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MAJOR ARTICLE

Fluoroquinolone Use Among Hospitalized Children: Diagnosis-Based Stratification to Identify Stewardship Targets

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Background. As FQ (fluoroquinolone) use has shifted in pediatric populations, better metrics are needed to guide targeted antibiotic stewardship interventions and limit development of adverse events and resistance, particularly in medically complex children. In this study, we identify high-utilization groups based on underlying medical conditions and describe their relative FQ use over time.

Methods. This study is a retrospective analysis of data from the Pediatric Health Information System database from 2016 to 2020. We identify high-utilization groups based on underlying medical conditions using *International Classification of Diseases, Ninth* or *Tenth Revision* codes. We delineate overall trends in the use of FQs in the inpatient setting, including rate and proportional use by each patient group.

Results. Patients with an oncology diagnosis represent a large (25%–44%) and rising proportion (+4.8%/year, $P = .001$) of national FQ use over the study period. Patients with intra-abdominal infections, including appendicitis, have had a significant increase in both their relative proportional use of FQs (+0.6%/year, $P = .037$) and proportion of FQ use per admission encounter over the study period (+0.6%/year, $P = .008$). Patients with cystic fibrosis represent a decreasing proportion of overall use (−2.1%/year, $P = .011$) and have decreasing FQ use per inpatient encounter (−0.8%/year, $P = .001$).

Conclusions. Patients with an oncology diagnosis and patients with an intra-abdominal infection appear to be targets for FQ stewardship. Patients with cystic fibrosis have decreasing inpatient FQ use.

Keywords. antimicrobial stewardship; cystic fibrosis; fluoroquinolones; hospitalized children.

Fluoroquinolones (FQs) are an important class of antibiotics, particularly for treating multidrug-resistant (MDR) organisms. However, widespread use has led to increasing rates of FQ resistance. Due to concerns about adverse events and antimicrobial resistance, the American Academy of Pediatrics released a clinical report outlining limiting FQ use in 2016 [1–3]. They recommend using FQs for (1) MDR infections without an acceptable alternative or (2) when there is no alternative oral agent for an infection that does not require intravenous therapy [2].

Despite these recommendations, FQs are still used in pediatric outpatient and inpatient settings, particularly in chronically ill children [4–7]. Fluoroquinolones are consistently within the top 5 broad-spectrum agents used for pediatric hospital-onset infections and represent >9% of total antibiotic-days each year for these indications since 2019 [8–10]. Antimicrobial stewardship initiatives directed at FQ use are key for prevention of emergence of resistant bacteria and the development of adverse events in this vulnerable population. Given the robust antimicrobial stewardship scaffolding present in the inpatient setting, describing and understanding FQ use in this population could be an important first step toward both inpatient and outpatient stewardship efforts.

Metrics such as days of therapy (DOT) per 1000 patient-days are standard for benchmarking antibiotic consumption between hospitals, including unit-level comparisons. However, these metrics do not include stratification by specific medical conditions and their relative antibiotic consumption. By describing FQ use in the context of specific underlying medical conditions, we created diagnostic groups to identify potential high-yield stewardship targets and relevant subspeciality providers that manage the medical care of these children.

METHODS

Data Source

We performed a retrospective database analysis using data from the Pediatric Health Information System (PHIS) database. This

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dataset provides inpatient data regarding antimicrobial utilization (including duration, agent, and route) and diagnosis codes associated with both patients and discrete encounters [11]. Data include the 9th and 10th revisions of the *International Classification of Diseases* (*ICD-9* and *ICD-10*, respectively) coding for medical diagnoses and procedures. The PHIS database contains details on clinical and resource utilization data from >50 children's hospitals. Hospitals that participated in the PHIS database during the study period (2016–2020) are in 29 states and include 10 million inpatient cases and 285.5 million total *ICD-9*/*ICD-10* codes [11]. The protocol for this study was approved by the local institutional review board.

Inclusion Criteria

All patients <18 years of age were included if they received a minimum of 1 dose of FQ therapy during an admission between 2016 and 2020. FQs were defined as moxifloxacin, ciprofloxacin, and levofloxacin delivered through an enteral or intravenous route.

