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Review Article

Common Bacterial Causes of Urethritis in Men: Diagnosis and Treatment

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Introduction

Sexually transmitted diseases (STDs) are caused by a large number of diverge microbial agents that are responsible for considerable morbidity and mortality world- wide. Urethritis is one of the most common STD syndromes diagnosed in men.[1] An estimated 340 million new cases of curable sexually transmitted infections occur world-wide each year, with the largest proportion in the region of South and South East Asia, followed by Sub-Saharan Africa, Latin America and the Caribbean.[2] In United States, approximately 15 million people become infected with one or more STDs each year, often causing severe consequences and adding billions of dollars to health care cost[3]. Neisseria gonorrhoeae and Chlamydia trachomatis are the two most common bacterial causes of STDs.[4] Gonorrhoea is one of the most common STDs in developing countries and is a global health problem.[5] Globally, 88 million new cases of gonorrhoea occur each year.[6] In the United States, gonorrhoea is consistently the second-most frequently notifiable infection with a rate of 100.8 cases per 100,000 population.[7] Sexually transmitted diseases are one of the most common causes of illness and are important causes of morbidity and mortality, particularly in developing countries.[1] Proper diagnosis and a standard treatment regimen need in community to eradicate the infection and to prevent the development of complications and also to keep important public health benefit to decreasing transmission and eliminating the reservoirs of infection.

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Microbial pathogens

The possible bacterial pathogens that can be transmitted sexually are *Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasmaurealyticum, Mycoplasma genitalium, Haemophylusducreyi* and *Treponemapallidum.*[8] Prevalance of gonorrhoea in adult males in 2005 in different WHO regions are 1.72% in Africa, 0.68% in region of America, 0.21% in European region, 1.10% in South East Asian region and 0.52% in Western pacific region.[6] Prevalence of *C. trachomatis* in India is 30.8% in 2003 among symptomatic men and women.[9] 21% in UK in 2002 among males with sterile pyuria[10], 12.3% in 2010 in South Africa among men with urethritis.[11] *Ureaplasmaurealyticum* has been implicated in many infections, including nongonococcal urethritis, urethroprostatitis and epididymitis in men.[12] Prevalance of *Ureaplasmaurealyticum* is 12.8% in Japan in 2005 among patients with non gonococcal urethritis.[13] Ureaplasma can be distinguished from mycoplasmas by their ability to produce the enzyme urease, which degrades urea to ammonia and carbondioxide. Detection of Ureaplasmas by PCR employs ureas gene as template for amplification.[14] *Mycoplasma genitalium* is first isolated from men with urethritis, but studies that attempted to asses its association with disease are inhibited by the difficulty of growing the organism in culture. The microorganism is detected mainly by PCR.[15] Prevalance of *M. genitalium* in Japan was 1%.[16] In a highly exposed female population in Kenya, the prevalence of *M. genitalium* was 16%.[17]

Clinical presentation

The commonest uncomplicated nongonococcaland-gonococcal genital infection in men is an acute urethritis and usually presented by urethral discharge in about 80% of the cases and burning sensation on micturation (dysuria) in about half of the time. The urethral discharge is purulent in 75% of the cases, cloudy in 20% and mucoid in about 5% of the cases[18]. In female,

primary gonococcal infection is present in the endocervix, with concomitant urethral infection occurring in 70-90% of the cases. After an incubation period of 8-10 days, patients may present with cervicovaginal discharge, abnormal or intermittent bleeding and pelvic pain. Ocular gonococcal infections, seen primarily among neonates who acquired the organism during passage through an infected birth canal (Ophthalmia-neonatorum) have been also reported. Infection of the eye often results in periorbital cellulitis, a profuse purulent discharge, conjunctival infection, eyelid oedema. Inadequate treatment of eye infections can lead to ulcerative keratitis, corneal perforation and blindness.[19]

Laboratory diagnosis of Gonorrhoea:

Gram staining

Detection of intracellular bean shaped gram negative diplococci in gram-stained smears, especially of urethral specimens from men is used widely for a presumptive diagnosis of gonorrhoea.[20, 21]

