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A Review on Antimicrobial Resistant Gonorrhoea

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ABSTRACT

The bacterium *Neisseria gonorrhoeae* causes the sexually transmitted infection (STI) gonorrhoea, which has an estimated global annual incidence of 86.9 million adults. Gonorrhoea can present as urethritis in men, cervicitis or urethritis in women, and in extra genital sites (pharynx, rectum, conjunctiva and, rarely, systemically) in both sexes [1:18:19:20]. Its causative agent, Neisseria gonorrhoeae, has shown a remarkable flexibility to adapt and become resistant to all antimicrobials introduced over the past century for gonococcal therapy. The currently last available first-line therapy that is recommended in most countries is ceftriaxone. However, resistance levels against ceftriaxone are rising globally and incidences of confirmed treatment failure are increasingly encountered, particularly with the global spreading of the ceftriaxone-resistant FC428 clone in recent years. Resistance against most antimicrobials has been the result of adaptive genomic mutations that reduce affinity of the antimicrobial to its target protein or rRNA [2]. Confirmation of the diagnosis requires microscopy of Gram- stained samples, bacterial culture or nucleic acid amplification tests. As no gonococcal vaccine is available, prevention relies on promoting safe sexual behaviors. Improved global surveillance of the emergence, evolution, fitness, and geographical and temporal spread of AMR in *N. gonorrhoeae,* and improved understanding of the pharmacokinetics and pharmacodynamics for current and future antimicrobials in the treatment of urogenital and extra genital gonorrhoeae, are essential to inform treatment guidelines. Key priorities for gonorrhoea control include strengthening prevention, early diagnosis, and treatment of patients and their partners; decreasing stigma; expanding surveillance of AMR and treatment failures; and promoting responsible antimicrobial use [1:18:19:20]. To ensure gonococcal treatment remains available in the future, both alternative clinically approved antimicrobials and novel antimicrobials have been intensely studied both in gonococcal susceptibility analyses and clinical efficacy trials. Although there have been some limited successes, all studied alternative therapies that reached clinical trials have displayed some shortcomings in their efficacy against pharyngeal infections and/or overlapping resistance determinants with previously or currently used antimicrobials. This review summarizes the development of gonococcal antimicrobial resistance over the past century, describes the mechanisms involved in antimicrobial resistance, and provides an overview of the alternative therapies that have been under investigation this past decade [2].

Keywords: Neisseria gonorrhoeae; Antimicrobial resistance; AMR; Ceftriaxone; Alternative therapy

Introduction

Gonorrhoea is defined as a set of clinical conditions involving infections with sexually acquired pathogen, Neisseria gonorrhea, identified microbiologically by its Gram-negative intracellular diplococcic *N. gonorrhoeae*may be acquired at multiple mucosal sites in the lower genital tract, including the urethra, cervix, Bartholin's and Skene's glands, as well as through the anorectal canal, pharynx, and conjunctivae. It may spread to the upper genital tract, uterine tubes, and abdominal cavity, as well as other systemic sites [6:7:8:9]. The systemic sites [6:7:8:9]. The bacteria are mainly found in discharge from the penis (semen) and in vaginal fluids [2]

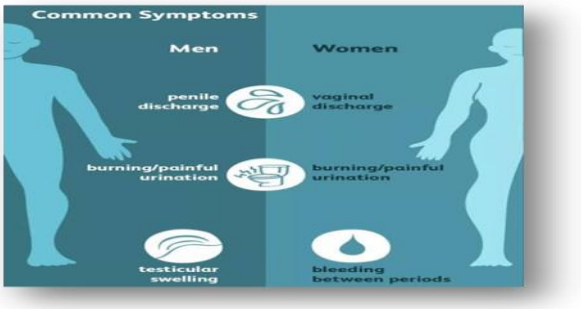

Fig.1: Signs and symptoms of gonorrhoea [23]

- Unprotected vaginal, oral or anal sex sharing vibrators or other sex toys that haven't been washed or covered with a new condom each time they're used
- Also symptomatic men usually have: Dysuria, urinary frequency, purulent urethral discharge.
- Women may have: abnormal vaginal discharge, dysuria, and/or vaginal bleeding during menstrual periods, diffuse pelvic inflammatory diseases (PID) may cause fever along with pain and

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tenderness of pelvic organs lower abdomen [3:4:5].

