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Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

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abstract

BACKGROUND AND OBJECTIVES: Postdischarge treatment of complicated pneumonia includes antibiotics administered intravenously via a peripherally inserted central venous catheter (PICC) or orally. Antibiotics administered via PICC, although effective, may result in serious complications. We compared the effectiveness and treatment-related complications of postdischarge antibiotics delivered by these 2 routes.

METHODS: This multicenter retrospective cohort study included children ≥2 months and <18 years discharged with complicated pneumonia between 2009 and 2012. The main exposure was the route of postdischarge antibiotic administration, classified as PICC or oral. The primary outcome was treatment failure. Secondary outcomes included PICC complications, adverse drug reactions, other related revisits, and a composite of all 4 outcomes, termed "all related revisits."

RESULTS: Among 2123 children, 281 (13.2%) received antibiotics via PICC. Treatment failure rates were 3.2% among PICC and 2.6% among oral antibiotic recipients and were not significantly different between the groups in across-hospital-matched analysis (matched odds ratio [OR], 1.26; 95% confidence interval [CI], 0.54 to 2.94). PICC complications occurred in 7.1%. Adverse drug reactions occurred in 0.6% of children; PICC antibiotic recipients had greater odds of adverse drug reaction in across hospital matched analysis (matched OR, 19.1; 95% CI, 4.2 to 87.3). The high rate of PICC complications and differences in adverse drug reactions contributed to higher odds of the composite outcome of all related revisits among PICC antibiotic recipients (matched OR, 4.71; 95% CI, 2.97 to 7.46).

CONCLUSIONS: Treatment failure rates between PICC and oral antibiotics did not differ. Children with complicated pneumonia should preferentially receive oral antibiotics at discharge when effective oral options are available.

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WHAT'S KNOWN ON THIS SUBJECT: Postdischarge treatment of complicated pneumonia includes antibiotics administered intravenously via a peripherally inserted central venous catheter (PICC) or orally. Postdischarge antibiotics administered via PICC, although effective, may result in serious complications.

WHAT THIS STUDY ADDS: Treatment failure rates were low (2.7%) and not significantly different between PICC and oral antibiotic therapy recipients. PICC complications occurred in 7.1% of children resulting in significantly higher adjusted revisit rates among those receiving PICC (17.8%) versus oral (3.1%) antibiotics.

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Community-acquired pneumonia is the most common, serious childhood infection requiring hospitalization.[1,2] Up to 15% of children hospitalized with pneumonia develop pleural effusion or empyema (ie, complicated pneumonia).[3,4] Treatment may include pleural drainage but almost always requires prolonged antibiotic therapy.[1,5,6] Antibiotics are typically administered intravenously during the hospitalization but can be continued either orally or intravenously via a peripherally inserted central catheter (PICC) after hospital discharge.

Prolonged intravenous antibiotics administered via PICC, although effective, may result in serious complications (eg, catheter-associated bloodstream infections, venous thrombosis) and additional health care utilization (eg, evaluation for fever necessitating hospital admission).[7–9] Oral antibiotics have proven effective compared with antibiotics via PICC for other bacterial infections such as acute osteomyelitis.[10] National guidelines do not directly address the preferred route of postdischarge antibiotic therapy in children with complicated pneumonia but instead highlight the risks of PICC complications and emphasize the safety and effectiveness of oral therapy in other serious infections.[1] Only 1 single-center study has addressed the effectiveness of PICC compared with oral antibiotic therapy in children with complicated pneumonia.[11]

Our objectives were to compare the effectiveness of postdischarge oral versus intravenous antibiotics delivered via a PICC for children with complicated pneumonia and to determine differences in treatment-related complications.

