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Traditional versus reverse syphilis algorithms: A comparison at a large academic medical center

Craig D. Dunseth, Bradley A. Ford, Matthew D. Krasowski*

Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

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ABSTRACT

Objectives: An increasing number of institutions are transitioning from the traditional syphilis testing algorithm (initial screening with nontreponemal tests) to the 'reverse' algorithm (initial screening with treponemal tests such as syphilis IgG). The aim of this study was to evaluate the switch in syphilis algorithm at an academic medical center with a population with low syphilis prevalence.

Design and methods: We performed a six-year retrospective study at the University of Iowa Hospitals and Clinics, an academic medical center, comparing the traditional algorithm (n = 12,612) with the reverse algorithm (n = 10,453). False positives were considered to be positive screens with negative confirmatory testing.

Results: Using the traditional algorithm, 93 samples (0.7% of total) screened positive with RPR, with 40 of these samples having negative TP-PA testing (43% of positive screens, 0.3% of total). Using the reverse algorithm, 110 screened positive with syphilis IgG (1.1% of total), and 33 of these samples had both negative RPR and TP-PA (30% of positive screens, 0.3% of total). In both algorithms, higher RPR titers and syphilis IgG values were associated with increased probability of positive confirmation.

Conclusions: In this study at an academic medical center, the reverse algorithm had significantly more total positive screens than the traditional algorithm. Both algorithms produced equivalent rates of active infection. The quantitative difference in positives between the two algorithms are the category of patients who are syphilis IgG positive, RPR non-reactive, and TP-PA reactive. Specimens with higher RPR titers and syphilis IgG values are more likely to confirm positive.

1. Introduction

Serologic testing has been the standard for syphilis diagnosis. Serologic testing is divided into two major groups: treponemal, which tests for specific antibodies to *Treponema pallidum* (the causative organism), and nontreponemal, which tests for antibodies formed in response to cellular damage [1]. The use of nontreponemal or treponemal tests in isolation is not ideal as each type of test has limitations; hence, there are two commonly used approaches for the serologic diagnosis of syphilis – traditional and 'reverse' algorithms [2].

The traditional testing algorithm for syphilis begins with a screening nontreponemal test such as rapid plasma reagin (RPR), with positive results followed by a confirmatory treponemal test such as fluorescent treponemal antibody or *T. pallidum* particle agglutination assay (TP-PA) [3]. RPR titers are sensitive, decrease with treatment, and have traditionally been more convenient and less expensive to perform than treponemal tests, rationalizing this algorithm. With increasing automation and decreasing cost, an

* Correspondence to: University of Iowa Hospitals and Clinics, Department of Pathology, C-671 GH, 200 Hawkins Drive, Iowa City, IA 52242, USA.
E-mail addresses: craig-dunseth@uiowa.edu (C.D. Dunseth), bradley-ford-1@uiowa.edu (B.A. Ford), mkrasows@healthcare.uiowa.edu (M.D. Krasowski).

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increasing number of institutions have adopted a reverse testing algorithm which first screens with a treponemal test (e.g., syphilis IgG); reactive samples are then tested by RPR which is used to assess disease activity [4]. Discordant syphilis IgG and RPR results are resolved by a second treponemal test (e.g., TP-PA), as recommended by the Centers for Disease Control and Prevention (CDC) for laboratories adopting the reverse algorithm [5]. In the setting of a positive syphilis IgG and non-reactive RPR, a nonreactive treponemal test result indicates a false positive syphilis IgG screen because TP-PA has higher analytical sensitivity than syphilis IgG screening [6]. Conversely, a reactive result suggests prior treated syphilis or late/latent syphilis for which the CDC recommends treatment to decrease possibility of developing tertiary syphilis [5].

