INVITED ARTICLE

Typhoid and Enteric Fevers in Intensive Care Unit

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Abstract

Enteric fever (typhoid and paratyphoid)is caused by *Salmonella typhi* and *Salmonella paratyphi*. It is spread by fecal-oral route, largely through contamination of water and foodstuff. Developing countries are the worst affected. It takes 7 – 21 days from ingestion of the organism to manifestation of symptoms which are generally Fever, relative bradycardia, and pain abdomen. Hepatosplenomegaly, intestinal bleeding, and perforation are the features at various stages of the disease. The bacteria invade the submucous layer and proliferate in the Payer's patches. Blood culture is the gold standard for diagnosis but it is only rarely positive. Fluroquinolones, cephalosporins, and azithromycin are antibiotics of choice. There is increasing evidence of the development of resistance to all antibiotics. *Salmonella* sepsis, though uncommon, can occur. Intestinal perforation, peritonitis, and secondary sepsis are complications that may require intensive care unit management.

Keywords: Ceftriaxone, Enteric fever, Fever, Fluoroquinolones, Gram-negative bacilli, ICU.

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Introduction

Typhoid fever remains an enigma even 137 years after the isolation of its bacterium by German Scientist Gaffky. Typhoid and paratyphoid (orsimply enteric fever) are caused by *Salmonella typhi* and *Salmonella paratyphi* (serotypes A, B, and C). Type A is the most common. Type B is seen in Europe. Type C is rare and only seen in Eastern Asia. Typhoidis endemic in many developing countries where there is a lack of safe drinking water and proper hygienic infrastructure. Approximately, 12 million people are affected with *S.typhi* and 4 millionwith *S. paratyphi*. More than 15,000 annual deaths occur worldwide due to typhoid fever.[1,2] In India, the annual incidence of enteric fever was seen to be 377 (178–801) and 105 (74–148) cases, respectively/100,000 persons, with children between 2 years and 4 years old having the highest incidence.[3] In India, the actual disease burden is difficult to estimate as different geographical areas have a difference in disease distribution along with deficiency of blood culture facilities in semiurban and rural areas. Even occasional outbreaks pose problems for the healthcare authorities to take stock of the disease prevalence. With mortality risk of about 0.2%, timely and appropriate antibiotic treatment yields good results.[4] When untreated or inappropriately treated, typhoid fever can be a prolonged life-threatening illness with a lot of morbidities.Patients developing one or more complications need intensive care unit (ICU) admission. With a failure to diagnose and treat early, complications are often seen in the second week onward.[5] Emergence of ciprofloxacin resistance and increasing trend of minimum inhibitory concentration (MIC) of ceftriaxone (present drug of choice) have made management difficult in India.

Pathophysiology

Pathophysiology begins with the transmission of the gram-negative bacilli via fecal–oral route. *Salmonella* is acid-sensitive and is destroyed in the stomach by gastric acid. Infection can only be acquired if a large dose of bacteria is consumed or patients are on long-term proton pump inhibitors or antacids. Following ingestion, *S. typhi* enters into the small bowel epithelium aided by the cystic fibrosis transmembrane conductance regulator (CFTR). Resistance to typhoid infection is seen in individuals with abnormal CFTR protein. There is a submucosal intracellular proliferation of the bacteria and recruitment of mononuclear cells and lymphocytes in the second part of the Peyer's patches, leading to hypertrophy of the Peyer's patches. Over the next 1 – 3 weeks, the bacteria are released in the bile and spreads to the reticulo-endothelial system through the lymphatic system and bloodstream. Bacterial proliferation in the reticuloendothelial system is characteristic of enteric fever and that contributes to most of its symptomatology.[6]

Figure 1 depicts the pathogenesis of enteric fever.

