

Etiological Profiles and Antibiotic Resistance of Urinary Tract Infections Among Different Age Categories in Children: A Retrospective Study of Xiamen Single-Center

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Purpose: To analyze the distribution of pathogens and drug resistance in children with urinary tract infections (UTIs) in a single center in Xiamen and to guide the selection of empirical antibiotics in the clinic.

Methods: Clinical data of 2001 children with UTIs in Xiamen Children's Hospital between 2014 and 2022 were retrospectively analyzed, grouped by age and comorbidities. Differences in pathogen distribution and drug sensitivity were compared with the chi-square test applied and significance set at $p < 0.05$.

Results: Of 2001 urine samples collected, 965 (42.73%) had positive results for common infections. Gram-negative bacteria predominated (644/965; 66.74%), with *Escherichia coli* being the most prevalent (432/965; 44.77%). The top five pathogens were *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*. The percentage of *Escherichia coli* was higher in simple UTIs than complex (54.01% vs 45.35%), and *Pseudomonas aeruginosa* (9.59% vs 2.74%) and fungi (7.27% vs 1.96%) were higher in complex UTIs ($p < 0.05$). Predominance of *Pseudomonas aeruginosa* and *Enterococcus faecalis* in boys and *Enterococcus faecalis* in girls. *Escherichia coli* had a significantly lower rate of resistance to ampicillin than *Klebsiella pneumoniae* ($p < 0.001$), and both had a high rate of resistance to cephalosporins (over 95% to cefazolin), but a low rate of resistance to amikacin and furotoxin. *Pseudomonas aeruginosa* had 100% resistance to most cephalosporins, but less than 7% to ceftazidime, cefepime and piperacillin tazobactam. *Enterococcus faecalis* had over 90% resistance to Ampicillin, Penicillin, Linezolid and 91.53% to tetracycline. No Tigecycline/Vancomycin-resistant enterococci were found. Both Gram-negative and Gram-positive bacteria maintained relatively low rates of resistance to Nitrofurantoin.

Conclusion: Pediatric UTIs in Xiamen show gender-based pathogen differences, mainly gram-negative. Nitrofurantoin is preferred for mild cases, and the clinical selection should be individualized by combining the regional pathogen spectrum and drug sensitivity.

Keywords: UTIs, children, pathogens, antibiotic resistance, urine pH

Introduction

Urinary tract infections (UTIs) is an inflammatory injury caused by bacteria invading urinary tract mucosa or tissue and is one of the common infectious diseases in children. Its incidence varies depending on gender, age and whether combined with urinary tract structural malformations. Most children have good prognosis after timely and correct anti-infective treatment, but if the treatment is not timely or not standardized such as inappropriate choice of antibiotics and insufficient course of treatment, it will lead to many complications, such as sepsis, abnormal renal function, renal scarring, renal hypertension and so on. Therefore, timely selection of effective antibiotics is the key to the treatment of

UTIs. Enterobacteriaceae is the most important causative organism in paediatric UTI. In recent decade, UTI caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) has become more prevalent.¹ The problem of drug resistance of Enterobacteriaceae bacteria (especially ESBL-positive strains) is becoming increasingly serious. But there is a lack of consensus in treating ESBL-E UTI. A recent international survey shows that the prevalence of UTIs caused by ESBL-E bacteria varies in different regions and there are significant variations in the management of UTI caused by ESBL-E bacteria between centres. In vitro susceptibility to the antibiotics remains an important management consideration.² Given that the distribution and drug resistance of pathogenic bacteria is affected by age, region and other factors, understanding the distribution of pathogenic bacteria and the characteristics of drug resistance in UTIs in this region has important reference and guidance for clinical drug use and reducing drug resistance of pathogenic bacteria.³ In this study, we retrospectively analyzed the clinical data, distribution of pathogenic bacteria and drug resistance of UTIs admitted to Xiamen Children's Hospital from June 2014 to December 2022, in order to provide a reference for the selection of empirical drugs for UTIs in this region.

Materials and Methods

Study Setup and Design

This retrospective cross-sectional study was conducted at the Department of Nephrology, Children's Hospital of Fudan University (Xiamen Branch), Xiamen Children's Hospital, from June 2014 to December 2022. The study analyzed urine samples from hospitalized children aged 0–17 years with suspected UTIs. The methodology used hospital medical records to gather patient demographic and clinical information.

Inclusion criteria: Children aged 0–17 years with a diagnosis of UTIs. The diagnostic criteria for UTIs refer to the Evidence-based Guidelines for the Diagnosis and Management of Urinary Tract Infections (2016).⁴

Exclusion criteria: (1) Children with only routine urinalysis without urine culture. (2) Children with asymptomatic bacteriuria. (3) Children with contaminated urine samples were considered in combination with clinical manifestation, laboratory examination and treatment effect.

Methodology

Clinical Data Collection

Clinical data of the children were collected through the electronic medical record system, including age, gender, clinical symptoms, urine routine, urine culture and drug sensitivity test results, urinary ultrasound, urography, and other laboratory test results.

