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Typhoid fever in children presenting to paediatric medical wards of Ahmadu Bello University Teaching Hospital Zaria: A 13-month review

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Abstract: Typhoid fever is a systemic infection caused by the Gram-negative bacilli *Salmonellae*, transmitted via the feaco-oral route. It commonly affects children, leading to complications and death if untreated. This is a report of typhoid fever admissions as seen at ABU Teaching Hospital Zaria over a 13-month period.
Objectives: To describe the clinical presentation and management outcomes of children admitted with typhoid fever during a 13-month period.
Materials and methods: A retrospective review of demographic, clinical presentation and treatment response of children managed for typhoid fever was conducted. Results were presented as means with standard deviation, proportions, tables, figures and Chi-squares with p values. The prevalence of typhoid fever admissions was obtained over the period from 2008-2011.
Results: A total of 779 children were admitted from 1st January 2011 to 31st January 2012, out of which 39 (4.9%) had a diagnosis of typhoid fever. There was a significant difference in prevalence of typhoid fever admissions from 2008-2010 compared to 2011 (X^2 = 5.6651; p <0.019). The mean age was 7.2 (SD ± 4.3) years and 71.8% resided in the same neighbourhood. All the children had pre-admission antibiotics, while 93.3% had abdominal pain, 64.1% had diarrhoea, 89.7% had fever and 69% had hepatomegaly. *Widal* test and blood cultures were positive in 46% and 10.3% respectively. Poor treatment response led to antibiotic switch for 61.1% started on chloramphenicol. Bowel perforation occurred in four (10.3%) who had laparotomy but there was no mortality, and all were discharged after recovery.
Conclusion: A surge was observed in typhoid fever admissions associated with widespread use of pre-admission antibiotics. Low rates of pathogen isolation and unaffordable costs precluded appropriate antibiotic choice for many at admission, and led to poor treatment response. Public health education should emphasize water hygiene and judicious use of antibiotics.

Key words: Typhoid fever; Enteric fever; Children; Hospital admission.

Introduction

Typhoid fever is a systemic infection caused by *Salmonella enterica serotype Typhi* (*S. Typhi*) and *S. enterica serotype Paratyphi (S. Paratyphi)* A, B, and C.[1] Hospital-based studies and reported outbreaks in sub-Saharan Africa indicate that non-typhi salmonellae especially *S. enterica* serotype *Enteritidis* and *S. enterica* serotype *typhimurium* that tend to cause less severe disease, are as important as *S. Typhi* and *S. Paratyphi* fever.[1-3] The organisms cause febrile illness in individuals residing in areas with poor environmental sanitation, sewage disposal with contamination of water supply and food.[1-3] The greatest disease burden is in children and young adults especially in Asia (Pakistan, India, and Bangladesh), sub-Saharan Africa and Latin America, with estimates of about 21 million annual cases and around 216,000 deaths.[2-5] The highest peaks of typhoid fever occur within the 5–19 years age range but the disease is also common under the age of 2 years in certain endemic areas of Asia.[1-5]

The diverse clinical manifestations in children often mimic other endemic infectious illnesses, cause delays in diagnosis and treatment, leading to severe complications and death.[2-4,6-8,9] Several limitations continue to make laboratory diagnosis challenging even with currently available diagnostic methods.[1,2,10] The isolation of *salmonella* in blood is difficult because it is fastidious, with many bacterial cells dying before inoculation, and thus cultures may turn out negative even with appropriate culture media.[10,11] Furthermore, bone marrow biopsy that is known to yield higher isolation rates from cultures of the organism is invasive and not feasible on a routine basis.[10] The age-old serologic *Widal* test is poorly specific due to cross reactivity with other *enterobacteriae*, while PCR is costly and not feasible in most endemic areas.[1,2,10]

The uncontrolled use of over-the-counter antibiotics for self-medication of presumed typhoid fever and other infections has continued to contribute to a growing global problem of antibiotic resistance, further causing treatment failure with severe/complicated disease and mortality in cases of confirmed typhoid fever. [2,3,11,12] Chloramphenicol has been used as first line drug of choice for the treatment of typhoid fever but recent studies have shown that drug resistance is a significant problem that has rendered it less effective with high rates of treatment failure, relapse and chronic carrier rates.[1-3,11,12]

We observed a trend of higher prevalence of typhoid fever in children admitted and managed in ABU Teaching Hospital in the period studied compared to the previous three years. Our aim is to describe the demographic variables, clinical presentation, management and outcome of children who presented with typhoid fever within the 13-month period.

