RESEARCH ARTICLE

Comparative Effectiveness of Oral Versus Outpatient Parenteral Antibiotic Therapy for Empyema

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ABSTRACT

BACKGROUND: Treatment of pediatric parapneumonic empyema (PPE) requires several weeks of antibiotic therapy that is typically completed in the outpatient setting. The route of outpatient therapy can be oral or intravenous (outpatient parenteral antibiotic therapy [OPAT]). No studies have compared outcomes between oral therapy and OPAT for PPE.

METHODS: We identified children <18 years hospitalized from 2005 to 2014 at Primary Children's Hospital with PPE and discharged with oral therapy or OPAT. The primary outcome was the percentage of children who experienced all-cause complications after discharge. Complications included those that were related to pneumonia (including treatment failure, defined as readmission with reaccumulation of pleural fluid or abscess requiring drainage) or antibiotic therapy (eg, allergy, line clot) resulting in either a hospital readmission or emergency department/urgent care visit. All-cause complications were compared between oral therapy and OPAT by using propensity score–weighted logistic regression.

RESULTS: A total of 391 children were hospitalized with PPE; 337 (86%) were discharged with OPAT; 35 (9%) children experienced an all-cause complication, including 5 with oral (9.3%) and 30 (8.9%) with OPAT. Pneumonia and treatment-related complications were comparable ($P = .25$ and .78, respectively). Two patients treated with OPAT (1%) experienced treatment failure. After adjustment using propensity score weighting, the frequency of complications was similar between groups (adjusted odds ratio 0.97, 95% confidence interval 0.23–4.65).

CONCLUSIONS: The frequency of complications was similar with oral therapy and OPAT for children with PPE. Oral antibiotics may be considered safe and effective for children with PPE who will be discharged to complete therapy in the outpatient setting.

www.hospitalpediatrics.org
DOI:10.1542/hpeds.2015-0100

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Hersh received funding from Agency for Healthcare Research and Quality grant K08HS023320. The content is solely the responsibility of the authors and does not necessarily represent the official view of the Agency for Healthcare Research and Quality. Dr Stockmann is funded by the American Foundation for Pharmaceutical Education's Clinical Pharmaceutical Sciences Fellowship. Dr Byington is funded through the H.A. and Edna Benning Presidential Endowment, the National Center for Advancing Translational Sciences of the National Institutes of Health (1ULTR001067), and the Centers for Disease Control and Prevention (5U50CI000866). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Parapneumonic empyema (PPE) is a severe complication of pneumonia in which pus accumulates in the pleural space.[1,2] The incidence of PPE has increased nationally over the past decade.[3–6] Children with PPE experience substantial short-term morbidity and accumulate significant medical expenditures related to hospitalization, invasive drainage procedures, radiologic studies, and antimicrobial therapy.[1,7–9] Despite the complexity of the care, clinical outcomes for PPE after hospital discharge are excellent and long-term complications or sequelae, including treatment failure, are rare.[9,10]

Most children with PPE require prolonged antibiotic therapy. Much of the treatment course may occur after the hospitalization in the home setting for as long as 2 to 4 weeks.[11] Antibiotic therapy is administered either as oral therapy or intravenously via outpatient parenteral antibiotic therapy (OPAT). There are no published studies that have compared outcomes, including rates of treatment failure and other treatment-related complications, between oral therapy and OPAT for children with PPE. As a result, there is considerable practice variability in the management of children with PPE, including the duration of therapy and the choice between oral therapy and OPAT.[12,13]

Recent guidelines from the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society of America recommend consideration of oral therapy instead of OPAT for children with PPE, although the evidence supporting this recommendation was judged to be of low quality.[11] The choice of intravenous versus oral therapy can significantly impact the experiences of family caregivers, with many parents reporting missing work after hospital discharge.[10,14] However, in the absence of better evidence, physicians may be reluctant to adopt oral therapy for the treatment of PPE due to concerns that clinical outcomes may be worse than those observed with OPAT. Therefore, the primary objective of this study was to compare the proportion of patients with PPE who experience a treatment- or pneumonia-related complication after hospital discharge while receiving oral therapy or OPAT. The secondary objective was to determine the frequency of antibiotic treatment failure as measured by suppurative complications or worsening empyema requiring additional medical encounters.

