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Authors

Dasgupta-Tsinikas, Shom
Zangwill, Kenneth M
Nielsen, Katherine
et al.

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Treatment and Epidemiology of Third-Generation Cephalosporin-Resistant Urinary Tract Infections

Shom Dasgupta-Tsinikas, MD[a,b], **Kenneth M. Zangwill, MD**[a,c], **Katherine Nielsen, MD**[d], **Rebecca Lee, DO**[d], **Scott Friedlander, MPH**[c], **Suzanne M. Donovan, MD**[e], **Tam T. Van, PhD**[f], **Susan M. Butler-Wu, PhD**[g], **Jagmohan S. Batra, MD**[h], **Sylvia H. Yeh, MD**[a,c] **Resistant UTI in Children Study Team***

[a]Division of Pediatric Infectious Diseases, Harbor-UCLA Medical Center, Torrance, CA

[b]Department of Public Health, County of Los Angeles

[c]Lundquist Institute at Harbor-UCLA Medical Center, Torrance CA

[d]Department of Pediatrics, Harbor-UCLA Medical Center

[e]Department of Medicine, Olive View-UCLA Medical Center

[f]Department of Pathology, Harbor-UCLA Medical Center

[g]Department of Pathology and Laboratory Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

[h]Miller Children's and Women's Hospital, Long Beach, CA

Abstract

Background: Limited data are available on the contemporary epidemiology, clinical management, and healthcare utilization for pediatric urinary tract infection (UTI) due to third generation cephalosporin-resistant Enterobacterales (G3CR) in the United States.

Objectives: To describe the epidemiology, antimicrobial treatment and response, and healthcare utilization associated with G3CR UTI.

Methods: Multi-site, matched cohort-control study including children with G3CR UTI versus non-G3CR UTI. UTI was defined as per American Academy of Pediatrics guidelines, and G3CR

Address correspondence to: Sylvia H. Yeh, MD, Liu Research Bldg (RB-3), 1124 W. Carson Street, Torrance, CA 9052. syeh@lundquist.org.

*A complete list of study team members appears in the Acknowledgments.

Contributors' Statement:

Dr. Dasgupta-Tsinikas conceptualized and designed the study, designed the data collection instrument, collected data, coordinated and supervised data collection, managed and analyzed data, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. Zangwill and Yeh conceptualized and designed the study, designed the data collection instrument, coordinated and supervised data collection, supervised data analysis, and reviewed and revised the manuscript.

Drs. Nielsen, Lee, Van, Butler-Wu, and Batra collected data, coordinated and supervised data collection, and reviewed and revised the manuscript.

Mr. Friedlander managed and analyzed data, and reviewed and revised the manuscript.

Members of the Study Team contributed to site-specific IRB applications and/or initial data acquisition.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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as resistance to ceftriaxone, cefotaxime or ceftazidime. We collected data from the acute phase of illness to 6 months thereafter.

Results: Among 107 children with G3CR UTI and 206 non-G3CR UTI with documented assessment of response, the proportion with significant improvement on initial therapy was similar (52% vs 57%, odds ratio (OR) 0.81, 95% confidence interval (CI) 0.44-1.50). G3CR-patients were more frequently hospitalized at presentation (38% vs 17%, OR 3.03, 95% CI 1.77-5.19) and for longer duration (8d vs 4d, p-value=0.05). In the follow-up period, more G3CR-patients had urine cultures (75% vs 53%, OR 2.61, 95% CI 1.33-5.24), antimicrobial treatment for any indication (53% vs 29%, OR 2.82, 95% CI 1.47-5.39), and subspecialty consultation (23% vs 6%, OR 4.52, 95% CI 2.10-10.09). In multivariate analysis, prior systemic antimicrobial therapy remained a significant risk factor for G3CR UTI (adjusted OR 1.91, 95% CI 1.06-3.44).

Conclusions: We did not observe a significant difference in response to therapy between G3CR and susceptible UTI, but subsequent healthcare utilization was significantly increased.

Introduction

Cephalosporins are among the most commonly prescribed antimicrobials for urinary tract infections (UTIs) in children, and the American Academy of Pediatrics (AAP) recommends these agents as first-line therapeutic options.[1–6] Increasing prevalence of third-generation cephalosporin-resistant Enterobacterales (G3CR) has been described, and the most recent national pediatric surveillance data documented an increase from 1.4% in 1999 to 3% in 2011.[7–12].

Some pediatric cohorts describe basic utilization and outcomes associated with drug-resistant Enterobacterales infections, but scant controlled data exist on choice of and response to initial antimicrobials, and no data on subsequent healthcare utilization exist for pediatric G3CR UTI. We sought to describe the contemporary epidemiology, clinical practice patterns, and outcomes for G3CR UTIs in an underserved pediatric population. We hypothesized that such children may: 1) exhibit a similar clinical response to initial antimicrobial therapy as seen among patients with drug-susceptible UTI; 2) experience excess healthcare utilization in the acute phase of illness and during the subsequent six months; and 3) not exhibit established risk factors for drug-resistance.

