Enteric fever: Diagnostic value of clinical features

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Abstract

Objectives: to evaluate the diagnostic value of clinical symptoms and signs in enteric fever and to propose a clinical diagnostic criterion.

Design: Prospective observational study

Setting: Kathmandu Medical College, Teaching Hospital, Kathmandu, Nepal

Materials and methods: febrile patients with clinical diagnosis of enteric fever were included in the study with the aim of confirming diagnosis with blood culture, or bone marrow culture and evaluating the diagnostic accuracy of various clinical signs and symptoms.

Results: 64% of the clinically diagnosed cases had blood/ bone marrow culture positive. The diagnostic accuracy of the various symptoms and signs excluding fever was between 42%-75.5%. Majority of the symptom and sign did not have very high diagnostic accuracy. Hence a diagnostic criterion was proposed and clinical features with diagnostic accuracy more than 50% were taken into consideration. Major criteria included fever with diagnostic accuracy of 64%, headache with accuracy of 75.5% and relative bradycardia with an accuracy of 66%. Minor criteria included vomiting, diarrhoea, Splenomegaly, chills and abdominal pain /discomfort with diagnostic accuracy of 57%, 55%, 55%, 53% and 51% respectively. Finally after combination of various major and minor criteria a final diagnostic criterion was proposed having an accuracy of 66% and including both major and minor clinical symptom and sign.

Conclusion: clinical diagnosis of enteric fever will be very helpful in a country like ours. Though none of the clinical symptoms and sign have very high diagnostic accuracy a diagnostic criteria may be helpful. Criteria including both major and minor signs and symptoms would be the most appropriate diagnostic tool as it includes the important abdominal symptoms and signs of enteric fever.

Key words: enteric fever, clinical features, diagnostic criteria

Enteric fever is a very common diagnosis for any fever coming to a general practitioner in the developing countries[1, 2,3]. Laboratory confirmation of diagnosis is not always feasible as it is either unavailable or unaffordable for the majority of our lower socio-economic class that bears the brunt of the disease. Hence clinical diagnosis is still important for us. Typhoid fever has a characteristic clinical syndrome, which differs clinically and pathologically from other septicemias by gram-negative bacteria[4]. However in country like ours where enteric fever is endemic, all fever more than a few days duration is considered to be enteric fever and treated. A large study done by Murdoch et al in Nepal [5]has shown that in only 25% of the 332 persons with clinical diagnosis of enteric fever, blood culture was positive and other diseases like rickettsial fever, leptospiral fever were also found to be prevalent. Hence confirmation of clinical diagnosis is important. Clinical features of typhoid fever have not changed much and are similar to those described at the beginning of the 20th century[6]. It can be still argued

that clinical diagnosis can be considered to be important. However there is no objective data on the value of individual signs and symptoms in diagnosis of enteric fever[7]. Hence we have done this study with an aim of evaluating the diagnostic value of clinical symptoms and signs. The objective was to determine the diagnostic accuracy of clinical features in diagnosis of enteric fever and to propose a clinical diagnostic criterion.

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Materials and methods

Patients admitted in the medical wards of Kathmandu Medical College Teaching Hospital from April 2004 to August 2005with provisional clinical diagnosis of enteric fever were included in the study. Admission was both from the emergency and medical outpatient department. The medical officer on duty filled the preformed performa that included all the known signs and symptoms of enteric fever[8] and also noted additional symptoms volunteered by the patients and not included on the performa. Symptom like cough and sore throat that was present in only one patient was not mentioned in the result. Two doctors noted clinical signs at presentation- on the day of the admission by the medical officer on duty and the next day the consultant who confirmed the findings. Similarly the medical officer sent blood for culture and sensitivity on the day of admission. If the patient was already on antibiotic a bone marrow culture was also sent on the day of admission. Patients with a prior blood culture diagnosis of enteric fever were excluded from the study. Blood culture and sensitivity was performed in the microbiology laboratory under department of pathology of KMCTH. In all the patients the symptoms and signs that were present were noted and for each, sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy[9] of the clinical features were calculated taking blood culture positive as the true positive or gold standard as shown. A Receiver-Operating Characteristic Curve (ROC) was plotted with sensitivity as Y-axis and 1-specificity as X-axis for each symptom and sign[10].

The signs and symptoms with accuracy more than 50% and lying above the 45-degree line of the ROC were taken as significant.

