Typhoid intestinal perforation in developing countries: Still unavoidable deaths?

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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 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

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.

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[6]. 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[2]. The majority of disease burden have been observed in South and South-East Asia[3] and in sub-Saharan Africa, primarily in the low income neighborhoods of the capital cities but also in rural areas[3,4]. Data collection is substantially underestimating the morbidity and mortality of typhoid[5,6], 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[7,8]. The true incidence of complications is unknown[9], but alarming problems may arise in 10% to 15% of patients, especially when the disease is lasting for two or more weeks[10]. The commonest GI complication is intestinal bleeding, usually not severe and managed conservatively[11], while typhoid intestinal perforation (TIP) is the most serious one[11,12]. It has been reported in 0.8% to 39% of patients[13-15], with a striking difference between high-income and poor resources countries[16,17]. A higher propensity to perforation has been observed in sub-Saharan Africa than in Asiatic countries, suggested to be consequent to more virulent agents[18], though likely more related to data coming from referral hospitals, where the very ill patients are seen, than to a true local disease virulence[19].

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[14]. The number and size of perforated ulcers do not affect the severity of the symptoms. Although the mortality consequent to TIP is certainly improved[20] when compared to the 58% of death rate almost 50 years ago in Nigeria[21], still the reported mortality rate is fluctuating from 5% in the best settings to 80% in peripheral facilities[10,22-26], with a not negligible death rate reported in tertiary hospitals[27-30]. 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[13,31,32].

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[33,34]. In the meantime fewer resources could be directed towards rural areas with lower population density where enteric fever is less common[35,36].

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[37]. 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[38]. 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[39,40]. The recently proposed Typhoid Risk Factor (TRF) index[41], 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
areas\textsuperscript{[42]}. 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\textsuperscript{[43]}, nearly 75% of \textit{S. Typhi} isolated from a population-based surveillance in Kenya were multi-drug resistant\textsuperscript{[36]}.

\textbf{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\textsuperscript{[44,45]}. Blood culture remains the gold standard for diagnosis, especially in the first week of illness\textsuperscript{[46]}, 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 infra-structure and might be a good diagnostic support, especially in the second week of disease, but misuse and misinterpretation can be critical\textsuperscript{[47]}. 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.

\textbf{Delay in surgical treatment}

A timely surgical treatment can prevent the severe peritoneal contamination observed in up to 70% of patients\textsuperscript{[18,22-25,48,49]}, associated with a high mortality rate\textsuperscript{[50,51]}. Moreover, early surgery might reduce the need for extensive surgical procedures, with their contribution to a high morbidity and mortality\textsuperscript{[52,53]}. 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\textsuperscript{[18]} 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\textsuperscript{[54]}. 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\textsuperscript{[55,56]}.

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\textsuperscript{[18]} before consulting the hospital.

\textbf{SURGICAL RELATED CONSTRAINTS}

Non-operative treatment has been proposed in the past in moribund patients or for long-standing perforations\textsuperscript{[22]}, 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\textsuperscript{[57]}.

\textbf{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\textsuperscript{[44,45,50,56,57-60]} 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.

\textbf{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.

\textbf{Surgical technique}

The type of the surgical procedure does not appear to influence the mortality of TIP\textsuperscript{[13,19,56]}; conversely, sound surgical judgment and experience are required to select the appropriate surgery according to the surgical

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\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Vaccination strategies} & \textbf{Countries} \\
\hline
Preemptive community-based routine vaccination & China, India \\
Preemptive community-based routine vaccination & 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 \\
\hline
\end{tabular}
\caption{Reported experiences with typhoid vaccination strategies\textsuperscript{[37,38,40,41]}}
\end{table}
CONCLUSIONS

Single layer vacuum assisted closure appears promising in such situations remains controversial since a long time.

Suitable ileostomy bags, with consequent skin damage with difficulty in austere environment and shortage of intestinal fluids from ileostomy can be managed in patients with critical conditions.

Retraction, parastomal hernia, mainly when performed by single or two suture layers. Simple repair has generally a lower mortality rate vs double layer repair, good closure of the perforation rather than single- or double-layer repair that determines the outcome in patients with enteric perforation.

Primary ileostomy is significantly preferred over resection anastomosis: ileostomy is a good life saving procedure (statistical evaluation not reported).

