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Changing patterns in sensitivity of causative organisms of septicaemia in children: the need for quinolones

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Summary

A review of the pattern and antibiotic sensitivities of blood culture isolates over a 3 year period in children presenting to the Paediatric Unit of Ahmadu Bello University Teaching Hospital, Kaduna is reported. Positive blood culture isolates were obtained in 26.9% of 1,982 children. The most prevalent isolates were *Staphylococcus aureus* (59.9%), *Escherichia coli* (16.9%) and *Klebsiella* (16.3%). There was a striking paucity of isolation of *Salmonella typhi* (1.3%) and *Streptococcus*. Sensitivity to commonly used drugs like ampicillin/cloxacillin, genticin, ceftazidime and chloramphenicol was low (8.0-50.0%), with a corresponding delayed fever resolution and prolonged hospital stay. 31.0-83.3% of the isolates were highly sensitive to pefloxacin, norfloxacin and ofloxacin, which were not generally recommended for use in paediatric patients. In two patients with no response to commonly used antibiotics, use of quinolones lysed their fever within 48 hours. This change of antibiotic sensitivity patterns calls for a thorough investigation into the potential role of these quinolones in paediatric chemotherapeutics either singly or in appropriate combinations with existing antibiotics.

Keywords: *Changing sensitivity patterns, septicamia in children, quinolones*

Résumé

La révue de la fréquence et la sensitivité des antibiotiques sur les isolats de sang cultivés obtenus des enfants visistant l'unité de pédiatric du centre universitaire hospitalier de l'université d'Ahmadou Bello était reporté durant une période de 3 ans. Les isolats étaient de 26.9% des 1,982 enfants. Les isolats contenaient plus fréquemment des *staphylococcus Aureus*(59.9%), *Escherichia coli* (16.9%),et *Klebsiella*(1.3%). Il y avait une paucité remarquable en isolation du *salmonella typhi* (1.3%) et streptococcus. La sensitivité des antibiotiques currente comme l'ampicillline , cloxacilline , gentamicine,ceftazidine et chloramphénicol était faible (8.0-50.0%), avec un retard correspondant de la résolution de la fiévre et prolongant la durée d'hospitalisation. 31.0-83.3%) des isolats étaient plus sensitive au pefloxacin, norfloxacin et ofloxacin qui étaient moins géneralement prescrit en pediatrie. L'usage des quinolones détruisent la fiévre en 48 heures a deux patients sans action aux antibiotiques currenment utilisés,. Ces changements de sensitivité d'antibiotiques demandent une compléte investigation sur le role potential ds quinolones en chimiothérapie pédiatriques soit en unique ou combinaison appropriée avec les antibiotiques existant.

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Introduction

There has been growing concern over resistance of bacterial organisims to antimicrobial agents like penicillins, aminoglycosides and even to third generation cephalosporins currently in use [1]. This resistance has continued to develop due to drug pressure, self medication with substandard dosages of antibiotics, use of drugs for shorter period of time than prescribed, fake and adulterated drugs [2].

Fluroquinolones, a new group of antibacterial agents have been introduced for adult patients since 1984.[3,4] and have a potent activity against a wide range of pathogens. These include aerobic Gram positive and Gram negative organisms including several nosocomial multi-resistant strains. Potential toxicity to articular cartilage has been described, based on observations of weight bearing synovial joints of some young animals with incomplete skeletal growth [5,6].As a result of this, there has been great caution and reluctance in the use of quinolones in children. However, in children with severe infections, quinolones have been used on a compassionate basis [5].

This study presents the current status of antibiotic sensitivity pattern to the most commonly isolated bacterial agents in children as seen in the Paediatric Department of Ahmadu Bello University Teaching Hospital, Kaduna, Nigeria.

Patients and methods

Blood culture isolates obtained from children presenting sick to the Department of Paediatrics, Ahmadu Bello University Teaching Hospital, Kaduna from January 1996 to December 1998 were reviewed. These children had presented to one of the 3 units of the Department – the Paediatric Outpatient Department (POPD), Special Care Baby Unit (SCBU) or Emergency Paediatric Unit (EPU). Blood cultures had been undertaken in them as part of the diagnostic investigations done for standard patient management.

The blood samples taken were all processed in the Microbiology Department of the hospital. Results of all the blood cultures done during the study period were retrieved. Those that had positive cultures were collated and analysed. The specific pathogens isolated as well as corresponding antibiotics sensitivity and resistance were noted.

The case-notes belonging to all children with the positive isolates were retrieved from the Medical Records Department and studied. Data relating to their age, presenting complaints, diagnosis, pathogen isolated in blood culture, antibiotic used for treatment, duration of hospital stay and final outcome were also collected and analysed.

Results

One thousand, nine hundred and eight-two (1,982) blood culture samples were taken from sick children and cultured from

January 1996 to December 1998. The ages of the children ranged from a few hours to 13 years and included 490 neonates. Five hundred and thirty-four (26.9%) of these samples were positive. These included 20.8% of the neonatal samples and 28.9% of those taken from older children (Table 1). In all, 19.1% of the positive cultures were obtained from neonates.

