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DIAGNOSTIC APPROACHES FOR SEXUALLY TRANSMITTED INFECTIONS IN CLINICAL MICROBIOLOGY: A COMPREHENSIVE REVIEW

ZAHRAA FALAH AZEEZ [1], ZAHRAA HAMID ALWAN AL-SAADI [2], QUSAY. K.M.AL MASOOD [3]

[1] COLLAGE OF BIOTECHNOLOGY, UNIVERSITY OF AL-QADISIYAH, IRAQ.

[2] COLLEGE OF SCIENCE, DEPARTMENT OF MICROBIOLOGY, AL-KARKH UNIVERSITY OF SCIENCE.

[3] IRAQI MINISTRIES OF EDUCATION, IRAQ.

ABSTRACT

Accurate and timely diagnostic methods for the management of sexually transmitted infections (STIs) are very esssential because such diseases pose a big threat to public health. This systematic review gives a detailed overview of the wide range of diagnostic approaches, technologies, challenges and future possible ways in the STI diagnosis. A review of the traditional laboratory methods, nucleic acid amplification tests (NAATs), point-of-care testing (POCT) and also new diagnostic technologies discuss their significant contributions to the revolution in STI diagnostics. Challenges including the antimicrobial resistance, evolving pathogens and also poor access to testing quality assurance have been identified which highlights the need for continued interventions aimed at addressing these challenges. Over the horizon, integrated syndromic approaches and further development of point-of-care testing technologies as well as precision medicine strategies based on novel biomarkers and technology present many exciting possibilities for improving the accuracy, accessibility, diagnoses usefulness. This review seeks to guide current and future practices in the clinical microbiology toward STI diagnosis, highlighting innovations and challenges that are key for patient welfare advancements in public health efforts against the STIs.

INTRODUCTION

STIs are still a major public health threat, with millions of people caught up in their wake every year. According to the WHO, one million STIs are contracted every day across the world and it is young adults who shoulder an unfair share of this burden as well. These infections do not only lead to high morbidity and the mortality rates but also contribute significantly towards chronic conditions such as infertility, pelvic inflammatory disease and increased risk of HIV infection [1, 2].

Accurate and timely diagnosis is very central to the effective management of any STIs. Early identification of the causative pathogens is very essential to ensure proper treatment initiation, contact tracing and also prevention for further transmission. But the variety of STI, its very diverse clinical manifestations and asymptomatic carriers render an accurate diagnosis very difficult for a healthcare provider [3].

The field of STI diagnosis has been revolutionized in recent years through notably marked progresses made recently on the diagnostic approaches for clinical microbiology. Long-term traditional laboratory tests such as microscopy, culture, and serological include inclusion of the following: Although these approaches have given us useful information regarding the STI epidemiology, they are also limited by their inadequate sensitivity specificity and TAT [4-5].

In order to address these challenges, nucleic acid amplification tests (NAATs) have been developed as highly accurate STI diagnostic tools. Methods including polymerase chain reaction (PCR), real-time PCR, and nucleic acid hybridization enable the direct detection of pathogen DNA or RNA in clinical specimens. These molecular approaches have transformed STI diagnostics by allowing early detection even in low-level infection and providing prompt reporting [6, 7].

In addition, the emergence of POCT has revolutionized STI diagnosis. The speed, convenience and simplicity of these rapid diagnostics tests makes them most appropriate in resource-poor settings as well as the community health care delivery systems. Antigen-based tests and portable molecular assays have proved to be fairly accurate, suggesting that they can even prove effective for POCT [8, 9].

NGS, microarrays and biosensors are potential emerging technologies aimed at further improvement of STI diagnosis based on the traditional approach developed by molecular level diagnostic technology. Technological tools at the forefront of development allow multidetector type pathogens and markers antibiotic resistance, leading in different ways to facilitate STI epidemiology [10, 11].

Even with these developments, obstacles persist in STI diagnosis such as antimicrobial resistance, mutating pathogens and a proper quality assurance program. This can only be

done by providing collaborative efforts from clinicians, researchers, policymakers and laboratory professionals to ensure standardized diagnostic protocols are available alongside reliable results [12, 13].

