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SYPHILIS: A SYSTEMATIC REVIEW WITH EMPHASIS ON CLINICAL, EPIDEMIOLOGICAL, DIAGNOSTICS AND TREATMENT

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ABSTRACT

Syphilis is a chronic, systemic bacterial infection caused by Treponema pallidum subspecies pallidum, a pathogen recognized as a major public health threat for centuries. Despite the availability of effective antimicrobial therapy, syphilis continues to impose a substantial global burden, with an estimated 5 million new cases reported annually, disproportionately affecting populations in low- and middle-income countries. Objective: This systematic review aimed to synthesize current evidence on the clinical spectrum, epidemiological trends, diagnostic modalities, and treatment strategies of syphilis, with particular emphasis on dermatological manifestations and dermoscopic evaluation. A systematic literature search was conducted across PubMed and Scopus databases using the following search terms: “syphilis,” “diagnosis,” “dermoscopy,” “management and treatment,” “laboratory tests and syphilis,” and “primary OR secondary OR tertiary OR congenital syphilis.” Of 100 articles initially identified, 47 met the predefined inclusion criteria and were incorporated into the final analysis. The review synthesized evidence on the full clinical spectrum of primary, secondary, tertiary, and congenital syphilis, with detailed characterization of cutaneous manifestations and dermoscopic features. Established and emerging diagnostic modalities were systematically evaluated with respect to their diagnostic accuracy and alignment with current clinical guidelines. Treatment and management strategies across all disease stages were critically appraised in accordance with applicable international guidelines. Syphilis represents a resurgent global public health challenge demanding strengthened advocacy, sustained community engagement, and increased research investment. Priority areas include the advancement of point-of-care diagnostics, the development of reliable treatment-response biomarkers, the reinforcement of public health surveillance infrastructure, and, ultimately, the development of an effective preventive vaccine.

Keywords: Syphilis; Epidemiology; Diagnosis; Treatment

INTRODUCTION

Syphilis is a systemic sexually transmitted infection caused by Treponema pallidum subspecies pallidum, a gram-negative spirochete belonging to the family*Treponema pallidum* is the etiological agent of syphilis, belongs to the family *Spirochaetaceae*. As a bloodborne pathogen capable of infecting virtually every organ system, T. pallidum produces a wide spectrum of clinical manifestations that closely mimic numerous infectious and non-infectious conditions, rendering accurate diagnosis particularly challenging. Given this diagnostic complexity, clinical assessment must be consistently corroborated by appropriate laboratory investigations [1-3]. Transmission of syphilis may occur through direct sexual contact with an infectious lesion, transfusion of contaminated blood or blood products, vertical transmission from an infected mother to her fetus during pregnancy or at delivery, or accidental occupational exposure [1, 3]. Following exposure to infectious material, an asymptomatic incubation period of approximately 21 days precedes the onset of clinical disease. The infection subsequently progresses through well-defined stages: primary syphilis, characterized by a painless, indurated genital, anal, or oral chancre at the site of bacterial entry; secondary syphilis, presenting with constitutional symptoms including fever, generalized lymphadenopathy, and a diffuse mucocutaneous rash; and late or tertiary syphilis, an often destructive stage in which patients may develop neurosyphilis, cardiovascular involvement, or gummatous lesions of the skin, bone, and visceral organs [2]. Accurate staging is fundamental to guiding appropriate therapeutic intervention.

