European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Carbapenem resistance in pediatric urinary tract infections, its prevalence, risk factors and emerging prescription trends: A comprehensive review

Article History:

Name of Author: Nadia Gul[1], Sudhair Abbas[2★], Huma Gul[3], Muhammad Bilal Khan[4], Naila Shahbaz[5], Peer Abdul Hanan[6], Nisar Zamin Shah[7]

Affiliation:
[1]*Faculty of Life Sciences, Department of Pharmacy, Sarhad University of Science and Information Technology Peshawar, Pakistan*
[2]*Bangash Faculty of Life Sciences, Department of Pharmacy, Sarhad University of Science and Information Technology Peshawar, Pakistan; sudhair.fls@suit.edu.pk*
[3]*FCPS peads Medicines, Fellow Pediatric Cardiology,DHQ Mardan*
4Department of Molecular Biology Islamia College University Peshawar;
[5]*Faculty of Life Sciences, Department Of Pharmacy, Sarhad University of Science and Information Technology Peshawar, Pakistan*
[6]*Faculty of Life Sciences, Department Of Pharmacy, Sarhad University of Science and Information Technology Peshawar, Pakistan*
[7]*Faculty of Life Sciences, Department Of Pharmacy, Sarhad University of Science and Information Technology Peshawar, Pakistan.*

Corresponding Author:
Sudhair Abbas
sudhair.fls@suit.edu.pk

Received: *16*-01-2026
Revised: *28*-01-2026
Accepted: *05*-02-2026
Published: *14*-02-2026

Abstract:
Carbapenem resistance in childhood urinary tract infection (UTIs) is a growing problem around the world pressing the viability of the last-line antibiotics in children. UTIs occur in pediatrics in large proportions of antibiotics and include infants and children with a history of underlying urology or healthcare exposures. This review was conducted as a summary of the available evidence on the problem of carbapenem-resistant uropathogens in pediatric UTIs, major patient- and healthcare-related risk factors, as well as emerging prescription trends. Increasing resistance is closely associated with the previous usage of broad-spectrum antibiotics and further dependence on carbapenems against serious infections. Urinary tract infections caused by carbapenem resistance in children are related to elevated failure rates of treatments, sepsis, renal issues, extended hospital stay, and high healthcare expenditures. The review emphasizes the role of early diagnosis, carbapenem-sparing interventions, and antimicrobial stewardship to maximize treatment responses and reduce the risk of additional resistance.

Keywords: Pediatric urinary tract infection; carbapenem resistance; antimicrobial resistance; risk factors; prescribing trends; antimicrobial stewardship.

INTRODUCTION

UTIs are widely recognized as the most frequent types of bacterial infections in children globally and one of the most alarming sources of morbidity, health care usage, and antibiotic exposure in children. (1) Estimates suggest that the proportion of girls and boys who develop at least one UTI in childhood is 7-8 percent and 2 percent respectively, and the prevalence rates are the highest in

infants and young children. (2) Urinary tract infections remain a common reason for pediatric emergency department presentations, representing nearly 2% of all pediatric emergency department (ED) visits, and contribute significantly to health care utilization in young children. (3) Pediatric urinary tract infections cause acute illness and long-term consequences, including recurrent infections and renal scarring, and in children with anatomical abnormalities may result in chronic kidney disease or hypertension, underscoring the need for timely diagnosis and management. (4) Pediatric urinary tract infections exhibit an uneven global burden, with disproportionately higher incidence and complications reported in low- and middle-income countries. (5, 6)

In low and middle income countries, empirical antibiotic therapy for pediatric urinary tract infections is often initiated without microbiological confirmation, which increases the risk of treatment failure and the emergence of drug-resistant organisms.(7,8) Antibiotic-resistant pediatric UTIs are associated with increased medical costs and longer hospital stays, highlighting a significant healthcare burden even in high-income countries. (8) Over the past two decades, antimicrobial resistance has increasingly affected pediatric UTIs, with traditionally used antibiotics such as ampicillin, trimethoprim-sulfamethoxazole, and early-generation cephalosporins showing high resistance, particularly in *Escherichia coli*, largely due to widespread inappropriate antibiotic use. (9) Children are particularly vulnerable to antimicrobial resistance due to their developing immune systems, higher infection rates, frequent early exposure to antibiotics, and limited pediatric-specific data and treatment options. (10)

Extended-Spectrum β-lactamse producing *E. coli* and *Klebsiella* are increasingly encountered in pediatric UTIs, and carbapenems, including imipenem, meropenem, and ertapenem, are recommended as preferred agents for severe or complicated infections caused by multidrug-resistant organisms. (11)

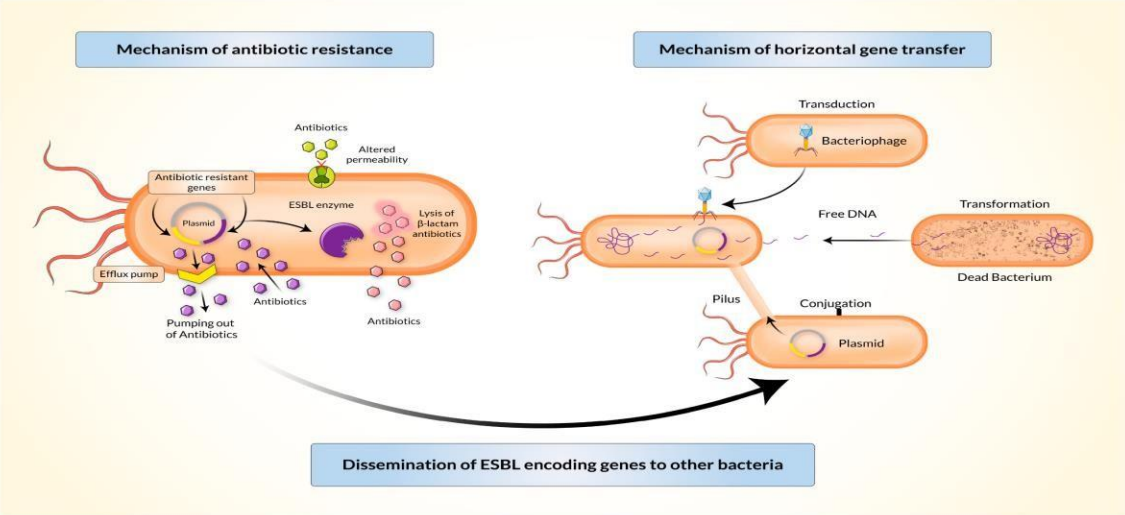

Figure 1 Extended-Spectrum β-Lactamases (ESBL) (12)

Carbapenems are broad-spectrum β-lactam antibiotics effective against ESBL-producing and resistant Gram-negative bacteria and are commonly used for severe infections, including complicated UTIs, sepsis, neonatal infections, and in immunocompromised pediatric patients. (13) Although carbapenems are life-saving, their increasing use raises concerns about the emergence of resistance. Children are particularly vulnerable, as repeated or prolonged exposure can disrupt the developing gut microbiome and promote colonization by resistant pathogens. (14, 15) In a recent pediatric surveillance study, the annual incidence of carbapenem-resistant Enterobacterales (CRE) was 0.47–0.87 cases per 100,000 children, whereas extended-spectrum β-lactamase (ESBL) producing Enterobacterales occurred at much higher rates (19.63–26.5/100,000), indicating that ESBL organisms remain substantially more prevalent than CRE in pediatric UTIs. (16) Carbapenem resistance in Enterobacterales arises through multiple mechanisms, including the production of carbapenemases, alterations in outer membrane porins often coupled with ESBL or AmpC β-lactamases, and the transfer of resistance genes via horizontal gene transfer. (17)

In pediatric populations, CRE infections are associated with multidrug resistance and poorer clinical outcomes; however, surveillance data indicate that carbapenem resistance in community-acquired pediatric UTIs remains relatively rare. (16) Continuous monitoring of ESBL and carbapenem resistance patterns is therefore essential to guide empirical therapy and strengthen antimicrobial stewardship practices. (18) Carbapenem-resistant Pseudomonas aeruginosa infections in children are associated with limited therapeutic options, higher rates of treatment failure, prolonged hospitalization, and increased mortality. (19) The emergence of carbapenem-resistant organisms in pediatric UTIs is particularly

challenging, as treatment options are limited by age-related safety concerns, incomplete pediatric pharmacokinetic and toxicity data, and restricted approval of agents such as polymyxins, tigecycline, or newer β-lactam/β-lactamase inhibitor combinations, making clinical decision-making more complex. (20) Moreover, resistance patterns and risk factors in children differ from those in adults due to unique anatomical, developmental, and healthcare-related factors, highlighting the need for separate evaluation and pediatric-focused antimicrobial stewardship. (21)

Despite the growing clinical importance of carbapenem resistance, most studies focus on adults, bloodstream infections, or ICU settings, leaving pediatric UTIs underrepresented, with prevalence, risk factors, and prescribing practices varying widely across regions and healthcare settings. (22) A pediatric-specific review is urgently needed to summarize carbapenem resistance prevalence in pediatric UTIs, highlight key risk factors, and assess emerging prescribing trends, supporting evidence-based practice, antimicrobial stewardship, and policy development globally. (23)

Rationale and Objectives

Rationale

Children are a uniquely vulnerable population in the context of urinary tract infections due to anatomical abnormalities, functional urinary tract disorders, and age-related susceptibility that contribute to higher infection risk in infancy and early childhood. (24, 25) Young children, especially infants, are particularly susceptible to urinary tract infections due to immature immune defenses and underdeveloped urinary tract anatomy. Congenital abnormalities, such as vesicoureteral reflux or other structural anomalies, further increase the risk of recurrent infections. These repeated infections often lead to higher exposure to antibiotics, which can contribute to the development of antimicrobial resistance in pediatric populations. (2, 26, 27) Early and repeated antibiotic exposure during critical periods of growth can significantly perturb the developing gut microbiome. Such disruptions have been associated with long-term consequences, including increased risk of metabolic disorders, immune dysregulation, and propagation of antimicrobial resistance genes. Evidence from birth cohort studies demonstrates that infants receiving antibiotics in the first year of life exhibit persistent alterations in gut microbial composition and an increased burden of resistance genes, highlighting the potential for future health impacts and treatment challenges. (28-30)

Treatment options for multidrug-resistant UTIs in children are limited due to scarce pediatric safety, dosing, and pharmacokinetic data for many antibiotics. Consequently, carbapenems are often reserved as last-line agents in severe cases, despite concerns about toxicity, ecological impact, and resistance selection.(31, 32) Carbapenem-resistant uropathogens in children represent a serious clinical challenge, reducing available safe and effective treatment options. Children carrying or infected with these resistant organisms can contribute to transmission in both community and healthcare settings, underscoring the importance of antimicrobial stewardship and judicious prescribing. (16) Although carbapenem-resistant uropathogens are increasingly reported in children, pediatric-specific data on their prevalence, risk factors, and prescribing patterns remain limited, underscoring the need for focused review and surveillance to inform clinical practice and antimicrobial stewardship. (33)

Objectives

This comprehensive review aims to define the current landscape of carbapenem resistance in paediatric urinary tract infections, with particular emphasis on epidemiology, determinants of resistance, and evolving treatment practices.

Primary Objective:

- To synthesize available evidence on the prevalence of carbapenem-resistant uropathogens in pediatric UTIs across diverse geographic regions and healthcare settings.

Secondary Objectives:

- To identify patient related, microbiological, and healthcare-associated risk factors contributing to carbapenem resistance in children.
- To evaluate emerging prescription trends, including carbapenem utilization, de-escalation approaches, and carbapenem-sparing strategies in pediatric practice.
- To highlight clinical and public health implications, supporting the development of paediatric-specific treatment guidelines and strengthening antimicrobial stewardship initiatives.

