Pediatric Urinary Tract Infections: Pathogen Prevalence, Antibiotic Susceptibility, and Cost-Effectiveness Analysis in a Tertiary Medical Center in Israel

Adir Alper MD MHA[1], Gadeer Jomaa Khateb MD[3], Edvin Konikov MD[4], and Eden Amir MD MSc MHA[2]

[1]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[2]Department of Management, Bar-Ilan University, Ramat Gan, Israel
[3]Department of Pediatrics, Galilee Medical Center, Nahariya, Israel
[4]Third Faculty of Medicine, Charles University, Prague, Czech Republic

ABSTRACT **Background:** Pediatric urinary tract infections (UTIs) are a significant health concern, with rising antibiotic resistance complicating treatment decisions. We investigated pathogen distribution, antibiotic susceptibility patterns, and the cost-effectiveness of treatment options among hospitalized children at a tertiary medical center in Israel.

Objectives: To assess antibiotic susceptibility patterns of UTI pathogens in hospitalized children and evaluate cost-effective alternatives to gentamicin.

Methods: A retrospective analysis of 1649 pediatric UTI cases (January 2010–May 2022) at Galilee Medical Center examined patient demographics, urine culture results, and antibiotic susceptibility. A cost-effectiveness analysis was performed using incremental cost-effectiveness ratios (ICERs), based on susceptibility rates from the study and antibiotic costs from the Israel Ministry of Health, with gentamicin as the comparator.

Results: *Escherichia coli* was the most common pathogen (63.7%). High susceptibility rates were observed for carbapenems and amikacin (> 99%), with lower rates for gentamicin (91.7%) and ceftriaxone (87.6%). Treatment costs ranged from US$2.54 (trimethoprim/sulfamethoxazole) to US$307.80 (ertapenem). Fosfomycin demonstrated higher susceptibility than gentamicin (94.2% vs 91.7%) and lower cost (US$3.77 vs US$8.05), dominating gentamicin in cost-effectiveness analysis. Piperacillin/tazobactam and ceftriaxone were dominated by gentamicin in terms of cost-effectiveness.

Conclusions: *E. coli* was the predominant pathogen in pediatric UTIs among hospitalized children. Carbapenems and amikacin showed high susceptibility but were costly. Fosfomycin demonstrated high susceptibility, favorable cost-effectiveness, and the advantage of oral administration, making it a promising option for empiric treatment. Empiric antibiotic selection should integrate susceptibility patterns, clinical context, and economic considerations.

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KEY WORDS: antibiotic susceptibility, cost-effectiveness, fosfomycin, gentamicin, pediatric urinary tract infection (UTI)

Pediatric urinary tract infections (UTIs) are predominantly caused by *Escherichia coli*, accounting for approximately 80% of cases. Risk factors include bowel and bladder dysfunction, anatomical abnormalities, and female gender [1]. Diagnosis relies on obtaining an uncontaminated urine sample, with urine culture serving as the gold standard [2]. Treatment typically involves a 7- to 10-day course of appropriate antibiotics, tailored to local resistance patterns, with options like cephalexin and parenteral agents like gentamicin [3]. However, gentamicin, an aminoglycoside antibiotic, although commonly used in the treatment of pediatric UTIs, is associated with side effects such as nephrotoxicity, ototoxicity and neurological effects [4]. Studies indicate that nephrotoxicity may affect 20–33% of pediatric patients receiving aminoglycosides [5], necessitating careful monitoring of renal function [6].

Long-term complications of UTIs in children include renal scarring, hypertension, and end-stage renal disease, particularly when infections are misdiagnosed or inadequately treated [7]. The risk is especially high in infants and young children, where symptoms may be nonspecific and often manifest as unexplained fever [8]. These risks emphasize the importance of effective management and prophylaxis in high-risk patients [3].

Cost-effectiveness analysis (CEA) is a critical tool in healthcare decision-making, enabling the comparison of medical interventions based on both costs and effectiveness. By incorporating a societal perspective and evaluating total costs and health outcomes, CEA helps clinicians and policymakers optimize the value of care and inform policy in an increasingly cost-conscious healthcare environment [9].

