Antibiotic Susceptibility Patterns of Uropathogenic Organisms in Febrile Under-Five Children at Federal Medical Centre, Owerri, Nigeria:Implications for Empiric Treatment Strategies

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ABSTRACT

Urinary tract infections (UTIs) in under-five children are often under-diagnosed, leading to potential adverse outcomes. This study investigates the antibiotic susceptibility patterns of uropathogenic organisms isolated from febrile under-five children at the Federal Medical Centre, Owerri, Nigeria. The research highlights the dynamic nature of antibiotic sensitivity, emphasizing the need for regular assessments and prudent antibiotic use. Findings reveal varying susceptibility to commonly used antibiotics, necessitating a reevaluation of empirical choices. Amikacin, gentamicin, and levofloxacin demonstrate high sensitivity, while co-trimoxazole and co-amoxiclav exhibit lower effectiveness. The study underscores the importance of regional considerations in managing UTIs and advocates for improved antibiotic stewardship.

Keywords: Uropathogenic organisms, febrile under-five children, antibiotic susceptibility, urinary tract infections and Nigeria

INTRODUCTION

Urinary tract infection (UTI) is a common cause of fever in under-five children, however it is grossly under-diagnosed and untreated [1]. Unrecognised UTI increases the likelihood of adverse short and long-term outcomes such as renal scarring, hypertension and chronic kidney disease (CKD) [2]. Furthermore, antibiotic sensitivity (or resistance) profile of UTI-causing organisms is a dynamic event, with global and regional data indicating reducing sensitivity to commonly used antibiotics; this creates a need for each practice environment to routinely assess the antibiotic sensitivity profile of common organisms [2-4]. The increasing resistance to antibiotics among uropathogens worldwide is a significant concern for clinicians, necessitating periodic reviews of empiric antibiotic choices [5-6]. This summary focuses on the sensitivity patterns of various antibiotics commonly used for urinary tract infections (UTIs) in febrile under-five children [7-9]. Nitrofurantoin:Initially effective for UTIs, but sensitivity varies with causative organisms and regions [10-11]. High sensitivity reported in Nigeria and Tanzania, possibly due to limited and controlled use. Some regions, like Sudan, show higher resistance, emphasizing the need for cautious use.Co-trimoxazole:Widely used in the 1970s, but indiscriminate use and prophylaxis may contribute to low sensitivity. Studies in India, Tanzania, and Nigeria report low sensitivity, indicating potential overuse and resistance [12-14]. Regional variations suggest differing susceptibility patterns and possible abuse rates. Amoxicillin-clavulanate: An alternative for UTI treatment, but changing resistance patterns are documented. Varying sensitivity across regions in Sudan, Tanzania, and Nigeria, indicating evolving resistance. Suggests the importance of monitoring and adjusting empirical choices [15-17]. Quinolones (Ciprofloxacin and

Levofloxacin):Initially not routine for children due to arthropathy risks, but studies show transient effects.Ciprofloxacin sensitivity varies across regions, with some studies indicating emerging resistance.Levofloxacin resistance patterns also show discrepancies among different regions. Aminoglycosides (Gentamycin and Amikacin):Potent antibiotics with high sensitivity [18-19]. Gentamycin shows varied sensitivity, possibly indicating regional differences. Amikacin consistently demonstrates high sensitivity, making it an effective option. Cephalosporins (Ceftriaxone, Cefixime, and Cefuroxime): Second and third-generation cephalosporins are commonly used but face waning potency. Ceftriaxone sensitivity varies across regions, with recent studies suggesting emerging resistance [20-25]. Cefixime and Cefuroxime exhibit reduced sensitivity in some regions, emphasizing the impact of indiscriminate use. The observed variations in antibiotic sensitivity underscore the importance of prudent antibiotic use, regular reviews of empirical choices, and regional considerations in managing UTIs in children. The emergence of resistance highlights the need for improved antibiotic stewardship and monitoring practices [26-30].

Aim and Objectives
The aim of this research was to determine the pattern of antibiotic susceptibility observed in uropathogenic organisms that were isolated in Febrile Under-Five Children at Federal Medical Centre, Owerri, Imo State, Nigeria.

