Performance Characteristics of Current-Generation Immulite 2000 TORCH Assays

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The performances of seven Immulite 2000 (Siemens Healthcare Diagnostics) TORCH (Toxoplasma gondii, other microorganisms, rubella virus, cytomegalovirus, and herpes simplex virus) assays were evaluated in comparison with the performances of the ETI-MAX 3000 (DiaSorin) TORCH assays. The two systems demonstrated good agreement, and given their sensitivity, specificity, and positive predictive value, they can be used with confidence for TORCH prenatal screening.

Congenitally acquired infections can result in serious and debilitating sequelae. Prenatal screening for antibodies to the TORCH complex—Toxoplasma gondii, other microorganisms (e.g., Treponema pallidum), rubella virus (RV), cytomegalovirus (CMV), and herpes simplex virus (HSV)—is an important tool for identifying susceptible women, especially those with acute maternal infection, for whom early treatment is essential. Discriminating between primary and recurrent infection also is very important but often difficult (1–3).

To facilitate the large workload that prenatal screening creates for the clinical laboratory, several automated random-access analyzers have been commercialized. The sensitivity and specificity of TORCH IgG and IgM assays on these systems vary, and manufacturers continue to reformulate assays to improve these characteristics. In our study, we evaluated the performance characteristics of seven TORCH assays (T. gondii, RV, and CMV IgG and IgM and HSV IgG) available on the Immulite 2000 immunoassay system (Siemens Healthcare Diagnostics Inc., Tarrytown, NY) and compared them to characteristics of the ETI-MAX 3000 TORCH assays (DiaSorin S. p. A., Saluggia, Vercelli, Italy), which are currently in use in our laboratory.

This study was performed on sera (one sample/patient) prospectively collected consecutively from pregnant women referred to our microbiology laboratory for prenatal screening from September 2009 to March 2010. Approximately 500 total sera were tested for each analyte. Blood samples were clotted and centrifuged prior to testing. Results for sera analyzed using the Immulite 2000 system (IMM) were compared to TORCH assays on the ETI-MAX 3000 system (EMAX). IMM is an automated immunoassay analyzer with continuous random-access capabilities that uses enzyme-amplified chemiluminescence chemistry; EMAX is a fully automated enzyme immunoassay (EIA) microtiter plate analyzer with photometric measurement.

IMM T. gondii IgG, RV IgG and IgM, CMV IgG, and HSV IgG assays are all 2-step, solid-phase, enzyme-enhanced immunoassays which have been described previously (4), whereas the T. gondii IgM and CMV IgM assays were recently reformulated and relicensed by Siemens. The T. gondii IgM assay employs a IgM-capture sandwich method, whereby patient IgM is captured by anti-IgM bound to the solid substrate. T. gondii IgM is then identified using a T. gondii IgM-specific antigen bound to the light-emitting agent alkaline phosphatase. The new Siemens T. gondii IgM assay uses P30 antigen as the capture antigen. This antigen has been shown to be well recognized by T. gondii IgM (5). The redesigned CMV IgM assay now includes removal of potentially interfering IgG using polyclonal anti-IgG (6–12). Sera were initially assayed singly (round 1). Quantitative results were used to generate qualitative results (positive, negative, or equivocal) on the basis of each assay’s cutoffs as supplied in each manufacturer’s instructions for use. If the qualitative IMM results did not agree with the qualitative EMAX results, sera were retested by both methods in duplicate (round 2). If the results were still discrepant following retesting, they were resolved using the fully automated Vitrek immunodiagnostic assay system (VIDAS; bioMérieux SA, Marcy l’Étoile, France) for IgG and IgM to T. gondii, RV, and CMV. This reference method has been described in detail in recently published comparative studies (4, 13, 14). The Enzygnost HSV assay (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) was used to resolve discrepant results between the IMM and EMAX HSV IgG assays. The numbers of each test requiring duplicate and/or discrepant resolution testing are presented in Table 1.

The relative sensitivities and specificities of IMM assays were estimated, both before and after resolution of discrepant results. Additionally, criteria published by Lebech et al. (15) for different...
tiating probable versus possible versus unlikely primary maternal toxoplasmosis were used to classify results and are synopsized in Table 2. As per Zotti et al. (16), results of IgG avidity testing was also used to help differentiate probable from unlikely primary T. gondii infection. IgG avidity testing (BEIA; Bouty S. p. A., Milan, Italy) was performed on all sera positive for T. gondii, RV, and CMV IgM by one or both methods and interpreted according to the manufacturer. Because prevalence of primary T. gondii, RV, and CMV infection in pregnant women is generally low, frozen sera from our collection (stored at −20°C for no more than 6 months) positive for either T. gondii IgM (39 samples), RV IgM (43 samples), or CMV IgM (13 samples) were also included in the study to improve the statistical significance of IgM detection for the purpose of calculating relative sensitivity and specificity.