METHODS

Human Subjects Protection

This study was reviewed and approved by the institutional review boards of the University of Utah and Primary Children's Hospital (PCH). A waiver of informed consent was granted for the retrospectively collected data presented in this study.

Setting

We identified children (<18 years of age) who were hospitalized for PPE at PCH between January 2005 and October 2014. PCH is a 282-bed children's hospital that serves as a quaternary care referral center for Utah, Idaho, Wyoming, Nevada, and Montana.

Study Design and Exposure Classification

Using methods adapted from Shah et al,[9] children with PPE were initially identified by the presence of an *International Classification of Diseases, Ninth Revision, Clinical Modification* code for empyema (510) in combination with ≥1 pleural drainage procedure codes (thoracentesis [34.91], chest tube placement [34.04], video-assisted thoracoscopic surgery [34.21], or thoracotomy [34.02 and 34.09]). We then performed a manual record review to confirm the diagnosis of PPE and to document the mode of antibiotic therapy at discharge (oral versus OPAT) and the antibiotics prescribed.

Data Sources

Demographic, microbiological, and clinical data were electronically extracted from PCH's Enterprise Data Warehouse. Data elements that were extracted included age, gender, race/ethnicity, ICU admission, mechanical ventilation, hospital length of stay, the number of imaging studies performed, laboratory studies (white blood cell count, C-reactive protein, and erythrocyte sedimentation rate), and inpatient admissions, emergency department visits, and urgent care visits within 30 days of discharge from the index hospitalization. Additionally, complex chronic medical conditions were identified by using methods described by Feudtner et al.[15] Microbiologic data from sterile site cultures (blood and pleural fluid) were manually reviewed and positive cultures were classified as *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant), Viridans group streptococci, or other organisms.

Primary Outcome

Despite high rates of PPE in the Intermountain West,[3,16] treatment failure occurs infrequently; thus, we had limited power to directly compare the frequency of treatment failure between oral- and OPAT-treated patients. Consequently, this comparative effectiveness study used a composite primary outcome of all-cause complications accounting for both pneumonia-related complications (including treatment failure) and treatment-related complications.

Pneumonia-Related Complications

These included any unplanned hospital readmission or emergency department/urgent care visits within 30 days of discharge from the index hospitalization where the primary reason for admission or presentation was related to pneumonia, including treatment failure as well as less severe presentations, such as new fever, shortness of breath, and hypoxia.

Treatment Failure

This was a subset of pneumonia-related complications defined as a hospital readmission for worsening pneumonia, including progression of empyema or development of a parenchymal abscess requiring a repeat drainage procedure or operative intervention. Other less severe presentations were also included as pneumonia-related complications, including new fever, shortness of breath, and hypoxia.

Treatment-Related Complications

These were defined as a hospital readmission or unplanned emergency

department/urgent care visit within 30 days of discharge for complications related to antibiotic therapy, including drug adverse events (eg, rash, diarrhea, cytopenia) or catheter-related complications (eg, occlusion/clotting, dislodgment, leakage, malfunctioning, and line infections).

All health care encounters within 30 days of the index hospitalization were electronically identified for all of the patients included in this study and manually reviewed. Classification of the primary outcome was performed blinded to the treatment method by ALH and treatment failures were confirmed by CS, KA, and ATP.

Secondary Outcomes

Prespecified secondary analyses included assessments of individual components of the composite primary outcome measure including (1) pneumonia-related complications, (2) treatment failure, (3) treatment-related complications, and (4) catheter-related complications.