RESEARCH QUESTION
What is the antibiotic susceptibility pattern among the isolated uropathogenic organisms?
Specific Objective
To determine the antibiotic susceptibility pattern among the isolated uropathogens.
METHODOLOGY
Study Area
The study was carried out at the Paediatric Outpatient Clinics and Emergency Paediatric Unit of the Federal Medical Centre Owerri, Imo state. The State is one of the five states of South-Eastern Nigeria and it is made up of 27 local government areas. Owerri is the capital of Imo State and it is made up of three local government areas namely: Owerri Municipal, Owerri North and Owerri West. The estimated population of Owerri is about 400,000. The projected population for 2020 is about 872,604. The Federal Medical Centre is a tertiary health facility located centrally in Owerri. It has two outreach centres located at Umunama-Mbaise and Izombe-Oguta and serves as a referral centre for hospitals from all over the state and the neighbouring states of Rivers and Anambra. The Paediatric Outpatient Clinics run from Mondays through Fridays between 8am and 4pm. An average of 70 patients are seen daily with an annual average of 13,000 patients. It is the first point of care for all sick children visiting the hospital except for emergencies and children who come to the hospital during the weekend who are managed in the emergency paediatric unit. Sick children presenting after 4pm are also seen at the emergency unit. The emergency paediatric unit runs a 24-hour service and an average of 300 patients seen monthly with an average of 4000 patients seen per annum.

Study Design
This was a hospital-based descriptive cross-sectional study.
Ethical Considerations
Ethical clearance and permission to carry out the study was obtained from the Research and Ethics Committee of the Federal Medical Centre Owerri. Also, parents and care givers of eligible children provided a written informed consent. The study was conducted in a manner that ensured that participation in the study did not result in undue delay of commencement of standard treatment or management. In addition, the results of children with positive urine culture were passed on to the team responsible for the care of the child as soon as it became available.
Study Population
The study population consisted of all febrile (axillary temperature > 37.5°C) children between the ages of 0 and 59 months attending the Paediatric Outpatient Clinics and Emergency Paediatric Unit that met the inclusion criteria.
Inclusion Criteria
1. Children between the ages of 0 and 59 months presenting with fever (axillary temperature > 37.5°C).
2. Children whose parents or caregivers provided written informed consent.
Exclusion Criteria
1. Very ill children requiring immediate resuscitation and commencement of antibiotics which would have delayed by participation in the study.
2. Children who received systemic (oral or parenteral) antibiotics within the previous 72 hours.

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Sample Size Calculation

The minimum sample size was estimated using the Cochran formula for prevalence studies.[115]

$$\text{Sample size, } n = \frac{Z^2 pq}{d^2}$$

Where n= sample size

    Z= Standard normal deviation at 95% confidence level= 1.96
    P= Prevalence of UTI in febrile under 5 children in Enugu[9] = 11%
    Q= (1-p)
    d =level of precision= 0.05

$$n = \frac{Z^2 pq}{d^2}$$

= [(1.96)² × 0.11 × 0.89] / (0.05)²
Therefore, the minimum calculated sample size=152
A further 10% (16) was added to the minimum sample calculated to factor in risk of attrition.
Therefore 170 children were recruited for the study.

Sampling Technique

Eligible children were recruited consecutively.

Study Procedure

Each recruited subject had a detailed history and physical examination. The findings were documented in the data entry form. The variables entered into the form included demographic data (research number, age, and gender), history of fever, presence of symptoms suggestive of urinary tract infections and treatment received prior to enrolment in the study. Other information recorded in the form included the temperature reading, the presence of bladder mass, ballotable kidneys, uncircumcised penile shaft, neural tube defects and the presence of other focus of infections.

Temperature

Body temperature was measured by using mercury in glass clinical thermometer. This was placed in contact with the skin on the subjects' axilla for four minutes after which reading was recorded. A subject was considered febrile when the temperature was above 37.5°C.