Table 1 : Distribution of children with blood culture samples taken.

	Number of children (%)		
	Neonates (0-1/12)	Others (>1/12 -13years)	Total
Culture Positive	102 (20.8)	432 (28.9)	534(26.9)
Culture Negative	388 (79.2)	1060 (71.1)	1448(73.1)
Total	490 (100.0)	1492 (100.0)	1982 (100.0)

Isolates

The bacterial pathogens isolated from the positive blood culture samples are as shown in Table 2. The commonest organisms were *Staphylococcus aureus, Eschericha coli* and *Klebsiella* and these accounted for over 90% of pathogens recovered. The distribution of isolates was similar in both neonates and older children. Of note is the fact that *Staphylococcus aureus* was the predominant organism at all age groups.

Table 2 : Types of pathogen isolated in childen

	Number of children (%)		
Pathogens isolated	Neonates (1/12)	Others (1/12 to 13years)	Total
Staphylococcus aureus	56 (54.9)	264 (61.1)	320 (59.9)
Eschericha coli	19 (18.6)	71 (16.4)	90 (16.8)
Klebsiella	20 (19.6)	67 (15.5)	87 (16.3)
Nonhemolytic Streptococcus (NHS)	4 (3.9)	14 (3.2)	18 (3.4)
Salmonella	-	7 (1.6)	7 (1.3)
Pseudomonas	1 (1.0)	2 (0.5)	3 (0.6)
Others	2 (2.0)	7 (1.6)	9 (1.7)
Total	102 (100.0)	432 (100.0)	534 (100.0)

Antibiotic sensitivity patterns

The antibiotics sensitivity pattern varied Table-3. There was generally a low sensitivity to commonly used antibiotics (ampicillin/cloxacillin, gentamycin, chloramphenicol and erythromycin, 8-50%) and highest with the quinolones (norfloxacin, perfloxacin and ofloxacin, 31-83%).Even sensitivity to a third generation cephalosporin- ceftazidime was surprisingly low (8.8-22%), except to *Salmonella species* .

Clinical features

The most predominant clinical features among the neonates were discharge from the eyes/umblicus or skin sepsis, jaundice and convulsions. In the older children fever, vomiting/ diarrhoea and abdominal pain were the predominant presentation. The diagnosis on admission was neonatal sepsis with / without jaundice and in the older children, septicaemia.

Outcome

The average hospital stay was 10 days (range of 7 – 14 days) in neonates and 12 days (range of 10 – 20) days in the other children. The first line drug therapy for septicaemia in the centre (parenteral ampicillin-cloxacillin and genticin) was instituted in these children on admission. Fever resolution took an average of 6 days (range of 4-9 days). In 40% of the older children who had not achieved fever resolution by the 5th day cephalosporins were given as second line therapy. Two children with unrelenting fever by the second week of admission were given trials of quinolones (norfloxacin). Their fever lysed within 48 hours. Overall, there was an unacceptably high rate (10%) of discharge against medical advice and case fatality rate of 4.8% among the children studied.

Discussion

This study highlights one of the major problems faced by clinicians in the developing countries, that of which antibiotic to use in a sick child. Just over a quarter of the children seen had positive blood cultures. Negative results could have been due to various reasons like previous antibiotic exposure, other causes of fever like malaria, viral infections and late presentation of children as in those with *Salmonellosis* by the second week when bacteraemia is intermittent or low.

However in those patients with positive cultures, the three commonest organisms isolated were the same in both neonates and older children: *S. aureus*, *E. coli* and *Klebsiella*. *Salmonella* species was isolated from only 1.3% of the samples and *Pseudomonas* from 0.6%. In the neonatal age group, *E. coli* and *Klebsiella* ranked with almost equal frequencies of about one third the number for *Staphylococcus*. *Salmonella* was not isolated from the neonatal group.

That *Staphylococcus aureus* is a leading cause of sepsis is no longer surprising as this has been documented in previous studies from this and other centers [7,8]. What is worrying and even alarming is the changing pattern of bacterial sensitivity from commonly used drugs to newer, more potentially harmful drugs. Previous studies done in this and other centres showed highest sensitivities to ampicillin -cloxacillin, genticin and cephalosporins[9]. In the present study, highest sensitivity to ampicillin -cloxacillin was 50.0%, genticin 39.0% and even ceftazidime had sensitivty of 21.4% except in *Salmonella* infection were 100% sensitivity was recorded. The clinical effect of this change in sensitivity was evident by delayed fever resolution, resulting in prolonged hospital stay, large number of discharges against medical advice, as well as high death rates. These clinical effects may be accounted for by prior misuse of antibiotics (from self medication) before presentation. Other reasons could be a changing sensitivity pattern of the pathogens as shown in this study or as a result of septicaemia overlying other special conditions e.g HIV/ AIDS or sickle cell anaemia.

Overall, perfloxacin, noroxin and ofloxacin had the highest sensitivities of about 2 – 3 times that of the commonly used ampicillin-cloxacillin /genticin combination (first line) and ceftazidime (second line drug) in our centre for management of septicaemia. It is noteworthy that ampicillin-cloxacillin was of particularly low sensitivity in the neonates and ceftazidime of low sensitivity to all pathogens except *Salmonella*.