History

Gonorrhoea is the second most prevalent sexually transmitted infection globally, which is caused by human-specific gram-negative bacterium Neisseria gonorrhoeae. In 1882 its first culture was performed by *Leistikow*. The World Health Organization estimates that there are annually 78–87 million new gonorrhoea cases. Gonorrhoeae usually colonizes and infects the genital tract, but the rectal or pharyngeal mucosa may also be colonized. In men, gonorrhoea most commonly manifests as urethritis and epididymo-orchitis, while women typically develop cervicitis, which is often asymptomatic. However, untreated female infections may lead to pelvic inflammatory disease, ectopic pregnancies, and infertility. Furthermore, complicated gonococcal infections can increase the risk of human immunodeficiency virus transmission and acquisition by increasing the human immunodeficiency virus loads in the genital tract, rectal infection, pharyngeal infection, complicated gonoccocal infection (local complications in men and women, systemic complications). In the absence of effective gonococcal vaccines, antimicrobial therapy has remained the principal for control of gonorrhoea infections. Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis manifesting as purulent ocular discharge and swollen eyelids. Untreated conjunctivitis may lead to scarring and blindness. Gonococcal treatment guidelines need to be updated in response to the changing antimicrobial susceptibility patterns of *N. gonorrhoeae*. Increased resistance to most antibiotics used to treat gonococcal infections has been rep the even development of untreatable gonococcal infections with serious sexual and reproductive health consequences. The previous WHO Guidelines for the management of sexually transmitted infections, published in 2003, include ciprofloxacin as a first-line treatment for gonorrhoea, even though high levels of resistance to quinolones are reported in most countries and these medicines have been withdrawn from all international guidelines. Decreased susceptibility to the extended spectrum (third-generation) cephalosporin's, another recommended first-line treatment in the 2003 guidelines, is becoming more widespread and several countries have reported treatment failures. Treatment recommendations must therefore be updated urgently to reflect the actual antimicrobial resistance (AMR) patterns of STIs, delay the further development of resistance to cephalosporin's and to include treatment options for cases of cephalosporin treatment failure. Gonorrhoea is usually treated with an antibiotic injection of ceftriaxone one time to the buttocks and a single dose of azithromycin by mouth. Once on antibiotics, you should feel relief within days. The antibiotics used for extended therapy are usually given once or twice a day. Some common antibiotics used include azithromycin and doxycycline. Scientists are working to develop vaccines to prevent gonorrhoea transmission.

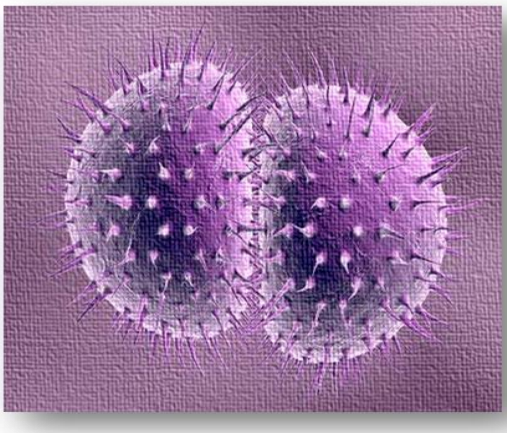

Fig. 2: Nissergonorrhoea

Pathophysiology

Step involved in pathogenesis:-

Adherence: Initial event, *N. gonorrhoeae* adhere to mucosal cells, mediated by Opa (opacity associated proteins) and other surface proteins.

Invasion: Organism is then pinocytosed by epithelial cells, which transport gonococci from mucosal surface to sub epithelial spaces. Simultaneous with attachment of gonococci to nonciliated epithelial cells, gonoccocal (endotoxin) impairs ciliary motility and contributes to destruction of surrounding ciliary cells. This process may promote further attachment of additional organisms.

Tissue damage: Progressive mucosal cell damage occurs and exudation of purulent material into lumen of the infected organ.

Dissemination: Decreaseability to resist the killing activity of antibodies and cause bacteremia illness with or without septic arthritis [3:4:5].