Specimen Collection

After recruitment into the study, the investigator labelled the sample bottles appropriately and midstream urine was collected by the researcher or the caregivers under supervision. This was done by voiding the initial part of the urine stream into the toilet or another container and at approximately the middle of the urine flow the specimen bottle was positioned to capture urine. However, in children not yet toilet trained, spot urethral catheterization was carried out under aseptic conditions. In collecting the sample by urethral catheter, the researcher or the assistant wore sterile gloves then the child was placed in supine position and the labia or penis was cleaned with antiseptic swab. In females, the labia was parted to expose the urethral opening, the catheter was lubricated with sterile anaesthetic gel (KY jelly) before insertion into the urethral opening upward until urine begins to flow out. For the male child, the penis was lifted and the foreskin retracted in the uncircumcised. The urethral opening was cleaned with antiseptic swabs in a circular motion from the urethral opening to the base of the penis and a sterile lubricant was applied to the catheter before insertion. The penis was held with slight upward tension and perpendicular to the child's body and the catheter was inserted. The size of the catheter to be used was French gauge (Fr) 6 for children under one year of age while French gauge (Fr) 8 was used in subjects older than one year. Urine specimen was collected into two sterile wide necked leak proof universal bottles. One sample was used for dipstick urinalysis and the other for microscopy, culture and sensitivity in the laboratory. Specimens for culture were sent to the laboratory within 15-20 minutes of collection. In cases where a delay was anticipated before processing, specimens were stored in the refrigerator for no longer than six hours.

Specimen Processing

A macroscopic examination was done for every urine sample to record the colour and nature (to assess whether the urine was clear or turbid). Urinalysis was also carried out qualitatively using chemstrip-10 dipsticks (Roche Diagnostics Montreal, Quebec Canada) to detect the presence of protein, blood, nitrite and leucocyte esterase. The strip was dipped for no longer than one second into the specimen and excess urine was removed by drawing the edge of the strip along the rim of the container, the test strip was turned on its side and placed on a piece of absorbent

paper to prevent mixing of chemicals. A timer was set for two minutes. After one minute, the strip was held close to the colour blocks printed on the reagent vial and read for protein, blood and nitrite while the leucocyte esterase was read at two minutes. Each test pad was carefully matched to its reference. All results were read and recorded between one and two minutes. Results were subsequently recorded in the questionnaire.

Urine Microscopy

Urine microscopy was carried out at the laboratory by the microbiologist with active participation of the investigator using a wet preparation. This was done using about 5 ml of well mixed urine which was aseptically transferred to a labelled conical tube and centrifuged at 2000 revolutions per minute (rpm) for five minutes. The supernatant was decanted into a second container. A drop of the well mixed sediment was transferred to a slide and covered with a cover glass. The preparation was viewed under a light microscope using 40x objective. Presence of pyuria (>5WBC/HPF) was regarded as significant and suggestive of UTI.

Urine Culture

A sterile calibrated wire loop that takes 0.001 ml of urine was used to inoculate a loopful of urine on blood agar and Cysteine Lactose Electrolyte Deficient (CLED) agar. Then the plate was incubated aerobically at 35^0C- 37^0C for18 - 24 hours, after which those with significant growth (colony count $\geq 10^5$ CFU/ml for MSU or $\geq$ 50,000 CFU/ml for catheter specimen) were identified by standard bacteriological methods, colonial morphology and *Microbact*® 12 A[116]. Urinary tract infection was defined as the presence of compatible clinical features and significant bacteriuria taking into consideration the mode of urine collection[8]. Urinary tract infection was defined as a growth of at least 50,000CFU/ml of a single organism in catheter specimen urine and at least 100,000 CFU/ml in midstream urine samples. The results of subjects with confirmed UTI was communicated to the managing team for treatment according to standard protocol and the subsequently referred to Nephrology clinic for follow-up.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was also done on the isolates from urine samples with significant bacteriuria. This was determined using Kirby Bauer discs diffusion method[114]. In this method, four colonies were inoculated into 5ml sterile normal saline compared with 0.5 McFarland standard (with approximate cell density of $1x10^8$ CFU/ml) to ensure equal turbidity and a sterile swab stick dipped into the suspension. The swab was streaked on the entire agar surface of Mueller Hinton agar and a known concentration antibiotics disks which have been equilibrated with the room temperature were placed gently equidistant to each other with five disks per 90mm petri dish. The plates were incubated aerobically at 35-37°C for 24 hours after which the diameter of the zones of inhibition were measured to the nearest millimetre using transparent calibrated ruler and compared to the Clinical and Laboratory Standards Institute (CLSI) 2014 interpretative chart[113]. The susceptibility test was carried out using these antibiotics co-trimoxazole (25/23 □g), nitrofurantoin (30 □g), ciprofloxacin (5 □g), co-amoxiclav (20/10 □g), gentamycin (10 □g), cefixime (30 □g) and cefuroxime (30 □g) the other antibiotics tested were levofloxacin (5 □g), amikacin (30 □g) and ceftriaxone (30 □g). The antibiotic susceptibility testing and all other procedures were quality controlled using ATCC 25923 *Staphylococcus aureus* and ATCC 25922 *Escherichia coli*.