Methods

Study Design and Setting.

We performed a retrospective, matched cohort-control study among patients 0-18 years of age with G3CR UTI at all public acute care facilities in Los Angeles (Harbor-UCLA Medical Center [site A], LAC+University of Southern California Medical Center [site B], and Olive View-UCLA Medical Center [site C]), and one not-for-profit hospital (Miller Children's and Women's Hospital [site D]). For sites A and D, the study period was November 1, 2014 to February 28, 2017, and for sites B and C it was November 1, 2015 to February 28, 2018, reflecting the availability of a fully operational electronic medical record system.

Inclusion and Exclusion Criteria.

We defined UTI as the presence of an abnormal urinalysis (pyuria and/or bacteriuria), plus a concomitant urine culture of a catheterized or clean-catch/midstream specimen with recovery of ≥10,000 colony-forming units/milliliter (cfu/mL) of an Enterobacterales isolate. Although a threshold of ≥50,000 cfu/mL is recommended for the diagnosis of UTI in children 2-24 months in the 2011 AAP Clinical Practice Guideline and its 2016 reaffirmation, a threshold of ≥10,000 cfu/mL is permitted for cultures with semiquantitative growth reported as 10,000 to 100,000 cfu/mL.[5,13] At each of our study sites, semiquantitative reporting was often used. We excluded results from specimens found to have squamous epithelial cells on microscopic examination or culture results deemed by study personnel to be consistent with asymptomatic bacteriuria. In addition, the urinalysis criteria were waived in rare circumstances based on clinical context if two or more study clinicians agreed unanimously that the incident could be confidently labeled as a UTI. Similarly, polymicrobial culture results could be included if two or more study clinicians agreed unanimously that the incident could be confidently labeled as a UTI.

The first identified G3CR UTI was considered the index UTI. For each G3CR-patient, we endeavored to select two non-G3CR UTI controls, matched by study site, sex, and age group (0-5yo, ≥6yo). To do so, we generated lists of patients with ≥10,000 cfu/mL of a non-G3CR Enterobacterales isolate at each study site and performed chart review to verify inclusion criteria.

Antimicrobial Susceptibility Testing.

Susceptibilities were performed using GN-69 or GN-73 cards on the VITEK® 2 automated testing platform (bioMérieux, Inc., Durham, NC). Third-generation cephalosporin-resistance was defined as resistance to ceftriaxone, cefotaxime, or ceftazidime. We defined non-G3CR as susceptible to all (and at least one) of the third-generation cephalosporins for which a result was reported. Carbapenem-resistant isolates were excluded due to the unique risk factors, treatment approaches, and outcomes among patients with such drug-resistant infections.[14,15] When available, minimum inhibitory concentrations (MICs) were recorded, as were phenotypic resistance mechanisms and method of confirmation. There were differences in reporting processes among study sites related to manual confirmation of extended-spectrum beta-lactamase (ESBL) phenotype, cascaded reporting, suppression of MIC values or susceptibility interpretations for beta-lactam agents, and VITEK® 2 prediction for ampC production. Time to finalization of culture and drug susceptibility results was counted in days; specimen collection date was day zero.

Clinical Data Collection and Definitions.

Using a standardized data collection instrument (see Supplement), we collected biosocial, clinical, and healthcare utilization information for the acute phase and the 6-month period thereafter. To complement other measures of diversity and biosocial determinants, race (Black/not-Black) and ethnicity (Hispanic/not-Hispanic) were recorded according to demographic fields in each chart. International exposure was defined as any recent personal (or current household contact) travel outside the United States. Prior acute healthcare utilization included any emergency department visit or hospitalization occurring before first

date of presentation for the index UTI. Duration of therapy was counted in days, with the date of the first antibiotic prescription considered day one. Anti-pseudomonal agents were defined as: ceftazidime, cefepime, piperacillin, meropenem, imipenem, ceftolozane, ciprofloxacin, levofloxacin, gentamicin, amikacin, tobramycin or aztreonam. Assessment of response to initial antimicrobial therapy was defined as "significant improvement" if there was: 1) resolution of fever and other vital sign abnormalities, for hospitalized patients; or 2) documentation of clinical improvement by treating physicians based on their assessment. We defined time to significant improvement as the earlier of these criteria. Utilization of genitourinary (GU) imaging was recorded, and exposure to GU imaging with ionizing radiation was defined as voiding cystourethrogram, ^{99m}Tc-labeled mercaptoacetyltriglycine renal scan, or dimercaptosuccinic acid scan (DMSA). Subsequent multidrug-resistant urine culture results included the isolation of Enterobacterales exhibiting G3CR or carbapenem-resistance. Subspecialty consultation included care from Nephrology, Urology or Infectious Diseases services. For five G3CR and five non-G3CR at every site, two investigators reviewed data entry for accuracy, and a third adjudicated discrepancies.

