

# Factors Associated with Perioperative Mortality in Typhoid Fever Patients with Intestinal Perforation in Nigeria

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## Abstract

**Objective:** Despite the availability of effective antibiotic treatment, patients in Nigeria continue to perish from complications of typhoid fever, including intestinal perforations. Given the preventable nature of these deaths, we attempted to identify pre-operative factors that may influence mortality in typhoid patients with intestinal perforation at Bowen University Teaching Hospital (BUTH) in Ogbomoso, Nigeria.

**Methodology:** All the charts of patients with typhoid admitted to BUTH for surgical repair of intestinal perforation were reviewed from January 2004 to March 2009. There were 173 patients treated during that period; however, adequate records were obtained for 144 patients. These were analyzed for statistical associations between patient characteristics and mortality.

**Result:** There were 32 deaths, yielding a mortality rate of 22.2%. Female gender ( $p=0.013$ ), presence of neurological symptoms on presentation ( $p=0.014$ ), delay in securing blood for patients requiring pre-operative blood transfusion ( $p=0.028$ ), length of that delay ( $p=0.037$ ) and duration of presentation-operation time interval ( $p=0.025$ ) were associated with increased mortality. There was no association between mortality and age, time from symptom onset to hospital presentation or any other sign/symptoms or laboratory values.

**Conclusion:** Delay in obtaining blood for patients requiring pre-operative transfusion and prolonged duration of presentation-operation interval were the only modifiable factors associated with increased mortality. Efforts to increase blood donation and decrease delay between hospital presentation and operation can ensure that patients with typhoid related intestinal perforations receive proper treatment as quickly as possible.

**Keywords:** Africa South; Sahara; Nigeria; Blood transfusion; Intestinal perforation; Preoperative period; Typhoid fever

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## Introduction

Typhoid is estimated to have caused greater than 160,000 deaths in the year 2013 [1]. Nigeria has an especially high burden of the disease due to high population density, poor sanitation and an inadequate number of water purification systems. Typhoid initially presents with little more than fever and headache, with more serious and characteristic gastrointestinal features such as diarrhea, constipation, and vomiting occurring several days later. The early nonspecific features of typhoid, along with an often-

overburdened healthcare system and lack of patient knowledge concerning where and when to seek healthcare, may lead patients in Nigeria to take actions that delay appropriate treatment. As a result, many patients with typhoid in Nigeria do not present to the hospital until their second week of symptoms, when there is a high chance that perforation of the small intestine has occurred,

leading to gastrointestinal bleeding and a potentially fatal peritonitis. Often, further delays await patients at the hospital as well. We sought to identify pre-operative factors predictive of mortality in patients presenting to Bowen University Teaching Hospital (BUTH) in Ogbomoso, Nigeria with typhoid related intestinal perforations.

## Materials and Methods

All charts of patients admitted to Bowen University Teaching Hospital (BUTH) (formerly Baptist Medical Centre) in Ogbomoso, Nigeria were reviewed for operative repair of intestinal perforations due to typhoid from January 2004 to March 2009. During that time period, there were 173 patients with intestinal perforation secondary to typhoid treated at the hospital; however, adequate records (which included descriptions of symptoms, vital signs, laboratory values and survival outcomes) were only able to be obtained for 144 patients. Data were entered into a Microsoft Excel™ (Redmond, WA) spreadsheet. The initial diagnosis of intestinal perforation secondary to typhoid was based solely upon clinical history and physical examination. For those 131 patients who survived until operation, the diagnosis was confirmed upon exploratory laparotomy. For the 13 patients who died before operation could be performed, the diagnosis of intestinal perforation secondary to typhoid was based on clinical evaluation alone, since no autopsies are conducted at the hospital. Internal review board (IRB) approval was granted by Vanderbilt University School of medicine IRB and BUTH IRB. Summary statistics (means, medians, percentiles, percentages, and frequencies), as well as associations between patient characteristics and mortality using Pearson and two-sample Wilcoxon tests were carried out by using R version 2.10.1.

