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ORIGINAL RESEARCH ARTICLE

Diagnosis of enteric fever in the emergency department: a retrospective study from Pakistan

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Abstract
Background Enteric fever is one of the top differential diagnoses of fever in many parts of the world. Generally, the diagnosis is suspected and treatment is initiated based on clinical and basic laboratory parameters.
Aims The present study identifies the clinical and laboratory parameters predicting enteric fever in patients visiting the emergency department of a tertiary care hospital in Pakistan.
Methods This is a retrospective chart review of all adult patients with clinically suspected enteric fever admitted to the hospital through the emergency department during a 5-year period (2000–2005).
Results A total of 421 emergency department patients were admitted to the hospital with suspected enteric fever. There were 53 cases of blood culture-positive enteric fever and 296 disease-negative cases on culture. The mean age in the blood culture-positive group was 27 years (SD: 10) and in the group with negative blood culture for enteric fever, 35 years (SD: 15) with a male to female ratio of 1:0.6 in both groups. Less than half (48%) of all patients admitted with suspected enteric fever had the discharge diagnosis of enteric fever, of which only 13% of the patients had blood culture/serologically confirmed enteric fever. None of the common clinical and laboratory parameters differed between enteric fever-positive patients and those without it.
Conclusion Commonly cited clinical and laboratory parameters were not able to predict enteric fever.

Keywords Enteric fever · Pakistan · Likelihood ratio · Emergency department

Introduction

Enteric fever (EF) encompasses both typhoid and paratyphoid fevers. Typhoid fever is caused by *Salmonella typhi*, whereas paratyphoid fever is caused by *S. paratyphi A*, *B*, and *C* [1]. Occurring largely in low income countries [2, 3], EF causes 16 million illnesses and 600,000 annual deaths worldwide [4]. It is one of the top differential diagnoses in patients with fever without an obvious source in many parts of the world. In high income countries, EF is suspected in patients with fever and recent history of travel to endemic areas [5].

The diagnosis of EF in the emergency department (ED) is based on clinical signs and symptoms, with basic or no laboratory testing. Neither the sensitivity of initial diagnosis by the physician is known nor is the diagnostic accuracy of clinical features used for such a diagnosis. This study explores the sensitivity, specificity, positive predictive value, and negative predictive value of common clinical and laboratory parameters used for diagnosing EF in the ED.

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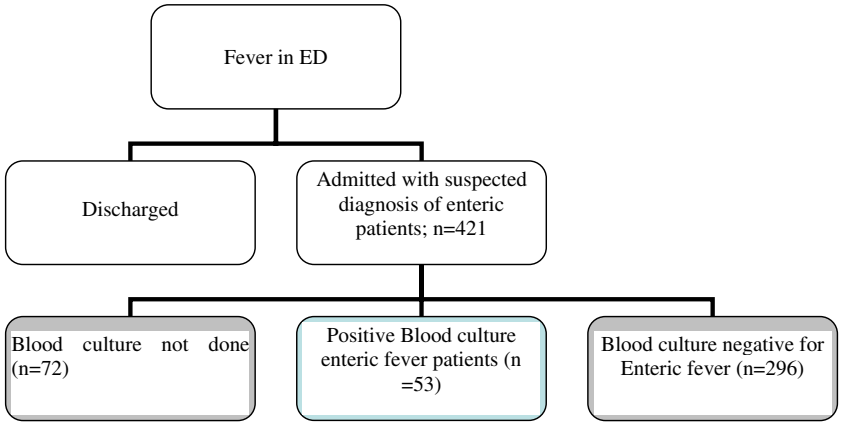

Fig. 1 Enteric patients enrolled in the study from the ED of the hospital (July 2000–June 2005)

Methods

Study design

A retrospective chart review study was conducted.

Study setting and sample

The Aga Khan University Hospital (AKUH) is a private, 540-bed tertiary care teaching hospital, located in Karachi, Pakistan. It is one of the many tertiary care hospitals serving a city of 17 million people. The Emergency Department at AKUH treats about 45,000 patients per year with an admission rate of 35%. Care is primarily provided by residents and medical officers under the supervision of senior faculty members. All patients with an admission diagnosis of suspected EF during the 5-year period (July 2000–June 2005) were included in the study (Fig. 1). The study was approved by the Ethics Review Committee of the Aga Khan University.

Study protocol

The hospital's health information system was used to identify patients admitted to the hospital through the ED with a suspected diagnosis of EF. Medical records were reviewed by trained research assistants. The completed questionnaires were rechecked by the principal investigator for missing information. Information was extracted on: age, gender, presenting signs and symptoms, comorbidities (for example, hypertension and diabetes), and laboratory parameters (for example, hemoglobin, white cell counts, sodium, potassium, and bicarbonate). Diagnosis of typhoid fever was confirmed by blood culture. Blood cultures are the standard diagnostic method. The sensitivity and specificity for identifying blood culture-positive cases of typhoid fever are 89 and 53%, respectively [6, 7].