Data Analysis

Data was coded and entered into a computer. It was analysed using IBM Statistical Package for Social Sciences (SPSS) version 20.0. Frequency tables, charts and figures were used to summarize variables as appropriately required. Mean and standard deviation were used to summarize quantitative variables that were normally distributed. Chi square (□²) and where necessary Fisher's exact test and likelihood ratio were used to test for association between categorical variables. A p-value of < 0.05 was considered statistically significant. Security of data was ensured as information on the data entry form was made anonymous by excluding names and phone numbers. The proforma were also kept safe and made available only to the researcher, supervisors and research assistants.

RESULTS
Demographic characteristics of study subjects

One hundred and seventy children aged 0-59 months were recruited for this study. One hundred and fourteen (67.1%) of the 170 subjects were males while 56 (32.9%) were females with a male-female ratio of 2:1. Fifty (29.4%) of the subjects were aged 0-11 months. The mean age was 24.0±16.1 months. (Table 1)

Table 1: Demographic characteristics of study subjects

Variables	Frequency n (%)
Gender	
Male	114 (67.1)
Female	56 (32.9)
Age Groups (months)	
0 − 11	50 (29.4)
12 − 23	39 (22.9)
24 − 35	37 (21.9)
36 − 47	22 (12.9)
48 − 59	22 (12.9)

Presenting complaints of febrile under-five children

Cough (103; 60.6%) and catarrh (93; 57.6%), were the most common symptoms at presentation to the hospital among the study participants. A small proportion of the children had symptoms suggestive of urinary tract infection; Twenty-three (13.5%), 4 (2.4%), and 4 (2.4%) had frequent urination, foul smelling urine and painful urination respectively. Most symptoms were non-specific (Table 2).

Table 2: Presenting complaints of febrile under-five children

Symptoms	Frequency n (%)
Fever	170 (100)
Cough	103 (60.6)
Catarrh	93 (57.6)
Vomiting	46 (27.1)
Abdominal pain	30 (17.6)
Frequent urination	23 (13.5)
Diarrhoea	14 (8.2)
Convulsions	5 (2.9)
Foul smelling urine	4 (2.4)
Painful urination	4 (2.4)
Jaundice	1 (0.6)

Overall Susceptibility of Organisms to Antibiotics

The susceptibility of the aetiologic agents were highest to Amikacin followed by levofloxacin and gentamycin (84.4% each). The antibiotics with the lowest sensitivity were co-trimoxazole and co-amoxiclav which had 21.9% and 28.1% respectively. The susceptibility of all isolated organisms to Ceftriaxone was 43.8% as shown in Figure 1.
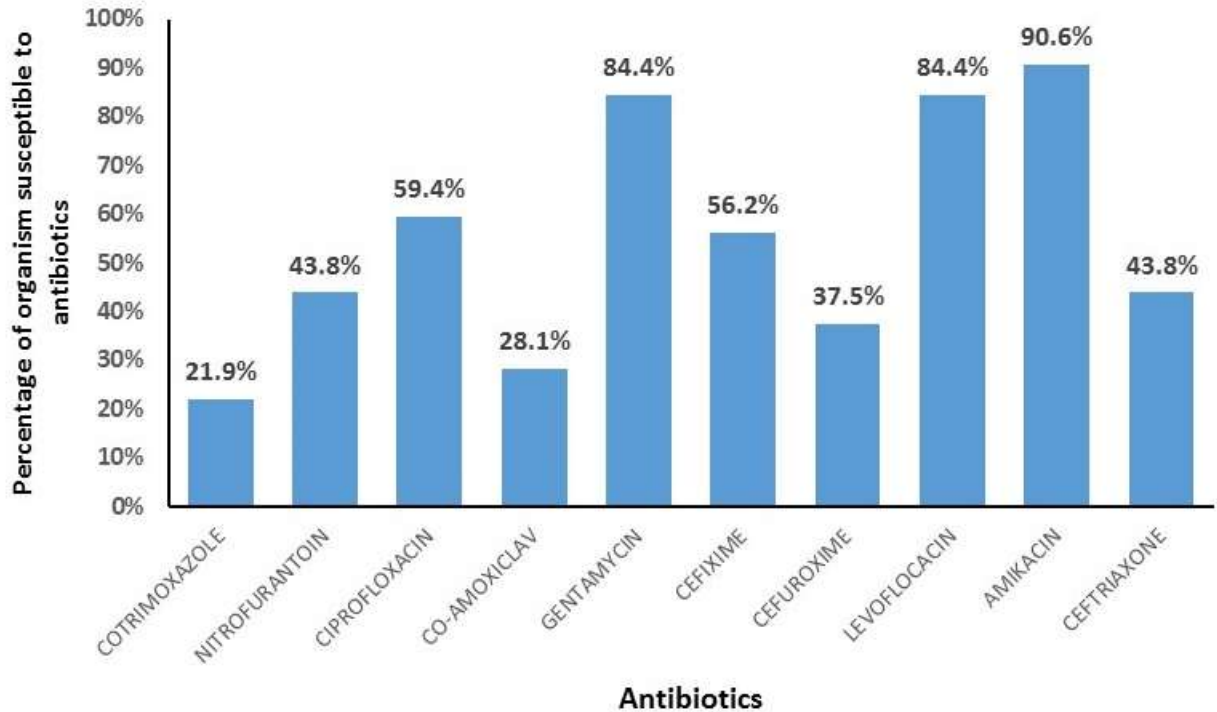
Figure 1: Overall susceptibility of Organisms to Antibiotics
Susceptibility pattern of aetiologic agents to antibiotics