Materials and Methods

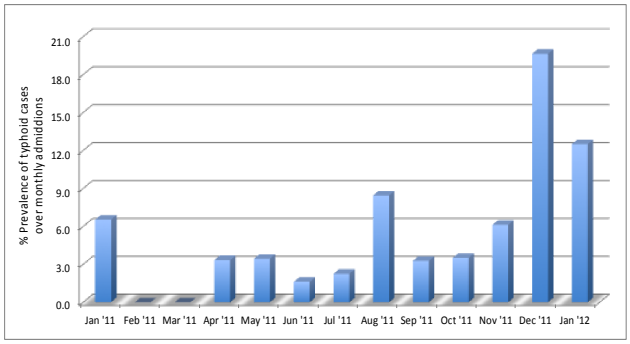
The admission registers of the *Emergency Paediatric Unit* (EPU) and the *Paediatric Medical ward* (PMW) were used to identify all cases with diagnoses of typhoid fever. A total of 55 children were admitted and managed for typhoid fever from 1st January 2011 to 31st January 2012. The case selection criteria for a diagnosis used a combination of clinical features and laboratory investigations that included cultures of blood, stool and urine, Widal agglutination test and satisfactory response to antibiotics. Cases were also categorised to belong to one of three diagnostic categories[1] as *confirmed* typhoid fever (suggestive clinical features plus positive salmonella culture), *probable* typhoid fever (suggestive clinical features, positive Widal test, negative cultures with satisfactory response to antibiotic therapy) or *possible* typhoid fever (suggestive clinical features, negative cultures and negative Widal test, with satisfactory response to antibiotic therapy). A total of 39 cases had complete records available, and data from these were analysed. The antibiotic treatment of typhoid fever in our facility involves the use of intravenous ceftriaxone or ciprofloxacin but where these were not immediately available intravenous chloramphenicol was used. Antibiotics were administered for periods ranging from 10-21 days as determined by overall clinical response and presence or absence of complications. Where clinical features of bowel perforation occured intravenous Metronidazole was also commenced prior to surgical intervention, during surgery and continued post-operatively. Poor response to treatment was considered if after 72 hours of regular antibiotic therapy a patient's condition has not improved, with persistent or deteriorating clinical features or development of features of septic shock.

Relevant information obtained from the records of the 39 eligible cases including biodata, clinical features, comorbidities, investigations, response to antibiotics and treatment outcome was collected into a semi-structured profoma. Data was entered in *Microsoft® Excel®* for *Mac 2011 (Version 14.1.0)*, which was also used for analysis and generating tables and charts.

Results

A total of 779 children were admitted into the Emergency Paediatric Unit (EPU) and Paediatric Medical ward (PMW) of the ABU Teaching Hospital over a period of 13 months from 1st January 2011 to 31st January 2012. Two peaks with higher prevalence of admissions due to typhoid fever occurred, the first in August 2011 with 8.5% and the second in December 2011/ January 2012 with 19.6% and 12.5% of admissions respectively (Fig 1).

Fig 1: Prevalence of typhoid fever as percentage of monthly admissions



The mean age of the children was 7.2 years (SD ± 4.3) and 20 (51.3%) of children were aged 6-10 years, while 12 (30.8%) were aged 1-5 years (Table 1). There were twice as many males (26) than females (13), giving a male:female ratio of 2:1. Majority of the children, 28 (71.8%) came from adjacent residential settlements.

Table 1: Age distribution of 39 children managed for typhoid fever

Age range (Years)	No	%
1-5	12	30.8
6-10	20	51.3
11-15	6	15.4
>15	1	2.5
Total	39	100.0

The annual prevalence of typhoid fever admissions relative to total admissions over the years from 2008 to 2011 revealed an increase from a range of 2.3-2.9% between 2008 and 2010, to 4.5% in 2011 as shown in Table 2. The difference in the prevalence of typhoid fever admissions between these two periods was statistically significant (X^2 = 5.6651; p <0.019).