The positive predictive values (PPVs) of the IgM tests for cases of probable/possible primary infection by T. gondii and CMV in pregnancy were calculated by dividing the number of true cases of probable/possible primary infection by the total number of IgM-positive cases. PPVs for the EMAX and IMM assays were compared both with and without the inclusion of the frozen samples.

The 95% confidence limits for proportions (sensitivity, specificity, agreement, and PPV) and for intermethod differences in PPV were calculated by Wilson’s method and by Newcombe’s method for unpaired data, respectively (17). Note that a difference is significant at the alpha 0.05 level only if the 95% confidence interval for that difference excludes zero.

Across the seven analytes, a total of 3,612 results were obtained. Even after reassaying of duplicate samples with initially discrepant

| TABLE 2 Criteria for possible, probable, and unlikely primary maternal infection (15) |
|---------------------------------|-----------------|
| Determination                  | Criterion                                  |
| Possible                       | Seroconversion (first sample taken within 2 months before conception) and/or significant rise of IgG titers and presence of IgM and/or IgA. High IgG titers, presence of IgM and/or IgA, and onset of lymphadenopathy during pregnancy. High IgG titers and presence of IgM and/or IgA in second half of pregnancy. |
| Probable                       | Stable high IgG without IgM in the second half of pregnancy. High IgG and presence of IgM and/or IgA in first half of pregnancy. |
| Unlikely                       | Stable low IgG, with or without IgM. Stable high IgG, without IgM, in early pregnancy. |

*Positivity for any one criterion is sufficient to make the corresponding determination.*

| TABLE 3 Relative sensitivity, specificity, and agreement for the IMM assays, before and after discrepancy resolutiona |
|---------------------------------|---------------------------------|-----------------|-----------------|
| Analyte (n)                    | Resolution status | EMAX result | No. of samples | % (95% CI) | Sensitivity | Specificity | Agreement |
|                                |                   | IMM neg | IMM pos |                |             |             |           |
| T. gondii Ig G (517)            | Before            | Neg    | 407    | 0              | 100 (96.6–100) | 100 (99.1–100) | 100 (99.3–100) |
|                                |                   | Pos    | 0      | 109             | 100 (96.6–100) | 100 (99.1–100) | 100 (99.3–100) |
| T. gondii IgM (560)             | Before            | Neg    | 498    | 2              | 70.2 (56–81.3)  | 99.6 (98.6–99.9) | 97.1 (95.3–98.2) |
|                                |                   | Pos    | 14     | 33              | 73.5 (59.7–83.8) | 96.8 (98.6–99.9) | 97.3 (95.6–98.3) |
| RV IgG (500)                   | Before            | Neg    | 31     | 5               | 100 (99.2–100)  | 86.1 (71.3–93.9) | 99 (97.6–99.6)  |
|                                |                   | Pos    | 0      | 453             | 100 (99.2–100)  | 91.2 (77–97)     | 99.4 (98.2–99.8) |
| RV IgM (512)                   | Before            | Neg    | 478    | 5               | 70 (48.1–85.5)   | 99 (97.6–99.6)   | 97.8 (96.1–98.8) |
|                                |                   | Pos    | 6      | 14              | 82.4 (59–93.8)   | 99 (97.6–99.6)   | 98.4 (96.9–99.2) |
| CMV IgG (503)                  | Before            | Neg    | 128    | 1               | 100 (99–100)     | 99.2 (95.7–99.9) | 99.8 (98.9–100) |
|                                |                   | Pos    | 0      | 374             | 100 (99–100)     | 99.2 (95.7–99.9) | 99.8 (98.9–100) |
| CMV IgM (521)                  | Before            | Neg    | 495    | 4               | 57.9 (36.3–76.9) | 99.2 (98–99.7)   | 97.7 (96–98.7)  |
|                                |                   | Pos    | 8      | 11              | 93.3 (70.2–98.8) | 99.8 (98.9–100)  | 99.6 (98.6–99.9) |
| HSV IgG (499)                  | Before            | Neg    | 105    | 19              | 100 (99–100)     | 84.7 (77.3–90)   | 96.2 (94.1–97.5) |
|                                |                   | Pos    | 0      | 372             | 100 (99–100)     | 92.1 (85.7–95.8) | 98.2 (96.6–99)  |

*Equivocal results were not tabulated.*
results, 97 discrepancies remained. To resolve the status of these discrepant results as true or false, the samples in question were then assayed by the reference method (Table 1). The comparative study results obtained both before and after resolution are presented in Table 3; equivocal results are not shown. Agreement between the two assays was good for all tests. Relative sensitivities for the Immulite T. gondii IgM, RV IgM, and CMV IgM were 70.2%, 70%, and 57.9% after round 2 (retesting in duplicate) but increased to 73.5%, 82.4%, and 93.3%, respectively, after resolution (retesting with the reference method). The low preresolution relative sensitivity (57.9% for Immulite CMV IgM) was caused by 15 discrepant CMV IgM sera. Following resolution, 10 were determined to be negative, four were positive, and one remained equivocal.