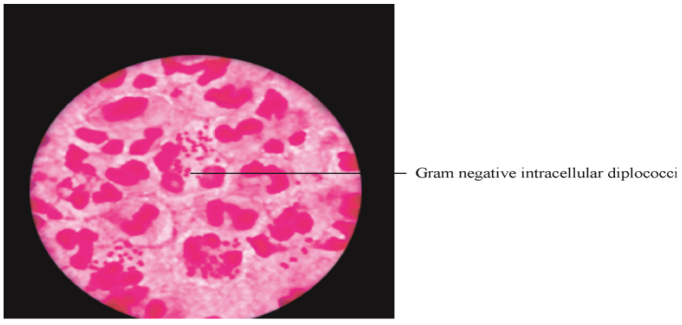

Figure I : Gram staining showing Gram negative intracellular diplococci.

Culture

Culture-based systems provide high specificity (virtually 100% if definitive identification procedures are applied), but are expensive and require personnel trained in the handling the fastidious gonococcus. In the contrary, culture method allows antibiotic susceptibility testing (AST) and characterization of the isolated strains. Culture identification of *N. gonorrhoeae* is the gold standard for definitive diagnosis of gonorrhea.[21]

Table I: Identifying criteria for *N. gonorrhoeae* grown on culture media

Test Procedure	Identifying criteria for *N.gonorrhoeae*	References
Colonycharacteristic observation	Small, glistening, raised, colourless dew-drop colony	
Gram staining	Gram-negative diplococci	39
Superoxol test	Positive	40
Oxidase test	Positive	29
Carbohydrate utilization test	Ferment glucose only	29

Identification of *Neisseria gonorrhoeae* colonies

After overnight incubation, typical colonies of *N. gonorrhoeae* of 0.5 mm in diameter appear and may vary from grey to white, transparent to opaque and raised convex to flat. Frequently a mixture of different colony types appears on a plate. Colonies exhibiting characteristic morphology are confirmed by Gram stain and oxidase reaction for preliminary identification. Subsequent confirmation by carbohydrate utilization tests are done for the full identification of *N. gonorrhoeae*.[22]

All isolates of oxidase-positive, gram-negative diplococci that are recovered from urogenital sites that grow on selective media are presumptively identified as *N. gonorrhoeae*. The superoxol test also provides an additional presumptive test for identifying the isolates.[18]

Serology/Immunological Diagnosis

Serological tests are of limited value for the diagnosis of gonococcal infection because gonococcireact poorly with the antibodies and further non-gonococcal isolates were often found to cross-react with gonococcal antibodies. In addition immunological identification tests include fluorescent antibody and coagglutination tests.

Polymerase Chain Reaction (PCR) :

It is the in vitro enzymatic amplification of a specific gene segment cppB that is present in the genome of all *N. gonorrhoeae*. The cppB gene originates from the 4.2 kb cryptic plasmid of the organism, which is found whole or part, integrated in the chromosome in all gonococci. The PCR method of detection of *N. gonorrhoeae* from clinical specimens showed sensitivity and specificity as 100% and 88.9% respectively, using the culture method as gold standard. The sensitivity of culture is 85-95%, so it is possible that there were false negatives for this method, which would lead to an underestimation of the specificity of the PCR. The advantage of choosing cppB gene sequence as primer is it is present even on the chromosome of plasmid-free strains, thus can overcome the limitation of using cryptic plasmid as probe in DNA hybridization for diagnosis of gonococcal infection.[23]

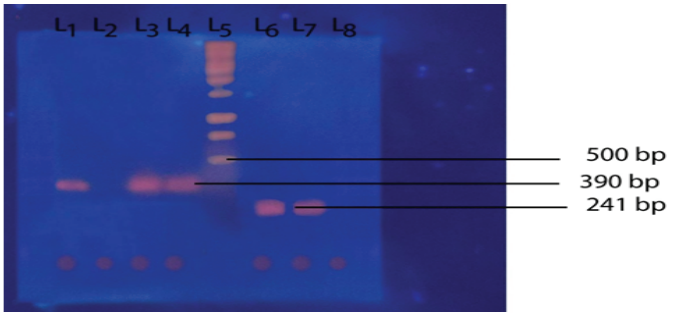

Figure-II: Multiplex PCR shows gel electrophoresis of amplified DNA of *N. gonorrhoeae* and *C. trachomatis*