Hospitals that did not contribute data to PHIS during the full study period or with incomplete *ICD-9* and *ICD-10* data were excluded. No patients were excluded based on individual patient characteristics.

Diagnostic Groups

We used a multistep algorithm to identify potential high-yield targets by underlying medical condition. Diagnostic groups for receipt of FQs were identified by a combination of expert opinion, single-center retrospective review of FQ use at our institution, and review of the most common diagnosis codes in PHIS associated with antibiotic FQ use. Based on these assessments, 5 diagnostic groups were identified: cystic fibrosis (CF), urologic abnormality, oncologic abnormality, tracheostomy, and intra-abdominal infection. All patients with FQ exposure were then stratified into these groups or into an "unassigned" category.

To increase sensitivity, a chronic condition was identified by including *ICD-9* and *ICD-10* diagnostic codes associated with encounters prior to the index encounter when FQs were prescribed (Supplementary Table 1). The antecedent length of time used for definition of groups varied by diagnosis. The lengths were chosen based on the chronicity of illness and their perceived contribution to potential microbial resistance. Patients were placed into the CF, tracheostomy, or urologic abnormality group if there was a diagnosis code for these conditions at any point since birth. Patients were placed in the oncology group if they had an oncologic diagnosis at or within 3 years prior to their receipt of a FQ. Patients were placed in the intra-abdominal infection group if they had an intra-abdominal code at or within 1 year prior to their receipt of a FQ.

If patients had multiple diagnostic group codes, they were stratified based on clinical priority as follows: All patients with CF diagnosis codes were placed in the CF group, all patients with oncology diagnoses (other than those with CF) were placed in the oncology group, and patients with codes for both tracheostomy and urologic abnormality were placed in the tracheostomy group. Intra-abdominal infection diagnoses were given the lowest priority. The prioritization schema was designed to select the chronic condition that was expected to be clinically relevant to the hospital admissions and associated antibiotic use. Our criteria prioritized conditions managed by subspecialty services that were most likely responsible for antibiotic decision making. This could help identify a primary specialist to collaborate for future antimicrobial stewardship initiatives.

Metrics Assessed

We first assessed the overall distribution of FQ use by diagnostic group for each year of the study. Proportional FQ use by each diagnostic group, as a percentage of total FQ use, was calculated for each study year at the encounter and patient level. Trends in proportion of use by each diagnostic group were determined for 2016–2020.

To further quantify antibiotic use, we calculated the total DOT for each diagnostic group per year. Additionally, DOT were calculated for each FQ (ie, levofloxacin, moxifloxacin, and ciprofloxacin). We then calculated the trends in FQ use per encounter to account for changes in patient volume for diagnoses.

The PHIS database does not capture antibiotic use prescribed after hospital discharge. Therefore, to estimate the potential use of FQs as transition agents to outpatient therapy, we determined the median duration of each encounter and the frequency of initial exposure to FQs in the final 2 calendar days of admission, stratified by diagnostic group.

Next, we determined the number of unique patients in each diagnostic group who received FQs within a calendar year. To determine the total number of patients per year in each of the 5 diagnostic groups, patients were assigned using the same stratification and time interval criteria described above; however, the first day of the year was used instead of the first day of FQ receipt to determine eligibility periods for assignment to diagnostic groups.

Statistical Methods

All continuous variables were described using median and interquartile range (IQR). Proportions were calculated and trends over time were assessed for statistical significance using linear regression modeling for each chronic condition. Multilevel generalized linear mixed models were used to assess statistical difference in odds ratios (ORs) of prescriptions for FQs written within the final 2 calendar days of hospital admission [12]. For this model, overall use was the reference and chronic conditions were the specific clusters. All statistical analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute,

Cary, North Carolina). All changes in percentage by year were obtained from the linear regression analysis.