Mortality is significantly affected by multiple perforations, severe peritoneal contamination and burst abdomen.

Mannheim Peritonitis Index and perforation-operation interval were found independent risk factors affecting morbidity.

ASA class is a significant predictor of mortality in patients treated for typhoid intestinal perforation. ASA class is a significant predictor of mortality in patients treated for typhoid enteric perforation with enteric perforation.

T-tube inserted into the bowel lumen after closing all distal perforations. T-tube inserted into the bowel lumen after closing all distal perforations. Few studies 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, and a poor surgical outcome is questionable. Enterocutaneous fistula is the most alarming complication, with a mortality up to 67% (71,72), that is likely underestimated because death can occur months after surgery.

Ileostomy is usually reserved to patients with severe disease, delayed presentation and very contaminated abdomen, with a high risk of suture contamination (64-66). Few studies 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, and a poor surgical outcome is questionable. Enterocutaneous fistula is the most alarming complication, with a mortality up to 67% (71,72), that is likely underestimated because death can occur months after surgery.

Ileostomy has been also described as a routine primary procedure (74), although it is associated with high morbidity rate and complications like prolapse, stricture, retraction, parastomal hernia, mainly when performed in patients with critical conditions (75). 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 (76), but to date the optimal method of closure in such situations remains controversial (77). Vacuum assisted closure appears promising but may not be feasible in peripheral facilities. Scheduled re-

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

| Ref. | Conclusions |
|------|-------------|
| Haider et al. (59), 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 et al. (57), 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 et al. (58), 2003 | Primary ileostomy vs simple repair vs resection anastomosis: ileostomy is a good life saving procedure (statistical evaluation not reported). |
| Shukla et al. (59), 2004 | Single layer vs 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 et al. (60), 2007 | Mortality is significantly affected by multiple perforations, severe peritoneal contamination and burst abdomen. |
| Gedik et al. (61), 2008 | Mannheim Peritonitis Index and perforation-operation interval were found independent risk factors affecting morbidity. |
| Mohil et al. (62), 2008 | Disease severity assessed by POSSUM score. Severity of disease rather than surgical procedure has a significant impact on the outcome. |
| Pandey et al. (63), 2008 | T-tube inserted into the bowel lumen after closing all distal perforations vs primary closure vs 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 et al. (64), 2011 | ASA class is a significant predictor of mortality in patients treated for typhoid enteric perforation. |
| Ibrahim et al. (65), 2014 | Single layer vs 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 et al. (66), 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 (25,60). 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 (21,61-63).

Simple repair has generally a lower mortality rate than resection, although death rate remains high when abdominal contamination is severe (64-66). Few studies 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 (27,48), and a poor surgical outcome is questionable (10,56,59). Enterocutaneous fistula is the most alarming complication, with a mortality up to 67% (71,72), that is likely underestimated because death can occur months after surgery (25).

Ileostomy is usually reserved to patients with severe disease, delayed presentation and very contaminated abdomen, with a high risk of suture contamination (21,61). Ileostomy has been also described as a routine primary procedure (74), although it is associated with high morbidity rate and complications like prolapse, stricture, retraction, parastomal hernia, mainly when performed in patients with critical conditions (75). 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 (76), but to date the optimal method of closure in such situations remains controversial (77). Vacuum assisted closure appears promising but may not be feasible in peripheral facilities. Scheduled re-

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 forcibly 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.

REFERENCES

1. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Kemik O, Dülger AC, Olmez A, Hasirci I, Kişli E. 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.

2. Buckle GC, Walker CL, Black RE. Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. J Glob Health 2012; 2: 010401 [PMID: 23198130 DOI: 10.7189/jogh.02.010401]

3. Azmatullah A, Qamar FN, Thaver D, Zaidi AK, Bhutta ZA. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. J Glob Health 2015; 5: 020407 [PMID: 26649174 DOI: 10.7189/jogh.05.020407]

4. Slayton RB, Date KA, Mintz ED. Vaccination for typhoid fever in sub-Saharan Africa. Hum Vaccin Immunother 2013; 9: 903-906 [PMID: 23563513 DOI: 10.4161/hv.23007]

5. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Andersen LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulahak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colhoun H, Colson KE, Condon J, Cooper LT, Corriere M, Chiu CH, Chugh SS, Coffeng LE, Colan SD, Colhoun H, Colson KE, Condon J, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhdarker KC, Dahodwala N, de Leo D, Dengenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorey ER, Driscoll T, Duber H, Ebelt B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Fox MP, Fullerton A, Furberg K, Gillum RF, González-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassem NA, Keran A, Khoo JP, Knowlton AD, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabeywejana J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsunari A, Matzopoulos R, Mayosi BM, McAnulty J, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mboob S, Mokdad AA, Moran A, Mulholland K, Nair SN, Nalim D, Narayan KM, Nassehi K, Norman P, O’Donnell M, Omer SB, Orbild K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivera AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, Porraini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushlon L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Siwe K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Toubon JA, Truelsen T, Undurraga EA, Venkatesubramanian N, Vijayarukam L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazrooa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095-2128 [PMID: 22345660 DOI: 10.1016/S0140-6736(12)61728-0]

6. Osoba KO, Iroh Tam PY, Mintz ED. The unrecognized burden of typhoid fever. Expert Rev Vaccines 2017; 16: 249-260 [PMID: 27797598 DOI: 10.1080/14760588.2017.1255553]

7. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004; 82: 346-353 [PMID: 15298225]

8. Chang YT, Lin JY, Huang YS. Typhoid colonic perforation in childhood: a ten-year experience. World J Surg 2006; 30: 242-247 [PMID: 16425068]

9. Qamar FN, Azmatullah A, Bhutta ZA. Challenges in measuring complications and death due to invasive Salmonella infections. Vaccine 2015; 33 Suppl 3: C16-C20 [PMID: 25921727 DOI: 10.1016/j.vaccine.2015.03.103]

10. Sümé A, Kernik O, Dülger AC, Olmez A, Hasirci I, Kişli E, Bayraktar B, Bulut G, Kotan C. Outcome of surgical treatment of intestinal perforation in typhoid fever. World J Gastroenterol 2010; 16: 4164-4168 [PMID: 20806433 DOI: 10.3748/wjg.v16.i33.4164]

11. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med 2002; 347: 1770-1782 [PMID: 12456854]

12. Bitar R, Tarpley J. Intestinal perforation in typhoid fever: a historical and state-of-the-art review. Rev Infect Dis 1985; 7: 257-271 [PMID: 3890908]

13. Atamanalp SS, Aydinli B, Ozturk G, Oren D, Basoglu M, Yildirgan MI. Typhoid intestinal perforations: twenty-six-year experience. World J Surg 2007; 31: 1883-1888 [PMID: 17629741]

14. Eggleston FC, Santoshi B, Singh CM. Typhoid perforation of the bowel. Experiences in 78 cases. Ann Surg 1979; 190: 31-35 [PMID: 464674]

15. Butler T, Knight J, Nath SK, Speelman P, Roy SK, Azad MA. Typhoid fever complicated by intestinal perforation: a persisting fatal disease requiring surgical management. Rev Infect Dis 1985; 7: 244-256 [PMID: 3890997]

16. Worku B. Typhoid fever in an Ethiopian children's hospital: 1984-1995. Ethiop J Health Dev 2000; 14: 311-316 [DOI: 10.4314/eqhd.v14i3.9904]

17. Chiu CH, Tsai JR, Ou JT, Lin YT. Typhoid fever in children: a fourteen-year experience. Acta Paediatr Taiwan 2000; 41: 28-32 [PMID: 10910556]

18. Ekenze SO, Okoro PE, Amah CC, Ikefuna AN. Typhoid ideal perforation: analysis of morbidity and mortality in 89 children. Niger J Clin Pract 2008; 11: 58-62 [PMID: 18689141]

19. Ameh EA. Typhoid ideal perforation in children: a scourge in developing countries. Ann Trop Paediatr 1999; 19: 267-272 [PMID: 10715713]

20. Ukwenya AH, Ahmed A, Garba ES. Progress in management of typhoid perforation. Ann Afr Med 2010; 9: 259-265 [PMID: 22064250 DOI: 10.4103/1596-3519.87040]

