Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Sociodemographic and Clinical Correlates of Multidrug-Resistant Uropathogens in Hospitalized Children

Khitam Muhsen[1], Sama Haleem[1], Bshara Mansour[2,3], Ma'anit Shapira[4,5], Milena Pitashny[4,5], Mohammad Masarwa[6], Muna Omar[1], Wasef Na'aminh[1,*], Eias Kassem[5,6,*]

[1]Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [2]Pediatric Department and Pediatric Nephrology Service, Saint Vincent de Paul Hospital, Nazareth, Israel; [3]The Azrieli Faculty of Medicine, Bar-Ilan University, Zefat, Israel; [4]Clinical Laboratory Division, Hillel Yaffe Medical Center, Hadera, Israel; [5]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [6]Department of Pediatrics, Hillel Yaffe Medical Center, Hadera, Israel

*These authors contributed equally to this work

Correspondence: Khitam Muhsen, Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, Tel +972-3-6405945, Fax +972-3-6409868, Email kmuhsen@tauex.tau.ac.il

Purpose: Antibiotic resistance in uropathogens causing urinary tract infections (UTIs) is increasing; nonetheless, evidence on multidrug-resistant (MDR) bacteria remains limited. We aimed to examine the prevalence and risk factors of Gram-negative MDR bacteria in pediatric UTIs and compared the hospitalization duration and cost between patients with and without MDR.

Patients and Methods: A retrospective single-center study was conducted among hospitalized children from 2015 to 2020. Sociodemographic (age, sex, population group, residential socioeconomic status), clinical (prior hospitalizations, antibiotic use, background diseases), and laboratory (complete blood count, C-reactive protein levels) data were collected from medical files. MDR was defined as non-susceptibility to ≥1 agent in ≥3 antimicrobial classes.

Results: The study included 506 children (81.8% girls; median age 11 months). Most (94.2%) isolates were Gram-negative. Resistance to ampicillin, trimethoprim/sulfamethoxazole, amoxicillin/clavulanic acid, nitrofurantoin, cefuroxime-axetil, and cefuroxime-sodium was 33.8%, 12.4%, 9.4%, 3.9%, 3.2%, and 2.5%, respectively. MDR prevalence was 6.9% (95% CI 4.8–9.5), and 50.8% (46.4–55.4) showed resistance/intermediate susceptibility to 1–2 antibiotic categories. Arab children had an increased likelihood of MDR (OR=3.29 (95% CI 1.49–7.25) than Jewish children, and children with vs. without a history of antibiotic use before hospitalization (5.06, 1.67–15.31). The likelihood of resistance/intermediate susceptibility to 1–2 antibiotic categories increased in relation to antibiotic use before hospitalization (2.68, 1.25–5.74) and in males vs. females (1.71, 0.99–2.94). No significant differences were found in hospitalization duration or cost between the MDR groups.

Conclusion: The prevalence of MDR and non-susceptibility/resistance to 1–2 antibacterial categories in Gram-negative uropathogens is concerning. Our findings underscore the need for tailored empirical therapy and targeted antibiotic stewardship interventions.

Keywords: urinary tract infection, children, uropathogens, antibiotic resistance, multidrug resistance

Introduction

Urinary tract infections (UTIs) are common among children, primarily caused by Gram-negative bacteria, with *Escherichia coli* (*E. coli)* accounting for >80% of infections.[1] The management of UTI in children involves administering empirical antibiotic treatment until the results of urine culture and antibiotic sensitivity testing are available, and adjusting the antibiotic treatment as needed.[2] Early antibiotic treatment is necessary to prevent renal injury.[3] The choice of empirical treatment is based on the local antibiotic susceptibility patterns of uropathogens.[4] Therefore, understanding antibiotic resistance patterns is essential.

https://doi.org/10.2147/IDR.S588989
Received: 23 December 2025
Accepted: 9 March 2026
Published: 8 April 2026

An increase in the incidence of UTIs caused by antibiotic-resistant bacteria has been observed worldwide over the past few years.[5–7] A systematic review on the global prevalence of antibiotic resistance in pediatric UTIs caused by *E. coli* showed lower rates in children from countries that belong to the Organization for Economic Cooperation and Development (OECD) vs. non-OECD countries.[5] Ampicillin resistance was estimated at 53.4% in OECD countries vs. 79.8% in non-OECD countries, while resistance to Ceftazidime was 2.5% vs. 26.1%.[5] Studies from Israel demonstrated a high prevalence of antibiotic resistance in uropathogens in children,[8,9] reaching 60% resistance to ampicillin and first-generation cephalosporins in *E. coli* urine isolates.[8] Extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae* are a key mechanism of resistance,[6] which prevalence has increased in urine cultures of children.[10–12]

Multidrug resistance (MDR) is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories,[13] with a prevalence range from 5% to 90% in bacteria isolated from urine cultures of children with UTIs,[14–19] resulting in difficult-to-treat infections.[14] Studies from Europe showed 18.4% and 34.1% prevalence of MDR in uropathogens in pediatric UTI in Greece and Romania, respectively,[15,19] compared to 78.4% and 80.0% in children from Ethiopia and China, respectively.[16,17] Risk factors for antibiotic-resistant UTIs in children include previous/recent antibiotic treatment, urinary tract anomalies, vesicoureteral reflux and related prophylactic antibiotics, and prior hospitalization.[14,15,19–21] However, evidence on the risk factors of MDR remains limited.