Data analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 14.0. Descriptive statistics were computed for categorical variables by computing their frequencies. The distribution of quantitative variables was assessed by computing their means and standard deviations. Some of the variables were not included in the analysis due to sparse cell count (for example, coated tongue, confusion, and vertigo). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios (LRs) with 95% confidence intervals (CIs) were calculated using standard formulas taking blood culture-positive typhoid cases as confirmatory tests (Table 1).

Results

A total of 421 ED patients were admitted to the hospital with suspected EF. There were 53 cases of blood culture-positive EF and 296 EF-negative cultures. In 72 cases,

Table 1 Measures of diagnostic test accuracy

Measures
Blood culture-positive EF patients and clinical symptom/sign positive (a)
Blood culture-negative and clinical symptom/sign positive (b)
Blood culture-positive EF patients/clinical symptoms and signs negative (c)
Blood culture-negative and clinical symptoms/signs negative (d)
Sensitivity = (a)/(a) + (c)
Specificity = (d)/(d) + (b)
Positive predictive value = (a)/(a) + (b)
Negative predictive value = (d)/(d) + (c)
+LR = [(Sensitivity)/(1 − Specificity)]
−LR = [(1 − Sensitivity)/Specificity]

Table 2 Comparison of laboratory indices among patients in the different groups (July 2000–June 2005)

Laboratory indices	Blood culture positive for EF, n=53		Blood culture negative for EF, n=296		
	Number	Mean	Number	Mean	p
Hemoglobin (g/dl)	52	13.1	293	13	=0.8
WBC ($\times 10^9$/l)	53	5.3	293	6.7	=0.001
Platelets ($\times 10^9$/l)	52	166	285	178	=0.3
Sodium (mmol/l)	52	134	277	134	=0.9
Potassium (mmol/l)	52	3.7	277	3.8	=0.4
Chloride (mmol/l)	34	103	191	104	=0.06
Bicarbonate (mmol/l)	37	22	197	21.6	=0.5
Creatinine (mg/dl)	47	1.09	255	1.1	=0.8
Urea (mg/dl)	39	15.2	229	12	=0.3

blood cultures were not performed. The mean age in the blood culture-positive group (n=53) was 27 years (SD: 10) and in the blood culture-negative group (n=296), 35 years (SD: 15) with a male to female ratio of 1:0.6 in both groups. The most common presenting symptoms of EF cases and disease-negative cases, respectively, were: vomiting (77%, 54%; p=0.002), abdominal pain (19%, 30%; p=0.1), chills (26%, 30%; p=0.7), diarrhea (17%, 19%; p=0.7), and cough/flu (13%, 21%; p=0.2). The abnormal vital signs reported were: tachycardia (57%, 45%; p=0.1), tachypnea (64%, 55%; p=0.2), and systolic blood pressure >120 (24%, 22%; p=0.6). The mean temperature at presentation in both groups was 38°C (SD: 1) and mean duration of fever was 7 days (SD: 6) in the first group and 14 days (SD: 33) in the second group. On physical examination, dehydration (45%, 33%; p= 0.09), anemia (13%, 23%; p=0.2), and palpable lymph nodes (6%, 5%; p=0.8) were the most common findings in both groups. Hypertension (2%, 10%; p=0.06) and diabetes (4%, 8%; p=0.3) were the most common comorbidities in the EF-positive and EF-negative groups. There were 2 EF cases with abnormal liver function tests (LFTs) compared to 14 in the disease-negative group (p= 0.7). Disseminated intravascular coagulation (DIC) was observed in one EF case compared to none in the disease-negative group. Less than half of the patients had taken antibiotics (penicillin, quinolones, cephalosporin, amino glycosides, sulfonamide, Flagyl, and chloramphenicol) prior to their visit to the ED; the intake percentage in both groups was 41 and 43%; p=0.7. The laboratory

Table 3 Likelihood ratios of clinical and laboratory parameters of blood culture-positive EF (n=53) versus blood culture negative for EF (n=296) (July 2000–June 2005)