Clinical Grouping

Children were divided into 5 groups according to their age, including age ≤ 28 d, 28d~1y, 1y~3y, 3y~5y, and >5y. According to the presence or absence of comorbid factors, they were divided into simple UTI and complicated UTI. And the diagnostic criteria for complicated urinary tract infection refer to the Chinese Expert Consensus on the Diagnosis and Treatment of Urinary Tract Infection (2015 Edition) - Complicated Urinary Tract Infection.⁵

① Strain culture, identification and drug sensitivity test: Bacterial isolation and culture were carried out with reference to the clinical laboratory operation procedure. The same child cultured the same pathogenic bacteria several times in one course of disease was regarded as one case. ② Criterion of pathogenic bacteria: Mid-stream urine culture with colony count $\geq 10^5$ cfu/mL is considered true bacteriuria, colony count $< 10^4$ cfu/mL may be contaminating bacteria, colony count of $10^4 \sim 10^5$ cfu/mL was suspected positive, and needs to be re-examined.⁶ If the result is the same, it is considered pathogenic, while suprapubic bladder puncture is meaningful as long as a colony is present.

Analytical Statistics

SPSS 25.0 was used to conduct statistical analysis. Count data expressed as number of cases and percentage. The chi-square test was employed for the statistical analysis, with a significance level set at $p < 0.05$ for all tests. Demographic data, including age, sex, bacterial isolates, antimicrobial susceptibility test results of admitted patients, and urine pH were analyzed.

Results

Epidemiological Characteristics of UTIs Samples and Patient

A total of 2001 children aged 2 hours to 17 years were recruited for this study, of which 855 had positive urine cultures, with a total colony count of 965 strains, and a positive rate of 42.73%. Among the 855 children, there were 458 boys and 397 girls, 19 (8.22%) were younger than 28 d, 570 (66.67%) were 28 d~1 year, 132 (15.44%) were 1~3 years, 64 (7.48%) were 3~5 years, and 70 (8.19%) were >5 years. The proportion of children aged 28d~1 year was much higher than that of other age groups, and the proportion of boys (55.09%, 314/570) was higher than that of girls (44.91%, 256/570).

Clinical Features

Clinical Symptoms

Fever was the main manifestation in 560 of the 855 children (65.5%, 560/855), of whom 501 were younger than 3 years old (89.5%, 501/560). There were 19 children aged \leq 28 days, 7 (36.8%) with skin jaundice, 6 (31.6%) with fever, 1 case each of diarrhea, abdominal distension, congenital hydronephrosis, congenital absence of anus, respiratory infection, and skin rash. Sixty-three cases of children with urinary tract irritation symptoms such as frequent urination, urgency, painful urination or abnormal urination as the main symptom, including 18 (28.6%) younger than 1 year, which mainly with urine odor, abnormal color of urine, and crying during urination, followed by 16 (25.4%) aged 1~3 years and then 29 (46.0%) older than 3 years. Thirty-six cases started with convulsions, including 23 (63.89%) aged 28d-1 year, 6 (16.67%) aged 1~3 years, 3 (8.33%) aged 3~5 years, and 4 (11.11%) aged >5 years, which accounted for 4.04% (23/570), 4.55% (6/132), 4.69% (3/64) and 5.71% (4/70), respectively, in the same age group of the children.

Merger Factors

Among the 855 children, 344 (40.2%) had complicated urinary tract infections, of which 273 (31.93%) had abnormal urinary tract structure. The most common being hydronephrosis in 117 (42.86%); followed by vesicoureteral reflux in 74 (27.11%); and then separated/widened renal pelvis in 46 (16.85%); duplicated kidney in 23 (8.42%), renal dysplasia in 7 (2.56%); posterior urethral valve in 3 (1.10%, of which 1 was postoperative), and ectopic kidney in 3 (1.10%). Other comorbid factors: 13 cases were double "J tube" indwelling, 24 cases of urinary tract stones, 7 cases of neurogenic bladder (Table 1).

Distribution of Pathogenic Bacteria and Drug Resistance Analysis of UTIs

Distribution of Pathogenic Bacteria of UTIs

Urine culture was positive in 855 children, with a total colony count of 965 strains and a positive rate of 42.73%. Gram-negative bacteria were 644 strains (66.74%), Gram-positive bacteria were 286 strains (29.63%) and Fungi were 35 strains (3.63%). The top five strains detected among all pathogenic bacteria were *E. coli* (432 strains, 44.77%), *E. faecium* (173 strains, 17.93%),

Table 1 Main Comorbid Factors in Children with UTIs in Different Age Groups [Cases (%)]

Age	Number of Cases	Hydronephrosis (%)	Vesicoureteral Reflux (%)	Other Abnormal Urinary Tract Structure (%)	Urethral Catheter/ Surgical History (%)	Urinary Stones (%)	Neurogenic Bladder (%)
\leq 28d	19	1 (5.26)	0 (0)	4 (21.05)	0 (0)	0 (0)	0 (0)
28d-1y	570	75 (13.16)	55 (9.65)	58 (10.18)	4 (0.70)	9 (1.58)	4 (0.70)
1-3y	132	16 (12.12)	11 (8.33)	10 (7.69)	2 (1.52)	2 (1.52)	1 (0.76)
3-5y	64	11 (17.19)	5 (7.81)	6 (9.37)	3 (4.69)	9 (14.06)	0 (0)
>5y	70	14 (0.20)	3 (4.28)	4 (5.71)	4 (5.71)	4 (5.71)	2 (2.86)
Total	855	117	74	82	13	24	7