Data Management and Statistical Analysis.

Approval was obtained from each participating site's Institutional Review Board, and data use agreements were in place permitting the entry of data into a secure online project-management platform (RedCAP™, Vanderbilt University, Nashville, TN). We performed descriptive statistics, and univariate analyses using differences in proportions for categorical variables, and differences in medians with interquartile ranges for continuous variables. Bivariate and multivariate logistic, linear, or Poisson regression analyses were performed, as appropriate. P-values < 0.05 were considered statistically significant. Sensitivity analyses restricted to patients with ≥50,000 cfu/mL were performed for robustness. All analyses were performed using Stata, version 13.1 (2013, StataCorp LP, College Station, TX).

Results

Study Population.

We identified 3,408 unique urine cultures with Enterobacterales isolates, of which 131 (3.8%) were G3CR (see Figure); two carbapenem-resistant isolates were excluded. There were no differences in G3CR prevalence between sites (range 3.2-4.1%). One hundred seven children were classified as G3CR-patients; *Escherichia coli* was the identified pathogen in 89 (83%), and 87 (81%) were ESBL-positive (Table 1). We identified 206 non-G3CR UTI as matched controls; of these, 194 (94%) were due to *Escherichia coli*.

Pyuria was present for 264 (84.3%) patients. Urinalysis criteria were waived for 20 (6.4%: 10 G3CR, 10 controls) for the following reasons: neutropenia/bone marrow failure; quantity not sufficient for urinalysis (but presence of UTI signs/symptoms and concomitant bacteremia with the same uropathogen without another identified focus). Thirty-one (9.9%) patients had >1 uropathogen isolated in urine culture, but with a single predominant Enterobacterales spp. deemed to represent the causative organism by unanimous consensus of clinical study personnel. Two hundred eighty-five (91.1%) patients had ≥50,000 cfu/mL of the uropathogen of interest, and 255 (81.4%) had ≥100,000 cfu/mL.

Antimicrobial Susceptibility Test Results.

Susceptibility to non-cephalosporin agents is detailed in Table 2. The effect of breakpoint changes on cephalosporin and fluoroquinolone MIC interpretation are provided in Supplemental Table 1. Six (5.6%) G3CR and zero controls were resistant to all oral beta-lactam agents, fluoroquinolones, and trimethoprim-sulfamethoxazole (p=0.001). Time to culture result was not different between groups: median and interquartile range (IQR) of 2 days (IQR 1-3). It was less common, however, for susceptibility results to be reported within 1 day for G3CR isolates versus non-G3CR (16% versus 37.1%, OR 0.32, 95% CI 0.18-0.58, p<0.001).

Clinical Characteristics and Risk Factors.

Clinical characteristics and risk factors associated with G3CR UTI included prior receipt of antimicrobial therapy, prior healthcare utilization, and presence of at least one underlying medical condition (Table 3). There were no differences when prior drug receipt occurred <30 days versus <60-90 days prior to index UTI (data not shown). Prior hospitalization was more common among G3CR (41%) than control-patients (17%, OR 3.30, 95% CI 1.77-6.13, p<0.001). After adjustment for study site and underlying medical conditions, the odds of G3CR UTI remained significant for prior antimicrobial treatment or prophylaxis (adjusted odds ratio (aOR) 1.9, 95% CI 1.1-3.4), but not for prior acute healthcare utilization (aOR 1.9, 95% CI 1.0-3.7).

Antimicrobial Treatment and Response.

Antimicrobial treatment was prescribed for the index UTI in 92.7% of susceptible patients and 87.9% of G3CR-patients (Table 4). Compared to controls, initial antimicrobials for G3CR-patients were less frequently given orally (62% versus 75.4%, OR 1.90, 95% CI 1.08-3.34, p=0.02) and less frequently exhibited *in vitro* activity against the patient's isolate (Table 4). Modifications of the initial antibiotic choice occurred in 55% of G3CR-patients versus 29% of controls (OR 2.93, 95% CI 1.70-5.05, p<0.001). Initial antibiotics included agents with anti-pseudomonal activity in 14 (15%) G3CR-patients versus 5 (3%) controls (OR 6.51, 95% CI 2.11-23.71, p<0.001). Eleven (23%) G3CR-patients who received initial antibiotics without anti-pseudomonal activity subsequently had their therapy modified to an anti-pseudomonal agent; this did not occur in any control-patient (p<0.001).

