American Journal of Medicine and Medical Sciences 2025, 15(8): 2496-2500
DOI: 10.5923/j.ajmms.20251508.15

Current Views on Seroresistance in Syphilis

K. M. Abzoirov

Republican Specialized Scientific and Practical Medical Center of Dermatovenerology and Cosmetology, Tashkent, Uzbekistan

Abstract In recent years, the prevalence of sexually transmitted diseases has been increasing worldwide. This process directly affects the epidemiological situation regarding syphilis (Lues). Recently, specific achievements have been made in syphilis infection, but nevertheless, seroresistance in syphilis remains a problem. Because the measures used in treating, diagnosing, and dispensary monitoring of patients with syphilis increase serological resistance, this creates additional burdens for dermatovenerological dispensary staff.

Keywords Syphilis, Seroresistance, Serological reactions, Treponema pallidum, Neurosyphilis, Cerebrospinal fluid, Wassermann reaction, Microreaction, TPIT (Treponema pallidum immobilization test), FTA-abs, Treatment failure

1. Introduction

Identifying the causes of seroresistance development in syphilis is of great importance. This work attempted to identify the aspects mentioned above, applied modern specific treatment, and also used new diagnostic methods to differentiate seroresistance from false-positive serological biological reactions [1,2].

As emphasized above, due to seroresistance in syphilis, there is an opinion among patients that syphilis is not completely cured, but only "subsides." This opinion develops due to positive serological reactions in the blood. Patients may remain under dispensary observation for a long time [3].

Many causes can be listed for the development of seroresistance in syphilis: according to the initially identified diagnosis, if incomplete treatment was conducted, if the patient has multiple comorbidities, when immunity is decreased, when nervous system damage is present, and other factors. Based on the above, to treat patients with seroresistance in syphilis, it is necessary to implement the following [4].

In recent years, the problem of seroresistance in syphilis has been increasingly described in specialized sources. Some scientists propose evaluating this condition as a separate nosological unit. Syphilidologist scientists working in the 70s-80s of the 20th century had many different opinions and theories about the development of seroresistance in syphilis, taking into account causal factors.

A.A. Studnitsin and M.N. Bukharovich focused on specific treatment, its quality and duration in the development of seroresistance, and also emphasized the importance of patients' comorbidities.

P.G. Nazarov noted the significance of the autoimmune state of the organism in patients with seroresistance in syphilis [5].

Seroresistance in syphilis can persist for a long time, with various changes observed in the immune system. During this period, antibodies and antigens are produced by "surviving treponema." Some authors emphasize that immunity decreases in seroresistance, and comorbidities, as well as alcoholism, drug addiction, and smoking, are of great importance. In healthcare practice, benzylpenicillin and its long-acting preparations are widely and freely used in treating syphilis; patients can purchase them from pharmacies and self-medicate. As a result, patients with syphilis may develop seroresistance due to existing visceropathology and nervous system syphilis. At the same time, patients themselves need additional quality specific treatment [6].

As a causal factor of seroresistance in syphilis, visceropathology and neurosyphilis have been indicated by various authors in different years from 1.5-2% to 10-12%. At the same time, researchers have indicated poor-quality specific treatment in the formation of seroresistance.

"Surviving treponema" present in the patient's body causes the development of serological positivity in patients' blood despite effective treatment. In such cases, evaluating seropositivity from practical and theoretical perspectives is difficult [7].

Sometimes in syphilidology practice, when additional specific treatment is prescribed, patients may develop Jarisch -Herxheimer reaction (fever, subjective sensations - headache, weakness, general malaise). This proves the presence of the pathogen - surviving treponema and changes in immunity status (K.A. Yuldashev) [8].

We studied for the first time the state of endogenous intoxication in patients with seroresistance in syphilis before specific treatment and found that all indicators were high. After additional treatment, the identified endogenous intoxication indicators decreased significantly, indicating improvement of endotoxicosis under the influence of the

Received: Jul. 7, 2025; Accepted: Jul. 27, 2025; Published: Aug. 4, 2025
Published online at http://journal.sapub.org/ajmms

conducted specific treatment (K.A. Yuldashev, K.M. Abzoirov, 2014).

Based on the "Standard for Treatment Diagnostics and Dermatovenereology" adopted in the Republic of Uzbekistan in 2021, seroresistance in syphilis is characterized as follows: "serological positivity in blood one year after receiving specific anti-syphilis therapy," where positive Wassermann reactions with cardiotreponemal and treponemal antigens, as well as positive titers of reagins in microreactions, are preserved.