RESULTS

Data from 89 hospitals and affiliated campuses were initially included, but 24 sites were excluded due to incomplete patient data. The excluded data represented 2.1% of total encounters and 2.5% of total patients. Overall, there were 89 993 patients with 112 546 encounters in which FQs were prescribed. There were 465 144 patients with 1 510 247 encounters associated with the diagnostic groups included in the study, independent of FQ prescription.

When proportional use by DOT was calculated, the 5 diagnostic groups accounted for 54.3%–64.3% of total use (Table 1). The next highest represented diagnosis groups seen included sickle-cell disease, antibiotic allergies, and pneumonia not otherwise specified. Within the oncology group, 5304 (45.2%) patients had leukemia as their qualifying diagnosis and 6437 (54.8%) had other oncologic qualifying diagnoses. The most frequently used FQ was ciprofloxacin (62%), followed by levofloxacin (37%), moxifloxacin (1%), and combination FQ use (0.3%). Overall, 53.9% (284 192 days) of the DOT was with oral FQs and 46.1% (243 378 days) with parenteral formulations. The median days of use were highest in the oncology (4–5) and CF (5–7) diagnostic groups (Table 2).

There was an increase in the percentage use by DOT over the study period in the oncology group (+4.8%/year, $P = .001$) and the intra-abdominal group (+0.6%/year, $P = .037$). There was a decrease in the percentage use by DOT over the study period in the CF group (−2.1%/year, $P = .011$) and the tracheostomy group (−0.6%/year, $P = .043$). There was no significant change in the urologic abnormality group ($P = .8$) (Table 1).

The percentage of encounters with FQ use increased over time among patients in the intra-abdominal infection group (+0.6%/year, $P = .008$) and the oncology group (+0.1%/year, $P = .047$). The percentage of encounters using FQs over time decreased among patients in the CF group (−0.8%/year, $P = .001$) and the tracheostomy group (−0.46%/year, $P = .002$). There was no significant change in the urologic abnormality group (Table 3).

Overall, 49.6% of FQ treatment courses began in the last 2 calendar days of admission (Figure 1). The intra-abdominal infection group (74.2%; OR, 3.24 [95% confidence interval {CI}, 1.63–6.47]) and the urologic abnormality group (64.4%; OR, 2.02 [95% CI, 1.01–4.03]) were more likely to first receive FQs in this time when compared to the overall frequency. This suggests that many of these prescriptions were prescribed as transition to oral therapy prior to discharge. However, the median duration of admission for these 2 groups (3 days for both) was also lower than that of the other groups assessed (CF, 11 days; tracheostomy, 6 days; oncology, 14 days).

DISCUSSION

Due to increases in infections caused by extended-spectrum β-lactamase–producing gram-negative organisms, especially in urinary tract infections, FQs have emerged as important options in the treatment of MDR infections [13, 14]. While there is more comfort with the use of FQs in pediatrics, long-term impacts on antibiotic resistance in pediatric populations are unknown [15, 16]. However, increased incidence and duration of FQ therapy is associated with the emergence of FQ-resistant pathogens, and there is conflicting evidence linking it to the emergence of MDR organisms [6, 17]. Based on our results, the epidemiology of inpatient FQ receipt has shifted among high-risk patient groups between 2015 and 2020 with clear trends via both changes in proportional use and use per encounter for the identified patient groups.

Measuring FQ use and its association with development of resistance in chronically ill children is challenging, and a more systematic approach is needed [13]. Existing benchmarking using DOT for institutional- and unit-level reporting may not detect increases in use among specific vulnerable populations. Implementation of additional metrics, such as proportional use by diagnosis, within antimicrobial stewardship could prove a useful tool for targeted initiatives, particularly among pediatric patients who require frequent antibiotics [18]. Our

Table 1. Percentage of Total Days of Therapy for Each Diagnostic Group by Year

	Diagnostic Group						
Year	CF	IA	ONC	TRACH	URO	UNASGN	Total DOT
2016	12.0%	3.5%	25.8%	10.9%	2.2%	45.7%	79 237
2017	11.7%	3.2%	28.2%	10.6%	2.3%	44.1%	82 932
2018	9.6%	3.6%	35.1%	9.6%	2.4%	39.6%	83 497
2019	7.6%	4.9%	38.3%	10.0%	2.4%	36.9%	94 342
2020	3.5%	5.7%	44.9%	8.0%	2.2%	35.7%	86 091
Change, % per year	−2.1%	+0.6%	+4.8%	−0.6%	+0.01%	…	…
P value	.011[a]	.037[a]	.001[a]	.043[a]	.8		…

Abbreviations: CF, cystic fibrosis; DOT, days of therapy; IA, intra-abdominal infection; ONC, oncology; TRACH, tracheostomy; UNASGN, unassigned; URO, urologic abnormality.