This review consolidates pediatric-specific evidence on the prevalence, risk factors, and prescribing patterns of carbapenem-resistant UTIs to inform clinical practice and antimicrobial stewardship.

METHODS OF THE REVIEW

Search Strategy

A comprehensive and systematic literature search was conducted to identify relevant studies addressing carbapenem resistance in pediatric urinary tract infections. Major electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Embase, were searched to ensure broad coverage of biomedical and public health literature. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to pediatric UTIs and antimicrobial resistance. Key search terms included *"pediatric urinary tract infection," "children," "infants," "carbapenem resistance," "carbapenem-resistant Enterobacterales," "multidrug-resistant*

uropathogens," and *"antibiotic prescribing trends."* Boolean operators (AND/OR) were used to refine searches. The timeframe was limited to studies published between January 2020 and November 2025 to capture contemporary resistance patterns, diagnostic approaches, and prescribing practices. Reference lists of eligible articles and relevant reviews were manually screened to identify additional studies that may not have been captured through database searching.

Eligibility Criteria

Research papers that met the following criteria were considered including:

(i) use of pediatric populations aged 1-18 years.
(ii) Reports of microbiologically confirmed UTIs
(iii) Reports of carbapenem resistance, use, or accompanying risk factors.

These were observational studies (cross-sectional, cohort, and case-control) as well as surveillance reports, interventional or stewardship-related studies which qualified to be included. Community-acquired and healthcare-associated UTI were both taken into consideration. Research that involved adults only or non-urinary infections or colonization in the absence of clinical infection was eliminated. Cases that contained less than five patients, conferences that had no full text on their abstracts and non-English articles were also excluded to maintain quality and interpretability of data.

Definitions and Outcomes

Urinary tract infection was characterized based on the standard pediatric requirements, such as the presence of clinical symptoms that are typical of UTI and the presence of significant bacterial growth on urine culture collected via an appropriate collection technique (Subcommittee on Urinary Tract Infection, 2021). The definition of carbapenem resistance relied on the reported susceptibility testing results based on the established standards, e.g., the Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (CLSI, 2023). The main findings were the occurrence of carbapenem-resistant uropathogens in childhood UTIs. The risks identified, the mechanisms of resistance, the patterns of antibiotic prescription and the clinical outcomes linked with the carbapenem-resistant infections were the secondary outcomes.

Data Extraction and Synthesis

The information was obtained with a standardized form that included characteristics of the studies, population demographics, setting, uropathogens, resistance pattern, and trends in prescribing. As there are likely to be diverse study designs, populations and outcome measures, a narrative synthesis method was employed. Results were summarized thematically in prevalence, risk factors and prescription practices. Quality and risk of bias in a study were estimated and determined with the help of the appropriate tools, i.e., Joanna Briggs Institute critical appraisal instruments of observations studies. Any discrepancies in the data extraction or interpretation were resolved via a consensus to further increase methodological rigor.

Epidemiology and Prevalence of Carbapenem Resistance in Pediatric Urinary Tract Infections

Urinary tract infections are among the most common bacterial infections in children, with Escherichia coli as the predominant pathogen. (34) Rising antimicrobial resistance, including multidrug-resistant and carbapenem resistant isolates, has increasingly complicated pediatric UTI management. (35, 36) Prevalence varies across regions and healthcare settings, highlighting the need to understand epidemiological patterns to guide empirical therapy, antimicrobial stewardship, and public health interventions.

Burden and Clinical Spectrum

Neonatal and young infant urinary tract infections often present with nonspecific symptoms such as fever, poor feeding, or irritability, which can delay diagnosis and treatment. (37) Older children with urinary tract infections typically present with more localized urinary symptoms such as dysuria, frequency, urgency, or flank pain, facilitating earlier recognition. (38) Boys are predominantly affected in the neonatal period due to congenital urinary tract anomalies, whereas postnatally, girls show higher prevalence because of anatomical and behavioral factors. (39)

The burden of pediatric urinary tract infections is compounded by multidrug-resistant and carbapenem resistant uropathogens, which limit effective antimicrobial options, prolong illness, increase hospitalization duration, and elevate the risk of complications due to challenges in empirical therapy and higher treatment failure rates. (40)

Early detection of resistance patterns is crucial to guide therapy, support antimicrobial stewardship, and improve pediatric outcomes.Pediatric urinary tract infections are classified as uncomplicated or complicated. Uncomplicated infections occur in otherwise healthy children with normal urinary anatomy and function, typically involving the lower urinary tract and manageable without extensive investigation or intervention. (41) Complicated UTIs involve structural or functional abnormalities, such as vesicoureteral reflux, obstructive uropathy, neurogenic bladder, or indwelling catheters or systemic involvement like pyelonephritis and urosepsis. (39) Children with chronic comorbidities are more susceptible, with higher hospitalization, recurrent infections, and broad-spectrum antibiotic exposure. Complicated UTIs are disproportionately associated with multidrug-resistant organisms, promoting antimicrobial resistance in pediatric populations. (42)

4.2 Common Pediatric Uropathogens

Carbapenem resistance in pediatric urinary tract infections is an increasingly recognized threat. Recent surveillance shows that carbapenem-resistant Enterobacterales (CRE) constitute a measurable proportion of pediatric UTI isolates, with 3.3% of Gram-negative uropathogens in a West Bank pediatric cohort exhibiting carbapenem resistance alongside high rates of multidrug resistance and ESBL production, underscoring the shrinking efficacy of frontline antibiotics in children. (36) Although comprehensive global pediatric prevalence data remain limited, CRE and ESBL-producing Enterobacterales have been documented in large pediatric populations with urine being the most common source, and incidence rates notably higher in infants compared with older children. (16) Risk factors for acquiring resistant pathogens include prior antibiotic exposure, hospitalization, invasive devices, and complicated or recurrent infections, which collectively contribute to therapeutic challenges and highlight the need for robust antimicrobial stewardship and resistance surveillance in pediatric UTI care. (16, 36)

Table 1. Common Uropathogens Causing Pediatric UTIs and Resistance Tendencies

Uropathogen	Approximate Prevalence in Pediatric UTIs	Key Resistance Features	Clinical Significance	Key References
Escherichia coli	~60–82% of isolates	High rates of ESBL production; emerging resistance trends	Primary community-acquired pathogen	(43)
Klebsiella pneumoniae	~10–15%	ESBL-producers; potential for carbapenemase genes (region-dependent)	Common in both community and hospital-acquired UTIs	(23)
Enterobacter spp.	~1.7–3%	AmpC, porin loss; potential CRE in healthcare settings	Often associated with complicated UTIs	(23)
Proteus mirabilis	~4–9%	Intrinsic resistance to nitrofurantoin; MDR Patterns seen	Linked with structural abnormalities	(44)
Pseudomonas aeruginosa	~3–7%	Intrinsic and acquired resistance (efflux, porins; carbapenem resistance in some regions)	ICU/complicated UTI pathogen	(43)
Acinetobacter baumannii	Rare (~<2%)	OXA-type carbapenemases; MDR common in severe settings	Severe nosocomial infections	(45)

Antibiotic use and healthcare exposure drive shifts in pediatric uropathogens. While *E. coli* dominates community-acquired UTIs, hospital-acquired infections increasingly involve multidrug-resistant organisms. This evolving epidemiology highlights the need for local surveillance to guide effective empirical therapy in children. (34, 36).

Link Between ESBL and Carbapenem Use

The global rise of extended-spectrum β-lactamase (ESBL) producing Enterobacterales has driven increased carbapenem use in pediatric UTIs. ESBLs confer resistance to penicillins and third-generation cephalosporins, historically first-line treatments, forcing clinicians to escalate therapy to carbapenems, particularly for severe or complicated infections. This creates a self-reinforcing cycle: higher carbapenem use applies selective pressure that favors the emergence of carbapenem-resistant organisms through mechanisms such as carbapenemase production or combined porin loss and β-lactamase activity. Consequently, children with prior ESBL infections, recurrent UTIs, or recent broad-spectrum antibiotic exposure are more likely to receive empirical carbapenems, further accelerating resistance. (12, 46, 47)

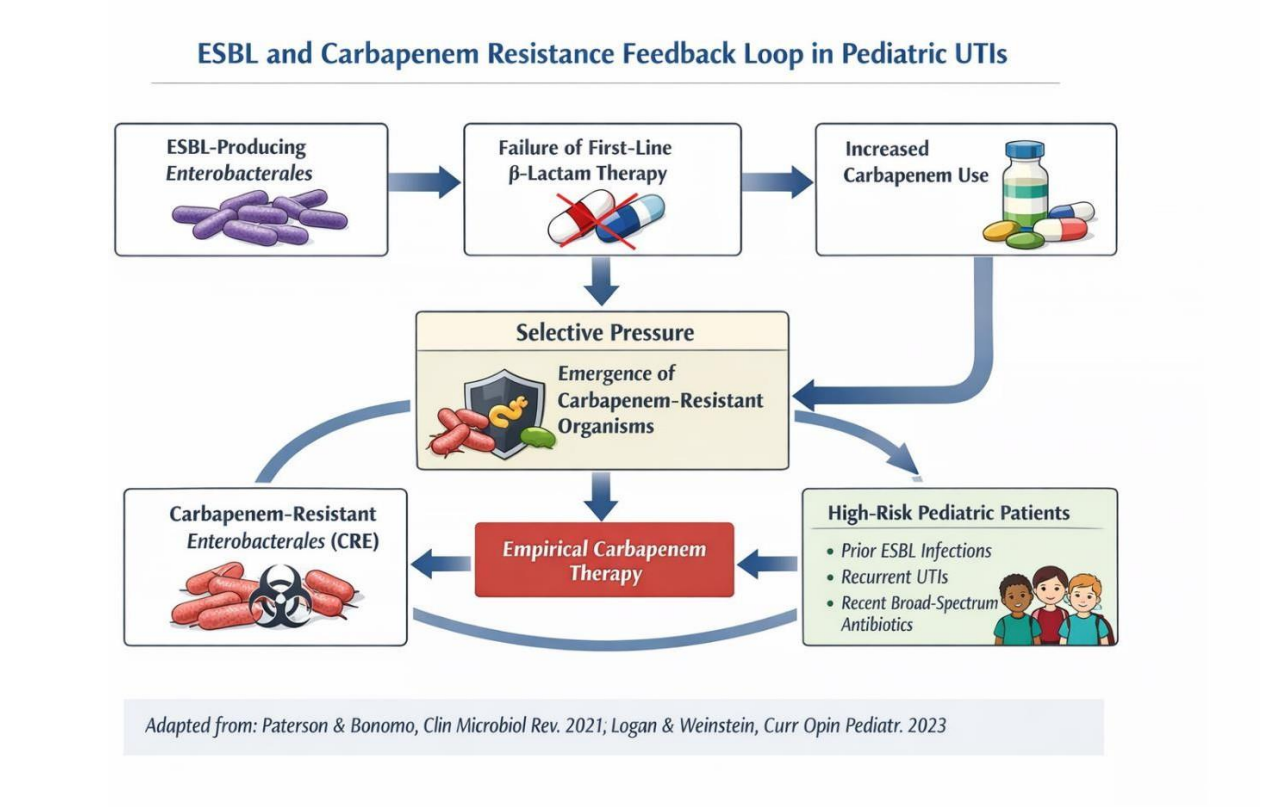

Figure 2 Mechanistic feedback loop linking ESBL prevalence to carbapenem resistance in pediatric UTIs. (48)