Of patients with documentation of response to initial therapy, there was no difference in the proportion with significant improvement between G3CR-patients (57%) and control-patients (52%, OR 0.81, 95% CI 0.44-1.50) (Table 4). Improvement was documented within a median of 2 days (IQR 1-5) in both groups, including 25 G3CR-patients receiving initial therapy without *in vitro* activity against their isolates (Supplemental Table 2). After adjustment for underlying medical conditions, *in vitro* susceptibility to initial antimicrobials did not increase the odds of significant improvement (aOR 1.17, 95% CI 0.42-3.25, p=0.77). In patients who were assessed to have had no significant improvement on initial antimicrobials, therapy was modified more often for G3CR (42%) than for susceptible UTI (15%, OR 4.20, 95% CI 1.61-10.95), but total duration did not differ (Table 4).

Hospitalization and Length-of-stay.

Multivariate analysis revealed that G3CR-patients were more frequently hospitalized upon presentation than controls (aOR 6.60, 95% CI 2.03-21.44, p=0.002) and that presence of an underlying medical condition was an independent predictor of hospitalization (aOR 2.44, 95% CI 1.11-5.36, p=0.03). Factors not associated with hospitalization in this analysis included highest presenting temperature, *in vitro* activity of initial antimicrobials, and study site. G3CR-patients were hospitalized longer than control-patients (median 8 days [IQR 4-15] versus 4 days [IQR 3-7], p<0.05, Table 3). Controlling for highest presenting temperature and presence of underlying medical condition, G3CR UTI (IRR 2.27, 95% CI 1.70-3.05, p<0.001), study site (IRR 1.54, 95% CI 1.09-2.16, p=0.01) and, paradoxically, susceptibility to initial antimicrobials (IRR 1.51, 95% CI 1.15-1.99, p=0.003) were associated with longer length-of-stay.

Healthcare Utilization During Subsequent 6 Months.

Seventy-one (66%) G3CR-patients and 134 (65%) control-patients had documented follow-up until 6 months after index UTI. No deaths occurred. G3CR-patients were more likely to have repeat urine cultures (75%) than control-patients (53%, OR 2.61, 95% CI 1.33-5.24). Among these, G3CR-patients had subsequent multidrug-resistant culture results more frequently than control-patients (26% vs 3%, OR 12.21, 95% CI 2.63-56.54). There were no significant differences between groups in orders for any imaging studies of the GU tract (Table 4) or exposure to GU imaging with ionizing radiation (data not shown). Subspecialty consultation was more common among G3CR-patients than control-patients, and the proportion of G3CR-patients receiving additional courses of antimicrobial therapy for any indication other than treatment of the index UTI was also higher than for control-patients (Table 4). After adjustment for underlying medical conditions (aOR 2.2, 95% CI 1.1-4.3, p = 0.02) and study site (not significant), the odds of G3CR-patients receiving any additional courses of antimicrobial therapy remained significant (aOR 2.63, 95% CI 1.41-4.91, p=0.002).

Sensitivity Analyses.

Restricting analyses to patients with ≥50,000 cfu/mL, results of univariate (Supplemental Tables 3–4) and adjusted/multivariate analyses were robust. Adjusting for presence of underlying conditions, multivariate analysis re-demonstrated that *in vitro* susceptibility to initial antimicrobials did not increase the odds of significant improvement on initial therapy (OR 1.19, 95% CI 0.40-3.52, p=0.75). There were no substantive changes in the direction of results for this or any other analyses.

Discussion

G3CR and ESBL-producing *Escherichia coli* are increasingly reported in patients with community-acquired infections, including UTI.[7,8,16,17] The most recent pediatric U.S. population data (2010-2011) reported a prevalence of G3CR and ESBL Enterobacterales of 3.0% and 0.9%.[7] Our data revealed a slightly higher prevalence of G3CR, with a majority exhibiting an ESBL phenotype. Our study included only patients with UTI, incorporated a

contemporaneous control group of children with susceptible UTI, and selected patients from a diverse population that was not skewed by a preponderance of medically complex children.

There are few pediatric outcomes data on G3CR UTI, and even fewer on clinical response to discordant therapy.[18–21] We present the largest, detailed outcomes data and statistical analyses demonstrating that first-line antimicrobials for UTI are equally likely to lead to significant improvement in children with G3CR versus susceptible isolates. Our data are consistent with a recent study in which 186 (80%) of 192 children with G3CR UTI who received discordant therapy had clinical improvement, as well as a European study that found no difference in clinical outcomes among 61 children on initially effective versus 77 on ineffective treatment for febrile G3CR UTI; neither study included a comparator group with susceptible UTI.[21,22]

Observed clinical response to discordant antimicrobials for UTI may be superior to predicted *in vitro* activity for at least two reasons. Interpretive criteria are often based upon small numbers of patients with severe, high-inoculum infections including bacteremia limiting generalizability to milder infections such as non-bacteremic UTI.[23–25] Also, the concentration of antimicrobials in the renal parenchyma or urine may result in exposures several-fold higher than an organism's MIC breakpoint, as illustrated by the Clinical and Laboratory Standards Institute's decision to establish a higher urine-specific breakpoint for cefazolin in 2014.[21,26] "Susceptible" and "resistant" categories reflect probabilities and expert consensus, which may not correlate perfectly with real-world clinical observations.[24].

