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Value of a Single-Tube Widal Test in Diagnosis of Typhoid Fever in Vietnam

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The diagnostic value of an acute-phase single-tube Widal test for suspected typhoid fever was evaluated with 2,000 Vietnamese patients admitted to an infectious disease referral hospital between 1993 and 1998. Test patients had suspected typhoid fever and a blood culture positive for *Salmonella typhi* ($n = 1,400$) or *Salmonella paratyphi* A ($n = 45$). Control patients had a febrile illness for which another cause was confirmed (malaria [$n = 103$], dengue [$n = 76$], or bacteremia due to another microorganism [$n = 156$] or tetanus ($n = 265$). An O-agglutinin titer of ≥100 was found in 18% of the febrile controls and 7% of the tetanus patients. Corresponding values for H agglutinins were 8 and 1%, respectively. The O-agglutinin titer was ≥100 in 83% of the blood culture-positive typhoid fever cases, and the H-agglutinin titer was ≥100 in 67%. The disease prevalence in investigated patients in this hospital was 30.8% (95% confidence interval, 26.8 to 35.1%); at this prevalence, an elevated level of H agglutinins gave better positive predictive values for typhoid fever than did O agglutinins. With a cutoff titer of ≥200 for O agglutinin or ≥100 for H agglutinin, the Widal test would diagnose correctly 74% of the blood culture-positive cases of typhoid fever. However, 14% of the positive results would be false-positive, and 10% of the negative results would be false-negative. The Widal test can be helpful in the laboratory diagnosis of typhoid fever in Vietnam if interpreted with care.

The signs and symptoms of uncomplicated typhoid fever are nonspecific, and an accurate diagnosis on clinical grounds alone is difficult (9). Although a definitive diagnosis can be made by isolation of *Salmonella typhi* from blood or bone marrow (10), in areas of endemicity, such as Vietnam, bacterial culture facilities are often unavailable and the Widal test is the only specific diagnostic investigation tool available. The Widal test has been in use for more than a century as an aid in the diagnosis of typhoid fever (7, 26). It is a tube dilution test which measures agglutinating antibodies against the lipopolysaccharide O and protein flagellar H antigens of *S. typhi*. The value of the test for the diagnosis of typhoid fever has been debated for as many years as it has been available (1, 15, 20). There is no consensus concerning diagnostic criteria for interpreting the test. Serological diagnosis relies classically on the demonstration of a rising titer of antibodies in paired samples 10 to 14 days apart. In typhoid fever, however, such a rise is not always demonstrable, even in blood culture-confirmed cases. This situation may occur because the acute-phase sample was obtained late in the natural history of the disease, because of high levels of background antibodies in a region of endemicity, or because in some individuals the antibody response is blunted by the early administration of an antibiotic (20). Furthermore, patient management cannot wait for results obtained with a convalescent-phase sample. For practical purposes, a treatment decision must be made on the basis of the results obtained with a single acute-phase sample. The cutoff for positivity chosen in a particular community depends on the background level of typhoid fever (i.e., the prior probability) and the level of typhoid vaccination, which may vary with time (4). The resulting Widal result may lack sensitivity and specificity, particularly in a community with endemic typhoid fever (12). Typhoid fever has been endemic in Vietnam for many years. We have evaluated the value of a single acute-phase Widal result for the diagnosis of typhoid fever in Vietnam.

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MATERIALS AND METHODS

Study groups. The Centre for Tropical Diseases (CTD), Cho Quan Hospital, Ho Chi Minh City, Vietnam, is a 500-bed infectious diseases referral center for southern Vietnam. Prospective studies of typhoid fever, septicemia, malaria, dengue, and tetanus have been in progress at the CTD since 1991. The following groups of patients admitted to CTD between May 1993 and January 1998 were studied.

(i) Group 1 (typhoid fever cases). A total of 1,400 patients with suspected enteric fever investigated with a blood culture and a Widal test had *S. typhi* subsequently isolated from the blood culture. Information concerning the duration of illness before admission, history of prior antibiotic therapy, and outcome was available for 500 of these patients.

(ii) Group 2 (paratyphoid fever cases). A total of 45 patients with suspected enteric fever investigated with a blood culture and a Widal test had *S. paratyphi* A subsequently isolated from the blood culture.

