Typhoid fever perforation in Kathmandu, Nepal
- A retrospective study of risk factors and antibiotic treatment

Author:  Isabel Vigmo, Medical Student at the Sahlgrenska Academy University of Gothenburg, Sweden

Supervisors:  Yogendra Singh, MD, PhD, Professor of Surgical Oncology Department of Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Göran Kurlberg, MD, PhD, Associating Professor of Surgery Sahlgrenska University Hospital/ Campus Östra, Göteborg, Sweden
Abstract

Introduction: Typhoid fever is a global health problem, causing significant morbidity and mortality throughout the developing world. A recent survey estimated a global number of 21.7 million illnesses and 217,000 deaths in the year 2000. Due to poverty and poor sanitary conditions, typhoid fever remains a major health problem in Nepal. A frequent complication of typhoid fever is perforation of the terminal ileum. Mortality rates rating from 20 - 40 % are most commonly reported.

Aims and objectives The aim of this study was to trace risk factors for enteric perforation in patients with typhoid fever as well as to assess health care factors that influence the outcome of these patients.

Methods and materials This retrospective study was conducted at the Tribhuvan University Teaching Hospital in Kathmandu, Nepal. The inclusion criteria for participation was the diagnosis ileal perforation due to typhoid fever in adult patients (≥ 16 years). During June 14th 2006 and May 22th 2010, 30 patients underwent surgery for ileal perforation due to typhoid fever and were therefore enrolled in the study. Using a collection form, data was abstracted from the medical records of these patients and then analyzed.

Results There were 22 males and eight females (male : female ratio 2.75 : 1) with a mean age of 28.1 ± 10.0 years. The mean duration of symptoms was 14 ± 11.0 days (range 5 - 60 days) and all patients suffered from fever and abdominal pain. A majority (16) of the perforations occurred in the second week of disease. Primary repair was applied to 18 patients, while 11 patients received wedge resection and one patient received ileostomy. Reperforation occurred in one patient and mortality developed in two (7 %) patients.

Conclusions Typhoid fever remains a major health problem in Nepal. The leading cause of mortality in typhoid fever is ileal perforation, which is a complication that possibly could be prevented. Identification and appropriate antibiotic treatment of typhoid fever would reduce morbidity and mortality. Early and appropriate surgical intervention is vital for the survival of typhoid fever perforation.

Keywords: Typhoid fever perforation, Risk factors, Antibiotic treatment
# Table of contents

1. Introduction................................................................................................................................. 1
   1.1 Microbiology............................................................................................................................. 2
   1.2 Transmission.............................................................................................................................. 2
   1.3 Epidemiology............................................................................................................................ 3
   1.4 Pathogenic mechanisms.......................................................................................................... 3
   1.5 Clinical features....................................................................................................................... 4
   1.6 Diagnostic methods................................................................................................................... 4
   1.7 Differential diagnoses............................................................................................................. 6
   1.8 Treatment.................................................................................................................................. 6
      1.8.1 Antimicrobial therapy........................................................................................................... 6
      1.8.2 Surgical management of intestinal perforation................................................................. 7
   1.9 Study area: Kathmandu, Nepal.................................................................................................. 7
2. Problem of interest.......................................................................................................................... 9
3. Aims and objectives....................................................................................................................... 10
4. Method and materials................................................................................................................... 11
5. Results.......................................................................................................................................... 12
6. Case report.................................................................................................................................... 18
7. Discussion...................................................................................................................................... 20
8. Conclusions.................................................................................................................................... 24
9. Acknowledgements...................................................................................................................... 25
10. References...................................................................................................................................... 26
1. Introduction

Typhoid fever is a global health problem causing great suffering in developing countries where unhealthy living conditions prevail. Also known as enteric fever, this potentially fatal multisystemic disease is caused by several serotypes of Salmonella Enterica including S. Typhi and S. Paratyphi. Untreated or suboptimally treated typhoid fever may lead to perforation of the terminal ileum. The complication requires surgical management and is still associated with considerable morbidity and mortality [1].

Whereas typhoid fever was a major cause of death in the United States and Europe in the 19th century, the provision of clean water and good sewage systems led to a dramatic decrease in the incidence of typhoid in these regions. Today, the disease remains endemic in many areas of the developing world where poor sanitary conditions remain and facilitate transmission. Typhoid fever is estimated to cause over 26 million infections and over 200,000 deaths annually. South-central Asia and south-east Asia have been identified as regions with high incidence of typhoid fever (>100/100,000 cases/year), whereas the rest of Asia, Africa, Latin America and Oceania excluding Australia and New Zealand are reported to have a medium incidence (10-100/100,000 cases/year) [2]. Most cases of typhoid fever in the developed world are attributed to travellers returning from endemic areas whilst domestically acquired disease is infrequently reported [3].