Global Prevalence Patterns

Carbapenem resistance among pediatric uropathogens varies significantly across continents due to differences in antimicrobial use practices, healthcare infrastructure, surveillance capacity, and infection prevention measures. In high-income regions such as the United States, CRE prevalence remains relatively low compared with ESBL-producing Enterobacterales, whereas several low- and middle-income countries report higher CRE incidence, particularly among hospitalized children with prior antibiotic exposure or limited infection control. Surveillance studies from Asia and Africa demonstrate a gradual but concerning rise in CRE, emphasizing the need for ongoing monitoring, antimicrobial stewardship, and targeted infection prevention strategies to curb the spread of resistant pathogens in pediatric populations. (16, 49-51) Carbapenem resistance in pediatric uropathogens is generally low in North America and Western Europe, reflecting strong antimicrobial stewardship and regulated antibiotic use. European Antimicrobial Resistance Surveillance network data show very low carbapenem resistance among *E. coli* (<1%) with variable rates in *K. pneumoniae*, while single-center pediatric studies report <1% carbapenem resistance in Enterobacterales. Sporadic outbreaks have been reported, highlighting the need for ongoing surveillance and stewardship. (52, 53)

Conversely, carbapenem resistance has been more prevalent in parts of Asia, the Middle East, and Southern Europe, with clinical surveillance showing high resistance burdens among key uropathogens such as Klebsiella pneumoniae and Acinetobacter baumannii. A systematic review reported pooled carbapenem resistance of ~31% among Gram-negative clinical isolates in Asia, and pediatric hospital data showed carbapenem-resistant K. pneumoniae and A. baumannii ranging from ~16–37% in children, underscoring the regional rise in resistance across diverse healthcare settings. (54, 55) High prevalence of extended-spectrum β-lactamase (ESBL) producers in these regions drives frequent carbapenem use, which in turn contributes to the selection of resistant strains. Rising carbapenem-resistant *Klebsiella pneumoniae* (CRKP) rates in Mediterranean countries have been linked to clonal dissemination of carbapenemase-producing organisms. (56)

Table 2. Global Prevalence of Carbapenem Resistance in Pediatric UTIs

Region	Reported Carbapenem Resistance Range	Dominant Resistant Pathogens	Key Setting	References
North America	**Very low incidence** (CRE incidence ~0.47–0.87/100,000 children) — overall proportion	*E. coli*, *Enterobacter*,	Pediatric surveillance & tertiary hospitals	(16)

	among Enterobacterales very low (<5% CRE relative to ESBL)	*K. pneumoniae* (CRE)		
Western Europe	Low CRE prevalence (<5–10% in general Enterobacterales clinical isolates)	*E. coli*, *K. pneumoniae*	Pediatric referral & general hospitals	(57)
South Asia e.g. China	~5–15% CRE detection in pediatric Enterobacterales isolates	*K. pneumoniae*, *E. coli*, *Enterobacter* spp.	LMIC tertiary hospitals & surveillance	(50)
Middle East and Africa	~5–10% CRE reported in Enterobacterales surveillance (varies by country)	CRE Enterobacterales	Hospitals/general clinical settings	(58)
Sub-Saharan Africa	5–15% CRE in clinical Enterobacterales isolates	*E. coli*, *K. pneumoniae*	Urban & referral hospitals	(58)
Latin America	CRE documented, heterogeneous prevalence reported in pediatric bloodstream and hospital infections (exact UTI data limited)	*K. pneumoniae*, *Serratia* spp.	PICUs/tertiary care	(59)

Limited data from Africa suggest the emergence of carbapenem resistance among pediatric Gram-negative pathogens, particularly in urban referral hospitals. Reported resistance rates range from 5% to 20%, although these figures are likely underestimated due to underdiagnosis and limited laboratory capacity. (60) In Latin America, carbapenem resistance among pediatric Gram-negative pathogens varies widely, with some countries reporting relatively low prevalence while others experience high burdens, particularly of Klebsiella pneumoniae, reflecting uneven access to antimicrobial stewardship and infection control resources. (59)

Global trends in carbapenem resistance among pediatric Gram-negative pathogens show marked regional differences. Resistance remains relatively low in North America and parts of Europe but is increasing in Asia, the Middle East, Africa, and Latin America, reflecting variations in antimicrobial use, stewardship, and healthcare infrastructure. These patterns highlight the global nature of the problem and the risk of international spread via travel and healthcare exposure. (61)

Regional and Low- and Middle-Income Countries (LMIC) Data

Carbapenem resistance in pediatric UTIs disproportionately affects low- and middle-income countries (LMICs), although its true burden remains difficult to quantify because of substantial surveillance gaps. Many LMICs lack comprehensive national antimicrobial resistance surveillance systems, and pediatric-specific data are often limited to single-center or short-term studies, leading to underestimation of resistance trends. In many South Asian settings, clinical studies have reported increasing carbapenem and last-resort antibiotic resistance among Gram-negative urinary isolates, reflecting limited diagnostic capacity and antimicrobial stewardship. Recent surveillance from resource-limited regions has further underscored the need to strengthen monitoring systems to better inform empirical therapy and infection control strategies in pediatric populations. (62-64) Thus, the prevalence rates reported are very diverse, and cannot be helpful to understand the level of resistance in the community.

Hospital-based studies from South Asia and sub-Saharan Africa report high carbapenem resistance among pediatric Gram-negative pathogens (>20–30%), particularly in tertiary referral hospitals managing complicated infections, reflecting an increasing resistance burden in these regions. (65, 66) In such environments, the inadequate diagnostic capability can frequently require a lengthy empirical treatment with general purpose anti-microbials leading to an unintended selective pressure favoring resistant organisms. Also, the availability of OTC antibiotics and under-treatment drug courses further increases the development of resistance.

Surveillance gaps are especially pronounced in rural and low-resource settings, where limited laboratory infrastructure and infrequent culture confirmation hinder the accurate documentation of antimicrobial resistance. Consequently, carbapenem resistance among community-acquired pediatric UTIs may be significantly underexplored, and until susceptibility testing and international breakpoints are standardized and consistently applied, comparisons across regions remain difficult. (64) The solutions to these gaps in the definition of the burden of carbapenem resistance in LMIC pediatric populations involve the reinforcement of laboratory networks and incorporation of pediatric data in domestic AMR action plans.

Hospital vs Community-Acquired Infections

Overall, hospital-acquired pediatric UTIs demonstrate significantly higher rates of carbapenem resistance compared with community-acquired infections, driven by prolonged hospital stays, intensive antibiotic exposure, use of indwelling catheters, prior surgeries, and ICU admissions. (36)
Conversely, carbapenem-susceptible E. coli still remains a major cause of community-acquired pediatric UTIs. Nonetheless, carbon resistance organisms develop in community settings recently, especially in children with prior occurrence of health care or hospitalization. (67) The diffusion of conventional boundaries between hospital-acquired and community-acquired resistance brings up the issue of the possibility of further spread of CRE outside of healthcare establishments.
The preeminence of nosocomial infection in carbapenem resistant pediatric UTIs underscores the significance of infection prevention and control strategies such as catheter management guideline, hand hygiene and environmental cleaning in curbing the spread in hospitals. (68)

Age-Stratified Prevalence
One of the determinants of prevalence of carbapenem resistance in UTIs in pediatrics is age. Neonates and young infants always have the highest rates of carbapenem-resistant infections, which are highly explained by the exposure to the hospital setting and invasive interventions during the first years of their lives. (69) One of the reservoirs of CRE has been found to be the neonatal intensive care units, where the outbreaks are often linked with the use of shared equipment or the spread of the infection by healthcare workers.

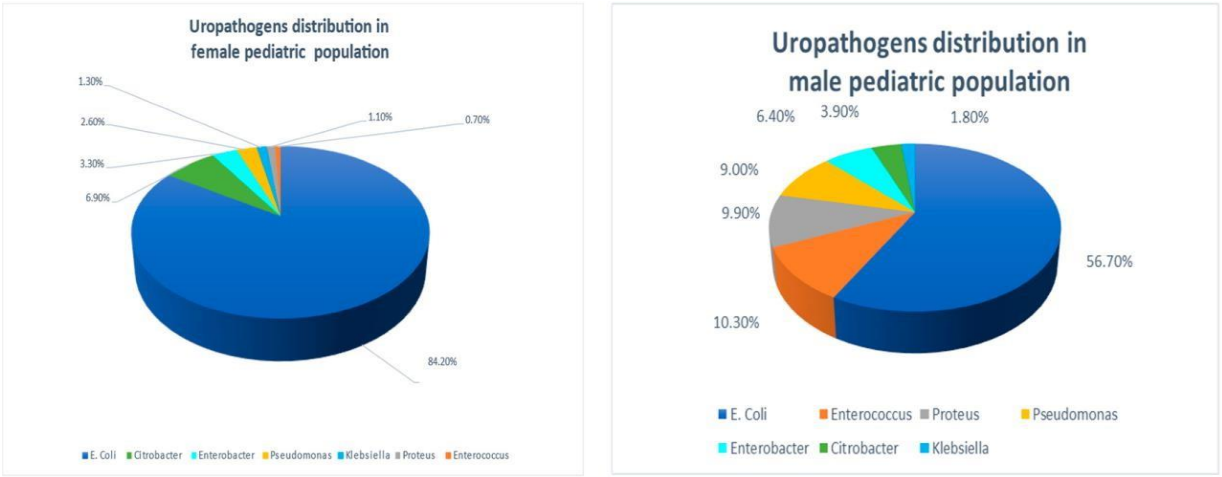

Figure 3 Pathogens Causing Pediatric Community Acquired Urinary Tract Infections and Their Increasing Antimicrobial Resistance (43)

Older children and adolescents generally exhibit a lower prevalence of community-acquired urinary tract infections. However, those with chronic illnesses, congenital or acquired urological abnormalities, or a history of recurrent infections remain at higher risk regardless of age. Additionally, repeated or prolonged exposure to antibiotics in this population can contribute to the development of antimicrobial resistance, including extended-spectrum β-lactamase (ESBL)-producing pathogens, which are associated with more complicated clinical outcomes. (70)
Such age stratified trends underscore justified surveillance and preventive targeted interventions in neonatal and infant cohorts, in which clinical implications of carbapenem resistance may be especially dreadful.

Temporal Trends Over Time
Longitudinal surveillance studies demonstrate a progressive increase in antimicrobial resistance among pediatric uropathogens over recent decades. A 20-year single-center analysis showed a steady year-on-year rise in resistant urinary isolates in children, largely driven by extended-spectrum β-lactamase–producing Enterobacterales, reflecting evolving epidemiological patterns over time. (71) Recent surveillance data indicate that carbapenem-resistant Enterobacterales (CRE) continue to be detected in pediatric populations over time, with annual incidence rates reported among children from 2016 to 2020 and a high proportion of CRE isolated from urine cultures, underscoring the ongoing emergence of carbapenem resistance in pediatric urinary tract infections. (72) This increased temporal trend has been strongly associated with the escalating use of carbapenem due to high levels of ESBL and few alternatives.
Several studies indicate that changes in antibiotic prescribing practices can rapidly influence resistance patterns, underscoring the sensitivity of antimicrobial resistance development to selection pressure. Evidence from high-income settings suggests that resistance rates in pediatric urinary tract infections may stabilize or modestly decline following the implementation of robust antimicrobial stewardship programs; however, such trends remain inconsistent or insufficiently

documented in many low- and middle-income countries. (73)
Comprehensively, time-based analyses indicate that unless world-wide stewardship initiatives and enhanced surveillance persist, the rates of carbapenem resistance among pediatric UTIs would continue their upward trend and, therefore, possibly further restrict therapeutic choices of a high-risk patient group.