As described above, by the criteria of Lebech et al. (15) and Zotti et al. (16), 15 serum samples indicated a probable/possible primary Toxoplasma infection (IgG*, IgM*, and low-avidity IgG). Only 12 of these sera were IgM positive according to both the IMM and EMAX assays, while three were IgM negative according to IMM but positive according to EMAX. Analysis by IMM of multiple sera collected before and after the study period from the same women consistently indicated that they were negative for IgM in two of the three discrepant cases (Tables 4 and 5).

Using all criteria (duplicate/resolved results, Lebech criteria, and avidity results), the PPVs of the T. gondii IgM test for primary toxoplasmosis were calculated to be 39.5% for IMM and 30.6% for EMAX if both the prospectively collected (fresh) and banked (frozen) samples were included in the analysis, increasing slightly to 45.5% and 38.5% if only fresh samples were included. Differences between the PPVs for each method were fairly similar regardless of whether all samples (8.9%) or only fresh samples (7%) were used. More important, for both sets, as indicated by the 95%

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**TABLE 4 Detection of T. gondii IgM in patient sera with discrepant IMM negative results**

| Patient and pregnancy week | T. gondii IgM result (index) | T. gondii IgM result (titer [UI/ml]) | IgG avidity | T. gondii IgM result (VIDAS) |
|-----------------------------|-----------------------------|-----------------------------------|-------------|-----------------------------|
|                             | IMM | EMAX | IMM | EMAX | (%) | IMM | EMAX |
| Patient 1                   |     |      |     |      |     |     |      |
| 10                          | Neg (0.4) | Pos (2) | ND | Pos (250) | L (10) | Pos |
| 12                          | Neg (0.4) | Pos (2) | ND | Pos (185) | ND | Pos |
| 32b                         | Neg (0.3) | Pos (2) | Pos (107) | Pos (127) | L (12) | Pos |
| 36                          | ND | Pos (2) | ND | Pos (137) | L (12) | ND |
| At delivery                 | Neg (0.2) | Pos (1.9) | ND | Pos (92) | L (11) | Pos |
| Patient 2                   |     |      |     |      |     |     |      |
| 11                          | Neg (0.5) | Pos (1.4) | ND | Pos (>250) | L (13) | Pos |
| 16                          | Neg (0.4) | Pos (1.2) | ND | Pos (>250) | L (13) | Equiv |
| 23                          | ND | Weakly pos | ND | Pos (232) | L (13) | ND |
| 31b                         | Neg (0.3) | Weakly pos (1.2) | Pos (196) | Pos (178) | B (16) | Equiv |
| At delivery                 | Neg (0.3) | Weakly pos (1) | ND | Pos (126) | L (13) | Neg |
| Patient 3                   |     |      |     |      |     |     |      |
| 13                          | Equiv (0.9) | Pos (2.8) | ND | Pos (184) | L (3) | Pos |
| 20                          | Equiv (0.9) | Pos (2.8) | ND | Pos (>250) | ND | Pos |
| 28                          | Equiv (0.9) | Pos (2.6) | ND | Pos (>250) | L (4) | Pos |
| 35                          | Equiv (0.9) | Pos (2.4) | ND | Pos (172) | ND | Pos |
| At deliverya                | Neg (0.8) | Pos (2.4) | ND | Pos (183) | L (4–5) | Pos |

*a* Neg, negative; Pos, positive; Equiv, equivocal; ND, not determined; L, low; B, borderline.

*b* Sample included in the study.

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**TABLE 5 Analysis of discrepant cases for CMV IgM**

| Patient and pregnancy week | CMV IgM | CMV IgG | IgG avidity | VDAS CMV IgM (AU/ml) | Result of: |
|---------------------------|---------|---------|-------------|----------------------|------------|
|                           | IMM (index) | EMAX (index) | IMM (index) | EMAX (IU/ml) | Antigenemia | Urine culture | Bronchial washing |
| Patient 1                 |         |         |             |                      |            |              |                |
| 10b                       | Pos (1.6) | Neg (0.6) | Pos (11) | Pos (4.5) | L (20–22) | Pos | ND | ND | ND |
| 11                        | ND | ND | ND | ND | ND | Neg | Pos | ND |
| Patient 2                 |         |         |             |                      |            |              |                |
| 9b                        | Neg | Pos (3) | Pos (9.2) | Pos (2.3) | L (13–15) | Neg | ND | ND | ND |
| 11                        | ND | Pos | ND | Pos (2.6) | L (15) | ND | Neg | Neg | ND |
| Patient 3                 |         |         |             |                      |            |              |                |
| 15b                       | Neg | Pos (13) | ND | Pos (1.7) | L (2) | Equiv | Neg | Pos | ND |

*a* Neg, negative; Pos, positive; Equiv, equivocal; ND, not determined; L, low.