(iii) Group 3 (febrile controls). A total of 290 patients had a febrile illness other than typhoid fever. This group included 103 adults with severe falciparum malaria and a negative blood culture; 76 children with a clinical diagnosis of dengue fever confirmed by positive dengue virus-specific IgM and IgG results (Dengue Rapid Test; PanBio, Windsor, Queensland, Australia) and whose symptoms resolved without antibiotic therapy; and 156 patients with possible typhoid fever investigated with a blood culture and a Widal test but in whom a bacterium or fungus other than *S. typhi* was isolated from the blood culture. The bacteria isolated (number) were *Escherichia coli* (45), *Klebsiella* spp. (9), *Salmonella cholerasuis* (5), other *Salmonella* spp. (5), *Pseudomonas aeruginosa* (3), *Acinetobacter* spp. (2), *Aeromonas hydrophila* (1), *Proteus mirabilis* (1), *Burkholderia pseudomallei* (1), beta-hemolytic streptococci (13), other streptococci (8), *Staphylococcus aureus* (15), *Cryptococcus neoformans* (2), and *Penicillium marneffei* (1).

(iv) Group 4 (other controls). A total of 265 adults and children were admitted to the hospital with tetanus.

The microbiology laboratory records were examined for the period from Feb-

TABLE 1. O and H agglutinins in each group of patients[a]

Group (no. of patients)	*S. typhi* antigen	No. (%) of sera showing the following reciprocal antibody titer:					
		0	100	200	400	800	>800
1 (1,400)	O	236 (17)	475 (34)	425 (30)	190 (14)	72 (5)	2
	H	456 (33)	315 (23)	232 (16)	190 (14)	115 (8)	92 (6)
	O or H	175 (13)	390 (28)	369 (26)	234 (17)	139 (10)	93 (6)
2 (45)	O	21 (47)	15 (33)	7 (16)	2	0	0
	H	35 (78)	4 (9)	3 (7)	1	2	0
	O or H	21 (47)	14 (31)	6 (13)	2	2	0
3 (290)	O	272 (82)	44 (13)	15 (4)	4 (1)	0	0
	H	307 (92)	18 (5)	4 (1)	2	3	1
	O or H	264 (79)	49 (15)	14 (4)	4 (1)	3	1
4 (265)	O	245 (93)	16 (6)	3 (1)	1	0	0
	H	262 (99)	3 (1)	0	0	0	0
	O or H	242 (92)	19 (7)	3 (1)	1	0	0

[a] For "O or H" entries, the patient's highest titer is shown.

ruary 1998 to May 1998 to find the proportion of 500 patients with suspected typhoid fever who had both a blood culture and a Widal test performed and in whom typhoid fever was subsequently confirmed by the isolation of *S. typhi* from the blood culture. This examination was done to provide an estimate of the prevalence of typhoid fever in the local population of patients being investigated to use in the calculation of the positive and negative predictive values of the Widal test.

Blood cultures were performed and cultured organisms were identified by customary methods (14). The Widal test was performed with standardized *S. typhi* O and H antigens (Sanofi Diagnostics Pasteur, Marnes la Coquette, France). Serial dilutions of sera starting at a dilution of 1:100 were made with 0.9% saline. Tubes containing O and H antigens and sera were incubated at 37°C for 1 h, centrifuged at 1,411 × *g* for 5 min, and examined for visible agglutination. Appropriate positive and negative control sera were included. The Widal test was performed as part of the routine diagnostic service of the laboratory by the laboratory scientific staff on rotation.

Analysis. Sensitivity (true-positive rate) was defined as the probability that the Widal test result would be positive when blood culture confirmed that typhoid fever was present (group 1). Specificity (true-negative rate) was the probability that the Widal test result would be negative when typhoid fever was not present (groups 3 and 4). Although the clinical features and management of paratyphoid fever are similar to those of typhoid fever, group 2 was not used for the calculations of sensitivity, specificity, and predictive value. The Mann-Whitney U test was used for the comparison of continuous variables, and the chi-square test with Yates' correction was used for categorical variables (SPSS for Windows version 7.5.1; SPSS Inc., Chicago, Ill.). The positive predictive value was the probability that typhoid was present when the test was positive, and the negative predictive value was the probability that typhoid was not present when the test was negative. Although the sensitivity and specificity were not affected by the prevalence of typhoid fever, the predictive values depended strongly on the prevalence. The predictive values could be calculated by use of the prevalence of typhoid fever in the population being investigated (p), with the following formulae: positive predictive value = (sensitivity) × p)/{(sensitivity × p) + [(1 − specificity)(1 − p)]} and negative predictive value = [specificity × (1 − p)]/{[(specificity × 1 − p)] + [(1 − sensitivity) × p]}.