Multidrug-resistant uropathogens might complicate treatment by delaying effective treatment, potentially resulting in prolonged hospitalizations and increased healthcare costs. Studies of ESBL-producing bacteria have shown that children with ESBL-positive UTIs experience longer hospital stays and higher hospitalization costs.[10,17,22–24] However, evidence remains elusive regarding MDR UTIs.

Therefore, this study aimed to examine the prevalence and risk factors of UTI due to Gram-negative MDR bacteria among children. We also compared children with UTI caused by MDR bacteria vs. non-MDR bacteria in hospitalization duration and cost, as objective measures of clinical severity and healthcare resource utilization.

Materials and Methods

Study Population and Design

A retrospective study was conducted using the medical records of children aged 0–17 years hospitalized with a positive urine culture at the pediatric department of Hillel-Yaffe Medical Center in Israel between 2015 and 2020.

Hillel Yaffe Medical Center is located in the Hadera sub-district, which, as of 2019, had an estimated population of 456,500 residents, of whom 43.6% were Israeli Arabs and 56.4% were Jewish.[25] Access to healthcare services in Israel is universal.[26]

Data Collection

Demographic, clinical, laboratory, and imaging data were obtained from medical records. Urine samples were obtained from the children on admission to the Pediatric Emergency Department or the Pediatrics Department at Hillel-Yaffe Medical Center.

Children who were not hospitalized, those with fungal infections, insignificant cultures (growths of fewer than standard colony-forming units/mL [CFU]), and bacterial growth considered contamination, were excluded from the study.

The definition of positive urine culture remains controversial.[27,28] Therefore, we followed commonly used cutoffs as follows: a positive urine culture was defined as the growth of >1000 CFU/mL from a urine sample obtained by suprapubic aspiration, >10,000 CFU/mL from a urine sample obtained by transurethral catheterization, or >100,000 CFU/mL from a clean-catch midstream sample.[27,28]

The study included 3 outcome variables: MDR, hospitalization duration, and cost. The main outcome variable was the presence of MDR Gram-negative isolates in urine cultures. Antibiogram results were interpreted as susceptible, intermediate, or resistant. MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories[13],(Supplementary Table 1. The “intermediate susceptibility” and “resistance” results were grouped into one group as follows: uropathogens were classified as either having i) resistance/intermediate susceptibility to ≥3 antibiotic categories (MDR), ii) resistance/intermediate susceptibility to 1−2 antibiotic categories, or iii) sensitive to all tested antibiotics. Hospitalization duration (in days) was calculated as the difference between the discharge and admission dates. Hospitalization costs were calculated as the per-night stay cost[29] multiplied by the hospitalization duration.

The independent variables included demographics, clinical, and laboratory characteristics. Demographics included the child's age (analyzed as a continuous variable and a categorical variable: 0–11 months, 12–59 months, and 5–17 years), sex, year of admission, population group (Arab or Jewish), and residential socioeconomic status rank.[30] Clinical and laboratory characteristics included a prior UTI, hospitalizations or emergency room visit in the month preceding the current hospitalization, background disease, anomalies in the urinary tract (hydronephrosis, vesicoureteral reflux, neurogenic bladder, parenchymal/functional kidney disorder, etc)., antibiotic treatment before hospitalization, treatment with penicillin, first and second generation cephalosporins before hospitalization, complete blood count and C-reactive protein (CRP) results on admission.

Additional data were collected on signs and symptoms (body temperature (fever was defined as a body temperature ≥38°C), vomiting, urinary tract complaints, antibiotic treatment, and kidney ultrasound during hospitalization.

Laboratory Methods

Urine cultures were performed at the microbiology laboratory of Hillel-Yaffe Medical Center. All samples were cultured on blood and CHROMagar™ Orientation agar plates (Hylab, Rehovot, Israel) according to standard procedures. The plates were incubated at 35°C for 16–24 hours, and bacteria from positive cultures were identified using standard methods. Bacterial identification was performed using the Bruker Daltonik MALDI-TOF MS system instrument, the Bruker Biotyper 3.1 Software, and Library version 4613. Contamination was defined as the growth of commensal bacteria, indicating inadequate sample collection. Antibiotic susceptibility was examined using the VITEK-2 automated system (bioMérieux, Marcy Etoile, France), cartridges GN395 and GN308. Interpretation of results followed the Clinical and Laboratory Standards Institute,[31] using the Advanced Expert System software version 1.9.0. Antibiogram results were interpreted as susceptible, intermediate, or resistant.

Statistical Analysis

Data were analyzed using SPSS software, version 29 (IBM Corp, Armonk, NY, USA). Categorical variables were presented as counts and percentages. Results for continuous variables were expressed as mean and standard deviation (SD) or, if variables were not normally distributed, as median and interquartile range (IQR). Bivariate analysis was performed to examine the correlates of MDR uropathogens in urine culture using the Kruskal–Wallis test, as the data did not meet the assumptions of normality. Post-hoc pairwise comparisons were performed to examine specific group differences using Dunn's, with Bonferroni adjustment for multiple comparisons. The chi-square test was used for categorical variables. Multivariable multinomial regression models were performed. A p-value<0.05 was considered statistically significant.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Tel Aviv University (Protocol number 0005388–1) and the Institutional Review Board of Hillel Yaffe Medical Center (Protocol number HYMC-0038-22) approved the study protocol and granted an exemption from obtaining written informed consent, given the retrospective study design. Patient data were kept confidential using secure platforms, and personal identification data were separated from the study data, with only coded data used without any personal identifiers.

