Antimicrobial sensitivity pattern of organisms causing urinary tract infection in children with sickle cell anemia in Maiduguri, Nigeria

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Abstract

Background: Patients with sickle cell disease have increased tendency to develop frequent and severe infections, especially of bones and urinary tract.

Objective: The knowledge of antimicrobial sensitivity pattern of common etiological agents will serve as a guide to empiric treatment while results of urine culture and sensitivity are being awaited.

Materials and Methods: Antimicrobial sensitivity test was carried out on bacterial isolates from the urine of febrile children with sickle cell anemia (SCA) and children with HbAA in Maiduguri. Urine specimens were collected and cultured by standard methods. Sensitivity to 15 antimicrobials (based on availability of sensitivity disc) was tested using the disc-diffusion technique of stokes.

Results: Significant bacteriuria was obtained from 65 (26%) of the 250 children with SCA and 51 (20.4%) of the 250 controls. The isolates were *E. coli, Klebsiella, Coliforms, Proteus, Staph aureus* and *Salmonella*. Sensitivity was highest to 3rd generation cephalosporins, followed by the quinolones: ciprofloxacin (86.2%), ofloxacin (83.1%), and peflacine (73.8%). Sensitivity of the organisms to some of the commonly used antibiotics like ampicillin, cotrimoxazole, and nalidixic acid was generally low. In general, the pattern of bacteriuria and their sensitivity in the SCA group was similar to the pattern in the control group.

Conclusion: Etiological agents of childhood urinary tract infections (UTI) in this environment are resistant to most of the drugs commonly recommended for its treatment. Amoxicillin/clavulanic acid, cefuroxime, and gentamicin, are recommended as first-line drugs for treatment of UTI while awaiting results of culture and sensitivity. Ceftriaxone and ceftazidime should be reserved for case of non response to first-line drugs and severe infections.

Key words: Antimicrobial agents, Nigeria, sickle cell anemia, urinary tract infections

Introduction

Urinary tract infection (UTI) is a significant cause of morbidity in childhood, and children with sickle cell disease (SCD) have been observed to have an increase risk of UTI. [1-4] Delay in instituting appropriate treatment may lead to formation of scar and subsequent renal impairment.[5,6] Knowledge of antibiotic sensitivity pattern of the common etiological agents is of great importance.

The knowledge will also serve as a guide to first-line treatment while the results of culture and sensitivity are being awaited. Prompt treatment will reduce the risk of renal scaring and other sequelae of UTI in sickle cell anemia (SCA) individuals such as precipitation of crisis and fatal septicemia.[7,8]

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This study is relevant since there is no previous report to guide antibiotic therapy for UTI in children with SCA in this environment. The study was therefore designed to determine the antibiotic sensitivity pattern of bacterial agents isolated from the urine of febrile SCA children seen at University of Maiduguri Teaching Hospital and State Specialist Hospital Maiduguri, North-Eastern Nigeria.

Materials and Methods

The study population consisted of 250 patients with SCA (Hemoglobin SS) aged 6 months to 15 years presenting with fever (temperature $\geq 37.5°C$) at the Pediatric Consultants Clinics or Children Emergency Wards of both the Teaching Hospital and the State Specialist Hospital, Maiduguri, between October 2005 and January 2008. Equal number (250) of children with HbAA matched for age and sex with fever were enrolled as controls. Children clinically suspected to have conditions with increased risk of UTI such as glomerulopathy, nephrotic syndrome, severe malnutrition, or obstructive uropathies were excluded from the study.[9,10] Children who had history of antibiotic intake in the last 7 days and dehydrated children were also excluded from the study.

