REVIEW

The Multisystemic Nature of Syphilis: Challenges in Diagnosis

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Abstract: Syphilis, a chronic systemic infection caused by Treponema pallidum, reemerges as a major global health concern due to its rising incidence and wide-ranging clinical presentations. While often regarded as a sexually transmitted infection confined to the genital tract, syphilis frequently involves multiple organ systems, particularly in its secondary and tertiary stages. This review highlights the key organ-specific manifestations of syphilis, focusing on cardiovascular, pulmonary, hepatic, renal, and neurological complications. Cardiovascular involvement may include aortitis, aortic regurgitation, and coronary ostial stenosis. Pulmonary syphilis, though rare, can mimic malignancies or granulomatous diseases. Hepatic syphilis often presents as cholestatic hepatitis and, in severe cases, may progress to fulminant liver failure. Renal complications range from mild proteinuria to nephrotic syndrome and glomerulonephritis. Neurosyphilis, previously considered a late-stage and uncommon outcome, is now increasingly recognized earlier in the disease course, with a wide rage of clinical symptoms. Effective diagnosis relies on a combination of serologic testing, imaging, histopathological evaluation and, in special cases, advanced molecular techniques such as metagenomic sequencing. Timely recognition and treatment with penicillin remain critical in preventing long-term organ damage. Given syphilis's ability to imitate various conditions and affect diverse populations, increased clinical vigilance and a multidisciplinary approach are essential for effective management.

Keywords*: Syphilis, Cardiovascular Syphilis, Hepatic Syphilis, Pulmonary Syphilis, Neurosyphilis.*

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INTRODUCTION

Syphilis, a chronic systemic infection caused by *Treponema Pallidum*, continues to represent a persistent public health burden, despite the existence of effective antibiotic treatment for decades. Primarily transmitted through sexual contact or from mother to child during pregnancy, the disease has experienced a notable global resurgence in recent years, with rising rates observed in both adults and newborns [1]. According to the World Health Organization, syphilis affected nearly 20 million people worldwide in 2016, with over 7 million new infections occurring annually [2].

Contrary to initial expectations following the discovery of Penicillin in the 1920s, syphilis incidence has risen notably in recent years. Several high-income countries have reported substantial increases in prevalence, driven by factors such as reduced condom use, evolving sexual behaviors, the widespread adoption of HIV pre-exposure prophylaxis (PrEP), and challenges in public health surveillance systems [3,4]. A retrospective study from Italy revealed a 265% increase in syphilis cases over a ten-year period, while data from the UK show that incidence has tripled over the past decade [5,6]. Similar upward trends have been observed in parts of Asia and Africa, where recent findings indicate alarming prevalence rates among blood donors and pregnant women attending antenatal clinics [7,8]. Congenital syphilis, considered a rare condition, is now re-emerging as a serious public health concern. In the United States, cases increased by 755% between 2012 and 2021, with almost 3,700 affected newborns reported in 2022 [9]. On a global scale, congenital syphilis is responsible for an estimated 350,000 adverse pregnancy outcomes each year, despite being easily detectable and treatable during pregnancy [10,11].

Frequently referred to as “the Great Imitator”, syphilis can present with a wide spectrum of clinical manifestations affecting various organs, especially in its tertiary stage, which may occur years after the initial infection if left untreated [12]. Increasingly, literature has documented organ-specific complications such as cardiovascular syphilis, neurosyphilis, and hepatic, renal, or pulmonary involvement—even in individuals who are immunocompetent or have previously received treatment [13,14]. The re-emergence of syphilis has been especially observed in certain vulnerable populations, including men who have sex with men (MSM) and individuals co-infected with HIV, in whom the disease often presents atypically and progresses more rapidly [14,15].

These factors highlight the need for clinicians in all specialties to remain highly suspicious for syphilis in patients presenting with unexplained organ-specific pathology. Given its diverse and sometimes deceptive clinical presentation, heightened awareness is especially crucial in internal medicine, where patients often present with nonspecific or unexplained systemic or organ-related symptoms [15].

1. CARDIOVASCULAR SYPHILIS (CVS)

Cardiovascular syphilis (CVS) is a potentially fatal, yet frequently underrecognized, complication of tertiary syphilis that typically manifests decades after the initial Treponema pallidum infection. Although modern antibiotic therapy has significantly reduced its prevalence, recent evidence and case reports suggest a slow but concerning resurgence, particularly among individuals with untreated or incompletely treated infections [1,16]. Syphilitic aortitis may occur in up to 70–80% of untreated syphilitic patients, although only 10–15% progress to major cardiovascular events such as aortic regurgitation (AR), thoracic aortic aneurysms or coronary ostial stenosis [17]. In a large autopsy series, more than 65% of individuals with syphilitic aortitis exhibited ≥75% stenosis in at least one epicardial coronary artery, with a predilection for the right coronary ostium in 15% of cases [18].