Table 2: Typhoid fever prevalence as percentage of annual admissions (2008-2011)

Year	Typhoid cases	Total Admissions	% Prevalence
2008	21	712	2.9
2009	17	755	2.3
2010	23	781	2.9
2011	33	738	4.5

X^2 = 5.67; df = 1; p = 0.019 (Fisher's exact)

There was history of domestic use of well water predominantly in nine (23.1%) of households of the children, but with another 23.1% of households (that originally relied predominantly on public pipe-borne water) that had to resort to other alternatives after their supply was disrupted. There was also occasional use of a particular brand of water sachets for domestic purposes in these neighbourhoods in 15 (38.5%) cases.

Clinical and laboratory findings

Time of presentation to hospital was within the second week of onset of illness in 18 (46.2%), while 15 (53.8%) presented either in the first or third week. Fever was a common complaint in all the children, while abdominal pain, headache and diarrhoea were accompanying complaints in 36 (92.3%), 26 (66.7%) and 25 (64.1%) patients respectively (Table 3). There was history of household contact with family members who had similar illness in four (10.3%), including three siblings that were managed for typhoid fever on admission in ABUTH but at different times during the review period (not shown in table).

Physical examination on admission showed that 35 (89.7%) patients were febrile with axillary temperatures >37.4^{0}C, while 13 (33.3%) were underweight. Cardiovascular examination showed that nine (23.1%) had tachycardia, three (7.7%) had congestive cardiac failure and two (5.1%) had septic shock. None of the patients had bradycardia. Although 19 (48.7%) children had tachypnoea none had features suggestive of pneumonia. Table 3 shows the major examination findings, with hepatomegaly and generalised tenderness being the commonest.

All patients (100%) had used at least one or more oral and/or parenteral antibiotics for variable periods ranging from 3-15 days prior to presentation, the commonest being amoxycillin, chloramphenicol and ciprofloxacin. Frequent combinations used included (cefuroxime + augmentin + co-amoxiclav); (amoxicillin + augmentin + ceftriaxone); (tetracycline + metronidazole + ciproflox-

Table 3: Clinical features in 39 children managed for typhoid fever

Symptom	Frequency	%
Fever	39	100.0
Abdominal Pain	36	92.3
Headache	26	66.7
Diarrhoea	25	64.1
Vomiting	23	59.0
Constipation	10	25.6
Blood in Stool	8	20.5
Physical Sign	**Frequency**	**%**
Hepatomegaly	27	69.2
Abdominal tenderness	21	53.9
Intestinal ileus	7	18.0
Splenomegaly	6	15.4
Abdominal distension	5	12.8
Guarding	4	10.3
Rebound tenderness	2	5.1

Laboratory evaluation revealed that 18 (46.2%) patients had positive *Widal* test result, five (12.8%) had negative results and 16 (41%) were not tested. Preliminary blood culture results for most patients was reported as showing no growth of organisms but later yielded *Salmonella typhi* in three (7.7%) cases and was negative in 29 (74.4%), while seven (18%) had no blood culture done. Of the stool cultures requested one (2.6%) yielded *Salmonella typhi* and none of urine samples cultured yielded any organism. The outcome by diagnostic categories revealed that possible typhoid diagnosis predominated, with 29 (74.4%) as against 18 (46.2%) probable and four cases (10.3%), three blood and one stool samples) confirmed, culture positive cases.
Anaemia was present in 27 (69.2%) cases out of which it was severe in five (12.8%) necessitating blood transfusion, moderate in 14 (35.9%) and mild in eight (20.5%) of the children respectively. Leukocytosis (predominant neutrophilia) was present in six (15.4%), leukopaenia in one (2.6%), while four (10.3%) children had absolute neutrophilia and none had relative lymphocytosis.