Neither AAP guidelines nor a recent state-of-the-art review provides treatment recommendations for drug-resistant UTI.[5,27] Interestingly, despite recommending avoidance of cefepime and piperacillin-tazobactam for ESBL isolates, Infectious Diseases Society of America permits continuation of either drug if initiated empirically when the patient improves clinically.[28]

We provide new information on healthcare utilization during the acute care phase, and the first utilization data during the 6 months after a G3CR UTI in children. G3CR-patients had a >6-fold adjusted odds of hospitalization at presentation for their index UTI and length-of-stay was twice as long as for controls. Total treatment duration correlated with study site and not study group, likely reflecting clinician preference rather than clinical indication. Similarly, G3CR-patients were more likely to have subsequent courses of antimicrobial therapy and repeat urine culture.

Subsequent multidrug-resistant isolates were recovered in approximately one-quarter of G3CR-patients who had repeat urine cultures, similar to a molecular epidemiology study at four pediatric centers which found that 14% had subsequent resistant infections.[29] A common clinical practice is to use prior susceptibility results to guide the choice of empiric therapy for subsequent incidents of suspected UTI.[30] This may result in exposure to inappropriately broad spectrum antimicrobials and may warrant reconsideration.

We identified several risk factors for G3CR UTI, some novel and others previously described.[7,18,20,31–35] Risk factors have included underlying medical conditions, prior acute healthcare utilization, and prior antibiotic exposure.[16,32,34,36–40] Our data reproduce these

findings in a diverse and underserved population in the U.S. While >50% of patients in either group had at least one underlying medical condition, the majority reflected common conditions including obesity, metabolic syndrome, and developmental delay. Unlike in prior studies, international exposure was not a significant risk factor despite being present in 22% of G3CR-patients compared to 11% of controls.[41,42]

Our findings are subject to several limitations. We used dichotomized age ranges that some may consider too broad, but this was decided *a priori* to ensure identification of enough matched controls. Data were missing for several variables, particularly biosocial risk factors previously unexamined for this condition. MICs were also missing due to variable suppression of results, although application of changing interpretive criteria would not have resulted in meaningful changes in study group classification (Supplemental Table 1). Generalizability may be limited due to our predominantly Medicaid patients in Los Angeles County, California that faces many barriers to healthcare access and continuity. We did not have complete data on initial treatment response, and documentation may have varied for non-hospitalized patients. We did not attempt to ascertain UTI relapse, as there is no widely accepted standard for distinguishing relapse from recurrence.[1] Patients may have sought care outside of our hospital systems, but it is highly likely that they would have been seen at one of our study hospitals.

Because we accepted semiquantitative cultures ≥10,000 cfu/mL (a minority of our study population), some patients may have had asymptomatic bacteriuria and not true UTI. Such cultures were included only if sufficient data were available to confidently label an incident as UTI according to guidelines and common clinical practice.[5,13,27] Sensitivity analyses restricted to patients with ≥50,000 cfu/mL did not reveal substantive changes in results (Supplemental Tables 3 and 4).

Since AAP guidelines target children 2-24 months, our study shares a limitation of pediatric UTI studies: the absence of a national consensus diagnostic definition outside of this age range.[5,13] Indeed, the definition of pyuria remains an area of active research, and one commentary has problematized the use of a strict cfu/mL cutoff.[43–45] We used a composite of urinalysis and urine culture, each performed in response to signs/symptoms attributable to UTI.[5,13,27] We could not reliably distinguish children with pyelonephritis beyond initial working diagnosis, as we did not collect sufficiently detailed physical examination data, and no child had a DMSA scan.

We describe clinical, epidemiologic, and utilization characteristics of G3CR UTI in an underserved pediatric population. Our data highlight the need for randomized controlled trials on safe and optimal treatment approaches for G3CR UTI. Future investigations should evaluate if such infections alter subsequent practice behaviors, reflecting priming by a prior drug-resistant UTI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ESBL	extended-spectrum beta-lactamase
G3CR	third-generation cephalosporin-resistant
IQR	interquartile range
MIC	minimum inhibitory concentration
UTI	urinary tract infection

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Table of Contents Summary:

Matched cohort-control study of risk factors, response to initial antimicrobial therapy, and healthcare utilization among children with UTI due to third-generation cephalosporin-resistant Enterobacterales.