Kathmandu, the capital city of Nepal, has previously been coined a typhoid fever capital of the world [4]. Whereas typhoid fever in rural areas is not uncommon, the living conditions of the urban centre of Kathmandu predispose for the constant transmission of the disease to a greater extent. Typhoid fever is largely an endemic disease but it has an epidemic potential. The disease also has a very high social and economic impact because of the hospitalization of patients with acute disease and the complications and loss of income attributable to the duration of the clinical illness.

If typhoid fever remains untreated, or if the antibiotic treatment is inadequate, the disease can cause fatal complications such as intestinal bleeding and ileal perforation. Despite the high morbidity, relatively little is known about risk factors for enteric perforation in patients with typhoid fever. Furthermore, the emergence of multi-drug resistant strains of S. Typhi and S. Paratyphi makes treatment increasingly difficult. Given the morbidity and mortality and considering the reduced effectiveness of commonly used antibiotics there is an increasing urgency to control the disease and its complications.
1.1 Microbiology

The majority of cases of typhoid fever are attributed to the gram-negative bacterium Salmonella Enterica serotype Typhi (S. Typhi). It is a rod-shaped facultative bacteria which belongs to the family Enterobacteriaceae. Only humans are affected by this highly virulent and invasive pathogen. For every ten cases of S. Typhi infection, there are one or two cases of paratyphoid fever, caused by the human-adapted S. Enterica serotypes Paratyphi A, Paratyphi B and Paratyphi C [5]. Whereas S. Paratyphi A infections occur in a significant and rising number, S. Paratyphi B and S. Paratyphi C are relatively uncommon [6].

The genes for virulence factors cluster in Salmonella pathogenesis islands (SPIs) and their expression is generally limited to specific host compartments. SPI-1 encodes a type three secretion system (TTSS) that translocates bacterial virulence factors into host cells during infection. This system is essential for the invasion of epithelial cells and it is activated under the conditions present in the intestinal lumen. SPI-2 is then required for the survival and replication of the bacteria in the host cells. Unlike most other Salmonella serotypes, S. Typhi expresses the Vi Polysaccharide capsule. It is an important virulence factor that increases the infectivity of S. Typhi and the severity of the disease [7].

1.2 Transmission

Humans are the only natural host and reservoir. Typhoid fever is transmitted the fecal-oral route by ingestion of food or water contaminated by excreta of patients and asymptomatic carriers and is therefore most common in areas with poor sanitary facilities. The highest incidence occurs where water supplies serving large populations are contaminated with faeces. The risk of infection increases as the size of inocula increases and the infectious dose varies between $10^3 – 10^8$ organisms given orally [3].

Food often eaten outside the home and handled by chronic or transient infected persons is also a common source of infection. Other risk factors for increased transmission include recent typhoid fever in the household, a lack of toilets in the household, drinking unboiled water, not using soap for hand washing, and sharing food from the same plates as others. Between 1 % and 5 % of patients with acute typhoid infection have been reported to become chronic carriers of the infection in the gall bladder, depending on age, sex and treatment regimen [8].
1.3 Epidemiology

Typhoid fever is a global health problem causing great morbidity and mortality. In 2000, typhoid fever caused an estimated 21.7 million illnesses and 217,000 deaths throughout the world, whereas paratyphoid fever caused an estimated 5.4 million illnesses [9]. However, its real impact is difficult to estimate since the clinical picture is easily confused with those of many other febrile diseases. The Indian subcontinent has previously been reported to have the highest incidence of typhoid fever worldwide [3]. A recent multicentre study in five Asian countries – China, India, Indonesia, Pakistan and Vietnam- showed that incidence rates were significantly higher in the south Asian sites (Pakistan and India) than in South East and North East Asian sites (Vietnam, Indonesia, China) [10].

Infections with S. Paratyphi A are emerging at a rapid rate and are responsible for a growing proportion of typhoid fever in a number of Asian countries [2]. A study performed by Maskey et al in Patan Hospital in Kathmandu confirms this trend; the proportion of enteric fever cases caused by S. Paratyphi A increased from 17.5 % in 1993 to 34 % in 2003 [11].

Multiple studies have highlighted the seasonal variation of typhoid fever. In Nepal, the heaviest burden is during the monsoon months from June to August where both the average temperatures and rainfall peak [4]. This association is believed to be due to contamination of water supply caused by an overwhelmed and inadequate sewage system.

1.4 Pathogenic mechanisms

After ingesting contaminated food or water, typhoid organisms pass through the pylorus and reach the small intestine. They penetrate the mucosal epithelium and arrive in the lamina propria, where they elicit an influx of macrophages that ingest the bacterium but generally does not kill them. Some bacteria remain within macrophages in the lymphoid tissue of the small intestine, whereas others are drained into mesenteric lymph nodes. The current opinion is that the typhoid bacteria then reach the bloodstream by drainage via mesenteric lymph nodes to the ductus thoracicus and then the general circulation. Within 24 hours the bacteria reach an intracellular location in the organs of the reticuloendothelial system, that is, the spleen, liver and bone marrow. They then reside here during the incubation period, usually 8-14 days [8]. Clinical symptoms start with bacteremia.