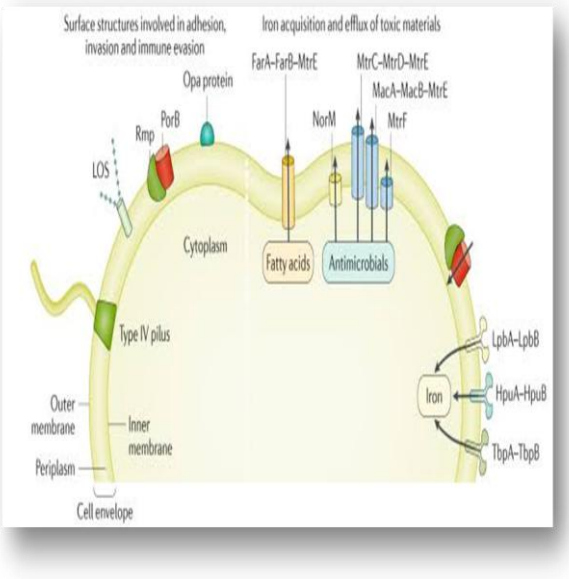

Fig. 2: N. gonorrhoea cell envelope structure [21]

Case Study

The United States has the highest prevalence of sexually transmitted diseases in the developed world. Control strategies should be aware of the most frequent reasons why curable sexually transmitted diseases are not treated by recommended therapy. They have selected 1631 patients of age group between 18-29 in various sites and screening was performed on these persons for gonorrhoea and chlamydial infections and surveys regarding past genitourinary symptoms. Additional interviews were conducted for those patients who had past history genitourinary infection. From these data they estimated the total number of persons who had gonorrhoea or chlamydial infection in previous years, the proportion of person treated and the primary reasons for non treatment.

Prevalence of gonorrhoea was found to be 2.3% and that of chlamydial Infections was 10.1%. They estimated that 77% and 45% of all cases of chlamydial infection and gonorrhoea, respectively were asymptomatic. The untreated gonorrhoea (86%) and chlamydial infection (95%) were untreated because they were also asymptomatic. The remaining 14% of gonorrhoeal

infection and 5% chlamydial infection remain untreated because persons did not receive medical care for symptoms. They concluded that the primary reason for untreated gonorrhoeal and chlamydial infection was that the infected persons were asymptomatic.

The secondary reason is drug resistance shown by most of patients. The routine *N. gonorrhea* is intrinsically resistant to wide variety of antimicrobials such as vancomycin, trimethoprim, colistin, penicillin, ceftriaxone etc. and this is mainly due to genomic mutations. Only β lactamase (penicillin) encoding blaTEM, which provides high level resistance to tetM gene which provide high level resistance to tetracycline. From some regions, gonococcal isolates were found with abundant TEN-135 variant which has propensity to evolve into an extended spectrum β-lactamase that is able to hydrolyze cephalosporin such as cefixime and ceftriaxone is one of the most important gonococcal antimicrobial resistance determinant that produce nonspecific resistance to penicillin, cephalosporin ,azithromycin ,tetracycline, ciprofloxacin & other hydrophobic or amphipathic drug. Also mosaic MtrRCDE alleles acquired from N. meningitidis & commensal Neisseria species appeared to contribute to multidrug resistance. Penicillin & cephalosporin target gonoccocal penicillin binding protein 2, encoding gene penA and provide increased resistance. Penicillin resistance has most commonly been results of an aspartate insertion at position 345. Cephalosporin resistance is generallyassociated with alanine 501 polymorphism or mosaic penA alleles with up to 70 amino acids polymorphisms. Strains such as A311V, T483S, T316P and/or A501P polymorphins with mosaic penA alleles have been found to show high level ceftriaxone resistance. Tetracyclines resistance has been shown to confer by V57M polymorphism in ribosomal protein S10. Spectinomycin resistance has been due to C11920 mutation in 16 rRNA or by mutation in ribosomal protein S5 encoded by rps6, namely deletion of valine of position 25 combined with K26E polymorphisms. Ciprofloxacin resistance arises from variety of mutations in GyrA & ParC subunit of exact resistance level are determined by specific combination of mutation. Sulfonamide resistance can arise from variety of folP point mutation in gonococcal infection. Azithromycin resistance is resulted from specific mutation in target loop V of 23S rRNA. Low level azithromycin resistance is caused by C2611T polymorphism while high level resistance is result from a A2059G polymorphism.To study antimicrobial resistance patterns, ensure treatment guidelines are adequate and to obtain insight into the epidemiology of resistance mechanism, the *N.gonorrhoeae* sequence typing for antimicrobial resistance tool was recently developed, which assigns sequence types (STs) and alleles based on polymorphism in penA, mtrR, porB, ponA, gyrA, parC, and 23S rRNA. These *N. gonorrhoeae* sequence typing for antimicrobial resistance STs are now commonly used and combined with the STs assigned by the *N. gonorrhoeae* multiantigen sequence typing and multilocus sequence typing methods [2].