[a]Changes that are significant ($P < .05$).

Table 2. Median Days of Therapy per Encounter of Each Diagnostic Group by Year

	Diagnostic Group					
Year	CF	IA	ONC	TRACH	URO	UNASGN
2016	7.0 (3.0–12.0)	2.0 (1.0–3.0)	4.0 (2.0–9.0)	3.0 (2.0–6.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
2017	7.0 (3.0–12.0)	2.0 (1.0–3.0)	4.0 (2.0–9.0)	3.0 (2.0–5.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)
2018	7.0 (3.0–13.0)	2.0 (1.0–3.0)	4.0 (2.0–11.0)	3.0 (2.0–6.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
2019	7.0 (3.0–12.0)	1.0 (1.0–2.0)	5.0 (2.0–12.0)	3.0 (2.0–6.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)
2020	5.0 (2.0–11.0)	1.0 (1.0–2.0)	5.0 (2.0–13.0)	3.0 (2.0–6.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)

Data are presented as median (interquartile range).

Abbreviation: CF, cystic fibrosis; IA, intra-abdominal infection; ONC, oncology; TRACH, tracheostomy; UNASGN, unassigned; URO, urologic abnormality.

Table 3. Percentage of Total Encounters Using Fluoroquinolones by Year

	Diagnostic Group					
Year	CF	IA	ONC	TRACH	URO	APPY
2016	5.5%	4.8%	2.2%	8.3%	3.6%	3.7%
2017	4.8%	4.8%	2.2%	7.6%	3.9%	3.9%
2018	4.1%	5.4%	2.5%	7.3%	4.5%	4.5%
2019	3.5%	6.3%	2.6%	7.0%	4.5%	6.4%
2020	2.3%	6.9%	2.6%	6.3%	4.0%	6.8%
Change, % per year	−0.8%	+0.6%	+0.1%	−0.5%	+0.2%	+0.9%
P value	.001[a]	.008[a]	.047[a]	.002[a]	.284	.013[a]

Abbreviations: APPY, appendicitis; CF, cystic fibrosis; IA, intra-abdominal infection; ONC, oncology; TRACH, tracheostomy; URO, urologic abnormality.

[a]Changes that are significant ($P < .05$).

diagnostic groups were created both to capture a large proportion of overall FQ use in pediatrics and to emphasize the need for understanding their use in these complex patient groups.

Electronic health record technology can be utilized to provide therapy to patients via rapid targeted risk assessments [19]. This has the potential to be used for stewardship initiatives such as risk factor-based antibiograms (ie, stratified by admission location, exposure history) or syndrome-based antibiograms [20]. Our methodology of antibiotic use stratified by medical condition can be used with these antibiograms to closely monitor antibiotic utilization and its association with antimicrobial resistance. By shifting the focus of antibiotic use from the institutional/unit level to patient group–specific use, we hope to increase individualized care, maximize stewardship initiatives for specific antibiotic classes, and inform stewardship efforts for vulnerable populations.

Our data identify specific, targetable populations that are undergoing shifts in FQ use. Patients within the oncology group have increasingly become the primary users of FQs within the hospital. This is likely driven by increased use of FQs for prophylaxis, as well as broader acceptance and experience with FQs as step-down therapy for pediatric oncology patients in general over the last decade [2, 21, 22]. However, while associated with fewer febrile episodes and bacterial infections when compared to no prophylaxis, there was no significant difference in these outcomes when compared to any other prophylaxis regimens [23, 24]. Additionally, recent studies have found increased incidence of MDR and FQ-resistant infections associated with their use, with resultant ineffective prophylaxis in some patients [17, 25]. Tracking FQ use in oncology patients and other medically complex children is important, as the emergence and transmission of FQ-resistant infections contributes to the burden of antimicrobial resistance hospital-wide and in the community [26].