Statistical Analysis

Descriptive statistics were used to characterize demographic and clinical characteristics. Categorical variables were compared by using the χ^2 or Fisher's exact test, as appropriate. Normally distributed continuous variables are expressed as the mean (±SD) and were compared by using Student's *t* test. Continuous nonparametrically distributed variables are expressed as the median (interquartile range [IQR]) and were compared by using the Wilcoxon log-rank test.

As the discharge mode of therapy was not assigned at random, baseline characteristics may have differed among the 2 treatment groups (oral versus OPAT). To account for these differences in baseline characteristics, we used propensity score weights that were derived by using boosted classification trees, which were then included as weights in a logistic regression model that compared the frequency of the composite primary outcome among oral- and OPAT-treated children with PPE.[17] Propensity score weighting is a well-established method used to account for the influence of potentially confounding variables when deriving estimates of the primary outcome in each treatment group.[18] Unlike the traditional method of propensity score matching, which results in the exclusion of many patients, this method improves the statistical power by retaining all patients in the final model while simultaneously reducing the influence (down-weighting) of those patients with markedly different pretreatment characteristics.[17] In this approach, the composite primary outcome was regressed on an indicator variable denoting treatment status (oral versus OPAT) in a propensity score–weighted logistic regression model. The effect of oral outpatient antibiotic therapy as compared with OPAT was determined by using the estimated regression coefficient from the fitted model and is expressed as the adjusted odds ratio (aOR) and the corresponding 95% confidence interval (95% CI). Propensity score balance measures for each variable included in the final, adjusted model are included in Supplemental Table 5. Covariates were considered to be balanced between the 2 groups if the standardized difference was <0.25.[19]

Statistical significance was set at $P < .05$ and all comparisons were 2-sided. All statistical analyses were performed in R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Propensity score weights were derived using the twang package and weighted logistic regression models were developed using the survey package in R.[17,20]

RESULTS

Demographic and Clinical Characteristics of the Study Population

From 2005 through October 2014, we identified 391 hospitalized children with PPE at PCH. The number of children discharged each year ranged from 20 to 63. The median age was 3.8 (IQR 2.2–7.5) years and the median length of stay during the initial hospitalization was 8.8 (IQR 6.9–11.3) days. Most patients were discharged with OPAT (86%); however, the proportion discharged with oral antibiotics increased in the latter years of the study (Fig 1A). Baseline demographic, clinical, and microbiological characteristics of the 2 treatment groups

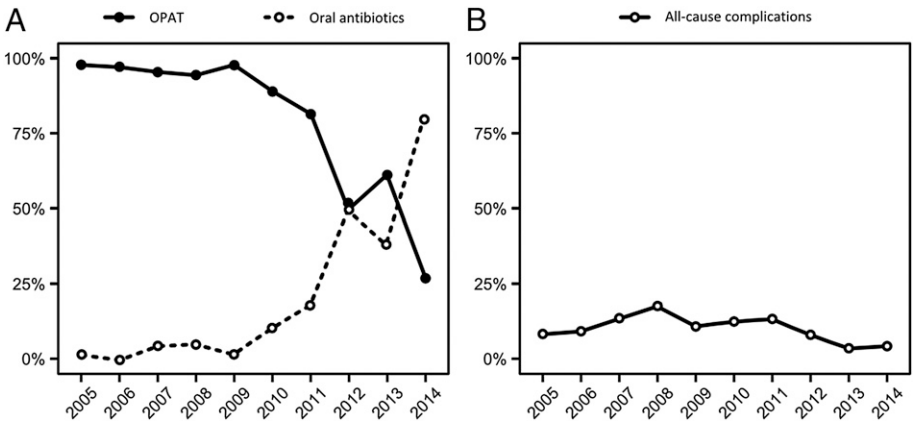

FIGURE 1 A, Annual trends in use of OPAT and oral antibiotics for PPE after hospital discharge. B, Annual trends in the percentage of PPE cases with all cause complications.