21. Dickson JA, Cole C. Perforation of the Terminal Ileum. A Review of 38 Cases. Br J Surg 1964; 51: 893-897 [PMID: 14226047]

22. van Basten JP. Stockenborgher R. Typhoid perforation: A review of the literature since 1960. Trop Geogr Med 1994; 46: 336-339 [PMID: 7892698]

23. Saxe JM, Cropsey R. Is operative management effective in treatment of perforated typhoid? Am J Surg 2005; 189: 342-344 [PMID: 15792765 DOI: 10.1016/j.amjsurg.2004.11.032]

24. Adesunkanmi AR, Ajao OG. The prognostic factors in typhoid
ileal perforation: a prospective study of 50 patients. J R Coll Surg Edinb 1997; 42: 395-399 [PMID: 9484395]

25 Osifo OD, Osigwesonyi SO. Typhoid ileal perforation in children in Benin city. Afr J Paediatr Surg 2010; 7: 96-100 [PMID: 20431219 DOI: 10.4103/1188-6725.69597]

26 Clegg-Lampley JN, Hodasi WM, Dakubo JC. Typhoid ileal perforation in Ghana: a five-year retrospective study. Trop Doct 2007; 37: 231-233 [PMID: 17988489 DOI: 10.1017/S00497507782323784]

27 Otegbayo JA, Daramola AO, Onyebutu HC, Albogun WF, Ogogoye OO. Retrospective analysis of typhoid fever in a tropical tertiary health facility. Trop Gastroenterol 2002; 23: 9-12 [PMID: 12170927]

28 Sarwar Khan J, Hassan H, Bhopal FG, Mehmood N, Taj N, Alam Khan J, Iqbal M. Typhoid Perforation: A ten year experience in a Surgical Unit. J Ralav Med Coll 2002; 6: 70-73

29 Talabi AO, Etonyeaku AC, Sowande OA, Olowookere SA, Adegoke OA. Predictors of mortality in children with typhoid ileal perforation in a Nigerian tertiary hospital. Pediatr Surg Int 2014; 30: 1121-1127 [PMID: 25280454 DOI: 10.1007/s00383-014-35929]

30 Mogasale V, Desai SN, Mogasale VV, Park JK, Ochiai RL, Wierzba TF. Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review. PLoS One 2014; 9: e93784 [PMID: 24743649 DOI: 10.1371/journal.pone.0093784]

31 Mock CN, Amaral J, Visser LE. Improvement in survival from typhoid ileal perforation. Results of 221 operative cases. Ann Surg 1992; 215: 244-249 [PMID: 154396] 32 Keenan JP, Hadley GP. The surgical management of typhoid perforation in children. Br J Surg 1984; 71: 928-929 [PMID: 6494468]

33 Sinha A, Sazawal S, Kumar R, Sood S, Reddath VP, Singh B, Rao M, Nafficy A, Clensons JD, Bhan MK. Typhoid fever in children aged less than 5 years. Lancet 1999; 354: 734-737 [PMID: 10475185 DOI: 10.1016/S0140-6736(99)0001-1]

34 Brooks WA, Hossain A, Goswami D, Nahar K, Alam K, Ahmed N, Naheed A, Nair GB, Mastroeni P, White NJ, Tran TH, Vo VH, Dougan G, Farrar JI, Wain J. A clinical, microbiological, and pathological study of intestinal perforation associated with typhoid fever. Clin Infect Dis 2004; 39: 61-67 [PMID: 15206054 DOI: 10.1086/s12879-016-2074-1]

41 Lee JS, Mogasale VV, Mogasale V, Lee K. Geographical distribution of typhoid risk factors in low and middle income countries. BMC Infect Dis 2016; 16: 732 [PMID: 27919235 DOI: 10.1186/s12879-016-2074-1]

42 Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. Lancet 2015; 385: 1136-1145 [PMID: 25458731 DOI: 10.1016/S0140-6736(15)00408-7]

43 Karikú S, Gordon MA, Fessey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. Vaccine 2015; 33 Suppl 3: C21-C29 [PMID: 25912288 DOI: 10.1016/j.vaccine.2015.03.102]

44 Ross IN, Abraham T. Predicting enteric fever without bacteriological culture results. Trans R Soc Trop Med Hyg 1987; 81: 374-377 [PMID: 3686311]

