Intestinal perforation due to typhoid fever in Karamoja (Uganda)

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INTRODUCTION: *This is a retrospective analysis of patients operated for typhoid perforation, aiming to analyze epidemiology, clinical-diagnostic and therapeutic aspects, mortality and prognosis.*
METHODS: *47 patients were operated at Matany Hospital from 2010 to 2016. We examined clinical files to collect data. Microbiological and isthological examinations were unavailable, so etiology was deducted operatively.*
RESULTS: *Median age: 17.85 years, 61.7% of patients were male, 74.47% perforated within two weeks from the onset of symptoms. Every radiological investigation (X-Rays and Ultrasound Scans) resulted positive. 40 patients underwent primary repair, 4 underwent resection. 72.34% experienced postoperative complications, SSI (Surgical Site Infection) occurred in 40.42%. Mortality rate reached 5.56% in patients without organ failure (vs 31.03%) and 11.76% (vs 20.51%) in patients operated within 24 hours from perforation. An MPI (Mannheim Peritonitis Index) score >30 was related with a mortality rate of 36% (vs 3.45%).*
CONCLUSIONS: *Peak of incidence occurs at the end of rainy season. Majority of patients are young men. Main symptoms are fever and signs of intestinal obstruction, with a shorter period before perforation. Primary repair is the technique of choice for single perforations, resection for multiple ones, right colectomy in case of cecal involvement, ileostomy for important peritoneal contamination. SSI are the most frequent complications, enteric fistulas the most severe ones. Mortality rate is around 21.28%. Important prognostic factors are time between perforation and operation and the presence of organ failure. An MPI score >30 is related with a poorer prognosis.*

KEY WORDS: Prognostic factors, Surgical treatment, Typhoid perforation, Uganda

Introduction

Typhoid fever is a sistemic infection caused by Gram negative bacillus, facultative anaerobic, *Salmonella enterica spp. enterica* serotype *typhi*, belonging to *Enterobacteriaceae* family and specifically human [1].

Nowadays, the heaviest disease burden belongs to Developing Countries, where sanitation and health conditions remain poor.
Reliable data from which to assess the real impact of this disease in these areas are difficult to find, since in many hospitals microbiological exams are still unavailable and up to 90% of patients with typhoid fever are treated as outpatients.
Nevertheless, it is likely that every year about 20-30 million cases of typhoid fever occur in the world, with a number of deaths between 200.000-500.000 per year[2]; perforation rates (the most severe complication) reported in Literature vary between 0.8% and 18% of cases[3-5] .
Typically, perforation (usually ileal) occurs during the

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second-third week of illness (although recent works showed a trend of earlier perforation), with an increase in morbidity and mortality [6].

Attempts of determining the epidemiology of the disease in Africa have been even more difficult [7]: Crump et al. [2] concluded that available data were so poor that only a mere incidence rate was achievable (100-1.000 cases over 100.000 people, in a population of about 820 millions)[8].

Global Burden of Disease Study of 2010 estimated similar percentages [9], as well as Buckle et al. [10] (724 cases over 100.000 inhabitants).

For what concerns antibiotic resistance, the first microorganisms resistant to chloroamphenicol became a major concern during 1970s, followed during 1980s by MDR (Multi-Drug Resistant) microorganisms resistant to chloroamphenicol, ampicilline and trimethoprim/sulfametoxazole and in the 1990s by microorganisms resistant to cephalosporines and quinolones [11].

The threat of multiresistant bugs, in a low-resource region with unavailable epidemiological and laboratory surveys points out the need of an international collaboration (as some programs already sponsored by WHO) and standardized diagnostic techniques in order to identify and analyze these pathogens [7].

Patients and Methods

47 patients were operated for typhoid perforation at the Surgical Department of St. Kizito Hospital (Matany), from January 2010 to April 2016.

29 patients (61.7%) were male and 18 (38.3%) female. Median age was 17.85 years (range 2-60): 18.24 years for male (range 3-60) and 17.28 years for female (range 2-54). 46.8% of patients was aged between 11 and 20 years old.

We examined the files of these patients to collect personal data, clinical aspects, radiological results, therapy and operative findings.

Many of the required data were difficult to find on the clinical files: particularly the details on the exact onset of symptoms, the preoperative duration of peritonitis, blood examinations (usually only hemoglobin level was tested before the operation) and death circumstances.

Microbiological and histhological data were unavailable.

The evaluation of organ failures was merely clincal, not instrumental.

Similarly to other studies [12], typhoid etiology was therefore suspected at the operation for the presence of typical ulcers on the antemesenteric side of the terminal ileum, in patients without any other possible cause of intestinal perforation.

All data have been processed using LibreOffice 4.4®.

Due to the few patients enrolled in this study, we didn't aim to achieve statistically significant results (which would require a broader analysis); therefore, data presented are rough percentages and even p-value would have been inappropriated.

Results

We noticed a seasonal trend of typhoid fever (whose most severe complication is intestinal perforation), related to the rainy season (in Karamoja the major one lasts from April to May and the minor one from October to November approximately).

Particularly, the observed peaks occurred at the end of rainy seasons (June and November, Fig. 1), despite weather conditions have recently become more irregular.

The majority of patients (Fig. 2) presented with abdominal pain and distension, fever (in the former period or at admission), ileus and vomit.

In many cases the presence or absence of abdominal guarding was not reported on the file as well as the presence of hepato/splenomegaly, often due to the short time forced by the emergency operation.

We underline the rare finding of relative bradycardia, diarrhea, digestive bleeding and confusion: we will discuss this result in the following chapter.

Despite the poor quality of anamnestic collection, contrarily to what we expected, perforation of the majority of patients occurred after about a week from the onset of symptoms (24 patients, which is to say 51.06%).

74.47% of patients (35 cases) perforated within two weeks from the onset of the first symptoms.

The average duration of the disease before perforation was 6.97 days (range 2-35).

In 9 cases it was not possible to date the onset of symptoms, since it was not specified on the file.

We could rely on scanty data from laboratory investigations, not only from a microbiological point of view, but also from first level diagnostic exams (e.g. complete blood count, renal and liver function, HIV test), probably seen as useless in an african district setting, where diagnosis are clinical and patients pay for each investigation performed.

The only exam which was routinely performed was preoperative hemoglobin count (35 patients, 74.47%) and sometimes the blood smear for malaria in febrile patients.

Hemoglobin count revealed anemia in 15 patients (42.86%) of the 35 tested, with an hemoglobin value lower than 10 g/dl (range 5,9-16,8, median 10.40), but none was transfused before the operation.