In this comprehensive review article, we will therefore discuss the different diagnostic methods used to detect STIs in clinical microbiology. Through critical analysis of long-standing methods, NAATs, POCT approaches, and innovative technologies we will offer a detailed exploration on the strengths weaknesses as wellas their applicability in diverse medical environments. We will also talk about a syndromic approach to STI diagnosis; quality assurance programs, difficulties that diagnostic laboratories faced along with future directions for improvement of the STD diagnostics.

This review article aims to add value to the current body of knowledge on STI diagnostics and inspire improvements that will help us fight these infections more successfully. Our focus on holistic diagnostic processes in clinical microbiology is intended to provide healthcare providers with guidance for rational STI management.

Commonly Tested STIs

STIs refer to various pathogens that mainly spread through sexual contact. It is crucial to understand the epidemiology, clinical presentation and complications of STIs commonly tested for in order to not only achieve accurate diagnosis but also ensure proper management. In this part we consider some of the most common STIs and their influence on public health [1, 14].

Chlamydia trachomatis

World over, one of the most prevalent bacterial STIs is Chlamydia trachomatis. It primarily affects the genital tract which causes infection in both males and female. However nearly all infected individuals are asymptomatic, which leads to under diagnosis and cases of poor outcomes if left unattended. In women, the untreated infection results in pelvic inflammatory diseases tubal abortions and infertility. The complications in men may include epididymitis and reactive arthritis. It is important to make early and accurate diagnosis before the disease takes root for control of spread, reducing long-term effects [15, 16].

Neisseria gonorrhoeae

One common bacterial STI with severe impact on public health is the Neisseria gonorrhoeae, also known as gonorrhea. It mostly affects the genital tract, rectum and pharynx. As with chlamydia, gonorrhea is often asymptomatic in many persons and therefore difficult to diagnose without routine screening. Gonorrhea if left unchecked may result in serious

complications like pelvic inflammatory disease, infertility and likelihood of HIV/AIDS transmission. A prompt detection and an appropriate treatment of the problem are also crucial for preventing a transmission as well as managing some complications that can come with **(17, 18)**.

Trichomonas vaginalis

It is one of the most prevalent STIs globally and an infection by Trichomonas vaginalis, a protozoan parasite. The predominant target of the disease is urogenital tract in both sexes. Symptoms of Trichomoniasis include vaginal discharge, itching, burning sensation and pain during intercourse. However, trichomoniasis has also been linked with an increased rate of HIV acquisition and transmission. Diagnosis in a timely manner is essential for effective and early treatment so as to interrupt transmission [19].

Human Papillomavirus (HPV)

HPV is the most common viral sexually transmitted infection in the world. It is made of a large viral family and these are more strains it includes cervical, anal, penile as well oropharyngeal cancers. And HPV infections may also cause genital warts. HPV vaccine programs have been developed in most countries as a preventive approach towards the prevalence of diseases induced by factors associated with HPV. Nonetheless, molecular diagnosis of HPV infections is important for early detection of high-risk strains as well as monitoring the success or failure rate associated with vaccination programs [20-22].

Herpes Simplex Virus (HSV)

Herpes Simplex Virus (HSV) infection is caused by two types: HSV-1 and HSV-2. Cold sores are mainly associated with HSV-1 while genital herpes is predominantly caused by 2HSV. They can induce orogenital infections and screening. Most HSV infected individuals are asymptomatic or have mild infection, which makes the diagnosis of disease without special tests difficult. It is crucial to recognize HSV infections early because of the implications that they have on managing symptoms, preventing transmission to partners or neonates and also lowering the chances of complications [11, 23, 24].

