Rapid diagnosis of typhoid fever

The article on prospective evaluation of Typhidot® test for typhoid fever in this issue¹, emphasizes the significance of the rapid diagnosis of typhoid fever and evaluates the Typhidot® as a rapid diagnostic tool. Typhoid fever is caused by *Salmonella* Typhi and is similar but often less severe than the disease caused by *Salmonella* serotype Paratyphi A. The clinical presentation of typhoid fever varies from a mild illness with low-grade fever, malaise, and slight dry cough to a severe clinical picture with abdominal discomfort and multiple complications. Severity and clinical outcome of the typhoid are controlled by the duration of illness before the initiation of appropriate therapy, the choice of treatment, age, previous exposure, the virulence of the bacterial strain, and the quantity of inoculum ingested. Host factors include infection with AIDS, other immunosuppressions or taking medications, e.g., antacids. Evidence of *Helicobacter pylori* infection also represents an increased risk of acquiring typhoid fever².

Typhoid fever is a global health problem. Its real impact is difficult to estimate because the clinical picture is confused with other febrile infections. Further, the disease is underestimated due to lack of bacteriology laboratories in most clinical settings of developing countries. Incidence of typhoid fever has been estimated as approximately 17 million cases with 600,000 associated deaths occurring annually³-⁵. Obviously, the disease has a very high social and economic impact⁶.

Acute typhoid fever is characterized by prolonged fever, disturbances of bowel function (constipation in adults, diarrhoea in children), headache, malaise and anorexia. Cough is common in the early stage of the illness⁷. Confirmed case of typhoid fever is defined, according to the World Health Organization (WHO), as a patient with fever (> 38°C) that has lasted for at least three days, with a laboratory confirmed positive culture of *S. Typhi*. Probable case of typhoid fever is a patient with fever (> 38°C) that has lasted for > 3 days, with a positive serodiagnosis or antigen detection test but without *S. Typhi* isolation. Chronic carrier is determined as excretion of *S. Typhi* in stools or urine for longer than one year after the onset of acute typhoid fever. Short-term carriers also exist but their epidemiological role is not as important as that of chronic carriers. Some patients excreting *S. Typhi* have no history of typhoid fever.

The infection is transmitted by ingestion of food or water contaminated with faeces. Epidemiological data suggest that water borne transmission of *S. Typhi* usually involves small inocula, whereas food borne transmission is associated with large inocula⁸. The definitive diagnosis of typhoid fever depends on the isolation of *S. Typhi* from blood, bone marrow or a specific anatomical lesion. Blood and bone marrow aspirate cultures are the gold standard for the diagnosis of typhoid fever⁹-¹². Duodenal aspirate culture has also proved highly satisfactory as a diagnostic test by author but has not found widespread acceptance because of poor tolerance of duodenal aspiration, particularly in children¹³.

Salmonellae can be characterized by their somatic (O) and flagellar (H) antigens. Some salmonellae also have an envelope antigen called Vi (virulence). H antigen is usually determined by means of the tube
agglutination test. Widal test measures agglutinating antibody levels against O and H antigens. The levels are measured by using serial dilutions of sera. Usually, O antibodies appear on days 6-8 and H antibodies on days 10-12 after the onset of the disease. The test is usually performed on acute and convalescent sera to detect the rising titres. The test has only moderate sensitivity and specificity\textsuperscript{14}.

It is, therefore, important to establish the antibody level in the normal population in a particular locality in order to determine a threshold above which the antibody titre is considered significant. This is particularly important if a single acute sample is available. If paired sera are collected, a four-fold rise in the antibody titre, between convalescent and acute sera, is diagnostic\textsuperscript{15}.

