

Typhoid fever in a Tertiary Hospital in Nigeria: Another look at the Widal agglutination test as a preferred option for diagnosis

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ABSTRACT

Background: Single Widal agglutination test rather than blood culture, is commonly employed to diagnose typhoid fever in Nigeria. We took another look at the Widal agglutination test as a preferred option for diagnosis of typhoid fever by determining the specificity and sensitivity of Widal agglutination test in febrile adult patients. **Materials and Methods:** Two hundred and seventy-one blood samples from consecutive adults (>18 years) with febrile illness attending the General Practice Clinic of the University of Benin Teaching Hospital were tested using the Widal agglutination test, blood culture, and malaria parasite test on each sample to establish the diagnosis of typhoid fever. **Results:** Of the 271 blood samples 124 (45.76%) were positive following a Widal agglutination test, 60 (22.10%) blood samples grew *Salmonella* organisms on blood culture while 55 (20.29%) blood samples showed a co-infection of typhoid fever and malaria. A sensitivity of 35%, specificity of 51%, positive predictive value of 17%, and a negative predictive value of 73% were observed for Widal agglutination test as a diagnostic modality for typhoid fever infection. **Conclusion:** A single Widal agglutination test is not a valid diagnostic option for typhoid fever while co-infection with malaria parasite is the preponderant microbiological finding in typhoid fever infections. The severity of malaria parasitemia is associated with positive titers on Widal test.

Key words: Co-infection, febrile illness, malaria, typhoid fever

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INTRODUCTION

Fever is a common cause for consultation in most healthcare facilities in the tropics and subtropics,¹ with infections accounting for most causes of fever.^{1,2} In the tropics, malaria and typhoid fever are among the common infectious diseases, with both being endemic in Nigeria.³⁻⁵

Typhoid fever is a life-threatening systemic infection⁶ caused by the bacterium, *Salmonella typhi*,⁷⁻¹¹ a Gram-negative, motile, aerobic, nonsporing, intracellular *Bacillus*.¹² It is a global public health problem with an estimated 21.6 million new cases of typhoid fever and 216,500 deaths

recorded globally in 2000.^{7,8} This is especially worse in the developing nations of the world where it is a significant contributor to morbidity and mortality.¹¹

Typhoid fever is spread by the faeco-oral route^{9,12,13} and commonly presents with nonspecific clinical features such as fever, headache, rigors, joint pain, nausea, vomiting, constipation, and diarrhea which are indistinguishable from other causes of fever such as malaria.^{1,3,7,14-16} The presence of clinical symptoms characteristic of typhoid fever or the detection of a specific antibody response is only suggestive of typhoid fever but not definitive.^{13,17} Culture and isolation of *S. typhi* is the gold standard for

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the diagnosis of typhoid fever.^{5,8,10,13,18-23} Blood culture is the most definitive method of diagnosing typhoid fever, especially in the 1st week of infection.^{2,5,13,18} About 80–90% of patients are likely to have positive blood cultures during the period of established disease, especially during the 1st week of illness.^{5,24}

In most parts of Africa, Nigeria inclusive, the Widal agglutination test (despite its limitations) is the most common diagnostic tool employed in the diagnosis of typhoid fever because of its relatively cheap cost and the fact that it is easy to perform and requires minimal training and equipment.^{25,26} However, a number of medical practitioners have often raised alarm on the apparently “high rate” of typhoid fever diagnosed in healthcare facilities in Nigeria and other parts of Africa.^{3,5,24,25}

This apparently “high rate” of typhoid fever may be due to the use and poor interpretation of the Widal test in making a diagnosis of typhoid fever.²⁷⁻²⁹

In view of the apparently “high rate” of typhoid fever, the controversial nature of the Widal agglutination test, and the dearth of studies on the validity of the Widal agglutination test as a diagnostic tool in the University of Benin Teaching Hospital (UBTH), this study was conducted to evaluate the validity of the Widal agglutination test as a diagnostic tool for typhoid fever by comparing it with blood culture (a standard method for diagnosing typhoid fever).

MATERIALS AND METHODS

This was a descriptive cross-sectional study carried out in the General Practice Clinic of the UBTH, Nigeria, after an ethical approval from the Ethics and Research Committee of the Teaching Hospital. The study population comprised febrile adult patients.

Blood samples were tested using Widal agglutination test. The samples were also cultured for *Salmonella* organisms while microscopy of thick blood film for malaria parasite was carried out.

Data were collected on a proforma and analyzed using the SPSS version 10 statistical software (SPSS version 10, Chicago, IL). Results were presented in statements and charts. Statistical significance was set at $P < 0.05$.