Sexually Transmitted Infection	Causative Pathogen	Clinical Manifestations	Complications	Impact
Chlamydia trachomatis	Chlamydia trachomatis	Often asymptomatic, urethritis, cervicitis, pelvic	Pelvic inflammatory disease, ectopic	Long-term reproductive health consequences

		inflammatory disease	pregnancy, infertility	
Neisseria gonorrhoeae	Neisseria gonorrhoeae	Urethritis, cervicitis, proctitis, pharyngitis	Pelvic inflammatory disease, infertility, increased risk of HIV transmission	Long-term reproductive health consequences, potential co-infection with HIV
Trichomonas vaginalis	Trichomonas vaginalis	Vaginal discharge, itching, discomfort during intercourse	Increased risk of HIV acquisition and transmission	Impact on reproductive health and HIV transmission
Human Papillomavirus (HPV)	Human Papillomavirus (Various strains)	Genital warts, cervical, anal, penile, oropharyngeal cancers	Development of cancers, including cervical cancer	Significant burden of cancer-related morbidity and mortality
Herpes Simplex Virus (HSV)	HSV-1, HSV-2	Oral or genital ulcers, flu-like symptoms during initial infection	Neonatal herpes, increased risk of HIV transmission	Neonatal morbidity and mortality, impact on reproductive health

Table 1. *(Overview of Commonly Tested Sexually Transmitted Infections (STIs))*

Traditional Diagnostic Methods

In clinical microbiology, the traditional diagnostic methods have continued to serve as a foundation for STI diagnosis over centuries. Although this method is very simple and commonly used, it has played a significant role in STI diagnosis and treatment. In this section, we will also elaborate on some of the more commonly used traditional diagnostic methods along with their relevant strengths and weaknesses [3].

Microscopy

Microscopy is one of the simplest techniques reserved for viewing microorganisms in a clinical sample. Most commonly, gram stain microscopy and wet mount microscopyare used to diagnose bacteria parasites and fungi in STI cases. In terms of effectiveness, gram stain microscopy is rather good for detecting the gram- negative diplococci like Neisseria gonorrhoeae and other viable organisms such as Staphylococcus aureus. By using wet mount microscopy, motile pathogens such as Trichomonas vaginalis can be detected. Despite microscopy providing results in a relatively short time, these limitations are determined by the

sensitivity and specificity that becomes vital when dealing with low-level infections or polymicrobial samples [25].

Culture

One of the traditional methods is culture, which refers to cultivation of microorganisms on selective or differential media. It is also often used for the detection and determination of bacterial pathogens responsible for STIs including Neisseria gonorrhoeae as well as Haemophilus ducreyi. It is culturing that makes it possible to conduct antimicrobial susceptibility testing required for developing the appropriate treatment. Nevertheless, culture-dependent techniques can take many days to grow bacteria, followed by identification. Furthermore, there are certain fastidious bacteria that have specialized growth needs hard to mimic in the lab [26].

Serological Tests

Through the use of serological tests, antibodies that are being produced by a host against a specific pathogen can be detected. It's majorly used for diagnosis of viral STIs such as HIV, HBV and syphilis. Serological methods involve enzyme immunoassays (EIAs), chemiluminescent assays and rapid lateral flow tests. This test is convenient because they have low cost, easy availability and short turn-around times. However, serological assays are unable to differentiate active and old infections even though confirmatory testing may be required. Cross reactivity or non-specific reactions results in false positive [27-29].

Biochemical Tests

Biochemical testing involves the identification of metabolite byproducts and enzymatic activities that arise from microorganisms. For example, biochemical assays including nitrate reduction and catalase tests can be used to differentiate the bacterial species in various ways. These tests are used in conjunction with other diagnostic techniques to confirm the identification of particular pathogens. Biochemical tests are incredibly useful in defining metabolic potential of microbes, however they do not always show sufficient resolution to differentiate closely related species [30].

Nevertheless, the traditional diagnostic methods have been widely used for STI diagnoses and with certain limitations. Such approaches usually require professional workforce, can be less rigorous as for molecular technique and may fail to identify people with low-grade infections or asymptomatic carriers. However, conventional diagnostic tools still have an important role to play even in limited resource settings where sophisticated high-end technologies may be beyond reach or unaffordable [31].