are featured in Table 1. Children discharged with oral antibiotics were more likely to be admitted to the ICU (57% vs 32%; $P < .001$), require mechanical ventilation (33% vs 13%; $P < .001$), and had longer lengths of stay (median 10.0 vs 8.7 days; $P = .01$) than children discharged with OPAT. The longer length of stay in the oral group was due to longer hospital stays for children who were admitted to the ICU. Other baseline characteristics were comparable between the 2 treatment groups. After propensity score weighting, the 2 treatment groups were balanced on all measured covariates (Supplemental Table 5). For children discharged with oral antibiotics, 63% received amoxicillin (Table 2). Among children discharged with OPAT, 89% received ceftriaxone or cefotaxime and 43% received combination therapy with clindamycin (either oral or intravenous) and another intravenous antibiotic.

Primary Outcome

Of the 391 children discharged from the hospital after hospitalization with PPE, 35 (9%) experienced the primary outcome (all-cause complications). The annual proportion of patients who experienced complications did not change ($P = .53$; Fig 1B). The frequency of all-cause complications was similar among children discharged with oral antibiotics (9.3%) and those discharged with OPAT (8.9%) (unadjusted OR 1.04, 95% CI 0.34–2.61) (Table 3). After adjustment for baseline demographic, microbiological, and clinical characteristics with propensity score weighting, the frequency of all-cause complications remained similar (aOR 0.97, 95% CI 0.23–4.65).

Secondary Outcomes

Pneumonia-related complications within 30 days of discharge occurred infrequently (7/391 [2%]). Two patients discharged on oral antibiotics (4%) and 5 patients discharged with OPAT (2%) were readmitted for pneumonia-related complications ($P = .25$). A summary of the clinical course of these patients is presented in Table 4. A total of 2 patients met the definition of treatment failure, both of whom received OPAT (1% of OPAT-treated patients).

TABLE 1 Characteristics of Children Hospitalized With PPE Who Were Discharged From the Hospital on Oral Antibiotics Versus OPAT

Characteristic	Complete Cohort, $n = 391$		
	Oral, $n = 54$	OPAT, $n = 337$	*P*
Age, y, median (IQR)	4.7 (2.6–9.1)	3.7 (2.0–7.0)	.16
Any complex chronic medical condition, *n* (%)	29 (54)	166 (49)	.56
Neurologic and neuromuscular	5 (9)	12 (4)	.07
Cardiovascular	11 (20)	23 (7)	.003
Respiratory	3 (6)	4 (1)	.06
Renal and urologic	2 (4)	3 (1)	.14
Gastrointestinal	0 (0)	2 (1)	.99
Hematologic or immunologic	0 (0)	8 (2)	.61
Metabolic	2 (4)	4 (1)	.19
Other congenital or genetic defect	5 (9)	14 (4)	.16
Malignancy	6 (11)	13 (4)	.03
Premature and neonatal	3 (6)	6 (2)	.11
Asthma, *n* (%)	5 (9)	29 (9)	.80
Positive culture from a sterile site, *n* (%)	16 (30)	111 (33)	.75
Staphylococcus aureus	2 (4)	16 (5)	.70
Blood culture	0 (0)	4 (1)	.99
Pleural fluid/pulmonary abscess	2 (4)	14 (4)	.99
Methicillin-resistant *S. aureus*	1 (2)	8 (2)	.99
Streptococcus pneumoniae	11 (20)	58 (17)	.99
Blood culture	5 (9)	32 (9)	.96
Pleural fluid/pulmonary abscess	8 (15)	35 (10)	.33
Streptococcus pyogenes	6 (11)	28 (8)	.28
Blood culture	0 (0)	7 (2)	.60
Pleural fluid/pulmonary abscess	6 (11)	24 (7)	.28
Viridans streptococci	0 (0)	5 (1)	.99
ICU admission, *n* (%)	31 (57)	107 (32)	<.001
Mechanical ventilation, *n* (%)	18 (33)	43 (13)	<.001
Length of stay, d, median (IQR)	10.0 (7.6–15.4)	8.7 (6.9–11.0)	.01