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Clinical Features

In the first week of illness, there may be rising (step-ladder) fever associated with chills. Also, pulse-temperature dissociation (or relative bradycardia) may be seen. Abdominal pain is common in the second week and "rose spots" may be seen.Subsequently, hepatosplenomegaly may be detected. Later in the third week, intestinal perforation due to ileocecal lymphatic hyperplasia may occur and this may lead to peritonitisand secondary sepsis.[7] Perforation is more common in males.[8] Such patients are admitted to ICU.

If a patient, after an acute infection, continues to excrete the bacteria in the stool or in urine for more than 12 months, a *chronic carrier state* should be diagnosed and then accordingly treated.[9]

Diagnosis

Blood culture remains the gold standard of diagnosis. Polymerase chain reaction (PCR), more so nested PCR, has high sensitivity

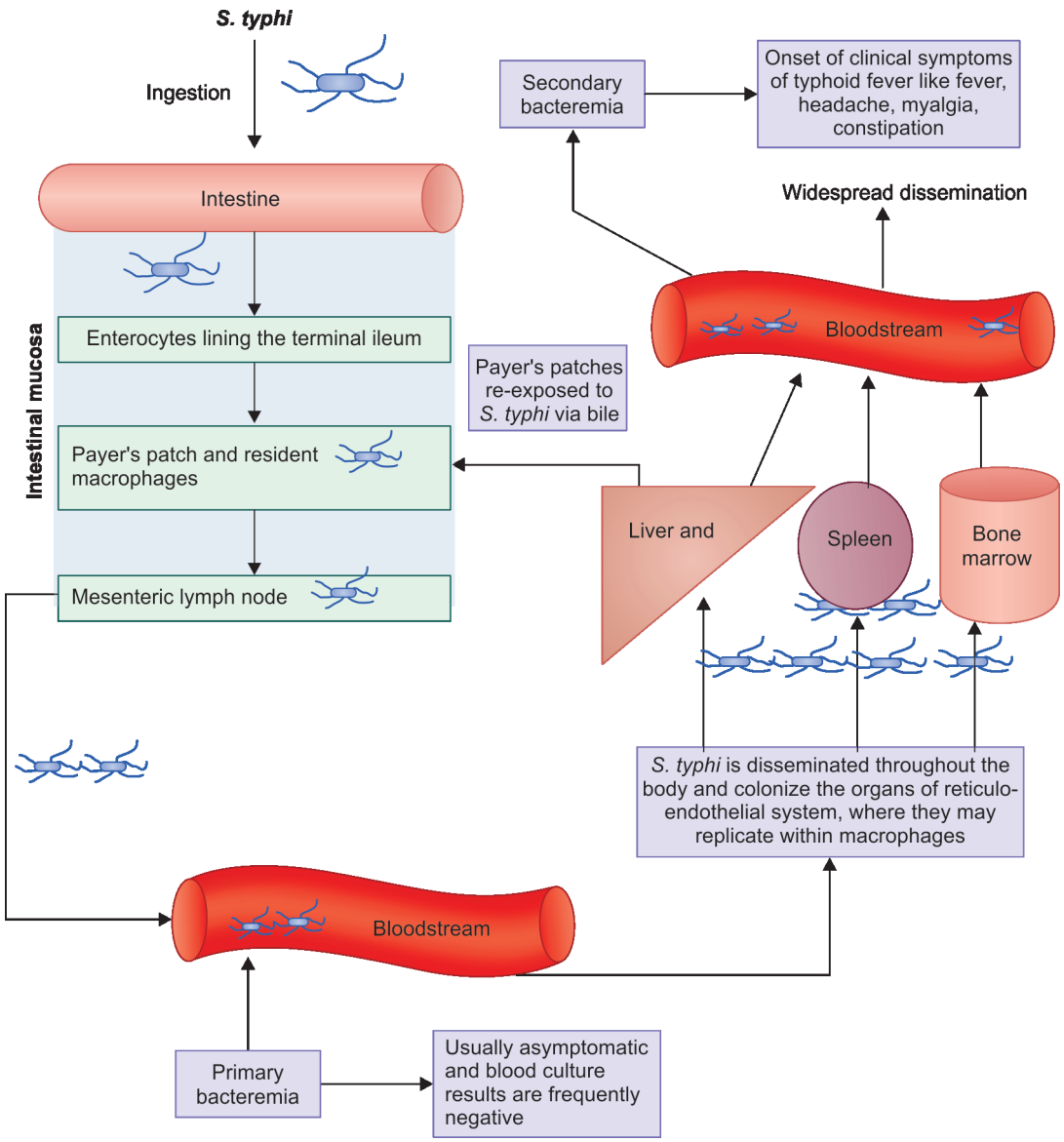

Fig. 1: Pathophysiology of typhoid fever

and specificity and can be used to detect"clinically suspected but culture negative cases."[10]

Serological test, like Widal (sensitivity, 47–77% and specificity, 50–92%), has better negative than positive predictive value.[11] Other tests, like Typhidot, Typhidot-M, IDL Tubex test, and IgM Dipstick, have varying sensitivity and specificity patterns in detecting active disease.

Metabolomics is a relatively new area of scientific research. These can be used to detect and measure minute quantities of chemicals in biological material. Metabolomics uses mass spectrometry technology to detect these chemical substances and may offer an alternative approach for accurate diagnosis of fever of unknown origin.[12]

Antimicrobial Susceptibility in Typhoid Fever

A retrospective analysis at AIIMS, New Delhi, showed that *S. typhi* infections was susceptible to chloramphenicol (87.9%), amoxicillin (75.5%)and cotrimoxazole (87.3%) while *S. paratyphi* A infections were succeptible 94.2, 90.1, and 94.2%, respectively.