Results

Overall, 869 children had a positive urine culture during 2015–2020; of those, 353 were not hospitalized, for 2, the medical records were not found, 2 had their culture classified negative by the attending physician when considering the urine sample collection method, and 6 had growth of unusual microorganisms in urine culture, thus were excluded, leaving in the analysis 506 participants (81.8% females) (Supplementary Figure 1 and supplementary Table 2). The participants' median age was 11 months (IQR=34 months), with 50.5% being 0–11-month-olds. Overall, 61.9% were Jewish and 38.1% were Arab children. A prior UTI, background diseases, emergency room visit in the preceding month, hospitalization in the preceding month, and congenital anomalies of the urinary tract were documented in 12.3%, 18.8%, 5.7%, 3.0%, and 9.3% of the participants, respectively. Antibiotic treatment was prescribed to 84.0% of participants during hospitalization and to 77.0% at discharge (Table 1). Symptoms differed according to age group (Supplementary Table 3).

Table 1 Demographic and Clinical Characteristics of the Study Participants

	N (%)
Total	506 (100.0%)
Age [a]	
0–11 months	255 (50.4%)
12–59 months	150 (29.7%)
5–17 years	100 (19.8%)
Sex	
Males	92 (18.2%)
Females	414 (81.8%)
Population group	
Jewish	313 (61.9%)
Arab	193 (38.1%)
Residential socioeconomic status rank	
Low	149 (29.9%)
Intermediate	256 (51.4%)
High	93 (18.7%)
Previous urinary tract infection (yes) [a]	62 (12.3%)
Previous hospitalization in the preceding month (yes) [b]	15 (3.0%)
Emergency room visit in the preceding month	29 (5.7%)
Fever (body temperature≥38 °C) (yes) [c]	308 (61.4%)
Co-bacterial infection (yes) [d]	42 (8.3%)
Indwelling urinary catheter or intermittent catheterization of the urinary bladder (Yes) [a]	3 (0.6%)
Congenital anomalies of the kidney and urinary tract (yes)	47 (9.3%)
Hydronephrosis	24 (4.7%)
Vesicoureteral reflux	9 (1.8%)
Neurogenic bladder	10 (2.0%)
Urological or anatomical anomaly	9 (1.8%)
Parenchymal or functional disorder of the kidney	7 (1.4%)
Background diseases (yes)	95 (18.8%)
Nephrological or genitourinary disorder	47 (9.3%)
Neurological disorder	17 (3.6%)

(*Continued*)

Table 1 (Continued).

	N (%)
Gastrointestinal disorder [e]	6 (1.2%)
Pulmonary or cardiovascular disorder	10 (2.0%)
Genetic disorder	7 (1.4%)
Other disorder	48 (9.5%)
Antibiotic use before hospitalization (yes) [c]	44 (8.8%)
Antibiotic use during hospitalization (yes)	425 (84.0%)
Antibiotic use after discharge (yes) [b]	388 (77.0%)

Notes: The percentages shown in the table refer to the entire sample. [a]Missing data for one child; [b]Missing data for 2 children; [c]Missing data for 4 children. [d] Included: pneumonia, lymphadenitis, tonsillitis, meningitis, otitis media, cellulitis, dysentery, and parapharyngeal abscess. [e]Gastrointestinal disorders included: gastroesophageal reflux, celiac disease, gastrostomy feeding, and hepatic ischemic injury due to birth asphyxia.

The median of hemoglobin level at admission was 11.2 gr/dL (IQR=2.0), and of leukocyte count was $15.7\times10^3/\mu L$ (IQR=9.5), and of CRP level was 58.3 mg/L (IQR=116.8) (Supplementary Table 4). Ultrasound of the kidney/urinary tract was performed during hospitalization for 223 (44.1%) participants; of those, 59.2% had findings consistent with UTI (Supplementary Table 5).

The collection technique of urine culture was mostly catheterization (59.4%), primarily in infants, followed by midstream catch (35.7%), mainly among 5–17-year-olds, and suprapubic aspiration (4.6%), exclusively among infants (Supplementary Table 6).

Overall, 521 uropathogens were identified; of those, 491 (94.2%) were Gram-negative (81.6% *Escherichia coli*) and 30 (5.8%) were Gram-positive (Supplementary Table 7). Fourteen children (2.8%) had mixed infections. We excluded Gram-positive isolates from further analysis.

Antibiotic treatment was prescribed to 44 (9.1%) participants before hospital admission, to 413 (85.7%) participants during hospitalization, and to 381 (79.1%) participants at discharge. The most commonly used antibiotics before hospital admission were amoxicillin (31.8%), cephalexin (25.0%), amoxicillin-clavulanic acid (18.2%), and cefuroxime (11.4%). During hospitalization, the most used antibiotics were gentamicin (55.5%) and ceftriaxone (39.9%). The common antibiotics prescribed on discharge were amoxicillin-clavulanic acid (40.2%), cephalexin (33.6%), and amoxicillin (18.4%) (Supplementary Table 8).