The pathogenesis involves endarteritis obliterans of the vasa vasorum, leading to ischemic damage of the aortic media. This process causes disruption of elastic fibers, followed by fibrosis, which weakens the aortic wall. Over time, these structural changes can result in ascending aortic aneurysms, progressive aortic valve insufficiency due to annular dilation or direct valvular damage, and bilateral coronary ostial stenosis [19,20].

Clinically, syphilitic cardiovascular involvement often remains silent for years, delaying its diagnosis. One of the earliest and most common manifestations is aortic regurgitation (AR), which may lead to progressive left ventricular dilation and congestive heart failure. In a large Taiwanese population-based cohort, patients that were serologically confirmed with syphilis had an 81% higher risk of developing AR compared to those syphilis-negative. Higher incidence of acute myocardial infarction, atrial fibrillation, heart failure, and stroke was also observed in these patients [16].

As the disease progresses, patients may experience clinical symptoms such as retrosternal chest pain, exertional dyspnea, angina or even acute coronary syndrome (ACS). Physical examination may reveal a high-pitched diastolic murmur suggestive of AR or a continuous murmur in cases involving rupture of a sinus of Valsalva aneurysm. Characteristically syphilitic coronary involvement is usually referred to the coronary ostia, sparing the distal coronary vessels, a distribution that differs from typical atherosclerotic disease. This distinct pattern should raise suspicion for syphilis particularly in younger individuals lacking conventional cardiovascular risk factors [20,21,22].

Myocardial involvement, despite the fact that it is less commonly reported, can include gummatous myocarditis or, more rarely, septic cardiomyopathy. Guo et al. described two young adults who developed acute heart failure (left ventricular ejection fraction <30%) during early-stage syphilis, despite having no prior cardiac history. Both required intensive care, including extracorporeal membrane oxygenation (ECMO), and achieved near-complete recovery of cardiac function following appropriate antibiotic therapy. These cases suggest that syphilis may trigger a reversible inflammatory myocardial dysfunction, potentially mediated by cytokine release, oxidative stress, and mitochondrial injury [23].

Diagnosing CVS requires a multidisciplinary approach. Initial assessment includes serologic testing with both non-treponemal (VDRL, RPR) and treponemal (TPPA, FTA-ABS) assays. Imaging also plays a major role: transthoracic and transesophageal echocardiography can reveal aortic regurgitation or chamber enlargement, while CT angiography and cardiac MRI are used to identify thoracic aneurysms and coronary ostial stenosis. In selected cases, positron emission tomography (PET) can detect active inflammation within the aortic wall [24].

Management centers on high-dose intravenous benzylpenicillin (18–24 million units per day for 10–14 days), often followed by intramuscular benzathine penicillin for extended suppression in certain scenarios. Surgical intervention is needed in cases of large or symptomatic aneurysms, severe AR, ruptured sinus of Valsalva, or coronary stenosis not responsive to medical treatment. When CVS is accurately diagnosed and properly managed, outcomes are favorable, with case series reporting two-year survival rates above 90% in patients receiving both antibiotic therapy and surgical intervention [21,22,25].

2. PULMONARY SYPHILIS

Pulmonary syphilis, although rare, is a clinically important manifestation of Treponema pallidum infection, most commonly seen during the secondary or tertiary stages. It is often underdiagnosed due to its nonspecific symptoms and ability to

mimic other pulmonary diseases, but nowadays it is now receiving renewed attention thanks to advancements in diagnostic imaging and molecular diagnostics [26]. Hematogenous dissemination of T. pallidum during early infection can lead to involvement of the pulmonary parenchyma and pleura, even in immunocompetent individuals [27].

Radiologically, pulmonary syphilis presents with a wide range of findings. Common features include peripheral subpleural nodules, solitary or multiple rounded opacities, interstitial infiltrates, and, less commonly, cavitary lesions [28]. A recent systematic review identified pulmonary nodules as the most consistent imaging finding in patients with confirmed secondary pulmonary syphilis [27]. These nodules often show a bilateral distribution, typically sparing the central lung zones. PET-CT scans frequently reveal FDG-avid nodules with elevated standardized uptake values (SUVs), which can be mistaken for malignancies, complicating the diagnostic process [28].