RESULTS

Table 1 shows the relationship between Widal agglutination test and blood culture diagnostic method, with the Widal agglutination test having a sensitivity of 0.35 (35%), specificity of 0.51 (51%), positive predictive value (PPV) of 0.17 (17%), and a negative predictive value (NPV) of 0.73 (73%).

Table 2 shows the relationship between malaria parasite infection and Widal agglutination test results among respondents. With an increase in malaria parasitemia, there was an increase in the proportion of blood samples with significant *Salmonella* antibody titers using the Widal agglutination test. There was a statistically significant association between the severity of malaria parasitemia and a positive Widal agglutination test ($P = 0.006$).

Table 3 shows the relationship between presence of malaria parasite and a positive blood culture for typhoid fever infection. From the data, it would seem that having malaria parasite infection does not presuppose a co-existing typhoid fever infection odds ratio (95% confidence interval [CI]) = 0.01 (0.001–0.03).

DISCUSSION

This study was aimed at determining the validity of the Widal agglutination test as a preferred option for the diagnosis of typhoid fever infection among adult febrile patients at the Family Medicine Department of the UBTH, Nigeria.

Table 1: Relationship between Widal test and blood culture method of diagnosis of typhoid fever

Widal test	Blood culture (%)		Total (%)
	Present	Absent	
Positive	21 (17)	103 (83)	124 (100.0)
Negative	39 (26.5)	108 (73.5)	147 (100.0)
Total	60 (22.1)	211 (77.9)	271 (100.0)

Sensitivity=0.35 (35%); Specificity=0.51 (51%); Positive predictive value=0.17 (17%); Negative predictive value=0.73 (73%)

Table 2: Relationship between malaria parasite infection and Widal test among respondents

Malaria parasite	Typhoid fever (Widal test) (%)		Total (%)
	Present	Absent	
++	72 (53.3)	63 (46.7)	135 (100.0)
+	28 (48.3)	30 (51.7)	58 (100.0)
Absent	24 (30.8)	54 (69.2)	78 (100.0)
Total	124 (45.8)	147 (54.2)	271 (100.0)

$\chi^2=10.33$, $df=2$, $P=0.006$. + (<10 *Plasmodium falciparum* parasites/100hpf), ++ (>10 *Plasmodium falciparum* parasites/100hpf), Absent (no *Plasmodium falciparum* parasites seen)

Table 3: Relationship between presence of malaria parasite and typhoid fever infection among respondents

Malaria parasite	Typhoid fever (blood culture) (%)		Total (%)
	Present	Absent	
Present	5 (2.6)	188 (97.4)	193 (100.0)
Absent	55 (70.5)	23 (29.5)	78 (100.0)
Total	60 (22.1)	211 (77.9)	271 (100.0)

$P < 0.001$, OR (95% CI)=0.01 (0.001-0.03). OR – Odds ratio; CI – Confidence interval

Comparing the Widal agglutination test results with the blood culture results, it was found that out of 124 (45.8%) study subjects that had a positive Widal agglutination test (using a cut-off *Salmonella* antibody titre of >1:80, in use in the Medical Microbiology Department of UBTH), 21 (17%) had blood culture confirmation of typhoid fever. However, out of 147 (54.2%) study subjects that had negative Widal agglutination test, 39 (26.5%) had blood culture confirmation of typhoid fever.

The calculated sensitivity of Widal test as a diagnostic tool for typhoid fever was 35%, with a 95% CI of 0.2312–0.4836. This shows that Widal agglutination test has a low sensitivity and a 35% ability to correctly identify individuals who actually have typhoid fever.

The calculated specificity of Widal agglutination test was 51%, with a 95% CI of 0.4425–0.5807. This shows that Widal agglutination test has a 51% ability to correctly identify individuals who do not have typhoid fever.

The calculated PPV of Widal agglutination test was 17%, with a 95% CI of 0.1080–0.2469. This shows that Widal agglutination test has a low PPV, with only a 17% ability to accurately determine the proportion of those who are truly positive for typhoid fever.

The calculated NPV of Widal test was 73%, with a 95% CI of 0.6557–0.8037. This shows that Widal test has a high NPV, with a 73% ability to accurately determine the proportion of those who are truly negative for typhoid fever.

The above findings are of great relevance, especially against the backdrop of controversies plaguing the use of Widal test in the diagnosis of typhoid fever.