Among the available diagnostic tools, direct detection of *Treponema pallidum* from lesion material by dark-field microscopy or polymerase chain reaction (PCR) represents the most definitive approach; however, serological testing remains the cornerstone of routine clinical practice [4, 5]. Two complementary categories of serological assays are employed: non-treponemal tests—including the rapid plasma reagin (RPR), the venereal disease research laboratory (VDRL) test, and the toluidine red unheated serum test (TRUST)—which are semi-quantitative assays detecting IgM and IgG antibodies against lipoidal antigens released from damaged host cells; and treponemal-specific tests, including the *Treponema pallidum*microhemagglutination assay (TPMA), the *Treponema pallidum* hemagglutination assay (TPHA), fluorescent treponemal antibody-absorbed (FTA-ABS) test, enzyme immunoassay (EIA), and chemiluminescence immunoassay (CLIA)—which detect antibodies directed against specific treponemal antigens [2, 6]. Seroconversion following initial infection requires approximately 3 to 6 weeks, rendering serology unreliable during the earliest phase of primary syphilis. Moreover, treponemal assays cannot distinguish between active, remote, or treated infection, and false-positive results may arise due to cross-reactivity in immunocompromised states or autoimmune disorders. Current guidelines therefore recommend a combined diagnostic strategy incorporating both non-treponemal and treponemal assays, with confirmatory testing essential to minimize diagnostic error [2, 6]. In contemporary practice, rapid immunochromatographic test strips simultaneously detecting both antibody classes have gained widespread adoption as point-of-care tools. Acknowledging the global resurgence of syphilis and the evolving complexity of its clinical and laboratory diagnosis, the present systematic review provides an integrated overview of the clinical presentations, epidemiological trends, diagnostic strategies, and treatment approaches for syphilis—with particular attention to dermatological manifestations and dermoscopic assessment—to support clinicians and public health practitioners in the management and control of this re-emerging infection. Of note, the specific *Treponema pallidum* antibodies they detect constitute part of the diagnostic evidence base synthesized herein.

METHODS

A literature review was performed in PubMed and Google Scholar, using the search phrases “syphilis,” “diagnosis,” “dermoscopy,” “management AND treatment,” “laboratory tests AND syphilis,” and “primary OR secondary OR tertiary OR congenital syphilis.” This analysis covered 47 publications from a total of 100.

Background: *Treponema pallidum* is the causative agent of syphilis, as well as a major blood borne microbial pathogen. During 15th century syphilis became to recognize as a new disease. There were two theories behind emergence of syphilis, may be through Columbus and his crew members during travelling from new world to Europe or else syphilis is already existed in Europe but undiagnosed [7-10]. In 1905, *Treponema pallidum* first found by Schaudinn and Hoffmann in lymph nodes and chancres of syphilis infected patient. Trponema is thread like, short, slender, spirals with pointed and rounded ends. Some of the treponemes are pathogenic and some are present as commensals in host [11].

Classification and morphological features: Spirochetes are slender, elongated, motile coil like flexible bacteria. Spirochetes are structurally more complex than other bacteria with characteristics endoflagella between the outer membrane and cell wall. This phylum is subdivided into three families, such as *Spirochetaecae*, *Brachyspiraecae* and *Leptospiraecae*. The genus Treponema comes under Spirochetaecae family and divided into 9 subtypes. The four major *Treponema spp* are pathogenic to human; such as *Treponema pallidum subsp. pallidum*, *Treponema pallidum subsp. endemicum*, *Treponema pertenue* and *Treponema carateum* [12-14]. Treponema pallidum a causative agent of syphilis is a thin delicate organism with pointed ends about 10 µm in length and 0.1-0.2 µm in width. It has about ten regular spirals at 1 µm of the regular interval. It is motile by endoflagella and rotates around long axis with backward and forward movement; look like cork and screw movement.

Genomic structure and metabolism: The Treponema pallidum genome is 1014 kb pairs of the small circular chromosome consisting 1041 open reading frames [15-17]. The genome of T. pallidum is smaller in size, similar to the genome of *Mycoplasma* and *Borellia*[18]. Depend on the SDS-PAGE findings Treponema pallidum protein pattern was prefix as TpN followed by molecular weight of the proteins, like TpN 47, TpN 17, TpN 15 and TpN 44 etc. The outer membrane of Treponema pallidum contains very low number of proteins and this outer membrane protein thought to be involved in membrane permeability. The genome of this bacterium does not contain any restriction modification gene or