METHODS

Study Design and Data Source

This retrospective cohort study used data from the Pediatric Health Information System (PHIS), which contains hospital administrative and billing data from children's hospitals affiliated with the Children's Hospital Association (Overland Park, KS).[12,13] We supplemented the PHIS data with information from the medical record to (1) confirm eligibility, (2) determine postdischarge antibiotic choice and route, (3) review reasons for return emergency department (ED) visits and rehospitalizations within 14 days after index discharge, and (4) identify causative bacteria from blood and pleural fluid culture. These data were collected and managed using secure, Web-based Research Electronic Data Capture (REDCap, Nashville, TN) tools and subsequently merged with PHIS data.[14]

Participants

We queried PHIS for children who (1) were ≥2 months and <18 years of age on the date of admission; (2) were discharged between January 1, 2009, and December 31, 2012; and (3) had an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) discharge diagnosis code for both pneumonia (480.×–483.×, 485.×–487.×) and pleural effusion (510.0, 510.9, 511.0, 511.1, 511.9) where the primary ICD-9-CM code was either pneumonia or pleural effusion (Fig 1).[15] If a child had multiple hospitalizations within a 14-day period, the first admission was considered the eligible encounter, whereas subsequent admissions were classified as readmissions.

We used PHIS data to exclude children from the study cohort if they (1) had a concurrent or previous ICD-9-CM code for a chronic condition that would increase the risk of treatment failure with either modality or preclude oral antibiotic use (ie, cardiovascular, respiratory, hematology, immunodeficiency, or malignancy)[16]; (2) were not admitted through the ED, thus excluding most children transferred from another hospital for whom pretransfer data would neither be available in PHIS nor consistently available in the medical records; (3) did not receive antibiotics on the first day of hospitalization, making it unlikely that they had bacterial pneumonia at presentation; (4) had a length of stay <4 days, which might increase the likelihood of discharge with intravenous antibiotics for prolonged therapy, or >14 days, which might increase the likelihood of discharge with oral antibiotics as planned antibiotic therapy was nearly complete; or (5) transferred to another facility or expired during their hospitalization (Fig 1).

Investigators from 38 hospitals attended a webinar to receive training on eligibility criteria, relevant data elements, and use of the REDCap database.[10] Sites received lists of patients and hospitalizations for medical record review based on eligibility criteria applied to PHIS data, including the index hospitalization (ie, eligible encounter) as well as all return visits (ED or hospitalization) up to 14 days after index discharge. Children were then excluded based on medical record review if they (1) had a medical record that was not reviewed, (2) had a record that could not be located, (3) did not have complicated pneumonia (to qualify for a diagnosis of complicated pneumonia on medical record review, a patient had to have pneumonia with pleural effusion or empyema documented on chest radiograph), (4) had exclusion criteria identified during medical record review (eg, transferred from another hospital, no antibiotics prescribed at discharge, comorbidities not identified by ICD-9-CM codes), or (5) had data quality issues (eg, intravenous antibiotics at discharge but no documentation of PICC placement).

Main Exposure

The main exposure, determined by medical record review, was the route of postdischarge antibiotic

