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Mini Review

New advances in the rapid diagnosis of typhoid fever

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For effective management of typhoid, diagnosis of the disease must be done with speed and accuracy. Laboratory diagnosis of typhoid fever requires isolation and identification of *Salmonella* enterica serotype *Typhi*. In many areas where the disease is endemic, laboratory capability is limited. Recent advances in molecular immunology have led to the identification of sensitive and specific markers for typhoid fever and technology to manufacture practical and inexpensive kits for their rapid detection. But their limitation paves way to continue to search for the ideal rapid tests to diagnose acute typhoid fever.

Key words: New advances, typhoid diagnosis, typhidot®, tubex®, fimbrial antigen.

INTRODUCTION

Typhoid is now regarded as a disease of history by many people living in developed countries. Typhoid fever is a systemic life-threatening infection caused by the bacterium *Salmonella* typhi. This is a highly adapted, human-specific pathogen occurring more frequently in underdeveloped regions of the world where overcrowding and poor sanitation are prevalent.

According to the best global estimates, there are atleast 16 million new cases of typhoid fever each year, with 6, 00,000 deaths (Ivanoff, 1995). Between 1 - 5% of patients with acute typhoid infection have been reported to become chronic carriers of the infection, depending on age, sex and treatment regimen. Furthermore this chronic carrier state has also been implicated in causation of carcinoma of the gall bladder.

DIAGNOSIS OF TYPHOID FEVER

The diagnosis of typhoid fever on clinical grounds is difficult, as the presenting symptoms are diverse (Stuart and Pullen, 1946) and similar to those observed with other common febrile illness, such as malaria and non-severe dengue fever. The isolation of serotype *typhi* from blood remains the method of choice for the laboratory diagnosis (Wain et al., 1998). However, the availability of microbiological culturing facilities is often limited in regions in which typhoid is endemic and blood cultures can be negative when patients have received prior anti-biotic therapy. Bone marrow culturing has a higher sensitivity than blood culturing (Farooqui et al., 1991; Vallenas et al., 1985), but is a more invasive procedure. Sero diagnosis of typhoid fever has been attempted since the late 19th century when Widal and Sicard showed that the serum of patients with typhoid fever agglutinated typhoid bacilli (Widal, 1896).

Unfortunately, neither the widal test, which remains in widespread use in the developing world, nor any of the serodiagnostic tests that have since been developed has proven sufficiently sensitive, specific and of practical value (Levine and Orenstein, 1999). Recent advances in molecular immunology have led to the identification of potentially more sensitive and specific markers in the blood and urine of patients with typhoid fever and enabled the manufacture of practical and inexpensive kits for their detection.

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RAPID TEST KITS FOR DIAGNOSIS OF TYPHOID FEVER

Typhidot® a test kit that makes use of 50 kD antigen to detect specific IgM and IgG antibodies to *S. typhi* (Ismail et al., 1991). It has undergone full - scale multinational clinical evaluation of its diagnostic value (Lu-Fong et al., 1999; Jackson et al., 1995; Choo et al., 1997). This dot EIA test offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values. Another variant of Typhidot® is Typhidot-M® and has shown that inactivation of IgG removes competitive binding and allows access of the antigen to the specific IgM when it is present. Evaluation of Typhidot® and Typhidot-M®in clinical settings showed that they performed better than the Widal test and the culture method (Bhutta and Mansurali, 1999). An evaluation of Typhidot® in India was 100% sensitive and 80% specific compared to a blood culture as "gold standard" (Jesudason et al., 2002). Looking at the other side of the picture one finds that Typhidot® relies more heavily on IgM results and so the sensitivity of Typhidot® is high in the first week of illness and decreases during the later stage of the disease.

IDL Tubex® is another test marketed by a Swedish company which reportedly can detect IgM O9 (or LPS in general) antibodies from patients within a few minutes. It exploits the simplicity and user friendliness of the widal and the slide latex agglutination tests but uses the separation of colored particles in solution to improve resolution and sensitivity. But for reasons yet to be elucidated, Tubex® detects IgM antibodies but not IgG. This makes it invaluable as an aid in the diagnosis of current infections. More over Tubex® test is the potential for difficulty in interpreting the results of hemolyzed samples.

The multi-test Dip-S-Ticks test (Panbio INDX Inc., Baltimore.Md.), is based on the binding of *S. typhi* specific –IgM antibodies in samples to *S. typhi* lipopolysaccharides (LPS antigen) and the staining of bound antibodies by an anti-human IgM antibody conjugated to colloidal dye particles. This test only detects IgG antibodies and has poor specificity.

DISCUSSION

It is possible that the rapid diagnostic tests are more sensitive than blood culture as "gold standard". If so, a result that appears to be a false positive test compared to a blood culture may in fact be a true- positive. This hypothesis requires further evaluation. Alternatively, a false-positive may be result of past infection with serotype *Typhi* or another nontyphoidal *Salmonella* serotype that shares common antigens.

In conclusion, researchers continue to search for the ideal rapid test to diagnose acute typhoid fever. Several urine assays have been developed (Rockhill et al., 1980), but none have proved optimal. With the sequencing of the entire serotype *Typhi* genome, it may be possible now to identify other antigens, such as *fimbrial antigens*, that may produce an antibody response to serotype *Typhi* (Wain et al., 2002). More sophisticated molecular techniques like PCR, are being explored. However, their utilization in the developing countries will most likely be limited.

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