Diagnostic Method	Technique	Pathogens Detected	Strengths	Limitations
Microscopy	Direct visualization of microorganisms in clinical samples	Neisseria gonorrhoeae, Trichomonas vaginalis, Staphylococcus aureus, etc.	Rapid results, visualization of motile pathogens	Limited sensitivity and specificity, challenges with polymicrobial samples
Culture	Growth of microorganisms on selective or differential media	Neisseria gonorrhoeae, Haemophilus ducreyi, etc.	Antimicrobial susceptibility testing, species identification	Time-consuming, specific growth requirements, delayed results
Serological Tests	Detection of antibodies produced by the host in response to a specific pathogen	HIV, HBV, syphilis, etc.	Relatively inexpensive, quick results	Cannot differentiate between current and past infections, false-positive results
Biochemical Tests	Detection of metabolic byproducts or enzymatic activities produced by microorganisms	Differentiating bacterial species	Metabolic characterization of microorganisms	May not be specific enough for closely related species

Table 2. *(Overview of Traditional Diagnostic Methods for Sexually Transmitted Infections (STIs))*

Nucleic Acid Amplification Tests (NAATs)

NAATs have revolutionized STI diagnostics because they are highly specific and sensitive in detecting pathogens involved in STIs. Among these molecular techniques assays to amplify and detect pathogen DNA or RNA molecules in clinical samples. In this sphere, we will address the terminology of NAATs and how they are applied to STI diagnosis with reference to their advantages [31].

Principles

The process of genomic nucleic acid sequencing, which is specific to STI pathogens and serves as the basis for NAATs. Among the popular methods used in NAATs, polymerase chain reaction (PCR), real-time PCR, transcription mediation amplification and nucleic acid sequence based amplification are worth mentioning. These approaches make possible exponential

multiplication of the target nucleic acids which are beneficial, when one works with low level infection specificity [32].

Applications

NAATs are technologies used for the detection of various STIs such as Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and Mycoplasma genitalium among others.

However, NAATs are distinguished from traditional diagnostic approaches by a number of unique characteristics. They are highly nuclease sensitive; detecting even small quantities of pathogen DNA and RNA is helpful in low-level infection cases or asymptomatic carriers. Furthermore, NAATs provide very high specificity rates that limit the number of false-positive outcomes. They are especially effective in practice because they provide results right away that respond promptly with medical treatment and contact tracing [33].

Advantages

NAATs have several distinct advantages over traditional diagnostic procedures. They show great sensitivity and can even detect a minute concentration of pathogen DNA or RNA that assists in low-level contamination cases as well patients who are asymptomatic carriers. Furthermore, NAATs have a high level of specificity and lead to fewer cases of false positives. Early medical intervention is possible thanks to their timely output as well, for contact tracing could be implemented soon [32].

Parallel with this, NAATs have also made it possible for the implementation of multiplex assays which diagnose more than one STI pathogen. The multiplexing characteristic simplifies the diagnostic process, reduces turn-around time and saves precious clinical specimens. Second, the introduction of automated platforms for NAATs has increased test throughput and eliminated human factors that assure complete efficacy in sample diagnosis.

Nucleic Acid Amplification Test	Principle	Applications	Advantages
Polymerase Chain Reaction (PCR)	Amplification of specific nucleic acid sequences	Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium, etc.	High sensitivity, high specificity, rapid results, multiplexing capability, automation
Real-time PCR (qPCR)	Real-time monitoring of DNA amplification	Various STI pathogens from diverse clinical samples	Rapid and quantitative results, multiplexing capability, automation

Transcription-Mediated Amplification (TMA)	Amplification of RNA molecules	Detection of STI pathogens such as Chlamydia trachomatis and Neisseria gonorrhoeae	High sensitivity, isothermal amplification, automation
Nucleic Acid Sequence-Based Amplification (NASBA)	Amplification of RNA sequences	Mycoplasma genitalium, HIV, HCV, HBV, etc.	Isothermal amplification, high sensitivity, automation, quantitative results

Table 3. *(Overview of Nucleic Acid Amplification Tests (NAATs) for Sexually Transmitted Infections (STIs))*

Point-of-Care Testing (POCT)

It was additionally discovered that point-of-care testing (POCT) is a reliable diagnostic method for the early and decentralized detection of sexually transmitted diseases. These tests aim to be performed at or near the patient's location to provide timely results and aid clinical decision-making. In this chapter, we will discuss POCT and how it is used to diagnose STIs [34].