Carbapenem Resistance in Pediatric UTIs
Clinical Significance
Carbapenem-resistant Enterobacterales (CRE) represent a serious emerging concern in pediatric urinary tract infections due to limited treatment options and potential for poor clinical outcomes. (11) National surveillance in the United States showed that CRE was consistently isolated from pediatric urine cultures, with annual incidence rates between 0.47 and 0.87 cases per 100 000 children and a higher burden in infants compared with older age groups, underscoring the emerging epidemiology of carbapenem resistance in pediatric urinary tract infections. Most CRE cases were healthcare-associated community-onset or community-associated, highlighting the importance of considering CRE beyond hospital settings. CRE infections in children have important implications for empirical therapy and infection control planning. (16)

Mechanism of Carbapenem Resistance
Carbapenem resistance in Enterobacterales is most often mediated by the production of carbapenemase enzymes such as KPC, NDM, and OXA-48-like variants that degrade carbapenem antibiotics. Additional mechanisms include combinations of extended-spectrum β-lactamase (ESBL) or AmpC β-lactamase production with reduced outer membrane permeability, contributing to clinical resistance. (17) These resistance determinants are frequently carried on mobile genetic elements, facilitating horizontal gene transfer across species. Although detailed pediatric mechanistic studies remain limited, regional resistance patterns in Enterobacterales support the role of these mechanisms in clinical isolates. (50, 74)

Laboratory Detection and Surveillance
Timely and accurate detection of carbapenem resistance in pediatric UTIs requires both phenotypic and molecular methods. Culture and minimum inhibitory concentration (MIC) testing serve as the foundation for identifying CRE phenotypes, while PCR and other molecular assays enable confirmation of specific carbapenemase genes, which remains the gold standard for definitive detection of resistance mechanisms. (75) Surveillance studies involving large networks (e.g., CHINET) have documented carbapenem resistance rates among pediatric Enterobacterales, with variations across age groups and bacterial species. Routine detection supports both clinical decision-making and public health tracking, although access to advanced diagnostics remains limited in many settings. (50)

Pediatric CRE in Special Populations
High-risk pediatric groups, such as children with malignancies, demonstrate a particularly concerning CRE burden. Implementation of rapid diagnostic techniques and targeted screening strategies in pediatric oncology has been associated with earlier initiation of effective therapy, illustrating the potential impact of improved surveillance on clinical outcomes. (76)

Risk Factors for Carbapenem-Resistant Pediatric UTIs
Patient-Related Factors
Pediatric patient characteristics strongly influence susceptibility to carbapenem-resistant UTIs. Neonates and young infants are at higher risk due to immature immunity, weaker mucosal defenses, and increased early-life hospitalizations. Genomic surveillance highlights the spread of carbapenem-resistant *Escherichia coli* in children, emphasizing its public health impact. (77). Premature infants are particularly vulnerable to carbapenem-resistant infections due to prolonged NICU stays, invasive lines, and exposure to broad-spectrum antibiotics, which promote colonization and infection with resistant organisms. (78)
Immunocompromised children, including those with primary immunodeficiencies, malignancies, or post-transplant immunosuppressive therapy, are at higher risk for recurrent and severe UTIs caused by multidrug-resistant pathogens. (70)
It has also been found that malnutrition, common in many low- and middle-income countries, weakens immunity and increases susceptibility to infections caused by resistant pathogens. (19). Chronic diseases, such as chronic kidney or neurological conditions, increase the risk of recurrent healthcare visits and repeated antibiotic exposure, promoting the emergence of multidrug-resistant infections. (79)

Table 3. Patient- and Disease-Related Risk Factors for Carbapenem-Resistant Pediatric UTIs

Risk Factor	Explanation	Strength of Association	References
Neonatal age	Immature immune system, frequent NICU exposure, invasive procedures	High	(80)

Prematurity	Increased Susceptibility, Frequent Health care exposure	High	(59)
Immunosuppression	Reduced immune defense, frequent healthcare contact	Moderate–High	(59)
Recurrent UTIs	Repeated antibiotic exposure increases chance of resistant/complicated infections	High	(31)
Malnutrition	Impaired immune defenses increase susceptibility to UTI	Moderate	(81)

All these factors related to patients indicate that biological vulnerability and clinical complexity intersect to augment the risk of carbapenem-resistant pediatric UTIs. The identification of high-risk patient profiles is thus vital to preventative aspects that are targeted and to sensibly prescribe antibiotics.

Urological and Anatomical Factors

Vesicoureteral reflux (VUR), characterized by retrograde urine flow from the bladder to the upper urinary tract, is a major predictor of recurrent UTIs in children. High-grade VUR often necessitates repeated antibiotic therapy, increasing selective pressure for carbapenem-resistant organisms. (82) Congenital urinary tract anomalies (e.g., hydronephrosis, posterior urethral valves, duplex systems) and functional disorders (neurogenic bladder, voiding dysfunction) predispose children to urinary stasis and incomplete bladder emptying, promoting bacterial persistence and biofilm formation, which contribute to carbapenem-resistant infections. (83). They often prescribe the prophylaxis or suppressive antibiotics to the children, which is meant to avoid the occurrence of the infection but, as a consequence, makes the antimicrobial resistance more likely to develop. Surgery on urological abnormalities is also associated with an exposure to hospital settings and perioperative antibiotics, and these are associated with resistant infections.

Non-E. coli pathogens, such as *Klebsiella* and *Enterobacter* species, which have higher rates of carbapenem resistance, are more likely to cause UTIs in children with structural urinary tract abnormalities. (84) In such a way, urological and anatomical factors not only enhance the risk of UTI but also define the resistance pattern of causative pathogens.

Healthcare-Associated Factors

Healthcare exposure is a major risk factor for carbapenem-resistant UTIs in children. Long-term hospitalization, particularly in ICUs or NICUs, increases susceptibility due to heavy antibiotic use, invasive procedures, and patient proximity (85).

Table 4. Healthcare-Associated and Antibiotic-Related Risk Factors

Factor	Mechanism	Impact on Resistance	References
Prior carbapenem use	Strong selective pressure	Very high	(86)
ICU admission	Cross-transmission and High antibiotic pressure	High	(86)
Indwelling catheters	Biofilm formation & breach of defenses	High	(87)
Prolonged hospitalization	MDR colonization & Health care exposure	Moderate–High	(86)
Antibiotic prophylaxis	Selection of resistant flora	Moderate	(87)

Indwelling urinary catheter use is a significant healthcare-associated risk factor for carbapenem-resistant UTIs. Catheters disrupt natural host defenses, facilitate ascending infection, and promote biofilm formation, which shields bacteria from host immunity and antimicrobial agents. Catheter-associated UTIs are frequently linked to multidrug-resistant organisms, and pediatric studies identify prolonged catheter duration, PICU stay, and prior MDR colonization as important risk factors for MDR-CAUTI. (88, 89) Urological or abdominal surgery or any surgical intervention that exposes an individual to perioperative exposure to antibiotics and temporary urinary drainage devices are associated with further increase of the

risk.

Other possible sources of resistance spread include frequent readmissions and inter-facility transfers which allow cross-transmission of resistant strains between healthcare environments. This risk is enhanced by poor infection prevention and control policies such as poor hand hygiene and environment cleaning. The following healthcare related factors frequently enhance the significance of strong infection control programs to prevent carbapenem resistant pediatric UTI.

Antibiotic Exposure

Previous antibiotic exposure is a major, modifiable risk factor for carbapenem-resistant UTIs in children. Even brief courses of carbapenems can exert strong selective pressure on urinary and gastrointestinal microbiota, promoting resistance. (70) This effect is increased further when repeat or prolonged courses are used, especially on children, with recurrent infection or chronic illness.

Third- and fourth-generation cephalosporin, fluoroquinolone as well as a combination of 2-lactam and 2-lactamase inhibitors have also been implicated in the resistance pathway that results in the use of carbapenems. These agents pick out extended-spectrum β-lactamase-producing organisms, which in most cases warrant an escalation to carbapenem when the infections take place. (90) Empirical broad-spectrum therapy is often initiated prior to the culture results in pediatric practice hence further unnecessary exposure.

The use of antibiotic prophylaxis to prevent recurrent UTIs is a controversial topic, and new evidence is indicating that long-term prophylaxis might lead to heightened resistance but with limited clinical goodwill (91). The exposure effects of being exposed to the antibiotic on repeated occasions and in healthcare settings underscores the imperative role that antimicrobial stewardship plays in mitigating the risk of carbapenem resistance.

Microbiological and Environmental Factors

Carbapenem-resistant UTIs are important precursors of microbiological colonization with resistant organisms. Enterobacteriaceae carriage of carbapenem-resistant gastrointestinal microbes has been established as a serious risk factor to further urinary infection especially among children in hospital settings (92) Colonization can linger on for long periods of time and is usually untapped unless active surveillance is conducted.

There is also spreading of resistance due to environmental factors. It has become increasingly clear that household transmission of resistant bacteria can occur as a result of the colonized family members, water sources, and animal or environmental reservoirs (93). Poor hygiene and the crowding of people in crowded areas make it easier to spread the illness and the chances are high that children will contract organisms that have developed resistance early in life.

These microbiological and environmental drivers demonstrate that not only is the problem of carbapenem-resistant pediatric UTI a hospital issue but also a complication between the healthcare system, community, and environment. To fulfill these factors, there should be integrated approaches based on One Health with clinical interventions.

Clinical Impact and Outcomes

Treatment Failure and Complications

In children, carriage of (UTIs) resistant to carbapenem in the urinary tract is linked to much worse clinical outcomes than infection by carbapenem-sympergic organisms. Among the most severe, resistance to antimicrobial therapy should be noted as a phenomenon that poses a significant danger of treatment failure (dependence or recurrence of infection despite the correct use of antimicrobial treatment). The delays in timely effective treatment are typical as the relevant empirical regimens do not include resistant pathogens, especially in those settings with no rapid diagnostics (94). These delays have the potential to cause localized UTIs to develop systemic infections.

Table 5. Clinical Outcomes of Carbapenem-Resistant vs Susceptible Pediatric UTIs

Outcome	Carbapenem-Susceptible UTIs	Carbapenem-Resistant UTIs	References
Treatment failure	Low	Significantly higher	(95)
Sepsis risk	Rare	Increased	(85)
Hospital stay	Short	Prolonged	(90)
Renal scarring	Occasional	More frequent	(96)
Healthcare costs	Lower	Substantially higher	(97)

Carbapenem-resistant pediatric UTIs are associated with a particularly serious complication known as sepsis, which is pronounced in infants and children with underlying comorbidities. The rate of intensive care admission, mechanical

ventilation, and mortality due to Gram-negative sepsis caused by carbapenem-resistant organisms have been found to be higher than those related to susceptible microbes. (69) Even though the mortality in pediatric UTIs is commonly low, the existence of the carbapenem resistance significantly predisposes the chance of unfavorable consequences.

Another vital issue is the renal complications. The results of recurrent or unsuccessfully managed UTIs recurrence in children may result in renal scarring that has long-term consequences such as hypertension, kidney proteinuria, and impaired renal functioning in adulthood (98) The infection that is resistant to carbapenem antibiotics can be accompanied by a long course of treatment and can be recurring, which further increases the overall risk of kidney damage. Therefore, resistance not only makes the acute management challenging, but also adds to the long-term morbidity in the affected children.

Health System Burden

In addition to patient outcomes, carbapenem-resistant UTIs have a significant costly impact on healthcare systems of pediatric patients. The children with resistant infections are associated with prolonged hospitalization because of the delay in proper treatment administration, intravenous antibiotics use, and addressing complications. Some of the studies have found that hospital stays which were caused by carbapenem-resistant Gram-negative bacteria are by two to three times shorter than those which were caused by susceptible bacteria (99)

The economic effect is equally high. The prolonged length of stay, use of costly last-line antibiotics, further diagnostic tests, and application of infection control measures all make healthcare costs higher. These costs are once again intensified in the pediatric department due to the requirements of specialized services, including multidisciplinary follow-up and pediatric intensive care units (19). Financial burden can also restrict access to the right treatment in the low- and middle-income countries, worsening inequity in health.

