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LETTER TO THE EDITOR

TYPHOID FEVER DIAGNOSIS IN DEVELOPING COUNTRIES: THE WIDAL TEST DILEMMA

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TYPHOID FEVER DIAGNOSIS IN DEVELOPING COUNTRIES: THE WIDAL TEST DILEMMA

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Dear Editor,

We would like to draw the attention of the scientific and clinical service community to the situation in the developing countries as regards the proper diagnosis of typhoid fever, and the implications on treatment and possible antibiotic resistance.

The State of Things

Typhoid fever is a systemic infection resulting from the invasion of the gastrointestinal tract by *Salmonella enterica*, serovar typhi, transmitted feco-orally. It is of global health significance, as about 11 to 21 million people are infected annually with 128,000 to 161,000 annual mortality worldwide [1]. It is particularly of concern to people living in developing countries; such as in Africa, the Americas, South-East Asia and the Western Pacific, where poverty, poor hygiene and lack of clean water continue to drive the infection[1,2]. The diagnosis of typhoid fever requires clinical and microbiological evidence. Symptoms though non-specific, include prolonged high-grade fever, abdominal pain, fatigue, headache, nausea, and constipation or diarrhoea. The gold standard for establishing the diagnosis of typhoid fever is isolating the organism from blood, stool, urine and aspirated bile via culture, typically after a week of infection. These cultures often take between 3-7 days for results to be made available [3].

The Widal test is a serologic test which is over a century old, and is based on the principle of agglutination (antigen-antibody reaction), developed to detect *Salmonella typhi* flagellar (H) and lipopolysaccharide (O) antigens in sera of infected individuals[4]. This test still holds sway in many parts of the world where

resources are limited and the endemicity of typhoid fever is high, and it is often the only test available for diagnosing the infection in these places [5]. This is because of the low cost, availability and low requirement for expertise of the Widal test when compared with some other tests. It is however known that several other illnesses which may share symptomatology with typhoid fever, have been shown to offer cross-reactivity on the Widal test especially in typhoid endemic areas, such as non-typhoidal salmonella infections, malaria, dengue fever, miliary tuberculosis, endocarditis, chronic liver disease and brucellosis [4]. Lack of standardization of the antigens used in the test, repeated exposure to *Salmonella spp.* over time, previous typhoid fever immunization, difficulty in establishing a steady-state baseline titre for the population are factors that contribute to the poor sensitivity and specificity of the test. A single Widal test may have some diagnostic relevance in an unvaccinated or unexposed patient in a non-endemic region, but its usefulness is questionable in typhoid endemic regions where repeated exposure to the organism would likely stimulate higher baseline antibody levels [6]. Studies have also shown that individuals with culture-positive typhoid fever may fail to show the expected reaction on Widal test, implying that a negative Widal test does not necessarily rule out typhoid infection [4]. Schroeder, in a study established that the Widal test is non-specific, poorly standardized, confusing and difficult to interpret [7]. Over-diagnosis and poor antibiotic stewardship are the resultant effects of continued use of this test. In this era of established resistance of *S. typhi* to former first line drugs such as ampicillin, chloramphenicol and sulfamethoxazole-trimethoprim, in addition to rising resistance to quinolones and third generation cephalosporins (the current first- and second-line medications)[8,9], is continued use of this test really beneficial to the patient and the community on the long run?

The way forward

The following are strategies that could be implemented by stake-holders in resource-poor settings for better diagnosis and management of typhoid fever.

- Widal test should only be considered useful in endemic regions if patients have four-fold or more increases in O or H agglutinin titres in serum specimens obtained 2 to 3 weeks [4].
- Establishment of a steady state or baseline titre at the community level, though tasking, will help set a reference point for interpreting results. This will increase suspicion of an actual typhoid infection [4].
- Standardization and maintenance of the antigens used can improve the value of the Widal test. Studies have shown however that irrespective of the composition and standardization of the antigens used, isolation of aetiologic agent will always be superior [10].

- Close communication between the managing physician and the laboratory should exist, as technique variation in individual laboratories may affect the Widal titres and thus the expected antibody titre rise may not be seen even in bacteriologically confirmed patients [4].
- It must be stressed that the role of Widal test is to increase the suspicion for typhoid fever, not to confirm it. Its diagnostic use should be limited to situations where no other confirmatory test is available.
- Rapid diagnostic tests with high specificity and sensitivity should be explored [11]. Research and development breakthroughs in this area would not only reduce diagnostic delays, but will reduce the overall cost and logistics required in diagnosing typhoid fever.
- Newer techniques such as co-agglutination have been found to be highly sensitive for diagnosing typhoid fever, and can be adopted for screening purposes. Polymerase chain reaction is highly specific and can be used for diagnosing typhoid fever in patients who are culture negative [12].
- In the absence of rapid kits, investments should be made by stakeholders (from health policy makers to hospital administrators) to provide needed infrastructure and personnel for accurate microbiological diagnoses to be made.

CONCLUSION

There is need for countries where the use of Widal test is prevalent, to explore and invest in alternative means of rapidly and accurately diagnosing typhoid fever, as this would have a positive effect on the war against antimicrobial resistance. If the Widal test must be used, it should be used to increase the suspicion of typhoid fever, especially when a four-fold rise in titre has been demonstrated in paired samples taken two weeks apart. Baseline titres should be established locally, to serve as a reference point when interpreting results.

CONFLICT OF INTEREST

There are no conflicts of interest to declare

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