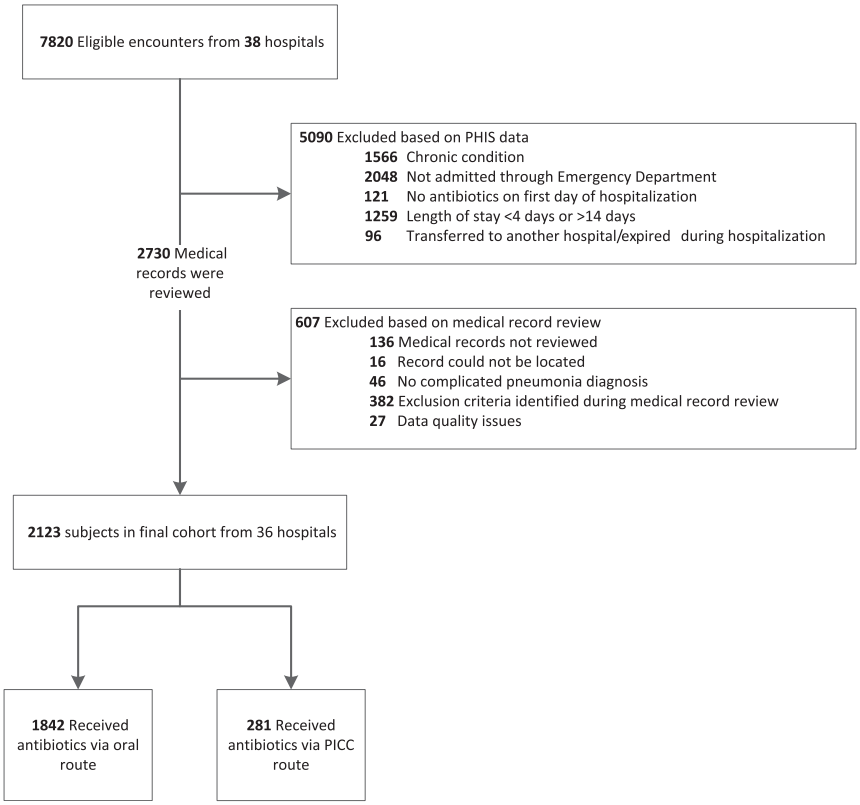

FIGURE 1
Flowchart of the study cohort.

administration, classified as PICC or oral. If a PICC was placed during the index hospitalization but removed before discharge and the child was prescribed oral antibiotics at discharge, the child was classified as receiving oral therapy. Our data-use agreement did not permit disclosure of individual hospital performance in an identifiable manner. Therefore, hospital-level PICC use is presented in a deidentified manner but grouped by US Census Bureau Census Divisions to permit geographic comparisons.[17]

Outcome Measures

Outcomes were verified by medical record review. The main outcome was treatment failure, defined as an ED revisit or rehospitalization that resulted in extension or change of antibiotic therapy or performance of pleural drainage. Secondary outcomes included (1) PICC complications, defined as fever evaluation, PICC insertion site or bloodstream infection, sepsis, or PICC thrombosis; (2) adverse drug reactions, defined as diarrhea, *Clostridium difficile* infection, rash, erythema multiforme or Stevens-Johnson syndrome, anaphylaxis, drug-induced neutropenia, drug fever, acute kidney injury, serum sickness, or other drug-related complications; (3) ED revisits or rehospitalizations not classified as treatment failure, PICC complication, or adverse drug reaction but plausibly related to the index encounter or treatment (eg, chest pain, chest tube site drainage); and (4) a composite outcome measure of treatment failure, PICC complication, adverse drug reaction, and other plausibly related ED revisits or rehospitalizations.

Covariates

PHIS provided information on age, sex, race/ethnicity, insurance, and pleural drainage procedures (ICD-9-CM procedure codes 34.04, 34.06, 34.09, 34.21, 34.51, 34.52, 34.91).[5] Pleural drainage was classified as none, chest tube, or surgical (ie, video-assisted thoracoscopic surgery or thoracotomy). Pleural drainage timing was classified as early (ie, performed ≤2 days after admission) or late (ie, performed >2 days after admission) based on the index procedure performed. Medical record review provided results of blood and pleural fluid cultures as well as discharge antibiotics. Cephalosporins, antistaphylococcal penicillins, and β-lactam/β-lactamase inhibitors (eg, ampicillin-sulbactam, amoxicillin-clavulanate) were classified as anti–methicillin-susceptible *Staphylococcus aureus* (MSSA) agents. Clindamycin, newer generation fluoroquinolones (eg, levofloxacin, moxifloxacin), linezolid, and vancomycin were classified as anti–methicillin-resistant *S. aureus* (MRSA) agents.

Statistical Methods

Matching

Matching balanced patient level covariates in the PICC and oral antibiotic groups. Patient-level covariates were incorporated in a logistic regression for whether a patient received PICC or oral antibiotics to generate a propensity score for treatment. This model included the following patient-level covariates: age, race, insurance, length of stay in days, blood culture results (culture negative vs culture positive), ICU admission, and timing and route of pleural drainage. To ensure the best matches on patient level factors, matching was done across hospitals because the number of patients assigned to PICC and oral groups within each hospital was sparse.

