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The aetiology of non-malarial febrile illness in children in the malaria-endemic Niger Delta Region of Nigeria

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PEER REVIEW

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Comments

In this study, the author probed into the other causes of non-malarial febrile illnesses and found that bacteria are often associated with the febrile illnesses. In addition, their sensitivity studies also revealed that the choice of antibiotics needs to be screened so that effective treatments can be administered. Although bacteria are found in some patients, it is not clear whether these are the causes of the illnesses. It is unknown whether these patients were treated with antibiotics and what are the outcomes of the treatments.

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ABSTRACT

Objective: Febrile illnesses are common in childhood and differentiating the causes could be challenging in areas of perennial malaria transmission. To determine the proportion of non-malarial febrile illness in children, the aetiological agents and their antimicrobial sensitivity pattern. **Methods:** Blood, urine, throat swab and ear swab samples were obtained from 190 febrile children aged 6 months to 11 years. Malaria parasite was detected by microscopic examination of thick and thin Giemsa-stained films. Smears from ear and throat swabs and urine specimen were cultured on appropriate media. Bacterial isolates were identified by Gram staining, morphology and biochemical tests. Antibiotic susceptibility was tested using the Kirby-Bauer disc diffusion method. **Results:** The prevalence of non-malarial febrile illnesses was 45.26% (95% *CI*: 38.21-52.31). Twenty-four patients (12.6%) had at least one sample that was bacterial culture positive. Samples from 62 patients (32.6%) were negative for both malaria parasite and bacterial culture. Urinary tract infection was responsible for 8.42%, otitis media 7.89% and pharyngitis 5.78% of the fevers. *E.coli*, *S. aureus* and *S. pneumoniae* were the commonest isolates from urine, ear swab and throat swab samples respectively. *S. pneumoniae* was responsible for all the positive throat cultures. Bacterial isolates exhibited different degrees of susceptibility to the antibiotics tested, but susceptibility of most of the isolates to oxacillin and cloxacillin was generally poor. **Conclusions:** Bacterial infections are responsible for a significant proportion of non-malarial febrile illnesses, and diagnostic facilities should be strengthened to detect other causes of febrile illness outside malaria.

KEYWORDS

Malaria, Perennial transmission, Fever, Bacteria, Children

1. Introduction

Fever is one of the commonest symptoms of disease/illness in children and has numerous causes. Infection with bacteria, viruses, protozoa or fungi can manifest as febrile illnesses. Since these febrile illnesses have some common overlapping manifestations, clinical diagnosis can be difficult. With the numerous differential diagnoses of fever in children, there can be diagnostic delay[1].

In the tropics and malaria-endemic regions, most fevers are presumed to be due to malaria and are treated empirically as such[2]. However, there is mounting evidence that a significant proportion of these febrile illnesses are due to other causes aside malaria[3,4]. These non-malarial febrile illnesses have been defined as "infectious diseases in patients who present with undifferentiated fever and require malaria rapid diagnostic tests/microscopy, but in whom these tests were negative"[5].

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Non-malarial febrile illnesses are important causes of morbidity and mortality as they have been shown to cause a higher mortality than malaria globally, even in malaria-endemic areas[4,6]. Studies have shown that many cases of clinically diagnosed malaria were due to other pathogens especially bacteria[3,4,7]. This means that with presumptive treatment of fevers as malaria, other causes of fevers are neglected and could lead to unwanted consequences. Overdiagnosis of malaria is usually associated with failure to treat alternative causes of severe infection[8], while overtreatment of malaria is believed to contribute to the rapid development of antimalarial drug resistance[9].

The World Health Organization advocates test-based management of malaria, with artemisin-based combination therapy (ACT) restricted to only parasitologically-confirmed cases[10]. However, empirical treatment of fevers continues in resource-poor settings. Rapid diagnostic tests (RDTs) are based on malaria antigen detection and are meant to differentiate malaria from non-malarial febrile illness and have been shown to be effective[11].

There is regional variation in the proportion of fever attributable to malaria[12]. The aetiology of non-malarial febrile illness is not well characterized in Nigeria generally and the Niger Delta region in particular.

The present study was therefore carried out to determine the current prevalence of non-malarial febrile illnesses in children presenting with acute fever at a tertiary health institution in Bayelsa state, Nigeria, as well as finding out the aetiological agents of the fever, and their antimicrobial sensitivity patterns with a view to impacting on policies on management of childhood febrile illnesses.

