Selected clinical information - TUBEX® TF for typhoid fever

Subject: **TUBEX, a new serologic test for rapid, simple and sensitive diagnosis of typhoid fever (*Salmonella typhi)*.**

Title: "One-step 2-minute test to detect typhoid-specific antibodies based on particle separation in tubex."

Authors: Lim P-L, Tam FCH, Cheong Y-M, Jegathesan M.

Source: *J Clin Microbiol 1998; 36: 2271-2278*

Summary: Typhoid fever is caused by *Salmonella typhi*. Correct diagnosis of the disease, which is vital before applying a suitable therapy, is possible by detection of anti-*S. typhi* antibodies in patient sera. However, the various methods that exist today are either not sensitive enough (Widal) and/or time-consuming, demand trained personnel and performance in a laboratory (Typhidot; ELISAs). TUBEX is a new diagnostic test, showing high sensitivity and specificity for typhoid fever, yet being fast and simple to perform. It is a semi-quantitative test, based on magnetic inhibition separation. TUBEX detects anti-*S. typhi* O-9 antibodies in patient serum by inhibiting the binding between anti-O-9 IgM, conjugated to colored latex particles, and *S. typhi* lipopolysaccharide, conjugated to magnetic latex particles. Upon forced magnetic sedimentation, the resultant supernatant color is read to obtain the result.
In a preliminary study of 16 sera from 14 patients with proven typhoid fever, and 75 individuals free of the disease, TUBEX was proven to be 100% sensitive and 100% specific. Also, 11 patients clinically diagnosed as having typhoid fever were all positive in the test.

Conclusion: "TUBEX appears to be well designed and well suited for use in the laboratory or by the bedside as a simple, rapid aid to the routine diagnosis of typhoid fever."

"We describe a new test (TUBEX) which has the advantages of the Widal test and the specificity normally accorded to ELISAs that utilize purified antigens for detection."

"TUBEX appears to be an ideal test to help in the diagnosis of typhoid fever. The test is fast, simple and easy-to-use. TUBEX can be used in developing countries where the disease is especially prevalent and where the cost of ELISA readers and other forms of instrumentation is prohibitive."

Subject: **TUBEX provides the sole detection of IgM, not IgG, O9-antibodies, thus enabling diagnosis of purely acute typhoid fever.**

Title: "The TUBEX typhoid test based on particle-inhibition immunoassay detects IgM but not IgG anti-O9 antibodies."

Authors: Tam FCH and Lim P-L

Source: *J Immunol Methods 2003; 282: 83-91*

Summary: The typhoid fever diagnostic test TUBEX detects the presence of antibodies in patient sera by their ability to inhibit the interaction between two types of reagent particles in the test. In short, these are: a) colored indicator latex particles carrying anti-O9 monoclonal antibodies; b) magnetic particles coated with *S. typhi* LPS (lipopolysaccharide). The reaction is performed in specially designed tubes. After a few minutes the tube is placed on a magnet and thus the magnetic particles settle to the bottom of the tube, together or without the indicator particles depending on if these have been inhibited from binding or not (anti-O9 antibodies present in the serum or not) Presented here is data showing that only IgM antibodies in the patient serum, and not IgG antibodies, can inhibit this reaction between the indicator and the magnetic particles. The reason for this is not completely clear, but likely the main reason is the structure of the respective antibodies, with IgM having a pentameric large structure as compared to the Y-shaped smaller IgG. Upon binding, the IgM molecules not only efficiently covers the indicators, but presumably also crosslink the particles. IgG on the other hand, upon binding likely leave gaps where indicator particles still can bind. Importantly, both IgM and IgG particles inhibit as efficiently when tested in other assay formats, like ELISA.

Conclusion: "Clinically, the finding that TUBEX detects IgM but not IgG antibodies is important. Detecting only the IgM antibodies enhances the specificity of the assay because, unlike IgG, these are found only in current infections."

"Whatever the mechanism differentiating the behavior of IgM antibodies from IgG, the TUBEX system appears ideally suited for the general diagnosis of infectious diseases, including dengue fever which can often be confused with typhoid fever clinically, where IgM antibodies constitute an important and reliable marker of the disease. The TUBEX system also provides a very rapid and simple means of detection."

Subject: **Comparative evaluation of diagnostic tests in acute serological diagnosis of typhoid fever (*Salmonella typhi)*.** *Centers for Disease Control & Prevention*

Title: "Evaluation of rapid diagnostic tests for typhoid fever."

