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Are enteric perforations caused by salmonella typhi?- A prospective clinical study to establish the etiology and optimum management of enteric perforations

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IN BRIEF

Background: Despite advances in diagnostic modalities, surgical approach, antimicrobiological therapy and intensive care support, ileal perforations continue to be a potentially fatal affliction in a tropical country. Most ileal perforations are considered to be of typhoid etiology simply based on the clinical presentation of fever of two weeks duration followed by an ileal perforation on the antimesenteric border of terminal ileum.While the surgical management of these perforations does not change a great deal when compared with other causes of ileal perforations, the antimicrobial therapy and the overall outcome is affected by the underlying etiology. Against this background a prospective study was conducted over a period of one year with an aim to establish the underlying pathology and whether these "suspected" typhoid perforations are truly of typhoid etiology.

Material and methods: A prospective cohort of forty-seven patients of ileal perforations of suspected typhoid etiology was evaluated over a period of one year. The surgical management was based on a standardized protocol using APACHE II scoring system. Blood culture, peritoneal fluid, ulcer edge and mesenteric lymph nodes biopsies were subjected to culture to determine the predominant aerobic bacterial isolate and its anti microbiological sensitivity.

Results :In this series male to female ratio was 36: 11, with an average age of 27.3 years. The average duration of fever was 6.67 days; average hospital stay was 10.14 days with a mortality rate of 17.72%. Salmonella typhi could be isolated in only 10.53% of the patients.

Conclusions: The classical presentation of these so called "typhoid perforations" is not commonly observed. Salmonella typhi is rarely isolated from the blood/tissue cultures and the diagnosis of typhoid perforations is essentially clinical. Since ileal perforations are the most common surgical emergency managed by a resident trainee particularly in the developing and underdeveloped countries, a trainee proof and standardized surgical protocol based on APACHE-II scoring system is recommended in order to reduce the mortality.

Key words: Typhoid, enteric, ileal, perforations

INTRODUCTION

The incidence of intestinal perforation in cases of typhoid fever is about 2-3%[1]. Serological testes (Widal test) although done routinely have been found to be non specific and difficult to interpret in areas where typhoid fever is endemic [2].

Diagnosis of typhoid is rarely confirmed and in majority of cases of enteric perforation, only a conjectural diagnosis is made based on the circumstantial evidence of terminal ileal, anti-mesenteric perforation in an adult running fever.

There is a need to study this problem, especially in a country like India; where the burden of ileal perforations is high and there is convincing data that absent or inadequate empirical and definitive antibiotic therapy results in both increased failure rates and increased mortality [3,4].

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It is hoped that establishing the diagnosis and not assuming the diagnosis can help save many lives by deciding the antibiotics to be started before surgery, since surgical intervention is unlikely to be influenced by the etiology.

MATERIAL AND METHODS

A prospective cohort of forty-seven patients of ileal perforations was included in the study for a period of one year from July 2003 to July 2004. Patients less than 12 years of age, those with gastric, duodenal, appendicular, or colonic perforations and those who died before resuscitation and surgery were excluded. All patients underwent a thorough clinical examination and relevant investigations for APACHE II scoring. In addition, in all such patients a routine blood culture was also sent before antibiotics were started.

Pre operative resuscitation included intravenous fluids, commencement of intra venous antibiotics and correction of electrolyte derangement when indicated. Adequate urinary output, normal serum electrolytes and urea were considered a good indicator of adequate resuscitation.

Based on the APACHE II scoring, patients were triaged into three management groups [5] (table 1).

Exploratory laparotomy was performed in all patients after adequate resuscitation, by a midline incision. Operative findings were recorded, and the amount of pus and fecal material were estimated and drained after collecting a sample for culture. Edge of the perforation was excised and preserved in Brain Heart Infusion broth. A draining lymph node in the mesentery was also excised and preserved in Brain Heart Infusion broth for culture. Based on APACHE II triaging appropriate surgery was performed. The peritoneal cavity was lavaged thoroughly by 2-3 liters of normal saline [6-9]. Drains were placed in the right paracolic gutter and the pelvic cavity.