The primary aims of this study were to demonstrate the current susceptibility patterns of UTI-causing pathogens in hospitalized children in Israel and to conduct a

cost-effectiveness analysis of the tested antibiotics. By exploring antibiotic susceptibility, we identified potential alternatives to gentamicin. Conducting a CEA using Incremental Cost-Effectiveness Ratio (ICER) will provide insights into the economic implications of different treatment options, aiding healthcare management in making informed resource allocation decisions.

PATIENTS AND METHODS

This retrospective study included pediatric patients hospitalized with UTIs at the Galilee Medical Center between January 2010 and May 2022. Inclusion criteria included patients younger than 18 years with a positive urine culture obtained in the emergency department. Exclusion criteria included patients 18 years of age or older, patients with a positive pregnancy history, patients who received empiric antibiotic treatment before urine culture collection,and patients without bacterial growth in urine culture.

Data were collected from medical records and laboratory results, and were anonymized to protect patient privacy, with the identities of patients represented by ascending serial numbers. Collected data included age, method of urine sample collection, culture results, and antibiotic susceptibility.

Antibiotic susceptibility was assessed according to CLSI M100 standards (32nd ed., 2022), classifying pathogens as susceptible, intermediate, or resistant based on MIC thresholds. Antibiotic costs were obtained from the Israel Ministry of Health's price list (as of 1 July 2024) and converted to US$ using the exchange rate on that date [10]. The analysis considered the least expensive generic alternatives and assumed a full treatment course for a 20 kg child.

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in cost between two antibiotics by the difference in their effectiveness, as measured by susceptibility rates, using gentamicin as comparator. The formula used was:

$$\frac{\text{cost of antibiotic 2} - \text{cost of antibiotic 1}}{\text{\% susceptibility of antibiotic 2} - \text{\% susceptibility of antibiotic 1}}$$

Descriptive statistics were used to summarize baseline characteristics, with continuous data described using mean and standard deviation, and categorical data described using frequencies and percentages. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25.0 (SPSS, IBM Corp, Armonk, NY, USA).

The study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the institutional review board at the Galilee Medical Center. Patient confidentiality was maintained throughout the study.

Table 1. Pathogen prevalence and distribution by age group

Pathogen	< 1 year	1–5 years	5–12 years	12–18 years	Frequency (N=1649)	Percent (%)
Escherichia coli	58.81% (444)	73.02% (314)	70.93% (205)	49.71% (87)	1050	63.7
Enterococcus faecalis	13.77% (104)	5.35% (23)	5.88% (17)	9.14% (16)	160	9.7
Klebsiella	11.92% (90)	6.05% (26)	5.88% (17)	8.00% (14)	147	8.9
Proteus mirabilis	3.84% (29)	5.81% (25)	3.11% (9)	12.00% (21)	84	5.1
Pseudomonas aeruginosa	3.05% (23)	5.12% (22)	5.88% (17)	2.29% (4)	66	4
Enterobacter	2.52% (19)	1.63% (7)	1.04% (3)	2.86% (5)	34	2.1
Citrobacter	2.12% (16)	0.23% (1)	0.35% (1)	1.71% (3)	21	1.3
Staphylococcus aureus	1.72% (13)	0.23% (1)	0.69% (2)	2.86% (5)	21	1.3
Acinetobacter	0.93% (7)	0.00% (0)	1.04% (3)	1.14% (2)	12	0.7
Coagulase-negative staphylococci	0.66% (5)	2.09% (9)	4.15% (12)	6.29% (11)	37	2.2
Streptococcus agalactiae (Group B)	0.66% (5)	0.47% (2)	1.04% (3)	4.00% (7)	17	1
Total isolates	755	430	289	175	1649	100