2. Materials and methods

2.1. Study design

This was a prospective descriptive study involving children between the ages of 6 months and 11 years presenting with acute fever at the Paediatric Unit of the Niger Delta University Teaching Hospital (NDUTH), Okolobiri. Between October 2011 and March 2012, 190 children were consecutively recruited for the study.

2.2. Study area

The NDUTH is situated in Bayelsa State in the Niger Delta region of Nigeria. It is the only teaching hospital and one of two tertiary health institutions in the state. The hospital also serves neighbouring communities in Rivers and Delta States. The Niger Delta region lies in the tropical rainforest belt and has perennial transmission of malaria.

2.3. Inclusion/exclusion criteria

Fever was defined as a having a measured axillary temperature $\geqslant$37.5 °C. Children with a history of fever of less than fourteen days were consecutively recruited for the study while those with fever of greater than fourteen days duration, or body temperature less than 37.5 °C as well as those who had received treatment with antimalarials or antibiotics within the preceding two weeks were excluded from the study.

2.4. Ethical clearance

Informed consent was obtained from the parents of the study subjects, and ethical approval for the study was obtained from the Ethics Review Board of the NDUTH.

2.5. Malaria parasite detection

Five milliliters of venous blood was collected into sterile EDTA-containing bottles. Thick and thin blood films were done for each sample for malaria parasite count and to identify parasite species respectively. Thin and thick smears were prepared by placing a drop or 3 drops of blood respectively, onto clean slides, which were then Giemsa-stained[13]. In order to confirm or rule out the presence of malaria parasite, each slide was read independently by two experienced microscopists and discordance between results were resolved by a third microscopist. A thick smear was declared negative if no parasites were seen after examination of at least 100 high power-fields.

2.6. Bacterial culture

A clean-catch urine sample, throat and ear swabs were obtained from each subject. A calibrated loopful of urine and smears from the throat and ear swabs were inoculated on Cystine lactose electrolyte-deficient agar, blood agar, chocolate agar and Macconkey agar respectively. The cultures were incubated aerobically at 37 °C for 24 to 48 h. The bacterial isolates were identified and classified using colonial morphology, Gram-staining and standard biochemical tests. Positive ear or throat cultures were defined as pure growth of a single pathogenic micro-organism, with a positive urine culture being the culture of $>10^5$ colony forming units per milliliter of urine.

2.7. Antibiotic susceptibility testing

Antimicrobial sensitivity was tested for each isolated organism using the disk diffusion method of Kirkby-Bauer as described by the National Committee for Clinical laboratory Standards (Clinical Laboratory Standard Institute)[14].

2.8. Statistical analysis

Statistical analysis was performed with the Graphpad Prism version 4® (Graphpad software, San Diego, CA). Differences between groups were determined by the one-way analysis of variance (ANOVA) or paired *t*-test with the level of significance set at $P<0.05$.

3. Results

One hundred and ninety children (190) presenting with fever were studied, with 78 female and 112 male children as shown in Table 1. The female:male ratio was 0.69:1. The age range was 6 months to 11 years, mean age of 2.81 years.

Table 1
Age and sex distribution of the study subjects.

Age (years)	Male	Female	Total
<1	24 (12.3%)	18 (9.47%)	42 (22.1%)
1 to 2	47 (24.73%)	33 (17.38%)	80 (42.1%)
3 to 4	18 (9.47%)	11(5.78%)	29 (15.26%)
5 to 6	15 (7.89%)	8 (4.21%)	23 (12.1%)
7 to 8	1 (0.5%)	3 (1.57%)	4 (2.1%)
9 to 10	3 (1.57%)	3 (1.57%)	6 (3.15%)
11	4 (2.1%)	2 (1.05%)	6 (3.15%)
Total	112 (58.95%)	78 (41.05%)	190 (100%)

3.1. Prevalence of non-malarial febrile illness

86 patients were malaria slide negative giving a prevalence of non-malarial febrile illness of 45.26% (95% *CI*: 38.21 – 52.31). Of these malaria slide negative patients, 62 were bacterial culture negative (72.1%) whilst 24 had at least one sample that was bacterial culture positive (27.9%). 16 urine samples (8.42%), 15 ear swab samples (7.89%) and 11 throat swab samples (5.79%) yielded significant bacterial growth (Table 2). Of the 104 malaria slide positive subjects, 12 had samples that yielded significant bacterial growth.

Table 2
Frequency of positive bacterial cultures.

