DIAGNOSING ENTERIC FEVER: A REAPPRAISAL

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INTRODUCTION

The diagnosis of enteric fever (EF) is mainly a clinical diagnosis confirmed whenever possible by bacteriological culture (Parry, 1979). Upto half the patients diagnosed as having EF can be culture negative (Sangpetchsong *et al.*, 1983). This may be due to, for example, the relative insensitivity of blood culture or partial treatment with antibiotics (Cook 1980; Escamilla *et al.*, 1984).

To help the clinician diagnosis, textbooks sometimes list 20 or more clinical and laboratory events associated with EF (Foote *et al.*, 1979). However, the diagnostic value of some of these events, particularly the Widal test, has been questioned (Zuerlein *et al.*, 1985).

The objective of this study was to determine which of these events were useful in discriminating EF from other causes of fever.

MATERIALS AND METHODS

Data were collected over an 18 month period from patients admitted to the University hospital with undiagnosed fever. Criteria for entrance into this study group were (i) a differential diagnosis list that included EF, (ii) the absence of a diagnosis of EF relapse, (iii) failure to exclude the diagnosis of EF by 24 hours after admission and (iv) the performance of blood and stool cultures. Application of criterium (iii) allowed exclusion of easily diagnosed causes of fever like malaria or tuberculosis.

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Cases of EF were derived from a consecutive sample of 150 patients. The 'gold standard' for EF was either a positive blood and/or stool culture for *S. typhi*, *S. paratyphi* A or *S. paratyphi* B, or a fourfold rise in the Widal O agglutinin titre in paired sera from a clinically diagnosed patient. Controls consisted of a random sample of 150 patients with other causes of fever. The latter group included diagnoses such as viral fever, shigellosis or tumour-related fever.

The results of 11 dichotomous and 8 numerical variables, said to be associated with EF (Kong, 1976; Foote *et al.*, 1979; Nelson, 1982; Nye, 1982), were recorded (Tables 1 and 2). The datum recorded for each variable, was the first obtained during the first 24 hours after admission.

The Widal test was performed using a tube agglutination technique with an initial screening dilution of 1 : 40 (Wellcome Diagnostics, United Kingdom). Titres less than this value were arbitrarily titred as 1 : 20.

Statistical analysis : To reduce the variable set to a manageable size for logistic regression analysis, x^2 testing was performed on dichotomous variables from an initial group of cases and controls. This eliminated 8 variables with the least value as predictors of EF.

The remaining 11 variables were related to the risk of EF by logistic regression analysis using the equation below.

$$\text{In } p_x/q_x = b_o + b_1x_1, \ldots \sum_{i=2}^{11} b_i x_i$$

Where In $p_x = q_x$ was the log odds of EF in the presence of the variables x_1, ..., x_{11},

Table 1

Frequency (expressed as percentage) of 8 variables recorded in EF cases and controls.

Variable	EF	Controls	Other Studies*
	n = 73**	n = 73	
Cough	37	29	11 to 86%
Acute coryza/sore throat	6	14	6 to 84%
Arthralgia	1	7	7 to 54%
Abdominal pain	35	21	19 to 84%
Diarrhoea	42	27	17 to 68%
Lymphadenopathy	7	8	
Lymphocytosis > 53%	19	12	Lymphocytosis
Relative bradycardia***	61	51	11 to 100%

* The frequencies reported from other studies of EF are also given. (Kong, 1976; Foote *et al.* 1979; Nelson, 1982; Nye, 1982).

** No significant diference between EF cases and controls, $X^2 < 7.2$ adjusted for multiple comparisons.

*** Seventy adult patients (>12 years) and their controls, $X^2 = 1.1$ $p > 0.05$.

Table 2

Maximum likelihood estimates of logistic parameters relating the risk of EF to 11 variables.

Variable	Coefficient	Standardized Coefficient
x_0 intercept	1.934	
x_1 age (years)	− 0.017*	− 0.261
x_2 duration of fever (days)	0.009+	0.072
x_3 hepatomegaly (coded 0 = no, 1 = yes)	− 0.003+	− 0.002
x_4 splenomegaly (coded 0 = no, 1 = yes)	0.102+	0.041
x_5 fever peak in first 24 hours (tenths of a degree above 37°C)	0.067*	0.611
x_6 fever pattern (coded 0 = intermittent, 1 = remittent or sustained)	0.486*	0.243
x_7 white blood cell count (per $1 \times 10^6/1$)	− 0.187*	− 0.901
x_8 Widal O agglutinins *S. typhi* (scored −4 = 1:20, −3 = 1:40, −2 = 1:80, −1 = 1:160, 0 = 1:320, −1 = 1:640, 2 = 1:1280, 3 = 1:2560, 4 = 1:5120)	0.418*	0.587
x_9 Widal H agglutinins *S. typhi* (scored as x_8)	0.362*	0.775
x_{10} Widal H agglutinins *S. paratyphi* A (scored as x_8)	0.644*	0.515
x_{11} Widal H agglutinins *S. paratyphi* B (scored x_8)	− 0.728*	-0.333
Maximized log likelihood	− 425	

* $X^2 > 11$, degrees of freedom = 1, $p < 0.001$.