K. pneumoniae (93 strains, 9.64%), *E. faecalis* (72 strains, 7.46%) and *P. aeruginosa* (47 strains, 4.87%). The other bacteria were 22 strains (2.28%) of *Proteus mirabilis*, 9 strains (0.93%) of *Morganella morganii*, 8 strains (0.82%) each of *Enterobacter cloacae* and *Enterococcus urinaria*, 7 strains (0.73%) of *Citrobacter freundii*, 6 strains (0.62%) each of *Klebsiella acidogenes*, *Staphylococcus epidermidis* and *Enterococcus quail*. Four strains (0.41%) each of *Enterobacter aerogenes* and *Corynebacterium glucoside*. Three strains (0.31%) each of *Proteus vulgaris*, *Enterobacter kobe*, *Salmonella typhimurium* and *Staphylococcus aureus*. Two strains (0.20%) each of Group B *Streptococcus*, *Enterococcus raffinose*, *Staphylococcus haemolyticus*, *Corynebacterium striatum* and *Streptococcus pharyngitis*. One strain (0.10%) each of *Enterobacter asburiae*, *Klebsiella acidogenes* (ESBL), *Raoul's bacillus ornithinolyticus*, *Enterobacter cloacae*, *Actinobacillus johannes*, *Staphylococcus saprophyticus*, *Streptococcus gallate*, *Staphylococcus lugdunensis*, *Staphylococcus hominis*, *Streptococcus dysgalactiae*, *Corynebacterium asepticum*. A total of 35 strains of Fungi were detected, including 20 strains (2.07%) of *Candida albicans*, 10 strains (1.03%) of *Candida tropicalis*, 2 strains (0.20%) each of *Candida smoothis* and *Pseudohyphae near-smoothis*, 1 strain (0.10%) of *Saccharomyces longispora*. There were 214 ESBL-positive strains, accounting for 22.18% (214/965), of which 186 were ESBL-E, accounting for 19.27% (186/965) (Table 2).

The detection rate of Gram-negative bacteria (66.74%) was higher than that of Gram-positive bacteria (29.64%). In children with simple UTIs, the detection rate of *E. coli* was significantly higher than that of complicated UTIs ($\chi^2 = 6.17$, $p = 0.013$). Meanwhile, the detection rate of *E. faecium*, *K. pneumoniae* and *E. faecalis* was also higher than that of complicated UTIs, but the difference was not statistically significant ($\chi^2 = 0.39, 0.01, 1.03$, $p = 0.531, 0.925, 0.311$). On the contrary, the detection rate of *P. aeruginosa* and Fungi in complicated UTIs was significantly higher than that in simple ($\chi^2 = 18.59, 14.77$, both $p < 0.001$) (Table 3).

Table 2 Species and Distribution of Pathogenic Bacteria [Strains (%)]

Gram-Negative Bacteria	Strains (%)	Gram-Positive Bacteria	Strains (%)
<i>E. coli</i>	432 (44.77)	<i>E. faecium</i>	173 (17.93)
<i>K. pneumoniae</i>	93 (9.64)	<i>E. faecalis</i>	72 (7.46)
<i>P. aeruginosa</i>	47 (4.87)	Other positive Bacteria	41 (4.25)
<i>Proteus mirabilis</i>	22 (2.28)	Fungi	35 (3.63)
Other negative bacteria	50 (5.17)	Total	965 (100)
ESBL-positive	214 (22.18)	ESBL-E	186 (19.27)

Abbreviations: *E. coli*, *Escherichia coli*; *E. faecium*, *Enterococcus faecium*; *K. pneumoniae*, *Klebsiella pneumoniae*; *E. faecalis*, *Enterococcus faecalis*; *P. aeruginosa*, *Pseudomonas aeruginosa*; ESBL, extended-spectrum beta-lactamase-producing; ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.

Table 3 Distribution of Simple and Complicated UTIs Caused by Major Pathogens [Strains (%)]

Main Pathogenic Bacteria	Number of Strains	Simple UTIs	Complicated UTIs	χ^2	p-value
<i>E. coli</i>	432	276 (63.89)	156 (36.11)	6.17	0.013
<i>E. faecium</i>	173	107 (61.85)	66 (38.15)	0.39	0.531
<i>E. faecalis</i>	72	39 (54.17)	33 (45.83)	1.03	0.311
<i>K. pneumoniae</i>	93	56 (60.22)	37 (39.78)	0.01	0.925
<i>P. aeruginosa</i>	47	14 (29.79)	33 (70.21)	18.59	<0.001
Fungi	35	10 (28.57)	25 (71.43)	14.77	<0.001

Note: p-value was calculated by the Chi-square test.