Due to the lack of blood available for transfusions and the high infective risk of these procedures, the majority of african guidelines recommend to transfuse patients only for very low hemoglobin levels or hemodynamic instability.

Moreover, even when blood is needed urgently for transfusions, it is usually unavailable.

White blood cell count (range 3.300-11.000, median 6070) was requested preoperatively in 9 patients only

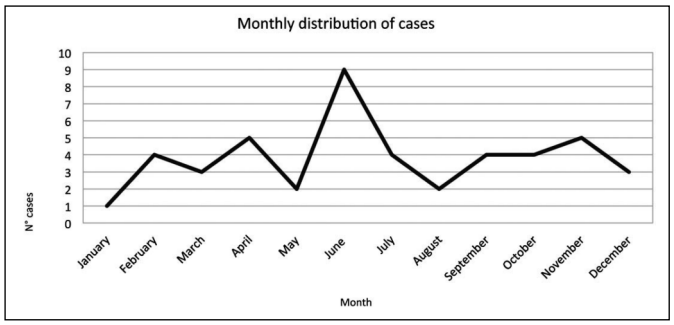

Fig. 1: Monthly distribution of cases.

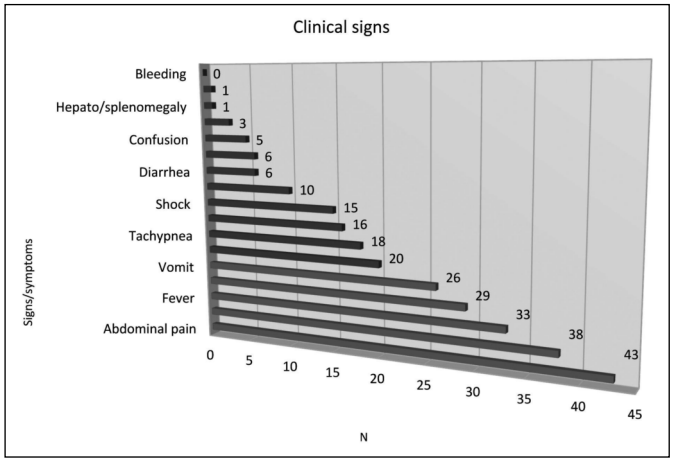

Fig. 2: Clinical signs.

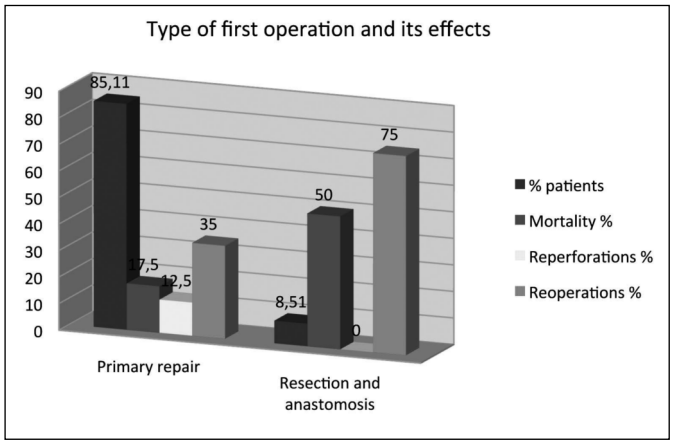

Fig. 3: Type of first operation and its effects.

(19.15%), and its values ranged between 4.000 and 10.000/mm^3 in 5 of them (55.56%), were lower than 4.000/mm^3 in 3 (33.34%) and higher than 10.000/mm^3 in 1 (11.12%).

Widal Test was carried out in 5 patients and its result was negative in 4 of them (one of these became positive later on) and positive in one case, confirming the unreliability of this test.

An important role for the management of the patients was undertaken by radiological investigations: ultrasound scan (US) and direct abdominal X-rays (XR), as computed tomography scan was obviously unavailable.

Specifically, 6 patients (12.77%) were studied with US, 17 (36.17%) with XR, 17 (36.17%) with both techniques and 7 (14.89%) were not evaluated with radiological investigations.

Every radiological exam performed was positive for pathological issues (pneumoperitoneum or free abdominal fluid).

Medical therapy set up was appropriated in every patient: both for what concerns fluid resuscitation and for what concerns preoperative and postoperative antibiotic coverage (basically: chloroamphenicol, ampicilline/gentamicin /metronidazole, ceftriaxone/metronidazole, ciprofloxacin/metronidazole). Naso-gastric tube and urinary cathether was placed in every patient before the operation.

Evaluating the kind of surgical procedure performed at first operation, every patient underwent median laparotomy.

Amazingly, no patient underwent an ileostomy at the first operation.

The only patient who underwent right colectomy finally died after a second operation performed for a new perforation.

Laparostomies were not performed in our hospital.

The most frequent techniques used were therefore primary repair of the perforation and ileal resection with anastomosis, both of them always associated with peritoneal washing and drainage.

Fig. 3 shows the effects of both these surgical techniques. The majority of patients [40] underwent primary repair, versus 4 patients who underwent resection.

Mortality was higher in this second group (2 deaths), probably due to a worse gravity of the disease too.

However, we noticed an high occurance of re-perforations [5] and re-operations [14] in the first group.

34 patients (72.34%) experienced postoperative complications, with a mortality rate of 29.41%.

Fig. 4 shows the main complications encountered and their outcomes.

8 patients suffered a re-perforation (17.02%) and 20 patients a second operation (42.55%), both for reconstructive surgery of the abdominal wall and for postoperative peritonitis, but the most frequent complication was surgical site infection (19 patients, 40.42%), due to important wound contamination at the operation.

Mortality rate was 80% (8 deaths) in the 10 cases complicated by septic shock after the surgical operation, 37.5% (3 deaths) in patients with a reperforation and 30% (6 deaths) in patients who underwent a second surgical operation.

The average hospital stay was 28.57 days (range 1-73).

Total mortality rate was 21.28% (10 patients over 47).

We finally reviewed the possible prognostic factors of this disease, starting from a peculiar aspect of typhoid

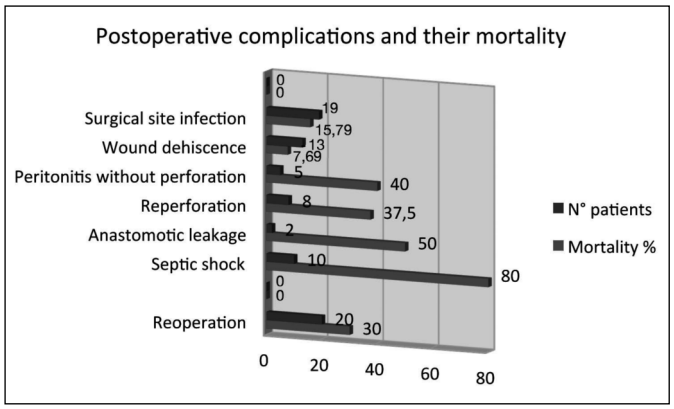

Fig. 4: Postoperative complications and their mortality %.