Typhoid fever is not a typical diarrhoeal disease and the intestinal pathology is characterized by interstitial inflammation with predominantly mononuclear infiltrates, while neutrophils are scarce [5]. S. Typhi therefore has the ability to cause a systemic infection without stimulating a significant
local inflammatory response but is transferred from the gastrointestinal lumen to the reticuloendothelial system in a relatively undetected way [12].

The mechanism of intestinal perforation in typhoid fever is hyperplasia and necrosis of Peyer's patches in the terminal ileum. The lymphoid aggregates of Peyer's patches extend from the lamina propria to the submucosa, so that in the presence of hyperplasia the distance from the luminal epithelium to the serosa is bridged by lymphoid tissue. Tissue damage in Peyer's patches occurs, resulting in ulceration, bleeding, necrosis and, in extreme cases, perforation. Both bacterial factors and the host inflammatory response are believed to contribute to the consequent tissue damage [6].

1.5 Clinical features

The symptoms of typhoid fever can vary broadly in severity and may be altered by co-existing morbidities and early administration of antibiotics [13]. Since typhoid fever and paratyphoid fever most often present with similar clinical symptoms and signs, the accurate diagnosis relies on laboratory confirmation [14].

Acute non-complicated typhoid fever is generally characterized with the sudden onset of prolonged fever, headache, abdominal discomfort and malaise. The disease often causes diarrhea, especially in younger children, whereas older children and adults commonly present with unaffected bowel motions or constipation. Bronchitic cough is common in the early stage of the illness. During the period of fever, up to 25% of patients show exanthema, on the chest, abdomen and back [8].

The most common complications are sepsis and dehydration. Around 10% of the patients also develop intestinal bleeding and ileal perforation [15]. The symptoms of intestinal perforation and peritonitis is characterized by abdominal tenderness, rebound tenderness, guarding and subsequent abdominal rigidity. This complication is usually accompanied by a sudden rise in pulse rate and hypotension. If untreated, ileal perforation leads to generalized peritonitis, septicemia as well as fluid- and electrolyte derangements.

1.6 Diagnostic methods

Isolation of the causative organism remains the most effective diagnostic method in suspected typhoid fever. The investigation of choice is therefore the culturing of blood or bone marrow. However, whilst considered routine, blood culturing of S. Typhi is expensive and requires specialist facilities and personnel. In addition, S. Typhi and S. Paratyphi A are not always culturable even if
good microbiological facilities are available [12]. Bone marrow is the most sensitive culture route but this is an invasive procedure and is seldom performed outside specialist hospitals. Stool and urine becomes positive after the first week of infection, but their sensitivity is significantly lower then the culturing of blood or bone marrow.

The diazo test is a simple bed side urine test that can be of great value in the early diagnosis of typhoid fever. It is particularly valuable in developing countries where laboratories are primitive. The principle of the test is a red colouration given by the foam of the urine when mixed with diazo reagent. The test is positive in about 90% of typhoid cases and previous administration of antibiotics does not interfere with the sensitivity of the diazo test [16].

The first typhoid diagnostic was the Widal test, which measures antibodies against O and H antigens of S. Typhi. This test is simple to perform, but has only moderate sensitivity and specificity. Another diagnostic challenge is the fact that many patients reach microbiological facilities at a late stage of infection or may be self treated with antimicrobials. Due to these reasons, the diagnosis of typhoid fever is often made on clinical criteria in resource-poor countries.

Leukopenia is known to be a common laboratory finding among patients with typhoid fever who do not have ileal perforation [6]. This may be explained by a shift of leukocytes from the circulation into the marginal or, alternatively, by a bone marrow depression. A study performed by Khan et al has identified leukopenia due to absolute neutropenia with a relative lymphocytosis as a laboratory finding highly suggestive of typhoid fever [17].

Typhoid fever without ileal perforation is also associated with trombocytopenia, which can be caused by a decreased production of trombocytes, an increased destruction by the reticuloendothelial system, or DIC [18].

Additional investigation is needed when ileal perforation due to typhoid fever is suspected. Abdominal ultrasonography, plain abdominal radiography and paracentesis are the recommended diagnostic methods. Typical findings for ileal perforation include free abdominal fluid, hepatosplenomegaly, air-fluid levels, and free air under the diaphragm [6]. Fecaloid or purelent fluid upon paracentesis is also consistent with this diagnosis. In some cases, the diagnosis is ultimately based on the typical intraoperative findings of a perforation of the antimesenteric border of the terminal ileum. A definitive confirmation of the diagnosis is obtained by an ulcer edge biopsy and a lymph node culture.
1.7 Differential diagnoses

As previously stated, the diagnosis of typhoid fever is often based on clinical features in developing countries. This poses a problem, since typhoid fever may mimic many common febrile illnesses. The differential diagnoses include malaria, sepsis with other bacteria pathogens and infections caused by intracellular organisms such as tuberculosis and brucellosis. Viral infections, such as dengue fever and acute hepatitis should also be taken into consideration [13]. Furthermore, infections with Rickettsia Typhi are common in Kathmandu and offer similar clinical symptoms on presentation [4].