Amikacin achieved more than 80% sensitivity in all organisms except *Acinetobacter baumanii*, levofloxacin was also found to be active against most organisms. *E. coli* was found to have more than 80% susceptibility to only gentamycin and Amikacin. Similarly, *S. aureus* had more than 80% susceptibility to only gentamycin and levofloxacin. The most common uropathogens *E. coli, Klebsiella spp and S. aureus* had low susceptibility to commonly used antibiotics such as co-trimoxazole and co-amoxiclav. Ceftriaxone, cefixime and cefuroxime had sensitivity of 43.8%, 56.3% and 37.5% respectively as shown (Table 3).

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Table 3: Susceptibility pattern of aetiologic agents to common antibiotics.

Antibiotics	Aetiologic Agents n (% susceptibility)							
	E COLI n = 12	KLEB n = 6	ENTERO n = 3	STAPH n = 5	ACTINO n = 3	CITRO n = 2	SERR n = 1	Total n = 32
COTRIMOXAZOLE	1 (8.3)	2 (33.3)	0 (0)	1 (20.0)	2 (66.7)	1 (50.0)	0 (0.0)	7 (21.9)
NITROFURANTOIN	4 (33.3)	6 (100)	0 (0)	2 (40.0)	1 (33.3)	1 (50.0)	0 (0.0)	14 (43.8)
CIPROFLOXACIN	6 (50.0)	5 (83.3)	2 (66.7)	3 (60.0)	1 (33.3)	1 (50.0)	1 (100)	19 (59.4)
CO-AMOXICLAV	4 (33.3)	1 (16.7)	2 (66.7)	1 (20.0)	0 (0)	1 (50.0)	0 (0.0)	9 (28.1)
GENTAMYCIN	11 (91.7)	6 (100)	1 (33.3)	5 (100)	1 (33.3)	2 (100.0)	1 (100)	27 (84.4)
CEFIXIME	8 (66.7	4 (66.7)	1 (33.3)	1 (20.0	1 (33.3)	2 (100.00	1 (100)	18 (56.3)
CEFUROXIME	3 (25.0)	4 (66.7)	1 (33.3)	2 (40.0)	1 (33.3)	1 (50.00	0 (0.0)	12 (37.5)
LEVOFLOCACIN	7 (58.0)	6 (100)	3 (100)	5 (100)	3 (100)	2 (100.0)	1 (100)	27 (84.4)
AMIKACIN	11 (91.7)	6 (100)	3 (100)	4 (80.0)	2 (66.7)	2 (100.0)	1 (100)	29 (90.6)
CEFTRIAXONE	5 (41.7)	4 (66.7)	1 (33.3)	1 (20.0)	0	2 (100.0)	1 (100)	14 (43.8)

