



## Typhoid intestinal perforation in developing countries: Still unavoidable deaths?

Sandro Contini

Sandro Contini, Former Professor of Surgery, Department of Surgical Sciences, University of Parma, 43123 Parma, Italy

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**Correspondence to:** Sandro Contini, MD, Professor, Department of Surgical Sciences, University of Parma, Strada S. Eurosia 45/B, 43123 Parma, Italy. [sandrocontini46@gmail.com](mailto:sandrocontini46@gmail.com)  
Telephone: +39-348-5656989  
Fax: +39-521-251019

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low-middle-income countries. Although the mortality rate consequent to TIP in resource-poor countries is improved in the last decades, it is still fluctuating from 5% to 80%, due to surgical- and not surgical-related constraints. Huge economic costs and long timelines are required to provide a short- to middle-term solution to the lack of safe water and sanitation. Inherent limitations of the currently available diagnostic tools may lead to under-evaluation as well as over-evaluation of the disease, with consequent delayed treatment or inappropriate, excessive antibiotic use, hence increasing the likelihood of bacterial resistance. There is a need for immunization programs in populations at greatest risk, especially in sub-Saharan Africa. Uniform surgical strategies and guidelines, on the basis of sound or prospective surgical studies and adapted to the local realities, are still lacking. Major drawbacks of the surgical treatment are the frequent delays to surgery, either for late diagnosis or for difficult transports, and the unavailable appropriate intensive care units in most peripheral facilities. As a consequence, poor patient's conditions at presentation, severe peritoneal contamination and unsuitable postoperative care are the foremost determinant of surgical morbidity and mortality.

**Key words:** Typhoid bacterial resistance; Typhoid fever; Typhoid intestinal perforation; Developing countries; Low- Middle-Income Countries; Postoperative care; Typhoid vaccination

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### Abstract

Typhoid fever is a public health challenge mostly concentrated in impoverished, overcrowded areas of the developing world, with lack of safe drinking and sanitation. The most serious complication is typhoid intestinal perforation (TIP), observed in 0.8% to 39%, with a striking rate difference between high-income and

**Core tip:** Typhoid perforation in low-middle-income countries has still a disappointing outcome, related to surgical and not surgical constraints: (1) safe water and sanitation are lacking in high risk settings like slums or overcrowded areas; (2) currently available diagnostic facilities have inherent limitations; (3) multiple drugs resistant bacteria are an increasingly

threatening problem; (4) vaccination programs in some high risk regions, like sub-Saharan Africa, have not yet been carried out; (5) surgery is often delayed; (6) in peripheral facilities postoperative intensive care is problematic and often unsuitable; and (7) surgical standards and guidelines are not available due to the lack of sound prospective studies.

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## INTRODUCTION

Typhoid fever is a public health challenge, mostly occurring in impoverished, overcrowded areas of the developing world, with lack of safe drinking and sanitation<sup>[1]</sup>. Although there is some evidence that typhoid fever incidence rates have declined over the past several decades, still the global estimation of typhoid fever episodes in 2010 was of 13.5 million<sup>[2]</sup>. The majority of disease burden has been observed in South and South-East Asia<sup>[3]</sup> and in sub-Saharan Africa, primarily in the low income neighborhoods of the capital cities but also in rural areas<sup>[3,4]</sup>. Data collection is substantially underestimating the morbidity and mortality of typhoid<sup>[5,6]</sup>, for the inherent limits of evaluations based on extrapolation of data across regions and age groups. Moreover, reliable data are particularly scanty where the burden of the disease is mostly concentrated.

### ***Typhoid fever and typhoid intestinal perforation***

Globally, typhoid fever has a case-fatality rate of 10%-30% without effective treatment, reduced to 1%-4% with appropriate management<sup>[7,8]</sup>. The true incidence of complications is unknown<sup>[9]</sup>, but alarming problems may arise in 10% to 15 % of patients, especially when the disease is lasting for two or more weeks<sup>[10]</sup>. The commonest GI complication is intestinal bleeding, usually not severe and managed conservatively<sup>[11]</sup>, while typhoid intestinal perforation (TIP) is the most serious one<sup>[11,12]</sup>. It has been reported in 0.8% to 39% of patients<sup>[13-15]</sup>, with a striking difference between high-income and poor resources countries<sup>[16,17]</sup>. A higher propensity to perforation has been observed in sub-Saharan Africa than in Asiatic countries, suggested to be consequent to more virulent agents<sup>[18]</sup>, though likely more related to data coming from referral hospitals, where the very ill patients are seen, than to a true local disease virulence<sup>[19]</sup>.