[13] Ciprofloxacin, of loxacin, and levofloxac insusceptibilities were 71.3, 70.8, and 0.9% for *S. typhi* and 58.1, 57.4, and 57.1% for *S. paratyphi* A, respectively. MIC_{50} and MIC_{90} were 8 and 12 µg/mL for *S. typhi* with azithromycin, with susceptibility of 98.9%. The study also showed that susceptibility to ceftriaxone and cefixime was 100% but it also demonstrated that there was a steady increase in ceftriaxone MIC50 and MIC90 values over time. MIC50 and MIC90 values for ceftriaxone, in 12 years (2005–2016) showed a creepy rise (MIC50 increased from 0.023 to 0.064 µg/mL) and MIC90 values also showed a rise from 0.038 to 0.19 µg/mL). This was an indication of evolving resistance ($p < 0.05$).[13] A retrospective study has shown cephalosporin resistance (1%) and macrolide resistance (9%).[14]

The AIIMS study showed a nonlinear change in the rate of culture-positive enteric fever with a maximum of 0.0087 in 1999 and a minimum of 0.0006 in 2014.[13]

Figure 2, adopted from the same article, depicts the trend.

The changing empiric antibiotic therapy over the years might be the reason attributed to the decrease and then further increase in the culture-positive cases and also an indicator of the development of multidrug resistance.

Figure 3 depicts the change in antibiotic usage for enteric fever in India from the year 2000 to 2015.

Drug-resistant enteric fever is more in developing countries, and the scenario is worsening over time. Improvement of public health, proper sanitation, clean drinking water, and programmed vaccination can decrease the disease spread and in turn prevent the development and spread of drug-resistant *Salmonella* infections.

Treatment Trends

Individual patient data were collected from four RCTs and analyzed.[15] Among 2090 patients with clinical suspicion of enteric fever, 855 (41%) were culture positive; of these, *S. typhi* was cultured in 28% ($n = 581$) and *S. paratyphi* A in 13%($n = 274$). The study showed 139 (6.6%) treatment failures which included one death. Among the culture-positive patients, those with *S. typhi* infection had higher temperatures (median, 39.0°C) compared to *S. paratyphi* A (38.0°C). Liver function tests showed a significant elevation of liver enzymes in culture-positive than in culture-negative patients. Treatment failure rates between various antimicrobial treatments were similar. The review also showed the change in antimicrobial susceptibility and MIC values of different antibiotics.The study also depicted that MICs for *S. paratyphi* A were significantly higher than those for *S. typhi* with all antibiotics except cefixime.