Clinically, pulmonary syphilis is often asymptomatic and may be discovered incidentally during routine imaging. When symptoms do occur, they are typically mild and nonspecific, including a dry cough, vague chest discomfort, or exertional dyspnea. Systemic signs such as fever, malaise, weight loss, and the characteristic rash, especially on the palms and soles, may suggest secondary syphilis involvement. Epidemiological data indicate a predominance among males aged 30 to 60 years, though cases in individuals outside this age range have also been documented [27,29]. Histological findings in pulmonary syphilis are often nonspecific, typically showing lymphoplasmacytic infiltrates, necrotizing or non-necrotizing granulomas, and features of organizing pneumonia. A rare histologic variant—cicatricial organizing pneumonia (CiOP)—was reported by Goda et al. in a case of secondary syphilis, marking the first such instance in the literature [28].

Diagnosis requires a multidisciplinary approach, integrating clinical history, physical findings, imaging, and serologic testing. Direct detection of T. pallidum in lung tissue remains challenging due to its inability to be cultured under standard conditions. However, molecular techniques such as PCR and metagenomic next-generation sequencing (mNGS) on bronchoalveolar lavage (BAL) fluid have facilitated pathogen identification, particularly when serology and imaging are inconclusive [27]. The diagnostic criteria by Coleman and Bell include: (1) clinical features suggestive of syphilis, (2) positive non-treponemal and treponemal tests, (3) radiographic evidence of lung involvement, (4) exclusion of other diseases such as malignancy, TB, or fungal infections, and (5) resolution after appropriate antibiotic therapy [31]. Lung biopsy is rarely needed, unless alternative diagnoses are suspected.

Pulmonary gummas, a hallmark of tertiary syphilis, are exceptionally rare and characterized by necrotizing granulomas, central fibrosis, and peripheral inflammation. These lesions are frequently misdiagnosed as malignancies or chronic infections and, if left untreated, may result in permanent structural lung damage. Alsobrooks and Huang described a case where delayed recognition of tertiary syphilis led to progressive pulmonary fibrosis [32].

Treatment follows stage-specific syphilis guidelines. For secondary syphilis with pulmonary involvement, a single intramuscular dose of Benzathine Penicillin G (2.4 million units) is recommended. In cases of more widespread or suspected tertiary disease, a 10–14 day course of intravenous penicillin G is advised. For penicillin-allergic individuals, doxycycline or ceftriaxone may be alternatives, although their effectiveness in treating pulmonary lesions is less clearly defined. Radiographic improvements often occur within weeks to months after starting therapy, providing retrospective diagnostic confirmation [29,32].

3. HEPATIC SYPHILIS

Hepatic involvement in syphilis typically emerges during the secondary stage and is rather an uncommon manifestation. Referred to as syphilitic hepatitis, this disease is characterized by cholestatic liver enzyme abnormalities. In some severe cases, it can progress to acute liver failure, a life-threatening condition that may necessitate liver transplantation [33,34].

The exact pathophysiology remains unclear but is thought to involve immune-mediated mechanisms. These include portal and periportal inflammation, lymphoplasmacytic infiltration, and bile duct injury, triggered by systemic dissemination of Treponema pallidum via the bloodstream or lymphatics [34,35]. In rare tertiary forms, hepatic gummas may develop, mimicking neoplastic or granulomatous conditions.

Clinically, syphilitic hepatitis is frequently underdiagnosed because of its nonspecific presentation, or it can be masked by the systemic signs of secondary syphilis such as rash, fever, malaise, or lymphadenopathy. Typical hepatic symptoms include jaundice, right upper quadrant discomfort, anorexia, dark urine, and fatigue. Laboratory findings typically reveal elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), along with mild increases in aminotransferases and conjugated hyperbilirubinemia [35].

A 2019 systematic review of over 70 cases revealed that nearly 90% of patients with syphilitic hepatitis presented during early syphilis, with 88% showing cholestatic liver enzyme elevations [36]. Rare fulminant cases have also been documented: Gondolesi et al. reported a 20-year-old woman who developed acute liver failure requiring transplantation, with biopsy confirming syphilitic etiology [33]. In another case, Oliveira et al. described a young man initially misdiagnosed with primary biliary cholangitis (PBC) due to elevated ALP and positive antimitochondrial antibodies. High-titer VDRL testing later confirmed secondary syphilis, and under medical treatment with penicillin, his liver enzymes normalized, and it also reversed the autoantibody positivity, highlighting syphilis' potential to mimic autoimmune liver diseases [37].