If patients have positive Wassermann reaction and microreaction in blood after therapy conducted for one year, but the reagin titer has a tendency to decrease 4-fold, such patients should remain under dispensary control for another 6 months [9].

In additional treatment of seroresistance, when choosing the treatment method, it is necessary to consider maintaining high concentration of antibiotic in blood for a long time. Based on this, using water-soluble benzylpenicillin for patients with seroresistance in syphilis is appropriate in these conditions, ensuring high concentration of antibiotic in blood and providing the possibility of antibiotic passage through the blood-brain barrier (BBB).

It is known that recently in Uzbekistan, early latent syphilis predominates in the epidemiological structure of morbidity (more than 70%). Taking this fact into account, the emergence of new methods and changes in observation periods become understandable. Sensitivity of serological reactions of blood in patients with seroresistance in syphilis/ Currently, a wide complex of blood seroreactions is used in syphilis diagnostics, and different sensitivities are noted in them [10].

Various positive serological reactions of blood are noted at different stages of syphilis infection, depending on immunity status and existing comorbidities in patients. At different stages of syphilis, simultaneous positivity of blood seroreactions occurs together with clinical manifestations. When anti-syphilis therapy is applied, the serological reactions mentioned above serve to judge treatment effectiveness. Here, serological reactions of blood are studied dynamically - before and after specific treatment. It is necessary to pay attention to the picture of blood seroreaction negativization, as well as to the decrease in reagin titers. Negativization of blood seroreactions and decrease in reagent titers are considered good indicators of the effectiveness of the conducted specific therapy [11].

During dispensary observation, it is necessary to monitor the dynamics of blood seroreactions, and when positivity persists, patients can be examined to identify comorbidities and can be treated with immunostimulators, hepato- and cardioprotectors added for these diseases. Here, blood should be tested for seroreactions before and after additional treatment [12].

Currently in Uzbekistan, serological examination and dispensary control of patients with syphilis is carried out based on the 2021 "Standard for Diagnostics and Treatment in Dermatovenereology." Based on the standard, microprecipitation reaction (MPR) is determined at the level of district medical institutions (offices, departments), and MPR and Wassermann reaction with treponemal and cardiolipin antigens are determined at city medical institutions (dermatovenerological offices, departments, and dispensaries).

In specialized regional dermatovenerological hospitals (regional dermatovenerological hospitals and city dermatovenerological institutions), the following are determined from seroreactions: microreaction (m/r), classical seroreactions, enzyme immunoassay (EIA), passive hemagglutination reaction (PHA), immunochromatographic analysis (ICA).

Research objective: To study modern concepts about "seroresistant state" in syphilis and medical-social aspects.

2. Research Materials and Methods

In our material, 110 patients with seroresistance in syphilis showed serological reactions at various positive levels. Wassermann reaction with cardiolipin antigen in blood was negative (-) in 54 patients, (+) in 6 patients, (2+) in 30 patients, (3+) in 14 patients, and (4+) in 6 patients. Wassermann reaction with treponemal antigen: negative (-) in 57 patients, doubtful (+) in 8 patients, weakly positive (2+) in 22 patients, positive (3+) in 11 patients, and sharply positive (4+) in 12 patients. At the same time, Wassermann reaction with cardiolipin antigen was more sensitive compared to treponemal antigen.

Microreaction was even more sensitive: negative (-) in 11 patients; (+) in 12 patients, (2+) in 34 patients, (3+) in 34 patients, and seroresistance (4+) in 19 patients.

In patients with seroresistance in syphilis, before starting additional treatment, specific reactions - Treponema pallidum immobilization test (TPIT) were positive: from 31% to 50% - 3 cases, from 51% to 70% - 6 cases, and from 71% to 100% - 100 patients.

FTA-200 was positive in blood of patients with seroresistance in syphilis: (+) - 1 patient, (2+) - 10 patients, (3+) - 34 patients, and (4+) - 65 patients.

FTA-abs was even more sensitive and positive in blood of patients with seroresistance: (2+) - 7 patients, (3+) - 7 patients, and (4+) - 54 patients.

Thus, among serological reactions of blood in patients with seroresistance in syphilis, microreaction and FTA-abs showed high positivity.

1. It is necessary to study all positive serological reactions in patient's blood dynamically;
2. Attention should be paid to patient's age; those over 60 years can be discharged from dispensary control;
3. Analysis of existing somatic diseases not accounted for alcoholism and drug addiction is required;
4. It is necessary to clarify the type and quality of anti-syphilis therapy conducted according to the initially identified diagnosis;
5. To determine whether clinical-serological observation was carried out timely and dynamically;
6. Were complications of syphilitic infection in patients studied through consultations with related specialists

(therapist, neurologist, ENT doctor, ophthalmologist, and radiologist)?