RESULTS

The median (95% confidence interval [range]) age of the patients was significantly lower in the typhoid fever group, 17 (4 to 38 [1 to 68]) years, than in the control group, 23 (6 to 70 [1 to 90]) years ($P < 0.001$). The Widal titers for the four groups of patients are shown in Table 1. The detailed Widal test results for the febrile control patients are shown in Table 2. The cases (group 1) and controls (group 3 and 4) were subdivided into children (<15 years old) and adults (≥15 years old), and the sensitivity and specificity at various cutoff values were calculated (Table 3). The test was more sensitive for children than for adults at each cutoff for both O and H antigens but was less specific at O- and H-antigen titers of 100. In adults, the sensitivity for both O and H antigens increased with the duration of illness before admission (P, 0.01). This finding was not seen in children. There was no significant relationship between the Widal test results and a history of prior antibiotic therapy.

Examination of the microbiology laboratory records showed that 154 of 500 (30.8%; 95% confidence interval, 26.8 to 35.1%) consecutive patients admitted to the hospital and investigated with a blood culture and a Widal test had a blood culture positive for *S. typhi*. The positive predictive and negative predictive values for the O- and H-antigen titers were

TABLE 2. Widal test results for the febrile control patients

Organism(s) (no.)	*S. typhi* antigen	No. of organisms for which the titer was as follows:				
		0	100	200	400	1,600
Acinetobacter spp. (2)	O	2				
	H	2				
Aeromonas spp. (1)	O	1				
	H	1				
Burkholderia pseudomallei (1)	O		1			
	H		1			
Cryptococcus neoformans (2)	O	1	1			
	H	1	1			
Escherichia coli (45)	O	37	6	1	1	
	H	43		1		1
Klebsiella spp. (9)	O	8		1		
	H	8			1	
Penicillium marneffei (1)	O	1				
	H	1				
Proteus mirabilis (1)	O	1				
	H	1				
Pseudomonas aeruginosa (3)	O	2	1			
	H	3				
Salmonella spp. (10)	O	7	2	1		
	H	7	2		1	
Staphylococcus aureus (15)	O	10	3	2		
	H	13	2			
Streptococci (21)	O	15	6			
	H	19	2			
Plasmodium falciparum (103)	O	100	1	1	1	
	H	103				
Dengue virus (76)	O	66	8	2		
	H	70	6			

TABLE 3. Comparison of the sensitivity (1,400 patients) and specificity (555 patients) of the Widal test at different cutoff values for children and adults and the positive and negative predictive values for a disease prevalence of 30%

Antigen	Titer	Sensitivity for:			Specificity for:			Predictive value for the indicated patients:					
								Positive			Negative		
		All patients	Children	Adults	All patients	Children	Adults	All patients	Children	Adults	All patients	Children	Adults
O	≥100	0.83	0.88	0.80	0.89	0.86	0.91	0.76	0.73	0.79	0.93	0.94	0.91
O	≥200	0.49	0.57	0.44	0.97	0.97	0.98	0.88	0.89	0.90	0.82	0.84	0.80
O	≥400	0.19	0.25	0.15	0.99	0.99	0.99	0.89	0.91	0.87	0.74	0.75	0.73
H	≥100	0.67	0.70	0.66	0.96	0.95	0.97	0.88	0.86	0.90	0.87	0.88	0.84
H	≥200	0.44	0.48	0.43	0.99	1.00	0.99	0.95	1.00	0.95	0.80	0.82	0.80
H	≥400	0.28	0.29	0.28	0.99	1.00	0.99	0.92	1.00	0.92	0.76	0.77	0.76
O or H	≥100	0.88	0.92	0.84	0.87	0.83	0.89	0.74	0.70	0.77	0.94	0.96	0.93
O or H	≥200	0.60	0.66	0.56	0.97	0.97	0.97	0.90	0.90	0.89	0.85	0.87	0.84
O or H	≥400	0.33	0.36	0.31	0.99	0.99	0.99	0.93	0.94	0.93	0.78	0.78	0.77
O or H	≥200 or ≥100[a]	0.74	0.79	0.71	0.95	0.92	0.96	0.86	0.81	0.88	0.90	0.91	0.89

[a] That is, O ≥ 200 or H ≥ 100.

calculated for a disease prevalence of 30% with different cutoff values (Table 3).