Typhoid fever perforation should be considered in patients presenting with a high fever for a long period and an acute abdomen. Common differential diagnoses are perforated appendicitis, duodenal ulcer or other forms of acute abdomen.

1.8 Treatment

General principles for the management of typhoid fever include adequate rest, hydration and correction of fluid-electrolyte imbalance. Antipyretic treatment is also required. More than 90 % of patients can be managed at home with oral antibiotics and reliable care [8]. Regular follow-ups are recommended in order to detect complications and clinical relapse [13].

1.8.1 Antimicrobial therapy

The prognosis for a patient with typhoid fever is dependent on the rapidity of diagnosis and accurate treatment. Appropriate antibiotic treatment is critical in curing typhoid with minimal complications. Furthermore, the outcome is also affected by the patient's age, general state of health and nutrition.

The current recommendation for the treatment of uncomplicated typhoid fever is the use of fluoroquinolones as a first line therapy. Fluoroquinolones, such as ofloxacin, ciprofloxacin, fleroxacin and perfloxacin are highly active and generally well tolerated when compared to the former first-line drugs chloramphenicol, ampicillin, amoxicillin and trimethoprim-sulfamethoxazole.

A challenge in the therapy of typhoid fever is the changing of antibiotic sensitivity patterns and the emergence of high level resistant cases. Multi-drug resistance (MDR) strains of S. Typhi – that is, resistance to chloramphenicol, ampicillin, amoxicillin and trimethoprim-sulfamethoxazole, have emerged. The widespread use of fluoroquinolones has also been associated with decreased
susceptibility as well as resistance to this class of drugs [2].

In the case of intestinal perforation due to typhoid fever, the administration of metronidazole and gentamicin or ceftriaxone is recommended if a fluoroquinolone is not being used to treat leakage of intestinal bacteria into the abdominal cavity [8].

### 1.8.2 Surgical management of ileal perforation

Patients with typhoid fever perforation most commonly show an imbalance in blood electrolytes and acid-base levels. Anemia is common and may be partially masked by dehydration. For these reasons, the patients have to go through hemodynamic stabilization before they undergo surgery. Studies have shown that proved that mortality and morbidity can be decreased if the patient undergoes a sufficient preoperative resuscitaion [19, 20].

All patients with generalized peritonitis must undergo surgery. The intestinal perforation has to be closed and a thorough peritoneal lavage needs to be carried out [19]. A variety of surgical procedures can be utilized in the treatment of enteric perforation: simple closure, resection of the perforation and closure, wedge resection and closure, resection of the affected terminal ileum and end-to-end anastomosis, loop or end-ileostomy, resection with ileotransverse colostomy, and resection with right colectomy [21].

In the case of a single perforation, primary repair is suggested after debridement of the perforation borders. Multiple perforations pose greater problems and the recommended surgical intervention is a resection of the affected intestine segment followed by an end-to-end anastomosis. Ileostomy is the suggested procedure for patients in a critical general condition with severe peritonitis [1]. Right hemicolecetomy is only recommended in cases of caecal perforation [21].

### 1.9 Study area: Kathmandu, Nepal

Nepal, officially the Federal Democratic Republic of Nepal, is a landlocked country in South Asia and the worlds youngest republic. The World Bank calculates that Nepal has a gross per capita income of 340 US $, which classifies the country as the poorest in Asia. Approximately 55 % of the population lives below the international poverty line of US $ 1.25 per day. Poverty and political instability have had obvious harmful effects on infrastructure; while 89 % of the population now has access to improved water sources, only 45 % of the population has access to improved sanitary conditions [22]. In 2007, the World Health Organization has estimated the life expectancy at birth to 63 years and the healthy life expectancy to 55 years [23].
The population of Nepal has increased over the past decade to 28.1 million people, a development that is particularly prominent in the capital city Kathmandu, where people flock in the search of employment. Almost two million people live in Kathmandu, which therefore is the most populated area of the country with a density of 1,100 people per square kilometer. Predisposing factors for typhoid fever are apparent in large parts of Kathmandu, where living conditions facilitate constant transmission of the disease [4].

The Tribhuvan University Teaching Hospital (TUTH) is a 482-bed tertiary care centre situated in the centre of Kathmandu. The hospital provides emergency and elective out-patient and in-patient services and is one of the biggest hospitals in the country. This study was conducted in the Department of Surgery of the TUTH during May - June 2010.
2. Problem of interest

The most frequent complication of typhoid fever, and also the principal cause of mortality, is perforation of the terminal ileum. The complication requires surgical management and remains a significant surgical problem. Early intervention is crucial and mortality rates increase as the delay between perforation and surgery lengthens. Perforation rates are reported with wide variation. Butler et al reviewed 15,980 cases of typhoid fever in the world's literature and reported an overall 2.8% perforation rate [24]. Mortality rates between 20 - 40% are most commonly reported for ileal perforation [24][36]. Relatively little is known about risk factors for enteric perforation in patients with typhoid fever. Male gender, short duration of symptoms and leukopenia has previously been reported as independent risk factors in a case-control study performed by Hosoglu et al [6].