After detailed history and clinical examination was carried out on each patient, midstream urine specimen were carefully collected in children that have achieved bladder control, while suprapubic bladder aspiration was carried out in infants. The urine specimens were put into two sterile Universal bottles; one was used for dipstick urinalysis using multistix 10G (Bayer Corporation 2501 NW 34th Place Pompano Beach, Florida, USA) for the nitrite test, and the other specimen were taken immediately to the microbiology department of the Teaching Hospital for culture. Urine specimen collected at the State Specialist Hospital were kept in refrigerator at 4°C for the period of the clinic (2-3 h) and later transported immediately to the Teaching Hospital's microbiology department, usually 10 to 20 minutes' drive. The specimens were cultured immediately by inoculation into blood and MacConkey agar and incubated at 37°C for 48–72 h.[11] Samples showing at least 10^5 colony-forming units of bacteria per mL were considered to indicate significant bacteriuria.[12] Identification of the organisms to species level was via systematic bacteriological and biochemical test using standard techniques.[13]

Antimicrobial sensitivity tests were performed using the dick-diffusion technique of stokes,[14] using Oxoids miltidiscs. The Oxoids sensitivity discs were impregnated with ampicillin 2 μg, cephalexin 10 μg, ciprofloxacin 10 μg, erythromycin 10 μg, Pefloxacin 10 μg, chloramphenicol 10 μg, nalidixic acid 30 μg, amoxicillin/clavulanic acid 10 μg, ceftriaxone 30 μg, ofloxacin 10 μg, cotrimoxazole 10 μg, gentamicin 10 μg, cefuroxime 30 μg, ceftazidime 30 μg, and amoxicillin 10 μg. The control method was set up using Oxford *Staphylococcus aureus* NCTC 1048 for Gram-positive bacteria and Oxford *Escherichia coli* NCTC 10896 for Gram-negative bacteria. The organisms were regarded as sensitive when the zone of inhibition measured using a calibrated ruler was compared to the control bacteria.

Results

The mean age of the children with SCA was 5.6 ± 4.4 years, while the mean age of the controls was 5.4 ± 4.3 years. There were 145 boys and 105 girls in the SCA group and the HbAA control group, giving a male:female ratio of 1.4:1. The prevalence of bacteriuria in the group with SCA was 26.0% (65 of 250) and was 20.4% (51 of 250) in the controls. The most frequently isolated organism in the SCA and the control group was *E. coli,* 18 (27.7%) and 19 (37.3%), respectively. Other organisms in the SCA group were *Klebsiella* 24.6%, *Proteus* 17%, *Staph aureus* 13.8%, *Coliforms* 13.8%, and *Salmonella* 3.1%, while in the control group were as follows; *Klebsiella* 11.8%, *Proteus* 3.9%, *Staph aureus* 21.6%, and *Coliforms* 25.4%.

Table 1 shows the sensitivity of the isolates from SCA patients. The drugs associated with least sensitivity were erythromycin 10.8%, ampicillin 16.9%, cotrimoxazole 21.5%, and nalidixic acid 23.1%. Sensitivity was generally higher to the 3rd generation cephalosporins, especially ceftriaxone 89.2%, followed by the quinolones; ciprofloxacin, ofloxacin, and peflacine (86.2%, 83.1%, and 73.8%, respectively), and

Table 1: Antimicrobial sensitivity pattern of urinary isolates among SCA children

Isolates	Sensitivity (%)														
	AMP	CPX	CIP	OFL	COT	ERY	PEF	CHL	GEN	CXM	NAL	AUG	CRO	AML	CAF
E. coli n = 18	5.6	22.2	94.4	83.3	16.7	16.7	66.7	50.0	61.1	55.6	38.9	38.9	83.3	33.3	72.2
Klebsiella n = 16	25.0	50.0	93.8	81.3	25.0	0	87.5	50.0	31.3	68.8	37.5	43.8	93.8	31.3	81.3
Proteus spp n – 11	18.2	27.3	72.7	81.8	18.2	0	63.6	36.4	45.5	63.6	18.2	9.1	90.9	0	81.8
Staph aureus n = 9	33.3	55.6	77.8	77.8	44.4	22.2	66.7	33.3	44.4	44.4	0	44.4	88.9	33.3	55.6
Coliforms n = 9	11.1	55.6	77.8	88.9	0	22.2	88.9	55.6	55.6	55.6	0	44.4	88.9	22.2	88.9
Salmonella spp n=2	0	0	100	100	50.0	0	50.0	100	50.0	50.0	0	100	100	50.0	100
Overall sensitivity *n*=65	16.9	38.5	86.2	83.1	21.5	10.8	73.8	46.2	47.7	58.5	23.1	38.5	89.2	26.2	76.9