Table 1: APACHE II triaging and management protocols

	Group I	Group II	Group III
APACHE II score	■ 10	11-20	ᴀA 21
Management (surgery)	Primary closure Resection Anastomosis	Resection Anastomosis exteriorized Ileostomy	Resuscitation Bilateral flank drains ICU care
Abdominal Closure	Layered	Skin left open, rectus closed with interrupted monofilament	Laparostomy

MICROBIOLOGICAL METHODS

All microbiological samples were processed immediately utilizing standard microbiological processes as per NCCLS (National Council for Clinical Laboratory Standards) 2000 guidelines. The specimens were cultured in blood agar and MacKonkey agar. Blood cultures were processed by automation (BacT alert 3D System) to decrease average time of culture recovery. Core biopsy of lymph nodes was utilized in the culture of lymph nodes. Cultures that were isolated in blood or in lymph nodes were taken as the causative organism. If no isolates were recovered from these, the growths from ulcer edge biopsy were considered as causative. Isolates from peritoneal fluids were utilized for antibiotic selection in cases of persistent infection or pus cavity.

Culture growths were tested for antibiotic susceptibility utilizing Muller-Hinton agar by Kirby- Bauer disc diffusion method as per NCCLS 2000 guidelines. Based on the sensitivity of organisms isolated the antibiotics were changed if required.

Analysis

The confounding variables, duration of fever, surgical outcome in terms of morbidity, hospital stay and mortality were compared within the three APACHE II groups.

RESULTS

There were 36 males (76.59%) and 11 females (23.4%) and their age ranged from 13 to 46 years with a mean age of 27.3 years (standard deviation: 6.72). Most of the patients presented with a short duration of fever in our series mean of 6.67 days (standard deviation: 2.58, range 4 to 16 days). The average hospital stay was 10.14 days (standard deviation: 5.21, range 5 to 37 days). Seven patients (14.39%) required ICU admission in the post-operative period. Seven patients (14.39%) developed septicemia and eight patients (17.72%) died in this series. The outcome was compared between three APACHE II groups as detailed in table 2. Group III patients not only had higher mortality as was predicted by APACHE II scores but more frequently required ICU care, had higher morbidity as shown by figure 1. Most of our data collaborates the findings of various other similar series, except the duration of fever is considerably lower (6.67 days). Although not significant, but interestingly group III had a shorter history of fever (septicemia5.82 days). It probably reflects a more virulent infection from the onset.

Blood culture was positive in thirteen patients (27.6%). Ulcer edge was positive in thirty-three patients (70.2%). Lymph node culture was performed in thirty patients only, but it was positive in twenty patients (66.7 %). Peritoneal fluids grew culture in twenty-seven patients (57.4%), but contaminants were seen in as many as twenty patients (42.5%).

Table 2: comparison of surgical outcome between APACHE II groups

	Group I	Group II	Group III
N	10	24	13
Fever	4.86days	6.71 days	5.82 days
Hospital stay	7.23 days	8.96 days	14.57 days
ICU care	-	2 (8.3%)	5 (38.4%)
Wound infection	2(20%)	22(91.6%)	13(100%)
Wound dehiscence	-	14(56.3%)	9(65.2%)
Septicemia	-	2(8.3%)	5(36.46%)
Mortality	-	2(8.3%)	6(46.15%)

Salmonella typhi, S. paratyphi A were isolated in only five patients (10.63%). E. Coli was isolated in ten patients (21.27%), Klebsiella spp in seven (11.49%), C. freundii in seven patients (11.49%), Enterococci spp. In eleven patients (23.4%), Acinetobacter and Alpha Streptococci in two patients (4.2%) each and Enterobacter spp in three patients (6.3%). Pattern of bacterial isolates and sensitivity profile of gram positive and gram negative is given in tables 3,4,5 respectively.

DISCUSSION

Although greater understanding of pathophysiology of intra abdominal infections, the introduction of timed surgical intervention and improvement in critical care have reduced the mortality rate associated with severe intra abdominal infections, the rate remains unacceptably high.