TABLE 2 Frequency of Antibiotics Prescribed at Discharge for 391 Children With PPE

Group	Antibiotic(s)	*n* (%)
Oral, $n = 54$	Amoxicillin alone	27 (50.0)
	Clindamycin	13 (24.1)
	Clindamycin alone	12 (22.2)
	Clindamycin and rifampin	1 (1.9)
	Amoxicillin/clavulanate alone	7 (13.0)
	Levofloxacin alone	4 (7.4)
	Others[a]	3 (5.6)
OPAT, $n = 337$	Ceftriaxone or cefotaxime overall	299 (88.7)
	Ceftriaxone or cefotaxime alone	151 (44.8)
	Ceftriaxone or cefotaxime and clindamycin	139 (41.2)
	Ceftriaxone or cefotaxime and others[a]	9 (2.7)
	Clindamycin	23 (6.8)
	Clindamycin alone	17 (5.0)
	Clindamycin and others[a]	5 (1.5)
	Others[a]	15 (4.5)

[a] Others includes ampicillin/sulbactam, azithromycin, cefazolin, ciprofloxacin, erythromycin, gentamicin, linezolid, meropenem, nafcillin, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, and vancomycin.

TABLE 3 Clinical Outcomes and Complications Among Children Hospitalized With PPE Who Were Discharged From the Hospital on Oral Antibiotics Versus OPAT

Outcome	Oral, $n = 54$, n (%)		OPAT, $n = 337$, n (%)		Unadjusted OR (95% CI)[a]	P	aOR (95% CI)[b]	P
	Yes	No	Yes	No				
All-cause complications	5 (9.3)	49 (90.7)	30 (8.9)	307 (91.1)	1.04 (0.34–2.61)	.99	0.97 (0.23–4.65)	.96
Pneumonia-related complications	2 (3.7)	52 (96.3)	5 (1.5)	332 (98.5)	2.55 (0.24–16.05)	.25	—	—
Treatment failure	0 (0)	54 (100)	2 (0.6)	335 (99.4)	—	—	—	—
Treatment-related complications	3 (5.6)	51 (94.4)	26 (7.7)	311 (92.3)	0.70 (0.13–2.43)	.78	—	—
Catheter-related complications	—	—	17 (5.0)	320 (95.0)	—	—	—	—

—, not applicable.

[a] Unadjusted ORs were derived using logistic regression.

[b] The aORs were derived by using propensity score–weighted logistic regression. The propensity scores were derived from the following variables: the number of chronic medical conditions (as defined by Feudtner et al[15]), ICU admission, mechanical ventilation, length of stay, and a positive microbiological culture from a sterile site.

Treatment-related complications that occurred within 30 days of discharge were identified in 29 (7%) of 391 children. The distribution of treatment-related complications was comparable among the 2 treatment groups (oral 6% versus OPAT 8%; $P = .78$). Catheter-related complications were identified in 5% of OPAT-treated patients.

DISCUSSION

We compared all-cause complications among children hospitalized with PPE who were discharged with oral antibiotics versus OPAT. We found that the frequency of all-cause complications after discharge was similar between these 2 groups in unadjusted analyses, after adjustment for differences in demographic and clinical characteristics with propensity score weights and across study years. Treatment failure was uncommon, occurring in 0 of 54 children treated with oral therapy and 2 of 337 children receiving OPAT. These findings suggest that the safety and effectiveness of oral antibiotic therapy is comparable to OPAT for the outpatient antibiotic management of pediatric PPE.