Table 3 : Pattern of antibiotic sensitivity of the pathogens isolated.

Drugs	Drug sensitivity of Pathogens isolated (%) in the children														
	Staphylococcus			E.coli			Klebsiella			NHS			Salmonella		
	N	O	T	N	O	T	N	O	T	N	O	T	N	O	T
Ampicillin-Cloxacillin	14.3	28.8	26.3	15.8	18.3	17.8	-	10.5	8.0	15.8	20.0	18.0	•	50.0	50.0
Genticin	28.6	41.3	39.0	31.6	38.0	16.7	30.0	38.8	36.8	-	-	-	•	33.3	33.3
Chloramphenicol	25.0	28.4	27.8	15.8	33.8	30.0	15.0	17.9	17.2	50.0	60.0	56.6	•	50.0	50.0
Erythromycin	28.6	31.4	30.9	36.8	4.2	11.1	-	13.4	10.3	15.8	15.2	15.7	•	14.3	14.3
Ceftazidine	8.9	8.7	8.8	10.5	23.9	21.4	15.0	20.9	19.5	50.0	40.0	44.1	•	100.0	100.0
Ofloxacin	55.4	36.0	39.3	68.4	25.4	34.4	35.0	29.8	31.0	-	-	-	•	-	-
Norfloxacin	67.9	65.5	66.0	52.6	71.6	71.1	70.0	74.6	73.6	50.0	20.0	50.0	•	83.3	83.3
Perfloxacin	78.6	70.0	71.6	47.4	87.3	78.9	50.0	62.7	60.0	50.0	80.0	22.2	•	50.0	50.0

Key N = Neonates O = Others T = Total • =Not tested - - Reststant NHS = Non haemolytic Streptococcus

Two children who had unrelenting fever, and prolonged stay in hospital were given quinolones (norfloxacin) cautiously. Fever was noticed to have lysed within 48 hours of commencement of medication. Clinical studies have shown the efficacy of quinolones over other classes of antimicobial agents in Gram negative septicaemia especially those secondary to urinary tract infection [10], shigellosis [11,12], salmonellosis [4,13], Gram positive cocci [14], mycobacterium especially multi- resistant ones[15,16] and even to fungi[17]. Specifically ciprofloxacin has been found to be more efficient against gram negative agents [4,18,19], where it precepitiously reduces endotoxin levels unlike other groups of antibiotics that cause an initial antibiotic – induced endotoxin release in the early phase of therapy. Perfloxacin and ofloxacin are effective against *staphylococci*. Only ciprofloxacin and Du6895a, (an investigational fluroquinolone agent in combination with amphoterian B and fluconazole) are very active against anaerobes [20]. However these latter are very toxic. Quinolones as a group are inactive or marginally active against anaerobic bacteria.

The use of norfloxacin after failure of initial antibiotics in children has been practiced by Augard *et al.* [3] where neonates had resistance to third generation cephalosporins and reduced sensitivity to aminoglycosides. Also Van Wijk *et al*; [21] had used it in children with complicated urinary tract infection with good results and no adverse side effects.

It has been reported that the repeated and continued use of quinolones in children gives rise to arthropathy after 4 – 6weeks [22] and this is one reason for caution in using these drugs in them. Magnetic resonance imaging of these patients on continuous use showed joint fluid effusions, however there was no visible cartilage damage. The potential toxicity of quinolones to articular cartilage occurs because quinolones accumulate in the cartilage and form chelate complexes with divalent cations thereby inducing a deficiency of functionally available magnesium [23]. However the blood levels of quinolones needed to produce this effect in vivo are 10-fold higher than therapeutic doses. Five years follow-up of these children did not reveal any progression to arthropathy [22,24]. Other side effects described, including rashes, anaphylactoid reactions, blood dyscrasias, benign intracranial hypertension, renal failure, seizures and photosensitivity are however not well established in paediatric populations.

Another factor in children that may preclude the use of quinolones may be cost. In the context of the results of this study their use may be cost effective when compared to other antibacterial agents but the use of other aptibiotics resulted in prolonged hospital stay.

This study was limited to children presenting at a tertiary centre, many of whom had received previous treatment elsewhere. It may not be representative of community acquired bacteraemia and the sensitivity patterns may be different. However it does point to the fact that in sick children in this environment, there is an emergence of resistance to the commonly used antibiotics. Other more effective drugs need to be used. The possibility in developing countries exists of the newer drugs like quinolones being abused by health care providers who are not medically trained and who do not know the special precautions to be taken with these drugs.

There is an urgent need for prospective case control clinical studies on the use of quinolones in paediatric infections especially in this environment. These studies would help determine factors that affect clinical use and adverse effects actually seen. It could also reveal the possible effects of combinations with other antibiotic groups in an effort to forestall drug resistance. Quinolones may in future prove to be useful drugs in paediatric infections and there is a definite indication to change from a compassionate to a more rational use of these drugs in paediatrics.

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