An expert advisory panel recommended fluoro quinolones (especially, ciprofloxacin and ofloxacin) and cephalosporins (specifically those of the third and fourth generations) as the first-line therapeutic agents.[9] The recommendations were based on the treatment recommendations by the World Health Organization,

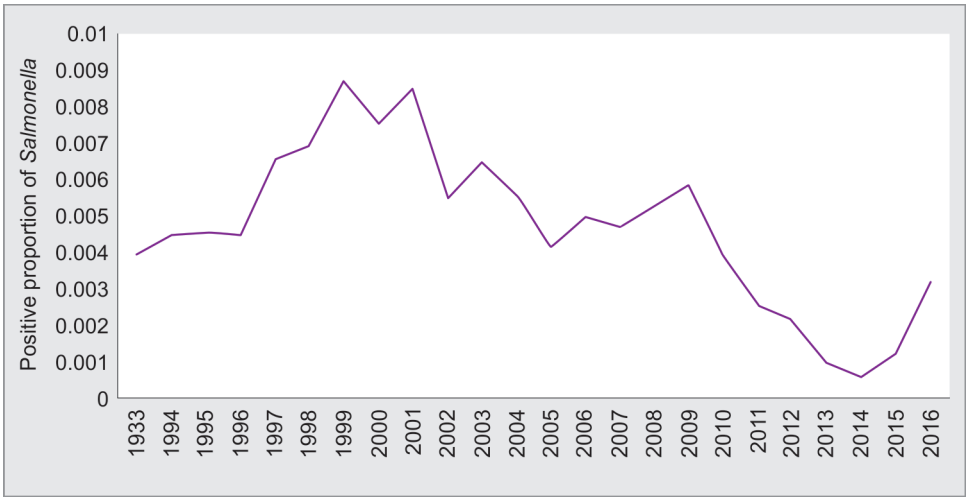

Fig. 2: Change in culture-positive cases over time

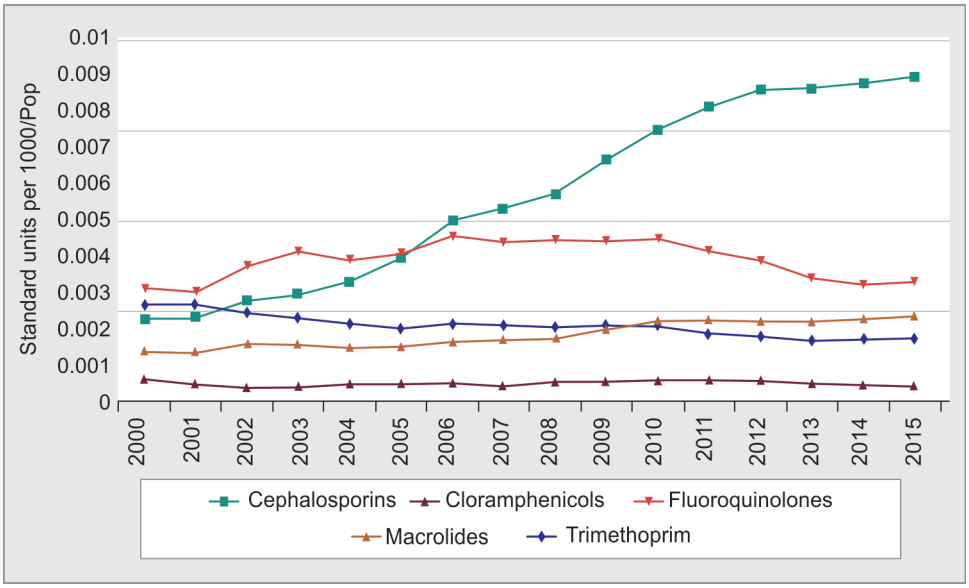

Fig. 3: Antibiotics used for the treatment of typhoid in India

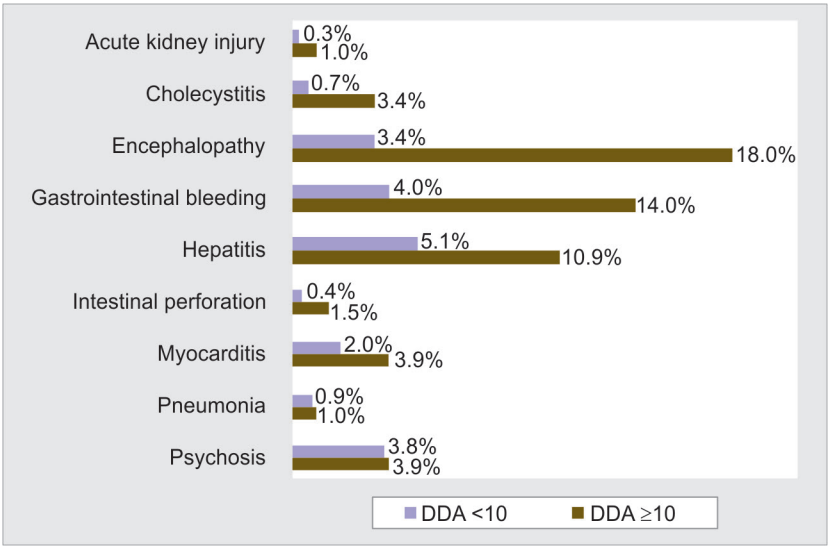

Fig. 4: Complication rates depending on disease onset to hospitalization

the Association of Physicians of India, and the Indian Association of Pediatrics.[9,16]

Table 1 elucidates the likely antibiotics to be chosen to initiate therapy.

It is recommended to initiate parenteral treatment in presence of comorbid conditions or extremes of age, dehydration, or intolerance to a particular drug. The idea is that when the patient stabilizes, therapy should be de-escalated to oral antibiotics. In case, there is evidence to believe that there is inappropriate response to treatment (e.g., fever persisting beyond 5 days), therapy can be escalated by choosing a different antibiotic or a second antibiotic may be added. However, at any point during the course of the treatment, the likelihood of possible complications should be closely watched.[17]

Complications, Morbidity, and Mortality

The average days from disease onset to hospitalization (DDA) in a meta-analysis were used as a surrogate to assess the effect of delay in treatment on the prevalence and risk of complications. This meta-analysis showed that the prevalence of complications in enteric fever in studies reporting DDA ≥10 was higher (36%) than studies reporting DDA <10 (16%). Chances of complications were three times higher in patients who had obtained delayed medical help.[5] Figure 4 depicts the complication rates in patients with "timely" compared to "delayed" admission.

A review and meta-analysis published in October 2020, has analyzed in detail, the complications and morbidity associated with typhoid fever.[17] Among 10,355 confirmed typhoid patients, 2,719 (26.3%) had complications with an overall case fatality ratio (CFR) of 2.0%. Among the complications most frequently encountered, intestinal perforation, GI bleeding, bronchitis, encephalopathy, and toxic myocarditis are most relevant. Among all the cases of typhoid intestinal perforation, the median CFR was 15.5% (6.7–24.1%). On the other hand, CFR among nonsurgical patients was 0.9 to 5.4% across different regions of the world.