There is a need for a quick and reliable diagnostic test for typhoid fever as an alternative to the Widal test. Recent advances include the IDL Tubex\textsuperscript{®} test by a Swedish company, which reportedly can detect IgM O9 antibodies. Another rapid serological test, Typhidot\textsuperscript{®}, takes three hours to perform. It was developed in Malaysia for the detection of specific IgM and IgG antibodies against a 50 kD antigen of \textit{S. Typhi}. A newer version of the test, Typhidot-M\textsuperscript{®}, was recently developed to detect specific IgM antibodies only. The dipstick test, developed in the Netherlands, is based on the binding of \textit{S. Typhi}-specific IgM antibodies in samples to \textit{S. Typhi} lipopolysaccharide (LPS) antigen and the staining of bound antibodies, by an anti-human IgM antibody, conjugated to colloidal dye particles.

The Tubex\textsuperscript{®} test is simple and rapid\textsuperscript{16}. It exploits the simplicity and user-friendliness of the Widal and the slide latex agglutination tests, but uses the separation of coloured particles in solution to improve resolution and sensitivity. Specificity is improved by means of an inhibition assay format and by detecting antibodies to a single antigen in \textit{S. Typhi} only. The O9 antigen used in the test is extremely specific because its immunodominant epitope is a rare dideoxyhexose sugar in nature. This antigen has been found in serogroup D salmonellae but not in other microorganisms. A positive result given by Tubex\textsuperscript{®} invariably suggests a \textit{Salmonella} infection, although the test cannot tell which group D \textit{Salmonella} is responsible. For reasons yet to be elucidated Tubex\textsuperscript{®} detects IgM antibodies but not IgG. This makes it invaluable as an aid in the diagnosis of current infections.

Typhidot\textsuperscript{®} test makes use of the 50 kD antigen to detect specific IgM and IgG antibodies to \textit{S. Typhi}. It has undergone full-scale multinational clinical evaluation of its diagnostic value\textsuperscript{17-19}. This dot enzyme immuno assay (EIA) test offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values. The detection of IgM reveals acute typhoid in the early phase of infection, while the detection of both IgG and IgM suggests acute typhoid in the middle phase of infection. In areas of high endemicity, where the rate of typhoid transmission is high, the detection of specific IgG increases. Since IgG can persist for more than two years after typhoid infection\textsuperscript{20}, the detection of specific IgG cannot differentiate between acute and convalescent cases. Evaluations of Typhidot\textsuperscript{®} and Typhidot-M\textsuperscript{®}\textsuperscript{21} in clinical settings showed that they performed better than the Widal test and the culture method\textsuperscript{22}.

In laboratory diagnosis of typhoid fever the method used as the gold standard should approach 100 per cent in sensitivity, specificity and positive and negative predictive values. Evaluation studies have shown that Typhidot-M\textsuperscript{®} is superior to the culture method\textsuperscript{19}. Although culture remains the gold standard, it cannot match up to Typhidot-M\textsuperscript{®} in sensitivity (>93%), negative predictive value and speed\textsuperscript{20}. Typhidot-M\textsuperscript{®} can replace the Widal test, when used in conjunction with the culture method, for the rapid and accurate diagnosis of typhoid fever. The high negative predictive value of the test suggests that Typhidot-M\textsuperscript{®} would be useful in areas of high endemicity.

The typhoid IgM dipstick assay is designed for the serodiagnosis of typhoid fever, through the detection of \textit{S. Typhi}-specific IgM antibodies in serum or whole blood samples. Tubex\textsuperscript{®} has not been evaluated extensively. In a preliminary retrospective study, the test performed better than the Widal test in both sensitivity and specificity\textsuperscript{15}. Evaluations of
the dipstick test in laboratory based studies in Indonesia and Egypt have shown consistent results. These studies indicated sensitivities up to 90 per cent for samples collected from culture-confirmed patients and specificities of 95 to 100 per cent.

In conclusion, infection caused by S. Typhi remains an important public health problem, particularly in developing countries. Morbidity and mortality, attributable to typhoid fever, are increasing with the emergence and worldwide spread of S. Typhi strains that are resistant to most useful antibiotics. As a consequence, there is renewed interest in understanding the epidemiology, diagnosis and treatment of typhoid fever. Public health authorities should largely make use of the available rapid, simple and reliable diagnostic tools of typhoid fever, especially in health units where culture technique is unavailable.

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References