Measures of diagnostic test accuracy

Blood culture positive and clinical symptom and sign positive= true positive (a)

Blood culture negative and clinical symptom and sign positive= false positive (b)

Blood culture positive and signs symptoms negative= false negative (c)

Blood culture negative and clinical signs and symptoms negative= true negative (d)

Prevalence $=a+c/a+b+c+d$

Sensitivity = true positive (a)/ true positive (a)+false negative(c)

Specificity= true negative (d)/ true negative (d)+false positive (b)

Positive predictive value= true positive (a) / true positive (a) + false positive (b)

Negative predictive value= true negative (d)/ true negative (d) +false negative (c)

Overall diagnostic accuracy= a+d/ a+b+c+d [9]

Statistical analysis was done using Pearson's χ^2 test with Yate's correction wherever applicable.

Results
Table 1: Patient profile

Characteristics	n=(%)	
Age (mean+ SD)	26.87±12.06	
Duration (mean+ SD)	10 ± 4.87	
Sex M: F	1.2:1	
Culture pattern		
Positive	34 (64.2)	
Blood	33	
Bone marrow	1	
Negative	19 (35.8)	
Total	53	
Frequency of symptoms	**Present**	**Absent**
Fever	53 (100)	00
Headache	41 (77)	12 (23)
Chills	39 (73)	14 (27)
Rigor	26 (49)	27 (51)
Constipation	7 (13)	46 (87)
Diarrhoea	24 (43)	29 (57)
Abdominal discomfort/pain	28 (53)	25 (47)
Distension of abdomen	4 (7.5)	49 (92.5)
Black stool	4 (7.5)	49 (92.5)
Vomiting	12 (22)	41 (78)
Dysuria	15 (28)	38 (72)
Myalgia	21 (39)	32 (61)
Loss of appetite	37 (69)	16 (31)
Frequency of signs	**Present**	**Absent**
Coated tongue	18 (34)	35 (66)
Relative bradycardia	40 (75)	13 (25)
Splenomegaly	30 (57)	23 (43)
Caecal gurgling	4 (7.5)	49 (92.5
Tender abdomen	4 (7.5)	49 (92.5)
Altered mentation	4 (7.5)	49 (92.5
Toxic look	5 (9.4)	48 (90.6)

Table 2: Presenting symptoms with results of blood culture

Symptoms	Blood Culture Positive Symptom positive n=(%) (a)	Blood Culture Negative symptom positive n =(%) (b)	Blood culture positive symptom negative n =(%) (c)	Blood culture negative symptom negative n =(%) (d)
Fever	34	19	0	0
Headache	31 (58.5)	10 (18.8)	3 (5.66)	9 (17)
Chills	24 (45.3)	15 (28.3)	10 (18.9)	4 (7.5)
Rigor	15 (28.3)	11 (20.8)	18 (33.9)	9 (17)
Constipation	5 (9.4)	2 (3.7)	28 (52.9)	18 (33.9)
Diarrhea	16 (30.2)	8 (15.1)	16 (30.2)	13 (24.5)
Myalgia	13 (24.5)	8 (15.1)	20 (37.7)	12 (22.7)
Distension of abdomen	3 (5.66)	1 (1.9)	31 (58.5)	18 (33.9)
Black stool	4 (7.5)	0	30 (56.7)	19 (35.8)
Vomiting	11 (20.8)	1 (1.9)	23 (43.4)	18 (33.96)
Dysuria	8 (15.1)	4 (7.5)	26 (49)	15 (28.4)
Pain abdomen	18 (33.96)	10 (18.9)	16 (30.2)	9 (16.98)
Loss of appetite	19 (35.8)	18 (33.96)	15 (28.4)	1 (1.9)

Table3: Presenting signs of the patients with results of blood culture

Signs	Blood Culture positive sign Positive (a)	Blood Culture negative sign positive (b)	Blood Culture positive sign negative (c)	Blood Culture negative sign negative (d)
Coated tongue	11(20.8)	7(13.2)	23(43.4)	12((22.6)
Relative bradycardia	28(52.8)	12(22.6)	6(11.3)	7(13.2)
Splenomegaly	20(38)	10(18.9)	14(26.4)	9(16.9)
Feel of abdomen (gurgling)	3(5.6)	0	31(58.5)	19(35.8)
Tenderness of abdomen	4(7.5)	0	30(56.6)	19(35.8)
Toxic look	4(7.5)	1(1.2)	30(56.6)	18(33.96)
Altered mentation	4 (7.5)	1 (1.9%)	30 (56.7%)	18 (33.96%)