RESULTS

A total of 1649 pediatric patients met the inclusion criteria. The ages of the patients ranged from 4 days to 18 years, with an average age of 4.1 ± 5.5 years. Urine samples were collected using different methods: mid-stream collection in 1035 cases (62.2%), catheterization in 572 cases (34.4%), suprapubic aspiration in 43 cases (2.6%), nephrostomy in 11 cases (0.7%), and cystoscopy in 3 cases (0.2%). The distribution of isolates by age group was as follows: < 1 year (45.8%, 755 isolates), 1–5 years (26.1%, 430 isolates), 5–12 years (17.5%, 289 isolates), and 12–18 years (10.6%, 175 isolates). Most isolates originated from children under 1 year, reflecting a higher incidence of infections or sampling in this age group.

Table 1 summarizes pathogen distribution. *E. coli* predominated (63.7%, 1050), followed by *Enterococcus faecalis* (9.7%), *Klebsiella* (8.9%), and *Proteus mirabilis* (5.1%).

Pathogen distribution across age groups is detailed in Table 1. *E. coli* was the predominant pathogen in all groups, peaking in the 1–5 year group (73.02%, 314 isolates) and lowest among adolescents aged 12–18 years (49.71%, 87 isolates). *E. faecalis* was more frequently isolated in infants under 1 year (13.77%, 104 isolates) compared to older groups. *P. mirabilis* showed an increase in the 12–18 years group (12.00%, 21 isolates), while the prevalence of coagulase-negative staphylococci rose with age, reaching 6.29% (11 isolates) in adolescents.

The antibiotic susceptibility results are summarized in Table 2. High susceptibility rates were observed for carbapenems (> 99%) and amikacin (99.4%), with lower rates for gentamicin (91.7%) and ceftriaxone 87.6%.

Table 3 details pathogen-specific susceptibility. *E. coli* (63.7%) showed high susceptibility to ertapenem, meropenem, amikacin (> 99%), and fosfomycin (98.8%), but lower to gentamicin (92.0%) and ceftriaxone (88.2%). *E. faecalis* (9.7%) was highly susceptible to carbapenems, amikacin, and nitrofurantoin (> 94%). *Klebsiella* (8.9%) had high susceptibility to ertapenem and amikacin (≥ 98%), less to ceftriaxone (79.3%). *P. mirabilis* (5.1%) and *Pseudomonas aeruginosa* (4.0%) showed strong susceptibility to amikacin and meropenem (> 96%).

The cost-effectiveness analysis is summarized in Table 4. Antibiotic treatment costs varied widely, ranging from $2.54 (trimethoprim/sulfamethoxazole) to $307.80 (ertapenem). Fosfomycin demonstrated dominance over gentamicin, being both more effective and less costly. Broad-spectrum agents such as ertapenem and meropenem had higher costs and marginal increases in effectiveness. Several antibiotics, including ceftriaxone and piperacillin/tazobactam, were dominated, being more expensive and less effective than gentamicin.

Table 2. Antibiotic susceptibility rates

Antibiotic	N	Susceptible (%)	Resistant (%)	Intermediate (%)
Ertapenem	1381	99.7	0.1	0.2
Meropenem	1194	99.5	0.4	0.1
Amikacin	1458	99.4	0.3	0.3
Fosfomycin	565	94.2	5.8	0.0
Gentamicin	1514	91.7	7.9	0.4
Piperacillin/ tazobactam	1443	90.9	2.9	6.2
Ciprofloxacin	1648	89.7	8.2	2.1
Ceftazidime	1459	87.9	11.6	0.5
Ceftriaxone	1403	87.6	12.1	0.3
Nitrofurantoin	1462	82.4	7.6	10.1
Cefuroxime	1337	80.3	16.1	3.6
Cephalexin	158	79.7	20.3	0.0
Cefazolin	205	78.0	19.0	2.9
Trimethoprim/ Sulfa	1497	74.6	25.4	0.0
Amoxicillin/ clavulanic acid	1329	73.3	11.4	15.3
Ampicillin	1484	40.4	59.4	0.5

DISCUSSION

In this study, we assessed pathogen distribution, antibiotic susceptibility, and cost-effectiveness of treatments in hospitalized pediatric UTI patients. Understanding local susceptibility profiles is essential for guiding empiric therapy, while cost-effectiveness analysis supports informed antibiotic selection, particularly in resource-limited settings.