## Results

Of the 144 cases reviewed, 90 patients were male and 54 were female. Their mean age was  $19.1 \pm 13.5$  years (range 2-80 years). The mean time interval between onset of symptoms and presentation was  $11.1 \pm 5.4$  days. A large majority of patients (127,88%) received some type of treatment prior to presentation at BUTH, which included treatment from a private clinic/patient medicine vendor, traditional healer, private hospital, public hospital or self-administration of an herbal remedy. Ninety-seven (76%) received one type of pre-presentation treatment and 30 (24%) received two types or more. Of the patients who had received previous treatment, 114 (80%) patients received treatment from a private clinic/patient medicine vendor, 12 (8%) received treatment from a traditional healer, 7 (5%) reported self-administration of an herbal remedy, 7 (5%) reported visiting a private hospital and 4 (3%) visited a public hospital. The most common signs and symptoms at presentation included abdominal pain, fever, abdominal distension, vomiting, diarrhea, and constipation (**Table 1**). On presentation, the mean temperature was  $38.4 \pm 1.1^\circ\text{C}$ , diastolic blood pressure was  $72.4 \pm 14.9$  mm Hg, systolic blood pressure was  $114.2 \pm 20.4$  mm Hg, and pulse was  $122 \pm 20$  beats per minute. In terms of laboratory values, the mean white blood cell count was  $8.2 \pm 3.8 \times 10^9/\text{L}$  and mean hematocrit was  $31.4 \pm 7.5\%$ .

There were 32 deaths yielding a mortality rate of 22.2%. Thirteen patients died before operation and three died intra-operatively. Excluding those patients who died before operation, there were 19 deaths, yielding a 14.8% (19/128) post-operative mortality rate. Upon presentation, the mean time interval until operation for all patients was  $15.8 \pm 10.9$  hours. Sixteen patients of 46 patients (35%) requiring pre-operative transfusion (i.e., hematocrit <30%) had a delay in obtaining necessary blood for transfusion before operation, which was defined as being greater than six hours. The mean duration of this delay was  $16.2 \pm 4.9$  hours.

Using the Pearson test for univariate analysis, statistically-significant associations with mortality were found with gender ( $p=0.013$ ), presence of neurological manifestations upon presentation (delirium, seizure or loss of consciousness) ( $p=0.014$ ), and delay in securing blood pre-operatively for patients requiring pre-operative transfusion ( $p=0.028$ ) (**Table 2**). No associations were found between mortality and the year the illness occurred, any sign or symptom besides neurological manifestations, or receiving pre-presentation treatment of any type.

Using the two-sample Wilcoxon test for univariate analysis, statistically-significant associations with mortality were found for duration of presentation-operation time interval ( $p=0.025$ ) and duration of delay in obtaining blood pre-operatively for patients requiring transfusion ( $p=0.037$ ) (**Table 3**). The mean time interval between presentation and operation was  $21.0 \pm 12.3$  hours in those who died and  $15.0 \pm 9.8$  hours in those who survived. The median delays in obtaining blood were  $19.5 \pm 6.3$  hours for those

**Table 1** Most common signs and symptoms reported by patients (n=144).

Signs and Symptoms	# of patients
Abdominal Pain	144 (100%)
Fever	142 (99%)
Abdominal Distension	107 (74%)
Vomiting	92 (64%)
Diarrhea	74 (51%)
Constipation	58 (40%)
Neurological manifestations	15 (10%)

**Table 2** Results of tests of associations between factors and mortality (nominal variables).

Variable	n	Died (n=31)	Survived (n=113)	P-value
Any pre-presentation treatment	127	28	99	0.63
Female Gender	54	17	37	0.013
Presence of abdominal distension	107	24	83	0.65
Presence of abdominal pain	144	31	113	0.56
Presence of constipation	58	11	47	0.54
Presence of diarrhea	74	17	57	0.66
Presence of fever	142	31	111	0.46
Presence of hypoactive/absent bowel sounds	94	22	72	0.17
Presence of neurological manifestations	15	7	8	0.014
Presence of vomiting	92	20	72	0.94
Pre-operative blood procurement delay	16	7	9	0.028

**Table 3** Results of tests of associations between factors and mortality (continuous variables).

Variable	All (n=144)	Died (n=31)	Survived (n=113)	P-value
Age (years)	19	19	19	0.26
Blood pressure- diastolic (mm Hg)	72	66	74	0.08
Blood pressure- systolic (mm Hg)	114	112	115	0.65
Duration of abdominal distension (days)	1	2	1	0.89
Duration of abdominal pain (days)	5	5	5	0.82
Duration of constipation (days)	4	4	4	0.41
Duration of diarrhea (days)	5	5	5	0.30
Duration of fever (days)	9	10	9	0.56
Duration of vomiting (days)	2	3	1	0.27
Duration of pre-operative blood delay (hours) (n=16, 5, 11 patients)	15	20	14	0.037
Duration of presentation-operation interval (hours)	16	21	15	0.025
Hematocrit (%)	31.4	30.1	31.7	0.43
Initial symptom to presentation at BUTH interval (days)	11	11	11	0.23
Pulse (beats per minute)	122	127	121	0.14
Temperature (°C)	38.4	38.3	38.5	0.59
White Blood Cell Count ( $\times 10^9/L$ )	8.2	7.2	8.3	0.32

with a delay who died and  $14.3 \pm 4.3$  hours for survivors who had a delay. No differences in mortality rates were observed for initial symptom to presentation at BUTH interval, ages, vital signs, duration of any sign or symptom and hematocrit or white blood cell count.