\+ Not significantly different from zero.

b_o was the intercept, b_1, ..., b_{11} the logistic parameters for each variable and x_1, ..., x_{11} the variables defined according to Table 2. The likelihood ratio test was used to test the significance of each regression coefficient (Schlesselman, 1982). The relative importance of these variables compared to each other was determined by ranking their standardized coefficients (Schlesslman, 1982).

RESULTS

There were 135 cases of *S. typhi*, 14 cases of *S. paratyphi A* and 1 case of *S. paratyphi* B. One hundred and thirty eight of these patients were culture positive. Eight of the dichotomous variables did not show a significant association with EF (Table 1). These variables were not furthur analysed.

The logistic regression model provided a good fit for the remaining 11 variables (x^2= 12. degrees of freedom = 8, $p > 0.05$) (Table 2), Eight variables had a significant, positive association with EF. These were, in order of importance, (i) a decreased white blood cell count, (ii) a raised *S. typhi* H agglutinin titre, (iii) a raised body temperature, (iv) a raised *S. typhi* O agglutinin titre, (v) a raised *S. paratyphi* A H agglutinin titre, (vi) a low *S. paratyphi* B H agglutinin titre, (vii) a young age and (viii) a non-intermittent fever pattern.

The relative importance of these variables and the relative odds of EF for a unit change in each variable, are shown in Table 3.

DISCUSSION

This study highlights events that can be used to distinguish EF from other causes of fever.

The ability to diagnose EF without knowledge of culture results is important for the following reasons; (i) blood culture incubation

Table 3

Relative odds of EF for each predictor variable. The variables are listed in decreasing order of importance.

Variable	Odds Ratio	Other Studies*
White blood cell count	0.83 (0.75-0.91)	leucopenia usual
Widal H agglutinins *S. typhi*	1.44 (1.20-1.72)	'not of value'
Peak temperature	1.07 (1.03-1.11)	fever > 39°C
Widal O agglutinins *S. typhi*	1.52 (1.14-2.03)	'least reliable method of diagnosis'
Widal H agglutinins *S. paratyphi* A	1.90 (1.12-3.25)	
Widal H agglutinins *S. typhi* B	0.48 (0.21-1.12)	
Age	0.98 (0.96-1.00)	75% of cases < 30 years
Fever type	1.63 (0.88-3.00)	Remittent fever

Values in parenthesis represent the 95% confidence interval.

* Assessments from other studies are also given (Kong, 1976; Foote *et al.*, 1979; Nelson, 1982; Nye, 1982).

can take from 1 to 21 days before yielding salmonella (Escamilla *et al.*, 1984), (ii) culture negative cases must be expected, unless more invasive, but often culturally unacceptable, tests like bone marrow or duodenal string capsule cultures are routinely performed (Cook, 1980), and (iii) confirmation of culture negative EF cases through either solitary or rising Widal agglutinin titres is unreliable (Kong, 1976).

Many of the manifestations of EF described in modern articles on EF, are subjective and of unproven value in diagnosis, for example, typhoid odour (Nelson, 1982). In our analysis there was no significant association with EF for 11, commonly cited events.

We have previously reported that a small number of objective, categorical variables can be used in Bayes' theorem to assist in the diagnosis of EF (Ross and Abraham, in press). Nevertheless, much of the value of numerical variables can be lost when transformed to a categorical form. For example, only 24% of EF cases had a leucopenia (normal WBC range $4.5\text{-}11\times10^6/1$), but the odds of EF in a febrile patient with a 'normal' count of $5\times10^6/1$ were three fold higher than the odds in a corresponding individual with a count of $10\times10^6/1$. Similar information was obtainable from the absolute value of the variables age and temperature.

The Widal O agglutination test has been described as the least reliable method of diagnosis (Nye, 1982), whilst, the H agglutinin titre has been dismissed as of no value in diagnosis (Foote, 1979). Despite this, the Widal H agglutinin titre for *S. typhi* was the second most important predictor of EF in our patients. Furthermore, the Widal test gave quantitative information in that the relative odds of EF increased by 44% for each rise in *S. tyhpi* H agglutinin titre. The superiority of H titres over O titres noted here, was also seen in the 1964 Aberdeen typhoid outbreak (Parry, 1979). The reduced odds of EF with a raised *S. paratyphi* B H agglutinin titre were due to the rarity of *S. paratyphi* B infection and a greater number of controls having background titres to this agglutinin than EF cases.

The findings of this study reflect EF manifested in our population. Nevertheless, they suggest that a probablistic diagnosis of EF might be made through logistic regression of a small number of objective, measured variables. This technique might also provide a more accurate way of confirming culture negative EF for epidemiological purposes.

SUMMARY

The diagnostic value of 19 clinical and laboratory events was assessed in 150 enteric fever cases. A logistic regession analysis revealed only 8 predicitive variables for the presence or absence of enteric fever. These were, in order of importance, (i) the white blood cell count, (ii) the *S. typhi* H agglutinin titre, (iii) body temperature, (iv) the *S. typhi* O agglutinin titre, (v) the *S. paratyphi* A H agglutinin titre, (vi) the *S. paratyphi* B H agglutinin titre, (vii) age and (viii) the fever pattern.

This study showed that objective variables like the Widal titres were useful in predicting enteric fever, whilst symptoms such as abdominal pain were unhelpful. Use of all 8 variables to calculate the probability of enteric fever might provide an accurate method of diagnosing or confirming enteric fever when culture results are unavailable or negative.

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