E. coli was the predominant pathogen across all age groups, consistent with existing literature [1], peaking at 73.0% in the 1–5 years group, likely due to environmental exposure in daycare settings, and declining in adolescents, possibly reflecting improved immunity. *E. faecalis* was more common in neonates, suggesting healthcare-associated infections, while *P. mirabilis* became more prominent in older children, potentially linked to complicated UTIs. These trends support tailoring empiric antibiotic therapy by age group.

Table 3. Antibiotic susceptibility by pathogen

Pathogen / antibiotic	CIP	GEN	NIT	TMP/S	AMI	AMC	AMP	CAZ	CRO	CXM	ETP	MEM	TZP	FOS	LEX	ZOL
Escherichia coli	939/1054 (89.1%)	969/1053 (92.0%)	928/979 (94.8%)	763/1054 (72.4%)	1050/1052 (99.8%)	754/1030 (73.2%)	377/1053 (35.8%)	931/1055 (88.2%)	930/1055 (88.2%)	853/1026 (83.1%)	1054/1054 (100.0%)	879/879 (100.0%)	955/1049 (91.0%)	424/429 (98.8%)	88/108 (81.5%)	120/143 (83.9%)
Enterococcus faecalis	147/160 (91.9%)	27/30 (90.0%)	145/154 (94.2%)	22/28 (85.7%)	30/30 (100.0%)	17/28 (60.7%)	138/156 (88.5%)	25/30 (83.3%)	24/28 (85.7%)	17/28 (60.7%)	28/28 (100.0%)	21/21 (100.0%)	27/29 (93.1%)	13/18 (72.2%)	NT	NT
Klebsiella	133/147 (90.5%)	125/147 (85.0%)	39/131 (29.8%)	123/147 (83.7%)	144/147 (98.0%)	113/138 (81.9%)	5/146 (3.4%)	117/147 (79.6%)	115/145 (79.3%)	104/135 (77.0%)	144/144 (100.0%)	105/106 (99.1%)	127/146 (87.0%)	46/55 (83.6%)	18/21 (85.7%)	22/29 (75.9%)
Proteus mirabilis	78/85 (91.8%)	81/85 (95.3%)	2/76 (2.6%)	73/85 (85.9%)	85/85 (100.0%)	59/62 (95.2%)	44/85 (51.8%)	84/85 (98.8%)	83/85 (97.6%)	78/81 (96.3%)	81/84 (96.4%)	68/69 (98.6%)	84/85 (98.8%)	31/34 (91.2%)	15/16 (93.8%)	11/13 (84.6%)
Pseudomonas aeruginosa	63/66 (95.5%)	62/66 (93.9%)	NT	1/37 (2.7%)	64/66 (97.0%)	NT	NT	61/65 (93.8%)	NT	NT	NT	59/61 (96.7%)	57/60 (95.0%)	NT	NT	NT
Coagulase-negative staph	33/37 (89.2%)	34/36 (94.4%)	35/36 (97.2%)	34/36 (94.4%)	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Enterobacter	33/35 (94.3%)	33/35 (94.3%)	9/33 (27.3%)	30/35 (85.7%)	35/35 (100.0%)	4/35 (11.4%)	NT	26/34 (76.5%)	26/35 (74.3%)	3/34 (8.82%)	32/33 (97.0%)	26/26 (100.0%)	27/34 (79.4%)	10/15 (66.7%)	NT	1/10 (10.0%)
Citrobacter	21/28 (75.0%)	27/28 (96.4%)	18/22 (81.8%)	26/28 (92.9%)	28/28 (100.0%)	21/24 (87.5%)	NT	27/28 (96.4%)	26/28 (92.9%)	13/24 (54.2%)	28/28 (100.0%)	21/21 (100.0%)	27/28 (96.4%)	NT	NT	NT
Staphylococcus aureus	20/21 (95.2%)	21/21 (100%)	21/21 (100.0%)	21/21 (100.0%)	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Streptococcus agalactiae	NT	NT	NT	15/15 (100.0%)	NT	NT	16/17 (94.1%)	NT	16/16 (100%)	NT	NT	NT	NT	NT	NT	NT
Acinetobacter	9/12 (75.0%)	9/12 (75.0%)	NT	9/11 (81.8%)	10/12 (83.3%)	NT	NT	9/12 (75.0%)	NT	NT	NT	NT	NT	NT	NT	NT