Age (years)	Ear swab +ve	Urine m/c/s +ve	Throat swab +ve
<1	–	3 (18.7%)	2 (18.2%)
1 to 2	10 (66.7%)	10 (62.5%)	4 (36.4%)
3 to 4	4 (26.7%)	–	2 (18.2%)
5 to 6	1 (6.67%)	3 (18.7%)	3 (27.3%)
7 to 8	–	–	–
9 to 10	–	–	–
11	–	–	–
Total	15	16	11

3.2. Aetiological agents

3.2.1. Urine

87.5% of the isolated bacteria were Gram-negative bacilli, with *Escherichia coli* (*E. coli*) being the most prevalent uropathogen accounting for 75% of the isolated bacteria (Table 3). *Staphylococcus aureus* (*S. aureus*) and *Klebsiella pneumoniae* (*K. pneumoniae*) each accounted for 12.5% of the isolates.

3.2.2. Ear swab

About 86.7% of the isolates were Gram-positive cocci. *S. aureus* was the commonest pathogen isolated accounting for 60% of the isolates. *Streptococcus pneumoniae* (*S. pneumoniae*) accounted for 26.7% and *Proteus mirabilis* (*P. mirabilis*) 13.3% of the isolates respectively.

Table 3
Frequency of isolated pathogens.

Sample	Pathogen isolated	Total	Male	Female
Urine	*E. coli*	12	6	6
	S. aureus	2	2	0
	K. pneumoniae	2	0	2
Ear swab	*S. aureus*	9	6	3
	S. pneumoniae	4	2	2
	P. mirabilis	2	2	0
Throat swab	*S. pneumoniae*	11	11	0

3.2.3. Throat swab

Only *S. pneumoniae* was isolated from the throat and all the subjects were male.

3.3. Antibiotic susceptibility

3.3.1. Urine

E.coli isolated from the urine was susceptible to the fluoroquinolones (ofloxacin and ciprofloxacin) and the cephalosporins (ceftazidime and cefexime), but resistant to cloxacillin (24.9% sensitivity) (Figure 1).

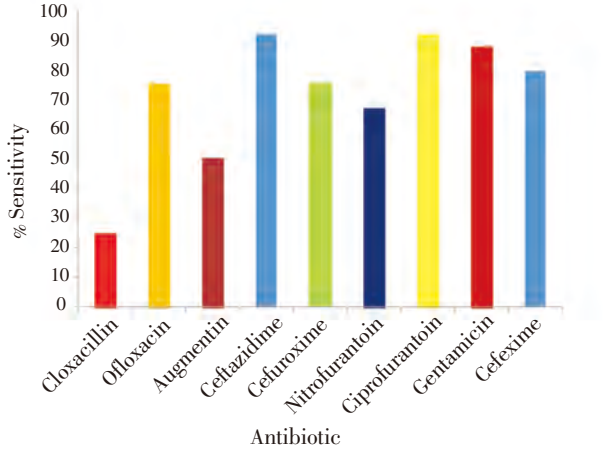

Figure 1. Susceptibility pattern of urinary *E.coli* to tested antibiotics. Least sensitivity was to cloxacillin.

3.3.2. Throat

S. pneumoniae was totally resistant to oxacillin, poorly susceptible to cloxacillin, ceftazidime and erythromycin. It was however susceptible to ceftriaxone (Figure 2).

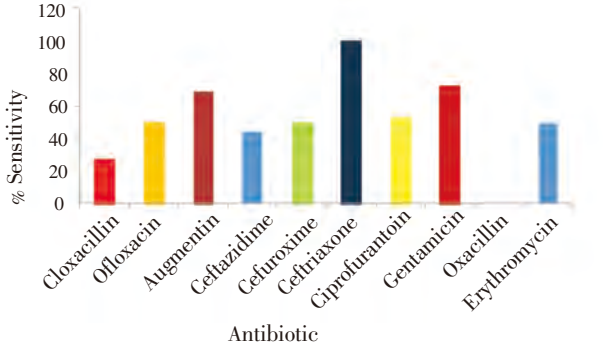

Figure 2. Sensitivity pattern of *S. pneumoniae* isolated from throat swabs.

3.3.3. Ear

S. aureus isolated from the ear was very susceptible to amoxicillin-clavulanic acid and gentamicin (Figure 3).

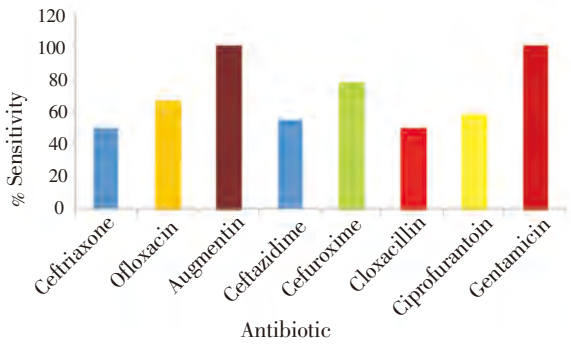

Figure 3. Susceptibility pattern of *S. aureus* isolated from ear swabs.