Table 2 lists out the complication rates seen in various geographical locations as revealed in the meta-analysis.[17]

Table 1: Treatment of enteric fever

Susceptibility	*Patient*	*Antibiotic*
Uncomplicated enteric fever		
Quinolone sensitive areas	Adult	Responders: Ciprofloxacin or ofloxacin or third generation cephalosporin, like cefixime Nonresponders: Chloramphenicol oramoxicillin
	Child	Responders: Thirdgeneration cephalosporin like cefixime Nonresponders: Chloramphenicol or amoxicillin
Quinolone–resistance areas	Adult	Responders: Cefixime Nonresponders: Azithromycin
	Child	Responders: Azithromycin Nonresponders: Cefixime
Complicated enteric fever	Adult	Responders: Third or fourth generation cephalosporins, like ceftriaxone or cefotaxime Nonresponders: Chloramphenicol orampicillin
Quinolone sensitive areas	Child	Responders: Cefotaxime or ceftriaxone Nonresponders: Chloramphenicol orampicillin
Quinolone resistance areas	Adult	Responders: Cefotaxime or ceftriaxone Nonresponders: Fluoroquinolones Cefotaxime or ceftriaxone
	Child	

Typhoid and Intensive Care

Intestinal perforation could be a frequent complication if enteric fever is not treated well and if the patient reports to a hospital quite

Table 2: Complications of typhoid fever, United Nations region wise, 1965 – 2018 (Source: https://www.journalofinfection.com/action/showFullTableHTML?isHtml=true&tableId=tbl0002&pii=S0163-4453%2820%2930690-3)

Complicationsa	*Africa*			*Americas*			*Asia*			*Oceania*			*Totalb*		
	n /	*N*	*(%)*	*n /*	*N*	*(%)*	*n /*	*N*	*(%)*	*n /*	*N*	*(%)*	*n /*	*N*	*(%)*
Abdominal															
Intestinal perforation	37 /	486	(7.6)	4 /	217	(1.8)	34 /	4,622	(0.7)	5 /	739	(0.7)	80 /	6,064	(1.3)
Gastrointestinal hemorrhage	11 /	320	(3.4)	0 /	0	—	87 /	2,809	(3.1)	21 /	739	(2.8)	119 /	3,868	(3.1)
Hepatitis	10 /	157	(6.4)	1 /	9	(11.1)	104 /	2,389	(4.4)	17 /	739	(2.3)	132 /	3,294	(4.0)
Cholecystitis	1 /	55	(1.8)	0 /	0	—	10 /	913	(1.1)	0 /	365	(0.0)	11 /	1,333	(0.8)
Cardiovascular															
Asymptomatic electrocardiographic changes	ND			ND			ND			ND			ND		
Myocarditis	2 /	191	(1.0)	0 /	0	—	30 /	1,979	(1.5)	1 /	365	(0.3)	33 /	2,535	(1.3)
Shock	0 /	14	(0.0)	0 /	0	—	59 /	3,580	(1.6)	17 /	365	(4.7)	76 /	3,959	(1.9)
Neuropsychiatric															
Encephalopathy	0 /	0	—	0 /	0	—	98 /	2,460	(4.0)	4 /	365	(1.1)	102 /	2,825	(3.6)
Delirium	34 /	277	(12.3)	0 /	0	—	650 /	2,027	(32.1)	21 /	344	(5.8)	705 /	2,648	(26.6)
Psychotic states	2 /	50	(4.0)	2 /	217	(0.9)	28 /	1,438	(1.9)	0 /	0	—	32 /	1,705	(1.9)
Meningitis	6 /	347	(1.7)	1 /	9	(11.1)	13 /	1,625	(0.8)	0 /	0	—	20 /	1,981	(1.0)
Impairment of coordination	ND			ND			ND			ND			ND		
Respiratory															
Bronchitis	0 /	0	—	0 /	0	—	32 /	407	(7.9)	0 /	0	—	32 /	407	(7.9)
Pneumonia	4 /	191	(2.1)	7 /	226	(3.1)	43 /	1,416	(3.0)	18 /	374	(4.8)	72 /	2,207	(3.3)
Hematologic															
Anemia	132 /	311	(42.4)	52 /	226	(23.0)	683 /	3,516	(19.4)	150 /	703	(21.3)	1,017 /	4,756	(21.4)
Disseminated intravascular coagulation	0 /	0	—	0 /	0	—	98 /	660	(14.8)	1 /	374	(0.3)	99 /	1,034	(9.6)
Other															
Focal abscess	1 /	47	(2.1)	0 /	0	—	0 /	0	—	0 /	0	—	1 /	47	(2.1)
Pharyngitis	ND			ND			ND			ND			ND		
Miscarriage	0 /	0	—	0 /	0	—	1 /	6	(16.7)	0 /	0	—	1 /	6	(16.7)
Relapse	6 /	171	(3.5)	2 /	129	(1.6)	71 /	2,166	(3.2)	0 /	0	—	79 /	2,466	(3.2)
Chronic carriage	ND			ND			ND			ND			ND		
Seizure or convulsionsc	14 /	125	(11.2)	0 /	0	—	94 /	4,224	(2.2)	0 /	0	—	108 /	4,349	(2.5)
Total complications	260 /	689	(37.7)	69 /	226	(30.5)	2,135 /	8,681	(24.6)	255 /	739	(34.5)	2,719 /	10,335	(26.3)
Total complications as described by study	116 /	348	(33.3)	24 /	327	(7.3)	401 /	3,028	(13.2)	128 /	739	(17.3)	669 /	4,442	(15.1)