Abbreviations: UTIs, Urinary tract infections; *E. coli*, *Escherichia coli*; *E. faecium*, *Enterococcus faecium*; *K. pneumoniae*, *Klebsiella pneumoniae*; *E. faecalis*, *Enterococcus faecalis*; *P. aeruginosa*, *Pseudomonas aeruginosa*.

Table 4 Distribution of Pathogenic Bacteria Among Children of Different Genders [Strains (%)]

Gram-Negative Bacteria	Boy (n = 534)	Girl (n = 431)	χ^2	p-value	Gram-Positive Bacteria	Boy (n = 534)	Girl (n = 431)	χ^2	p-value
E. coli	220	212	6.16	0.013	E. faecium	68	105	21.92	<0.001
K. pneumoniae	51	42	<0.01	0.919	E. faecalis	56	16	15.85	<0.001
P. aeruginosa	36	11	9.03	0.003	E. avium	2	7	4.03	0.045
P. mirabilis	17	5	4.38	0.036	S. epidermidis	3	0	0.07	0.792
M. morganii	9	0	7.33	0.007	Other Gram-positive bacteria	18	9	2.88	0.090
E. cloacae	6	2	1.26	0.261	Fungi	23	12	1.58	0.208
Other Gram-negative bacteria	25	9	4.72	0.030	Total	534	431	-	-

Note: p-value was calculated by the Chi-square test.

Abbreviations: E. coli, Escherichia coli; E. faecium, Enterococcus faecium; K. pneumoniae, Klebsiella pneumoniae; E. faecalis, Enterococcus faecalis; P. aeruginosa, Pseudomonas aeruginosa; E. avium, Enterococcus avium; S. epidermidis, Staphylococcus epidermidis; E. cloacae, Enterobacter cloacae; P. mirabilis, Proteus mirabilis; M. morganii, Morganella morganii.

Among the 965 strains of pathogenic bacteria, there were 534 strains in boys and 431 strains in girls, and the distribution of pathogens in different genders was different. Of the Gram-negative bacteria, the detection rates of *P. aeruginosa*, *Proteus mirabilis* and *Morganella morganii* in boys were significantly higher than girls, while *E. coli* was significantly lower. ($\chi^2 = 9.03, 4.38, 4.72, 6.16$, and $p = 0.003, 0.036, 0.008, 0.013$, respectively). Among Gram-positive bacteria, the detection rates of *E. faecium* and *E. avium* in girls were significantly higher than boys, but *E. faecalis* was obviously lower ($\chi^2 = 21.92, 4.03, 15.85$, and $p < 0.001, = 0.045, < 0.001$). There was no statistically significant difference in the sex distribution of fungal infection ($\chi^2 = 1.58, p = 0.208$) (Table 4).

Analysis of Drug Resistance of Main Pathogenic Bacteria

Among 855 urine culture-positive cases, the top five pathogenic bacteria were selected for drug sensitivity test, of which 36 strains of *E. coli* and 12 strains of *K. pneumoniae* were not tested for drug susceptibility. The resistance rate of *E. coli* to Ampicillin, Ampicillin sulbactam and Cefazolin was more than 50% (81.61%, 52.90% and 95.87%, respectively), followed by Cotrimoxazole and Ceftriaxone was 40% to 48.36%, and then Aztreonam and Ciprofloxacin was about 34%, Ceftazidime, Levofloxacin and Gentamicin was 20% to 30%, while Nitrofurantoin, Piperacillin tazobactam, Cefotetan, Tobramycin and Imipenem were all less than 10%. There were 190 strains of extended-spectrum β -lactamases (ESBL)-producing *E. coli* and 26 strains of (ESBL)-producing *K. pneumoniae*. The detection rate of (ESBL)-producing *E. coli* (47.86%, 190/397 vs 32.10%, 26/81) was significantly higher than that of (ESBL)-producing *K. pneumoniae* ($\chi^2 = 6.75, p = 0.009$). There was no significant difference between *E. coli* and *K. pneumoniae* in the resistance rate to Ampicillin sulbactam, Cotrimoxazole, Ciprofloxacin, Piperacillin tazobactam, Cefepime, Ceftriaxone, Ceftazidime, Cefazolin (all $p > 0.05$). The resistance rate of *K. pneumoniae* to Ampicillin, Nitrofurantoin and Cefotetan was significantly higher than that of *E. coli* (all $p < 0.05$), and both maintained a low resistance rate to Amikacin (1.51% and 1.23%, respectively) (Table 5).

P. aeruginosa drug sensitivity test showed (47 strains in total, with 1 strain had no drug sensitivity test) 100% resistance to Ampicillin (5/5), Ampicillin sulbactam (6/6), Cotrimoxazole (7/7), Ceftriaxone (46/46), and Cefazolin (5/5), followed by Nitrofurantoin 97.73% (43/44), Cefotetan 87.50% (7/8), Cefepime 6.52% (3/46), Levofloxacin 6.67% (3/45) and Amikacin 2.17% (2/46), and then Gentamicin, Piperacillin tazobactam, Ceftazidime, Tobramycin were all 4.35% (2/46). Two strains resistant to Cefoperazone sulbactam and 1 strain resistant to Meropenem.