The other group identified with increasing absolute and relative proportional FQ use were patients with intra-abdominal infections. This group included patients with diagnosis codes for intra-abdominal abscess and appendicitis. There are conflicting data and recommendations regarding appropriate antibiotics for these conditions, specifically related to the need for empiric therapy for *Pseudomonas aeruginosa.* Multiple recent large retrospective studies suggest there is no difference in readmission rates, organ space infection, and resource utilization when using piperacillin-tazobactam compared to ceftriaxone and metronidazole in both complicated and uncomplicated appendicitis, despite the former regimen targeting both *Pseudomonas* and enterococci [27, 28]. These studies suggest that fewer FQs could be used in children with intra-abdominal infections, instead of the nearly 2-fold increase observed in our study. Of note, a recent 2-center randomized trial comparing ceftriaxone and metronidazole versus piperacillin-tazobactam for treatment of perforated appendicitis showed decreased development of abscess and return emergency department visits with use of piperacillin-tazobactam [29]. However, the contribution of *Enterococcus* species, *P aeruginosa*, and other resistant gram-negative rods was not ascertained, as no cultures were obtained in the study. (It is unclear how helpful these cultures would be in terms of antibiotic selection for this patient population [30, 31].) In our findings, the primary driver of the increase in FQ use in intra-abdominal infections may be ease of transition to oral therapy. Given that the PHIS database does not capture outpatient prescriptions, our numbers likely underestimate the proportional contribution of FQ therapy in children with intra-abdominal infections. Future studies should examine whether the increased use of FQs for oral step-

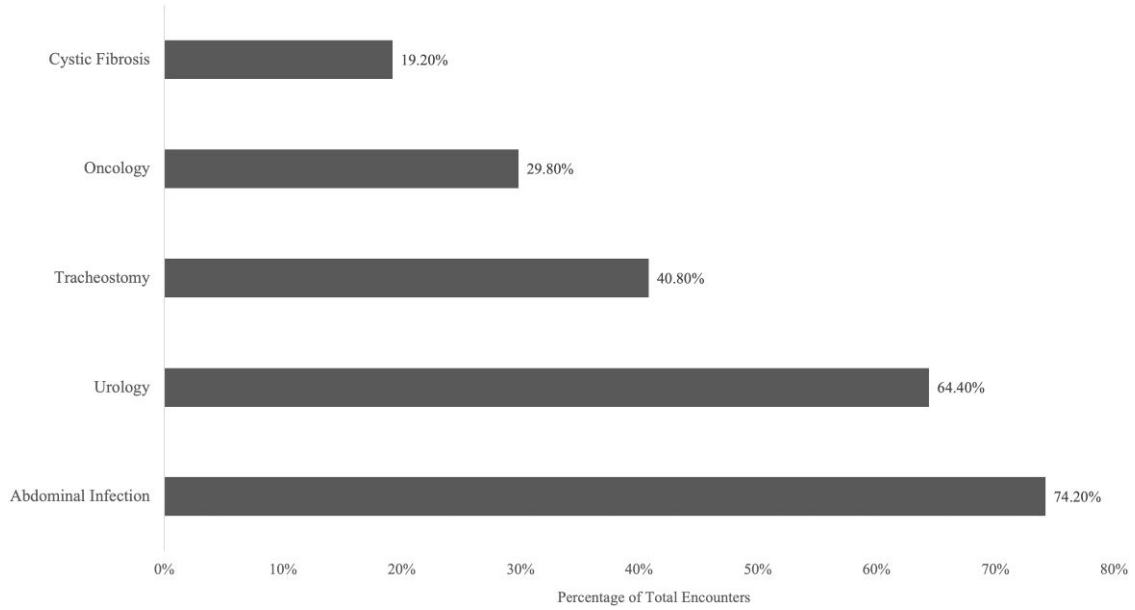

Figure 1. Percentage of encounters with first receipt of antibiotics 2 days prior to discharge.

down therapy has an impact on treatment failure and acquisition of antibiotic-resistant organisms.