### ***Clinical features and mortality of TIP***

Clinical features may be misleading: Peritoneal irritation can be almost absent before perforation, and peritoneal

response delayed afterward. Unlike other perforations, the omentum does not migrate to the perforation site<sup>[14]</sup>. The number and size of perforated ulcers do not affect the severity of the symptoms. Although the mortality consequent to TIP is certainly improved<sup>[20]</sup> when compared to the 58% of death rate almost 50 years ago in Nigeria<sup>[21]</sup>, still the reported mortality rate is fluctuating from 5% in the best settings to 80% in peripheral facilities<sup>[10,22-26]</sup>, with a not negligible death rate reported in tertiary hospitals<sup>[27-30]</sup>. Conversely, developed countries observed a decline in mortality to less than 5%, due mainly to timely surgery and appropriate pre- and post-operative intensive care<sup>[13,31,32]</sup>.

Several constraints contribute to this disappointing death rate, either related to the surgical management or linked to local settings and primary health care strategies.

## NON SURGICAL RELATED CONSTRAINTS

### ***Lack of water and sanitation, overcrowding***

A more diffuse access to water safety and sanitation is fundamental for the control of typhoid fever, but the related huge economic costs and long timelines will not allow a short- to middle-term solution. Healthcare systems of poor resources countries, especially when affected by internal or external conflicts, may not afford the cost of these socioeconomic improvements. Conversely, targeted interventions on densely populated urban communities like slums, where typhoid fever is a serious problem, could be a possible way out<sup>[33,34]</sup>. In the meantime fewer resources could be directed towards rural areas with lower population density where enteric fever is less common<sup>[35,36]</sup>.

### ***Inadequacy of immunization programs***

Almost all public health typhoid vaccination programs in the groups of populations at greatest risk have been performed in Asia (Table 1), with the strongest impact in endemic settings and in the short- to medium-term<sup>[37]</sup>. The oral vaccine was found to be highly cost-effective when targeting ages 1-14 years in high-burden/high-risk districts, as well urban slums and rural areas without improved water<sup>[38]</sup>. Remarkably, no vaccination experience has been reported from sub-Saharan Africa, where emerging threats, including multidrug resistance and increasing urbanization, would warrant concentration on immunization programs<sup>[4,39,40]</sup>.

The recently proposed Typhoid Risk Factor (TRF) index<sup>[41]</sup>, which takes into account the drinking water sources, toilet facility types, and population density, seems a reliable tool to evaluate variations in the disease burden, helping decision makers to identify high risk areas and prioritize the right populations for vaccination.

### ***Increasing antibiotics resistance***

Resistance to commonly used antibiotics in typhoid fever is becoming an emergent problem in endemic

**Table 1** Reported experiences with typhoid vaccination strategies<sup>[37]</sup>

Vaccination strategies	Countries
Preemptive community-based routine vaccination	China, India
Preemptive community-based routine vaccination campaign	China, India, Pakistan, Vietnam
Preemptive disaster-response community-based vaccination campaign	Fiji, India Pakistan
Preemptive school-based vaccination	Chile, China, Indonesia, Nepal, Pakistan, Vietnam
Reactive (outbreak response) community-based vaccination campaign	Fiji, Tajikistan
Reactive (outbreak response) school-based vaccination	China

areas<sup>[42]</sup>. In resource-limited countries the few remaining effective antimicrobials are either unavailable or too expensive and at the moment the development of new effective low-cost drugs has a little short-term perspective. More than one third of patients in many endemic areas are affected by Multi Drug Resistant (MDR) bacteria<sup>[43]</sup>: nearly 75% of *S. Typhi* isolated from a population-based surveillance in Kenya were multi-drug resistant<sup>[36]</sup>.

### Delay in diagnosis

Since clinical features are not always reliable, typhoid may be differentiated with difficulty from other co-endemic acute febrile illnesses. Validated prediction rules from clinical features and laboratory results are not available<sup>[44,45]</sup>. Blood culture remains the gold standard for diagnosis, especially in the first week of illness<sup>[46]</sup>, but with a large range of sensitivity (40%-80%) and is less reliable during antibiotic treatment. Stool cultures have lower sensitivity (< 40%). Widal test can be performed with minimal laboratory infrastructure and might be a good diagnostic support, especially in the second week of disease, but misuse and misinterpretation can be critical<sup>[47]</sup>. Poorly reliable tests may lead either to under-evaluation or over-evaluation of the disease, delaying a correct treatment or leading to inappropriate and excessive antibiotic use.