Lane 1 and 3: *N. gonorrhoeae* positive sample; Lane 2: Streptoccoucus pneumoniae (negative control); Lane 4: *N. gonorrhoeae* (positive control); Lane 5: 100bp DNA ladder; Lane 6: *C. trachomatis* (positive control); Lane 7: *C. trachomatis* positive sample; Lane 8: *H. influenzae* (negative control).

Antimicrobial Susceptibility testing (AST):
Progressive mutational events among *N. gonorrhoeae* strains have led to increased antimicrobial resistance.To recognize these drug resistant strains, several methods, including various modifications of disk diffusion and dilution tests, have been developed. Susceptibility testing of isolates of *N. gonorrhoeae* provides useful epidemiological information that is essential for formulating treatment guidelines. Occasional monitoring of susceptibility patterns over a period of time is used to detect the development of antibiotic resistance, and may indicate the need for a change in treatment guidelines.[24]

Laboratory Diagnosis of chlamydial infection:
Several methods have been used for diagnosis of chlamydial infection which include, A) Direct cytological examination: Immunofluorescence using monoclonal antibodies, Giemsa staining technique,Iodine staining technique, Papanicolaou staining. B) Leukocyte esterase test C) Isolation procedure: such as, Isolation in cell culture, Yolk Sac isolation D) newernon culture diagnostic tests: such as,enzyme immunoassay, immunochromatographic test), nucleic acid amplipication test, E) Serological tests such as, complement fixation test,micro immunofluorescence, single antigen immunofluorescence etc.

Nucleic acid amplification test:
The development of tests based on nucleic acid amplification technology has been the most important advance in the field of chlamydial diagnosis. The most widely known of DNA amplification technology is PCR.[25]

PCR can be genus, species, group or strain-specific depending on primer design. Since all nucleic acid amplification technologies detect nucleic acid targets, so they do not depend on viability or any intact state of organism for positive result as culture procedure.[26]

Diagnostic consideration of *Mycoplasma genitalium*:
Mycoplasma genitalium is a slow-growing organism. Only a few laboratories in the world are able to recover clinical isolates by culture. Therefore, NAAT (polymerase chain reaction) is the preferred method for *M. genitalium* detection.[27]

Diagnostic consideration of *Ureaplasma urealyticum*:
PCR is more sensitive than culture for diagnostic purposes, even for organisms such as *M. hominis* and *Ureaplasma* species, which are relatively easily and quickly cultivated.[28]

Treatment
An accepted definition of gonococcal treatment efficacy requires a cure rate of over 95% and a change in the treatment regimen is recommended when the prevalence of antimicrobial resistance exceeds 5% for a specific antibiotic.[29,30]

The current recommended regimens for uncomplicated gonococcal infections of the cervix, urethra, and rectum with ceftriaxone, 250 mg as a single intramuscular dose, plus either azithromycin, 1 gram orally in a single dose, or doxycycline, 100 mg orally twice daily for 7 days. If ceftriaxone is not available, CDC recommends cefixime, 400 mg orally, plus either azithromycin, 1 gram orally, or doxycycline, 100 mg orally twice daily for 7 days. For patients with a severe allergy to cephalosporins, CDC recommends a single 2 gram dose of azithromycin orally. In both circumstances, when ceftriaxone is not used, CDC recommends a test of cure for these patients one week after treatment. This is an important change in the treatment guidelines.[27]

Treatment should be initiated as soon as possible after diagnosis. Azithromycin and doxycycline are highly effective for chlamydial urethritis. NGU associated with M. genitalium currently responds better to azithromycin than doxycycline.[31]