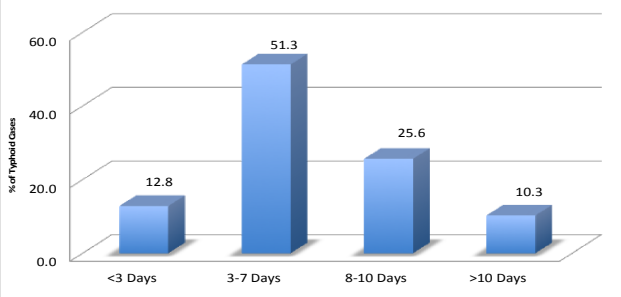
Blood films for malaria parasite microscopy (carried out as a routine for all admitted children with febrile illnesses), was positive in three (7.7%) cases and negative in 36 (92.3%). The three patients had negative specimen cultures and they received oral antimalarial therapy (coartem) from admission, in spite of which they remained ill with persistent fever and other clinical features suggestive of typhoid fever, but with negative repeat malarial parasite blood films after the completed courses of antimalarials.

Treatment outcomes

Regarding the duration of fever on admission, 20 (51.3%) patients had fever resolving within 3-7 days and 10 (25.6%) within 8-10 days. Fever resolved within less than three days in five (12.8%) and after 10 days of admission for (10.3%) patients respectively (Fig 2). The three children that had positive blood films for malaria parasites were also treated with oral ACT

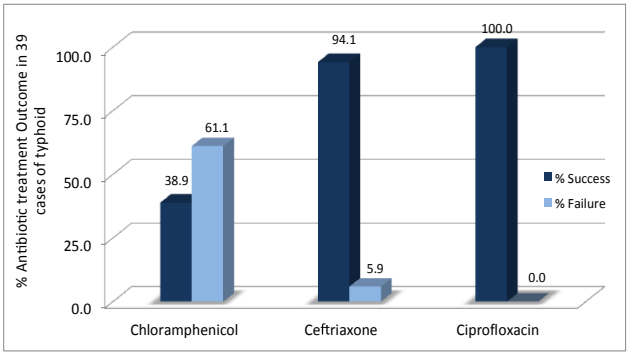
(*Coartem* tablets) for three days after which repeated blood films were reported as negative.

Fig 2: Duration of fever on admission in 39 children managed for typhoid fever



Out of seventeen children started on intravenous ceftriaxone from admission, one (5.9%) was switched to ciprofloxacin (on fourth day with poor response). In contrast, out of the 18 children that were started on intravenous chloramphenicol 11 (61.1% of 18) were switched over to ciprofloxacin or ceftriaxone (as above), while none of four patients started on ciprofloxacin required switching (Fig 3).

Fig 3: Antibiotic treatment outcome in 39 children managed for typhoid fever



There was no mortality recorded but four (10.3%) children had their illness complicated by bowel perforation and peritonitis necessitating exploratory laparotomy and bowel excision. These children had uneventful recovery and continued follow-up in the Surgical Outpatient clinic. Severe anaemia requiring blood transfusion and septic shock occurred in five (12.8%) and two (5.1%) children respectively. All the 39 patients eventually recovered and were discharged with no problems identified at follow up.

Discussion

This study revealed that majority of children (71.8%) that were managed for typhoid fever in the period reviewed resided in a stretch of adjacent settlements in Zaria, where pipe-borne water supply got interrupted through the rainy season. Several reports and reviews have described typhoid fever outbreaks in association with lack of potable water, some of which were related with the rainy season.[1,5,9,13,14] Although up to 23.1% of children resided in households that predominantly used well water, an equal proportion resided in households that predominantly used pipe-borne water before its supply was interrupted. This may have led to more use of well water and other unsafe alternatives that may have been contaminated. The cluster of children that presented from the adjacent settlements could explain the higher prevalence of typhoid fever admissions in 2011 compared to the previous three years.

The 6-10 year-old peak age conforms with what has previously been reported about peak age of occurrence of typhoid disease in children.[2-5,7,9,14] Although there were no infants amongst our patients, a significant proportion (30.8%) were within the 1-5 year age group. This is in contrast to findings in reports of studies in Asia where infants constituted significant (even though still smaller) proportions of patients compared to older age brackets of children.[5.] Our observations of fever as a common complaint in all the children, though documented on examination in 89.7%, and diarrhoea being commoner than constipation (64.1% versus 25.6%) were similarly found in other reports of typhoid fever in children. [7-9,14]