E.coli : Esscherichia coli, KLEB : Klebsiella spp, ENTERO : Enterobacter cloacae, STAPH : Staphyloccocus aureus, ACTINO : Acinetobacter baumanii, CITRO : Citrobacter fruendii, SERR : Serratia liquefacin

DISCUSSION

The majority of the isolates were sensitive to amikacin, gentamycin and levofloxacin. This is comparable to the report by Saravan [31] in India as well as some Nigerian researchers [9,10,11,32,33,34-39]. The possible low rate of abuse in Nigeria and uncommon use of aminoglycosides and levofloxacin in children may explain this finding. Conversely, West *et al* [40] in Port Harcourt and Muoneke *et al* [15] in Abakaliki Nigeria observed low sensitivity to gentamycin. This study was a cross-sectional type and therefore was able to identify the prevailing sensitivity pattern unlike Muoneke *et al* [15] in Abakaliki which was retrospective with possible missed cases due to under-diagnosis. In addition this finding may signify an emerging resistant pattern in these localities. Ciprofloxacin had good sensitivity to all isolated uropathogens in this study. Ciprofloxacin is increasingly being used in the empiric treatment of UTI and other bacterial infections in recent years as studies have shown that the arthropathy which was the major contraindication was found mostly in rats and the arthralgia when it occurs is usually transient and resolves with the discontinuation of the antibiotic. Several authors have also documented similar high sensitivity to ciprofloxacin [10,28,33]. However, Muoneke *et al* [15] in Abakaliki Nigeria reported low sensitivity of the uropathogens to ciprofloxacin. Whereas this study was carried out in an area with low quinolones use among children, attributed their finding to its frequent use as antibiotic of choice in the treatment of UTI in the community. The observed sensitivity pattern may present the need for in-patient use of gentamycin or amikacin and oral ciprofloxacin as empiric out-patient treatment for UTI among under-five children within and around the study locality, until the availability of urine culture result.

The sensitivity to ceftriaxone by all isolated uropathogens in this study was below 50%. This may suggest an emerging resistance to ceftriaxone which could be as a result of its wide use and possible abuse in the management of variety of bacterial infections in children. This trend is becoming a great cause of concern with regards to antibiotic stewardship [34]. This corroborates the findings by Ntukula in Tanzania, and other reports from different regions of Nigeria [35,40]. This however differs from the findings by [33] in Ibadan and Ibeneme [9] in Enugu Nigeria. This study was done recently when ceftriaxone appears to be one of the most commonly used antibiotics in the treatment of bacterial infections in children, the studies by Adebowale [33] and Ibeneme *et al* [9] were carried out over a decade ago and may possibly account for the high sensitivity to ceftriaxone as opposed to this study that reported low ceftriaxone sensitivity. Hence on account of this finding, the use of ceftriaxone empirically for suspected UTI may need to be reconsidered since it may mean that more than half of children will be receiving a potentially ineffective medication.

The isolated uropathogens in this study were least sensitive to cotrimoxazole and amoxicillin-clavulanate, drugs which were previously the antibiotics of choice in the treatment of UTI in children. The emerging widespread resistance could be attributed to the practice of self-medication among care givers, easy access to antibiotics via over-the counter purchase and a possible spill-over effect of the use of cotrimoxazole as prophylaxis for *Pneumocystis jiroveci* pneumonia in HIV/AIDS [9, 10, 34, 35]. This agrees with the observation by some Tanzanian [30,38] and Nigerian [9,10,11,35] authors. However, Okunola *et al* [10] in Benin –City and West *et al* [40] in Port Harcourt Nigeria documented high sensitivity to co-amoxiclav by the isolated uropathogens among febrile under-five children. The difference in the characteristics of the study participants as well as the period of the research may have accounted for this difference. Therefore, in view of this development, the use of cotrimoxazole and amoxicillin – clavulanate in the empiric treatment of UTI among febrile under-five children should be re-evaluated.

CONCLUSION

The study highlights the varying antibiotic susceptibility patterns among uropathogenic organisms in febrile under-five children, emphasizing the importance of prudent antibiotic use and regular reviews of empirical choices. Amikacin, gentamicin, and levofloxacin demonstrate notable sensitivity, while co-trimoxazole and co-amoxiclav show lower efficacy. The findings advocate for a reevaluation of empirical treatment strategies, considering the regional context. The emergence of resistance underscores the need for enhanced antibiotic stewardship practices to ensure effective management of urinary tract infections in this vulnerable population.

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