What's Known on This Subject:

Urinary tract infections due to third-generation cephalosporin-resistant Enterobacterales (G3CR) represent a persistent global and domestic threat. There are limited controlled data from the United States on the contemporary epidemiology, clinical management, outcomes, and healthcare utilization for these infections among children.

What This Study Adds:

This study reveals increased healthcare utilization for drug-resistant pediatric urinary tract infection. Clinical response to initial antimicrobial therapy did not differ between patients with UTI due to G3CR compared with susceptible isolates.

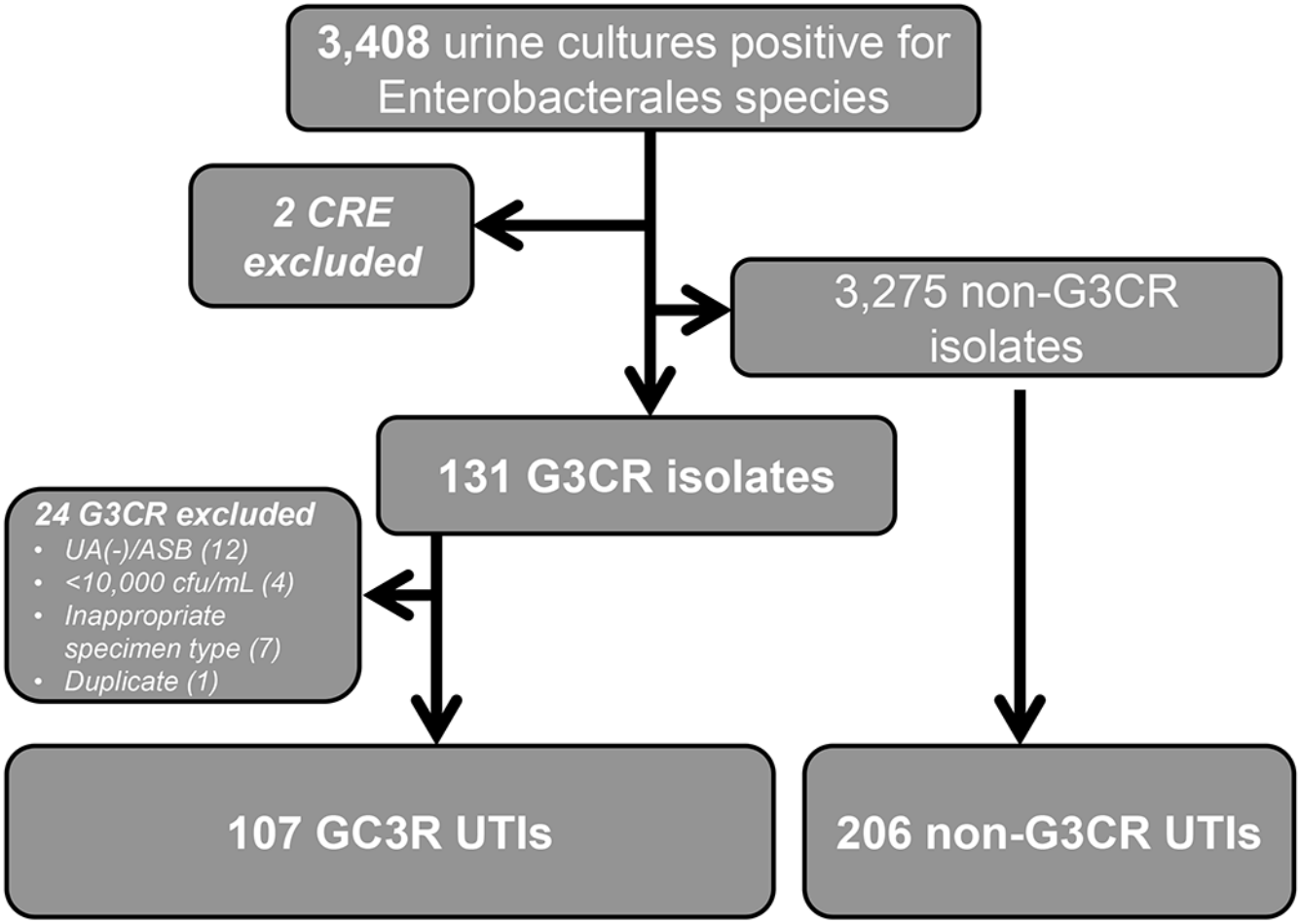

FIGURE 1:

Flow diagram for cohort-control study of pediatric UTI due to third-generation cephalosporin-resistant Enterobacterales.

ASB, asymptomatic bacteriuria. cfu/mL, colony-forming units per milliliter. CRE, carbapenem-resistant Enterobacterales. G3CR, third-generation cephalosporin-resistant. UA(−), urinalysis criterion not fulfilled. UTI, urinary tract infection.