Diagnosis should be taken into consideration, particularly in individuals with known risk factors for syphilis or those presenting with systemic manifestations. Serological tests remain essential, as they confirm the infection. In uncertain cases, liver biopsy may support diagnosis by demonstrating the characteristic histologic findings, although they are not pathognomonic. Advanced imaging such as MRCP may be useful if biliary involvement or obstruction is suspected, but rapid normalization of liver function following penicillin therapy is used as both a diagnostic and therapeutic confirmation. Standard treatment follows guidelines for systemic syphilis. Secondary syphilis with hepatic involvement is treated with benzathine penicillin G 2.4 million units IM once, while intravenous penicillin is reserved for severe cases. In instances of fulminant hepatic failure, early liver transplantation may be necessary if antimicrobial therapy fails to produce timely clinical improvement [36].

4. RENAL SYPHILIS

Renal involvement in syphilis represents a clinically meaningful and potentially reversible manifestation, associated with the secondary or tertiary stages of the disease. Its clinical presentation varies widely, from mild abnormalities such as asymptomatic proteinuria to severe forms like nephrotic syndrome, rapidly progressive glomerulonephritis, or even acute kidney injury (AKI) [38,39].

One of the largest biopsy-based studies to date, including 102 patients with active syphilis and renal involvement, revealed a diverse array of histopathologic patterns. Notably, over 55% of these patients were co-infected with HIV, highlightning the higher

risk in immunocompromised individuals. Most patients presented with AKI, with an average serum creatinine level of 4.7 mg/dL at the time of diagnosis [38].

Recent data showed that membranous nephropathy (MN) was the most common glomerular lesion in syphilis-related kidney disease, found in 28.4% of biopsied patients—significantly higher than in the general population [38]. These cases were typically negative for PLA2R (a marker of idiopathic MN), but they presented positive for neuron-derived neurotrophic factor (NDNF), suggesting an infectious or autoimmune origin. Immunofluorescence frequently revealed a "full-house" pattern (IgG, IgA, IgM, C3, C1q), commonly seen in lupus nephritis. Other renal findings included collapsing glomerulopathy, IgA nephropathy, and infection-associated GN. Tubulointerstitial lesions were also prevalent, with acute tubular injury in 24% and acute interstitial nephritis in 10% of cases [38]. In a case series by Sciaudone et al., two HIV-positive patients presented with nephrotic-range proteinuria and AKI. Though initially suspected of having HIV-associated nephropathy (HIVAN), biopsies confirmed MN with interstitial lymphoplasmacytic infiltrates and spirochetes, consistent with syphilitic nephropathy [39]. Similarly, Hazim et al. described a young man with severe proteinuria and hypoalbuminemia, initially diagnosed with idiopathic MN. High-titer syphilis serology led to treatment with benzathine penicillin, in both cases resulting in full clinical recovery [40].

Definitive diagnosis requires a combination of positive serologic testing, among compatible clinical and laboratory findings, and in many cases, renal biopsy to identify characteristic histopathological features, playing a key role. Spirochetes may be visualized using silver stains such as Warthin-Starry in renal tissue, although it is infrequent. Therapeutic management follows standard syphilis guidelines: intravenous Penicillin G is the treatment of choice in severe or tertiary disease, administered over 10–14 days, with or without adjunctive intramuscular therapy. Most patients experience significant renal recovery after antibiotic therapy, but a delayed diagnosis may lead to irreversible damage, such as fibrosis [39,40].

5. NEUROSYPHILIS

Neurosyphilis represents one of the most serious complications of Treponema pallidum infection, occurring as the bacteria invades the central nervous system (CNS). Despite the fact that is traditionally considered a late-stage manifestation, it can develop at any point during the course of syphilis, especially in immunocompromised patients. The clinical spectrum is diverse, ranging from asymptomatic inflammation to severe cognitive, motor, or psychiatric impairment [41,42].

Recent epidemiological data show a rising incidence of neurosyphilis alongside the global resurgence of syphilis. In Australia, cases rose from 0.97 to 2.47 per 100,000 between 2007 and 2016, while in New Zealand, neurosyphilis now represents about 5% of reported syphilis complications [43].

The pathophysiology involves the hematogenous dissemination of T. pallidum into the CNS, leading to chronic inflammation. Histopathological findings show microglial activation, perivascular lymphocytic infiltration, and meningeal thickening. Recent studies have highlighted elevated CSF biomarkers, such as soluble TREM2 (sTREM2), as indicators of neuroinflammation and microglial dysfunction, implicating both innate and adaptive immune responses [44].