CIP = ciprofloxacin, GEN = gentamicin, NIT = nitrofurantoin, TMP/S = trimethoprim/sulfamethoxazole, AMI = amikacin, AMC = amoxicillin/clavulanic acid, AMP = ampicillin, CAZ = ceftazidime, CRO = ceftriaxone, CXM = cefuroxime, ETP = ertapenem, MEM = meropenem, TZP = piperacillin/tazobactam, FOS = fosfomycin, LEX = cephalexin, ZOL = cefazolin

*Results with fewer than 10 valid entries (S = sensitive, I = intermediate, R = resistant) were marked as not tested (NT) and excluded

Carbapenems and amikacin were highly effective (> 99% susceptibility), while fosfomycin (94.2%) offered high susceptibility and oral administration benefits, outperforming gentamicin (91.7%) and ceftriaxone (87.6%). Oral fosfomycin, although not routinely used, has achieved clinical success in complicated UTIs, including pyelonephritis [11], and intravenous fosfomycin demonstrated superior microbiological eradication compared to piperacillin-tazobactam [12].

Across pathogens, carbapenems and amikacin consistently exhibited high susceptibility, while agents like ampicillin and cefuroxime showed variable effectiveness, emphasizing the need for pathogen-specific antibiotic selection.

Compared to a study from Diyarbakır, Turkey [13], our cohort had lower *E. coli* prevalence (63.7% vs. 85.8%) but higher ceftriaxone susceptibility (88.2% vs. 72.8%). Fosfomycin and amikacin showed similar high susceptibility in both. Our cohort also showed higher *Klebsiella* susceptibility to ceftriaxone (79.3% vs. 58%) and piperacillin-tazobactam (87.0% vs. 73.1%), underscoring the importance of local antibiograms to guide empiric therapy.

The ICER analysis evaluated the economic impact of antibiotic choices, balancing cost with clinical effectiveness. Gentamicin was selected as the reference due to its widespread use, urinary efficacy, and high susceptibility