[a]Complications from Parry etal., Table1; ND, no data. Data could not be abstracted as these complications were not described in any of the included articles;

[b]Europe not shown due to the single study from Europe including participants diagnosed with stool and urine cultures, therefore it was not possible to distinguish complications among those diagnosed by culture of a normally sterile site;

[c]Complication not listed by Parry etal.

late. Diagnosis is clinical and confirmed by point-of-care-ultrasound with the presence of pneumo peritoneum and pneumoretro peritoneum along with bubbles in peritoneal fluid and oedematous bowel loops.[18,19]

In a prospective observational study, 67 consecutive patients who had exploratory laparotomy for typhoid perforation between August 2009 and October 2012 in the main operating theatre of the University College Hospital, Ibadan, were studied.[20] Twenty-five patients (37.3%) out of 67 required critical care. Indications for ICU admission were poor respiratory effort,delayed recovery from anesthesia, sepsis, and septic shock. Twenty-one patients (84%) required mechanical ventilation. The mean ventilator days were

2.14 days (range 1–5 days). The length of ICU stay ranged from 1 to 15 days (mean 4.32 days) and 14 patients required inotropic support. Six patients (24%) expired. Hence, it can be observed that there is a high rate of ICU admission in patients who develop typhoid perforation and require active critical care involving mechanical ventilation, inotropic and ancillary supportive care.

Due to low yield from blood cultures (median of 1 CFU/mL of blood), *Salmonella* septicemia is uncommon. Adu-Gyamfi et al., reported a case of *Salmonella* sepsis in November 2019.[21] The patient was operated on for a ruptured appendix after a 6 days history of fever and pain abdomen. Preoperatively, he was delirious and in the postop period, he developed septic shock with acute kidney injury with dyselectrolytemia, leucocytosis, and thrombocytopenia. His C-reactive protein was raised and he had an admission APACHE II of 31 and SOFA score of 10. The blood and intra-abdominal specimens isolated *S.typhi* which was sensitive to ciprofloxacin and the patient improved with it.

Additionally, patients who develop other systemic complications and/or secondary sepsis often require management in the critical care unit with appropriate antibiotic therapy along with cardiovascular, respiratory, renal, and other organ system support. It is imperative to check, identify and implement the quint essential care needed in all critically ill patients and this can be done by routine check of "FAST HUG BID" and ensuring its implementation adequately.

Supplemental image 1 depicts the subtle differences in the FAST HUG BID in medical and surgical ICUs.[22]

Prognostic markers like APACHE II and SOFA scores would aid in identifying the criticality of illness in patients with complications of enteric fever who require ICU care.

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