Although a randomized controlled trial would be the optimal way to compare the efficacy of OPAT with oral therapy for children with PPE after hospital discharge, recent Infectious Diseases Society of America guidelines highlight that no such trials have been performed. The guidelines identify the need to compare the effectiveness of these modes of therapy as a priority area for research.[11] These guidelines also state that conversion to oral therapy for outpatient treatment is preferable to OPAT, as oral antibiotics are simpler to administer and less costly. Another advantage of oral therapy relates to

TABLE 4 Mode of Antibiotic Therapy, Microbiological Findings, and a Clinical Synopsis for the 7 Children With PPE Who Were Readmitted Within 30 Days of Discharge From Their Index Hospitalization

Patient No.	Mode of Antibiotic Therapy	Microbiological Findings (Source)	Treatment Failure?	Synopsis
1	OPAT	Viridans group *Streptococcus* (pleural fluid)	Yes	14-y-old readmitted 9 d after discharge with fever and reaccumulation of pleural fluid. Underwent operative drainage.
2	OPAT	Negative	No	14-y-old with trisomy 21 readmitted 1 d after initial discharge with new oxygen requirement and presumed aspiration event. During the hospitalization, antibiotic therapy was expanded to target anaerobes.
3	OPAT	Methicillin-sensitive *Staphylococcus aureus* (pleural fluid)	No	3-mo-old readmitted 6 d after discharge with a spontaneous pneumothorax.
4	OPAT	*Streptococcus pneumoniae* (blood)	No	3-y-old readmitted 5 d after discharge with increased work of breathing for observation. Symptoms resolved without an intervention or change in treatment.
5	OPAT	*Streptococcus pyogenes* (blood)	Yes	2-y-old readmitted 4 d after discharge with reaccumulation of pleural fluid. Underwent operative drainage.
6	Oral	Negative	No	5-y-old readmitted 1 d after initial discharge with a hydropneumothorax requiring chest tube placement.
7	Oral	*S pneumoniae* (pleural fluid)	No	4-y-old readmitted 18 d after discharge with a veno-pleural fistula and presumed thrombus.

the potential to reduce selection for antibiotic resistance. Ceftriaxone is the most commonly used agent for OPAT, in part due to dosing convenience, but it has a broader spectrum of activity than amoxicillin, which is the recommended oral agent in most cases.[11] However, concerns about the effectiveness of oral therapy for completing treatment relative to OPAT may remain and prevent some physicians from using oral step-down therapy. We found that treatment failure, strictly defined to be development of a lung abscess or reaccumulation of pleural fluid that required drainage, was an extremely rare outcome in a large sample of patients with PPE. Although the sample size of children who received oral antibiotics was somewhat limited, this study provides support to consider oral outpatient therapy for children with PPE.

Previous studies examining the long-term outcomes of children with PPE have also reported that hospital readmission occurs infrequently.[9,10] In 1 study conducted in a large network of freestanding children's hospitals, the overall readmission rate was 3% but varied widely across centers.[9] The authors did not report the clinical details of the rehospitalizations and therefore it is not possible to estimate the rate of treatment failure among the children who were readmitted. Nonetheless, this is similar to the 2% we observed among children who were readmitted for pneumonia-related complications. In a study by Cohen et al,[10] 6 (7%) of 84 patients with PPE required readmission after the index hospitalization, including 3 (4%) with persistent pleural effusion requiring intervention, which is suggestive of treatment failure. However, the mode of outpatient antibiotic therapy (intravenous versus oral) was not reported.

A strength of our study is that we were able to review the medical records for each patient who required readmission or visited an emergency department/urgent care after the index hospitalization for PPE. This enabled a precise classification of the reasons for rehospitalization, allowing us to distinguish children with treatment failure versus those with other types of complications, such as air leak or fistula formation. This shows the potential lack of specificity of using hospital readmission as a surrogate outcome for treatment failure in comparative-effectiveness studies; in this study only 2 (29%) of 7 pneumonia-related readmissions were classified as treatment failures.