DISCUSSION

The specific purpose of this study was to develop local recommendations for the interpretation of Widal test results. However, the results have implications for other regions where typhoid is endemic. Although the Widal test is widely used in Vietnam to diagnose typhoid fever, no previous study has been designed to evaluate its usefulness. There are various difficulties associated with an evaluation of the Widal test. First, the levels of agglutinins detectable in the noninfected populations of different areas vary considerably (12, 15, 17, 19–21, 23). This variation depends on the degree to which the disease is endemic in each area, a fact which may change over time, as has occurred in Papua New Guinea (4). It also depends on the level of infection due to other salmonellae with cross-reacting antigens. It is therefore critical to evaluate the Widal test in the area in which it is to be used. A second issue is the choice of a satisfactory gold standard for diagnosis and the selection of an adequate control group. In this study, we have chosen blood culture-positive patients as the confirmed typhoid fever cases. However, some patients with typhoid fever will be blood culture negative, particularly in areas such as Vietnam, where antibiotic pretreatment is common. Bone marrow culturing would be a better gold standard (10), but this test is not routinely performed at the CTD. The ideal control group would be patients with an illness compatible with typhoid fever and investigated with a Widal test but who are then found not to have typhoid fever. However, it can be difficult to choose patients who are blood culture negative and who definitely do not have typhoid fever. Septicemia, malaria, and dengue are common causes of admission with fever at the CTD, and each may be confused with typhoid fever but may be diagnosed following investigation (9): malaria with a positive smear and a negative blood culture; dengue with a compatible clinical history, recovery without antibiotics, a negative blood culture, and a positive dengue serological test (25); and septicemia by the isolation of an organism other than *S. typhi* from the blood. We have used a group of adults and children with tetanus to indicate the levels of agglutinating antibodies in the population as a whole.

This study confirms the presence of detectable agglutinins in a hospital-based population without typhoid fever. O agglutinins were present at a titer of ≥100 in 7% and H agglutinins were present at a titer of ≥100 in 1% of 265 adults and children with tetanus. The levels of agglutinins are similar to those found in other studies in this region (4, 13, 15, 16, 21). Pang and Puthucheary, for example, found O agglutinins at a titer of 160 or more in 5% and H agglutinins at a titer of 160 or more in 2% of 300 noninfected individuals in Malaysia (15).

Salmonellae are divided into serological groups on the basis of O or somatic antigens. Group D organisms, including *S. typhi*, possess O-antigen 9. Fifty-nine of the 78 group D organisms, including *S. typhi*, and group A and B organisms, such as *S. paratyphi* A, also have antigen 12. Other salmonellae share the H, flagellar, and antigen d with *S. typhi*. Cross-reactions, producing a false-positive O-antigen titer in the Widal test, can therefore occur with any of these serotypes (16, 18). Paratyphoid fever due to *S. paratyphi* A resulted in a positive O-antigen titer of ≥100 in 53% of patients and a positive H-antigen titer of ≥100 in 22%. However, a positive Widal test for these patients would still have resulted in appropriate management. There is evidence that the proportion of disease, both bacteremia and gastroenteritis, due to other *Salmonella* serotypes is low in this area (9). In this series, only 10 (0.7%) of the 1,455 salmonellae isolated from the blood cultures were nonenteric fever salmonellae. The level of stimulation of the immune system by other salmonellae with shared antigens may therefore also be low. Previous typhoid vaccination may contribute to elevated agglutinins in the noninfected population. However, such vaccination is not a factor in the population that we studied. There is no national program of typhoid vaccination in Vietnam, typhoid vaccine is not generally available, and it is extremely rare for patients to have a history of typhoid vaccination.

