 442 (6673–16 448)	.01

IQR, interquartile range.

TABLE 3 Regression Model Revealing Predictors of LOS and Costs of Hospitalizations in Pediatric Patients Hospitalized With Osteomyelitis

	Multivariate predictor of LOS[a]					Multivariate predictor of costs of hospitalizations[a]				
	Estimate	SE	LL	UL	*P*	Estimate	SE	LL	UL	*P*
Year	−0.3	0.4	−1.1	0.5	.45	345	672	−972	1662	.61
Sepsis	1.9	0.5	0.9	2.9	<.001	4958	1095	2811	7104	<.001
Bone debridement	0.9	0.6	−0.2	2.0	.11	4138	1183	1818	6458	<.001
PICC	1.2	0.4	0.4	2.1	.006	1890	911	105	3674	.04

LL, lower limit, UL, upper limit.
[a] Additionally, the model was adjusted for year, age, sex, insurance type, hospital location, and teaching status, and bed-size.

differences.[1,2] It is intriguing to note that despite the increase in the cases of acute osteomyelitis, there was a reduction in rates of sepsis and surgical interventions. Earlier diagnosis preventing invasive infections may have contributed to this decline.[33,34]

Another finding of our study was the precipitous drop in overall PICC placements. Recently, in a multicenter study involving tertiary children's hospitals, researchers demonstrated comparable effectiveness of oral and intravenous antibiotics on discharge in children hospitalized with acute osteomyelitis.[6,35,36]

The authors of this study also discussed increased complication rates in children discharged with PICC placements, thereby favoring early transition to oral antibiotics. These findings were corroborated in another study that revealed a consistent reduction in the use of intravenous antibiotics on discharge in children with osteomyelitis over an 18-year period.[37] The mounting evidence of improved outcomes with early transition to oral antimicrobial therapy demonstrates that despite the rise in acute osteomyelitis in children, national emphasis on value-driven clinical practices and quality improvement initiatives like "Choosing Wisely" may be associated with PICC placement reduction.[38]

We found that overall LOS remained stable for acute osteomyelitis hospitalizations at 4.6 days, which is similar to the previous study in which researchers used the Kids' Inpatient Database.[2] This duration may be justified by the time needed for diagnostic workup, continuation of intravenous antibiotics until the finalization of blood culture results, and monitoring response in a hospitalized setting for children with acute osteomyelitis. However, on adjusted analysis, PICC placements and sepsis were associated with higher LOS by 1.2 days and 1.9 days, respectively, likely because of severity of disease and additional resource use with PICC placement such as sedation services, PICC-trained nursing team, home health services, and insurance approvals.[39–41]

Despite reduction in PICC placements, the inflation-adjusted cost of hospitalization remained stable during the study period. In contrast, PICC placements increased the hospitalization cost with a stable LOS. Previously, studies have revealed that administrative processes and variation in professional or physician fees lead to the cost differences.[42,43] Additionally, 50% to 70% of total hospitalization cost is attributed to room charges and LOS, whereas the nonroom charges are determined by a physician's decision on the basis of a specific treatment and workup plan. Because of wide variability in patient care among physicians, the nonroom costs may be contributing to this higher cost while providing no added clinical benefit.[44] Although earlier use of confirmatory diagnostics has improved the outcomes for patients with severe infections, there is still a dearth of clinical consensus on the optimal duration for intravenous therapy and transition to oral antibiotic therapy. Initiatives targeting the wide variability in care delivery will optimize treatment strategies, diagnosis, and follow-up planning across hospital systems, which will create standardization in practice to augment cost savings.

Because this was a retrospective study based on ICD coding from an administrative database, the results of our study should be interpreted with caution because of several limitations. Large databases such as the NIS are susceptible to coding errors, omissions, and duplications. A major limitation of most of the administrative databases is reliance on administrative coding without confirmation from patient level data. For example, some complicated bone-related diseases such as orbital cellulitis affecting adjacent facial bones could be coded as primary or secondary osteomyelitis. However, the HCUP has instituted mechanisms to ensure the validity of the data in the NIS database.[45] In the NIS database, every encounter is considered a distinct entity, and a higher number of admissions could be an overestimation due to readmissions being counted separately. With our study design, we attempted to minimize this by excluding several conditions known to contribute to recurrent hospitalizations. One could surmise that readmissions indicate failure of treatment, which would be associated with increased PICC usage, a longer LOS, and an increase in surgical intervention; however, this was not the case in our study. Moreover, although we excluded a few major comorbidities so not to overly limit the study, this does not exclude every possible comorbidity. Additionally, we are also limited by lack of Current Procedural Terminology codes to accurately identify PICC placement. Clinical data such as imaging, inflammatory markers, or follow-up information are not available in the NIS database, so we were unable to study the long-term outcomes of osteomyelitis-associated hospitalizations. Despite these limitations, the NIS database is uniquely equipped to capture inpatient

osteomyelitis hospitalizations across the country. This is because most children with acute osteomyelitis require inpatient care for intravenous antibiotics, and because the NIS database is the largest inpatient care database in the United States, it is likely to include most osteomyelitis cases.

This study not only reveals the declining trends in PICC placements in hospitalized children but also provides an understanding of the economic health care burden of acute osteomyelitis. Future studies may be required for correlation of our findings with other databases assessing for epidemiology and readmission rates. Nationally concerted efforts addressing the duration of therapies, early imaging, and clear criteria for transition to oral antibiotics may help to shift the paradigm. We suggest the establishment of national clinical guidelines to promote safe practice, cost control, and antimicrobial stewardship.

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