Parameters	Sensitivity	Specificity	PPV	NPV	+ LR (95% CI)	− LR (95% CI)
Abdominal pain	0.89	0.17	0.29	0.81	1.08 (0.99–1.18)	0.59 (0.31–1.13)
Epigastric pain	0.03	0.92	0.71	0.14	0.44 (0.14–1.37)	1.04 (0.96–1.13)
Anorexia	0.82	0.15	0.06	0.92	0.97 (0.80–1.17)	1.15 (0.45–2.92)
Vomiting	0.54	0.22	0.79	0.08	0.68 (10.58–0.83)	2.02 (1.21–3.38)
Diarrhea	0. 86	0.15	1.92	0.83	1.02 (0.91–1.13)	0.87 (0.45–1.70)
Chills	0.86	0.15	0.20	0.73	1.01 (0.92–1.12)	0.89 (0.50–1.57)
Cough	0.20	0.86	0.89	0.16	1.56 (0.75–3.22)	0.91(0.81–1.03)
Headache	0.89	0.15	0.11	0.92	1.06 (0.94–1.19)	0.66 (0..25–1.74)
Past history of EF	0.77	0.14	0.04	0.92	0.91 (0.71–1.17)	1.50 (0.60–3.69)
Dehydration	0.33	0.54	0.80	0.12	0.73 (0.52–1.02)	1.22 (0.94–1.58)
Anemia	0.21	0.86	0.9	0.16	1.61 (0.78–3.32)	0.90 (0.80–1.02)
Palpable lymph nodes	0.05	0.94	0.83	0.15	0.89 (0.26–2.98)	1.00(0.93–1.08)
Leukopenia	0.31	0.77	0.88	0.17	1.36 (0.80–2.30)	0.89(0.76–1.05)
Neutropenia	0.31	0.77	0.88	0.16	1.37 (0.81–2.32)	0.89 (0.75–1.05)
Thrombocytopenia	0.42	0.59	0.85	0.15	1.05 (0.74–1.51)	0.95 (0.75–1.22)

results in the ED showed an average WBC count of 5.3 (SD: 2) and 6.6 (SD: 4) × 10^9/l, hemoglobin of 13 (SD: 1 and 2) g/dl, and a platelet count of 166 (SD: 63) and 178 (SD: 107) × 10^9/l (Table 2).

Of all 421 patients suspected of having EF, a little less than half (48%) were discharged with the diagnosis of EF. The diagnoses of the remaining 52% patients were viral fever (21%), malaria (6%), invasive gastroenteritis (5%), urinary tract infection (4%), and upper respiratory tract infection (3%).

Individual clinical and laboratory findings in the ED did poorly in differentiating patients of the two groups. Diarrhea LR (+1.02, 95% CI: 0.91–1.13), dehydration LR (+0.73, 95% CI: 0.52–1.02), leukopenia LR (+1.36, 95% CI: 0.80–2.30), and abdominal pain LR (+1.08, 95% CI: 0.99–1.18) etc. were not able to differentiate between these two groups (Table 3).

Discussion

Our study shows that in an endemic country like Pakistan, about less than half of patients admitted with the diagnosis of suspected EF actually have EF. In non-endemic parts of the world, clinical diagnostic sensitivity is likely to be much lower. In this study, one of the largest ED-based studies, no single clinical or laboratory indicator had a positive LR high enough to help clinical decision-making.

A number of small, non-ED-based studies have looked at the clinical diagnosis of EF. In Indonesia, in a prospective outpatient clinic-based study of 82 pediatric and adult typhoid/paratyphoid patients, Vollaard et al. found a low sensitivity of presenting symptoms. The study failed to find a clinical prediction rule [8]. Similarly, in Nepal, a prospective observational study conducted at a teaching hospital emergency and outpatient department showed that the majority of the symptoms and signs of typhoid in 53 adult cases were without a very high diagnostic accuracy [9]. Many other studies failed to show much difference in the clinical profiles of patients [10–17], though none of these studies evaluated the accuracy of emergency physicians in diagnosing EF.

There were at least two studies where some clinical and laboratory features were found to be highly predictive. In Bangladesh, Haq et al. prospectively studied 106 adult patients with microbiologically confirmed EF comparing them to 170 adult patients with other established febrile illnesses. The study found that history of a stepladder pattern of rise in temperature, loose motions, relative bradycardia, and coated tongue proved to be powerful markers of EF with high specificity (100, 94.7, 94.7, and 94.1%, respectively) [18]. In a study of 130 adult cases, Hosoglu et al. created a prediction rule using seven predictors. These predictors were age <30 years, abdominal distention, confusion, leukopenia, relative bradycardia, positive Widal test, and a typhoid tongue [19]. This prediction rule was validated in the same region where it was developed.

Limitations

There are several limitations of our study. First, this was a single-center study and may not represent the findings at other centers in Karachi or Pakistan. Second, being an ED-based study, our findings are likely to be applicable to more severe cases as only those who required admission to the hospital were included in this study. Third, due to the retrospective nature of the study, we were limited not only by the completeness of documentation by the treating physician but were also not able to assess all the variables (for example, relative bradycardia). Fourth, there may have been other patients with EF admitted through the ED, but because the clinician did not consider this diagnosis at the time of admission they were not included in this analysis. Fifth, a large number of blood culture negatives could be due to the fact that sensitivity of blood cultures decreases after the first week of illness and also due to prior use of an antibiotic.

Conclusion

In endemic settings, accurate diagnosis of EF via clinical and laboratory findings is difficult in an ED of a tertiary care teaching hospital.

Conflicts of interest None.

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