Authors: Olsen SJ, Pruckler J, Bibb W, Thi My Thanh N, My Trinh T, Thi Minh N, Sivapalasingam S, Gupta A, Thu Phuong P, Tran Chinh N, Vin Chau N, Dac Cam P, Mintz ED.

Source: *J Clin Microbiol 2004; 42: 1885-1889*

Summary: Confirmed laboratory diagnosis of typhoid fever requires isolation and identification of S. typhi, which can be problematic in many endemic countries with limited laboratory capabilities. Here, three commercially available diagnostic tests were evaluated: Multi-Test Dip-S-Ticks (IgG detection), TyphiDot (IgG and IgM) and TUBEX (sole IgM detection). Patients presenting with ≥ 4 days of fever were enrolled; in total 59 patients and 21 controls. Patients were cases with serotype Typhi isolated from blood samples, and controls were patients with other laboratory-confirmed illness.

The sensitivity and specificity findings were 89 and 53% for Multi-Test Dip-S-Ticks, 79 and 89% for TyphiDot, and 78 and 94% for TUBEX. Widal sensitivity varied between 61 – 64%; specificity 76 - 100% depending on test site. Sensitivity was highest for all assays during the second week of illness.

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Conclusion: "Two rapid kits, TyphiDot and TUBEX, demonstrated promising results."

"Although all three assays were relatively easy to use, the TUBEX was the simplest."

"Although the sensitivity of the Multi-Test Dip-S-Ticks was quite high (89%), it had low specificity (50%). The TyphiDot and the TUBEX both had high sensitivities (79 and 78%, respectively) and specificities (89 and 94%, respectively). The Widal test was the least sensitive of the assays, and the results varied by place performed"

SEROLOGICAL DIAGNOSIS OF TYPHOID FEVER IN CHILDREN: A COMPARATIVE EVALUATION OF SALMONELLA TYPHI O-9 ANTIGEN BASED RAPID ASSAY.

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OBJECTIVE AND METHODS: To evaluate the Salmonella typhi O-9 antigen based-rapid assay (TUBEX) for serological diagnosis of typhoid fever in children. A total of 103 children with clinically suspected typhoid fever were included in the study. Twenty six children with other febrile illnesses were included as controls. Both male and female patients, 2 to 17 years of age, were investigated. The efficacy of TUBEX was compared with Typhidot and Widal test.

RESULTS: Out of 103 patients with suspected typhoid fever, 28 (27.18%) patients had blood culture-proven typhoid, while 75 (72.82%) cases had negative blood culture and thus had clinical typhoid. None of these patients with non-typhoidal illness had blood culture positive for S. typhi / paratyphi.

In the entire cohort of 103 cases (clinical and culture proven typhoid), TUBEX was positive in 89 (86.41%), Typhidot in 77 (74.76%) and Widal test in 72 (69.90%) of the patients, respectively. In the non-typhoid group TUBEX was positive in 4 (15.38%), Typhidot in 1 (3.85%) and Widal test in 7 (26.92%) patients, respectively.

Comparative evaluation of the serological tests in the entire cohort (n=103) showed that the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TUBEX were 86.41%, 84.62%, 95.70% and 61.11%, respectively. Values for Typhidot were sensitivity 74.76%, specificity 96.15%, PPV 98.72% and NPV 49.02%. Widal test had sensitivity of 69.90%, specificity 73.08%, PPV 91.14% and NPV 38.00%.
Evaluation of the serological tests in the culture-proven typhoid fever group revealed that TUBEX had sensitivity of 89.29%, specificity of 84.62%, PPV 86.21% and NPV 88.00%. Typhidot had sensitivity of 82.14%, specificity 96.15%, PPV 95.83% and NPV 83.33%, while Widal test had sensitivity, specificity, PPV and NPV of 64.29%, 73.08%, 72.00% and 65.52%, respectively.

Analysis of results according to the duration of fever showed that the maximum number of TUBEX (80.36%) and Typhidot (80.36%) were positive in patients with 7 to 14 days of fever, while Widal test was mostly positive in children with fever of more than 14 days.

CONCLUSIONS: It is concluded that TUBEX test, with a reasonable sensitivity and specificity, is a useful serological diagnostic test for typhoid fever in children.

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