## Discussion

Our results demonstrate that delays in the interval between hospital presentation and operation, as well delays in obtaining donated blood for transfusion, are associated with increased mortality in typhoid patients with intestinal perforation. Previous studies of typhoid patients with intestinal perforations in Nigeria have demonstrated associations with pre-operative factors including female gender, presenting systolic blood pressure less than 90 mm Hg, abdominal tenderness, prolonged time interval between presentation and operation [2], duration of abdominal pain [3], presenting temperature greater than  $38.5^\circ\text{C}$  [4] and age  $<5$  years [5]. It is unclear why female gender was associated with increased mortality in our study, though this is not the first time this association has been observed [2]. The association of neurological symptoms and mortality we found is not unexpected, as these manifestations (such as delirium, seizure and loss of consciousness) often indicate severe sepsis or blood loss, and precede death for many medical conditions.

Most patients were anemic, with the mean hematocrit of all patients being 31.4%. Typhoid leads to anemia through bone marrow suppression, hemophagocytosis, occasionally hemolysis, and intestinal hemorrhage [6]. Prior to operation, patients in our study who had a hematocrit of less than 30% required transfusion. Despite longstanding evidence that adequate resuscitation of patients who are planned to undergo emergency surgeries can be accomplished in under 6 hours [7], the average presentation to operation interval in our study for all patients was nearly 16 hours. Delays in obtaining blood for pre-operative transfusion were a large contributor to this prolonged interval.

Blood banking is a problem at BUTH and other hospitals in Nigeria

due to low donation rates [8]. Reasons for reluctance to donate in a study in Lagos [9] included fear of contracting HIV or hepatitis from donation, weight loss, sexual failure, high blood pressure, sudden death, and seizure. A study on attitudes towards blood donation in a rural Nigerian village found a number of similar misconceptions being held by participants including beliefs that the participant did not have enough blood to donate and that donation would shorten their lifespan, cause them to lose libido, increase their risk of infection, or put them at risk since their blood might be exposed to rituals/witchcraft [10].

It is likely that such attitudes are present in Ogbomoso as well, which makes maintaining adequate levels of donated blood at BUTH difficult. Because of this, patients' families are often required to scramble to find blood donors of the correct blood type among their family and friends at the time of a patient's hospital presentation. Not having enough blood on hand thus presents a significant and deadly barrier to patients being able to undergo timely corrective operation. A study in Cross Rivers State, Nigeria found that offering non-cash incentives, such as certificates of honor, free blood screening and assurance that any blood donated would first go to the donor's family should they need it, more than doubled blood donations at two separate facilities [11]. Such changes could also lead to increased blood donation at BUTH if implemented. The lack of blood donations at BUTH and other Nigerian hospitals could also be addressed by carrying out school and community-wide education campaigns to dispel myths surrounding donation.

Though blood procurement delay plays a large role in prolonged presentation to operation interval, it is only one of many factors. Lack of operative theatre space, electricity, water, sterile gowns, anesthetic drugs, and patients' inability to pay necessary operative deposit fees were associated with prolongation of this interval in a 2003 Nigerian study [12]. Another study found that inability to pay the operative deposit fee accounted for the majority of cases of patients (65%) with acute abdominal emergencies having a prolonged period between presentation and operation [13]. The authors of that study suggested the creation of a short-

term credit system that allows for immediate emergency surgical care through the use of a revolving fund and requires patients to repay before they can be discharged. In a resource constrained setting such as Ogbomoso, a system like this could shorten wait times and result in decreased mortality if implemented in BUTH's emergency department, while still allowing the hospital to remain financially solvent.

Though our study is retrospective and small, it reveals modifiable factors that, if improved, could result in decreased mortality in typhoid patients with intestinal perforation and likely many other types of patients requiring operations. Future research in this area should assess mortality in patients with intestinal perforation or other surgical emergencies before and after establishing interventions to reduce presentation to operation interval and delays in obtaining blood for transfusion. We anticipate that such interventions would surely lead to decreased loss of life in patients requiring emergency abdominal operations in Nigeria and elsewhere in Africa.

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