transposons. There is higher level of nucleotide sequence homology between all the subspecies of *Treponema*. The single nucleotide differences between Treponema subspecies are described by Sanger sequencing and restriction fragment length polymorphism (RFLP) analysis. Although there is sequence similarity, but clinical features are not similar between the subgroups. Usually, pathogenic bacteria share their virulence features by horizontal gene transfer, plasmid mediated gene transfer, bacteriophage-mediated or transposons mediated gene transfer. But these mechanisms are not applicable for *Treponema* as they lack of these gene. The main feature of *Treponema* is, they can live inside the host but cannot replicate outside environment. Till now it has'nt been understandable that, why Treponema is not resistant to penicillin drug, after its long-term use; since 1943 and why it is not possible to culture the bacteria in artificial culture media rather than human or rabbit host. Treponema pallidum only depends on the host for their growth requirements; such as energy production based on the glycolysis as they lack of enzymes act on electron transport chain and tricarboxylic acid cycle. Therefore, multiplication time required for the Treponema is around 30-33 hrs both in in-vitro or in-vivo. Treponema pallidum is micro-aerophilic, requires 1.5-5% oxygen for the growth. The organism growth and survival depend on the temperature; Treponema can grow at 32-36ºC and killed at 45ºC. In human Treponema can be isolated frequently from skin lesions and very few from blood, because skin is cooler than blood. The heat sensitivity of Treponema is due to lack of heat shock gene [16-18].

Cultivation: The pathogenic strains of Treponema pallidum cannot cultivate artificially. The Nichol's strain one of the most virulent strains can be maintained by several serial passage in rabbit's testicle. The non-pathogenic treponemes (Reiter strain) can be cultured artificially in thioglycollate broth containing serum. The Reiter strain is widely used as antigen in the antibody specific treponemal test for the detection of syphilis infection [19].

Syphilis epidemiology and mode of transmission: Syphilis is one of the sexually transmitted disease prevalent worldwide. An estimated 18 million syphilis cases were reported globally and 5.6 million syphilis infected individuals were between 15-49 years age groups. The perinatal morbidity and mortality were higher in syphilitic pregnant women, around 1.36 million syphilis infected pregnant women were reported in the year 2008. In 2016, approximately 88,042 new cases of syphilis were reported. Syphilis can transmit through person-to-person direct contact with chancre. Sexual contact is the most common way to transmit the infection. Syphilitic mother to her child transmission is the second most common mode of transmission [20-21].

Pathogenesis and clinical features: Syphilis is sexually transmitted disease caused by *Treponema pallidum*. It has various infective stages with distinct clinical features and pathology. The various clinical stages of syphilis classified as; primary, secondary, late or tertiary syphilis and congenital syphilis. In the primary stage, after few hours of initial entry bacteria disseminate throughout the body. The skin surrounding the primary lesion or at the point of entry forms an edematous lesion consist of inflammatory cells. The base of the lesion is fibrotic, and the centre of the chancre consists of hyaluronic acid and chondroitin sulphate. Within 1-5 weeks the lesions disappear. The inguinal lymph nodes may be slightly enlarged. Bacteria can be demonstrated from the serous discharge, but specific antibodies to treponemes can be detected after 1-4 weeks of development of chancre. The secondary stage of syphilis, the bacterial invasion takes place in every organ of the body. Non-specific symptoms may develop include fever, sore throat, headache, anorexia, skin rash, condylomatalata etc. The pathogenesis of late syphilis is not clearly understood, but symptoms may appear after 10-20 years of initial infection. The gumma may develop on skin, mucosa, bones, viscera, ocular structure and muscles [22-26]. The prevalence of neurosyphilis was reported 6.5% in syphilis infected individual. The syphilitic meningitis may develop during the secondary stage but usually a characteristic feature of late syphilis. In neurosyphilis, may develop endarteritis and granular ependymitis with vascular occlusion, thrombosis and cerebral infarction. Therefore, obstruct the flow of CSF and develop hydrocephalus. In congenital syphilis bacteria directly invade the fetal circulation, so there is no primary stage of infection. The common clinical manifestations are seen in congenital syphilis; cutaneous lesions, osteochondritis, hepatosplenomegaly and deafness, blindness, snuffles. The symptoms may develop after 3 weeks to 6 months of infection and 50% of the infant are asymptomatic at birth [27-30].

Laboratory diagnosis of syphilis: The diagnosis of syphilis divided into 4 groups; direct microscopic examinations for detection of treponemes from lesions, non-treponemal test, and treponemal antibody test and direct antigen detection.

Apart from that nucleic acid-based assays are the gold standard technique for the detection of specific *Treponema pallidum* gene.