Bacteria	Blood	Ulcer edge	Intestinal fluid	Lymph node
Salmonella typhi (3)	3	0	0	3
Salmonella paratyphi A (2)	2	0	0	2
Escherichia coli (10)	0	9	6	3
Citrobacter freundii (7)	0	7	4	0
Klebsiella *species.* (7)	0	4	4	6
Acinetobacter *species.* (2)	0	1	2	1
Enterobacter *species.* (3)	3	1	1	0
Enterococci *species.* (8)	5	11	6	2
Alpha Streptococci (2)	0	0	1	2
Staphylococcus aureus (3)	0	0	3	0
No Growth	34	9	0	10
Contaminants	0	5	20	0
Not Done	-	-	-	17
Total N=47	5+34	33+9+5	27+0+20	20+10

Table 4: Sensitivity Profile of Gram Negative isolates

Bacteria	Natlimycin	Amp	Cot	Cefix	Pc	Cftzd	Ci	Cefo	G	Nt	Ak	Cip	Of	Cefo +Sulb	Pc+Tazo	Mero
E.coli	-	0	-	-	1	2	2	5	0	4	9	0	2	9	9	4/4
Klebsiella.	-	0	-	-	0	1	1	1	2	3	3	0	0	7	5	2/2
Citrobacter.	-	0	-	-	0	0	0	0	0	0	0	0	0	6	6	4/4
Acinetobacter.	-	-	-	-	2	2	2	2	2	2	2	2	2	2	2	2/2
Enterobactor.	-	0	-	-	0	0	0	0	0	0	1	0	0	3	2	1/1
Proteus.	-	0	-	-	0	0	0	0	0	0	0	0	0	2	2	1/1
S.typhii	3	3	3	3	-	-	-	-	-	-	-	3	3	-	-	-
S.par	2	2	2	2	-	-	-	-	-	-	-	2	2	-	-	-
Total N=34	5/5	5/5	5/5	5/5	3/29	5/29	5/29	8/29	4/29	9/29	15/29	7/34	9/34	29/29	26/29	14/14

Table 5. Sensitivity Profile of Gram Positive Isolates

Bacteria	PenicillinG	Ox	Em	G	Ciproflox.	Vanco	Teicoplanin	Linez	Clindamycin
Entero. N=8	1	-	0	7(high level	2	7	7	7	-
S.aurues N=3	0	2	0	3	3	3	2	2	2
Alpha Strep N=2	2	-	2	-	2	2	2	-	2
Total N=13	3/11	2/3	2/11	10/10	7/11	12/12	11/11	9/10	4/4

Patients were young adults and males, which supports the reports from another Indian centre [10]. Typhoid perforation was common in males and occurred most frequently during the early second or even the first week of illness, but not in the third week as Christie described [11,24].

Therapies for patients with intra abdominal infection are divided into:

1) "Source control" or operative treatment and

2) "Supportive measures" that include antibiotics. Operative management is more important than supportive therapy and often includes percutaneous or surgical drainage, debridement, and repair of anatomical pathology. However, antibiotics are often part of the supportive therapy for patient with secondary peritonitis. In addition to antibiotics, fluid resuscitation, hemodynamic monitoring, adequate tissue oxygen delivery, and nutritional and respiratory support are vital components of therapy [12].

Blood culture has been found to detect S. typhi in 44 to 83%of patients [2] with typhoid fever; however, the number of organism, stage of the disease, type of culture medium, incubation period and presence of growth inhibitors in blood limit its usefulness.

E. Coli is the most common isolate in peritoneal fluid cultures. S. Typhi is only occasionally isolated[13]. Peiris et al [14] were able to isolate S. typhi in only 4 out of 25 samples. Inoculating in enrichment medium can increase peritoneal fluid culture yield.

Peiris et al [14] found the highest rate of isolation of S. typhi (74%) was from mesenteric lymph nodes, even after taking antibiotics for as many as five days.

Numerous studies have cast serious doubt on the value of Widal test especially in endemic countries because of high prevalence of antibody titers in healthy adults and Anamanestic response seen in any fever [2,15,16].

The APACHE II score measuring the severity of disease, age, and chronic health status of the patients, is of value in predicting outcome and stratification of patients with intra abdominal infection. It is independently associated with the rate of mortality. For example, patients with an APACHE II score of more than 25 have a risk of death of about 50%[17,18]. The Surgical Infection Society adopted the APACHE II scoring system as the best available (although not ideal) method of risk stratification in intra abdominal infections [19].

Our own experience in using APACHE II triaging to decide the modality of surgery especially in doing ileostomy in most of group II and group III patients and comparing the outcomes with other units in our institute had shown significant reduction in mortality in-group II patients [5].