Results of drug sensitivity test of main enterococci (13 strains of *E. faecalis* and 38 strains of *E. faecium* without drug sensitivity test) displayed, the resistance rates of *E. faecalis* to Ampicillin, Penicillin and Erythromycin were 6.78% (4/59), 10.34% (6/58) and 67.80% (40/59), respectively, as *E. faecium* were 98.52% (133/135), 98.52% (133/135) and 67.91% (91/135) to the above drugs, and both to Clindamycin were 100% (20/20, 61/61). No *E. faecalis* resistant to

Table 5 Antimicrobial Resistance Rate Analysis of *E. coli* and *K. pneumoniae* [Strains (%)]

Drugs	<i>E. coli</i>	<i>K. pneumoniae</i>	χ^2	p-value
Amikacin	6 (1.51)	1 (1.23)	0.03	0.850
Ampicillin	324 (81.61)	81 (100)	17.58	<0.001
Ampicillin sulbactam	210 (52.90)	43 (53.09)	0.01	0.975
Aztreonam	138 (34.76)	24 (29.63)	0.79	0.374
Ertapenem	1 (0.26) ^d	0 (0.00) ^e	0.20	0.656
Nitrofurantoin	7 (1.77) ^a	29 (35.80)	111.60	<0.001
Cotrimoxazole	177 (44.8) ^b	33 (40.74)	0.45	0.502
Ciprofloxacin	137 (34.6) ^a	21 (25.92)	2.28	0.131
Piperacillin tazobactam	3 (1.77) ^a	3 (3.70)	2.63	0.105
Gentamycin	119 (29.97)	12 (14.81)	7.77	0.005
Cefepime	59 (14.86)	13 (16.05)	0.07	0.785
Ceftriaxone	192 (48.36)	33 (40.74)	1.57	0.210
Ceftazidime	84 (21.16)	24 (29.62)	2.76	0.097
Cefotetan	9 (2.28) ^c	7 (8.75) ^f	6.60	0.010
Cefazolin	325 (95.87) ^e	62 (95.38) ^h	0.03	0.860
Tobramycin	29 (7.32) ^a	4 (4.94)	0.594	0.441
Imipenem	4 (1.01)	2 (2.47)	0.28	0.597
Levofloxacin	113 (28.61) ^b	9 (11.11)	10.80	0.001

Notes: p-value was calculated by the Chi-square test; ^a396 strains, ^b395 strains, ^c394 strains, ^d389 strains, ^e339 strains, ^f80 strains, ^g77 strains, ^h65 strains.

Abbreviations: *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*.

Nitrofurantoin, whereas *E. faecium* was 8.27% (11/135), and both not resistant to Tetracycline and Vancomycin. The resistance rates of *E. faecium* to Ampicillin, Gentamicin, Ciprofloxacin, Linezolid, Moxifloxacin, Penicillin and Levofloxacin were obviously higher than that of *E. faecalis*, while significantly lower to Tetracycline and Streptomycin (all $p < 0.05$). No statistically significant differences were observed in resistance rates to Nitrofurantoin and Erythromycin between the two species ($p > 0.05$) (Table 6).

Table 6 Comparison of Antimicrobial Resistance Rates Between *E. faecalis* and *E. faecium* [Strains (%)]

Drugs	<i>E. faecalis</i> (n = 59)	<i>E. faecium</i> (n = 135)	χ^2	p-value
Ampicillin	4 (6.78)	133 (98.52)	166.5	<0.001
Nitrofurantoin	0 (0.00)	11 (8.27)	3.69	0.055
High concentration streptomycin	16 (27.59) ^e	10 (7.52) ^b	13.83	<0.001
High concentration gentamicin	24 (41.38) ^e	81 (60.45) ^a	5.94	0.015
Erythromycin	40 (67.80)	91 (67.91) ^a	<0.01	0.988

(Continued)

Table 6 (Continued).

Drugs	<i>E. faecalis</i> (n = 59)	<i>E. faecium</i> (n = 135)	χ^2	p-value
Ciprofloxacin	9 (15.25)	112 (82.96)	80.20	<0.001
Clindamycin	20 (100) ^g	61 (100) ^d	-	-
Linezolid	0 (0.00) ^f	128 (99.22) ^c	175.20	<0.001
Moxifloxacin	9 (15.25)	110 (82.09) ^a	77.40	<0.001
Penicillin	6 (10.34) ^e	133 (98.52)	156.50	<0.001
Tetracycline	54 (91.53)	66 (49.25) ^a	31.13	<0.001
Tigecycline	0 (0.00)	0 (0.00) ^a	-	-
Vancomycin	0 (0.00)	0 (0.00)	-	-
Levofloxacin	9 (15.25)	105 (77.78)	66.23	<0.001

Notes: p-value was calculated by the Chi-square test; ^a134 strains, ^b133 strains, ^c129 strains, ^d61 strains, ^e58 strains, ^f51 strains, ^g20 strains.

Abbreviations: *E. faecalis*, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*.