Antimicrobial Drug Resistance in Gram-Negative Urine Isolates

Among all Gram-negative isolates, the highest resistance was found for ampicillin (33.8%), trimethoprim/sulfamethoxazole (12.4%), and amoxicillin-clavulanic acid (9.4%). Intermediate susceptibility to these antibiotics was 19.8%, 4.9%, and 11.6%, respectively. (Supplementary Table 9). Results were similar when considering only *E. coli* (Supplementary Table 10). Considering antibiotic classes, resistance was highest to penicillins (37.8%), followed by sulfonamides (12.0%), nitrofurantoin (3.7%), and second-generation cephalosporins (3.3%). Combining resistance and intermediate susceptibility results into one category (non-susceptibility) revealed prevalence rates of 51.0%, 16.0%, 7.5%, and 7.1%, respectively (Table 2).

Among 482 children with a single Gram-negative isolate, 33 met the MDR definition, yielding a prevalence of 6.9% (95% CI 4.8–9.5), while 245 (50.8%, 95% CI 46.35–55.4%) had resistance/intermediate susceptibility results to 1–2 antibiotic categories and the rest (42.3%) had susceptible isolates to all tested antibiotics.

Correlates of MDR Gram-Negative Urine Isolates

Children with MDR Gram-negative uropathogens were older than those with isolates non-susceptible to 1–2 antibiotic categories and those with sensitive isolates to all tested antibiotics, with a median age of 19.0, 11.0, and 11.0 months,

Table 2 Antimicrobial Resistance and Non-Susceptibility of the Gram-Negative Isolates by Antibiotic Categories

Antibiotic class	Resistance N (%)	Non-Susceptibility[a] N (%)
Penicillin	182 (37.8%)	246 (51.0%)
First-generation cephalosporins	1 (0.2%)	6 (1.2%)
Second-generation cephalosporins	16 (3.3%)	34 (7.1%)
Third-generation cephalosporins	1 (0.2%)	5 (1.0%)
Fluoroquinolones	10 (2.1%)	18 (3.7%)
Aminoglycosides	15 (3.1%)	22 (4.6%)
Nitrofurantoin	18 (3.7%)	36 (7.5%)
Sulfonamides	58 (12.0%)	80 (16.0%)
Carbapenems	0 (0.0%)	0 (0.0%)

Notes: N=482; [a]Combining resistance and intermediate susceptibility results.

respectively (P=0.163), but the difference was not statiscally signficant. Within the MDR group, the proportion of Arab children was (P=0.003) higher (63.6%) than those with non-susceptibility to 1–2 antibiotic categories (38.0%), and the sensitive isolates group (32.4%). A similar distribution was observed in the proportions of residents from low-socioeconomic-status communities (51.5%, 32.0%, and 24.0%, respectively; P=0.010). Background diseases were more common in the MDR group than in the groups with non-susceptibility to 1–2 antibiotic categories and the all-sensitive isolates group (30.3%, 15.1%, and 21.6%, respectively, P=0.048). The trend was similar for congenital anomalies of the kidney/urinary tract (24.2%, 5.7%, and 11.3%, respectively, P=0.001), and use of antibiotics before hospitalization (21.9%, 0.7%, and 5.4%, respectively, P=0.006). The corresponding percentages for penicillin use were 12.5%, 5.7%, and 2.0%, P=0.014. Median levels of hemoglobin and CRP were lower in the MDR group (P<0.05). No significant differences (P>0.05) were found between the groups for sex, previous UTI, previous hospitalization, emergency room visits, use of first- or second-generation cephalosporins before hospitalization, leukocytes, neutrophils, lymphocytes, and platelet levels (Table 3).

Table 3 Associations of Socio-Demographic, Clinical Characteristics, Length of Stay and Hospitalization Cost with Antibiotic Resistance in Gram-Negative Urine Culture Isolates of Hospitalized Children 0–17 years Old

Variable	Resistance/Intermediate Susceptibility to≥ 3 Antibiotic Categories	Resistance/Intermediate Susceptibility to 1–2 Antibiotic Categories	Sensitive To all Antibiotic	P value [a]
Total	N=33	N=245	N=204	
Age (months), median (IQR)	19.0 (78.0)	11.0 (26.0)	11.0 (34.0)	0.163 [b]
Population group				0.003
Jews	12 (36.4%)	152 (62.0%)	138 (67.6%)	
Arab	21 (63.6%)	93 (38.0%)	66 (32.4%)	
Sex				0.148
Male	7 (21.2%)	45 (18.4%)	25 (12.3%)	
Female	26 (78.8%)	200 (81.6%)	179 (87.7%)	

(*Continued*)

Table 3 (Continued).