45 Kuvandik C, Karagoonlan I, Namiduru M, Baydar I. Predictive value of clinical and laboratory findings in the diagnosis of the enteric fever. New Microbiol 2009; 32: 25-30 [PMID: 19382666]

46 Wain J, Deep TS, Ho VA, Walsh AM, Nguyen TT, Parry CM, White NJ. Quantification of bacteria in blood of typhoid fever patients and relationship between counts and clinical features, transmissibility, and antibiotic resistance. J Clin Microbiol 1998; 36: 1683-1687 [PMID: 9620400]

47 Andrews JR, Ryan ET. Diagnostics for invasive Salmonella infections: Current challenges and future directions. Vaccine 2015; 33 Suppl 3: C8-15 [PMID: 25937611 DOI: 10.1016/j.vaccine.2015.02.030]

48 Abantanga FA, Namiko B, Amoah M. The range of abdominal surgical emergencies in children older than 1 year at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. Ann Afr Med 2009; 8: 236-242 [PMID: 20139546 DOI: 10.4103/1596-3519.59578]

49 Akgun Y, Bac B, Boylu S, Aban N, Tacyildiz I. Typhoid enteric perforation. Br J Surg 1995; 82: 1512-1515 [PMID: 8558066]

50 Adesunkanmi AR, Oseni SA, Adejuyigbe O, Aghakwuru EA. Acute generalized peritonitis in African children: assessment of severity of illness using modified APACHE II score. ANZ J Surg 2003; 73: 275-279 [PMID: 12752281]

51 Meier DE, Tarpley J. Typhoid intestinal perforations in Nigerian children. World J Surg 1998; 22: 319-323 [PMID: 9494426]

52 Nguyen QC, Everest P, Tran TK, House D, March S, Parry C, Connerton P, Phan VB, To SD, Mastroeni P, White NJ, Tran TH, Vo VH, Dougan G, Farrar JI, Wain J. A clinical, microbiological, and pathological study of intestinal perforation associated with typhoid fever. Clin Infect Dis 2004; 39: 61-67 [PMID: 15206054 DOI: 10.1086/s12879-016-2074-1]

53 Aja OG. Typhoid perforation: factors affecting mortality and morbidity. Int Surg 1982; 67: 317-319 [PMID: 7160899]

54 Younis SN. The role of abdominal ultrasound in the diagnosis of typhoid fever: an observational study. Travel Med Infect Dis 2014; 12: 179-182 [PMID: 24144450 DOI: 10.1016/j.tmaid.2013.09.004]

55 Edino ST, Yakubu AA, Mustapha A, Abubakar I. Prognostic factors in typhoid ileal perforation: a prospective study of 53 cases. J Natl Med Assoc 2007; 99: 1042-1045 [PMID: 17913115]

56 Hassan F, Sinha RKr, Pratap V, Sinha DK. Ileostomy in management of typhoid enteric perforation presenting late: an experience at tertiary-care hospital, Jharkhand, India. Pak J Surg 2010; 26: 108-110

57 Mohil RS, Singh T, Arya S, Bhatnagar D. Risk adjustment is crucial in comparing outcomes of various surgical modalities in patients with ileal perforation. Patient Saf Surg 2008; 2: 31 [PMID: 19025633 DOI: 10.1186/1754-9403-2-31]

58 Gedik E, Girgin S, Tacyildiz IH, Akgun Y. Risk factors affecting morbidity in typhoid enteric perforation. Langenbecks Arch Surg 2008; 393: 973-977 [PMID: 18026981 DOI: 10.1007/s00423-007-0244-8]

59 Tade AO, Olatuje SO, Osinupoib IA, Salami BA. Typhoid Intestinal Perforations in a Tropical Tertiary Health Facility: A Prospective Study. East Cent Afr J Surg 2011; 16: 72-79

60 Haider W, Majid A, Khanum A, Bhutta A. The prognostic factors in Typhoid Ileal Perforation. Pak Postgrad Med J 2002; 13: 4-8

61 Abantanga FA, Wolfe-Addai BB. Postoperative complications after surgery for typhoid perforation in children in Ghana. Pediatr Surg Int 1998; 14: 55-58 [PMID: 9880697]