Distribution of Pathogenic Bacteria and Urine pH

Total 965 strains pathogens were isolated from urine culture, including 644 Gram-negative bacteria, 286 Gram-positive bacteria and 35 Fungi. Comparing the urine pH of the three pathogenic bacteria, there was no significant difference between Gram-negative bacteria and Gram-positive bacteria ($p > 0.05$), while the urine pH of Fungal infections was obviously acidic ($p < 0.05$) (Table 7).

Table 7 Distribution of Pathogenic Bacteria and Urine pH (n = 965 Strains)

Pathogens	Number of Strains	Composition Ratio (%)	Urine pH ($\bar{X} \pm S$)
Gram-Negative Bacteria	644	66.74	6.45 \pm 0.81
<i>E. coli</i>	432	44.77	6.44 \pm 0.51
<i>K. pneumoniae</i>	92	9.53	6.47 \pm 0.52
<i>P. aeruginosa</i>	46	4.77	6.42 \pm 0.44
<i>P. mirabilis</i>	21	2.18	6.51 \pm 0.56
Other Gram-Negative Bacteria	53	5.49	6.48 \pm 0.58
Gram-Positive Bacteria	286	29.64	6.41 \pm 0.44
<i>E. faecium</i>	173	17.93	6.42 \pm 0.42
<i>E. faecalis</i>	72	7.46	6.43 \pm 0.48
<i>E. avium</i>	8	0.83	6.49 \pm 0.36
<i>S. epidermidis</i>	6	0.62	6.52 \pm 0.43
Other Gram-Positive Bacteria	27	2.80	6.49 \pm 0.49

(Continued)

Table 7 (Continued).

Pathogens	Number of Strains	Composition Ratio (%)	Urine pH ($\bar{X} \pm S$)
Fungi	35	3.62	6.39 \pm 0.44
Candida	26	2.69	6.32 \pm 0.45
Other fungi	9	0.93	6.27 \pm 0.38

Note: p-value was calculated by the Chi-square test.

Abbreviations: E. coli, Escherichia coli; E. faecium, Enterococcus faecium; K. pneumoniae, Klebsiella pneumoniae; E. faecalis, Enterococcus faecalis; P. aeruginosa, Pseudomonas aeruginosa; E. avium, Enterococcus avium; S. epidermidis, Staphylococcus epidermidis; P. mirabilis, Proteus mirabilis.

Discussion

Urinary tract infections is a common disease in children's urinary system, which is second only to respiratory tract infection in pediatric infectious diseases.⁷ Our study showed that the incidence of UTIs in children varied greatly at different ages, and the proportion of children aged 28d~1 year was much higher than other ages, accounting for 66.67%, with higher percentage in boys (55.09% vs 44.91%) than girls, which suggests that this age is the high prevalence of UTIs in children with a gender difference. In addition, clinical symptoms of acute UTIs vary markedly in children of different ages. Fever is the most common clinical manifestation, accounting for 65.5% of children with positive urine culture. Older children may be accompanied by typical urinary tract irritation such as urinary frequency, urgency, pain, or abnormal urination, while younger children usually lack typical symptoms and signs, especially small babies, sometimes only fever, or accompanied by non-specific symptoms such as abdominal distention, diarrhea, crying, lethargy, convulsions, feeding difficulties, jaundice, and developmental delay.⁸⁻¹⁰ As a result, it is easy to be overlooked clinically, therefore, clinicians should pay more attention to the presence of underlying UTIs in this group of children.

Pathogenetic results demonstrated that gram-negative bacteria and enterococci were the most common pathogens of UTIs in children in Xiamen, with E. coli ranked first, which was similar to Yu Lingfang's literature report, followed by Enterococcus, K. pneumoniae and P. aeruginosa.¹¹ Drug sensitivity test showed that E. coli maintained low resistance to Piperacillin tazobactam and Nitrofurantoin (both less than 5%), and could be considered as empirical drugs, while Ampicillin and Ampicillin sulbactam were 52.89% to 81.61%. There were differences in the resistance rates of the three generations of Cephalosporin, with Cefazidime 21.16%, Ceftriaxone 48.36%, but it was sensitive to Cefotetan. Although Ciprofloxacin and Levofloxacin are not commonly used in children, the resistance rates are up to 28.61%~34.6%, which is similar to the reports of E. coli to Ciprofloxacin in Shanghai, Panzhihua, and foreign areas (33.8%, 39.29% and 36%, respectively).¹²⁻¹⁴ Therefore, attention should be paid to the selection of antibiotics. Both E. coli and K. pneumoniae maintained low resistance rates to Amikacin, similar to the results of the Kim and Huang studies.^{15,16} Followed by Gentamicin 29.97% and 14.81%, respectively, which was related to the presence of ear and renal toxicity side effects of aminoglycosides, and were less used in China. Although the detection rate of K. pneumoniae was much lower than that of E. coli, its resistance rate to Ampicillin reached 100%, and obviously higher to Nitrofurantoin than that of E. coli. In addition, displayed 40.74%~95.38% to Ceftriaxone and Cefazolin, which was similar to the studies in some foreign areas.^{17,18} Therefore, antibiotic options are more limited in K. pneumoniae infection. There was a significant difference in the resistance rate to Ampicillin between E. faecium and E. faecalis (98.52% vs 6.78%). The low resistance rate of E. faecalis to Ampicillin may be related to the fact that it is not the first choice for E. faecalis infection. No Vancomycin-resistant enterococci have been found, so it can be considered for critical children with enterococcal infection, however, Vancomycin has hepatorenal toxicity, and a small number of Vancomycin-resistant strains have been found in some areas.¹⁹ Consequently, clinicians should strictly grasp the indications of the drug to prevent the emergence of drug-resistant bacteria. Both E.coli and gram-positive bacteria exhibit low resistance rate to Nitrofurantoin, and the drug maintains high concentrations in urine, orally convenient and cost-effective. Therefore, it can be considered as the first choice of treatment or later sequential therapy for children with UTIs caused by these pathogens. P. aeruginosa displayed