The validity of a diagnostic tool mainly depends on its sensitivity and PPV. The low (35%) sensitivity and low (17%) PPV of the Widal agglutination test found in this study clearly demonstrate that a single Widal agglutination test is not a valid diagnostic tool for typhoid fever. This is also supported by findings from other studies which cast doubt on the validity and use of the Widal agglutination test.^{8,13,25,27,30,31}

In determining the relationship between Widal agglutination test and malaria parasite infection, it was observed that there was a significant statistical association ($P < 0.05$) between the presence of malaria parasites and a positive Widal agglutination test. Out of a total of one hundred and ninety-three study subjects that had a positive malaria parasite test, 100 (52.4%) had a positive Widal agglutination test, while only 5 (2.6%) had typhoid infection confirmed by blood culture.

The high prevalence of malaria parasitemia found in this study may imply that the presence of malaria parasites in a patient could produce a positive Widal test result. This

is supported by findings from previous studies which documented the fact that the presence of malaria parasite in a patient could produce a false positive Widal test result^{25,27} on account of the fact that some undefined antigenic determinants possessed by the malaria parasite could cross-react with those of *S. typhi*, thus producing *Salmonella* antibodies. It may also explain the apparently “high rate” of typhoid fever diagnosed in private healthcare facilities in Benin City on the basis of a single Widal test result.

In determining the relationship between malaria parasite infection and typhoid fever infection (as confirmed by blood culture), it was found that there was a significant statistical difference ($P < 0.05$) between those who had only typhoid or malaria infection alone and those who had both typhoid fever and malaria co-infection. Out of 193 study subjects who had a positive malaria parasite test, only 5 (2.6%) had typhoid fever infection (as confirmed by blood culture), while 188 (97.4%) had no blood culture confirmation of typhoid fever infection. Of the 78 respondents (28.8%) that had negative malaria parasite test, 55 (70.5%) of them had blood culture confirmation of typhoid fever infection, while 23 (29.5%) had no blood culture confirmation of typhoid fever infection.

This shows that there is a statistically significant difference between those who had malaria and typhoid fever co-infection and those who had only malaria or typhoid fever infection alone, with most of the individuals likely to have either typhoid fever infection or malaria alone than malaria and typhoid fever co-infection.

The above findings and observations are supported by some previous studies such as the one conducted by Onuigbo²⁴ who found that out of 15 patients clinically diagnosed as typhoid fever, 70% had malaria while the remaining 30% remitted spontaneously. Similarly, in a study to determine the prevalence of typhoid fever in febrile patients with symptoms clinically compatible with typhoid fever in Cameroon, Nsutebu *et al.*¹ diagnosed malaria in 47% of the two hundred patients recruited for the study. In a study conducted in Nigeria, Smith *et al.*³² found malaria parasites in 64.3% of the patients recruited for the study. However, Tanyigna *et al.*³³ found malaria parasites in 27.4% of study patients. Akinyemi *et al.*³⁴ in their evaluation of blood collected from clinically diagnosed typhoid fever patients in the metropolis of Lagos, Nigeria, found malaria in 37.2% of the study subjects.

CONCLUSION

This study recommends the need to discourage exclusive reliance on a single Widal agglutination test for the diagnosis of typhoid fever, as it is not evidence based. All febrile patients suspected to have typhoid fever should be properly evaluated and investigated by Physicians with

bacteriological culture methods, as bacteriological isolation of *S. typhi* remains the most accurate means of confirming typhoid fever infection.

There is an overwhelming need for government, professional bodies, media houses, and other stakeholders to organize and promote public health enlightenment programs and campaigns to massively educate and enlighten members of the public on typhoid fever infection. Such programs and campaigns will greatly help to enlighten the general public on the use of valid diagnostic tools in the diagnosis and management of typhoid fever, and thus prevent them from being exploited or exposed to the complications of misdiagnosis or poor management of their febrile illnesses.

Compared with the blood culture as a diagnostic test for typhoid fever infection, this study found that the Widal agglutination test as a diagnostic modality for typhoid fever infection had a low sensitivity (35%) and a low PPV (17%).

The low sensitivity (35%) and low PPV (17%) of the Widal agglutination test, cast doubt on the validity of the Widal agglutination test as a preferred option for the diagnosis of typhoid fever infection.

On account of the above findings, this study concludes that a single Widal agglutination test is not a valid diagnostic option for typhoid fever.

Limitations

This study may be limited by the fact that other bacteriological cultures such as stool, urine, and bone marrow aspirate cultures were not conducted, especially as bone marrow aspirate culture is known to give a high yield of *Salmonella* even when blood and urine cultures of patients treated with antibiotics are negative.⁸

In addition, the findings of this study may unlikely be reflective of the findings in the community on account of the fact that it was a hospital based study. Further researches, particularly community-based studies, are therefore recommended.

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Conflicts of interest

There are no conflicts of interest.

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