Direct microscopic technique: Demonstration of treponems from syphilitic lesions by microscopic method is a gold standard method. Primary syphilis can be detected by darkfield microscopy. The organism can be detected several weeks before the appearance of antibodies to treponemes. The negative direct microscopy does not exclude the syphilis infection. In dark field microscopy dark field condenser are needed to perform the test. The light ray reflects from an object only enter in to the microscope, so only illuminated organism can be seen under microscope against a dark back ground. This method is useful during primary, secondary and early congenital syphilitic stage, when viable treponemes are more in number [25, 31].

Direct fluorescent antibody technique (DFA-TP): DFA-TP test is antigen-antibody reaction, detect the specific antibody against *Treponema pallidum*. A fixed smear is stained with fluorescein-isothiocyanate labelled anti-*Treponema pallidum* globulin and absorbed with FITC-conjugated mouse monoclonal antibody. This method can be used to detect *T. pallidum* subspecies in body fluids, secretions, lesion exudates and tissues [32-33].

Immunohistochemical method: It is a staining technique, uses a color reaction to identify the treponemes. Enzyme used in this method is either alkaline phosphatase or peroxidise. The slides are counterstained with hematoxylin to identify the treponemes and tissue morphology under bright-field microscopy [34-38].

Serological diagnosis: The easiest method to detect syphilis is serological based assays. This method is subdivided in to two; such as non-treponemal test and Treponemal antibody test. The non-treponemal tests are rapid, inexpensive easy to use methods to the diagnosis of syphilis. The principle of the test based on the detection of IgM and IgG antibodies against lipoidal proteins released from damaged host cells. The cardiolipin attached with cholesterol and lecithin to form an active antigen used in non-treponemal test (Venereal Disease Research Laboratory). In unheated serum regain (USR) extra addition of choline chloride and EDTA avoid to heat the serum specimen prior testing. Rapid plasma reagin (RPR) test is modification in USR; charcoal is added to the antigen mixture. The modification of RPR test is toludine red unheated serum test (TRUST). This flocculation method is the screening test for the qualitative and semi-quantitative detection of antibodies to treponemes. The capture-S solid phase red-blood-cell adherence assay used to detect the non-treponemal antibody in patient serum or plasma. The microtitre well coated with the VDRL antigen, patients' serum added to the well, presence of non-treponemal antibody react with the antigen [39-40]. The indicator red cells coated with antihuman IgM and IgG added to the well if antigen- antibody complex present it produces the mat of cells. The non-treponemal test has certain limitations; such as prozone phenomenon, false positive test result. In contrast the treponemal antibody tests are more specific for the detection of syphilis. Usually agglutination tests, fluorescent antibody tests and enzyme immune assays are commonly used in diagnostic laboratories. The fluorescent treponemal antibody-absorption (FTA-ABS) test is an indirect fluorescent antibody test for the diagnosis of syphilis. The test sera are bound with the treponemes, if there is antigen-antibody reaction FITC-labelled antihuman immunoglobulin attach with the complex. FITC-stained treponemes are visible under fluorescence microscopy. Syphilis can be diagnosed also by hemagglutination assay. The presence of specific antibody to *Treponema pallidum* in patient serum can be detected by indirect agglutination of sensitized erythrocytes and formation of the mat. *Treponema pallidum* hemagglutination assay (TPHA) and Microhemagglutination assay for antibodies to *Treponema pallidum* (MHA-TP) are the two indirect hemagglutination assays for the diagnosis of syphilis. In particle agglutination assay for the detection of the treponemal antibody, instead of erythrocytes, gelatin is used in agglutination reaction. The enzyme immunoassay proved to be highly specific and sensitive technique in syphilis diagnosis. Several modifications happened in enzyme immune assay. Currently most of the enzyme immune assay relies on recombinant protein-based diagnosis. The most frequently used recombinant proteins in enzyme immune assay are TpN17, TpN15 and TpN47. Western blot technique is one of the standard methods in the diagnosis of syphilis. In this method nitrocellulose membranes are coated with specific proteins of *Treponema pallidum* according to their molecular weight. If the patient serum contains the specific antibody, it will bind to that coated antigen and form a visual band on the strip. But it is not useful in routine diagnostic purpose. Immunochromatographic test strips are useful as point of care diagnostic assay for syphilis. A membrane filter paper is coated with specific treponema antigen in a lateral flow device. Test serum contains specific antibody makes an antigen-antibody complex and it can be visualized as color band on the