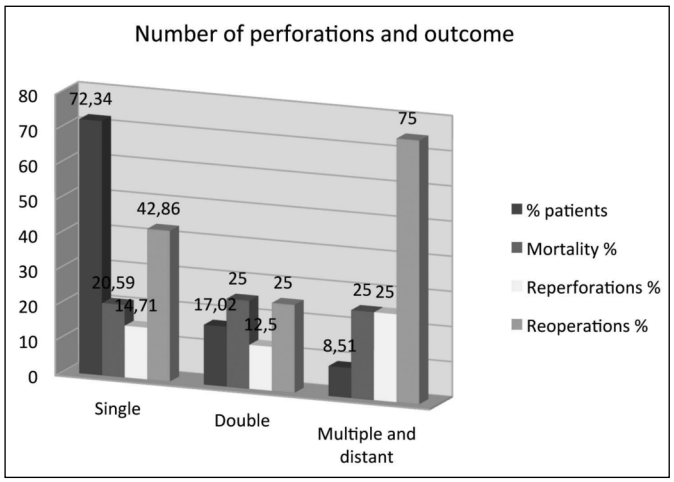

Fig. 5: Number of perforations and outcome.

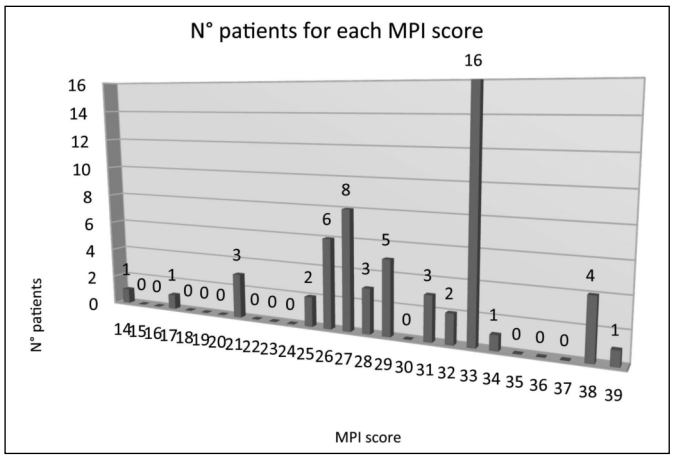

Fig. 6: Number of patients for each MPI score.

perforations: the impact of the number of perforations on the outcome of our patients.
As we can see in figure 5, the number of patients decreases with the increase in number of perforations, but mortality, the occurrance of re-perforations and the percentage of re-operations increase with the increase in number of perforations.
In detail, mortality rate reached 20.59% for single perforations and 25% for multiple ones.
We notice that one patient, operated for peritonitis, wasn't perforated at first laparotomy, but perforation occurred in a second time. In the multiple and distant' perforations group we included 4 patients, respectively with 4, 23 (ulcers), 8 and 3 perforations.
The median age observed was 19.4 years (range 2-60) in the single perforation group, 13.42 years when perforations were double or multiple (range 3-25).
Our evaluation continued studying the single impact on mortality of classical prognostic factors of peritonitis, expressed by Mannheim Peritonitis Index (MPI) score system [13-22] (except from the presence of cancer, since none of our patients was affected by this pathology), in order to compare their reliability even for peritonitis secondary to typhoid perforation.
Concerning the gender, in our study male were more affected than female (29 versus 18). Mortality rate was slightly higher in female with 4 deaths (22.23%) versus 6 deaths in male (20.69%).
The median age of survivors was 16.51 years, versus 22.9 years of deceased patients. The total median age (17.85 years) was closer to the age of survivors.
If we consider mortality rate in every age group, we can observe how this percentage considerably increases over 20 years of age.
For this reason, for the young median age of our patients and for the low number of patients older than 50 years old in our study, we decided to compare mortality rate in patients older than 20 years old and in younger than 20 years old: 35.29% in the first group (6 deaths over 17 patients) versus 13.34% in the second one (4 deaths over 30 patients).
The classical age cut-off of 50 years, although not significant for the low number of patients of this age (2 over 47), was nevertheless characterized by poor outcome: 50% of mortality versus 20% in patients younger than 50 years old.
In patients without signs of organ failure the risk of death was very low: only one patient over 18 died (5.56%), while mortality rate in patients with at least one organ failure at the admission reached 31.03% (9 deaths over 29).
Patients operated within 24 hours from the onset of abdominal signs were at lower risk of death (2 over 17 infectious episodes: 11.76%), while after this period mortality rate reached 20.51% (8 deaths over 39 episodes).
Since every case reached the hospital with diffuse peritonitis, it was not possible to understand the impact of the extension of peritonitis on mortality.
The presence of fecal contamination of the peritoneal cavity worsened the outcome (9 deaths over 46

episodes, with a mortality rate of 19.56%). In case of purulent peritonitis, instead, only one patient died (11.12%).
At last, the prognostic factors described above have been summarized using Mannheim Peritonitis Index.
MPI score was calculated for each peritonitic episode: results are shown in Fig. 6.
The high number of cases with a score of 16 is greatly influenced by the presence of female patients, who mainly regrouped in this value.
In fact, for female patients, MPI score increases by 5 points.
The average MPI score of deceased patients was 34.1 (range 29-39), versus 28.36 (range 14-38) of survivors.
An MPI score higher than 30 was related with a much higher mortality rate: 36% versus 3.45% for scores lower than 30.

Discussion

Seasonality

Our data confirm those observed by other Authors[23-25] concerning the relationship between the highest incidence of typhoid perforations and the end of the rainy season; particularly, in his study, Eggleston showed that more than half of the patients were admitted during this period.
Indeed, oro-fecal transmission of this disease in countries with inadequate sewerage can be increased by an inappropriate water disposal.

Sex

According to other studies[3,12, 23-42], typhoid perforation occur more frequently in male than in female population, with a ratio of 1.62.
The reason of this is not clear, although men might be at higher risk of exposure since they usually eat street food.