Table 4: Diagnostic value of the clinical features

Symptoms At presentation	Sensitivity a/a+c %	Specificity d/d+b %	Positive predictive value a/a+b %	Negative predictive value d/d+c %	Overall Accuracy a+d/a+b+c+d in %
Fever	100	0	100	0	64%
Headache	91	47	75.6	75	75 .5%
Chills	71	21	62	28	53%
Rigor	45	45	58	33	45%
Myalgia	39.4	60	62	38	47%
Diarrhoea	50	62	66.7	44.8	55%
Distension	9	95	75	37	40%
Vomiting	32.4	95	91	44	55%
Constipation	15	90	72	39	43%
Blood in stool	12	100	100	39	43 %
Dysuria	23	79	67	37	43%
Pain abdomen	53	47.4	64	36	51%
Loss of appetite	56	5.26	51	6.3	38%
Signs at presentation					
Coated tongue	32	63	61	34	43%
Relative bradycardia	82	37	70	54	66%
Splenomegaly	59	47	66	39	55%
Altered mentation	12	100	100	39	43%
Feel of the abdomen	57	100	100	38	43%
Caecal gurgling	9	100	100	38	42%
Tenderness	12	100	100	39	43%
Toxic look	12	95	80	38	41

Table 5: True positive and False negative rate

| Symptoms at presentation	Sensitivity (True positive rate) %	1-Specificity (False positive rate) %
Fever	100	0
Headache	91	53
Chills	71	79
Rigor	45	55
Myalgia	39.4	40
Diarrhoea	50	38
Distension	9	6
Vomiting	32.4	6
Constipation	15	10
Blood in stool	12	0
Dysuria	23	21
Pain Abdomen	53	53
Loss of appetite	56	95
Signs at presentation		
Coated tongue	32	37
Relative bradycardia	82	63
Splenomegaly	59	53
Altered mentation	12	0
Feel of the abdomen		
Caecal gurgling	9	0
Tenderness	12	0
Toxic look	12	5

Receiver Operating Curve (ROC)
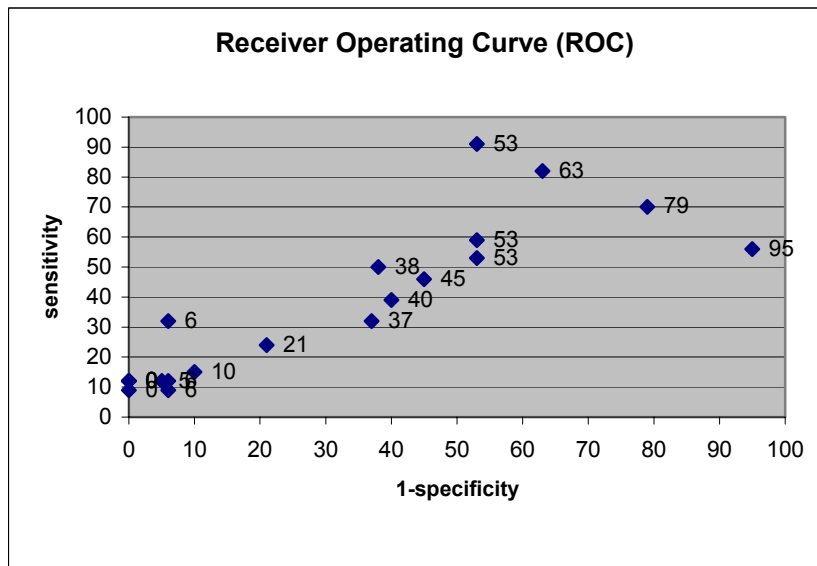
Table 6: Clinical features with diagnostic accuracy of >50%

Major criteria Accuracy >60%	Minor criteria Accuracy >50%	Proposal for Diagnosis of enteric fever
Fever (64%)	Vomiting (57%)	1.Three major 2.Three major plus three minor
Headache (75.5%%)	Splenomegaly (55%)	3.three major plus 2 minor
Relative bradycardia (66%)	Diarrhoea (55%)	4. Two major plus three minor
	Chills (53%)	5.Two major plus one minor
	Pain Abdomen (51%)	