Screening and diagnosis of gonococcal infection

Because gonorrhea is often asymptomatic in women, screening is critical for the identification of infection and the prevention or limitation of upper genital tract spread, and horizontal and vertical transmission [6:7:8:9]. Screening general populations for gonococcal infections is not indicated. However, screening or opportunistic testing can be considered for individuals at higher risk of gonococcal infection. These populations include the sexually active youth, sexual contacts of individuals having a suspected gonococcal infection, MSM, individuals with new or multiple sexual partners, individuals with HIV infection or a history of STIs, sex workers and their sexual partners, inconsistent condom use or human immunodeficiency virus infection with sexual activity [1:18:19:20]. Pharyngeal gonococcal infections are common in some segments of the population, especially

adolescents, and pharyngeal culture screening is responsible for identification of up to one-quarter of infected adolescent women who would likely be missed with traditional genital tract screening.1and women (≤35 years of age) and men (≤30 years of age) at initial admission to a correctional facility. All pregnant women at risk for gonorrhea or living in an area in which the prevalence of *N. gonorrhoeae* is high should be screened at the first prenatal visit for *N. gonorrhoeae* Pregnant women who test positive should be retested within approximately 3–6 months, and those who remain at high risk for gonococcal infection, including adolescents, should be retested also during the third trimester [6:7:8:9]. Main prevention efforts include education regarding symptomatic and asymptomatic gonorrhea and other STIs; promotion of safe sexual behaviors' (for example, increased condom use through condom-promotion education and campaigns); behavior change communication programs (for example, promoting fewer unknown, casual and unprotected sexual contacts and early health-seeking behavior); improved sexual partner notification and treatment; and expansion of targeted interventions, including screening in some settings for vulnerable populations (sex workers, MSM, adolescents and patients with STIs and their sexual partners) [1:18:19:20]. Specific testing for *N. gonorrhoeae* is recommended because of the subtle and nonspecific nature of presentation in most women as well as the availability of highly sensitive and specific testing modalities. Although there are three ways to diagnose gonorrhea, i.e., traditional culture, nucleic acid hybridization, and nucleic acid amplification tests (NAATs), NAATs are considered the standard for screening and diagnostic purposes currently. Culture requires collection of actual cells from infected mucosal surfaces, and is the only methodology approved for detection of *N. gonorrhoeae* from both genital (endocervical, urethral) and nongenital (anorectal, pharyngeal, and conjunctival) mucosal surfaces. Cultures can provide antimicrobial susceptibility results, and should be the test of choice in cases of suspected or documented treatment failure. Nucleic acid hybridization tests detect gonococcal DNA and some brands also test for chlamydial DNA; they are recommended for use on specimens collected from genital tract surfaces, including genital tract, vagina, and urine. The principal types of NAATs, i.e, transcription-mediated amplification, polymerase chain reactions, and strand displacement amplification, detect and copy gonococcal DNA to enhance detection. NAATs have demonstrated improves sensitivity and specificity compared with culture for the detection of *N. gonorrhoeae* at rectal and oropharyngeal sites among men. Although the standard female genital screening tool at most public health clinics is urine NAAT testing, there is growing support for vaginal swabs collected by providers and patients in clinical and nonclinical settings. Vaginal swab specimens perform at least as well as with other approved specimens using NAATs, and women find this screening strategy highly acceptable [6:7:8:9].