Table 4. Cost and cost-effectiveness analysis

Antibiotic treatment	Cost per treatment in ₪	Cost per treatment in US$	ICER Δ cost of treatment in US$ / Δ antibiotic susceptibility	Interpretation vs. gentamicin
Ertapenem	1121.62₪	$307.80	$\frac{(307.8-8.05)}{99.7-91.7}=\frac{299.75}{8}=\mathbf{37.47}$	Higher cost, higher effectiveness
Piperacillin/ tazobactam	371.89₪	$102.06	$\frac{(102.06-8.05)}{90.9-91.7}=\frac{94.01}{-0.8}=\mathbf{-117.51}$	Dominated
Meropenem	337.06₪	$92.50	$\frac{(92.5-8.05)}{99.5-91.7}=\frac{84.45}{7.8}=\mathbf{10.83}$	Higher cost, higher effectiveness
Nitrofurantoin	278.53₪	$76.44	$\frac{(76.44-8.05)}{82.4-91.7}=\frac{68.39}{-9.3}=\mathbf{-7.35}$	Dominated
Ceftazidime	229.92₪	$63.10	$\frac{(63.1-8.05)}{87.9-91.7}=\frac{55.05}{-3.8}=\mathbf{-14.49}$	Dominated
Ceftriaxone	178.04₪	$48.86	$\frac{(48.86-8.05)}{87.6-91.7}=\frac{40.81}{-4.1}=\mathbf{-9.95}$	Dominated
Amikacin	94.52₪	$25.94	$\frac{(25.94-8.05)}{99.4-91.7}=\frac{17.89}{7.7}=\mathbf{2.32}$	Higher cost, higher effectiveness
Cefazolin	64.94₪	$17.82	$\frac{(17.82-8.05)}{78-91.7}=\frac{9.77}{-13.7}=\mathbf{-0.71}$	Dominated
Ampicillin	63.8₪	$17.51	$\frac{(17.51-8.05)}{40.4-91.7}=\frac{9.46}{-51.3}=\mathbf{-0.18}$	Dominated
Gentamicin	29.35₪	$8.05	–	Reference
Amoxicillin/clavulanic acid	20.51₪	$5.63	$\frac{(5.63-8.05)}{73.3-91.7}=\frac{-2.42}{-18.4}=\mathbf{0.13}$	Lower cost, lower effectiveness
Ciprofloxacin	16.97₪	$4.66	$\frac{(4.66-8.05)}{89.7-91.7}=\frac{-3.39}{-2}=\mathbf{1.70}$	Lower cost, lower effectiveness
Cefuroxime	14.18₪	$3.89	$\frac{(3.89-8.05)}{80.3-91.7}=\frac{-4.16}{-11.4}=\mathbf{0.36}$	Lower cost, lower effectiveness
Fosfomycin	13.73₪	$3.77	$\frac{(3.77-8.05)}{94.2-91.7}=\frac{-4.28}{2.5}=\mathbf{-1.71}$	Dominates gentamicin
Cephalexin	10.15₪	$2.79	$\frac{(2.79-8.05)}{79.7-91.7}=\frac{-5.26}{-12}=\mathbf{0.44}$	Lower cost, lower effectiveness
Trimethoprim/ Sulfamethoxazole	9.24₪	$2.54	$\frac{(2.54-8.05)}{74.6-91.7}=\frac{-5.51}{-17.1}=\mathbf{0.32}$	Lower cost, lower effectiveness

Dominated = more expensive and less effective than gentamicin
Dominates gentamicin = more effective and less costly
ICER = incremental cost-effectiveness ratios

rates against uropathogens. Although other empiric options like ceftriaxone and piperacillin-tazobactam are recommended by the European Society for Pediatric Infectious Diseases guidelines, gentamicin showed superior sensitivity and remains a common first-line intravenous therapy for pediatric UTIs [14]. A positive ICER reflects improved effectiveness at a higher cost or reduced effectiveness at a lower cost, while a negative ICER may indicate dominance or inferiority compared to the comparator.

Fosfomycin dominated gentamicin, being both more effective (94.2% susceptibility) and less costly, supporting its consideration for empiric use. Ciprofloxacin showed lower cost and slightly reduced susceptibility but is limited in pediatric use due to musculoskeletal risks [15]. Amikacin, with high susceptibility (99.4%) and a low ICER ($2.32), emerged as an effective and affordable alternative compared to more expensive carbapenems. Several antibiotics, including piperacillin/tazobactam, nitrofurantoin, ceftazidime, and ceftriaxone, were dominated, while lower-cost agents like amoxicillin/clavulanic acid, cefuroxime, cephalexin, and trimethoprim/sulfamethoxazole had reduced effectiveness, limiting their role in empirical therapy.

These findings highlight the importance of considering cost-effectiveness thresholds (CETs), which represent the maximum amount a decision-maker is willing to pay for an additional unit of health outcome [16]. In scenarios with lower CETs, fosfomycin emerges as a dominant choice. Amikacin also presents a highly effective and economically favorable option, whereas carbapenems may only be justified at higher thresholds given their high costs.