4. Discussion

In this study, we determined the current proportion of non-malarial febrile illnesses due to bacterial infection in children in a malaria-endemic area of Nigeria. Almost half of the children were malaria slide negative and the fever could be attributed to causes other than malaria. This is in line with an earlier observation that about half of children presenting with fever in Africa do not have malaria[15]. This makes a case for other causes of fever. Studies characterizing non-malaria febrile illnesses are few and there is a need to determine the proportion of these illnesses due to bacterial causes.

Our observation of *E. coli* as the predominant uropathogen was not surprising as *E. coli* has been documented as the major organism in uncomplicated UTI[16,17]. Its resistance to cloxacillin was also not surprising as cloxacillin is a component of Ampiclox, one of the most abused self-prescription antibiotics in Nigeria[18].

The reason for the male preponderance of *S. pneumoniae* throat infection is not known and needs further investigation.

Early diagnosis and prompt and adequate treatment is capable of reducing and preventing morbidity/mortality of not only malaria but also other causes of fever.

Overdiagnosis of malaria is usually associated with failure to treat alternative causes of severe infection[8]. A study observed that there was higher mortality in malaria slide-negative patients than slide-positive patients, although the study couldn't determine if deaths could have been prevented by antibiotics[8]. Strict adherence to malaria rapid tests results, without incorporating other tests, is therefore capable of leading to a neglect of other dangerous diseases[19]. A positive malaria parasite test does not confirm the absence of non-malarial febrile illness, as evidenced by the 12 subjects who were malaria slide positive in addition to positive bacterial cultures. To resolve this, bacterial culture should be requested in all cases of febrile illness in children in addition to malaria detection tests (microscopy or RDTs).

With the global decline in the incidence of malaria[20,21], and presently no evidence of a decline in childhood mortality, there is a need to address the other causes of childhood deaths outside malaria.

Millennium development goal 4 (MDG4) aims to reduce by two-thirds infant and child mortality by the year 2015. For this to be possible in countries like Nigeria, which is among the 5 countries responsible for 49% of child deaths[4], the proportion of illnesses and deaths due to other causes outside malaria have to properly identified and addressed.

There is still a dearth of diagnostic facilities and trained staff in most parts of subSaharan Africa in terms of microscopy, RDTs and bacterial culture. Concerted efforts have to be made to make these tests available and affordable for MDG4 to be realised. Paedatricians and other health workers treating children should ask for symptoms of urinary, throat and ear infections when clerking children with acute fever, and physicians should be encouraged to request these tests before treatment.

Just as parasitological evidence is required before ACT, culture results should be required before antibiotic therapy.

We call for more efforts in improving the diagnosis and treatment of bacterial infections in children in order to reduce morbidity resulting from undiagnosed or misdiagnosed bacterial infections.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Non-malarial febrile illnesses constitute a major threat to the health of children in malaria endemic tropical regions and are often mistreated for malaria, which may lead to severe consequences

Research frontiers

This study was performed in the malaria-endemic Niger Delta region of Nigeria, where a total 190 children with febrile diseases were recruited and examined for malaria and bacterial infections.

Related reports

The results from this study contrast significantly with a recent study performed in Southeast Asia, where dengue, typhi and Japanese encephalitis were identified as the major pathogens. The difference might be due to regional prevalence of different pathogens and different study methods used.

Innovations & breakthroughs

The interesting finding from this study is that bacterial infections might be the major causes of non-malarial febrile infections. Another alarming note is that some bacteria have also shown increased resistance to some antibiotics used in the study region.

Applications

A potential application of the finding is that a rigorous malaria diagnosis by microscopy or RDTs needs to be performed before the patient is treated with antimalarials. Presumptive treatments need to be avoided in the future.

Peer review

In this study, the author probed into the other causes of non-malarial febrile illnesses and found that bacteria are often associated with the febrile illnesses. In addition, their sensitivity studies also revealed that the choice of antibiotics needs to be screened so that effective treatments can be administered. Although bacteria are found in some patients, it is not clear whether these are the causes of the illnesses. It is unknown whether these patients were treated with antibiotics and what are the outcomes of the treatments.

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