Neurosyphilis encompasses a range of clinical syndromes that vary depending on the timing and severity of central nervous system involvement. Asymptomatic neurosyphilis is the most frequently observed form, identified by abnormal cerebrospinal fluid (CSF) findings in patients who lack neurological symptoms. Meningeal neurosyphilis typically

occurs within the first year of infection and may present with symptoms such as headache, nausea, photophobia, and cranial nerve deficits. Meningovascular neurosyphilis tends to develop later and can lead to cerebrovascular events, including strokes, particularly in younger patients without conventional risk factors. General paresis is a progressive neuropsychiatric syndrome marked by cognitive decline, personality changes, and psychiatric disturbances. Tabes dorsalis, a late manifestation of tertiary syphilis, involves degeneration of the dorsal columns of the spinal cord, resulting in ataxia, sharp shooting pains, sensory loss, and bladder dysfunction [45,46].

Diagnosing neurosyphilis requires a multiple approach, including both systemic and cerebrospinal fluid (CSF) assessment. Serum treponemal tests such as TPPA and FTA-ABS are highly sensitive, while the CSF-VDRL remains the most specific test despite its lower sensitivity. Diagnostic indicators include elevated CSF protein levels, lymphocytic pleocytosis, and a reactive CSF-VDRL. In cases with unclear or atypical presentations, advanced molecular techniques like metagenomic next-generation sequencing (mNGS) and 16S rRNA PCR have been promising in detecting T. pallidum DNA directly in the CSF [47].

Neuroimaging findings vary depending on the form of neurosyphilis. Meningovascular involvement may reveal cerebral infarcts in unusual territories, general paresis often shows frontal or temporal lobe atrophy, and tabes dorsalis is associated with signal changes in the spinal cord [48]. Additionally, the chemokine CXCL13 has emerged as a potential biomarker in CSF, correlating with disease activity and offering value in monitoring treatment response [49].

The standard treatment consists of intravenous aqueous crystalline penicillin G (18–24 million units per day) for 10–14 days. Corticosteroids may be administered in order to reduce the risk of a Jarisch-Herxheimer reaction [42]. Clinical reports highlight the disease's varied presentation: for instance, Zhang et al. described a patient with psychosis and cognitive decline diagnosed with general paresis, who showed partial neurological improvement after antibiotic therapy [44]. Another case involved a middle-aged man with recurrent strokes and no vascular risk factors, ultimately diagnosed with meningovascular neurosyphilis and successfully treated with penicillin [48].

CONCLUSIONS

Syphilis has re-emerged as a major global health challenge, complicating diagnosis and management due to its diverse clinical presentations and ability to imitate a wide range of diseases. Once considered under control in high-income countries, its resurgence across all regions is fueled by changing sexual behaviors, inadequate screening, shifting epidemiological trends, and frequent co-infection with HIV.

Alarmingly, there is growing recognition of its systemic complications—including cardiovascular, pulmonary, hepatic, renal, and neurological involvement—which may appear alone or as part of a broader multisystemic syndrome, with an insidious evolution. Cardiovascular syphilis may remain undetected until severe outcomes such as aortic aneurysm or coronary ostial stenosis occur. Pulmonary syphilis can resemble malignancy or granulomatous disease, while hepatic involvement usually presents as cholestatic hepatitis, occasionally progressing to acute liver failure. Renal complications, particularly membranous nephropathy and glomerulonephritis, often mimic autoimmune conditions, complicating diagnosis. Neurosyphilis, once associated with late-stage disease, is increasingly seen earlier, with symptoms ranging from mild cognitive impairment to psychiatric disturbances or stroke-like episodes.

Accurate diagnosis requires a high degree of clinical suspicion and a multidisciplinary approach. Serologic testing remains the cornerstone, complemented by targeted investigations such as imaging, biopsy, and

CSF analysis based on organ involvement. Despite its complexity, syphilis remains highly responsive to antibiotic treatment, with penicillin G as the first-line therapy. When diagnosed in time, severe complications can be reversible, whereas a delayed recognition may result in permanent damage or death.

In conclusion, syphilis is not a disease of the past, and its resurgence demands clinical awareness, timely diagnosis, and interdisciplinary collaboration. Continued research into its pathophysiology, improved diagnostics, and optimized treatment strategies will be essential to managing this persistent and adaptable pathogen.

Author Contributions:

M.I.M. conceived the original draft preparation. M.I.M. and C.C.D. were responsible for the conception and design of the review. M.I.M., T.C.C. and A.L.T. were responsible for the data acquisition and for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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