Through analysis of the above-mentioned measures, it becomes necessary to identify errors made and thus develop a quality additional treatment regimen under patient control.

We studied patients with seroresistance in syphilis and causal factors of this condition development at the Republican Specialized Scientific-Practical Medical Center of Dermatovenerology and Cosmetology of the Ministry of Health of the Republic of Uzbekistan in various years.

The first group of examined patients included 110 patients with seroresistance, distributed according to primary diagnosis: secondary syphilis was identified in 9 patients and early latent syphilis in 101 patients.

The second group of patients with seroresistance included 125 people (56% men, 44% women), who were similar to Group I patients according to data. Before starting additional treatment, the following were observed in patients with seroresistance: Wassermann reaction with cardiolipin antigen in up to 41% of patients, Wassermann reaction with treponemal antigen in up to 50%, microreaction in up to 84.6%. TPIT, FTA-200, FTA-abs were positive at various degrees in 100% of patients.

At the same time, we studied the condition of 349 patients with early latent syphilis. When these patients were carefully examined using ultrasound examination of internal organs, ECG, REG, EEG of the nervous system, and cerebrospinal fluid examination, the following was identified:

- Aortitis was noted in 4.2% of 75 patients with early latent syphilis and syphilitic myocarditis in 3.5%;
- Deviations from the nervous system were noted in 8.4% of 349 patients with early latent syphilis;
- Cerebrospinal fluid (CSF) was examined in 48 patients with early latent syphilis, and pathology of various degrees indicating nervous system damage was identified in 42 cases;
- Various degrees of liver damage were identified through biochemical examinations and ultrasound in 63 out of 112 patients with early latent syphilis.

The data obtained above indicates that latent syphilis does not always remain "latent," and various deviations can be identified when carefully examined. This causes the development of seroresistance in syphilis.

Often, patients with early latent syphilis receive specific treatment in outpatient settings, where regimen violations occur, causing disruption of therapeutic concentrations of antibiotics in patients' blood. This also causes the development of seroresistance in syphilis in patients over 40 years old.

In 47 (42.7%) out of 110 patients with seroresistance in syphilis, diagnosis was identified at late stages and specific treatment was conducted poorly with standard violations.

Despite established diagnoses, patients were treated late in outpatient conditions, some applied antibiotics did not cross the blood-brain barrier, which occurs with neurosyphilis development, and positive blood seroreactions persist, also causing seroresistance development.

Comorbidities in patients cause the development of seroresistance in syphilis.

Thus, comorbidities were identified in 73 (66.3%) out of 110 patients with seroresistance in syphilis. We studied the structure of identified diseases.

Patient ages ranged from 19 to 68 years (males-37, females-36). Patients up to 20 years - 1 person, from 21 to 30 years - 14 people, from 31 to 40 years - 17 people, from 41 to 50 years - 18 people, from 51 to 60 years - 13, and 61 years and older - 10 patients with seroresistance in syphilis.

It should be emphasized that patients at 40 years had 5-6 nosological units, and most diseases were chronic in nature.

In patients with seroresistance in syphilis, serological appearance of blood was positive at various degrees and more expressed. Wassermann reaction with treponemal antigen showed positivity in 47.9% of patients, while Wassermann reaction with cardiolipin antigen showed positivity in 45%. Microreaction (m/r) was more sensitive, observed in 88.5% of patients. TPIT, FTA-200, and FTA-abs were positive in all 100% of cases.

In addition to serological blood tests, patient history was studied and functional and instrumental examinations were conducted - ultrasound, ECG, rheoencephalography (REG), electroencephalography (EEG), and other methods.

In addition to the above studies, patients were consulted with therapist, neurologist, ophthalmologist, ENT doctor, and radiologist based on functional test results.

Smears were taken from urethra in men and from 3 points (urethra, vagina, and cervix) in women for bacteriological and bacterioscopic examinations for diagnosing other STIs.

3. Research Results

In patients with seroresistance in syphilis, comorbidities were identified based on thoroughly conducted instrumental studies and consultations with relevant specialists. Changes were observed in cardiovascular system (CVS), nervous, genitourinary system, visual organ, and STIs.

As a result of gastrointestinal tract examination in patients with seroresistance in syphilis, comorbidities were identified in 52 (72.2%) cases, including: 31 (43%) chronic cholecystitis, 12 (16.6%) liver steatosis, 2 (2.7%) chronic splenohepasitis, 5 (6.9%) chronic persistent hepatitis, 2 duodenal ulcers.