To make use of all possible observations while minimizing differences across observations, we used full matching based on these propensity scores.[18–20] Full matching links each PICC-treated child to the oral therapy-treated child with the closest propensity score, or vice versa, in a manner that results in varying numbers of matches in each resulting set. Then we weighted children receiving oral antibiotics in each matched set to standardize results to the characteristics of the PICC children. Finally, we compared the weighted characteristics of the PICC and the oral therapy children to determine the degree of balance between the 2 samples. Propensity score modeling and full matching were implemented using the program fullmatch in the R software package version 3.1 (https://github.com/markmfredrickson/optmatch).

Response Models

Both stratified approaches and marginal models were used to generate the results for the response model. The stratified approaches condition on the matched set but dropped subjects if a matched set did not contain patients with differing outcomes. By contrast, marginal models used all patients without stratification, thus matching and the weighting resulted in 2 groups of patients who were similar except for route of antibiotic therapy on discharge.

Odds ratios were generated by the conditional logistic regression. As a secondary analysis, we used weighted logistic regression to estimate standardized risk differences for the effect of PICC on outcomes.[21] All variance estimates and confidence bounds were confirmed using robust variances.[22] All response models and resampling was performed using the programs logit, clogit, and bootstrap, and with a custom program for this application, all using Stata v 13.1 (Stata Corp, College Station, TX).

TABLE 1 Study Population Characteristics Pre- and Postmatch

Characteristic[a]	Prematch		Postmatch[b]	
	Oral	PICC	Oral	PICC
n	1842	281	1842	281
Age <5 y	56.0	61.6	61.1	61.6
White race	57.7	65.5	62.4	65.5
Government payer	54.0	36.3	35.3	36.3
Length of stay (d)	7.2	9.1	9.2	9.1
Culture positive	12.4	24.6	23.9	24.6
ICU admission	18.1	26.3	27.0	26.3
Drainage procedure				
No drainage	61.0	24.6	24.5	24.6
Late surgical drainage	11.7	15.3	14.8	15.3
Early surgical drainage	14.9	19.2	21.4	19.2
Late chest tube drainage	4.6	15.3	12.1	15.3
Early chest tube drainage	7.9	25.6	27.2	25.6

[a] Values presented as percentages except for length of stay, for which mean values are presented.
[b] Percentages are weighted.

RESULTS

We identified 7280 eligible encounters from 38 hospitals. We excluded 4550 encounters that met exclusion criteria derived from PHIS and an additional 607 encounters that met exclusion criteria derived from medical record review, including 103 encounters from the 2 hospitals that did not review any records and 33 encounters from 2 hospitals that were unable to review records for some patients in the required study timeframe (Fig 1). The remaining 2123 children from 36 hospitals were included. Of these, 1241 (58.5%) were white, 338 (15.9%) black, 135 (6.5%) Asian or Native American, and 409 (19.3%) other race (Table 1); 498 (23.5%) were classified as Hispanic ethnicity. The median age was 5.0 years (interquartile range, 2.0–8.0).

Pleural drainage was performed in 931 (43.9%) children. A pathogen was identified in blood or pleural fluid culture in 305 (14.4%) children. The most common pathogens were *Streptococcus pneumoniae* (*n* = 175), *Staphylococcus aureus* (*n* = 77), *Streptococcus pyogenes* (*n* = 21), and *Streptococcus milleri* group bacteria (*n* = 9). MRSA comprised 56 (72.7%) of the *S aureus* isolates. The median hospital length of stay was 7 days (interquartile range, 5–10). The hospital-level median length of stay ranged from 5 to 9.5 days, with a median of hospital medians of 7.0 days.