TABLE 1:

G3CR UTI patients by sex, age-group, study site, and organism/phenotype.

	Site A (n = 28)	Site B (n = 32)	Site C (n = 7)	Site D (n = 40)	Total Case-Patients (N=107)
Sex/Age group					
Female, 0-5yo	15	9	2	19	45
Female, ≥6yo	4	17	4	13	38
Male, 0-5yo	8	2	1	6	17
Male, ≥6yo	1	4	-	2	7
Organism, Phenotype					
E. coli, ESBL(+)	24	23	6	26	79
E. coli, ESBL(−)	1[b]	3	-	6	10
K. pneumoniae, ESBL(+)	-	2	-	2	4
K. pneumoniae, ESBL(−)	-	-	-	-	-
K. oxytoca, ESBL(+)	-	2	1	-	3
K. oxytoca, ESBL(−)	-	-	-	-	-
P. mirabilis	2[c]	1	-	1	4
Other uropathogen[a]	1	1	-	5	7

[a]Other uropathogen(s), by study site: site A, *Enterobacter cloacae* subspp. *cloacae*; site B, Klebsiella (Enterobacter) aerogenes; site D, Enterobacter cloacae complex (4), Citrobacter youngae (1).

[b]Isolate reported as AmpC beta-lactamase-producer.

[c]One P. mirabilis isolate reported as ESBL+.

TABLE 2:

Antibiotic susceptibility profile for selected non-cephalosporin agents, G3CR UTI versus non-G3CR UTI.

DRUG	Non-G3CR UTI, n (%[a])	G3CR UTI, n (%[a])	OR, 95%CI	p-value
Ciprofloxacin				
Resistant	19 (9.4)	62 (58)	13.34, 6.99-35.85	<0.001
Susceptible	184 (90.6)	45 (42)		
Levofloxacin				
Resistant	14 (11)	37 (54)	9.80, 4.46-21.95	<0.001
Susceptible	115 (89)	31 (46)		
Gentamicin				
Resistant	12 (5.9)	46 (43.8)	12.34, 5.90-27.10	<0.001
Susceptible	190 (94.1)	59 (56.2)		
Amikacin				
Resistant	0 (0)	1 (2)	-	1.0
Susceptible	13 (100)	49 (98)		
Piperacillin-tazobactam				
Resistant	4 (2.9)	13 (19.4)	8.06, 2.33-35.07	<0.001
Susceptible	134 (97.1)	54 (80.6)		
Trimethoprim-sulfamethoxazole				
Resistant	70 (34.5)	57 (53.3)	2.17, 1.31-3.59	0.002
Susceptible	133 (65.5)	50 (46.7)		
Nitrofurantoin				
Resistant	15 (7.3)	18 (17)	2.59, 1.17-5.78	0.01
Susceptible	190 (92.7)	88 (83)		

[a]Denominators may differ due to missing information.

TABLE 3:

Clinical characteristics and biosocial risk factors, G3CR UTI versus non-G3CR UTI, univariate analyses.

	Non-G3CR, n (%[a]) or median (IQR)	G3CR, n (%[a]) or median (IQR)	OR, 95%CI	p-value
Duration of presenting symptoms, days	2 (1-3)	2 (1-4)	-	0.79
Fever	121 (58.7)	64 (60)	1.05, 0.65-1.68	0.90
Maximum temperature, C°	37.3 (36.8-38.7)	38.2 (37.0-39.0)	-	0.07
Initial working diagnosis: Pyelonephritis	39 (18.9)	26 (24)	1.37, 0.78-2.41	0.30
Initial working diagnosis: simple/uncomplicated cystitis or UTI, site not specified	128 (62.1)	43 (40)	0.41, 0.25-0.66	<0.001
Positive blood culture	3 (1.5)	3 (3)	1.95, 0.39-9.84	0.67
Race, Black	15 (7.3)	4 (4)	0.49, 0.12-1.61	0.32
Ethnicity, Hispanic	173 (85.2)	82 (77)	0.57, 0.31-1.03	0.06
Preferred language, English	86 (42.0)	48(45)	1.13, 0.68-1.85	0.63
Medicaid recipient	179 (87.3)	95 (90)	1.25, 0.57-2.94	0.59
Number of siblings in household	1 (1,2)	1 (0,2)	-	0.22
Non-US-born	7 (5)	9 (13)	2.85, 0.89-9.43	0.05
International travel/exposure	13 (11)	13 (22)	2.15, 0.84-5.45	0.08
Foster/adopted child	6 (3.5)	5 (6)	1.73, 0.40-7.02	0.51
Homeless	1 (0.6)	0 (0)	-	1.0
History of systemic antimicrobial therapy	69 (36)	60 (59)	2.63, 1.56-4.45	<0.001
Allergy to beta-lactam antibiotic	1 (0.5)	4 (4)	7.96, 0.89-72.14	0.05
Prior acute healthcare utilization[b]	114 (58)	77 (77)	2.47, 1.39-4.46	0.001
History of hospital-acquired infection	5 (2.4)	5 (5)	1.97, 0.56-6.96	0.32
History of infection or colonization with other multidrug resistant organism	7 (3.4)	7 (7)	1.99, 0.68-5.83	0.25
Indwelling or intermittent bladder catheterization	9 (4.4)	12 (11)	2.76, 1.13-6.79	0.03
Central venous catheter, gastrostomy/jejunostomy, or tracheostomy	13 (6.3)	6 (6)	0.88, 0.33-2.39	1.0
Household contact who works in healthcare?	4 (7)	7 (21)	3.77, 0.86-18.87	0.05
History of acid-modifying anti-reflux therapy	13 (6.5)	9 (9)	1.42, 0.52-3.75	0.48
Delayed immunization	10 (5)	7 (7)	1.35, 0.42-4.06	0.60
Birth history				
Cesarean delivery	27 (30)	19(43)	1.75, 0.77-3.93	0.18
Low birthweight or pre-term	11 (5.3)	10 (9)	1.83, 0.75-4.45	0.23
Maternal intrapartum antibiotic exposure	16 (29)	8 (62)	4.00, 0.96-17.69	0.05
Underlying medical condition(s)				
At least one present	108 (52.4)	71 (66)	1.79, 1.07-3.00	0.02
Recurrent UTI	36 (17.5)	24 (22)	1.37, 0.77-2.44	0.29
Structural, functional or other genitourinary abnormalities[c]	20 (9.7)	17 (16)	1.76, 0.88-3.52	0.14