Most surgeons in order to reduce the degree of bacterial contamination and to remove blood, fecal matter and necrotic tissue perform intra operative peritoneal lavage with saline regularly [6]. The addition of antibiotics to the lavage solution appears to be without clear benefit; the addition of antiseptic may even produce toxic effects [7,8].

It is clear that intra abdominal infections are caused by the presence of bacteria endogenous to the intestinal tract. The micro flora of the intestine is very complex, both in numbers and variety of species present. The small bowel shows increasing numbers of bacteria from jejunum (10^3 to 10^4 CFU/ml) to the lower ileum (10^6 CFU/ml), with a change in composition of flora near the ileocaecal valve. It is in the distal ileum that gram negative species begin to out number gram positive species, with aerobic gram negative organisms consistently present along with anaerobic bacteria such as Bacteroides, Bifidobacterium, fusobacterium, Clostridium and Eubacterium [20].

Although E.coli and B. fragilis are considered the most significant intra abdominal pathogens, the data indicates that this is true of only lower GI spillage. The exception to this pattern was infection caused by ischaemic small bowel, where C. perfrigens and E.coli predominate [21].

As per the guidelines of The Infectious Disease Society of America and The Surgical Infection Society 2003[22], therapy depends on whether intra abdominal infections are community acquired or health care associated.

For community-acquired infections the location of the gastrointestinal perforation defines the infecting flora. Infections beyond proximal ileum are usually caused by a variety of anaerobic microorganisms. Given the activity of common regimens against the anaerobic microorganisms, microbiological work up should be limited to identification and susceptibility testing of facultative and aerobic gram-negative bacilli. These infections may be managed with a variety of single and multiple agent regimens.

For patients with community-acquired infections mild to moderate severity, agents that have a narrower spectrum of activity and that are not routinely used for nosocomial infections, such as cefuroxime plus metronidazole or quinolones plus metronidazole are preferable. Patients with severe infections, as defined by accepted physiological scores, or immuno-suppresed may benefit from regimens with broad spectrum of activity against facultative and aerobic gram-negative organisms, such as meropenem, imipenem/cilastatin, cefotaxime, ceftriaxone, cefipime plus metronidazole, ciprofloxacin plus metronidazole and piperacillin/tazobactum.

Health care associated infections (nosocomial / post operative) are caused by more resistant flora, which may include Pseudomonas aeruginosa, Enterobacter species, Proteus species, methicillin resistant Staphylococcus aureus, enterococci and Candida species. These infections, complex multidrug regimens are recommended.

Local nosocomial resistance patterns should dictate empirical treatment, and treatment should be altered on the basis of the results of a thorough microbiologic workup.

The appropriateness of initial anti-bacterial therapy and the response of surgeons to peritoneal culture results were examined in 480 patients with peritonitis[3]. Patients receiving inappropriate initial antibiotics had worse outcomes than patients receiving appropriate therapy. Montravers et al [23] have reported similar results in 100 patients with postoperative peritonitis.

CONCLUSIONS

*Based on our experience of ileal perforations, microbiological studies to demonstrate the predominant causative organism, it may be infered that even in a tropical country like India which is still endemic for typhoid fever, the ileal perforations behave like secondary peritonitis of any other etiology.

*We strongly recommend use of APACHE II or any other physiological scoring system for triaging patients to decide modality of surgery after adequate resuscitation has been done as residents perform most of these emergency surgeries.

*Antibiotics based on the local pattern of organisms cultured, and not empirical use of anti typhoid drugs, is seen to be more appropriate. Based on our data of sensitivity and IDSA 2003 guidelines we recommend the following pre-operative antibiotics, which should be changed according to cultures.

Despite all these efforts the mortality in-group III patients continues to be high, the answer for which lies probably in better supportive measures like ICU care and a change in the mind set to establish the diagnosis and not assume.

	Group I	Group II	Group III
Antibiotics	Cephalosporins (ceftriaxone, cefotaxime/sulbactum)	Cephalosporins (ceftriaxone, cefotaxime/sulbactum, cefipime) + metronidazole	Cefipime + amino glycosides + metronidazole
	Ciprofloxacin + metronidazole		Piperacillin/ Tazobactum + amino glycosides + metronidazole

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