Age

Our results match those of Chalya et al.[26], where the median age of patients studied was 18.5 years, with a peak between 11 and 20 years (47.1% of cases).
Caronna et al.[12] too showed a median age of 17.7 years, with 54.9% of patients younger than 15 years.
Other studies [6,24,26,27,29,32,35,43-47] showed similar results.
Asian Authors [3,23,25,39-42] describe a higher median age (20-40 years), but this can reflect so different realities.
As underlined above, young men are usually at higher risk of eating unhealthy food outside and using public toilets.
The high incidence of this disease in youth surelly plays a negative impact on the economies of these Countries.

Signs and Symptoms

Symptoms of intestinal obstruction and fever, as observed in many other studies [3,6,12,23,26-29,35,42,46], were the classical clinical presentation of the majority of our patients.
Sumer et al.[3] underlines how none of his patients showed relative bradycardia, digestive bleeding or hepatosplenomegaly.
These symptoms rarely appeared even in the study of Agu et al. [6] (0, 8 and 26% respectively), who also reports the presence of diarrhea in 28% of cases only (29% in Ugochukwu's study[24]).
Particularly, the so well-known relative bradycardia, seems to be a more common sign in early stages of uncomplicated typhoid fever[48-51]: with the onset of peritonitis, other microorganisms take part to the infective process, altering clinical presentation.
The late presentation of our patients with perforation might have contributed to the uncommon finding of this sign in our data[6].
The above studies didn't focus on the presence of confusion, with the exception of Ugochukwu et al.[24], who reports a prevalence of 17.4% (similarly to our results).

Onset of Symptoms

Chalya et al. [26] observed the onset of symptoms less than 14 days before the perforation in 80.8% of its patients, with a very similar percentage to ours.
In Ugochukwu's study[24], almost one third of patients perforated within two weeks from the onset of first symptoms.
Similar results have been reported by others [31,36,43,44,52,54].
Typhoid perforation usually occurs during the second and third week of disease, due to the necrotic process of Peyer's patches [4,23,25,55], but in the Developing Countries cases have been reported of early perforations within the first week of disease[53].
The reason of this feature is still unclear, but it might be secondary to a low immunity (e.g. in cases of anemia or malnutrition), an increased virulence of the microorganism, an hypersensitivity of Peyer's patches.
Indeed, many factors can contribute to the process leading to the tissutal damage, involving both bacterial and host inflammatory response [24,30,55].

Laboratory Investigations

All the studies on this topic were heavily supported by laboratory investigations: particularly, routine blood examinations, microbiological analysis (from blood, urine and stools), serological tests (often including HIV test and eventually CD4 count) and sometimes hystological exams too.
The majority of these investigations was unavailable for our patients: both for real lack of devices and for a mere

clinical approach to the patient, typical of Surgery in an african district hospital.
The total lack of HIV test was really disappointing, since it should have been performed almost routinely in a surgical ward of an high prevalence region.
Studying the prognosis of typhoid perforation in HIV patients would have been really interesting.
Similarly to what we described, Caronna [12] reported that 44.2% of the patients presented anemia and 50% showed a normal leukocyte count.
The average leukocyte count was normal in Eggleston's study[23] too (8200/mm^3).
Therefore, this exam was not a reliable tool for the evaluation of these patients.
In our study, Widal test was performed in only 5 patients and it was unrelevant for their subsequent management, providing only further doubts in the following diagnostic and therapeutic path of these patients.
Huckstep points out how this test can result negative in patients with typhoid fever, blood can be sterilized within few hours from antibiotic administration and stool cultures can result negative up to the third week of disease.
Widal test can also result negative at the beginning of typhoid fever: Kim et al.[25] described many patients with low titres but positive blood or stools cultures.
In Verma's study[42] the test was positive in 36.6% of patients only.

Radiological Investigations

Conversely, a crucial role was played in the management of our patients by radiological investigations (abdominal ultrasound scans and direct abdominal X-rays): 85.11% of cases underwent these studies and US and XR exam found out pathological issues in all of them.
This aspect confirms Chalya's data [26], whose patients underwent abdominal X-Rays in 95.2% of cases (which resulted positive in 74.7% of patients) and abdominal US in 53.8% of cases (positive 85.7%).
Totally, radiological investigations correctly diagnosed 80-90% of his cases, with a superiority of US over XR.
Other Authors reported similar results [24,42,56-58].

Medical Therapy

Our preoperative medical treatment was the same of the above studies.
However, as in the mentioned works, it wasn't possible to trace the therapies administered prior to the admission in our center.
In those studies, an adequate and early resuscitation, correction of hydroelectrolitic imbalances, endovenous administration of appropriated broad-spectrum antibiotics and blood transfusions when indicated before the operation proved to be essential prognostic factors [3,24,32,36-38,53,55,59,60]. For what concerns antibiotics, chloramphenicol associated with metronidazole used to be the antibiotic of choice [27,35] and is still used in many hospitals [28].
With the increasing resistance of microorganisms to chloramphenicol, cephalosporines (e.g. ceftriaxone) and quinolones (e.g. ciprofloxacine) became the antibiotics of choice associated with metronidazole for anaerobial coverage and with gentamicin for gram-negative bacteria [26].
Carbapenems too (e.g. meropenem) showed activity against this bacterium, but these drugs are not available in these low-resources settings, due to their high costs.

Surgical Technique of the First Operation

If early surgical therapy is with no doubt the best therapeutic option, the technique of choice is however still controversial [3,53].
Many surgical techniques have been used, from simple peritoneal drainage under local anaesthesia in moribound patients [27], to the excission of the edges of the perforation with transverse double layer primary repair, to intestinal resection and anastomosis especially for multiple perforations, to right colectomy in cases of cecal involvement.
The role of laparostomy in the management of this disease was studied by Caronna [12] only and should be better assessed in the future.
Laparoscopic approaches have been recently described [61,62], but they cannot obviously be performed in these settings.
Briefly [6,25,26,32,36,59,63,64], primary repair should be considered the technique of first choice for single perforations, resection with anastomosis for multiple ones (especially when close to each other), right emicolectomy for cecal involvement.
Ileostomy should be reserved for patients with severe and prolonged peritoneal contamination [4,26,28,29,31,34,65].
We take the opportunity to remember that, in African rural areas, ileostomy bags are difficult to find (both beacause they are unaffordable for the patients and because of difficult supplies) [12,26,29].
In addition to this, ileostomies can induce a constant dehydration in patients at risk of malnutrition and living in a tropical area.
Further more, we remember the need of a second operation in order to close the ileostomy, operation which must be performed by a skilled surgeon.
Similarly to what we observed in our study, Chalya [26] performed primary repairs in 78.8% of cases, resections in 9.6%, right colectomies in 7.7% and exteriorizations in 1.9%. Other Authors [6,12,24] describe similar results.
Caronna[12] observed a mortality of 40% in the resections group versus 31% in the primary repairs group, with a not statistically significant difference (50% and 17.5% respectively in our patients).