Variable	Resistance/Intermediate Susceptibility to≥ 3 Antibiotic Categories	Resistance/Intermediate Susceptibility to 1–2 Antibiotic Categories	Sensitive To all Antibiotic	P value [a]
Socioeconomic status				0.010
Low (1–3)	17 (51.5%)	78 (32.0%)	49 (24.0%)	
Medium (4–6)	11 (33.3%)	126 (51.6%)	107 (52.5%)	
High (7–10)	5 (15.2%)	40 (16.4%)	48 (23.5%)	
Previous urinary tract infection, yes	3 (9.1%)	32 (13.1%)	26 (12.7%)	0.812
Hospitalization in the preceding month	1 (3.0%)	10 (4.1%)	4 (2.0%)	0.436
Emergency room visit in the preceding month	0 (0.0%)	18 (7.3%)	10 (4.9%)	0.183
Background diseases	10 (30.3%)	37 (15.1%)	44 (21.6%)	0.048
Nephrological or genitourinary disorder	8 (24.2%)	14 (5.7%)	23 (11.3%)	0.001
Antibiotic use before hospitalization	7 (21.9%)	26 (10.7%)	11 (5.4%)	0.006
Penicillin use before hospitalization	4 (12.5%)	14 (5.7%)	4 (2.0%)	0.014
1st or 2nd generation cephalosporin use before hospitalization	1 (3.1%)	7 (2.9%)	5 (2.5%)	0.955
Hemoglobin (g/dL), median (IQR)	11.8 (1.2)	11.1 (1.6)	11.1 (2.3)	0.025 [bc]
Platelets (103/μL), median (IQR)	344.0 (192.3)	331.5 (156.3)	342.5 (172.5)	0.237 [b]
Leukocytes (103/μL), median (IQR)	14.1 (7.8)	16.2 (10.4)	16.0 (10.0)	0.167 [b]
Neutrophils (103/μL), median (IQR)	7.3 (7.1)	9.4 (7.5)	9.0 (8.5)	0.312 [b]
Lymphocytes (103/μL), median (IQR)	4.3 (3.5)	4.4 (3.9)	4.4 (4.4)	0.486 [b]
C-reactive protein (mg/L), median (IQR)	23.8 (94.5)	69.7 (119.0)	61.0 (113.0)	0.033 [bd]
Length of stay (days), median (IQR)	3.0 (2.0)	3.0 (2.0)	3.0 (2.0)	0.441 [b]
Hospitalization Cost (NIS), median (IQR)	8169.0 (5446.0)	8169.0 (5446.0)	8169.0 (5446.0)	0.441 [b]

Notes: P value was obtained by [a] chi-square test; [b] the Kruskal–Wallis test. IQR: Interquartile range. [c] Pairwise adjusted p value for multiple comparisons p=0.021 and p=0.054 comparing children with resistance/intermediate susceptibility to≥ 3 antibiotic categories vs. those with isolates sensitive to all antibiotics, and those with resistance/ intermediate susceptibility to 1–2 antibiotic categories, respectively. [d] Pairwise adjusted p value for multiple comparisons p=0.049 and p=0.028 comparing children with resistance/intermediate susceptibility to≥ 3 antibiotic categories vs. those with isolates sensitive to all antibiotics, and those with resistance/intermediate susceptibility to 1–2 antibiotic categories, respectively. Other pairwise comparisons were not statistically significant.

Multivariable analysis showed that Arab children had an increased likelihood of MDR (OR=3.29, 95% CI 1.49–7.25) than Jewish children, as well as children with a history of antibiotic use before hospitalization compared to children without antibiotic use before hospitalization (5.06, 1.67–15.31). The likelihood of resistance/intermediate susceptibility to 1–2 antibiotic categories also increased in relation to antibiotic use before hospitalization (2.68, 1.25–5.74), and in males vs. females (1.71, 0.99–2.94) (Table 4).

Hospitalization Duration and Costs

The median hospitalization duration was 3 days, and the median hospitalization cost was 9,966.0 NIS, with no significant differences (p >0.05) by MDR status (Supplementary Table 11).

 https://doi.org/10.2147/IDR.S588989

https://doi.org/10.2147/IDR.S588989

Table 4 Multinomial Regression Model of Factors Associated with Antibiotic Resistance in Gram-Negative Isolates in the Urine Culture of Hospitalized Children 0–17 years Old

Variable	**Resistance/Intermediate Susceptibility to 1–2 Antibiotic Categories**				**Resistance/Intermediate Susceptibility to≥ 3 Antibiotic Categories**			
	Unadjusted OR (95% CI)	**P value**	**Adjusted OR (95% CI)**	**P value**	**Unadjusted OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Population group (Arabs vs. Jews)	1.28 (0.87–1.89)	0.20	1.30 (0.87–1.94)	0.20	3.66 (1.70–7.88)	0.001	3.29 (1.49–7.25)	0.003
Age, months, continuous variable	0.99 (0.99–1.00)	0.20	0.99 (0.99–1.00)	0.30	1.01 (0.99–1.01)	0.10	1.00 (0.99–1.00)	0.80
Sex (Male vs. female)	1.61 (0.95–2.73)	0.08	1.71 (0.99–2.94)	0.05	1.93 (0.76–4.90)	0.20	2.35 (0.88–6.22)	0.09
Antibiotic use before hospitalization (Yes vs. no)	2.08 (1.00–4.33)	0.05	2.68 (1.25–5.74)	0.01	4.89 (1.74–13.76)	0.003	5.06 (1.67–15.31)	0.004
Background diseases (Yes vs. no)	0.65 (0.40–1.05)	0.08	0.58 (0.35–0.97)	0.04	1.58 (0.70–3.57)	0.030	1.13 (0.46–2.79)	0.80

Notes: N=478; The base-category (reference group) was sensitive to all antibiotics.

Discussion

We examined the prevalence and correlates of MDR in Gram-negative bacteria in children hospitalized with UTIs and estimated the cost associated with these infections.

Our findings demonstrate relatively high resistance rates to the main antibiotics used for treating UTIs in children, with the highest resistance to ampicillin (33.8%), followed by trimethoprim/sulfamethoxazole (12.4%) and amoxicillin-clavulanic acid (9.4%). Interestingly, resistance to first and second-generation cephalosporins was low (1.7% and 3.3%, respectively). Overall, 6.9% of the isolates were classified as MDR, within the lower limits of reported MDR estimates in pediatric UTIs.[14] We found a high percentage of 50.8% of isolates exhibited resistance/intermediate susceptibility to 1–2 antibiotic categories. These findings are crucial for informing the clinical care of children with UTIs and for updating empirical antibiotic guidelines.