CDC has recommends for non-gonococcal urethritis with azithromycin 1 gram orally in a single or Doxycycline 100 mg orally twice a day for 7 days. Alternative regimens are Erythromycin base 500 mg orally four times a day for 7 days Or Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days Or Levofloxacin 500 mg orally once daily for 7 days or Ofloxacin 300 mg orally twice a day for 7 dayst.[27]

A number of different antibiotics have been used to treat *M genitalium* infections with varying degrees of success. Tetracyclines initially looked promising but more recent studies suggest that failure to fully eradicate the infection occurs in a high proportion of cases treated with these agents. Macrolides, in particular azithromycin, offer the best chance of cure with a 84% clearance in a recent randomised controlled trial performed in men with *M genitalium* urethritis.[32]

The newer quinolones, such as moxifloxacin, also have good activity against *M genitalium* in vitro (although ciprofloxacin and ofloxacin are less effective).[33] Because *M genitalium* grows very slowly a prolonged course of

therapy may be required to eradicate it. In a preliminary open study from Scandinavia a trend towards improved outcome with longer duration of therapy was observed-azithromycin 1g immediately eradicated 85% (11/13) of the *M genitalium* infections whereas a dose of 500 mg on day 1 followed by 250 mg daily for 4 days eradicated 95% (19/20) of infections.[34]

A single 1 gram dose of azithromycin is approved for treatment of urethritis due to Chlamydia trachomatis and works as well clinically as 7 days of doxycycline in persons with urethritis due to *Ureaplasmaspecies*. Clarithromycin, although active against *Ureaplasma species* in vitro at concentrations comparable to or lower than erythromycin, has not been approved for use in the treatment of urogenital infections.[35]

Prevention and control

There is no effective vaccine for prevent gonorrhoea. The development of an effective vaccine has been hampered by the lack of a suitable animal model and the fact that an effective immune response has never been demonstrated. Control of gonorrhoea (and other STDs) requires a complex, integrated and comprehensive strategy of education, counseling, diagnosis, treatment and case-finding. Key elements are prevention through promotion of safer sexual practices and the availability of health care services. Condoms were found effective in preventing the transmission of gonorrhoea.[36]

The control measures for gonococcal infection listed in the STD treatment guidelines by the CDC include the following: i) education and counselling of persons at risk on ways to avoid gonorrhea through changes in sexual behaviours and includes abstinence and reduction of sex partners, and use of condoms during sexual act; ii) identification of asymptomatically infected persons and of symptomatic persons unlikely to seek diagnostic and treatment services can be implemented. iii) effective diagnosis and treatment of infected persons include an established surveillance system equipped with the personnel and logistics to carryout diagnosis of the cases of gonorrhea. For development of an effective treatment regimen, an organized antimicrobial surveillance system is essential; and iv) evaluation, treatment, and counseling of sex partners of persons who are suffering from gonorrhea can be implemented by partner notification by the infected persons seeking treatment.[27]

Post exposure propylaxis

Gonorrhoea is the 2nd most communicable disease in the United state. The transmission rate of gonorrhoea after sex with someone who has it ranges from 50% to 93%. When prescribing post exposure prophylaxis for gonorrhoea, it is essential to consider the risk of antimicrobial resistance and local susceptibility data. Chlaymydia is the most commonly reported communicable disease in the Unitedstases. The rise of transmission after sexual intercourse with a person who has an active infection is approximately 65% and increased with the number of exposures.[37]

Post exposure prophylaxis of sexually transmitted infection for adults and older children and adolescents: for protection against gonorrohoea and Chlamydia-1) Tab. Azitromycin 1gm orally, Single dose under supervision. 2) Tab. Cefixime 400 mg orally single dose.[38]

Conclusion

Prevention of urethritis is obviously an important goal. *N. gonorrhoeae* continues to be the most common bacterial pathogens in most of the studies of urethritis and has aroused concern because of the dramatic increase in the rates of resistance to antimicrobial agents among the isolates. So we should concern about the current guidelines for the judicious use of antimicrobial agents. Proper diagnosis and a standard treatment regimen will help to eradicate the infection and will keep an important role in public health benefit.

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