Carbapenem-resistant infections strain at a system level consumes already limited resources of healthcare and distract attention toward preventive services. The rising rate of resistance presents the significance of the stewardship programs alongside the facility of clinical interventions as well as cost-reduction techniques in a bid to maintain healthcare sustainability.

High-Risk Pediatric Groups

Some pediatric subpopulations face an unduly burden of the negative consequences of carbapenem-resistant UTIs. Immunative systems are immature, invasive measures are a frequent practice, and neonates often spend considerable time in the neonatal intensive care units (NICUs) with broad-spectrum antibiotics, which puts them at an extremely high risk (70) Carbapenem-resistant infections are connected with a shortage of treatment and deterioration of the condition in a relatively short period in this group.

Another high-risk group is the children with cancer treatment. These patients with oncology are frequently immunosuppressed due to chemotherapy and are repeatedly hospitalized, have central venous access, and take empirical antibiotic therapy, which all make the individual susceptible to resistant infections (100). Carbapenem-resistant UTIs may break life-saving treatments, extend hospitalization, and harm the overall prognosis significantly in those vulnerable populations.

Emerging Prescription Trends in Pediatric UTIs

Changes in Empiric Therapy

Over the last decade, empiric antibiotic treatment of pediatric urinary tract infections (UTIs) has changed significantly, in large part due to increasing levels of antimicrobial resistance. Traditionally, the oral agents involved in empiric regimens included amoxicillin-clavulanate or first- and second-generation cephalosporins. Nevertheless, the growing resistance to these agents, especially with the organisms producing extended-spectrum β-lactamase (ESBL), has prompted clinicians to consider the use of broader-spectrum treatments at the earlier phases of patient care. (101) Empiric usage of carbapenems as part of tertiary-care initial treatment of children with a history of severe UTIs, prior healthcare exposure, or known colonization with resistant organisms is now common in most tertiary-care settings.

This increased dependence on carbapenems is particularly noticeable among hospitalized children as well as children who appear with pyelonephritis or sepsis. Existing research based on pediatric referral centers has shown that empiric use of carbapenems has been rising progressively, even in the absence of microbiological support, because clinicians are concerned about the development of treatment failure in high-risk patients (102). Even though this strategy can enhance short term clinical outcomes, selective pressure towards carbapenem resistant organisms is also enhanced.

The movement of the emphasis of the coverage of the empiric to a wider area is based on a conflict between a timely and effective treatment of the patient and the maintenance of the available effectiveness of antibiotics. Clinicians going to settings with no strong local resistance data might resort to carbapenems to protect themselves. This tendency highlights the necessity to enhance risk stratification tools and real-time surveillance data as a means of adopting empiric therapy in UTIs in children.

Carbapenem-Sparing Strategies

Carbapenem-sparing strategies are now becoming visible in the treatment of UTI in children, as a consequence of the fear

that there is increasing carbapenem use. The application of β-lactam/β-lactamase inhibitors (BL/BLI) combinations, including piperacillin-tazobactam or that of newer and stronger activity against resistant Gram-negative bacteria, is one of the most popular ones. Some evidence shows that in selected pediatric patients that have ESBL-producing uropathogens, BL/BLI combinations can be viable substitutes to carbapenems in case of confirmed susceptibility (103)

Aminoglycosides are also found in an important role in carbapenem-sparing regimens, especially severe UTIs or urosepsis. Amikacin is also an agent that stays active and effective against a variety of multidrug-resistant uropathogens, and it is commonly used as monotherapy in the form of short courses or in collaboration with 8-lactams. (104) Daily-dose and once-daily dosing regimens have enhanced safety but the issue of nephrotoxicity and ototoxicity still exists particularly in young children.

Other means of sparing would be, optimization of dosing, reduced therapy periods and selective choice of patients in terms of clinical and microbiological stability. Taken together, these measures will help to maintain the efficacy of carbapenems, yet acceptable clinical outcomes are observed. Intense desire, however, mandates the timely susceptibility testing and confidence of the clinicians in other alternatives.

De-escalation and Step-Down Therapy

The de-escalation and step-down therapy became the most prominent elements of the contemporary antimicrobial practice in pediatrics. De-escalation is defined as reducing the antibiotic coverage as soon as culture and susceptibility tests are obtained, whereas the step-down therapy implies switching intravenous drugs to oral ones when the clinical conditions permit. Culture-directed de-escalation is demonstrated to cause no harm to unnecessary exposure to broad-spectrum antibiotics and no rise in treatment failure rates in pediatric UTIs. (105)

A number of studies prove that even in cases of the resistant organism, children who started on carbapenems can successfully be de-escalated to narrower-spectrum agents once their susceptibilities establish the susceptibility, which is a safe practice. (106) Early switching to oral therapy has been observed to be especially effective in reducing the length of stay in the hospital, limiting intravenous line related complications as well as enhancing the comfort of the patient.

De-escalation practices are not consistently implemented, even despite the strong supporting pieces of evidence. Obstacles are reported delays on culture, concerns by clinicians over relapse and oral availability of options against resistant pathogens. This is imperative in consolidating laboratory-clinical relationships and establishing effective de-escalation policies to integrate these interventions into the standard care of pediatric UTI.

Stewardship Program Influence

Antimicrobial stewardship program (ASP) has greatly impacted the trends in the prescribing of pediatric UTIs. Some of the interventions aiming to promote guideline-based prescribing in ASPs include prospective audit and feedback, formulary restriction and clinical decision support tools. Stewardship programs in pediatric hospitals have been linked to a decrease in carbapenem use and a rise in the use of evidence-based approaches to the treatment of UTI (107)

The adoption of guidelines has a special significance in the standardization of empiric therapy and promotion of carbapenem-sparing alternatives. Guidelines addressing children specifically focus more on risk-based empiric therapy, regular review of antibiotics at 4872 hours, and timely de-escalation (108). These bases are also strengthened by education of clinicians and trainees and promote the culture of judicious use of antibiotics.

Notably, the use of stewardship is not confined to hospitals, and one can also work in outpatient and emergency environments where pediatric UTIs are mostly inappropriately prescribed. ASPs are not only involved in the improved treatment results of patients but also the long-term security of the carbapenem resistance in the area due to the connection between prescribing practices and local resistance data and national guidelines.

Therapeutic Options for Carbapenem-Resistant UTIs

Table 7. Therapeutic Options for Carbapenem-Resistant Pediatric UTIs

Antibiotic	Activity Against CRE	Pediatric Limitations	References
Colistin	High	Nephrotoxicity	(109)
Fosfomycin	Moderate–High	Limited pediatric dosing data	(110)
Amikacin	High	Oto/nephrotoxicity	(111)
Ceftazidime–avibactam	High (KPC)	Limited approval	(112)
Cefiderocol	Broad	Case-series evidence only	(113)

Available Antibiotic Options

Management of carbapenem-resistant urinary tract infections (UTIs) in children is particularly challenging due to limited therapeutic options and pediatric-specific safety considerations. When carbapenem resistance is confirmed, treatment selection must balance antimicrobial efficacy with age-appropriate dosing and toxicity profiles. Polymyxins, particularly colistin, have been used as salvage therapy against carbapenem-resistant Gram-negative uropathogens. Although colistin demonstrates in vitro activity against many resistant strains, its use in children is constrained by nephrotoxicity and neurotoxicity, necessitating close monitoring and careful dose adjustment (114)

Fosfomycin has emerged as a valuable option for lower UTIs caused by carbapenem-resistant Enterobacterales, especially *Escherichia coli*. Its favorable safety profile and oral formulation make it attractive in pediatric practice, although data on optimal dosing in children remain limited. **Smith M et al. (2023)** reported high clinical cure rates and good tolerability of fosfomycin for pediatric UTI, including infections with resistant organisms, while noting the need for further dosing research. (115) Tigecycline exhibits broad activity against multidrug-resistant organisms but is generally avoided for UTIs due to poor urinary concentrations and limited pediatric experience.

Aminoglycosides such as amikacin retain activity against many carbapenem-resistant uropathogens and are frequently used either alone for uncomplicated infections or as part of combination therapy. Pediatric dosing strategies emphasize once-daily administration to reduce toxicity risk, though renal function monitoring is essential. (116)

Overall, available antibiotic options are few, often toxic, and supported by limited pediatric data, highlighting the need for individualized treatment decisions guided by susceptibility results.

Combination vs Monotherapy

The use of combination therapy versus monotherapy in carbapenem-resistant pediatric UTIs remains an area of ongoing debate. Combination regimens, often including two or more active agents such as a polymyxin plus an aminoglycoside or fosfomycin, are frequently employed in severe infections to enhance bacterial killing and reduce the risk of resistance emergence. (117)

Observational studies in pediatric and mixed-age populations suggest that combination therapy may be associated with improved microbiological clearance in critically ill patients, although definitive survival benefits remain uncertain.

Monotherapy, when guided by susceptibility testing and used in clinically stable patients with localized UTIs, may be sufficient and preferable in children, reducing toxicity, simplifying administration, and lowering costs. However, concerns about resistance development during therapy persist, especially with agents that have narrow therapeutic windows. Consensus guidelines recommend adjusting therapy based on urine culture and sensitivity, with targeted monotherapy once susceptibility is known in most uncomplicated pediatric cases. (118)

In pediatric practice, the choice between combination therapy and monotherapy is often influenced by infection severity, site of infection, host factors, and available antimicrobial options. Given the scarcity of randomized pediatric trials, treatment decisions rely heavily on extrapolation from adult data and expert consensus, underscoring the need for pediatric-specific evidence.

Novel and Emerging Agents

Novel β-lactam/β-lactamase inhibitor combinations, such as ceftazidime-avibactam and meropenem-vaborbactam, have demonstrated efficacy against certain carbapenemase-producing *Enterobacterales* in adult populations, and emerging pediatric observational data suggest similar promise in children with carbapenem-resistant infections, although optimal dosing, regulatory approvals, and real-world pediatric evidence remain limited. (119)

Cefiderocol, a siderophore cephalosporin with activity against a broad range of carbapenem-resistant Gram-negative bacteria, represents another promising option. Its unique mechanism of iron-mediated bacterial entry circumvents many resistance pathways. However, pediatric experience is currently limited to small case series and compassionate use reports, precluding definitive recommendations. (120)

Despite these advances, significant evidence gaps persist regarding optimal dosing, safety, and long-term outcomes in children. Ethical and logistical challenges in conducting pediatric antimicrobial trials further slow progress. Expanding pediatric clinical trials and post-marketing surveillance is essential to ensure that emerging agents can be safely and effectively integrated into the treatment of carbapenem-resistant pediatric UTIs.

Challenges, Knowledge Gaps, and Future Directions

Surveillance and Research Gaps

Despite growing recognition of carbapenem resistance in pediatric urinary tract infections (UTIs), substantial surveillance and research gaps persist. One major limitation is the scarcity of pediatric-specific antimicrobial resistance (AMR) data. Many national and international surveillance systems aggregate pediatric data with adult infections or prioritize bloodstream infections, resulting in underrepresentation of pediatric UTIs and incomplete characterization of resistance patterns in children. (121)

In addition, heterogeneity in study design, laboratory methods, and resistance definitions complicates cross-study comparisons and limits the generalizability of findings.

Despite increasing recognition of carbapenem-resistant pediatric UTIs, major surveillance and research gaps remain. Pediatric-specific antimicrobial resistance (AMR) data are limited, as most surveillance systems

aggregate pediatric infections with adult data or prioritize invasive infections, leading to underrepresentation of UTIs. In many regions, restricted access to diagnostic microbiology further contributes to underreporting and underestimation of resistance prevalence. (122) Moreover, the lack of longitudinal, multicenter pediatric studies hampers understanding of resistance trends, transmission dynamics, and the long-term impact of antibiotic exposure in children. (123, 124) Clinical trials evaluating treatment strategies for carbapenem-resistant pediatric UTIs are scarce, leading to reliance on adult data or observational studies.