Appropriate antibiotic treatment is critical in curing typhoid fever with minimal complications. When patients diagnosed with typhoid fever receive an adequate antibiotic treatment, the development of enteric perforation will be prevented [1]. However, the emergence of S. Typhi and S. Paratyphi bacteria with decreased susceptibility as well as resistance to recommended antibiotics pose a therapeutic problem and increase the risk of complications. The impact on the disease burden by multi-drug resistance and the emergence of recent fluoroquinolone resistance has not been estimated. It is however clear that the median time to fever clearance, relapse rates and faecal carriage rates are higher in patients infected with drug resistant strains than for those with drug sensitive strains [3]. In addition, it increases the pool of patients and carriers who can potentially transmit the disease.
The aim of this study was to trace risk factors for enteric perforation in patients with typhoid fever as well as assess health care factors that influence the outcome of these patients.

Objectives:

- To determine age, sex and geographical distribution of the patients
- To evaluate various parameters such as temperature, pulse and white blood cell count on admission
- To assess socioeconomic status defined by occupation
- To study how antibiotic treatment influences the outcome of these patients
- To study the seasonal variation of ileal perforation due to typhoid perforation
4. Methods and materials

This retrospective study was conducted at the Tribhuvan University Teaching Hospital in Kathmandu, Nepal. The inclusion criteria for participation was the diagnosis ileal perforation due to typhoid fever in adult patients (≥ 16 years). During June 14th 2006 and May 22th 2010, 29 patients underwent surgery for ileal perforation due to typhoid fever and were therefore enrolled in the study. Using a collection form, data was abstracted from the medical records of these patients. In order to determine risk factors for ileal perforation in patients with typhoid fever, the following parameters were examined: age, sex, district, clinical presentation, duration of symptoms, month of the year, temperature and pulse on admission, antibiotic treatment, duration of hospital stay, white blood cell count (WBC), lymphocytes, neutrophils, histopathology, widal test, operative findings, type of surgery, district, occupation and outcome of the patient.

Duration of symptoms were defined in days from the onset of symptoms to hospital admission. The diagnosis was in most cases based on a pre-perforation history consistent with typhoid fever combined with typical operative findings of antimesenteric ileal perforation.
5. Results

There were 30 patients with the intraoperative diagnosis of typhoid ileal perforation during the study period. The mean age of the patients was 28.1 ± 10.0 years. There were 22 males and eight females, giving a male : female ratio of 2.75 : 1 (Figure 1). The mean duration of symptoms was 14.1 ± 11.0 days (range 5-60 days) and all patients suffered from fever and abdominal pain (Table 1).

A majority (53 %) of the perforations occurred in the second week of disease. (Table 2)  The Widal test was performed in seven patients only and proved positive in three of these cases. A histopathologic confirmation of the diagnosis was obtained in six patients.

<table>
<thead>
<tr>
<th>Table 1. Most common symptoms in patients with typhoid fever perforations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Nausea - Vomit</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
</tbody>
</table>
Table 2. **Duration of illness** *

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Duration in weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Survivals</td>
<td>6</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
</tr>
</tbody>
</table>

* Defined as the time from onset of disease until surgical treatment.

Takycardia (>100 bpm) was present in 15 patients and fever (>38.0 °C) in 10 patients. (Table 3)

The mean white blood cell count (WBC) was 10074 ± 4814 cmm³ (range 2200 – 22300 cmm³). Four patients (13 %) showed leukopenia (WBC <4000 cmm³) , 15 (50 %) showed leukocytosis (WBC > 11000 cmm³) and 11 (37 %) showed normal WBC. The mean neutrophil count was 73.3 ± 15.5 % (range 25 – 93%) and the mean lymphocyte count 23.3 ± 14.8 % (range 3- 70 %).

Table 3. **Laboratory findings and vital signs on admission**

<table>
<thead>
<tr>
<th>Leukocyte count</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within normal range</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 36.0 °C</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>36.0 - 38.0 °C</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>&gt; 38.0 °C</td>
<td>10</td>
<td>33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulse</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 100 bpm</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>61- 99 bpm</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>≤ 60 bpm</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Leukopenia defined as WBC <4000 cmm³ and leukocytosis defined as WBC > 11000 cmm³. Information on pulse on admission was missing for one patient.
The majority of perforations were located more than 30 cm from the ileocecal junction (range 10-120 cm) (Figure 2) and most perforations were smaller than 2 x 2 cm (Figure 3).
A single perforation was seen in 28 patients, whereas one patient had multiple perforations and one patient had a sealed perforation (Table 4). The applied surgery types were: primary repair to 18 patients (60%), Wedge resection and anastomosis to 11 patients (37%) and resection and ileostomy to one patient (3%).