test strip. Although treponemal antibody tests are specific and sensitive method for the diagnosis of syphilis but there is chance to get false positive result due to cross reaction with other diseases; such as autoimmune disorders, HIV, etc. Therefore, it is recommended that syphilis diagnosis can be performed by using non-treponemal and treponemal antibody test simultaneously to overcome the diagnostic bias from the single type assay. Another highly specific and sensitive test for syphilis is molecular based assay. The polymerase chain reaction is highly sensitive technique to detect bacterial specific genes by using nucleic acid amplification [39-44].

Treatment of syphilis: Before the advent of penicillin, a variety of treatments for syphilis were utilized, ranging over the centuries to include purgatives, thermal therapies, and infectious agents. In the 19th century, mercury was widely used in oral medications, topical ointments, injections, and even fumigation, although treatments might require years to demonstrate effectiveness. In 1908, Paul Ehrlich was awarded the Nobel Prize for his discovery of arsphenamine (Salvarsan), an arsenic-derived compound considered the first contemporary antimicrobial agent [43]. It was introduced in the early 1910s as the first effective treatment for syphilis and African trypanosomiasis. Salvarsan was administered together with bismuth or mercury, with more than 30 doses recommended to prevent relapse and thought to effectively reduce the risk of neurosyphilis, although this progress occurred in many patients nonetheless. In 1927, Julius Wagner-Jauregg was awarded a Nobel Prize for developing malariotherapy to treat neurosyphilis, based on the concept that infecting patients with Plasmodium vivax induced a fever that could eradicate heat-sensitive T. pallidum bacteria [45]. Since 1943, penicillin has successfully treated syphilis; with no reported resistance cases to date, it remains the preferred treatment option. Benzathine penicillin G is the treatment of choice for syphilis in all stages [36-40]. However, it is important to take into account the treatment regimen depending on the stage, any pregnancy status, existing allergies, or if the patient experiences neurosyphilis, otic syphilis, or ocular syphilis. In any allergic scenario, it is advised to give doxycycline 100 mg twice daily for 14 days in early syphilis and for 28 days in the late stage. Physicians should consider empiric treatment when the clinical signs and epidemiological risk suggest increased suspicion, particularly when follow-up is unpredictable. It is essential to note that CDC treatment guidelines for every stage, including neurosyphilis, otic syphilis, and ocular syphilis, are unaffected by HIV status or nontreponemal test titer [44]. The treatment regimen should also be communicated to the patient’s partners accordingly. The response to treatment is assessed through clinical and serological methods [44, 46]. The treatment for primary, secondary, and early latent syphilis includes a single dose of 2.4 million units of benzathine penicillin G administered intramuscularly. The therapy involves administering benzathine penicillin G 2.4 million units intramuscularly once weekly for 3 straight weeks. Neurosyphilis, otic syphilis, and ocular syphilis necessitate therapy with intravenous aqueous crystalline penicillin G for a duration of 10–14 days. Since benzathine penicillin G is the sole treatment with proven effectiveness for both the pregnant person and the fetus, pregnant patients need to be desensitized and receive penicillin therapy [44, 46]. Patients should be advised to seek care if symptoms do not improve within 2 weeks. Suspected treatment failure requires further assessment and management that exceeds what is covered in this article. Absence of titer reduction (known as serologic nonresponse) impacts 12–20% of individuals with primary and secondary syphilis and is linked to reduced baseline nontreponemal titer, advanced age, late-stage disease, and potentially HIV infection. Furthermore, increasing titers in a patient recently treated may suggest reinfection, which is relatively frequent in individuals with a syphilis history [42,47].

CONCLUSION

This review article emphasizes the revival of syphilis globally, the alterations in its epidemiology, and the difficulties in preventing and managing the infection. To address the resurgence and spread of syphilis globally, it is crucial to implement new strategies—namely, enhancing prevention and control capabilities in healthcare facilities, utilizing new testing and diagnostic methods, introducing innovative interventions for older adults, adolescents, and young adults, as well as encouraging doxy-PEP and creating vaccines.

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