Table 7: Diagnostic accuracy of the proposed criterion

Criterion	Sensitivity	Specificity	Positive predictive value with 95% CI= ( )%	Negative predictive value with 95% CI=( )%	Diagnostic accuracy
A	98.79%	52.63%	74.28% (57.93-85.83)	58% (36.005-78.38)	69.23%
B	58.9%	78.95%	83.33 % (64-93)%	51.7% (34.4-68.6)	66%
C	69.7%	50%	69.7% (52.66-82.62)	50% (29.92-70.70)	62%
D	42.427%	85%	82.4% (58.9-93.8)%	47.22% (31.9-62)	58.5%
E	60.6%	70%	76.92% (57.9-88.9)%	51.9% (33.95-69.4)%	64.15%
F	93.94%	15%	64.58%(50.43-76.6)	60%(23.7-88.23)	64.2%

Comparison of diagnostic value of individual symptom and sign was done using a receiver-operating characteristic curve plotted between sensitivity in Y-axis and 1-specificity as X-axis.

Majority of the sign and symptom did not have very high diagnostic accuracy and were lying around the 45degree line of ROC. Hence a diagnostic criterion is proposed with symptom/sign with accuracy of more than 60% and lying above the 45 degree line of ROC [10] as major criteria and those with accuracy more than 50% and lying above the 45 degree line of ROC as minor criteria.

Criterion A and B have good diagnostic accuracy. Criterion B incorporates gastrointestinal features[8, 9] considered to be very important in diagnosis of enteric fever and hence appears most appropriate diagnostic criteria.

Discussion
According to Manson's Tropical Diseases[11], third edition, the five cardinal features of enteric fever are fever, relative bradycardia, toxaemia, splenic enlargement and rose spots. The first three followed by abdominal distension, pea soup diarrhoea and intestinal hemorrhage should confirm the diagnosis of the disease. Unfortunately in its new edition the paragraph on diagnosis does not include clinical features at all[12]. Though some studies have shown that clinical diagnosis is not always useful other studies confirm the persistence of these clinical features of enteric fever[13,14,15,16]. In a study done by Haq SA et al symptoms and signs like step ladder rise in temperature, loose motions, relative bradycardia and coated tongue had high specificity (100%, 94.71%, 94.71%, 94.12%) and predictive values[7]. Another study has concluded that the clinical features were that of febrile gastroenteritis with headache[17]. Yet another study has made the conclusion that headache, pain abdomen, nausea, anorexia and fever were the most common clinical feature of enteric[14]. A

recent study done in Nepal says that fever, chills, cough and pain abdomen were the common presenting symptoms and Splenomegaly was present in only 2.7 % of cases[18]. Though various studies have again and again emphasized the persistence of these clinical features [19,20,21], none have given objective data on the value of individual symptoms and signs. Our study fulfills this objective. In our study 64% (n=34) of the patients diagnosed clinically had disease. But majority of the symptoms and signs in our study did not have very high predictive accuracy. Symptoms like headache, chills and relative bradycardia had very high sensitivity and positive predictive value but lacked specificity. Similarly abdominal distention, vomiting, constipation, altered mentation, Caecal gurgling and abdominal tenderness on palpation had very high specificity but low positive predictive value and sensitivity. Hence we have proposed diagnostic criterion to include important time tested clinical features for clinical diagnosis of enteric fever. Criterion B in-cooperates all the important clinical features of enteric fever and has good specificity (78.9%), sensitivity (58.8%) and positive predictive value (83%). Hence appears most useful for clinical diagnosis. Criteria A that includes all the major criteria has better diagnostic accuracy but lacks any gastrointestinal features considered important in diagnosis of enteric fever. Moreover when criteria B was applied for clinical diagnosis versus blood culture the p value was < .01(χ^2 =7.4 with df=1) i.e. statistically significant. Hence we want to highlight the usefulness of clinical diagnosis of enteric fever and usefulness of diagnostic criteria. This will help people in areas were laboratory facilities are not there and also make empirical therapy which is the most used form of therapy in our country, more scientific. However we want to emphasize the preliminary nature of this conclusion and want to inform that we have an ongoing study that is applying the diagnostic criteria.

Conclusion

Enteric fever is a commonly diagnosed febrile illness. Clinical diagnostic criteria will be very useful to lessen our dependence on time consuming expensive laboratory tests. Hence we propose clinical diagnostic criteria that can be utilized for diagnostic purpose.

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