<table>
<thead>
<tr>
<th>Type of surgery and mortality</th>
<th>PC</th>
<th>WRA</th>
<th>RI</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of perforations</td>
<td>18</td>
<td>10</td>
<td>1</td>
<td>29</td>
<td>97</td>
</tr>
<tr>
<td>Single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Severity of contamination</td>
<td>6</td>
<td>4</td>
<td>-</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>11</td>
<td>1</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

PC: Primary closure; WRA: wedge resection and anastomosis; RI: resection and ileostomy. Peritoneal contamination was accepted as severe when the drainage amount was more than 1,000 ml, whereas the contamination was accepted as moderate when the amount was between 500 and 1,000 ml, and mild when the amount was less than 500 ml. Information of some factors was missing for two patients.

Complications requiring a second surgical treatment developed in two patients (7%). A perianastomotic abscess with interloop adhesions and pyoperitoneum developed in one patient and one patient suffered a reperforation as well as multiple abscesses and adhesions.

Mortality developed in two patients (7%). The cause was sepsis with ARDS and bronchopulmonal fistula and septic chock with ARDS, respectively.

The mean duration of stay in the hospital was 12.8 ± 9 days (This information was lacking for two patients.).
Prior unspecified antibiotic treatment had been given to eight patients before hospital admission. In the hospital, most patients were administered a combination antibiotic therapy consisting of metronidazol and a third generation cephalosporin, most commonly Ceftriaxone (Table 5).

The two patients that deceased had both received antibiotic treatment prior to hospital admission. In the hospital, they received combination therapies consisting of Klindamycin, Amikacin, Vankomycin and Cefotaxim, Metron, Clavum and Amikacin, respectively.

Table 5. **Outcome of different antibiotic regimes**

<table>
<thead>
<tr>
<th>No.</th>
<th>3rd generation cephalosporin + metronidazol</th>
<th>3rd generation cephalosporin + metronidazol + amikacin</th>
<th>Two third generation cephalosporins + metronidazol</th>
<th>Other combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivals</td>
<td>28</td>
<td>19</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Third generation cephalosporins e.g. Ofromax, Ceftriaxone, Infexime and Xone.

A majority of the ileal perforations occurred during the time period February to May (Figure 4).
Six patients were residents of Kathmandu, whereas 24 patients came from other districts. (Figure 5) The most common occupation was labouring and farming. (Table 6)

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labourer</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Unemployed / Unknown</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Farmer</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Housewife</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Student</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

Fig 5. Geographic distribution of the patients
6. Case report

A majority of the patients with typhoid fever perforation present with a solitary perforation. However, a reperforation of the ileum is seen in some cases and one study reported a reperforation rate of 12 % [25]. It is important to consider the possibility that the recurrent peritonitis is truly a persistent peritonitis due to missed perforations.

This case report demonstrates a case of re-perforation in a Nepali woman with typhoid fever.

A 35-year-old Nepali woman was admitted to the Tribhuvan University Teaching Hospital on April 27th 2010 feeling generally unwell, with a 12 day history of fever, abdominal pain, anorexia and loose stool. She also suffered from nausea and vomiting. Her temperature was 39.0°C, blood pressure 100/70 mmHg and pulse rate 108 bpm. Upon examination the patient was ill-looking but oriented. Her abdomen was normal shaped but showed guarding, board-like rigidity and rebound tenderness during palpation. Bowel sounds were absent on ascultation.

Analysis of blood showed Na⁺ 136.0 mEq/L, K⁺ 3.9 mEq, HbsAg reactive, creatinine 69.0 mmol/L, WBC 4200 cmm with the differential count neutrophils 62 % and lymphocytes 33 %.

An abdominal ultrasound was carried out but proved inconclusive. Gynecologic disease was ruled out by a consulting gynecologist.

Based on clinical findings and laboratory results, ileal perforation or perforated appendicitis was suspected. After resuscitation with intravenous fluids and administration of intravenous Xone and Metron, an exploratory laparotomy was carried out. A solitary 1 x 0.5 cm perforation was localized in the antimesenteric border of the distal ileum, 35 cm proximal to the ileo-caecal junction. Multiple enlarged mesenteric lymphnodes were found in the distal ileum and two litres of dirty fluid was present in the peritoneal cavity and pelvis. The peritoneal fluid was collected and the diseased bowel segment was resected with wedge resection and a two – layer anastomosis. The enlarged mesenteric lymphnodes were extracted.

The patient’s condition improved and was planned for discharge. However, upon stich removal on May 10th 2010, profuse serosanguinous discharge from the wound was noticed and bowelloops were visible. The patient was diagnosed with wound dehiscence and rushed to the operation theater where an exploratory laparotomy was performed. A new perforation measuring 1 x 1 cm was found on the antimesenteric border of the ileum, 25 cm from the ileo-caecal junction and 10 cm distal to the previous anastomosis. Multiple interloop abscesses and adhesions as well as an abscess in the subcutaneous plane were present. A peritoneal washing was performed and the interloop abscesses
and adhesions released. The perforation was repaired in a two – layer anastomosis and the previous repair site strengthened with a seromuscular suture. The wound was then closed with a tension suture. Pus was sent for culture and sensitivity test, showing Escheria Coli sensitive to Amikacin only, whereafter treatment with intravenous Amikcain was initiated.