The incubation period for urogenital gonorrhea ranges from ~2 days to 8 day. At least 90% of men with gonococcal urethritis are symptomatic, presenting with obvious urethral discharge and dysuria, a fact that permits the application of syndromic diagnosis (based on a set of symptoms and signs that are characteristic of a clinical manifestation) in many settings as both a time-saving and cost-saving measure. For men with symptomatic urethritis, Gram stain may be used to support symptom evaluation. Although ~40% of women with gonococcal cervicitis may report abnormal vaginal discharge, this symptom is unreliable for syndromic diagnosis of Gonorrhoea, as many other equally or more common genitourinary infections in women (for example, bacterial vaginosis, trichomoniasis and vaginal candidiasis) may cause the same symptoms.

Traditional Diagnostic Methods

Microscopy: In resource-limited settings, light microscopy of Gram-stained samples is often the only method available to diagnose infection with *N. gonorrhoeae* presumptively. The sensitivity and specificity of the Gram stain, which tests for the presence of characteristic Gram-negative diplococci within PMNLs, can vary substantially between studies and depends upon the specimen; the highest sensitivity and specificity were reported with urethral swab samples from symptomatic, whereas the sensitivity was as low as 40–50% in urethral specimens from asymptomatic males, and in endocervical or urethral specimens from women. This difference can probably be explained by a reduced bacterial load, particularly in these urethral samples, and by the presence of many other bacterial species in the endocervical samples. Gram stain, and similar high sensitivity and specificity were reported for diagnosing gonococcal urethritis in men.

Culture: Prior to the introduction of NAATs, culture of the organism was the gold standard and this remains the only diagnostic method available in some settings as it is a low-cost method. Culture performance is dependent upon factors such as anatomical site of the cultured sample, method of specimen collection, media and condition used to transport the sample to the diagnostic centre83,87,89, nonselective and/or selective culture media, conditions of incubation and species confirmatory tests. Cultures obtained too soon after exposure (<48h) may give false-negative results13, and a repeated culture sample some weeks later is sometimes considered. Pharyngeal and rectal specimens are much lower. Presumptive identification of cultured *N. gonorrhoeae* isolates is frequently accomplished by typical colony appearance on selective media, Gram-stained microscopy and the oxidase test, which detects the presence of cytochrome oxidase. For definitive *N. gonorrhoeae* identification, immunological tests frequently targeting PorB sugar utilization tests or other biochemical tests Finally, DNA extraction from cultured isolates is also currently the best method to obtain DNA for genomic analysis, as clinical specimens often either do not contain sufficient concentrations of DNA, or contain too much DNA from other bacterial species or human cells. Furthermore, methods for genomic DNA purification from clinical specimens have not been sufficiently developed or standardized.

NAATS: NAATs are currently recommended for Gonorrhoea diagnosis in most high-income countries. NAATs are now the preferred diagnostic test because specimen collection is noninvasive (urine or self-collected particularly vaginal swabs); viable organisms are not required for detection, permitting less stringent transportation and storage methods, most have superior sensitivity with maintained high specificity (which vary between NAATs and anatomical site tested) compared with culture; they produce more rapid results (many later generation NAAT platforms allow for high through put and automation); and many can simultaneously detect other STI-associated pathogens (particularly Several studies indicate that many additional NAATs are more sensitive, with maintained high specificity, than culture for diagnosing *N. gonorrhoeae* from pharyngeal and rectal specimen; however, such tests should be used only after rigorous local performance evaluations, and additionally a confirmatory NAAT with a different target should be used for such specimens as other Neisseria species, which can be frequently present especially in the pharynx, could be misidenti-fied as *N. gonorrhoeae. Th*us, when using NAATs to detect *N. gonorrhoeae*, it is important to choose the test or the testing strategy so that the positive predictive value (which is calculated based on the sensitivity and specificity of the test and on the local prevalence of the pathogen, and the last two parameters substantially affect the positive predictive value) is >90%. The introduction of NAATs for *N. gonorrhoeae* has substantially reduced the number of cultured patient samples. FDA-approved

NAATs are more expensive than culture-based methods, and are mostly used in high income countries.

A major disadvantage of commercial NAATs is the inability to perform AMR testing on gonococcal specimen. In many regions, >80% of gonorrhoea cases are diagnosed by NAATs and, therefore, crucial information regarding AMR and gonococcal strain biology is lost. There are no recommended molecular tests for the prediction of anti-microbial susceptibility or resistance; however, a PCR-based test that also detects ciprofloxacin susceptibility status has received the European Conformity in Vitro Diagnostic mark and several NAATs in the pipeline are also being developed to detect both *N. gonorrhoeae* and its ciprofloxacin susceptibility status. This type of test could be important particularly in regions in which ciprofloxacin susceptible strains are still spreading and, therefore, ciprofloxacin could be used for treatment as a lower cost, oral alternative to ceftriaxone plus azithromycin that is to spare the use of these antimicrobials and decrease the selective pressure for resistance. This concept has been tested clinically with success.