AMP = Ampicillin; ERY = Erythromycin; NAL = Nalidixic Acid; CPX = Cephalexin; PEF = Pefloxacin; AUG = Amoxicillin/clavulanic acid; CIP = Ciprofloxacin; CHL = Chloramphenicol; CRO = Ceftriaxone; OFL = Ofloxacin; GEN = Gentamicin; AML = Amoxicillin; COT = Cotrimoxazole; CXM = Cefuroxime; CAF = Ceftazidime

Table 2: Antimicrobial sensitivity pattern of urinary isolates among controls

Isolates	Sensitivity (%)														
	AMP	CPX	CIP	OFL	COT	ERY	PEF	CHL	GEN	CXM	NAL	AUG	CRO	AML	CAF
E. coli n = 19	10.5	31.6	78.9	78.9	26.3	5.3	68.4	42.1	63.2	57.9	42.1	15.8	100	21.1	84.2
Klebsiella n = 6	16.7	33.3	100	100	16.7	0	33.3	33.3	66.7	50.0	16.7	16.7	100	0	100
Proteus spp n = 2	0	0	100	100	0	0	50.0	50.0	100	100	0	0	100	0	100
Staph aureus n = 11	9.1	45.5	90.9	63.6	27.3	36.4	72.7	72.7	81.8	63.6	54.5	63.6	100	9.1	90.9
Coliforms n = 13	7.7	23.1	100	84.6	0	7.7	53.8	69.2	61.5	53.8	38.5	30.8	92.3	15.4	84.6
Overall sensitivity *n* = 51	9.8	31.4	90.2	80.4	17.6	11.8	60.8	54.9	68.6	58.8	39.2	29.4	98.0	13.7	88.2

AMP = Ampicillin; ERY = Erythromycin; NAL = NalidixicAcid; CPX = Cephalexin; PEF = Pefloxacin; AUG = Amoxicillin/clavulanic acid; CIP = Ciprofloxacin; CHL = Chloramphenicol; CRO = Ceftriaxone; OFL = Ofloxacin; GEN = Gentamicin; AML = Amoxicillin; COT = Cotrimoxazole; CXM = Cefuroxime; CAF = Ceftazidime

for second generation cephalosporin cefuroxime was 58.2%, comparable to chloramphenicol, which was 46.2%.

Table 2 shows the sensitivity of the microbial isolates in the controls. Those associated with least sensitivity were erythromycin 10.8%, ampicillin 16.9%, cotrimoxazole 21.5%, and nalidixic acid 23.1%. Sensitivity to amoxicillin was 26.2%, but when augmented with clavulanic acid it was enhanced to 38.5%. Sensitivity to gentamicin was 47.7%.

Discussion

SCA patients are prone to infections, and UTI is a known morbidity in them. Since several workers have reported increased risk of UTI in this group of individual, it is, therefore, necessary to have a guide to appropriate first-line drugs to institute early treatment.

This study reports the sensitivity of urinary isolates to 15 antimicrobials. The spectrum of isolates from the SCA children was grossly similar to that from the control group. In the SCA group, most isolates were resistant to ampicillin, which is similar to finding by Brown *et al.*[15] in Ibadan and by Elbashier and Badu[3] in Saudi Arabia. There was also a high level of resistance to cotrimoxazole in the present study, which is apparently in agreement with the study done in Ibadan.[16] Other workers in Nigeria[9,17,18] have reported similar level of resistance of pathogens isolated from the urinary tract to cotrimoxazole. In a study by Obaseiki-Ebor[19] in Benin, Nigeria, 80% of *E. coli* isolates and 74% of *Klebsiella* isolates were resistant to cotrimoxazole. Adeyemo *et al.*[16] in Ibadan observed that 100% of *E. coli* isolates and over 90% of *Klebsiella* isolates were resistant to cotrimoxazole and ampicillin.[16] In a study in Saudi Arabia, it was reported that *E. coli* and *Klebsiella* were highly susceptible to cotrimoxazole.[3] The reason for the contrast may be that cotrimoxazole is not a common on-the-counter drug in Saudi Arabia; meanwhile, it is very common in Nigeria. Thus, resistance easily develops.