Concept

POCT derives from the concept that testing might be done closer to a patient or what is otherwise referred as point of care, and more at immediate community setting. POCT devices are mainly portable, easy to operate and deliver results within minutes. These tests reduce the requirement of elaborate centralized laboratory facility, and allows initiation treatment at once in low-resource settings or remote places. The convenience and fast results of POCT have made it a desirable option for STI diagnosis in different medical settings [35].

Methods

The POCT methods for STI diagnostics use various technologies such as the lateral flow assays, immunochromatographic assays and nucleic acid amplification-based tests along with biosensor-based systems. These tests are designed to test antigens, antibodies or nucleic acid directly from the samples that have been clinically collected (blood urine vaginal swab and oral swabs etc). The fact that POCT devices are easy to use and can be operated by non-laboratory personnel enables appropriate diagnostic outcomes for STI in short times [36].

Applications

POCT of STI diagnosis is widely applicable to different healthcare settings such as primary care clinics, emergency department, community health centers and outreach program or resource-

limited environment. These tests are especially useful in the detection, diagnosis as well managing STI who have access to peripheral laboratories. Moreover, POCT performs an important function in enabling immediate treatment start-up, contact tracing and public health interventions aimed at determining STI spread [37].

Advantages

POCT has a series of benefits for the diagnosis of STIs. The POCT tools give rapid data, which improves clinical judgments at bedside and treatment with precise objectives for the patients. In addition, POCT provides same-day testing and treatment thus reducing the LTFU risk while improving patient outcomes. The POCT also provides the degree of decentralization so that susceptible patients to STI can get rapid diagnosis as well treatment. Additionally, POCT devices are portable and simple to operate in a multitude of healthcare facilities that do not have large lab infrastructure [37].

Point-of-Care Testing Method	Concept	Methods	Applications	Advantages
Lateral Flow Assays	Rapid and decentralized testing at or near the patient's location	Detection of specific STI antigens or antibodies	Primary care clinics, emergency departments, community health centers, outreach programs	Immediate results, ease of use, same-day testing and treatment
Immunochromatographic Assays	Bringing diagnostic testing closer to the patient, particularly in resource-limited or remote settings	Detection of specific STI antigens or antibodies	Screening, partner notification, public health interventions	Rapid turnaround time, decentralized nature, access to timely diagnosis
Nucleic Acid Amplification-Based Assays	Portable and user-friendly testing with immediate results	Amplification and detection of STI nucleic acids directly from clinical samples	Resource-limited settings, diverse healthcare settings without extensive laboratory infrastructure	On-the-spot clinical decision-making, immediate provision of appropriate care

Biosensor-Based Platforms	Facilitating immediate treatment initiation and public health interventions	Detection of specific STI antigens or antibodies	Timely diagnosis and intervention, overcoming barriers to access	Portability, simplicity, decentralized testing

Table 4. *(Overview of Point-of-Care Testing (POCT) Methods for Sexually Transmitted Infections (STIs)).*

Novel Diagnostic Technologies

New diagnostic technologies are very important for the development of quick and precise STI diagnosis since they introduce new technological approaches to the identification of pathogens or determining antibiotic resistance. The second section will discuss the principles, uses and implications of novel diagnostic technologies that underlie STI detection [38].

Next-Generation Sequencing (NGS)

Novel diagnostic tools are also critical for effective STI diagnosis as they introduce new technological avenues in pathogen detection and identification, antibiotic resistance determine. Consequently, this section will look into the principles of application and implications of inventing diagnostic technologies for STI diagnostics [39].

The advent of next-generation sequencing technologies has revolutionized the genomic landscape, and these approaches are now used to screen for genetic abnormalities in STI diagnostics. Using NGS, millions of DNA fragments from microbial ecosystems can be parallel sequenced which allows a deep profiling analysis on clinical samples. In the context of STIs, NGS can help determine pathogen diversity and evolution as well as antimicrobial resistance phenotypes. Additionally, there are a number of NGS-based metagenomic approaches that can identify novel or unculturable pathogens implicated by STI and some hitherto unknown causative agents [40].