Overall, 281 (13.2%) children received antibiotics via PICC postdischarge. PICC use

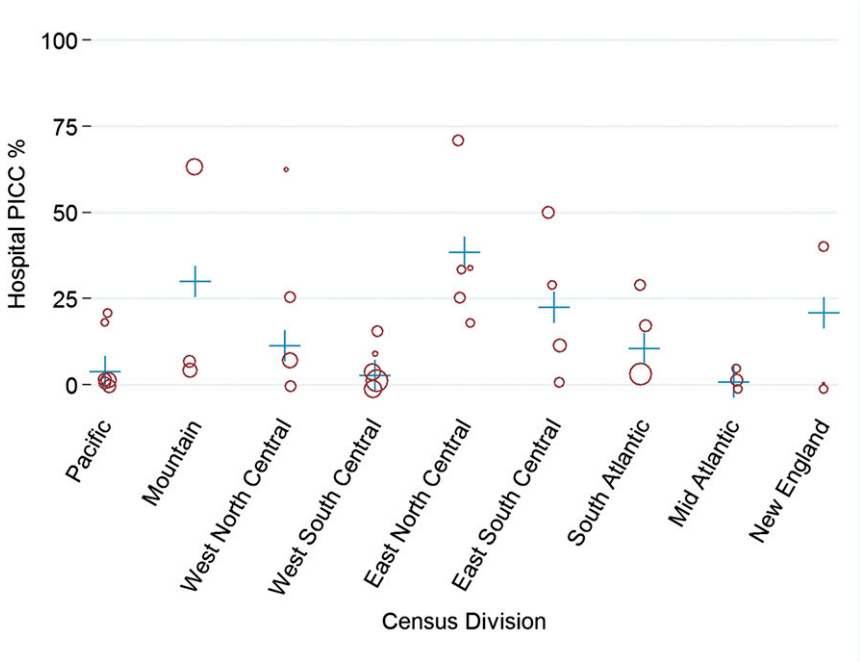

FIGURE 2
Variation within and across the 9 US Census Divisions in hospital-level PICC rates at discharge for treatment of pneumonia (n = 36 hospitals). Circles (individual hospital PICC %) have sizes proportional to the number of patients in the sample, and they are slightly jittered to view overlapping hospitals. Census division percentages (+) represent the PICC rates for all patients in the region.

postdischarge varied across hospitals, ranging from 0% to 71%. PICC use also varied within and among census regions (Fig 2). The most common antibiotics administered via PICC were anti-MSSA antibiotics alone (n = 117, 41.6%); an anti-MSSA antibiotic plus an anti-MRSA antibiotic (n = 73, 26.0%); and anti-MRSA antibiotics alone (n = 42, 14.9%). The most common antibiotics administered orally were anti-MSSA agents alone (n = 462, 25.1%); anti-MRSA agents alone (n = 422, 22.9%); anti-MRSA agent in combination with an anti-MSSA agent (n = 261, 14.2%); and amoxicillin alone (n = 214, 11.6%). Postdischarge antibiotics were prescribed for a median of 14 days (interquartile range, 7–14 days); 5% of subjects were prescribed 21 or more days of antibiotics postdischarge. No patient in whom a pathogen was identified received discordant therapy at discharge.

Before matching, children with postdischarge PICC antibiotic therapy had higher rates of surgical drainage, ICU admission, and positive cultures (Table 1). Treatment failure before matching occurred in 57 (2.7%) children overall, 3.2% in those with PICC antibiotic therapy and 2.6% in those with oral antibiotic therapy (Table 2). No treatment failures occurred among the 77 patients with *S aureus* isolated. Among children discharged with oral antibiotic therapy for culture-negative infection, treatment failure occurred in 1.4% and 1.9% of those discharged with amoxicillin and anti-MRSA antibiotics, respectively. Management of treatment failure included pleural drainage (n = 28, 49.1% of treatment failures), change in antibiotics for new or persistent symptoms (n = 18, 31.6%), extension of antibiotic course for persistent symptoms (n = 3, 5.3%), or other reasons (n = 8, 14.0%). Three children (0.1%), 2 receiving oral antibiotics and 1 receiving PICC antibiotics, developed a bronchopleural fistula.