Future research priorities should include standardized pediatric AMR surveillance, integration of genomic epidemiology, and multicenter studies focused specifically on UTIs. Expanding pediatric participation in antimicrobial clinical trials is essential to generate robust evidence that can guide safe and effective management strategies.

Policy and Stewardship Challenges

Policy and stewardship challenges are particularly pronounced in low- and middle-income countries (LMICs), where the burden of carbapenem resistance in pediatric UTIs is often highest. Limited laboratory capacity, inconsistent antibiotic supply chains, and shortages of trained healthcare professionals constrain the implementation of effective antimicrobial stewardship programs (ASPs), undermining efforts to optimize antibiotic use and control resistant infections. (125) In many LMICs, antibiotics remain available without prescription, facilitating inappropriate use and accelerating resistance development.

National AMR action plans frequently lack pediatric-specific components, and stewardship efforts tend to focus on adult inpatient care. Furthermore, financial constraints may limit access to newer, carbapenem-sparing antibiotics and rapid diagnostic technologies, reinforcing reliance on empirical broad-spectrum therapy. Weak regulatory frameworks and inadequate surveillance infrastructure further undermine policy effectiveness.

Addressing these challenges requires context-specific stewardship models, investment in laboratory systems, and integration of pediatric considerations into national AMR strategies. International collaboration and sustainable funding mechanisms are critical to support capacity building and ensure equitable access to effective UTI management for children in resource-limited settings.

CONCLUSION

Carbapenem resistance in paediatric urinary tract infections (UTIs) represents an escalating global health challenge with significant clinical and public health implications. Prevalence is highest among neonates, children with urological abnormalities, immunocompromised patients, and those with prior healthcare or antibiotic exposure, particularly in hospital settings and low- and middle-income countries. The emergence of carbapenem-resistant organisms is often preceded by earlier resistance mechanisms, such as extended-spectrum β-lactamase production, and reflects increasing reliance on carbapenems as last-line therapy.

The clinical burden of carbapenem-resistant paediatric UTIs is substantial, including higher rates of treatment failure, sepsis, renal complications, prolonged hospitalization, and increased healthcare costs, particularly among high-risk populations such as NICU and oncology patients.

Multifactorial risk factors including patient vulnerabilities, structural urinary tract anomalies, healthcare-associated exposures, and environmental determinants interact to facilitate the emergence, persistence, and dissemination of resistant organisms.

Emerging prescription trends highlight a gradual shift towards carbapenem-sparing strategies, de-escalation based on susceptibility data, and stewardship-driven empiric therapy in high-risk paediatric populations. Optimizing antibiotic use while maintaining clinical efficacy is critical to mitigating selective pressure and curbing further resistance.

Addressing this challenge requires strengthened paediatric-specific surveillance, rapid and accurate diagnostic capacity, robust antimicrobial stewardship programs, and inclusion of children in clinical trials for novel therapeutics. A coordinated, evidence-based approach that integrates clinical management, responsible prescribing, and policy-level interventions offers the best pathway to preserve carbapenem efficacy and ensure optimal outcomes for children with UTIs globally.

REFERENCES

1. Mattoo TK, Shaikh N, Nelson CP. Contemporary Management of Urinary Tract Infection in Children. Pediatrics. 2021;147(2).
2. Maringhini S, Alaygut D, Corrado C. Urinary Tract Infection in Children: An Up-To-Date Study. Biomedicines. 2024;12(11).
3. Gottlieb M, Amponsah T, Nguyen N, Shukla O, Bernard K, Moyer E. Epidemiologic Trends in Pediatric Urinary Tract Infections Among United States Emergency Departments from 2016-2023. Clin Exp Emerg Med. 2025.
4. Hughes K, Cannings-John R, Jones H, Lugg-Widger F, Lau TMM, Paranjothy S, et al. Long-term consequences of urinary tract infection in childhood: an electronic population-based cohort study in Welsh primary and secondary care. Br J Gen Pract. 2024;74(743):e371-e8.
5. Zuo X, Fang C, Wang C, Fang Z, Liang Q, Dai Z, et al. Global trends in childhood urinary tract infections, 1990–2021: results from the GBD study. Frontiers in Public Health. 2025;Volume 13 - 2025.
6. Zhang Y, Huang S, Wang Y, Huang W, Chen X, Su C, et al. Temporal trends and geographical variations in pediatric urinary tract infections: a comprehensive analysis using the global burden of disease study 2021. Tropical Medicine and Health. 2025;53.

7. Onyango HA, Sloan DJ, Keenan K, Kesby M, Ngugi C, Gitonga H, Hammond R. The appropriateness of empirical antibiotic therapy in the management of symptomatic urinary tract infection patients-a cross-sectional study in Nairobi County, Kenya. JAC Antimicrob Resist. 2024;6(4):dlae118.
8. 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.
9. Mekonnen S, Tesfa T, Shume T, Tebeje F, Urgesa K, Weldegebreal F. Bacterial profile, their antibiotic susceptibility pattern, and associated factors of urinary tract infections in children at Hiwot Fana Specialized University Hospital, Eastern Ethiopia. Plos one. 2023;18(4):e0283637.
10. Saleem Z. Editorial: Antimicrobial use and stewardship in pediatrics. Frontiers in Pediatrics. 2023;Volume 11 - 2023.
11. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, Van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). Clinical Infectious Diseases. 2022;75(2):187-212.
12. Husna A, Rahman MM, Badruzzaman ATM, Sikder MH, Islam MR, Rahman MT, et al. Extended-Spectrum β-Lactamases (ESBL): Challenges and Opportunities. Biomedicines. 2023;11(11).
13. Dong SW, Sharma TS, Sue PK. Approach to multidrug resistant infections in pediatric transplant recipients. Frontiers in Pediatrics. 2023;Volume 11 - 2023.
14. Luchen CC, Chibuye M, Spijker R, Simuyandi M, Chisenga C, Bosomprah S, et al. Impact of antibiotics on gut microbiome composition and resistome in the first years of life in low- to middle-income countries: A systematic review. PLoS Med. 2023;20(6):e1004235.
15. Wurm J, Curtis N, Zimmermann P. The effect of antibiotics on the intestinal microbiota in children - a systematic review. Frontiers in Allergy. 2024;Volume 5 - 2024.
16. Grome HN, Grass JE, Duffy N, Bulens SN, Ansari U, Campbell D, et al. Carbapenem-Resistant and Extended-Spectrum β-Lactamase-Producing Enterobacterales in Children, United States, 2016-2020. Emerg Infect Dis. 2024;30(6):1104-14.
17. Caliskan-Aydogan O, Alocilja EC. A Review of Carbapenem Resistance in Enterobacterales and Its Detection Techniques. Microorganisms. 2023;11(6):1491.
18. Ruppé É, Woerther PL, Barbier F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. Ann Intensive Care. 2015;5(1):61.
19. Huang W, Wei X, Xu G, Zhang X, Wang X. Carbapenem-resistant Pseudomonas aeruginosa infections in critically ill children: prevalence, risk factors, and impact on outcome in a large tertiary pediatric hospital of China. Frontiers in Public Health. 2023;11:1088262.
20. Kawalec A, Józefiak J, Kiliś-Pstrusińska K. Urinary tract infection and antimicrobial resistance patterns: 5-year experience in a Tertiary Pediatric Nephrology Center in the Southwestern Region of Poland. Antibiotics. 2023;12(9):1454.
21. Aguilera-Alonso D. It is time for pediatric antimicrobial stewardship programs. Enfermedades infecciosas y microbiologia clinica (English ed). 2021;39(3):113-4.
22. Sivarajan V, Ganesh AV, Subramani P, Ganesapandi P, Sivanandan R, Prakash S, et al. Prevalence and genomic insights of carbapenem resistant and ESBL producing Multidrug resistant Escherichia coli in urinary tract infections. Scientific Reports. 2025;15(1):2541.
23. Amleh T, Salah A, Hamayel R, Ibrahim BA, Sayeh H, Hamshari S, Qadi M. Bacterial etiology and antimicrobial resistance patterns of pediatric UTIs in the West bank, Palestine: a cross-sectional study. BMC pediatrics. 2025;25(1):725.
24. Agrawal P, Paunikar VM. Urinary Tract Infection in Children: A Narrative Review. Cureus. 2024;16(1):e51469.
25. U T, M S, Y PC, Yerikala R, Venugopalaiah P. A review on urinary tract infection on pediatric and womens health. International Journal of Health Care and Biological Sciences. 2025;6(1):1-5.
26. Boulanger V, Vincent H, Laghdir Z, Barrieras D, Franc-Guimond J, Potvin E, Quach C. Children with recurrent urinary tract infections: who are they and why do we need better prevention options? BMC Pediatrics. 2025;25(1):895.
27. Isac R, Doros G, Stolojanu C-A, Steflea RM, Stroescu RF, Olariu I-C, et al. General Characteristics and Current State of Antibiotic Resistance in Pediatric Urinary Tract Infection—A Single Center Experience. Antibiotics. 2024;13(8):684.
28. Li P, Chang X, Chen X, Wang C, Shang Y, Zheng D, Qi K. Early-life antibiotic exposure increases the risk of childhood overweight and obesity in relation to dysbiosis of gut microbiota: a birth cohort study. Ann Clin Microbiol Antimicrob. 2022;21(1):46.
29. Reyman M, van Houten MA, Watson RL, Chu MLJN, Arp K, de Waal WJ, et al. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. Nature Communications. 2022;13(1):893.
30. Lebeaux RM, Karalis DB, Lee J, Whitehouse HC, Madan JC, Karagas MR, Hoen AG. The association between early life antibiotic exposure and the gut resistome of young children: a systematic review. Gut Microbes. 2022;14(1):2120743.
31. 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. The Pediatric Infectious Disease Journal.