	Non-G3CR, n (%[a]) or median (IQR)	G3CR, n (%[a]) or median (IQR)	OR, 95%CI	p-value
Chronic renal insufficiency, or renal transplant recipient	1 (0.5)	3 (3)	5.91, 0.61-57.55	0.12
Diabetes, overweight/obesity, or metabolic syndrome	31 (15.0)	17 (16)	1.07, 0.56-2.03	0.87
Neurologic disorders[d]	28 (13.6)	19 (18)	1.37, 0.73-2.59	0.40
Immunodeficiency or malignancy	7 (3.4)	11 (10)	3.26, 1.22-8.67	0.02

[a] Denominators may differ due to missing information in medical records.

[b] Defined as any emergency department visit or in-patient hospitalization occurring before first date of presentation to care for index UTI.

[c] Includes patients with prior diagnosis of vesicoureteral reflux, urinary tract obstruction, indwelling stent, nephrostomy, other urinary diversion, and bowel/bladder dysfunction.

[d] Includes patients with prior diagnosis of seizure disorder, cerebral palsy, neurodevelopmental delay, spina bifida, spinal cord injury, neurogenic bladder, or other neurologic abnormality.

TABLE 4:

Treatment, outcomes and healthcare utilization for G3CR UTI versus non-G3CR UTI, univariate analyses.

	Susceptible UTI, n (%[a]) or median (IQR)	G3CR UTI, n (%[a]) or median (IQR)	OR, 95%CI	p-value
Antimicrobials prescribed for index UTI?	191 (92.7)	94 (88)	0.57, 0.24-1.36	0.21
Isolate susceptible to initial antimicrobials?	163 (95)	15 (28)	0.02, 0.01-0.05	<0.001
Assessment of clinical response to initial antimicrobials?	176 (92)	65 (69)	0.19, 0.10-0.38	<0.001
Significant improvement?	101 (57)	34 (52)	0.81, 0.44-1.50	0.56
If no improvement, first antimicrobials modified?	11 (15)	13 (42)	4.20, 1.61-10.95	0.004
Total duration of antimicrobials?	10 days (7, 10)	9 (3, 10)	-	0.16
Level of care, index encounter				
Ambulatory	170 (83.3)	66 (62)		
Hospitalized	34 (16.7)	40 (38)	3.03, 1.77-5.19	<0.001
Length of stay	4 days (3,7)	8 (4,15)	-	0.05
Repeat urine culture(s)?	71 (53)	53 (75)	2.61, 1.33-5.24	0.003
Subsequent multidrug-resistant urine culture isolate?	2 (3)	14 (26)	12.21, 2.63-56.54	<0.001
Imaging studies of genitourinary tract ordered?	56 (42)	33 (46)	1.21, 0.65-2.25	0.56
Subsequent additional courses of antimicrobial therapy?	37 (28)	37 (53)	2.82, 1.47-5.39	0.001
Subspecialty consult[b]	13 (6)	25 (23)	4.52, 2.10-10.09	<0.001

[a] Denominators may differ due to missing information in medical records.

[b] Defined as documented consultation by Nephrology, Urology, or Infectious Diseases services.