PICC complications, which occurred in 20 (7.1%) children, included PICC thrombosis resulting in malfunction (n = 11), PICC dislodgement or breakage (n = 4), insertion site cellulitis (n = 1), and fever evaluation (n = 1); details of the complications were not available for 3 patients. No PICC-associated bloodstream infections were reported. Adverse drug reactions occurred in 13 (0.6%) children overall; 6 had a rash, 2 had gastrointestinal symptoms (abdominal pain), and 1 each developed serum sickness, drug-induced neutropenia, drug fever, heparin-induced thrombocytopenia, and joint pain. Other related visits occurred in 73 (3.4%) of children. The most common reasons included respiratory complaints (eg, tachypnea, cough; n = 29), vomiting/dehydration (n = 18), chest pain (n = 10), chest tube site drainage (n = 4), abdominal pain (n = 2), and seizure (n = 2).

Matching resolved differences in patient characteristics, including rates and timing of pleural drainage (Table 1). After matching, there were no significant differences in treatment failure rates between PICC and oral antibiotic recipients (matched odds ratio [OR], 1.26; 95% confidence interval [CI], 0.54 to 2.94) (Table 2). In matched analysis, adverse drug reactions, other related revisits (ie, revisits not related to treatment failure, adverse drug reactions, or PICC complications), and all revisits related to complicated pneumonia remained significantly higher in those receiving antibiotics via PICC compared with the oral route (Table 2).

DISCUSSION

This multicenter study included >2000 children with complicated

TABLE 2 Outcomes of Children With Complicated Pneumonia

Outcome	Unadjusted Rates, % (*n*)	Matched OR (95% CI)[a]	*P*	Adjusted Rates, %[b]	Matched Risk Difference (95% CI)[c]	*P*
Treatment failure						
PICC	3.2 (9)	1.26 (0.54 to 2.94)	>.2	3.2	1.8% (–0.4 to 3.9)	.1
Oral	2.6 (48)	—	—	1.4	—	—
PICC Complications						
PICC	7.1 (20)	—	—	—	—	—
Oral	N/A	N/A	N/A	N/A	N/A	N/A
Adverse drug reaction						
PICC	3.2 (9)	19.1 (4.2 to 87.3)	<.001	3.2	3.1% (0.01 to 5.2)	.003
Oral	0.2 (4)	—	—	0.01	—	—
Other related revisits						
PICC	6.1 (17)	3.27 (1.65 to 6.48)	.001	6.0	4.4% (1.5 to 7.4)	.003
Oral	3.0 (56)	—	—	1.6	—	—
All related revisits						
PICC	17.8 (50)	4.71 (2.97 to 7.46)	<.001	17.8	14.8% (10.1 to 19.3)	<.001
Oral	5.8 (106)	—	—	3.1	—	—

N/A, not applicable; —, X.

[a] ORs estimated from condition logistic regression stratified by the matched sets. An OR >1 means that the PICC route has a higher risk for the adverse outcome.

[b] Rates are standardized by weighting matched sets by the number of PICC patients and analyzed using weighted logistic regression with robust variance estimates translated to probabilities and their differences

[c] Estimated using weighted logistic regression. A risk difference of greater than 0 means that the PICC route has the higher risk for the adverse outcome.

pneumonia treated at 36 children's hospitals. Although PICC use was not common overall, there was substantial variation in postdischarge PICC use across participating hospitals. Treatment failure rates were not significantly different between those treated with PICC versus oral antibiotics at discharge. However, children discharged with PICCs experienced a high rate of PICC complications and adverse drug reactions, resulting in high rates of ED revisits and hospital readmissions.

We found substantial variation in PICC use in children with complicated pneumonia. Although patient and disease characteristics contribute to such variation, clustering of treatment strategies by hospital suggests that institutional factors are major determinants of care practices. Highlighting these differences in PICC use is a first step toward reducing unwarranted variation.