Per the above discussion, it is important to distinguish analytical false positive results from clinical false positive results. A positive syphilis IgG screen with negative RPR and TP-PA confirmatory testing can be considered an analytical false positive. A positive syphilis IgG with positive TP-PA and negative RPR may be an analytical false positive due to cross-reacting antibodies or an analytical true positive result in late/latent syphilis or past/treated syphilis with persistent anti-syphilis IgG. Patients with or without signs and symptoms of syphilis and a positive/negative/positive set of results are empirically treated given that there is no definitive gold standard for diagnosis of latent syphilis, treatment with penicillin G benzathine is inexpensive, and personal and public health consequences of a missed opportunity to treat can be large. For the reverse algorithm, we therefore refer to syphilis IgG-positive, RPR-negative, TP-PA negative patients as “false positive”; and syphilis IgG-positive, RPR-negative, TP-PA positive patients as “positive”. For the traditional algorithm, we refer to a reactive RPR with a nonreactive TP-PA as "false positive", and a reactive RPR with positive TP-PA as “positive”.

As defined above, multiple studies have noted an increased rate of false positives with the reverse compared to the traditional syphilis algorithm [4,7–10]. This represents one of the major potential limitations of the reverse algorithm [11]. False positives can cause anxiety for providers and patients and potentially lead to unnecessary treatment. Previously undetected patients with positive syphilis IgG, negative RPR, and positive TP-PA also contribute to the burden of anxiety and treatment. Though there is no gold-standard test to adjudicate these results, this set of patients is more likely to have syphilis if they belong to a population where syphilis is more prevalent.

The University of Iowa Hospitals and Clinics (UIHC), a state academic medical center, switched from the traditional to the reverse syphilis algorithm in February 2013. According to data from the CDC, the incidence of primary and secondary syphilis in the state of Iowa has increased from 0.8 per 100,000 to 3.4 per 100,000 from 2009 to 2013, with the increase primarily in men who have sex with men [12], similar to overall national trends [13]. There were no cases of congenital syphilis reported in Iowa from 2009 to 2013 [12]. In the present study, we performed a six year retrospective analysis of syphilis testing results before and after the switch to the reverse syphilis algorithm at UIHC. A main focus of our study was how the reverse algorithm performed over a multi-year timeframe with respect to the distribution of positive and false positive results. A secondary aim was to evaluate whether higher syphilis IgG quantitative values and RPR titers associated with increased rates of positive TP-PA testing.

2. Materials and methods

2.1. Study population

With approval from the University of Iowa Institutional Review Board (protocol # 201501705), a retrospective study comparing results from the traditional syphilis algorithm (n = 12,612 screening tests; May 1, 2009 to February 24, 2013) with the reverse algorithm (n = 10,453 screening tests; February 25, 2013 to October 12, 2015) was performed for UIHC (see Fig. 1). UIHC is a 734 bed tertiary care academic medical center that includes an emergency department, adult and pediatric inpatient floors, and multiple intensive care units (cardiovascular, medical, neonatal, pediatric, and surgical/neurologic). Primary care and specialty outpatient clinics are provided at the main medical campus as well as at clinics throughout the local region. UIHC is a regional center for high-risk obstetric and neonatal care.

2.2. Laboratory analyses

Syphilis IgG testing was performed on a Bioplex 2200 analyzer (Bio-Rad Laboratories, Hercules, CA, USA) using the Syphilis IgG (*T. pallidum*) assay in the UIHC core clinical laboratory. Samples are run 24 h a day and results can auto-verify if quality criteria are met [14]. Following the information in the assay package insert, the following were the reference ranges for the syphilis IgG assay using units of antibody index (AI): 0.8 AI or lower, negative; 0.9–1.0 AI, equivocal; 1.1 AI or greater, positive. RPR and TP-PA tests were referred to a commercial reference laboratory (ARUP Laboratories, Salt Lake City, UT, USA). After UIHC switched to the reverse algorithm, stand-alone RPR testing was available to order only as a follow-up test to check for treatment response [termed “Syphilis treatment follow-up (RPR with reflex titer)” in the electronic order entry system], as the reflex confirmation following an equivocal or positive syphilis IgG result, or for specific protocols (e.g., some organ transplant donor evaluations) that do not allow the use of reverse algorithm. Screening recommendations for syphilis at UIHC did not change during the retrospective time periods. For obstetric patients, the goal was universal testing unless specifically refused by the mother.

2.3. Retrospective chart review

Clinical histories were reviewed for patients who screened positive or equivocal for screening tests in either algorithm. Chart review included prior documented history of syphilis, prior treatment for syphilis, and treatment following results. Screening values/