Ugochukwu [24] too observed a higher mortality in the resections group (27.7%) comparing to the primary repairs group (11.5%). In our study, mortality of patients in the ileostomies group was 28.6% and it reached 50% in patients who underwent right colectomy.

Postoperative Complications

Eggleston [23] described a higher rate of postoperative complications (81% of his patients versus 72.34% of ours).
Surgical site infection has been reported in Literature as the most frequent complication [3,26,27,35,36,43,60,64], due to the high contamination of laparotomic wound during the operation and to the low resistance of the patients.
In our study too, this was the most frequent complication (40.42%, compared to 44% of other studies [6,26]).
Enteric fistula (12.77% of our patients, versus 6.5% of Chalya's [26] and 6% of Agu's [6]) was the most severe complication [3,23], with a mortality rate of 33.34% in our study. Indeed, this is the clinical presentation of a second perforation (17.02% of our patients, versus 6% described by Agu [6]).
Agu[5] observed the occurance of a postoperative septic shock in 20% of cases, with a mortality rate of 100% (in our study it occurred in 21.28% of cases, with a mortality rate of 80%).
Laparotomy dehiscence occurred in 27.66% of our cases (3.2% [26] - 15% [24]) and postoperative intra-abdominal infections (without perforation) in 10.64% of patients (6.5%[26] - 19.7%[24]).
In our study, patients underwent a re-operation more frequently than what described Chalya [26] (42.55% versus 7.7%).

Average Hospital Stay and General Mortality Rate

Average hospital stay of our patients was the same of others [23,26] (28 days in both studies).
Despite mortality rate of typhoid perforations in Western Countries decreased between 0 and 2% [66,67], in the Developing Countries it still ranges between 9 and 22% [26-28,68] (although it can reach 80% in case of late surgical treatment [12]).
Among tropical countries, however, we must differentiate mortality observed in African Countries from the lower mortality of Asian ones (e.g. Nepal 6.8% [69], India 10.5%[70]).
The following list summarizes the recent improvement of mortality for typhoid perforation in African Countries.
About 30%: Archampong [36] (1976), Eggleston [23] (1979), Butler [71] (1985), Van der Werf [59] (1990), Adesunkanmi [31] (1997), Meier [65] (1998), Koume [29] (2004).
About 20%: Ameh [52] (1999), Otegbayo [68] (2002), Saxe [32] (2005), Adeniran [72] (2005), Chalya [26] (2012), Ugochukwu [24] (2013).
It is remarkable how surgery alone reduced mortality rate from the former 80-100% to about 30%; the most recent improvements in abating mortality are probably secondary to safer resuscitation techniques, availability of more powerful broad-spectrum antibiotics and better postoperative care, which greatly developed in the last decade [24].
The average mortality rate of our patients was 21.28%, in line with the most recent studies performed in Africa.

Mortality and Number Of Perforations

62% of perforations observed by Agu [5] were single, 28% were double and 10% were multiple.
84.6% of Chalya's patients [26] showed a single perforation, while 15.4% showed more than one.
Similar rates were recorded in our study and by other Authors [24,25,27,35,52,53].
In his study too (as in others [64,73]), the median age of patients with single perforation was higher than for patients with multiple perforations (45 versus 14 years); the reason for this relationship remains unclear.
Chalya [26] relates the number of perforations and mortality with statistical significance (mortality rate 43.8% in patients with multiple perforations, 19.3% in case of single perforation), in line with our results.
The number of perforations can be interpreted as a sign of severity of the disease.
This issue is nevertheless controversial in Literature, as many Authors support its prognostic value [26,31,37,59,63,65,71], while others do not confirm it [4,44,70].

Mortality and Sex

Mortality was slightly higher in our female patients than in male ones.
This reflects Chalya's result [26] (mortality rate of 24.1% in female gender versus 22.7% of mortality in male one), but differs from other Authors' results [27,28,31].
The importance of this prognostic factor is therefore still controversial.

Mortality and Age

Likewise other Authors [12,26,65], we noticed a higher mortality in older patients (e.g. Chalya [26]: 28.6% over 40 years of age versus 22.6% beneath it), confirming the reliabilty of this MPI factor.

Mortality and Organ Failure

We reported a mortality rate of 31.03% in presence of organ failure, versus 5.56% in its absence.
Many Authors [6,23,36-38] noticed that the average HR and the average RR were significantly higher at presentation in patients who subsequently died.

Some studies [23,26] proved a strong relationship between shock and mortality (38.9% in shocked patients versus 14.7% in absence of cardiovascular failure).
Tachypnea and tachycardia can be initial clinical manifestations of sepsis, which can evolve in septic shock (the major cause of death in these patients).
Indeed, mortality is heavily influenced by the lack of ICU [12,53,60]: where these Units are available, mortality rate is lower than 5% [4,63,66].
These parameters of the MPI can be therefore considered important factors affecting the prognosis of patients with typhoid perforation.

Mortality and time from operation

Many Authors report that the majority of patients reaches the hospitals late and in weak general conditions [26,27,56].
In low-resources countries, diagnostic and transport/referral difficulties often lead to a late presentation of rural inhabitants at health facilities (and particularly at district hospitals) [26,27,31,43,55].
Sociocultural factors can delay access to health structures too (e.g. trust on traditional medicine [12, 24]).
Several Authors consider the late admission as a relevant factor of increased mortality [4,25,26,34,43,44,60].
More specifically, early surgical operation was indicated by many as a major determinant on patients' outcome [23,24,27,28,31,32,36-38,46,53,56,63,70].
In Chalya's study[26], for example, mortality rate reached 24.4% when the operation was performed after more than 24 hours from perforation (while it was 14.3% in patients operated before 24 hours).
We obtained similar results (20.51% after 24 hours versus 11.76% before 24 hours).
Together with the presence of organ failure, this factor proves to be one of the most important of the MPI score.

Mortality and Spread of Peritonitis

Regardless of the number of perforations, the operative finding of diffuse peritonitis is described as very frequent in Literature [12] (e.g. Chalya [26]: 92.3% of patients); in our case it made up the totality of the patients and is generally related to a late hospital presentation.
Some Authors [36-38] identified the extension of peritonitis as a prognostic factor too.
This underlines again the importance of early surgical management in these patients.

Mortality and type of abdominal fluid

Likewise what other Authors described [23, 24], in our experience prognosis was worse in presence of fecal contamination (ileal or colic) compared to purulent contamination of the peritoneal cavity.