100% resistance to Ampicillin, Ampicillin sulbactam, Cefazolin, Ceftriaxone and Cotrimoxazole, followed by Nitrofurantoin (97.73%). While less than 10% to Ceftazidime, Cefepime, and Piperacillin tazobactam, which can be used as clinical empirical drugs for *P. aeruginosa*.

Enterobacteriaceae are the primary pathogens responsible for UTIs in children. According to a recent global survey, approximately 50% of participating medical centers reported that more than 10% of infant UTIs were caused by ESBL-producing Enterobacteriaceae (ESBL-E), highlighting the growing challenge of antibiotic resistance in clinical practice. Our research shows that the positivity rate of ESBL among pathogens of UTI in single-center children in Xiamen is 22.18% (214/965), and ESBL-E accounts for 19.27% (186/965). The frequency of ESBL-E-related UTIs varies by region. Among the 226 centers surveyed: 48.2% (109 centers) estimated that $\leq 10\%$ of UTIs were caused by ESBL-E, 34.1% (77 centers) reported a prevalence of 11–20%, 17.7% (40 centers) observed rates exceeding 20%. Notably, centers in Asia, the Middle East, and Africa had a significantly higher proportion of cases ($>20\%$) compared to other regions ($p < 0.01$). The selection of initial antibiotic therapy was influenced by local ESBL-E prevalence. In centers with high ESBL-E rates ($>20\%$), third-generation cephalosporins were the preferred choice (65.0%, 26/40). Their usage decreased in areas with lower prevalence: 44.2% (34/77) in the 11–20% group and 31.2% (34/109) where ESBL-E rates were below 10%. Conversely, penicillin combined with β -lactamase inhibitors was more commonly prescribed in centers with lower ESBL-E prevalence: 28.4% (31/109) for $<10\%$, 14.3% (11/77) for 11–20%, and only 7.5% (3/40) for $>20\%$ ($p = 0.018$). Although second- and third-generation cephalosporins are the most commonly prescribed first-line antibiotics (used in $>60\%$ of cases), ESBL-E bacteria show *in vitro* resistance to them. This antibiotic selection pressure encourages the proliferation of ESBL-resistant clones, driving the growing incidence of ESBL-E-related UTIs.²⁰

Although this study showed resistance to third-generation cephalosporins (eg, ceftriaxone) *in vitro*, previous studies have shown that some pediatric patients with ESBL-UTI may still have a good clinical response to cephalosporin therapy and do not necessarily need to upgrade to carbapenems (eg, meropenem).^{21–24} This difference may be due to higher concentrations of antibiotics in the urine (eg, ceftriaxone in urine far exceeding plasma MIC values) or the influence of host immune factors. Even if the drug is allergic to ESBL, if the child has mild clinical symptoms (no fever and hemodynamic stability), oral fosfomycin, nitrofurantoin, or amoxicillin-clavulanic acid (if sensitive) may be considered rather than direct carbapenems. In the presence of sepsis, urinary tract malformations, or immunocompromised, a combination of carbapenems or β -lactamase inhibitors based on susceptibility is still recommended.

Currently, the optimal treatment option for ESBL-UTI is still controversial. Some studies support a selective deescalation' strategy (ie, adjusting treatment based on clinical response rather than drug sensitivity alone), while others emphasize "precision medication" (avoiding treatment failure based on drug sensitivity). This study found that the positive rate of ESBL in Xiamen was high (22.18%), but clinicians still need to make comprehensive judgments based on the individual conditions of the children (such as age, comorbidities, and severity of infection) rather than relying solely on *in vitro* drug susceptibility results.

Our study showed that the proportion of urinary tract structural abnormalities was 31.93%. Compared with simple UTIs, conditional pathogenic bacteria caused a significantly higher proportion of complicated UTIs, especially *P. aeruginosa* (70.21%, $p < 0.001$) and fungi (71.43%, $p < 0.001$), suggesting that attention should be paid to *P. aeruginosa* and fungi in the treatment of complicated UTIs, and empirically select more targeted antibiotics or antifungals. Since *P. aeruginosa* and fungi can produce a variety of different bacterial toxins and have high rates of drug resistance, it is necessary to be highly vigilant for the production of drug-resistant bacteria in abnormal urinary tract structure or the widespread use of antibiotics. In addition, actively improving imaging examinations such as urological ultrasound, MR, and excretory urography are of indispensable significance for the diagnosis of urinary tract structural malformations, especially for low-age children with UTIs.