Among comorbidities, cardiovascular system (CVS) occupied a special place, and disorders of cardiac automatism, excitability, and conductivity were noted. These were identified through ECG, EchoCS, EchoKG application and confirmed by therapist and cardiologist consultation.

At the same time, aortitis was identified in 3 (4.1%) out of 25 patients with seroresistance in syphilis involved in examination, and myocarditis in 4 (5.4%).

Through neurophysiological examinations (REG, EEG) and neurologist examination of patients, changes in the nervous system were identified in 19 (26.3%) cases. The following pathologies were identified in 19 (26.3%) patients: CNS sanitation - 2 cases (2.9%), vegetative dystonia of vessels -

3 (4.1%), dyscirculatory encephalopathy - 8 (11.1%), chronic cerebral leptomeningitis - 3 (4.1%), psychosis - 1 (1.3%), astheno-neurotic syndrome - 1 (1.3%), CNS intoxication - 1 (1.3%) case.

As a result of careful examination of patients with seroresistance in syphilis, various comorbidities were identified in 28 (38.8%) of examined patients. Among them: 2 (2.7%) chronic prostatitis, 7 (9.7%) chronic pyelonephritis, 1 (1.3%) chronic adnexitis, 4 (5.4%) bacterial urethritis, 1 (1.3%) uterine fibroma, 3 (3.9%) chronic endocervicitis, 2 (2.7%) chronic endometritis, and 8 (11.1%) chronic colpitis were identified.

The following STI pathogens were identified: 8 cases (11.1%) ureaplasmosis, 3 (4.1%) cases chlamydiosis, 1 (1.3%) case gonorrhea, 1 (1.3%) case trichomoniasis, 6 (8.3%) cases gardnerellosis, 11 (15.2%) cases genital candidiasis.

The following diseases were identified from the visual organ: myopia in 1 (1.3%) patient, senile presbyopia in 1 (1.3%) patient, and retinal angiopathy in 1 (1.3%) patient.

The following dermatoses were identified in examined patients: vitiligo in 1 (1.3%) case and toxicoderma in 7 (9.6%) cases.

Interestingly, in patients with seroresistance in syphilis, comorbidities in nosological units: 5 diagnoses in 2 (2.7%) patients, 4 diseases in 3 (4.1%) patients, 3 nosologies in 8 (11.1%) patients, 2 diagnoses in 22 (29.7%) patients, and 1 diagnosis in 25 (33.6%) patients were identified.

Comorbidities, especially when the nervous system is damaged, are of great importance in the occurrence of seroresistance in syphilis.

The syphilis pathogen "surviving treponema" is an anaerobic microbe that multiplies well in the lymphatic system and nerve endings; this process can continue for years. As a result, neurosyphilis develops, and the following are necessary for its diagnosis:

- Repeated blood testing in seroreactions, immunological examinations, clinical changes from the nervous system, and most importantly, cerebrospinal fluid examination is of great importance in diagnosis. This method is considered very sensitive. Cerebrospinal fluid examination is of great importance and has been used for a long time, indicating central nervous system damage by syphilis and is considered the only method in venereology practice. Even in the initial period of syphilis, changes in its indicators can be identified through cerebrospinal fluid examination.

In addition, the total amount of protein in CSF and its coefficient are determined, and Pandy, Nonne-Apelt globulin reactions are also conducted. CSF is examined in serological reactions: Wassermann reaction, microreaction, specific reactions - TPIT, FTA-CSF (with whole CSF).

Normal indicators are as follows: formed elements - no more than 7 per 1 mm^3, total protein amount - no more than 0.33‰ (per mille), protein coefficient - 0.2, Nonne-Apelt and Pandy globulin reactions - negative, and serological reactions such as Wassermann reaction, microreaction, TPIT, FTA-CSF should also be negative.

CSF pathology was identified in 38 patients treated for seroresistance in syphilis at the dermatovenerology and cosmetology hospital of the Republican Scientific Research Institute of Emergency Medicine of the Ministry of Health of the Republic of Uzbekistan. Among them: primary syphilis was identified in 4 patients, secondary syphilis in 11 patients, early latent syphilis in 20 patients, and late latent syphilis in 3 patients.

In the study, the most sensitive indicator was cytosis - increase in formed elements, which was noted in 34 out of 38 patients (89.4%). In 33 out of 38 examined patients (86.8%), an increase in total protein amount up to 1.66‰ was identified. The protein coefficient remained almost unchanged.