### Delay in surgical treatment

A timely surgical treatment can prevent the severe peritoneal contamination observed in up to 70% of patients<sup>[18,23-25,48,49]</sup>, associated with a high mortality rate<sup>[50,51]</sup>. Moreover, early surgery might reduce the need for extensive surgical procedures, with their contribution to a high morbidity and mortality<sup>[52,53]</sup>. From 30% to 100% of perforated patients may wait a long period before surgery, especially in rural areas and peripheral facilities. Indeed the diagnosis can be challenging in very young patients, in those who perforate while on medical treatment<sup>[18]</sup> or in presence of a generalized septic state, but if symptoms are evocative, diagnostic confirmation by either abdominal x-ray or ultrasound,

should not delay surgery<sup>[54]</sup>. Similarly, adjustment of electrolytes and fluids imbalance or anemia correction should postpone surgery only for a short time as prolonged resuscitation can adversely affect the outcome<sup>[55,56]</sup>.

Frequent causes of surgical delay are protracted or late referral from inadequate health facilities, difficult transport systems (both ambulances and roads), difficulties sourcing funds for treatment and diversion of patients to alternative medical therapies<sup>[18]</sup> before consulting the hospital.

## SURGICAL RELATED CONSTRAINTS

Non-operative treatment has been proposed in the past in moribund patients or for long-standing perforations<sup>[22]</sup>, but there is now uniform agreement that the ultimate treatment for TIP should be a surgical one, although the best surgical management remains controversial. Actually, the type of surgical technique might have limited influence on the outcome, that is likely more related to the preoperative clinical conditions of the patients, to the degree of abdominal contamination and to the quality of pre- and post-operative care<sup>[57]</sup>.

### Scarcity of prospective studies and guidelines

Several surgical solutions have been proposed for the treatment of TIP, with a consequent variability of morbidity and mortality. Indeed, explicit surgical guidelines, particularly aimed to resource-poor countries, are lacking. Most reports are retrospective, often including a small number of patients with not rarely incomplete data and poor statistical analysis. Surgical morbidity and mortality are often reported without any risk adjustment based on the severity of the disease, delay of treatment *etc.* The few available prospective<sup>[50,55,57-60]</sup> studies highlighting that patient's conditions have a more significant impact on patient's outcome than the type of surgical procedure, are shown in Table 2, which is including all prospective studies found in the literature about TIP.

### Unavailable appropriate postoperative care

Postoperative care may be quite complex in these very fragile patients, frequently presenting with a septic state, coexistent diseases and an impaired immunological status. Moreover, intensive care units supplied for possible renal or respiratory failures, with available appropriate antibiotics for overwhelming infections and with accessible tools for nutritional support, are found infrequently in resource-poor countries, especially in peripheral or rural settings.

### Surgical technique

The type of the surgical procedure does not appear to influence the mortality of TIP<sup>[13,19,56]</sup>; conversely, sound surgical judgment and experience are required to select the appropriate surgery according to the surgical

**Table 2** Prospective studies reported in literature about surgical management of typhoid intestinal perforation

Ref.	Conclusions
Haider <i>et al</i> <sup>[60]</sup> , 2002	Late presentation, delay in operation, multiple perforations, and drainage of copious quantities of pus and fecal material from the peritoneal cavity adversely affected the incidence of fecal fistula and the mortality rate.
Adesunkanmi <i>et al</i> <sup>[50]</sup> , 2003	Peritonitis assessment by APACHE II score (50% perforations). A modified APACHE II score greater than 15 was associated with a significantly greater mortality.
Bashir <i>et al</i> <sup>[67]</sup> , 2003	Primary ileostomy <i>vs</i> simple repair <i>vs</i> resection anastomosis: ileostomy is a good life saving procedure (statistical evaluation not reported).
Shukla <i>et al</i> <sup>[68]</sup> , 2004	Single layer <i>vs</i> double layer repair: good closure of the perforation rather than single- or double-layer repair that determines the outcome in patients with enteric perforation.
Edino <i>et al</i> <sup>[53]</sup> , 2007	Mortality is significantly affected by multiple perforations, severe peritoneal contamination and burst abdomen.
Gedik <i>et al</i> <sup>[58]</sup> , 2008	Mannheim Peritonitis Index and perforation-operation interval were found independent risk factors affecting morbidity.
Mohil <i>et al</i> <sup>[57]</sup> , 2008	Disease severity assessed by POSSUM score. Severity of disease rather than surgical procedure has a significant impact on the outcome.
Pandey <i>et al</i> <sup>[69]</sup> , 2008	T-tube inserted into the bowel lumen after closing all distal perforations <i>vs</i> primary closure <i>vs</i> resection. In children with multiple perforations and poor general condition, the use of T-tube may be an effective management option (statistical evaluation not reported).
Tade <i>et al</i> <sup>[59]</sup> , 2011	ASA class is a significant predictor of mortality in patients treated for typhoid intestinal perforation.
Ibrahim <i>et al</i> <sup>[70]</sup> , 2014	Single layer <i>vs</i> double layer repair: single layer repair of the perforated ileum due to typhoid enteric perforation with peritonitis in children was effective by reducing complication rates.
Chaudhary <i>et al</i> <sup>[75]</sup> , 2015	Temporary loop ileostomy for perforation peritonitis due to benign systemic diseases like typhoid fever and tuberculosis confers a very high morbidity.

findings and especially in advanced diseases<sup>[25,60]</sup>.