There is a growing recognition that OPAT is overused and that overuse can be minimized through antimicrobial stewardship.[21,22] This is supported by an expanding evidence base indicating that the effectiveness of oral therapy is equivalent to OPAT for a variety of serious pediatric infections frequently treated with OPAT, including complicated appendicitis and osteomyelitis.[23–26] In a recent study comparing oral therapy with OPAT for osteomyelitis, rates of treatment failure were similar between groups.[25] However, the rate of adverse drug events was higher in patients treated with OPAT.[25] In that study, 15% of patients treated with OPAT experienced a catheter-related complication, of which 85% required an emergency department/urgent care visit or rehospitalization.

It is notable that in our study of PPE, we observed catheter-related complications in only 5% of patients treated with OPAT, which is lower than has been reported in other studies.[26,27] Several reasons may exist for this difference. First, we only included complications that resulted in a hospitalization or emergency department/urgent care visit and likely underestimated the true rate of complications. Certain complications (eg, administration of tissue plasminogen activator for a clotted central line) could be managed by a home health nurse without requirement for an acute care visit and were not captured by our analysis. Additionally, catheter dwell time is an established risk factor for complications, and thus the difference in catheter-related complication rates may be due to differing durations of treatment of PPE as compared with other infectious conditions.[28]

Several additional factors strongly favor oral antibiotics for outpatient antibiotic therapy that are not accounted for in our or other comparative-effectiveness studies. Most prominently, these include economic considerations, including both direct and indirect costs. For patients receiving OPAT with Intermountain Healthcare, the weekly cost for OPAT administration, exclusive of drug costs, is nearly $1000, a direct medical cost that is entirely avoided with oral therapy.[21] The costs of most intravenous antimicrobial agents greatly exceed the cost of oral agents, especially when comparing the most commonly used agents for the treatment of pneumonia: ampicillin or ceftriaxone versus amoxicillin. The caregiver time burden to administer OPAT also may be substantial, including time spent administering the antibiotic along with routine line care. This could lead to missed work or other activities. A formal economic evaluation comparing the direct and indirect medical costs of oral therapy to OPAT for pediatric PPE would complement comparative-effectiveness studies.

This was a retrospective, observational study and has several limitations. Treatment assignment was not random, resulting in some differences between the patient populations who were discharged from the hospital with oral antibiotics and those who were discharged with OPAT. Propensity score weights were used to improve balance between these 2 populations for several important clinical parameters; however, we were unable to fully account for temporal trends with our model due to the high proportion of patients treated with OPAT early in the study period. The increase in the number of patients discharged with oral antibiotics later in the study period was likely due, at least in part, to changes in our routine practice of using OPAT for most children with PPE and the introduction of the 13-valent pneumococcal conjugate vaccine. Additionally, although we adjusted for several important clinical factors, unmeasured confounders could remain (eg, radiographic differences). Emergency department/urgent care visits and rehospitalizations could not be identified if they occurred outside of the Intermountain Healthcare system. However, because Intermountain Healthcare facilities accounted for 75% to 85% of all pediatric hospitalizations in Utah over the study period, the number of missed events is likely to be low. We had a relatively small

number of patients treated with oral therapy as compared with OPAT, which limited our ability to detect potentially small differences in treatment outcomes, including treatment failures. Additionally, the total duration of antimicrobial therapy was not assessed and the number of days of parenteral therapy administered to the patients discharged on oral antibiotics is unknown. The most commonly cultured organism in our cohort was *S pneumoniae*. However, due to our limited sample size, we cannot exclude the possibility that higher rates of treatment failure or other complications may occur among cases of PPE caused by other organisms, such as *S aureus*.

CONCLUSIONS

In summary, we found that the frequency of all-cause complications among children with PPE who were discharged from the hospital to complete therapy with oral antibiotics and OPAT were similar. Treatment failure was extremely rare (<1%), and the 2 cases we identified occurred among children who were discharged with OPAT. Oral antibiotics should be considered for children with PPE who require completion of antibiotic therapy at home.

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