Point-of-care tests (POCTs): Development of appropriate rapid point-of-care tests (POCTs) is a high priority for the diagnosis of gonorrhoea. POCTs could provide a definitive, rapid diagnosis to guide specific treatment in situations where this is not currently possible, such as in settings in which only syndromic management is available, in cases where patients may not return for treatment and for screening asymptomatic patients116–118. Ideally, POCTs should meet the 'ASSURED' criteria, that is, be affordable, sensitive, specific, user-friendly, robust and rapid, and equipment free or requiring minimal equipment powered by solar or battery sources. However, all diagnostic tests that provide rapid test results and correct treatment during a single clinical visit could be defined as POCTs. The Gram stain is an oft-used POCT; its benefits and limitations have been described above122, 123. Other POCTs developed for *N. gonorrhoeae* include lateral flow immunochromatographic and optical immunoassay tests based on antigen detection, as well as a near-POCT NAAT — the Xpert CT/NG assay. Recent reviews of the performance of several POCTs have shown that immunochromato graphic-based and optical immunoassay-based POCTs had highly suboptimal sensitivities, some as low as 12.5%, and specificities ranging from 89% to >97 and, therefore, are not recommended. However, mathematical modeling has shown that the sensitivity required for POCTs to be effective may be lower in settings where there is a high risk for transmission because treatment is delayed pending testing results or patients do not return for treatment [1:18:19:20].

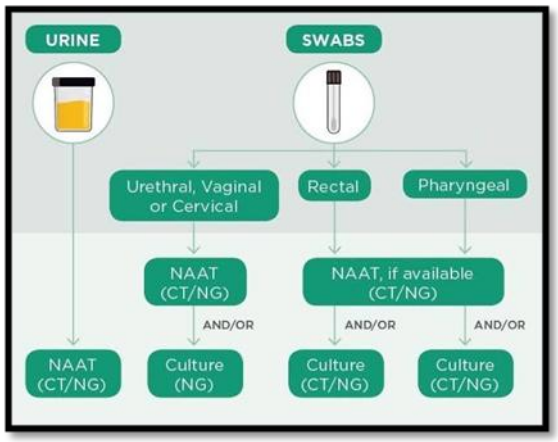

Fig. 3: Diagnosis of Gonorrhoea

Treatment

Treatment of gonococcal infection

Gonorrhea treatment is complicated by the ability of N. gonorrhoeae to develop resistance to antimicrobial therapies. In 1986, the CDC developed a national surveillance program called the Gonococcal Isolate Surveillance Project to monitor gonococcal isolate resistance patterns in the US among selected STI clinics in approximately Gonococcal Isolate Surveillance Project sentinel sites and 4–5 regional laboratories. Penicillin was the original treatment choice for gonococcal infections until the discovery in 1976 of resistance mediated by

plasmid production of β-lactamase. Rates of penicillinase-producing *N. gonorrhoeae* have risen steadily since then, and chromosomal-mediated resistant N. gonorrhoeae has emerged to tetracycline, cephosporins, spectinomycin, and aminoglycosides.38 newer findings include plasmid-mediated tetracycline resistance resulting from acquisition of a tet-M gene38–40 and fluoroquinolone resistance.