62 Mallick S, Klein JP. [Management of typhoid perforation of the small bowel: a case series in Western French Guiana]. Med Trop
Contini S. Typhoid intestinal perforation in developing countries

(1931; 61: 491-494 [PMID: 11980398]

Onen A, Dokucu AI, Cigdem MK, Ozturk H, Otsu S, Yucesan S. Factors effecting morbidity in typhoid intestinal perforation in children. *Pediatr Surg Int* 2002; 18: 696-700 [PMID: 12598967]

Caronna R, Boukari AK, Zaongo D, Hessou T, Gayito RC, Ahononga C, Adeniran S, Priuli G. 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 Gastroenterol* 2013; 13: 102 [PMID: 23782915 DOI: 10.1186/1471-230X-13-10]

Kouame J, Kouadio L, Turquin HT. Typhoid ileal perforation: surgical experience of 64 cases. *Acta Chir Belg* 2004; 104: 445-447 [PMID: 15469159]

Harouna YD, Bazira L, Vanneuville G. [Typhoid perforation of the small intestine at the Niamey Hospital, Niger]. *Ann Chir* 2001; 126: 179-181 [PMID: 11284112]

Bashir M, Nadeem T, Iqbal J, Rashid A. Ileostomy in Typhoid Perforation. *Ann King Edward Med Uni* 2003; 9: 1-3

Shukla VK, Sahoo SP, Chauhan VS, Pandey M, Gautam A. Enteric perforation—single-layer closure. *Dig Dis Sci* 2004; 49: 161-164 [PMID: 14992453]

Pandey A, Kumar V, Gangopadhyay AN, Upadhyaya VD, Srivastava A, Singh RB. A pilot study on the role of T-tube in typhoid ileal perforation in children. *World J Surg* 2008; 32: 2607-2611 [PMID: 18825454 DOI: 10.1007/s00268-008-9746-y]

Ibrahim M, Getso KI, Yashuwa AH, Mohammad AM, Anyanwu LJ. Single-layer closure of typhoid enteric perforation: Our experience. *Afr J Paediatr Surg* 2013; 10: 167-171 [PMID: 23866070 DOI: 10.4103/0189-6725.115046]

Agu K, Nzewu 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: 2514-2518 [PMID: 24858189 DOI: 10.1007/s00268-014-2637-5]

Memon AA, Siddiqui FG, Abro AH, Agha AH, Lubna S, Memon AS. An audit of secondary peritonitis at a tertiary care university hospital of Sindh, Pakistan. *World J Emerg Surg* 2012; 7: 6 [PMID: 22423629 DOI: 10.1186/1749-7922-7-6]

Malik AK, Nomani AZ, Qureshi AU, Gondal KM. Factors Associated with Survival in Patients of Enteric Perforations; A Retrospective Analysis of 73 Patients. *Ann King Edward Med Univ* 2010; 16: 233-236

Zida M, Ouedraogo T, Bandre E, Bonkoungou GP, Sanou A, Traore SS. [Primary ileostomy for typhoid-related ileal perforation: a 62-case series in Ouagadougou, Burkina Faso]. *Med Trop* (Mars) 2010; 70: 267-268 [PMID: 20734596]

Chaudhary P, Nabi I, Ranjan G, Tiwari AK, Kumar S, Kapur A, Arora MP. Prospective analysis of indications and early complications of emergency temporary loop ileostomies for perforation peritonitis. *Ann Gastroenterol* 2015; 28: 135-140 [PMID: 25609137]

Bernard HR, Cole WR. Wound infections following potentially contaminated operations. Effect of delayed primary closure of the skin and subcutaneous tissue. *JAMA* 1963; 184: 290-292 [PMID: 13970973]

Chen Y, Ye J, Song W, Chen J, Yuan Y, Ren J. Comparison of Outcomes between Early Fascial Closure and Delayed Abdominal Closure in Patients with Open Abdomen: A Systematic Review and Meta-Analysis. *Gastroenterol Res Pract* 2014; 2014: 784056 [PMID: 24987411 DOI: 10.1155/2014/784056]

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: 122-124 [PMID: 15471016]

Sinha R, Sharma N, Joshi M. Laparoscopic repair of small bowel perforation. *JSLS* 2005; 9: 399-402 [PMID: 16381353]

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