Hepatomegaly was common amongst the studied children even though with a higher frequency than was reported from Asia and other sub-Saharan African countries (69.2% versus range of 27-42%). [5,7-9,14] In contrast however, the proportion of children with splenomegaly in our report was only about half as many as was found in these reports (15.4% versus 30-40%). [5,7-9,14] This difference could have been due to the limitation of our study, with fewer subjects compared to these other studies. Although our analysis did not include sleeping pulse rate, none of our patients had bradycardia. However, reports that had documentation of sleeping pulse rates monitored on admission did not observe relative bradycardia,[8,15] which is a recognised feature of typhoid fever in adults, but is uncommon in children.[16]

Convulsions, coma or features of meningitis were not amongst the presenting features of typhoid fever in this report, but auditory and visual hallucinations were observed in just 5.1% of children. A wide range of central nervous system features including convulsions, coma, neuropsychiatric manifestations and meningitis have been documented in previous reports[16-18] but the fewer number of subjects in our report makes comparison with these other reports difficult.

The finding of anaemia in up to 69.2% of the cases conforms to what was documented in an older report[14] where anaemia was seen in 57% of under-five children and in a similar report from Ethiopia.[19] Anaemia results partly from immune-mediated red blood cell destruction and the effect of toxins liberated in the overwhelming sepsis caused by salmonella infection. [16] Leucopenia was uncommon, documented in only one patient (2.6%), much less than what was observed in previous studies in South Africa (18%) and Nigeria (14.2%). [9,14] On the other hand, leucocytosis (WBC count >10,000/mm^3)

occurred in 15% of our cases as similarly noted in the same studies. [9,14]

Isolation of *salmonella* in cultured specimens, the most important diagnostic tool and gold standard,[1,10,12] was not a predominant finding in our study, with only 10.3% positive culture for *Salmonella typhi*. Although blood culture was done in 82.1% of patients due to logistic challenges, the yield was still much lower than what was reported in similar but older reports that had findings in the range of 60-85% positive cultures.[7-9,14] The poor yield from cultures could have been partly due to pre-admission antibiotic use, often with multiple drugs, common to all the children studied. In the same manner, Widal test was positive in only 46.2% of our cases, a frequency less than that in other reports.[7-9,14] Use of antibiotics before hospital presentation is known to depress typhoid antibody production resulting in low titres detectable by Widal test just as it also leads to inhibition of growth of *salmonellae* on culture media.[10,11,12,20]

The switch to ceftriaxone or ciprofloxacin in 61.1% of children initially started on chloramphenicol at time of admission suggests a significant reduction in clinical efficacy of the latter drug. The negative preliminary culture results in majority of cases could be partly attributed to the observed indiscriminate use of antibiotics. These findings concur with observations that resistance to chloramphenicol constitutes a significant problem that has rendered it less effective with high rates of treatment failure, relapse and chronic carrier rates.[1-3,11,12]

There was no mortality even though potentially life-threatening complications of bowel perforation and progression to progression to bowel perforation (in 10.3%) and septic shock (in 10.3%) occurred with severe anemia in 12.8% of the child. The indiscriminate antibiotic use, delayed presentation and choice of less effective antibiotic at admission could have contributed to a higher rate of bowel perforation in up to 10.3% of our cases compared to a rate of 0.5–1% observed to result from inappropriate or delayed therapy.[6]

The limitations of this study include amongst others, being a retrospective review that reported on a limited number of children. Because ABUTH is a tertiary referral facility in Zaria, some other children ill with typhoid fever could have been treated in other lower level and private health facilities or at home. A community-based investigation of disease outbreak in the residential settlements of the children could have best revealed the epidemiological pattern of the problem, including the detection of milder cases and chronic carriers of *Salmonella typhi*.[1,5] Nevertheless, our findings suggest that typhoid fever had assumed public health importance in the settlements from where these children resided in the reporting period, a significant proportion of whom were aged under-5. The findings support a need for provision of adequate uninterrupted potable water supply, environmental sanitation, inclusion of vaccination against *Salmonellae* for infants in the National Immunization Schedule and public health education on water and food hygiene.[1,4,5,13,21]

Author contributions

Umar LW: Literature search and review, data analysis and initial draft and final manuscript writing.
Adelaiye H, Adebiyi M, Adeoye GO, Ahmad HR, Giwa F: Coordination of data collection

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