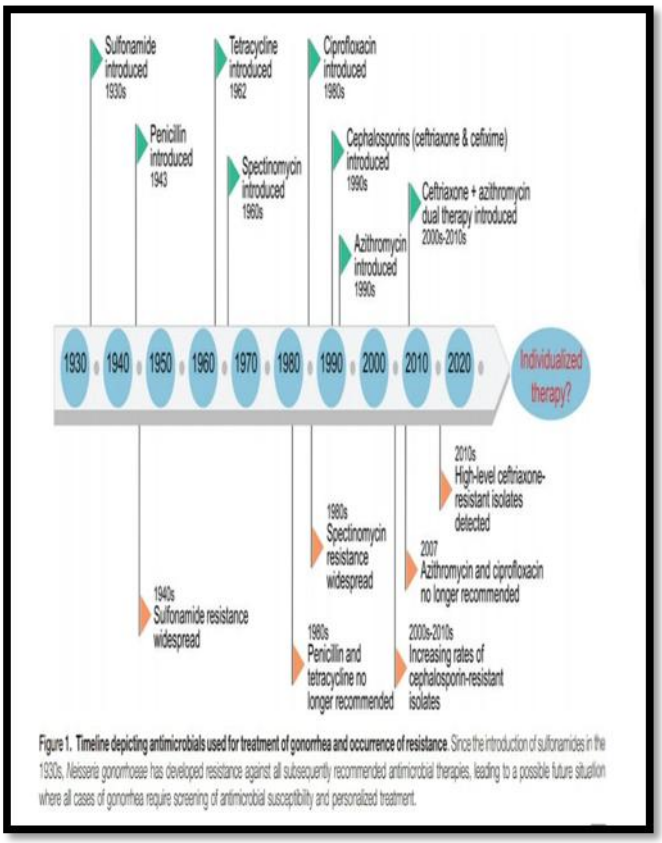

Fig. 4: Treatment History [2]

Treatment with quinolones used to be the mainstay of *N. gonorrhoeae* treatment in the US, but resistant strains spread throughout the US and the world, leading to removal of that class of drugs from recommendations for the treatment of gonorrhea and pelvic inflammatory disease in April 2007.Provider compliance has been excellent, with the proportion of Gonococcal Isolate Surveillance Project patients treated with fluoroquinolones (ciprofloxacin, ofloxacin, or levofloxacin) at 0.5% and the proportion treated with cephalosporins at 96.2% in 2009. By 2009, 23.5% of isolates collected from Gonococcal Isolate Surveillance Project sites were resistant to penicillin, tetracycline, or ciprofloxacin. To ensure appropriate antibiotic therapy, clinicians should ask patients testing positive for gonorrhea about recent travel to and sexual activity in these countries. Two cases of suspected treatment failure with ceftriaxone have been reported. Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations [6:7:8:9]. The CDC hosted a STD Treatment Guidelines Expert Consultation meeting in April 2013, where >60 experts in the fields of STD,infectious disease, epidemiology, and medicine discussed the latest developments in STD clinical and preventive services [10:11:12:13].

Antimicrobial regimens

While gonorrhea is a bacterial infection that responds to a number of antibiotics, resistance to all antibiotic treatments currently recommended for the treatment of gonorrhea has been documented and complicate therapeutic strategies. The CDC released new STI treatment guidelines in 2010, with evidence-based antibiotic regimens designed to treat gonorrhea by anatomic site of infection. The recommended treatment of gonorrhea has been limited to a single class of drugs, the cephalosporins. Treatment should be administered or dispensed at the time of diagnosis to maximize patient adherence. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms [6:7:8:9].

1. **Alternative clinically approved antimicrobial:**
   Due to the declining ceftriaxone susceptibility levels and the increasing incidence of treatment failure, alternative gonococcal therapies are

urgently required. Therefore, the World Health Organization recently included *N. gonorrhoeae i*n their priority list of multidrug-resistant bacterial pathogens to support research and development of effective drugs and therapies. For this purpose, gentamycin ertapenem, tigecycline, fosfomycin, fusicacid gemifloxacin, doxycycline, and rifampicin have all been investigated for their effectiveness as replacement therapy. However, based on recent comprehensive gonococcal susceptibility analyses, fosfomycin, gemifloxacin, doxycycline, and rifampicin are unlikely to be suitable as alternative therapies. In recent years, the best-studied alternative antimicrobial for treatment of gonorrhea has been gentamicin, which has undergone several clinical trials as part of dual therapy and more recently also as single therapy. A multicenter trial performed in the USA over the period 2010–2012 studied the efficacy of gentamicin 240mg intramuscularly combined with 2 g oral azithromycin for treatment of urogenital gonorrhea.116 a 100% cure rate was demonstrated in all 202 participants, which also included 10 pharyngeal and 1 rectal infections. However, a multicenter trial performed in the UK over the period 2014–2016 that studied efficacy of 240mg intramuscular gentamicin combined with 1g oral azithromycin showed inferiority compared with ceftriaxone/azithromycin therapy for treatment of gonorrhea. Of the 292 patients included in the gentamicin/azithromycin group, only 267 were cured (91%), which compared with a 98% efficacy in the ceftriaxone/azithromycin group. Treatment failure did not appear to be the result of gentamycin-resistant isolates, since all isolates displayed gentamicin MIC values of 4–8mg/L. These values are in line with a recent large-scale gonococcal gentamicin susceptibility study performed over the period 2015–2016 in the USA, which showed that 71% of the tested isolates displayed a gentamicin MIC of 8mg/L and 24% a MIC of 4mg/L.