In this study, there was a high level of resistance to amoxicillin, but sensitivity was improved when augmented

with clavulanic acid, which was in keeping with finding by Brown *et al.*[15] Amoxicillin/clavulanic acid improved sensitivity by 12.3% in this study, while in Ibadan study it improved by 22.3%. With the high level of resistance to common antimicrobials observed in this study, it will seem unsafe to recommend the use of cotrimoxazole, ampicillin, amoxicillin, and nalidixic acid as the first-line drugs in empirical treatment for UTI in this environment. There was relatively lower sensitivity of the isolates to cefuroxime compared to report by other workers.[3,16] This falling in sensitivity even to cephalosporins may mean that the organisms are developing resistance even in the normal inhibitory concentration of the drugs or there is increasing abuse or misuse of these drugs.

Finding of high sensitivity to quinolones (pefloxacin, ciprofloxacin, and ofloxacin) in this study is similar to finding by Brown *et al.*[15] and Adeyemo *et al.*[16] The quinolones are generally not recommended in young children. They may be of use in multi-drug resistant infections.[20] This practice was demonstrated in a *Pseudomonas* infection treated with quinolones in Ibadan.[15] While the risk of joint damage from quinolones had caused clinicians to exercise caution in prescribing these agents in children, close monitoring of pediatric patients receiving ciprofloxacin, a quinolone, has failed to reveal cartilage toxicity.[21] Other studies evaluating joint changes using magnetic resonance imaging, skeletal function tests, high-velocity laboratory testing, and physical examinations have revealed no abnormal development.[20-22] In the case of pefloxacin whose use has been associated with arthropathy, it is reversible and subsides after the drug is discontinued.[24] In addition, the incidence of arthropathy following the use of this drug seems to be age-related, being greater when the drug is first used between 15 and 20 years of age.[23] Therefore, it seems relatively safe to use it in multi-drug resistant infections below the age of 15 years; more so, since the review of available data on the pharmacokinetics of the quinolones in children suggest no risk of nephropathy, it may be considered a potentially useful drug in the treatment of childhood UTI.[24]

The greater sensitivity to ceftriaxone in this study is similar to findings by Elbashier and Badu[3] in Saudi Arabia where they found 93%, sensitivity of *E. coli* and *Klebsiella* to this drug. The explanation for this high sensitivity of this drug to urinary isolate in this environment may be that the drug cannot easily be abused because of it cost and route of administration. In this environment, most parents cannot afford the drug even when it is prescribed. Further implication of this high sensitivity means that the drug should be prescribed only when it is seriously indicated, either in a severe infection or based on sensitivity testing, so as to preserve its sensitivity to bacterial agents causing UTI.

Conclusion

There is similarity in the pattern of bacteriuria and antimicrobial sensitivity and resistance observed among SCA and control group; this study calls for a review of the drugs routinely used as first-line in the treatment of UTI in this environment. Amoxicillin/clavulanic acid, cefuroxime, and gentamicin are recommended for empiric treatment drug while awaiting the results of urine culture and sensitivity. Because of cost and non-availability of oral formulations, ceftriaxone and ceftazidime should be reserved for case of non-response to first-line drugs or in severe infections. There is a need to review the indication for the use of quinolones, particularly in infections caused by multi-drug resistant organisms, when third-generation cephalosporins cannot be purchased because of cost, especially in a developing world like Nigeria. Consideration should be given to pefloxacin and ciprofloxacin as potential drugs for the treatment of UTI in such cases, though the effect of quinolones on growing end of bones may limit their use.

Acknowledgment

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