Mortality and Mpi

In our evaluation, we didn't report any death below MPI values of 20 or lower, while we found that an MPI value higher than 30 was related to a mortality rate of 36% (versus 3.45%).
These results confirm the reliability of MPI as a prognostic tool [13-22].

Conclusions

An accurate epidemiological evaluation of this disease is actually impossible due to the lack of data, secondary to the several difficulties in carrying out epidemiological and microbiological analysis in the Developing Countries, of which this infection is typical.
Hence, the need of more detailed statistical studies, sponsored by international organisms and supported by laboratory examinations, in order to better define the real impact of this disease.
We noticed a seasonal trend of this pathology, related to the rainy season.
This indirectly underlines even the lack of good sanitation and clean water facilities available for these populations.
The majority of patients are young men (with a further impact on local economies) and the main symptoms described are fever and the typical signs of intestinal obstruction, with a shorter period between the onset of symptoms and the intestinal perforation, suggesting a more aggressive disease.
This aspect should deserve further investigations, in order to better understand its eventual causes.
Laboratory and microbiological investigations are usually poorly helpful in this setting: this implies the lack of knowledge on antibiotic-resistance patterns too in these areas.
Widal test is unreliable for the evaluation of these patients; HIV test, which should be performed for every surgical patient, is nevertheless still a goal to be reached in many surgical wards.
On the other hand, abdominal XR and US represent a strong diagnostic support for therapeutic decision-making.
Moreover, both these methods are available, affordable and appropriate for these settings.
Preoperative resuscitation and antibiotic therapy are crucial for therapeutic management of these patients.
Alas, the absence of safe anesthesiological procedures, postoperative monitoring and intensive care units has a negative impact on the outcome of the patients.
Primary repair should be considered the technique of first choice for single perforations, resection with anas-

tomosis for multiple ones (especially when close to each other), right emicolectomy for cecal involvement.
Ileostomy should be reserved for patients with severe and prolonged peritoneal contamination.
The role of laparostomy in these perforations should be better assessed in the future.
The choice of the technique is however secondary to the experience and skills of the surgeon, who is seldom a specialist in these hospitals.
Postoperative complications are quite common: surgical site infections and 'burst abdomens' are the most common ones, while enteric fistulae (secondary to re-perforations or to new ones) are the most severe ones. Postoperative septic shock is usually related to a poor prognosis.
Mortality in our centre (21.28%) was similar to the one described in other African facilities, confirming its reduction trend during the last decade; however, this rate is still too high, even in comparison with the rate of Western Countries.
Important prognostic factors revealed to be time between perforation and surgical operation and the presence of organ failure at the admission: both of these aspects still reflect a logistic deficiency. This consideration favours 'open and see' strategies over 'wait and see' ones, especially in African District Hospitals.
MPI showed to be a reliable prognostic tool in typhoid perforations, easy to use and appropriate for low-income settings; an MPI score of 30, in our study, was related with a worse outcome.

Critical Aspects

Our study is a retrospective one and the number of cases is too low to gain statistically significant results.
Epidemiological studies in developing countries have always been difficult due to incomplete and usually rough data.
The selection of patients for the study was based upon clinical and operative features, not on clear disease-definition criteria, due to complete lack of microbiological investigations.
The majority of patients is often lost at postoperative follow-up in these settings, we couldn't therefore collect data on long-time morbidity.

Riassunto

Lo scopo di questo studio retrospettivo su pazienti operati per perforazione tifoidea è stato analizzarne l'epidemiologia, la clinica e l'iter dianostico-terapeutico, i fattori prognostici e la mortalità.
Abbiamo pertanto analizzato le cartelle cliniche di 47 pazienti, operati presso l'Ospedale di Matany da Gennaio 2010 ad Aprile 2016.
Dal momento che gli esami microbiologici e istopatologici non erano disponibili, l'eziologia era presunta al tavolo operatorio.
Abbiamo notato un picco di incidenza correlato con la stagione delle piogge.
La maggioranza dei pazienti erano giovani maschi (età media 17.85 anni, 61.7% dei pazienti erano di sesso maschile) e i principali sintomi riportati sono stati la febbre e sintomi occlusivi, con un periodo minore tra l'insorgenza della sintomatologia e la perforazione (entro due settimane nel 74.47% dei casi).
La radiografia diretta dell'addome e l'ecografia si sono dimostrati importanti strumenti diagnostici, riscontrando note patologiche nella totalità dei casi.
La raffia (eseguita in 40 pazienti) è considerata la tecnica di prima scelta per le perforazioni singole, la resezione intestinale (eseguita in 4 pazienti) per quelle multiple, l'emicolectomia destra in caso di interessamento cecale e l'ileostomia nei casi caratterizzati da importante contaminazione peritoneale.
Le complicanze postoperatorie sono state molto frequenti (72.34% dei casi); in particolare, le infezioni della ferita chirurgica hanno costituito quelle più comuni (verificandosi nel 40.42% dei pazienti), mentre le fistole enteriche sono state quelle più severe.
Il tasso di mortalità è risultato pari al 21.28%, in linea con i tassi riportati in altri centri africani.
La precocità dell'intervento chirurgico e la presenza di insufficienza organica al ricovero hanno costituito importanti fattori prognostici.
Un punteggio MPI >30 era correlato con una prognosi peggiore (36% vs 3.45%).

References

1. Su LH, Chiu CH: Sa*lmonella: Clinical importance and evolution of nomenclature.* Chang Gung Medical Journal, 2007; 30(3), 210-19.

2. Crump JA, Luby SP, Mintz ED: *The global burden of typhoid fever*. Bull World Health Organ, 2004; 82:346-53.

3. A. Sumer, Kemik O, Dulger AC, et al.: *Outcome of surgical treatment of intestinal perforation in typhoid fever.* World J Gastroenterol, 2010; 16(33):4164-168.

4. Atamanalp SS, Aydinli B, Ozturk G, Oren D, Basoglu M, Yildirgan MI: *Typhoid intestinal perforations: Twenty-six year experience*. World J Surg, 2007, 31:1883-888.

5. Kotan C, Kosem M, Tuncer I, Kisli E, Sönmez R, Çıkman Ö, Söylemez Ö, Arslantürk H: *Typhoid intestinal perforation: Review of 11 cases.* Kolon Rektum Hast Derg, 2000; 11:6-10.

6. Agu, Nzegwu M, Obi E: *Prevalence, morbidity, and mortality patterns of typhoid ileal perforation as seen at the university of nigeria teaching hospital enugu nigeria: An 8-year review.* World J Surg, 2014; 38:2514-518.

7. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL: *Typhoid fever.* Lancet, 2015; 385:1136-145.

8. Bhutta. ZA: *Current concepts in the diagnosis and treatment of typhoid fever.* BMJ, 2006; 333:78-82.

9. Lozano R, Naghavi M, Foreman K, et al.: *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysisfor the Global Burden of Disease Study 2010.* Lancet, 2012; 380:2095-128.

10. Buckle GC, Walker CI, Black RE: *Typhoid fever and paratyphoid fever: systematic review to estimate glboal morbidity and mortality for 2010*. J Glob Health, 2012; 2:10401.

11. Parry CMT, Hien TT, Dougan G, White NJ, Farrar JJ: *Typhoid fever*. N Engl J Med, 2002; 347(22):1770-782.

12. Caronna R, Boukari AK, Zaongo D, et al.: *Comparative analysis of primary repair vs resection and anastomosis, with laparostomy, in management of typhoid intestinal perforation: Results of a rural hospital in northwestern Benin*. BMC Gastroenterology, 2013, 13:102.

13. Billing A, Frohlich D, Schildberg FW, and the Peritonitis Study Group: *Prediction of outcome using the Mannheim Peritonitis Index in 2003 patient*s. Brit J Surg, 1994; 81, 209-13.

14. Van Laarhoven CJ, Hoofwijk AG, van Vroonhoven TJ: *The Mannheim peritonitis index: A valuable method in predicting the outcome of severe peritonitis*? Neth J Surg, 1988; 40:168.

15. Seifert J, Schirrmacher E: *Retrospective comparison of two peritonitis scores on 195 patients with diffuse purulent peritonitis.* Theor Surg, 1990; 5:33-5.

16. Maqbool Qureshi A, Zafar A, Saeed K, Quddus A: *Predictive of Mannheim peritonitis index*. JCPSP, 2005; 15(11):693-69.

17. Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgadari A, Gui D,, et al.: *Prognosisi in intra-abdominal infections. Multivariate analysis on 604 patients*. Arch Surg, 1996; 131:641-45.

18. Sokmen S, Coker A, Unek T, Tuncyurek P, Bora S: *Effectiveness of the Mannheim peritonitis index in patients with peritonitis.* Ulus Travma Derg, 2001; 7:100-3.

19. Bracho-Riquelme R, Melero-Vela A, Torres-Ramirez A: *Mannheim peritonitis index validation study at the Hospital General de Durango (Mexico)*. Cir Ciruj, 2002; 70:217-25.

20. Grunau G, Hecmken R, Hau T: *Predictors of outcomes in patients with post-operative intra-abdominal infection.* Eur J Surg, 162, 619-25, 1996.

21. Liverani A, Correnti SF, Paganelli MT, Antonini G, Mercati U: *Mannheim index in prognosis and treatment of acute peritonitis.* Minerva Chir, 1998; 53:385-89.

22. Ohmann C, Hau T: *Prognostic indices in peritonitis*. Hepatogastroenterology,1997; 131:641-45.

23. Eggleston FC, Santoshi B, Singh CM: *Typhoid perforation of the bowel. Experiences in 78 cases*. Ann Surg, 1979; 190:31-35.

24. Ugochukwu AI, Amu OC, Nzegwu MA: *Ileal perforation due to typhoid fever e Review of operative management and outcome in an urban centre in Nigeria*. International Journal of Surgery, 2013; 11:218-22.

25. Kim JP Oh SK F, Jarrett F: *Management of ileal perforation due to typhoid fever*. Ann Surg, 1975; 181:88-91.

26. Chalya PL, Mabula JB, Koy M, et al.: *Typhoid intestinal perforations at a University teaching hospital in Northwestern Tanzania: A surgical experience of 104 cases in a resource-limited setting*. World Journal of Emergency Surgery, 2012; 7(4): 1-11.

27. Ugwu BT, Yiltok SJ, Kidmas AT, Opalawa AS: *Typhoid intestinal perforation in North Central Nigeria*. West Afr J Med, 2005, 24:1-6.

28. Edino ST, Mohammed AZ, Uba AF, Sheshe AA, Anumah M, Ochicha O, Yakubu AA, Alhassan SU, Mamman M: *Typhoid enteric perforation in North Western Nigeria.* Nig J Med, 2004, 13:345-49.

29. Koume J, Kouadio L, Turquin HT: *Typhoid ileal perforation: surgical experience of 64 cases*. Acta Chir Belg, 2004; 104:445-47.

30. Van Basten JP, Stockenbrugger R: *Typhoid perforation: A review of literature since 1960.* Trop Geogr Med, 1994; 46:336-39.

31. Adesunkanmi ARK, Ajao OG: *Prognostic factors in typhoid ileal perforation: A prospective study in 50 patients.* JR Coll Surg Edinb, 1997, 42:395-99.

32. Saxe JM, Cropsey R: *Is operative management effective in treatment of perforated typhoid?* Am J Surg, 2005; 189:342-44.

33. Yildirgan MI: *Typhoid intestinal perforations: Twenty-six year experience*. World J Surg, 2007; 31:1883-888.

34. Onen A, Dokucu AI, Ci dem MK, Oztürk H, Otçu S, Yücesan S: *Factors effecting morbidity in typhoid intestinal perforation in children.* Pediatr Surg Int, 2002; 18:696-700.

35. Agbakwuru EA, Adesunkanmi AR, Fadiora SO, Olayinka OS, Aderonmu AO, Ogundoyin OO: *A review of typhoid perforation in a rural African hospital*. West Afr J Med, 2003; 22:22-25.

36. Archampong EQ: *Typhoid ileal perforation: Why such mortality?* Br J Surg, 1976; 63:317-21.

37. Parry EHO: *Typhoid fever*. In: Parry EHO (ed) : *Principles of medicine in Africa,* 2nd edn. Oxfotd, UK: Oxford University Press, 1984; 268-76.

38. Olurin FO, Ajayi OO, Bohrer SP:*Typhoid perforation*. J Coll Surg Edinb, 1972; 17:253-63.

39. Jhobta RS, Attri AK, Kaushik R, Sharma R, Jhobta A: *Spectrum of perforation peritonitis in India. Review of 504 consecutive cases*. World Journal of Emergency Surgery, 2006; 1:article 26

40. Patil V, Vijayakumar A, Ajitha MB, Kumar SL: *Comparison between tube ileostomy and loop ileostomy as a diversion procedure.* ISRN Surgery, 2012, Article ID 547523, 5 pages.