Microarray Technology

The microarray technology makes possible not only the detection but also characterization of multiple genetic targets within one assay. Regarding STI diagnostics microarrays can be fabricated to detect and distinguish distinct pathogens, establish antimicrobial resistance profiles, identify virulence factors. Microarrays are attractive tools for the complete diagnostics of STI due to their high throughput and ability in multiplexing features, especially when a polymicrobial or multiple resistance determinants need to be evaluated [41].

Biosensors

Biosensors are analytical devices that make use of biological recognition elements together with transducing components to recognize particular analytes. Regarding STI diagnosis, biosensors can be engineered to sense pathogen-specific nucleic acids, proteins or antigens directly from clinical samples. The biosensor-based platforms provide the benefits of rapid detection, high sensitivity and portability features suitable for POC applications as well as the resource poor settings. Furthermore, biosensors can be combined with microfluidic platforms for automation of sample workup and analysis to increase the efficiency in STI diagnostics [42].

Impact and Applications

These novel technologies can change the entire diagnostic landscape for STIs by offering greater insight into pathogen population diversity, antimicrobial resistance and host-pathogen interactions. They also perform routine diagnostic testing, surveillance of STI epidemiology as well as outbreak investigations and monitoring treatment outcomes. Moreover, the capacity for prompt identification of pathogens and their resistance patterns can guide targeted antimicrobial therapy and results in personalized medicine during STI management [4].

Novel Diagnostic Technology	Principle	Applications	Advantages
Next-Generation Sequencing (NGS)	Comprehensive sequencing of DNA fragments from clinical samples	Pathogen diversity characterization, antimicrobial resistance profiling, identification of novel pathogens	High throughput, simultaneous analysis of millions of DNA fragments, potential for uncovering unculturable pathogens
Microarray Technology	Simultaneous detection and characterization of multiple genetic targets within a single assay	Multiplex pathogen detection, antimicrobial resistance determination, virulence factor identification	High throughput, comprehensive analysis of polymicrobial infections and resistance determinants
Biosensors	Integration of biological recognition elements with transducing components for specific analyte detection	Rapid pathogen-specific nucleic acid or antigen detection directly from clinical samples, point-of-care applications	High sensitivity, portability, integration with microfluidic systems for automated analysis

Table 5. *(Overview of Novel Diagnostic Technologies for Sexually Transmitted Infections (STIs))*

Challenges and Future Directions:

Challenges in STI Diagnosis	Description
Antimicrobial Resistance	Emergence of resistance among STI pathogens, impacting treatment efficacy and diagnostic test utility
Evolving Pathogens	Continuous evolution of STI pathogens, including new strains and variants, challenging diagnostic assays
Access to Testing	Limited access to reliable STI testing, particularly in resource-limited or marginalized communities, hindering early diagnosis and treatment
Quality Assurance	Need for high standards of quality assurance, proficiency testing, and standardization of testing protocols across diagnostic laboratories

Future Directions in STI Diagnosis

Future Directions in STI Diagnosis	Description
Integrated Syndromic Approach	Advancement and implementation of integrated syndromic approaches considering clinical signs, symptoms, and epidemiological data for accurate STI diagnosis
Point-of-Care Testing Innovations	Continued innovation in portable molecular assays, multiplexed rapid tests, and point-of-care technologies to expand access to timely STI diagnosis
Precision Medicine Strategies	Integration of precision medicine principles into STI diagnosis, including targeted antimicrobial therapy guided by pathogen genotyping and resistance profiling
Novel Biomarkers and Technologies	Exploration of novel biomarkers, host-based diagnostics, metabolomics, and advanced imaging techniques for enhanced sensitivity and specificity in STI diagnosis

CONCLUSION

In summary, the STI diagnostic approach addresses that NAATs and POCT are going to revolutionize pathogen identification whereas antimicrobial resistance development #pathogen evolution is a hindrance. The main road to the future of STI diagnosis involves integrated syndromic approaches, innovations in point-of care testing technologies precision medicine strategies and pursue new biomarkers technology. In conclusion, addressing these challenges and adopting the above new directions is necessary to improve STI diagnosis

accuracy, accessibility as well impact on patient outcomes while supporting public health initiatives aimed at fighting STIs.

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