2025;44(6):e211-e23.
32. Nelson Z, Aslan AT, Beahm NP, Blyth M, Cappiello M, Casaus D, et al. Guidelines for the Prevention, Diagnosis, and Management of Urinary Tract Infections in Pediatrics and Adults: A WikiGuidelines Group Consensus Statement. JAMA Network Open. 2024;7(11):e2444495-e.
33. Grome H, Grass J, Duffy N, Bulens S, Jacob J, Smith G, et al. Epidemiology of carbapenem-resistant and extended-spectrum beta-lactamase-producing Enterobacterales in US children, 2016–2020. Antimicrobial Stewardship & Healthcare Epidemiology. 2023;3(S2):s16-s.
34. Işık G, Öner P. Pathogenic microorganisms and antimicrobial resistance patterns in the pediatric age group with urinary system infections. Trends in Pediatrics. 2024;5(1):14-9.
35. Attar GBE, Ahmed S, Shree N, Khan A, Saha N, Khan MA. An observational study on multidrug resistance in pediatric patients with urinary tract infections. Naunyn Schmiedebergs Arch Pharmacol. 2025.
36. Amleh T, Salah A, Hamayel R, Ibrahim BA, Sayeh H, Hamshari S, Qadi M. Bacterial etiology and antimicrobial resistance patterns of pediatric UTIs in the West bank, Palestine: a cross-sectional study. BMC Pediatr. 2025;25(1):725.
37. Kamel AS, Abd El Moktader AM, Abd El Reheem F, Sayed MA. Incidence and risk factors of urinary tract infection in neonatal sepsis. Beni-Suef University Journal of Basic and Applied Sciences. 2022;11(1):87.
38. Priya, Ameta G, Singh M, Saini M. Clinical, etiological and radiological profile of paediatric patients with urinary tract infection: a tertiary care hospital based prospective studypital based prospective study. International Journal of Contemporary Pediatrics. 2025;12(6):960-8.
39. Daniel M, Szymanik-Grzelak H, Sierdziński J, Podsiadły E, Kowalewska-Młot M, Pańczyk-Tomaszewska M. Epidemiology and Risk Factors of UTIs in Children-A Single-Center Observation. J Pers Med. 2023;13(1).
40. El Zein Z, Boutros CF, El Masri M, El Tawil E, Sraj M, Salameh Y, et al. The challenge of multidrug resistance in hospitalized pediatric patients with urinary tract infections. Front Cell Infect Microbiol. 2025;15:1570405.
41. Alsaywid BS, Alyami FA, Alqarni N, Neel KF, Almaddah TO, Abdulhaq NM, et al. Urinary tract infection in children: A narrative review of clinical practice guidelines. Urol Ann. 2023;15(2):113-32.
42. Collingwood JD, Yarbrough AH, Boppana SB, Dangle PP. Increasing Prevalence of Pediatric Community-acquired UTI by Extended Spectrum β-Lactamase-producing E. coli: Cause for Concern. Pediatr Infect Dis J. 2023;42(2):106-9.
43. Shkalim Zemer V, Ashkenazi S, Levinsky Y, Richenberg Y, Jacobson E, Nathanson S, et al. Pathogens Causing Pediatric Community Acquired Urinary Tract Infections and Their Increasing Antimicrobial Resistance: A Nationwide Study. Pathogens. 2024;13(3):201.
44. Shaaban OA, Mahmoud NA, Zeidan AA, Kumar N, Finan AC. Prevalence and Resistance Patterns of Pediatric Urinary Tract Infections in Bahrain. Cureus. 2021;13(12):e20859.
45. Zhang Y, Xu G, Miao F, Huang W, Wang H, Wang X. Insights into the epidemiology, risk factors, and clinical outcomes of carbapenem-resistant Acinetobacter baumannii infections in critically ill children. Front Public Health. 2023;11:1282413.
46. Nivesvivat T, Piyaraj P, Thunyaharn S, Watanaveeradej V, Suwanpakdee D. Clinical epidemiology, risk factors and treatment outcomes of extended-spectrum beta-lactamase producing Enterobacteriaceae bacteremia among children in a Tertiary Care Hospital, Bangkok, Thailand. BMC Res Notes. 2018;11(1):624.
47. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J Infect Dis. 2017;215(suppl_1):S28-s36.
48. Alshehail BM, Alwezzeh MJ, Al Jamea Z, Alsalem F, Alabkari F, AlAtayah M, et al. Effectiveness of Carbapenem-Sparing Antibiotics Versus Carbapenems for Treating Non-Bacteremic Extended-Spectrum Beta-Lactamase-Producing Enterobacterales Infections. Infect Drug Resist. 2025;18:6113-28.
49. Githii S, Maingi JM, Nyaga T, Ndungu C, Nyongesa KW, Musyoki AM. Gastrointestinal carriage of carbapenemase-producing enterobacterales among inpatient and outpatient children in Kenya. Scientific Reports. 2024;14(1):30684.
50. Pan F, Wang C, Yang Y, Guo Y, Zhu D, Zhang H, et al. Trends in antimicrobial resistance in Enterobacterales isolated from children: data from the China Antimicrobial Surveillance Network (CHINET) from 2015–2021. One Health Advances. 2024;2(1):21.
51. Otaigbe II. Carbapenem resistant enterobacterales: a covert menace in low and middle income countries. Discover Public Health. 2025;22(1):544.
52. Alvisi G, Curtoni A, Fonnesu R, Piazza A, Signoretto C, Piccinini G, et al. Epidemiology and Genetic Traits of Carbapenemase-Producing Enterobacterales: A Global Threat to Human Health. Antibiotics. 2025;14(2):141.
53. Wanke-Rytt M, Sobierajski T, Lachowicz D, Seliga-Gąsior D, Podsiadły E. Analysis of Etiology of Community-Acquired and Nosocomial Urinary Tract Infections and Antibiotic Resistance of Isolated Strains: Results of a 3-Year Surveillance (2020-2022) at the Pediatric Teaching Hospital in Warsaw. Microorganisms. 2023;11(6).
54. Jayathilaka N, Shehana S, Nakkawita D, Senaratne T. Prevalence and molecular epidemiology of carbapenem resistance in Asia: a systematic review and meta-analysis. Syst Rev. 2025;14(1):123.
55. Jian X, Li Y, Wang H, Li C, Li F, Li J, et al. A comparative study of genotyping and antimicrobial resistance between carbapenem-resistant Klebsiella pneumoniae and Acinetobacter baumannii isolates at a

tertiary pediatric hospital in China. Frontiers in Cellular and Infection Microbiology. 2024;Volume 14 - 2024.
56. Hu Y, Yang Y, Feng Y, Fang Q, Wang C, Zhao F, et al. Prevalence and clonal diversity of carbapenem-resistant Klebsiella pneumoniae causing neonatal infections: a systematic review of 128 articles across 30 countries. PLoS Medicine. 2023;20(6):e1004233.
57. Piotrowski M, Alekseeva I, Arnet U, Yücel E. Insights into the Rising Threat of Carbapenem-Resistant Enterobacterales and Pseudomonas aeruginosa Epidemic Infections in Eastern Europe: A Systematic Literature Review. Antibiotics. 2024;13(10):978.
58. Karlowsky JA, Bouchillon SK, El Mahdy Kotb R, Mohamed N, Stone GG, Sahm DF. Carbapenem-resistant Enterobacterales and Pseudomonas aeruginosa causing infection in Africa and the Middle East: a surveillance study from the ATLAS programme (2018–20). JAC-Antimicrobial Resistance. 2022;4(3).
59. Ruvinsky S, Voto C, Roel M, Portillo V, Naranjo Zuñiga G, Ulloa-Gutierrez R, et al. Carbapenem-Resistant Enterobacteriaceae Bacteremia in Pediatric Patients in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. Antibiotics. 2024;13(12):1117.
60. Thomson K. Assessment of antibiotic resistance in pathogens causing neonatal sepsis, associated mortality and recommended treatment options in low-and middle-income countries: Cardiff University; 2022.
61. Wise MG, Karlowsky JA, Mohamed N, Hermsen ED, Kamat S, Townsend A, et al. Global trends in carbapenem- and difficult-to-treat-resistance among World Health Organization priority bacterial pathogens: ATLAS surveillance program 2018-2022. J Glob Antimicrob Resist. 2024;37:168-75.
62. Majigo MV, Mshana S, Komba E, Moremi N, Matee M. Protocol for surveillance of antimicrobial-resistant bacteria causing community-acquired urinary tract infections in low-income countries. PLoS One. 2024;19(5):e0304388.
63. Khursheed N, Adnan F, Khan MA, Hatif R. Regional insights on the prevalence and antimicrobial susceptibility pattern of carbapenem and colistin-resistant gram-negative bacteria: an observational cross-sectional study from Karachi, Pakistan. BMC Infectious Diseases. 2025;25(1):186.
64. Karna S. Burden of antibiotic resistance in urinary isolates: a retrospective cross-sectional study from a tertiary center in Far-Western Nepal. BMC Infectious Diseases. 2025;25(1):1634.
65. Jayathilaka N, Shehana S, Nakkawita D, Senaratne T. Prevalence and molecular epidemiology of carbapenem resistance in Asia: a systematic review and meta-analysis. Systematic Reviews. 2025;14(1):123.
66. Sisay A, Asmare Z, Kumie G, Gashaw Y, Getachew E, Ashagre A, et al. Prevalence of carbapenem-resistant gram-negative bacteria among neonates suspected for sepsis in Africa: a systematic review and meta-analysis. BMC Infect Dis. 2024;24(1):838.
67. Wanke-Rytt M, Sobierajski T, Lachowicz D, Seliga-Gąsior D, Podsiadły E. Analysis of Etiology of Community-Acquired and Nosocomial Urinary Tract Infections and Antibiotic Resistance of Isolated Strains: Results of a 3-Year Surveillance (2020–2022) at the Pediatric Teaching Hospital in Warsaw. Microorganisms. 2023;11(6):1438.
68. Shrestha R, Luterbach CL, Dai W, Komarow L, Earley M, Weston G, et al. Characteristics of community-acquired carbapenem-resistant Enterobacterales. Journal of Antimicrobial Chemotherapy. 2022;77(10):2763-71.
69. Al Mana H, Sundararaju S, Tsui CK, Perez-Lopez A, Yassine H, Al Thani A, et al. Whole-genome sequencing for molecular characterization of carbapenem-resistant Enterobacteriaceae causing lower urinary tract infection among pediatric patients. Antibiotics. 2021;10(8):972.
70. He X-T, Chang C-N, Yu C-H, Wang C-C. The risk factors, antimicrobial resistance patterns, and outcomes associated with extended-spectrum β-lactamases-Producing pathogens in pediatric urinary tract infection. Pediatrics & Neonatology. 2024;65(3):242-8.
71. Dejonckheere Y, Desmet S, Knops N. A study of the 20-year evolution of antimicrobial resistance patterns of pediatric urinary tract infections in a single center. European Journal of Pediatrics. 2022;181(9):3271-81.
72. Grome HN, Grass JE, Duffy N, Bulens SN, Ansari U, Campbell D, et al. Carbapenem-Resistant and Extended-Spectrum β-Lactamase–Producing Enterobacterales in Children, United States, 2016–2020. Emerging Infectious Diseases. 2024;30(6):1104.
73. Esposito S, Biasucci G, Pasini A, Predieri B, Vergine G, Crisafi A, et al. Antibiotic resistance in paediatric febrile urinary tract infections. Journal of global antimicrobial resistance. 2022;29:499-506.
74. Livermore DM, Nicolau DP, Hopkins KL, Meunier D. Carbapenem-resistant Enterobacterales, carbapenem resistant organisms, carbapenemase-producing Enterobacterales, and carbapenemase-producing organisms: terminology past its “sell-by date” in an era of new antibiotics and regional carbapenemase epidemiology. Clinical Infectious Diseases. 2020;71(7):1776-82.
75. Tüzemen NÜ, Önal U, Merdan O, Akca B, Ener B, Akalın H, Özakın C. Performance comparison of BD Phoenix CPO detect panel with Cepheid Xpert Carba-R assay for the detection of carbapenemase-producing Klebsiella pneumoniae isolates. BMC microbiology. 2024;24(1):168.
76. Madney Y, Mahfouz S, Bayoumi A, Hassanain O, Hassanain O, Sayed AA, et al. Carbapenem-Resistant Enterobacteriaceae (CRE) in Children with Cancer: The Impact of Rapid Diagnostics and Targeted Colonization Strategies on Improving Outcomes. Microorganisms. 2025;13(7):1627.
77. Li Y, Zhang Y, Sun X, Wu Y, Yan Z, Ju X, et al. National genomic epidemiology investigation revealed the spread of carbapenem-resistant Escherichia coli in healthy populations and the impact on public health.