The earliest serological response in acute typhoid fever is a rise in the titer of the O antibody, with an elevation of the H-antibody titer developing more slowly but persisting longer than that of the O-antibody cutoff titer (1). In this study, 17% of patients with blood culture-positive typhoid fever had no detectable O antibodies at a cutoff titer of 100, and 33% had no detectable H antibodies at a cutoff titer of 100. Although these patients may have had antibodies at a lower titer, it is well recognized that patients with confirmed typhoid fever may have a negative Widal test throughout the course of their illness, although the proportion has varied in different reports (2, 5, 15, 19, 23, 24). This lack of antibody response among patients with blood culture-positive typhoid fever has been attributed to undefined host or bacterial factors or prior antibiotic treatment (20). In this study, there was no relationship

between a history of prior antibiotic treatment and the Widal test results. Some patients were investigated in the first week of the disease, and this early investigation might be thought to have contributed to the proportion of patients with negative results (11, 24). However, the traditional view that the test becomes positive only in the second week of the illness is not supported by our data. The test was positive (titer to O and/or H antigen of ≥100) in 90% of patients with blood culture-positive typhoid fever and admitted during the first week of their illness. This result may reflect a population immunologically sensitized by regular subclinical exposure to *S. typhi*.

The level of agglutinins was correlated with age, with a higher level of agglutinins in children than in adults, as others have observed (12). Although the titer increased with the duration of illness in adults, it did not do so in children. These differences may reflect different proportions of IgM and IgG antibodies to *S. typhi* antigens at different ages.

False-positive Widal test results have been reported for patients with nonenteric fever salmonellae infections, malaria, typhus, *C. neoformans* meningitis, immunological disorders, and chronic liver disease (8, 15, 21, 22). In this study, elevated levels of agglutinins were found in patients with a variety of other bacteremic illnesses, including those caused by other *Salmonella* spp., *E. coli*, *Klebsiella* spp., and *S. aureus*. In general, the level of O antibodies in these patients was higher than that of H antibodies. The elevated levels may have been due to cross-reacting antigens or an anamnestic response. There are more than 40 cross-reacting antigens between *S. typhi* and other *Enterobacteriaceae* (6). The levels of agglutinins were low in adults with malaria and in children with dengue.

Some authors have claimed that the level of H agglutinins is unhelpful in the diagnosis of typhoid, maintaining that the H-agglutinin titer remains elevated for a longer period than the O-agglutinin titer after an episode of typhoid fever and also may rise as a nonspecific response to other infections (11, 20). Others, however, have proposed that the H-agglutinin titer is as useful as or more useful than the O-agglutinin titer (2, 5, 15, 23). In this study, H agglutinins were less sensitive but more specific than O agglutinins and yielded better positive predictive values.

The predictive value of a diagnostic test depends on the sensitivity and specificity of the test and on the prevalence of the disease in the population being tested. The performance of the Widal test will vary according to the likelihood of typhoid in the group of patients being investigated. If the test were used as a screen for all febrile patients admitted to the CTD, the typhoid fever prevalence would be less than 1%. A negative result would have a good predictive value for the absence of disease, but a positive result would have a very low predictive value for typhoid fever. The result would be virtually useless for diagnosing typhoid fever. The test should be restricted to those who have a reasonable probability of having typhoid fever. At the CTD, the disease prevalence was approximately 30% in those investigated with a blood culture and a Widal test. At a prevalence of 30%, a negative O- and H-antigen titer has a 94% probability of excluding typhoid. A positive H-antigen titer of 200 or more has a 100% probability of confirming typhoid in children and a 95% probability of doing so in adults but would only confirm the diagnosis in 28% of blood culture-positive typhoid cases. A positive cutoff for an O- or H-antigen titer of ≥100 is frequently used at the CTD. At this cutoff, 88% of patients with blood culture-positive typhoid fever would be correctly diagnosed. However, 6% of the negative results would be false-negative and 26% of the positive results would be false-positive. With a positive cutoff for an O-antigen titer of ≥200 or an H-antigen titer ≥100, 74% of blood culture-positive patients would be correctly diagnosed, 10% of the negative results would be false-negative, and 14% of the positive results would be false-positive.

Overall, the level of H agglutinins was found to be more helpful than the level of O agglutinins. When the O-agglutinin titer is ≥400 or the H-agglutinin titer is ≥200, typhoid can be diagnosed with reasonable confidence. An O-agglutinin titer of ≥200 and an H-agglutinin titer of ≥100 in an appropriate clinical context is likely to indicate typhoid in an area such as Vietnam. A negative Widal test result in a patient with a clinical history compatible with typhoid does not exclude the disease. Although new serological tests for the diagnosis of typhoid fever are becoming available, they must be carefully validated in each region before being used widely (3). In a region of endemicity such as Vietnam, we can conclude that elevated levels of agglutinating O and H antibodies as measured in the Widal test can be helpful in making a presumptive diagnosis of typhoid fever if interpreted with care.

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