Older age, Arab ethnicity, lower socioeconomic status, underlying comorbidities, pre-existing urinary tract anomalies, antibiotic use before hospitalization, and initiation of new penicillin treatment were positively associated with MDR in Gram-negative uropathogens. Adjustment for confounding showed that Arab children had a threefold increased risk of MDR infections compared with Jewish children. Moreover, antibiotic use before hospitalization significantly increased MDR risk by 5-fold, and the risk of having resistance/intermediate susceptibility to 1–2 antibiotic categories. A trend toward higher resistance was observed in males compared with females. These findings are important for identifying risk groups for treatment failure and better planning of antibiotic stewardship interventions.

Ampicillin resistance was most common in our study and was similarly high in other studies, making it a less effective empirical treatment.[8,15,19] While resistance to ampicillin was 33.8% and to trimethoprim/sulfamethoxazole 12.4%, another study from Israel reported higher estimates in *E. coli* urine isolates of over 55% and 25%,[32] respectively, likely because intermediate resistance was considered equivalent to resistance in this study.[32] Moreover, a significant increase in resistance to ciprofloxacin, cefuroxime, and ceftriaxone was observed during 2007–2021.[32] Zaitoon et al reported a significant difference in resistance to cephalexin (19.3% vs. 13.4%, P=0.03) between children with complicated and non-complicated UTI.[33] Collectively, these findings are essential for guiding healthcare providers in selecting appropriate empirical treatments for children with UTI.[8,32,33]

We found that antibiotic use before hospitalization and initiation of new penicillin treatment were significant risk factors for MDR, corroborating findings from previous studies.[21,34] A study from Philadelphia showed that use of amoxicillin within up to 60 days before UTI episodes predicted ampicillin resistance, and up to 30 days predicted amoxicillin-clavulanate resistance.[34] While antibiotic use before hospitalization might have been medically justified, educational interventions should be implemented to reduce unnecessary antibiotic use.

Interestingly, we found associations between multiple sociodemographic factors and MDR. Older age has been reported as a predictor of MDR in children.[35] In our study, age was not associated with MDR in multivariable models, suggesting that it may be a proxy for other factors, such as cumulative antibiotics exposure, that can directly affect the development of resistance. Arab ethnicity was associated with MDR. Another study showed that Arab ethnicity was associated with increased risk of community-acquired ESBL-UTI in children from Jerusalem.[12] This might be due to antibiotic prescribing and consumption habits that might vary across population groups and regions.[36,37] Collectively, these findings underscore the need for targeted antibiotic stewardship interventions.

Male sex was positively associated with increased risk of non-susceptibility to 1–2 antibiotic categories; however, the association was not statistically significant. This trend confirms previous reports showing increased MDR Gram-negative UTIs in males.[38,39]

In bivariate analysis only, we found that comorbidities and pre-existing urinary tract anomalies or diseases were significant risk factors for MDR. A study conducted in Romania involving pediatric patients with UTIs demonstrated that urinary tract malformations were a significant risk factor for MDR UTIs,[19] corroborating our findings. Another study from Greece showed that vesicoureteral reflux was significantly associated with MDR.[15] Background diseases and pre-existing urinary tract anomalies likely predispose patients to recurrent infections and antibiotic use, which are primary drivers of resistance.[15,19]

The median hospitalization duration in our study was 3 days, and the median cost was 9,966.0 NIS (~USD 3000), with no significant differences in these parameters by MDR status, unlike prior reports,[40–42] possibly due to methodological variations and patient case-mix.

Antibiotic treatment was prescribed to 84.0% of participants during hospitalization and to 77.0% at discharge (Table 1). At the studied hospital, antibiotic therapy begins during hospitalization and continues in the community, lasting 7–14 days. Discharge with antibiotic therapy generally occurred in clinically stable patients who demonstrated improvement in signs and symptoms. Antibiotic treatment was prescribed at discharge to complete the recommended course, given a median hospital stay of 3 days. Post-discharge clinical outcomes were not captured in our study. However, discharge decisions were based on clinical improvement, including decreased fever, white blood count, and CRP level.

Our study has limitations. This was a single-center study, which can limit the generalizability of our findings. However, the risk factors can be generalized to other populations. Our study included hospitalized children who might differ in disease severity from those in outpatient settings. The retrospective collection of data from medical records may have included incomplete information and variability in medical staff documentation.

The study strengths include a 5-year period and comprehensive data collection, thus providing robust results and a deep understanding of the prevalence and risk factors of MDR among uropathogens isolated from hospitalized children. In Israel, access to care is universal, thereby limiting the potential for selection bias. In addition, the study population comprises both Jewish and Arab children and a wide range of socioeconomic levels, thereby enhancing the generalizability of our findings. Laboratory methods were validated and performed by qualified staff, which ensures the reliability of microbiological results.

Conclusion

Our study underscores the burden of antibiotic non-susceptibility and MDR in Gram-negative uropathogens in hospitalized children. These findings are crucial for supporting evidence-based clinical care of children with UTIs and for updating empirical antibiotic guidelines. Antibiotic use before hospitalization was a strong predictor of MDR, and Arab ethnicity was independently positively associated with MDR, likely due to differential antibiotic use patterns in this population. Prescription of antibiotic treatment at discharge was high, reflecting improvement in patients' signs and symptoms and the need to complete the treatment course at home, given a median hospital stay of 3 days. These findings have important clinical and public health implications, particularly for planning antimicrobial stewardship and educational programs to reduce the burden of antibiotic resistance.