Among globulin reactions, Nonne-Apelt reaction was positive in 28 (73.7%) patients with seroresistance in syphilis. Among them, Nonne-Apelt reaction showed 2 (+) results in 22 cases and (4+) results in 6 cases.

Pandy reaction was positive in 32 (84.2%) cases. Among them: 2 cases (+), 28 cases (23.7%) (2+), and (3+) results were noted in 2 patients.

Serological reactions in CSF (Wassermann reaction, microreaction, TPIT, FTA-CSF) showed specific sensitivity and were positive in 30 (78.9%) cases. Among them: Wassermann reaction gave positive results in 2 (5.2%) patients, TPIT in 12 (31.6%) patients, and FTA-CSF in 26 (68.4%) patients. It was determined that the above serological reactions have high sensitivity in CSF.

We evaluated pathological changes in CSF according to G.V. Robustov and M.P. Frishman (1975) classification and divided them into types I and II.

As a result of careful examination of the above-mentioned patients and consultations with neurologist and other specialists, various pathological signs were identified from neurosymptomatology: pupil symptoms, cranial nerve damage, and pathological reflexes. At the same time, neurological symptomatology occurred together with pathological changes from CSF.

4. Conclusions

It should be emphasized that sometimes CSF may be changed, but neurological signs may not be identified. This condition is interpreted as "asymptomatic meningitis." Thus, identifying changes in the nervous system in seroresistant conditions is very difficult, although they can be included among direct causes of the above condition development. Here, initially conducted treatment and treatment methods with antibiotics that do not cross the blood-brain barrier (BBB) are of great importance. Therefore, treatment conducted according to primary diagnosis should be implemented qualitatively, and preference should be given to antibiotics that cross the BBB to prevent neurosyphilis development that may cause seroresistance development in syphilis. Most scientists have paid special attention to immune status in the development of seroresistance in syphilis. We studied some aspects of cellular immunity.

REFERENCES

[1] Workowski K.A., Bachmann L.H., Chan P.A., et al. Sexually Transmitted Infections Treatment Guidelines, 2021 // MMWR Recommendations and Reports. – 2021. – Vol. 70, № 4. – P. 1-187.

[2] Ho E.L., Lukehart S.A. Syphilis: using modern approaches to understand an old disease // Journal of Clinical Investigation. – 2011. – Vol. 121, № 12. – P. 4584-4592.

[3] Radolf J.D., Tramont E.C., Salazar J.C. Syphilis (Treponema pallidum) // Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. – Philadelphia: Elsevier Saunders, 2015. – P. 2684-2709.

[4] Seña A.C., Zhang X.H., Li T., et al. A systematic review of syphilis serological treatment outcomes in HIV-infected and HIV-uninfected persons: rethinking the significance of serological non-responsiveness and the serofast state after therapy // BMC Infectious Diseases. – 2015. – Vol. 15. – P. 479.

[5] Clement M.E., Okeke N.L., Hicks C.B. Treatment of syphilis: a systematic review // JAMA. – 2014. – Vol. 312, № 18. – P. 1905-1917.

[6] Jinno S., Anker B., Kaur P., et al. Predictors of serological failure after treatment of early syphilis // Clinical Infectious Diseases. – 2013. – Vol. 56, № 12. – P. 1776-1781.

[7] Pastuszczak M., Jakiela B., Jaworek A.K., et al. Elevated cerebrospinal fluid interleukin-17A and interferon-γ levels in early asymptomatic neurosyphilis // Sexually Transmitted Diseases. – 2013. – Vol. 40, № 10. – P. 808-812.

[8] Tuddenham S., Ghanem K.G. Emerging trends and persistent challenges in the management of adult syphilis // BMC Infectious Diseases. – 2018. – Vol. 18, № 1. – P. 606.

[9] Janier M., Hegyi V., Dupin N., et al. 2014 European guideline on the management of syphilis // Journal of the European Academy of Dermatology and Venereology. – 2014. – Vol. 28, № 12. – P. 1581-1593.

[10] Marra C.M., Maxwell C.L., Smith S.L., et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features // Journal of Infectious Diseases. – 2004. – Vol. 189, № 3. – P. 369-376.

[11] French P., Gomberg M., Janier M., et al. IUSTI: 2008 European Guidelines on the Management of Syphilis // International Journal of STD & AIDS. – 2009. – Vol. 20, № 5. – P. 300-309.

[12] Ghanem K.G., Erbelding E.J., Wiener Z.S., Rompalo A.M. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics // Sexually Transmitted Infections. – 2007. – Vol. 83, № 2. – P. 97-101.