Primary repair is usually performed for single or isolated perforations-by single or two suture layers. Segmental resection and anastomosis is preferred in presence of multiple adjacent perforations, while wedge resection is reported infrequently<sup>[21,61-63]</sup>. Simple repair has generally a lower mortality rate than resection, although death rate remains high when abdominal contamination is severe<sup>[64-66]</sup>. Few studies<sup>[67-70]</sup> evaluated prospectively single *vs* double layer repair without achieving definite conclusions, as shown in Table 2. The correlation between a high number of perforations, perhaps due to a highly virulent causative organism<sup>[17,18]</sup>, and a poor surgical outcome is questionable<sup>[12,56,59]</sup>. Enterocutaneous fistula is the most alarming complication, with a mortality up to 67%<sup>[71,72]</sup>, that is likely underestimated because death can occur months after surgery<sup>[73]</sup>.

Ileostomy is usually reserved to patients with severe disease, delayed presentation and very contaminated abdomen, with a high risk of suture leakage<sup>[11,13]</sup>. Ileostomy has been also described as a routine primary procedure<sup>[74]</sup> although it is associated with high morbidity rate and complications like prolapse, stricture, retraction, parastomal hernia, mainly when performed in patients with critical conditions<sup>[75]</sup>. Moreover, loss of intestinal fluids from ileostomy can be managed with difficulty in austere environment and shortage of suitable ileostomy bags, with consequent skin damage around ileostomies, not rarely induces the patient to a self-limitation of food intake.

Delayed primary closure of the abdominal wall has been recommended for heavily contaminated wounds since a long time<sup>[76]</sup>, but to date the optimal method of closure in such situations remains controversial<sup>[77]</sup>. Vacuum assisted closure appears promising but may not be feasible in peripheral facilities. Scheduled re-

laparotomies, allowing early recognition of complications and a more appropriate cleaning the abdominal cavity, have been performed with a positive impact on survival<sup>[64]</sup>. However, this policy has the disadvantage to submit the patients to multiple surgical trauma and increases the workload of the operative theater.

A laparoscopic approach to TIP has been occasionally carried out with acceptable results<sup>[78,79]</sup>. There is no evidence that laparoscopy is more advantageous than open surgery, although it could be considered as an advantageous diagnostic tool in doubtful abdomens. A concern is the need of a highly technological equipment and of an appropriate maintenance, often lacking in poor resources countries.

## CONCLUSION

Treatment and outcome of the TIP are still unsatisfactory in LMICs, with barriers related to local settings, local health strategies and specific surgical issues. An estimate of the burden of enteric fever and enteric fever drug resistance, especially in sub-Saharan Africa, is still inadequate. Local public health planning in high risk settings is essential to improve safe water availability and sanitation, but this compulsory achievement will be forcedly slow. Selected immunization programs, should be considered in areas at high risk, like slums or overcrowded places, especially in sub-Saharan Africa, where vaccination programs were never carried out despite the high burden of the disease. The recently proposed TRF index may help decision makers to identify high risk areas. Currently available diagnostic tools for typhoid fever have limitations in terms of speed, sensitivity, infra-structure requirements, and suitability. New approaches are needed to address many of these limitations for resource-poor countries. The emergence of multiple drugs resistant bacteria is



a threatening problem for the already overstretched health care systems of LMICs, taking into account the scarce resources to pay for effective antibiotics. A long delay before surgery, either due to a late diagnosis or to a protracted referral time, may strongly condition the surgical outcome. Prospective studies about surgical treatment of TIP in LMICs are lacking and should be encouraged in order to provide clear-cut surgical standard and guidelines. No one single surgical procedure can be recommended as a standard treatment on the basis of sound surgical studies. Any timely surgery carried out in a short time and allowing a swift clearing of peritoneal contamination, is the most likely to give the best outcome. A problematic pre- and post-operative care, due to lack of intensive care units, especially in peripheral hospitals, is a further shortcoming affecting the surgical outcome, independently on the type of surgery.

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