National guidelines recommend 2 to 4 weeks of antibiotic therapy for complicated pneumonia.[1] The optimal route of antibiotic therapy has been a source of considerable debate. National guidelines highlight the effectiveness of oral antibiotics for other serious bacterial infections but emphasize the absence of comparative data in children with complicated pneumonia.[1] Although effective treatment of children with complicated pneumonia requires adequate antibiotic concentrations in the lung and pleural space, parenteral therapy may not be necessary. Antibiotics such as amoxicillin, clindamycin, and linezolid have excellent bioavailability after oral ingestion and provide appropriate coverage for salient pathogens. Only 1 previous study compared oral with intravenous antibiotics for complicated pneumonia.[11] Stockmann et al examined outcomes of 391 children hospitalized with complicated pneumonia at a single center; 337 (86%) children received antibiotics via PICC.[11] Postdischarge pneumonia-related complications, using a comparable treatment failure definition, occurred in 5 (2%) patients discharged with antibiotics via PICC and 2 (4%; *P* = .25) patients discharged with oral antibiotics. In our multicenter study, differences in treatment failure rates between the PICC and oral antibiotic groups were not significant. For the matched analysis, children on oral antibiotics had a 1.8 percentage point lower risk of treatment failure. Although this result is not significant at conventional levels, the lower bound of the 95% CI (–0.4% points) suggests that we can rule out oral antibiotics as having a greater risk of treatment failure of clinical importance.

We divided therapy complications into PICC-associated complications and adverse reactions from antibiotics. The high rate of PICC complications (7.1%) contributed to the significantly high rate of all revisits among children receiving antibiotics via PICC. In contrast, Stockmann et al found that while PICC complications occurred in 5% of patients with complicated pneumonia, differences in overall treatment-related complications between patients receiving oral (5.6%) or PICC (7.7%, *P* = .78) antibiotics were not significant.[11] In our study, adverse drug reactions, while low overall, occurred more commonly among those receiving antibiotics via PICC. Although

adverse drug reactions are often considered unavoidable, our data highlight that the route of therapy, primarily by virtue of antibiotic selection, can contribute to their preventability.

This study had several limitations. First, as with any observational study, we could not account for some variables associated with illness severity, such as size and character of the pleural effusion or presence of necrotizing pneumonia. These variables may be associated with both treatment decisions (eg, need for pleural drainage) and outcomes. We believe that our large multicenter sample and the analytic approaches to address confounding minimize the impact of this limitation. A randomized clinical trial may better balance unmeasured confounders than our observational study. However, we believe that such a trial is unlikely given ethical considerations and institutional bias to participation as suggested by clustering of postdischarge PICC use by center. Second, we matched across hospitals because the paucity of patients with PICCs at some hospitals precluded within hospital matching. This limitation made it more challenging to account for hospital-level differences; however, matching across hospitals more effectively accounts for confounding by indication than matching within hospitals. The influence of hospital-level factors on outcomes is mitigated by the low rate of treatment failures overall. Third, the frequency and severity of adverse drug events depend, in part, on the antibiotic received. Thus, the differences in the types of antibiotics received rather than the route of antibiotic therapy per se may explain the higher rates of adverse drug reactions in those receiving antibiotics via PICC. Nevertheless, the higher rate of adverse drug reactions in the PICC group should be considered when determining route of antibiotic therapy postdischarge. Finally, we were not able to assess revisits to primary care. Children receiving oral antibiotics may be more likely than those receiving intravenous antibiotics to seek care in the primary setting when adverse events occur. If some of these adverse events did not result in an ED revisit or rehospitalization, we may have underestimated the occurrence of adverse drug events or other complications in the oral therapy group. However, such events may be less serious, an important consideration when weighing risks and benefits of oral versus PICC antibiotic treatment options.

CONCLUSIONS

Differences in treatment failure rates between PICC and oral antibiotic recipients were not significant. However, adverse drug reactions and PICC-associated complications contributed to the higher rates of reutilization among PICC antibiotic recipients. Although antibiotics via PICC may be appropriate for select patients, our study highlights the importance of preferentially treating children with complicated pneumonia with oral antibiotics at discharge when effective oral options are available.

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ABBREVIATIONS

CI: confidence interval
ED: emergency department
ICD-9-CM: *International Classification of Diseases, 9th Revision, Clinical Modification*
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-susceptible *Staphylococcus aureus*
OR: odds ratio
PHIS: Pediatric Health Information System
PICC: peripherally-inserted central catheter
REDCap: Research Electronic Data Capture

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