Few studies have assessed the cost-effectiveness of treatment for pediatric UTIs. Some focused on long-term antimicrobial prophylaxis in children with vesicoureteral reflux [17,18]. In adults, cost-effectiveness analyses examined management strategies and empirical antibiotic choices [19,20]. Wang [19] emphasized the impact of local resistance patterns on treatment selection, while Sadler [20] showed that resistance rates substantially influence relative cost-effectiveness. These findings underscore the relevance of our pathogen-specific analysis in hospitalized children, guided by local susceptibility data.

CLINICAL IMPLICATIONS AND LIMITATIONS

Clinical decisions should balance susceptibility and cost-effectiveness with co-morbidities, infection severity, and risks of broad-spectrum antibiotics. For example, in cases of suspected sepsis, life-threatening infections, or catheter-associated UTIs, agents with the highest sensitivity should be prioritized, regardless of the associated cost. In kidney disease or hearing impairment, aminoglycosides should be avoided.

Limitations of this study include its retrospective design and regional, single center setting, which may restrict the generalizability of the findings. In addition, the analysis is based on in vitro susceptibility data, which may not reflect clinical effectiveness.

CONCLUSIONS

E. coli was the predominant pathogen in pediatric UTIs among hospitalized children in a tertiary medical center in Israel. Carbapenems and amikacin demonstrated the highest susceptibility rates but were costly. Fosfomycin's high susceptibility, cost-effectiveness, and oral administration make it suitable for resource-limited settings, outperforming gentamicin, while ceftriaxone and piperacillin-tazobactam were less cost-effective. Empiric antibiotic selection should integrate pathogen susceptibility patterns, clinical context, and economic considerations to optimize outcomes. Further multicenter studies are warranted to validate these findings across different healthcare settings and to monitor evolving resistance trends.

Correspondence

Dr. A. Alper
Azrieli Faculty of Medicine, Bar-Ilan University, Safed 1321504, Israel
Email: alperadir@hotmail.com

References

1. Simões E Silva AC, Oliveira EA, Mak RH. Urinary tract infection in pediatrics: an overview. *J Pediatr (Rio J)* 2020; 96 Suppl 1 (Suppl 1): 65-79.
2. Roberts KB. The diagnosis of UTI: liquid gold and the problem of gold standards. *Pediatrics* 2015; 135 (6): 1126-7.
3. Mattoo TK, Shaikh N, Nelson CP. Contemporary management of urinary tract infection in children. *Pediatrics* 2021; 147 (2): e2020012138. Erratum in: *Pediatrics* 2022; 150 (4): e2022059259.
4. Lerner SA, Seligsohn R, Matz GJ. Comparative clinical studies of ototoxicity and nephrotoxicity of amikacin and gentamicin. *Am J Med* 1977; 62 (6): 919-23.
5. McWilliam SJ, Antoine DJ, Smyth RL, Pirmohamed M. Aminoglycoside-induced nephrotoxicity in children. *Pediatr Nephrol* 2017; 32 (11): 2015-25.
6. Le TA, Hiba T, Chaudhari D, et al. Aminoglycoside-related nephrotoxicity and ototoxicity in clinical practice: a review of pathophysiological mechanism and treatment options. *Adv Ther* 2023; 40 (4): 1357-65.
7. Karavanaki KA, Soldatou A, Koufadaki AM, Tsentidis C, Haliotis FA, Stefanidis CJ. Delayed treatment of the first febrile urinary tract infection in early childhood increased the risk of renal scarring. *Acta Paediatr* 2017; 106 (1): 149-54.