Abbreviations

CFU, colony-forming units; *E. coli, Escherichia coli*; ESBL, Extended-spectrum beta-lactamases; IQR, interquartile range; MDR, multidrug-resistant; NIS, New Israeli Shekel; OECD, Organization for Economic Co-operation and Development; SD, standard deviation; UTIs, urinary tract infections.

Data Sharing Statement

Individual-level data cannot be made publicly available due to legal and ethical restrictions. Aggregate data might be provided upon reasonable request to the corresponding author.

Acknowledgment

Wasef Na'aminh and Eias Kassem are co-senior authors for this study. This work was performed in partial fulfillment of the requirements for a Master's in Public Health (MPH), of Dr. Sama Haleem, at the School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Israel.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding
No external funding was available for this study.

Disclosure
The authors declare no relevant financial or non-financial interests in this work.

References

1. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J*. 2008;27(4):302–308. doi:10.1097/INF.0b013e31815e4122
2. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610. doi:10.1542/peds.2011-1330
3. Shaikh N, Mattoo TK, Keren R, et al. Early antibiotic treatment for pediatric febrile urinary tract infection and renal scarring. *JAMA Pediatr*. 2016;170(9):848–854. doi:10.1001/jamapediatrics.2016.1181
4. Le Saux N. Antimicrobial stewardship in daily practice: managing an important resource. *Paediatr Child Health*. 2014;19(5):261–270. doi:10.1093/pch/19.5.261
5. Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ*. 2016;352(i939). doi:10.1136/bmj.i939
6. Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing enterobacteriaceae in paediatric urinary tract infections: a systematic review and meta-analysis. *J Infect*. 2016;73(6):547–557. doi:10.1016/j.jinf.2016.07.014
7. Edlin RS, Shapiro DJ, Hersh AL, Copp HL. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. *J Urol*. 2013;190(1):222–227. doi:10.1016/j.juro.2013.01.069
8. Yakubov R, van den Akker M, Machamad K, Hochberg A, Nadir E, Klein A. Antimicrobial resistance among uropathogens that cause childhood community-acquired urinary tract infections in central Israel. *Pediatr Infect Dis J*. 2017;36(1):113–115. doi:10.1097/inf.0000000000001373
9. Shaki D, Hodik G, Elamour S, et al. Urinary tract infections in children < 2 years of age hospitalized in a tertiary medical center in Southern Israel: epidemiologic, imaging, and microbiologic characteristics of first episode in life. *Eur J Clin Microbiol Infect Dis*. 2020;39(5):955–963. doi:10.1007/s10096-019-03810-w
10. Dayan N, Dabbah H, Weissman I, Aga I, Even L, Glikman D. Urinary tract infections caused by community-acquired extended-spectrum β-lactamase-producing and nonproducing bacteria: a comparative study. *J Pediatr*. 2013;163(5):1417–1421. doi:10.1016/j.jpeds.2013.06.078
11. Graif N, Abozaid S, Peretz A. Trends in distribution and antibiotic resistance of bacteria isolated from urine cultures of children in northern Israel between 2010 and 2017. *Microb Drug Resist*. 2020;26(11):1342–1349. doi:10.1089/mdr.2020.0111
12. Megged O. Extended-spectrum β-lactamase-producing bacteria causing community-acquired urinary tract infections in children. *Pediatr Nephrol*. 2014;29(9):1583–1587. doi:10.1007/s00467-014-2810-y
13. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268–281. doi:10.1111/j.1469-0691.2011.03570.x
14. Mahony M, McMullan B, Brown J, Kennedy SE. Multidrug-resistant organisms in urinary tract infections in children. *Pediatr Nephrol*. 2020;35(9):1563–1573. doi:10.1007/s00467-019-04316-5
15. Kalaitzidou I, Ladomenou F, Athanasopoulos E, Anatoliotaki M, Vlachaki G. Susceptibility patterns of uropathogens identified in hospitalized children. *Pediatr Int*. 2019;61(3):246–251. doi:10.1111/ped.13772
16. Zhang K, Zhang Y, Chao M, Hao Z. Prevalence, pathogenic bacterial profile and antimicrobial susceptibility pattern of urinary tract infection among children with congenital anomalies of the kidney and urinary tract. *Infect Drug Resist*. 2023;16:4101–4112. doi:10.2147/idr.S399442
17. Zerefaw G, Tadesse S, Derbie A. Bacterial uropathogens, antimicrobial susceptibility profile and associated factors among pediatric patients in Bahir Dar, Northwest Ethiopia. *Ethiop J Health Sci*. 2022;32(1):81–92. doi:10.4314/ejhs.v32i1.10
18. Elale AK, Manilal A, Tadesse D, Seid M, Dubale A. Magnitude and associated factors of bacterial urinary tract infections among paediatric patients in Arba Minch, southern Ethiopia. *New Microbes New Infect*. 2023;51:101083. doi:10.1016/j.nmni.2023.101083
19. Duicu C, Cozea I, Delean D, Aldea AA, Aldea C. Antibiotic resistance patterns of urinary tract pathogens in children from Central Romania. *Exp Ther Med*. 2021;22(1):748. doi:10.3892/etm.2021.10180
20. Selekman RE, Shapiro DJ, Boscardin J, et al. Uropathogen resistance and antibiotic prophylaxis: a meta-analysis. *Pediatrics*. 2018;142(1). doi:10.1542/peds.2018-0119
21. Raman G, McMullan B, Taylor P, Mallitt KA, Kennedy SE, Multiresistant E. coli urine infections in children: a case-control study. *Arch Dis Child*. 2018;103(4):336–340. doi:10.1136/archdischild-2017-312831
22. Nieminen O, Korppi M, Helminen M. Healthcare costs doubled when children had urinary tract infections caused by extended-spectrum β-lactamase-producing bacteria. *Acta Paediatr*. 2017;106(2):327–333. doi:10.1111/apa.13656
23. Dotis J, Printza N, Marneri A, Gidaris D, Papachristou F. Urinary tract infections caused by extended-spectrum betalactamase-producing bacteria in children: a matched casecontrol study. *Turk J Pediatr*. 2013;55(6):571–574.
24. Begaj X, Lee H, Noor A, et al. Clinical outcomes of children with extended-spectrum ß -lactamase urinary tract infection receiving discordant empiric antibiotic: a comparative study of fever duration, length of stay, and readmissions. *Clin Pediatr*. 2023;62(4):338–344. doi:10.1177/00099228221129029