41. Batra P, Gupta D, Rao S, Narang K, Batra R: *Spectrum of gastrointestinal perforation peritonitis in rural central India.* Journal of Mahatma Gandhi Institute of Medical Sciences, 2013; 18(1):44-48.

42. Verma H, Pandey S, Sheoran KD, Marwah S: *Surgical audit of patients with ileal perforations requiring ileostomy in a tertiary care hospital in india.* Surgery Research and Practice, Article ID 351548, 1-4.

43. Tade AO, Olateju SO, Osinupebi OA, Salami BA: *Typhoid intestinal perforations in a tropical tertiary health facility: A prospective study.* East Cent Afr J Surg, 2011; 16(2):72.

44. Rahman GA, Abubakar AM, Johnson AW, Adeniran JO: *Typhoid ileal perforation in Nigerian children: An analysis of 106 operative cases.* Pediatr Surg Int, 2001; 17:628-30.

45. Pang T, Levine MM, Ivanoff B, Wain J, Finlay BB: *Typhoid fever: Important issues still remain*. Trends Microbiol, 1998; 6:131-33.

46. Ameh EA, Dogo PM, Attah MM, Nmadu PT: *Comparison of three operations for typhoid perforation*. Br J Surg, 1997; 84:558-59.

47. Amed HN, Niaz MP, Amin MA, Khan MH, Parhar AB: *Typhoid perforation still a common problem: Situation in Pakistan in comparison to other countries of low human developme*nt. J Pak Med Assoc, 2006; 56:230-32.

48. Haq SA, Alam MN, Hossain SM, et al.: *Value of clinical features in the diagnosis of enteric fever.* Bangladesh Med Res Counc Bull, 1997; 23:42-46.

49. Kuvandik C, Karaoglan I, Namiduru M, et al.: *New Microbiol.* 2009; 32:25-30.

50. Hoshino Y, Masuda G, Negishi M, et al.: *Predictive value of clinical and laboratory findings in the diagnosis of enteric fever. Clinical and bacteriological profiles of patients with typhoid fever treated during 1975–1998 in the Tokyo Metropolitan Komagome Hospital.* Microbiol Immunol, 2000; 44:577-83.

51. Neopane A, Poudel M, Pradhar B, et al.: *Enteric fever: Diagnostic value of clinical features*. Kathmandu Univ Med, 2006; J 4:307-15.

52. Ameh EA: *Typhoid ileal perforation in children: A scourge in developing countries*. Ann Trop Paediatr, 1999; 19:267-72.

53. Uba AF, Chirdan LB, Ituen AM, Mohammed AM: *Typhoid intestinal perforation in children: A continuing scourge in a developing country*. Pediatr Surg In, 2007; 23:33-9.

54. Nuhu A, Dahwa S, Hamza A: *Operative management of typhoid ileal perforation in children.* Afr Paed Surg, 2010; 7(1):9-13.

55. Hosoglu S, Aldemir M, Akalin S, Geyik MF, Tacyildiz IH, Loeb M: *Risk factors for enteric perforation in patients with typhoid Fever.* Am J Epidemiol, 2004; 160:46-50.

56. Khan SH, Aziz SA, Ul-Haq MI: *Perforated peptic ulcers: A review of 36 cases.* Professional Med J, 2011; 18(1):124-27.

57. Lee CW, Yip AW, Lam KH: *Pneumogastrogram in the diagnosis of perforated peptic ulcer.* Aust NZJ Surg, 1993; 63:459-61.

58. Chen SC, Yen ZS, Wang HP, Lin FY, Hsu CY, Chen WJ: *Ultrasonography is superior to plain radiography in the diagnosis of pneumoperitonium.* Br J Surg, 2002; 89:351-54.

59. Van Der Werf JS, Cameron FS: *Typhoid perforation of ileum: A review of 59 cases at Agogo hospital Ghana between 1982 and 1987*. Trop Geog Med, 1990; 40:330-36.

60. Abantanga FA, Wiafe-Addai BB: *Postoperative complications after surgery for typhoid perforation in children in Ghana.* Pediatr Surg Int 1998; 14:55-58.

61. Ramachandran CS, Agarwal S, Dip DG, Arora V: *Laparoscopic surgical management of perforative peritonitis in enteric fever: A preliminary study*. Surg Laparosc Endosc Percutan Tech, 2004; 14: 122-24.

62. Sinha R, Sharma N, Joshi M.: *Laparoscopic repair of small bowel perforation.* JSLS, 2005; 9:399-402.

63. Mock CN, Amaral,J, Visser, LE: *Improvement in survival from Typhoid ileal perforation.* Annals of Surgery, 1992; 215(3): 244-49.

64. Ekenze SO, Okoro PE, Amah CC, Ezike HA, Ikefuna AN: *Typhoid ileal perforation: Analysis of morbidity and mortality in 89 children.* Niger J Clin Pract, 2008, 11:58-62.

65. Meier DE, Tarpley JL: *Typhoid intestinal perforations in Nigerian children*. World J Surg, 1998; 22:319-23.

66. Carmeli Y, Raz R, Scharpiro JAC: *Typhoid fever in Ethiopian immigrants to Israel and native. Born Israelis: A comparative study*. Clin Inf Dis, 1993, 16:213-15.

67. Chang YT, Lin JY: *Typhoid colonic perforation in childhood: A ten year experience*. World J Surg, 2006, 30:242-47.

68. Otegbayo JA, Daramola OO, Onyegbatulem HC, Balogun WF, Oguntoye OO: *Retrospective analysis of typhoid fever in a tropical tertiary health facility*. Trop Gastroenterol, 2002; 23:9-12.

69. Karmacharya B, Sharma VK: *Results of typhoid perforation management: our experience in Bir Hospital, Nepal.* Kathmandu University Med J, 2006; 4:22-24.

70. Beniwal US, Jindal D, Sharma J, Jain S, Shyman G: *Comparative study of operative procedures in typhoid perforation.* Indian J Surg, 2003, 65:172-77.

71. Butler T, Knight J, Speelman P, et al.: *Typhoid fever complicated by intestinal perforation: A persisting fatal outcome requiring surgical management*. Rev Infect Dis, 1985; 7:244-56.

72. Adeniran JO, Taiwo JO, Abdur-Rahman LO: *Salmonella intestinal perforation: (27 perforations in one patient, 14 perforations in another). Are the goal posts changing?* J Indian Assoc Pediatr Surg, 2005; 10(issue 4).

73. Kella N, Radhi PK, Shaikh AR, Leghari F, Qureshi MA: *Factors affecting the surgical outcome in typhoid intestinal perforation in children*. Paed Surg, 2010; 16(4):567-70.