Genome Medicine. 2024;16(1):57.
78. Houlihan E, McCormick A, Connor CO, Knowles SJ. Prevalence study of antimicrobial resistant organisms in very preterm neonates. Irish Journal of Medical Science (1971-). 2025;194(2):623-9.
79. González-Anleo C, Girona-Alarcón M, Casaldàliga A, Bobillo-Perez S, Fresán E, Solé-Ribalta A, et al. Risk factors for multidrug-resistant bacteria in critically ill children and MDR score development. European Journal of Pediatrics. 2024;183(12):5255-65.
80. Chiotos K, Han JH, Tamma PD. Carbapenem-Resistant Enterobacteriaceae Infections in Children. Curr Infect Dis Rep. 2016;18(1):2.
81. Uwaezuoke SN, Ndu IK, Eze IC. The prevalence and risk of urinary tract infection in malnourished children: a systematic review and meta-analysis. BMC Pediatrics. 2019;19(1):261.
82. Zhang Y, Xu G, Miao F, Huang W, Wang H, Wang X. Insights into the epidemiology, risk factors, and clinical outcomes of carbapenem-resistant Acinetobacter baumannii infections in critically ill children. Frontiers in Public Health. 2023;11:1282413.
83. Yin L, Lu L, He L, Yan G, Lu G, Zhai X, Wang C. Non-carbapenem-producing carbapenem-resistant Pseudomonas aeruginosa in children: Risk factors, molecular epidemiology, and resistance mechanism. Journal of Infection and Public Health. 2025;18(2):102634.
84. Lin Y, Peng Q, Li W, Chen B. Analysis of antibiotic resistance and risk factors of extended-spectrum beta-lactamases-producing Escherichia coli in hospitalized children with community-acquired urinary tract infections. International Urology and Nephrology. 2025;57(7):2271-8.
85. Jean S-S, Harnod D, Hsueh P-R. Global threat of carbapenem-resistant gram-negative bacteria. Frontiers in cellular and infection microbiology. 2022;12:823684.
86. Palacios-Baena ZR, Giannella M, Manissero D, Rodríguez-Baño J, Viale P, Lopes S, et al. Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review. Clin Microbiol Infect. 2021;27(2):228-35.
87. Mbele S, Vasaikar SD. Risk factors for Carbapenem-resistant Enterobacterales infections: A case-control study. S Afr Fam Pract (2004). 2025;67(1):e1-e10.
88. Oumer Y, Regasa Dadi B, Seid M, Biresaw G, Manilal A. Catheter-associated urinary tract infection: Incidence, associated factors and drug resistance patterns of bacterial isolates in southern ethiopia. Infection and drug resistance. 2021:2883-94.
89. González-Anleo C, Girona-Alarcón M, Bobillo-Perez S, Fresán-Ruiz E, Solé-Ribalta A, Ciutad-Celdrán M, et al. Risk Factors for Multiresistant Catheter-Associated Urinary Tract Infection in the Paediatric Critical Patient. Acta Paediatr. 2025;114(10):2624-32.
90. Wang C, Feng L, Chen R, Chen Y. Retrospective Case-Control Study of Risk Factors for Carbapenem-Resistant Klebsiella pneumoniae Infection in Children in China. Pathogens. 2024;13(12):1106.
91. Jent P, Berger J, Kuhn A, Trautner BW, Atkinson A, Marschall J, editors. Antibiotics for preventing recurrent urinary tract infection: systematic review and meta-analysis. Open Forum Infectious Diseases; 2022: Oxford University Press.
92. Karampatakis T, Tsergouli K, Behzadi P. Carbapenem-resistant Klebsiella pneumoniae: virulence factors, molecular epidemiology and latest updates in treatment options. Antibiotics. 2023;12(2):234.
93. Carpenter RE. Metabolic and microbial crossroads: Sodium-glucose cotransporter-2 inhibitors and urinary tract infections in (Asian) diabetes care. Health Sciences Review. 2025:100226.
94. Chen R, Wang G, Wang Q, Zhang M, Wang Y, Wan Z, et al. Antimicrobial resistance and molecular epidemiology of carbapenem-resistant Escherichia coli from urinary tract infections in Shandong, China. International Microbiology. 2023;26(4):1157-66.
95. Alarcón-Millán J, Bonilla-Delgado J, Fernández-Tilapa G, Nieto-Velázquez NG, Sierra-Martínez M, Alvarado-Castro VM, Cortés-Malagón EM. Helicobacter pylori Virulence Factors and Clarithromycin Resistance-Associated Mutations in Mexican Patients. Pathogens. 2023;12(2):234.
96. Aguilera-Alonso D, Escosa-García L, Saavedra-Lozano J, Cercenado E, Baquero-Artigao F. Carbapenem-resistant gram-negative bacterial infections in children. Antimicrobial agents and chemotherapy. 2020;64(3):10.1128/aac. 02183-19.
97. O'Donnell JN, Putra V, Maring BL, Ozer EA, Belfiore GM, Rhodes NJ. Effect of omadacycline alone and in combination with meropenem against carbapenem-resistant Acinetobacter baumannii isolates. Journal of Global Antimicrobial Resistance. 2022;29:147-9.
98. Bologna E, Licari LC, Manfredi C, Ditonno F, Cirillo L, Fusco GM, et al. Carbapenem-resistant Enterobacteriaceae in urinary tract infections: from biological insights to emerging therapeutic alternatives. Medicina. 2024;60(2):214.
99. Jo KJ, Yoo S, Song JY, Kim SH, Park SE. Non-carbapenem antimicrobial therapy in young infant with urinary tract infections caused by community-acquired extended-spectrum β-lactamase-producing Escherichia coli. Pediatrics & Neonatology. 2021;62(3):271-7.
100. Yin L, Wu N, Yan G, Lu L, Qian H, Yang W, et al. Carbapenem-resistant gram-negative bacterial prevention practice in nosocomial infection and molecular epidemiological characteristics in a pediatric intensive care unit. Heliyon. 2023;9(8).
101. Autore G, Neglia C, Di Costanzo M, Ceccoli M, Vergine G, La Scola C, et al. Clinical outcome of discordant empirical therapy and risk factors associated to treatment failure in children hospitalized for urinary tract infections. Children. 2022;9(2):128.
102. Forster CS, Almaazi A, Hamdy R, Harik N. Predictors of empiric antibiotic use in the emergency department in children without urinary tract infections. Pediatric emergency care. 2022;38(5):e1251-e6.
103. El Masri M, Haddad N, Saad T, Rizk NA, Zakhour R, Kanj SS, Zeenny RM. Evaluation of carbapenem use

before and after implementation of an antimicrobial Stewardship-Led carbapenem-Sparing strategy in a Lebanese tertiary hospital: A retrospective study. Frontiers in Cellular and Infection Microbiology. 2022;12:729491.
104. Kato T, Yagi Y, Maruyama T, Hamada Y. Pharmacokinetics/Pharmacodynamics-Based Repositioning of Cefmetazole and Flomoxef in Extended-Spectrum β-Lactamase-Producing Enterobacterales Treatment: An Injectable Carbapenem-Sparing and Outpatient Strategy. Antibiotics. 2025;14(8):737.
105. Muratore E, Baccelli F, Leardini D, Campoli C, Belotti T, Viale P, et al. Antimicrobial stewardship interventions in pediatric oncology: a systematic review. Journal of Clinical Medicine. 2022;11(15):4545.
106. Morgan JE, Phillips B, Haeusler GM, Chisholm JC. Optimising antimicrobial selection and duration in the treatment of febrile neutropenia in children. Infection and drug resistance. 2021:1283-93.
107. Mascarenhas D, Ho MSP, Ting J, Shah PS. Antimicrobial stewardship programs in neonates: a meta-analysis. Pediatrics. 2024;153(6):e2023065091.
108. Harun MGD, Sumon SA, Hasan I, Akther FM, Islam MS, Anwar MMU. Barriers, facilitators, perceptions and impact of interventions in implementing antimicrobial stewardship programs in hospitals of low-middle and middle countries: a scoping review. Antimicrobial Resistance & Infection Control. 2024;13(1):8.
109. Eljaaly K, Bidell MR, Gandhi RG, Alshehri S, Enani MA, Al-Jedai A, Lee TC, editors. Colistin nephrotoxicity: meta-analysis of randomized controlled trials. Open forum infectious diseases; 2021: Oxford University Press US.
110. Baquero-Artigao F, del Rosal Rabes T. Fosfomycin in the pediatric setting: evidence and potential indications. Revista Española de Quimioterapia. 2019;32(Suppl 1):55.
111. Sizar O, Rahman S, Sundareshan V. Amikacin. StatPearls [Internet]: StatPearls Publishing; 2023.
112. Eslami M, Safaripour A, Banihashemian SZ, Nikjoo Niaragh S, Hemmati MA, Shojaeian A, et al. Innovative antibiotic therapies for carbapenem-resistant gram-negative bacterial infections: clinical efficacy, safety, and comparative studies. Microorganisms. 2025;13(2):295.
113. Falcone M, Tiseo G, Nicastro M, Leonildi A, Vecchione A, Casella C, et al. Cefiderocol as rescue therapy for Acinetobacter baumannii and other carbapenem-resistant Gram-negative infections in intensive care unit patients. Clinical Infectious Diseases. 2021;72(11):2021-4.
114. Ustundag G, Oncel EK, Sahin A, Keles YE, Aksay AK, Ciftdogan DY. Colistin treatment for multidrug-resistant gram-negative infections in children: caution required for nephrotoxicity. Sisli Etfal Hastan Tip Bul. 2022;56(3):427-34.
115. Purcell R, Yeoh D, Bowen A, Britton PN, Carr JP, Chen M, et al. A multicentre, retrospective audit of fosfomycin use for urinary tract infections in Australian children and adolescents. Journal of Antimicrobial Chemotherapy. 2023;78(7):1616-21.
116. Cura Yayla BC, Bedir Demirdağ T, Tapısız A, Atikel YÖ, Tezer H, Şahin EA, et al. Comparison of Carbapenem vs. Amikacin Antimicrobial Therapy for Pediatric Acute Pyelonephritis Caused by Extended-Spectrum B-Lactamase-Positive Enterobacteriaceae. Children. 2025;12(7):945.
117. Lai C, Ma Z, Zhang J, Wang J, Wang J, Wu Z, Luo Y. Efficiency of combination therapy versus monotherapy for the treatment of infections due to carbapenem-resistant Gram-negative bacteria: a systematic review and meta-analysis. Systematic Reviews. 2024;13(1):309.
118. Buettcher M, Trueck J, Niederer-Loher A, Heininger U, Agyeman P, Asner S, et al. Swiss consensus recommendations on urinary tract infections in children. Eur J Pediatr. 2021;180(3):663-74.
119. Meng H, Zhao Y, An Q, Zhu B, Cao Z, Lu J. Use of Ceftazidime-Avibactam for Suspected or Confirmed Carbapenem-Resistant Organisms in Children: A Retrospective Study. Infect Drug Resist. 2023;16:5815-24.
120. Schmid H, Brown L-AK, Indrakumar B, McGarrity O, Hatcher J, Bamford A. Use of Cefiderocol in the Management of Children With Infection or Colonization With Multi-drug Resistant Gram-negative Bacteria: A Retrospective, Single-center Case Series. The Pediatric Infectious Disease Journal. 2024;43(8):772-6.
121. Al Dabbagh M, Alghounaim M, Almaghrabi RH, Dbaibo G, Ghatasheh G, Ibrahim HM, et al. A Narrative Review of Healthcare-Associated Gram-Negative Infections Among Pediatric Patients in Middle Eastern Countries. Infect Dis Ther. 2023;12(5):1217-35.
122. Gandra S, Alvarez-Uria G, Turner P, Joshi J, Limmathurotsakul D, van Doorn HR. Antimicrobial resistance surveillance in low-and middle-income countries: progress and challenges in eight South Asian and Southeast Asian countries. Clinical microbiology reviews. 2020;33(3):10.1128/cmr. 00048-19.
123. Dejonckheere Y, Desmet S, Knops N. A study of the 20-year evolution of antimicrobial resistance patterns of pediatric urinary tract infections in a single center. Eur J Pediatr. 2022;181(9):3271-81.
124. Organization WH. Global antimicrobial resistance and use surveillance system (GLASS) report 2022: World Health Organization; 2022.
125. Abbas S. The challenges of implementing infection prevention and antimicrobial stewardship programs in resource-constrained settings. Antimicrobial Stewardship & Healthcare Epidemiology. 2024;4(1):e45.