*b* Sample included in the study.
confidence limits, there was no statistically significant difference between the IMM and EMAX PPVs. Because many laboratories may base results on only a single assay method run singly, we also evaluated PPVs for both assays on only the initial (round 1) results. When only these results were considered, PPVs were remarkably similar to PPVs calculated following two rounds of assays and third (resolution) assay (Table 6). The difference between the IMM and EMAX assays under these conditions also was not statistically significant.

According to the CDC, diagnosis of CMV primary infection is supported when at least one of three conditions is met: sera are IgG⁺ and IgM⁺ and demonstrate low-avidity IgG, positive CMV antigenemia is demonstrated, or CMV is identified by PCR or viral culture (18). Thirteen cases met these criteria; of these, 10 were identified as IgM positive using IMM on the basis of a single serum sample, with full agreement being observed between the IMM and EMAX methods. For fresh and frozen samples combined, analysis of discrepant sera yielded a PPV of 86.7% for primary CMV infection using the IMM CMV assay, regardless of whether only round 1 or round 2 with resolution data was used, versus 68.4% for the EMAX method. When only fresh samples were used, the IMM and EMAX PPVs were identical using only round 1 results, whereas the PPV of IMM was greater than that of EMAX when all data were applied. As with the T. gondii IgM assay, none of the differences in PPV between IMM and EMAX were statistically significant (Table 6).

A reliable diagnosis of acute T. gondii, RV, or CMV infection in pregnant women is the main objective of the TORCH diagnostic assays. Sensitivity and specificity for routine serological diagnosis vary depending on the commercial test used. Generally, detection of IgM antibodies is a sensitive indicator of an ongoing or recent infection; however, poor sensitivity or the presence of residual IgM can make diagnosis of primary infection challenging (19–21). Improvements in IgM and IgG avidity assays assist the clinician in detecting acute infection and distinguishing between a primary and secondary immune response (22–25).

Sensitivity is a very important parameter of an IgM test; detection of IgM not related to a primary infection generates concern, however, and the PPV of the test should also be considered in evaluating its performance (26).

In our evaluation, we found that the Immulite 2000 T. gondii and CMV IgM assays had PPVs which, although low, as would be expected in a low-prevalence population, were not statistically significantly different from that of the comparison method (ETI-MAX), in spite of the lower relative sensitivity of IMM T. gondii IgM and IMM CMV IgM. It is possible that improvement in the PPV of the new IMM T. gondii IgM over that of the previous assay may be related to the inclusion of the P30 antigen used to specifically capture IgM, but ascertaining if this hypothesis is correct is beyond the scope of our laboratory (5, 27).

Regarding RV, no primary infection occurred during the study period, and all discrepant IgM-negative and IgM-positive sera contained high-avidity IgG. In addition, most of the discrepant IgG-positive sera (responsible for the low relative specificity) and most of the discrepant IgM-negative sera (responsible for the low relative sensitivity) matched the reference method results.

The performances of the Immulite 2000 assays for T. gondii, CMV, RV, and HSV IgG detection were also considered. The Immulite 2000 T. gondii IgG and CMV IgG assays showed good concordance with the comparison method, probably because of the design similarity between these assays. The low relative specificity of the Immulite 2000 RV IgG could be ascribed to problems in assigning the cutoff for the comparison method, since of the five discrepant IgG-positive sera, two were confirmed by the reference method and three were equivocal. Differences in assay reagents could explain the low relative specificity of the Immulite 2000 HSV IgG assay: the Immulite 2000 assay incorporates the McIntyre inactivated strain and G strain, whereas the comparison assay uses purified gB-1 protein. However, most of the discrepant IgG-positive sera matched the reference method results.

The current-generation Immulite 2000 TORCH assays show performance that is similar to (15, 28–32) or better than (4) those previously reported in comparative studies, as well as being similar to the performance of the ETI-MAX assays commonly used in our laboratory, confirming that these assays are suitable for routine prenatal screening. In the case of IgM positivity, however, the IgG avidity test is still mandatory for discriminating between primary infection occurring before and early in pregnancy.

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