Interestingly, there has been a decrease in both the percentage DOT and overall percentage use in CF patients. This is an encouraging finding, as patients with CF have higher reported rates of antibiotic allergies/hypersensitivity, compared to other medically complex children, which limits available agents for serious respiratory infections [32, 33]. Additionally, there is recent evidence that suggests that the addition of FQs for combination therapy to *P aeruginosa* may not be associated with improved outcomes [7]. Our study is limited to inpatient antibiotic use, and thus may have missed use of FQs in CF patients in outpatient settings. Last, elexacaftor-tezacaftor-ivacaftor, a novel agent that alters cystic fibrosis transmembrane conductance regulator protein function to decrease pulmonary disease progression for CF patients, has also been shown to decrease overall use of antibiotics [34]. The broader use of these medications will likely further decrease the need for antibiotic use.

The PHIS database does not contain microbiology data, including antibiotic susceptibility. However, although the American Academy of Pediatrics guidelines have specific recommendations for FQ use based on antibiotic-resistant organisms, the patient populations we examined varied considerably in how microbiologic data inform antibiotic selection [2]. For example, a substantial proportion of FQ use in the oncology populations may be for prophylaxis, and thus not reliant on microbiology data. Similarly, many patients in the intra-abdominal infection group may receive empiric therapy without surgical cultures to guide therapy. In contrast, providers for patients in the urologic abnormality and tracheostomy groups are likely to use culture results to select antibiotic therapy, even when the isolated organisms may reflect colonization. With these considerations in mind, it is difficult to postulate that antibiotic resistance was the primary driver for selection of antimicrobial therapy.

There were limitations to our study. PHIS is an inpatient administrative database and thus does not capture outpatient prescriptions. For patients who may have received FQs as transition to outpatient therapy, the full duration likely was not captured. Nonetheless, initial inpatient stewardship interventions in medically complex children may lead to further longitudinal collaboration with subspecialists including stewardship in outpatient and skilled nursing facility settings. The PHIS database also represents a select group of children's hospitals in North America, which are more likely to have complex patients, robust antibiotic stewardship programs, and availability of infectious diseases consultation. Another limitation is the potential inaccuracy of *ICD-9* and *ICD-10* diagnostic codes. Providers may not reliably include all diagnosis codes or may inaccurately code encounters, limiting both specificity and sensitivity to capture diagnostic groups. Furthermore, because the prioritization schema for patient with multiple diagnostic groups relied on *ICD* coding in PHIS, there was a risk of misclassification. Finally, there has been a noted increase in rates of community-acquired extended-spectrum β-lactamase–resistant organisms between over the last several years [35–37]. These increases could have contributed to increased rates of overall use of FQs but would be unlikely to explain increased proportional use by underlying conditions.

Through identification of longitudinal use of FQs by diagnostic groups, we have utilized a novel method for measuring antibiotic use and identifying potential stewardship targets. The patient groups identified represent high-risk groups for recurrent antibiotic exposure, harboring of antibiotic-resistant organisms, and serious infections. This method also fosters identification of subspecialist partners for promoting judicious antibiotic use.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. S. P.-J. conceptualized the framework of the manuscript, drafted the initial manuscript, and participated in the manuscript revision process. S. S. contributed to all statistical analyses and consultations and participated in the manuscript revision process. T. S. participated in the manuscript revision process. S. J. P. oversaw the project, helped conceptualize the framework of the manuscript, and participated in the manuscript revision process. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Patient consent. This study was a database study without the use of or access to specific patient identifiers and thus did not require individual study participant consent. The design of this study conforms to standards currently applied in the United States and was authorized by the Ann and Robert H. Lurie Children's Hospital of Chicago Institutional Review Board.

Potential conflicts of interest. All authors: No reported conflicts.

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