The postoperative recovery was uneventful and the patient was discharged with oral antibiotics on May 17th 2010, 20 days after hospital admission.
In this study, a majority of the patients with ileal perforation were males. This finding is consistent with previous reports where a high male : female ratio amongst patients with typhoid fever perforation was documented [1] [6]. It does however remain unclear why typhoid fever perforation is more commonly seen in males than in females. In a study by Santillana et al [25], immune mechanisms and genetic predisposition factors were suggested as possible underlying factors. It has been proposed that individuals with genetic governance of the immune response to the S. Typhi antigen could undergo an exaggerated hyperplastic response of the Peyer's patches, leading to an increased risk of perforation. The male predominance would then be explained by a predisposing genetic pattern. Additional support for the genetic predisposition in the pathogenesis of typhoid perforation is given by a case report written by Vyas et al who reported typhoid fever perforation in two identical twin brothers aged 21 years in India [26].

It is also possible that men spend more time outside of the home which increases the risk of exposure to S. Typhi.

Typhoid fever perforation is generally seen in the second and third decade of young adolescents [27, 28]. As previously suggested, multiple exposures to S. Typhi may be required for the activation of the enhanced immune system producing ileal perforation. This theory is further supported by the virtual elimination of typhoid fever perforation in developed countries where the disease is seen in returning travellers, making multiple exposures to the bacteria almost impossible. The requirement of multiple exposures would explain the increasing incidence of ileal perforation parallell with age.

In this study, the number of patients in the age group 17 - 39 years constitute a majority of the total number of patients. A possible explanation for the age-dependent incidence is that people in this age group might be in touch with the environment more often and eat more food outside of the home, thereby increasing the exposure to S. Typhi. The young and the elderly may spend more time at home whereas people of working age naturally spend more time outside the home.

The finding of a peak incidence in perforations in the second week of disease agrees with reports from the world literature [6] [25]. This suggests that time is required for the bacteria to invade the tissue and also for the immune system to contribute to the pathogenesis of the intestinal lesions. Clearly, patients seek health care late in the course of their illness. This delay might be explained by several factors. Febrile disease is very common in Nepal, which makes it difficult to identify and differentiate between harmful diseases. It is therefore likely that the disease is often initially
misdiagnosed as a cold and self-medicated with over the counter medicine or traditional treatment. Moreover, a large part of the population has a poor access to health care with insufficient infrastructure leading to transport difficulties. Many of the patients included in this study had traveled two-three days to reach the TUTH. Furthermore, the expenses of hospital treatment may impede typhoid patients from seeking professional medical care or wait to the point where complications such as ileal perforation have already occurred. Finally, the people may be accustomed to social hardship and withstand the disease symptoms for a longer period of time, thereby delaying the time to appropriate treatment.

Leukopenia is a common laboratory finding in patients with uncomplicated typhoid fever. A study by Khan et al, in which five of 21 patients had intestinal perforation, the rate of leukopenia was higher amongst patients with no complications [29]. Santillana et al reported leukocytosis in 59.5 % of a total of 96 patients diagnosed with typhoid fever perforation [25]. In this study, 15 out of 29 patients showed leukocytosis, whereas only three patients showed leukopenia. The likely explanation is that the ileal perforation leads to secondary peritonitis and consequently, a rise in the white blood cell count.

Fever ( >38.0 °C) was not a striking admission finding. All patients presented with a history of prolonged fever, but only 10 patients had an elevated body temperature upon examination. It is likely that a majority of the patients had received antipyretic drugs before hospital admission. The vast majority of the patients presented with a solitary perforation. However, when searching the literature, multiple perforations are not infrequently reported [30, 31].

Out of the 30 patients enrolled in this study, two patients (7 %) deceased due to complications following the ileal perforation. This number is lower than the typical mortality rates of 20- 40 % that are most commonly reported [24] [31, 32, 33]. There is, however, a wide range in these figures. Studies conducted in countries with better economic conditions, including South Korea [34] and South Africa [35] have showed mortality rates as low as 9 %. These outcomes have been achieved by the addition of close electrolyte and blood gas monitoring, intensive care nursing, central venous pressure monitoring and the use of total parenteral nutrition. A possible explanation for the low mortality in this study is the fact that most patients were referred from other health centres. Furthermore, patients with a rapid and aggressive progress of typhoid fever may not reach the hospital in time and decease at home. These patients can therefore not be included and consequently, the overall mortality in typhoid fever perforation may be higher than indicated in this study.
Multiple studies have previously highlighted the seasonal variation of typhoid fever. Karkey et al reported an incidence peak in Nepal during the monsoon months from June to August [4]. This is an association that is well known amongst physicians in Nepal. However, in this study, the majority of ileal perforations took place during February to May. This is the period of spring with limited rainfall and not a typical time for the onset of typhoid fever.