25. Israel Central Bureau of Statistics. Statistical abstract of Israel 2019.
26. Clarfield AM, Manor O, Nun GB, et al. Health and health care in Israel: an introduction. *Lancet*. 2017;389(10088):2503–2513. doi:10.1016/s0140-6736(17)30636-0
27. Gnech M, Bujons A, Radmayr C, et al. Update and summary of the EAU/ESPU paediatric guidelines on urinary tract infection in children. *J Pediatr Urol*. 2025. doi:10.1016/j.jpurol.2025.06.016
28. Hilt EE, Parnell LK, Wang D, Stapleton AE, Lukacz ES. Microbial threshold guidelines for UTI diagnosis: a scoping systematic review. *Pathol Laborat Med Int*. 2023;15:43–63. doi:10.2147/PLMI.S409488
29. Israel Ministry of Health. The Ministry of Health's price list for ambulatory and hospitalization services. Available from: https://www.gov.il/he/departments/dynamiccollectors/moh-price-list. Accessed March 19, 2026.
30. Israel Central Bureau of Statistics. Characterization and classification of geographic units by the socio-economic level of the population 2017. 2021. Available from: https://www.cbs.gov.il/he/publications/DocLib/2021/socio_eco17_1832/e_print.pdf. Accessed March 19, 2026.
31. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing. CLSI Supplement M100-S25 to M100-S30*. Wayne (PA): CLSI; 2015–2020.
32. Shkalim Zemer V, Ashkenazi S, Levinsky Y, et al. Pathogens causing pediatric community acquired urinary tract infections and their increasing antimicrobial resistance: a nationwide study. *Pathogens*. 2024;13(3). doi:10.3390/pathogens13030201
33. Zaitoon H, Garkaby J, Nassrallah B, et al. Insights into hospitalized children with urinary tract infections: epidemiology and antimicrobial resistance patterns in Israel-a single center study. *Children*. 2024;11(9). doi:10.3390/children11091142
34. Paschke AA, Zaoutis T, Conway PH, Xie D, Keren R. Previous antimicrobial exposure is associated with drug-resistant urinary tract infections in children. *Pediatrics*. 2010;125(4):664–672. doi:10.1542/peds.2009-1527
35. El Zein Z, Boutros CF, El Masri M, et al. The challenge of multidrug resistance in hospitalized pediatric patients with urinary tract infections. *Front Cell Infect Microbiol*. 2025;15:1570405. doi:10.3389/fcimb.2025.1570405
36. Arcavi L, Okasha D, Trepp S, et al. Appropriate antibiotic prescribing pattern in hospitalized children. *Curr Drug Saf*. 2010;5(3):194–202. doi:10.2174/157488610791698343
37. Israel Ministry of Health. Health inequalities report, 2023: differences by population groups and trends over time. 2025. Available from: https://israelhealthindicators.org/wp-content/uploads/2025/05/NPQICH_GapsReport_May11_2025_Electronic.pdf. Accessed March 19, 2026.
38. Gomila A, Shaw E, Carratalà J, et al. Predictive factors for multidrug-resistant gram-negative bacteria among hospitalised patients with complicated urinary tract infections. *Antimicrob Resist Infect Control*. 2018;7:111. doi:10.1186/s13756-018-0401-6
39. Nedbal C, Mahobia N, Browning D, Somani BK. Variability in profiles and prevalences of Gram-negative bacteria in urinary tract infections: a population-based analysis. *J Clin Med*. 2024;13(17). doi:10.3390/jcm13175311
40. Uzodi AS, Lohse CM, Banerjee R. Risk factors for and outcomes of multidrug-resistant Escherichia coli infections in children. *Infect Dis Ther*. 2017;6(2):245–257. doi:10.1007/s40121-017-0152-3
41. Vallejo-Torres L, Pujol M, Shaw E, et al. Cost of hospitalised patients due to complicated urinary tract infections: a retrospective observational study in countries with high prevalence of multidrug-resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study. *BMJ Open*. 2018;8(4):e020251. doi:10.1136/bmjopen-2017-020251
42. Zhu NJ, Weldegiorgis M, Carter E, Brown C, Holmes A, Aylin P. Economic burden of community-acquired antibiotic-resistant urinary tract Infections: systematic review and meta-analysis. *JMIR Public Health Surveill*. 2024;10(e53828). doi:10.2196/53828