8. 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): 848-54.
9. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-effectiveness in health and medicine. New York: Oxford University Press; 2016.
10. Ministry of Health. Drug price lists. [Available from https://www.gov.il/he/departments/dynamiccollectors/drug-prices]. [Accessed 1 July 2024]. [Hebrew].
11. Zhanel GG, Zhanel MA, Karlowsky JA. Oral and intravenous fosfomycin for the treatment of complicated urinary tract infections. *Can J Infect Dis Med Microbiol* 2020; 2020: 8513405.
12. Hatlen TJ, Flor R, Nguyen MH, Lee GH, Miller LG. Oral fosfomycin use for pyelonephritis and complicated urinary tract infections: a 1 year review of outcomes and prescribing habits in a large municipal healthcare system. *J Antimicrob Chemother* 2020; 75 (7): 1993-7.
13. Samancı S, Çelik M, Köşker M. Antibiotic resistance in childhood urinary tract infections: a single-center experience. *Turk Pediatri Ars* 2020; 55 (4): 386-92.
14. Bryant PA, Bitsori M, Vardaki K, Vaezipour N, Khan M, Buettcher M. Guidelines for complicated urinary tract infections in children: a review by the european society for pediatric infectious diseases. *Pediatr Infect Dis J* 2025; 44 (6): e211-e223.
15. Li S, Chen Z, Huang L, et al. Safety of quinolones in children: a systematic review and meta-analysis. *Paediatr Drugs* 2022; 24 (5): 447-64.
16. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press; 2015.
17. Palmer LS, Seideman CA, Lotan Y. Cost-effectiveness of antimicrobial prophylaxis for children in the RIVUR trial. *World J Urol* 2018; 36 (9): 1441-7.
18. Shaikh N, Rajakumar V, Peterson CG, et al. Cost-utility of antimicrobial prophylaxis for treatment of children with vesicoureteral reflux. *Front Pediatr* 2020; 7: 530.
19. Wang R, LaSala C. Role of antibiotic resistance in urinary tract infection management: a cost-effectiveness analysis. *Am J Obstet Gynecol* 2021; 225 (5): 550.e1-550.e10.
20. Sadler S, Holmes M, Ren S, Holden S, Jha S, Thokala P. Cost-effectiveness of antibiotic treatment of uncomplicated urinary tract infection in women: a comparison of four antibiotics. *BJGP Open* 2017; 1 (3): bjgpopen17X101097.

Capsule

Axonal injury is a targetable driver of glioblastoma progression

Glioblastoma is an aggressive and highly therapy-resistant brain tumor. Although advanced disease has been intensely investigated, the mechanisms that underpin the earlier, likely more tractable, stages of glioblastoma development remain poorly understood. **Clements** and colleagues identified axonal injury as a key driver of glioblastoma progression, which is induced in white matter by early tumor cells preferentially expanding in this region. Mechanistically, axonal injury promotes gliomagenesis by triggering Wallerian degeneration, a targetable active program of axonal death, which the authors showed increases neuroinflammation and tumor proliferation. Inactivation of SARM1, the key enzyme activated in response to injury that mediates Wallerian degeneration, was sufficient to break this tumor-promoting feedforward loop, leading to the development of less advanced terminal tumors and prolonged survival in mice. Thus, targeting the tumor-induced injury microenvironment may suppress progression from latent to advanced disease, thereby providing a potential strategy for glioblastoma interception and control.

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Eitan Israeli

Capsule

Targeting PD-L1-CMTM6 interactions in myeloid cells triggers PD-L1 degradation and enhances cytotoxic T-cell expansion

Hsu et al. developed a new anti-PD-L1 antibody (H1A) that disrupts PD-L1 recycling and redirects it toward degradation. Due to the loss of available PD-L1 protein, H1A effectively prevents PD-L1 intrinsic signaling. Using in vivo humanized PD-1/PD-L1 mouse tumor models, the authors evaluated the therapeutic efficacy of H1A against current FDA-approved PD-L1 blocking antibodies. H1A demonstrated improved tumor control and established immunological memory responses in vivo in the treatment of tumors with moderate immunogenicity that are less responsive to current immunotherapies. This finding was supported by enhanced activation of myeloid cells (major histocompatibility complex (MHC)-II and CD80) and frequencies of effector T-cell populations found intratumorally. Human myeloid cells treated with H1A were also observed to have increased activation (MHC-II and CD80) and cytokine secretion. Similar to in vivo findings, human peripheral blood lymphocyte cultures demonstrated increased frequencies of effector T-cell populations and greater tumor cell killing.

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Eitan Israeli