Urine is a good medium for pathogenic bacteria. Urine pH reflects the ability of the kidneys to regulate the acid-base balance of body fluids, and its small changes can create conditions for pathogenic bacterial infection. Differences in urine pH corresponding to UTIs caused by different pathogenic bacteria.^{25–27} This study showed that urine pH of gram-negative bacteria and gram-positive bacteria were roughly the same, and there was no significant difference between them, whereas fungal urine pH was obviously more acidic, which is statistically significant compared with the above two bacterial profiles. Both *E. coli* and *Enterococcus* can produce acid, can tolerate a certain degree of acid and alkali, and

can survive in normal urine, while fungi like acid and can ferment sugars to produce acid. Therefore, the acidic environment of urine is a high-risk factor for fungal UTIs. Studies have shown that children with diabetes are more likely to cause acidic urine environment, which is a risk factor for fungal UTIs, so they should be more vigilant for fungal UTIs. Different pathogenic bacteria have different urine pH in children with UTIs, mainly affected by the nature of food, for meat eaters, protein decomposition produces phosphate excreted with the urine and making the urine acidic, while vegetarians excrete more bases, so the urine is alkaline. Urine has an inhibitory effect on bacterial growth, the inhibition is more pronounced, especially when urine pH is low. Significantly inhibited the proliferation of *E. coli* and significantly down-regulated the expression of *E. coli* virulence factors papC, fimH, and hlyA proteins when urine pH was below 5.0.²⁸ Research had showed that Ciprofloxacin and Fosfomycin had different MIC distributions against *E. coli* and *K. pneumoniae* in Miller-Hinton broth (MHB) and urine at different pH (5, 7, 8), and different antibacterial and bactericidal activities against isolated strains, and acidic urine was associated with symptomatic UTIs episodes caused by *E. coli*.²⁹ The sensitivity of pathogenic bacteria to antibiotics can be changed by regulating urine pH.³⁰ Therefore, adjusting urine pH according to the detected causative organisms can achieve the optimal effect of inhibiting the growth of the causative organisms, so as to improve the therapeutic effect of UTIs in children.³¹

This study retrospectively analyzed the composition and drug resistance rate of common pathogens in children with UTIs in Xiamen Children's Hospital, clarified the pathogenic bacteria of UTIs and their drug resistance, and provided a reference for the selection of clinical antibacterial drugs for children with UTIs in the region. However, there are differences in the composition and drug resistance of pathogenic bacteria in different regions, sensitive antibiotics should be reasonably selected according to the local pathogenic bacteria spectrum to effectively control infection as soon as possible and reduce the production of drug-resistant bacteria. In addition, dynamic monitoring of the distribution, migration and drug resistance of pathogenic bacteria provides reliable guidance for clinical drug use.³²

Our study has several limitations. First, this study was a retrospective study, there were inherent flaws in the retrospective design (such as reliance on medical records, inability to control for confounding factors such as antibiotic use history), medical records may be incomplete or inaccurate. We adopt data quality control methods such as standardized data extraction processes, exclusion of cases with missing key information (eg, lack of urine routine, urine culture), and dual data entry and logical verification to reduce recording errors in the process of collecting clinical data to ensure data integrity and accuracy. Furthermore, this study is a single-center retrospective study in Xiamen. The research results can only partially explain the characteristics of children's UTI in this region. It is not universal and cannot represent the characteristics of children's UTI in other regions. In the future, multi-regional and multi-center research will be needed to obtain more representative research results. Thirdly, the study was single-center data, and the sample size of certain age groups is small, which may affect the effectiveness of subgroup analysis. Lastly, the initial treatment of some children was outside the hospital, and the use of antibiotics was not provided at the time of admission. Some urine cultures lacked drug sensitivity tests and could not be analyzed for the correlation of antibiotic resistance.

Conclusion

The pathogens of UTIs in Xiamen are different and diverse, and the distribution of pathogens among children of different genders are different. Gram-negative bacteria are still the main pathogens of UTIs in children. Nitrofurantoin could be the priority drug for mild or lower UTIs. This study provides important data on the pathogenesis and drug resistance of UTIs in children in Xiamen, but clinical treatment decisions should be made based on in vitro drug sensitivity, clinical manifestations of children and local epidemiology to avoid over-reliance on carbapenems to reduce the further spread of drug resistance.

Ethical Information

The Scientific Ethics Committee of Xiamen Children's Hospital approved this study (Approval No. Xiamen Pediatrics Lun Shen [2024] No. 91). All guardians of the study participants have signed a "Letter to Parents of Children" at the time of hospitalization, in which section 13 informs them that clinically relevant information about the child during hospitalization may be used for scientific research. Before the examination, patient data was anonymized. The Declaration of Helsinki's guiding principles were followed in this investigation.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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