One explanation for the high incidence of ileal perforation during this time period could be that physicians misdiagnose the disease since it is not commonly seen in this time of year. Therefore, the disease may remain undiagnosed and consequently untreated, increasing the risk for ileal perforation.

Early administration of efficient antimicrobial treatment is essential for the successful treatment of typhoid fever. In this study, eight of 29 patients had received previous antibiotic treatment prescribed by physicians prior to admission to the TUTH. Previous studies have suggested that an adequate antibiotic treatment will prevent the development of ileal perforation in patients with typhoid fever [6] [24]. This is further illustrated by the fact that ileal perforation among patients with typhoid fever has been extremely rare in developed countries during the era of antibiotic use [24] [6]. However, for these eight patients, the chosen antimicrobial treatment could not prevent the development of intestinal perforation. This may be due to misadministration of an inappropriate antibiotic, antibiotic resistance or to a delay in administration.

It is important to highlight the association between inadequate antibiotic treatment and intestinal perforation, since this is a factor that is potentially modifiable.

Out of the 30 patients included in the study, six patients were residents of Kathmandu whereas 24 patients came from smaller villages on the countryside. It appears, that a majority of the patients that received care at the TUTH were residents of areas with a higher standard of living. There were no patients from the far west of Nepal, which is the most economically deprived area of the country. Therefore, it is reasonable to assume, that these patients are treated at regional hospitals which are not properly equipped. There were no patients from the southern districts close to the Indian border. One possible explanation is that these patients may seek medical care at Indian hospitals instead of coming to Kathmandu.

As previously stated, antibiotic resistance is becoming a major problem and treatment is becoming increasingly difficult, leading to patients taking longer to recover, suffering more complications and continuing to spread the disease to their family and to their community. In Nepal, many cases of typhoid fever may be self-treated, with patients using unprescribed
antibiotics from medical shops. A wide range of medications are available prior to consultation with a physician, which makes it difficult to know if the selected antimicrobial treatment is appropriate. Furthermore, a majority of patients diagnosed with typhoid fever are treated as out-patients, which makes it difficult to control the compliance to treatment.

In this study, most patients received treatment with intravenous Xone and Metronidazol and had a good outcome after the surgical treatment. This indicates that the antibiotic treatment with third generation cephalosporins was adequate and that resistance development did not pose a problem for these patients.

As previously stated, a majority of the patients came from villages outside the city of Kathmandu. In these areas, the access and exposition to antibiotics is limited, especially when compared to the situation in Kathmandu. It is likely that self-medication is more common in the city, whereas traditional medicine has a bigger impact in the villages. This might be the explanation for the overall successful antibiotic treatment in these patients. It is however important to control the prescribing and over the counter sales of antibiotics and to monitor antibiotic susceptibility patterns in Kathmandu.

The two interventions for the control of typhoid fever are treatment of the already infected and preventive measures. Ultimately, resources should be allocated towards prevention strategies that reduce the transmission of the disease. Prevention is based on ensuring access to safe water and by promoting safe food handling practices. The setting up and maintenance of the needed modern water system is essential as well as collection and treatment of sewage, especially during the monsoon season. Behaviour change with regard to hygiene is a cornerstone in the prevention of typhoid fever. In order to raise public awareness of typhoid fever and the recommended prevention measures, health education is important.

Many challenges remain for the control and management of typhoid fever in Nepal and the rest of the developing world. Especially when taking the young age of patients with typhoid fever perforation in consideration, the typical morbidity and mortality is unacceptably high. It also is important to study typhoid fever from a broader context of society and acknowledge poverty as a determinant for health.
8. Conclusions

Typhoid fever remains a major health problem in Nepal. The leading cause of mortality in typhoid fever is ileal perforation, which is a complication that possibly could be prevented. Identification and appropriate antibiotic treatment of typhoid fever would reduce morbidity and mortality. Early and appropriate surgical intervention is vital for the survival of typhoid fever perforation.

A majority of the patients in this study were young males and this finding is consistent with previous reports.
9. Acknowledgements

This study was supported by grants from the Minor Field Study Programme of the Swedish International Development Agency (SIDA) and the University of Gothenburg.

I would like to address warm and grateful thanks to all whom in different ways have contributed to the development and realization of this project.

First of all I want to thank my supervisors Dr. Göran Kurlberg, Dr. Yogendra Singh and Dr. Bikhal Ghimire for their input and assistance throughout the planning, researching and writing of this thesis.

My family and my partner deserve special recognition for supporting me in all circumstances and providing me with a foundation to feel comfortable in new environments.

Finally, I am very thankful to the Nepali people – for their kindness and welcoming attitudes, and not least for sharing their personal experiences of typhoid fever with me.
10. References