The carbapenem b-lactam ertapenem has been included in several antimicrobial susceptibility studies using collections of clinical isolates. Compared with ceftriaxone, the ertapenem MIC values were generally equal or higher.Although, MIC90 values for ertapenem were slightly lower them ceftriaxone MIC9 values in a recent study investigating isolates from China, which was suggested to be related with the generally higher ceftriaxone MIC values observed in that study.**93** Importantly, there was a poor correlation between ceftriaxone and ertapenem MIC values, suggesting that cross-resistance between ceftriaxone and ertapenem is poor.**93** Therefore, ertapenem was suggested as an alternative antimicrobial for particularly the ceftriaxone-resistant isolates. Particularly, high-level ceftriaxone-resistant isolates with penA alleles 37 (HO41)89 and 42 (F89 are still susceptible to ertapenem. Ertapenem has also been successfully used for treatment of gonorrhea caused by high-level ceftriaxone resistant strains, and even for strains displaying combined ceftriaxone and high-levelertapenem azithromycin resistance. Importantly, strains containing penA allele 60 appear to still be susceptible to ertapenem, which therefore might serve as an alternative therapy for the internationally spreading ceftriaxone-resistant FC428 clone. Of note, based on fractional inhibitory concentration index analyses, ertapenem and ceftriaxone do not appear to display any interactions, 115 indicating that they could also be used in combination therapies.

Thus far, only a few studies have investigated susceptibility of gonococcal isolates to the glycylcycline tigecycline. Recent analysis of 504

contemporary clinical isolates from China showed that all isolates were susceptible to tigecycline (MIC 0.5mg/L) and the correlation with susceptibility to tetracycline and doxycycline was poor, 93 indicating that the rpsJ V57M, porB1b, and mtrR resistance determinants for tetracycline or doxycycline, 92 which were highly abundant in the studied strain collection, do not provide resistance against tigecycline. Therefore, tigecycline might be an interesting antimicrobial for further evaluation of efficacy in clinical studies, possibly as part of a dual therapy, given that previous fractional inhibitory concentration index analyses indicated that tigecycline does not interact with other antibiotics.

2. Novel antimicrobials against gonorrhea

Even though many major pharmaceutical companies seemed to have abandoned their novel antimicrobial development pipelines due to limited success and expected profits, novel therapies are urgently required for many multidrug-resistant bacterial pathogens, including *N. gonorrhoeae*. Although some new therapeutic strategies, like macrophage cell therapy, or revived "old" strategies, like phage therapy. Although several novel compounds with antimicrobial activity against *N. gonorrhoeae* have been identified in recent years, the most promising novel antimicrobials for anti-gonococcal therapy that were already tested in clinical trials are Solithromycin, Zoliflodacin, and gepotidacin.The fluoroketolide Solithromycin (CEM-101) is the latest class of macrolide antibiotics with high activity against a variety of Gram-positive and Gram-negative bacteria and which retained high affinity for bacterial ribosomes.134 Solithromycin displayed good activity against a collection of clinical isolates from Canada (2008–2011) and Sweden (2011) and international reference strains, with a MIC90 of 0.125–0.25mg/L.135,136 However, isolates displaying high-level azithromycin resistance still displayed resistance against Solithromycin, with MIC values of 4–32 mg/L. Therefore, Solithromycin will not be a suitable alternative therapy in countries or regions with a high incidence of high-level azithromycin-resistant *N. gonorrhoeae*.

Zoliflodacin (ETX0914, AZD0914) is a novel spiropyrimidinetrione that targets bacterial type II topoisomerases with a distinct mechanism from quinolones such as ciprofloxacin Antimicrobial susceptibility of *N. gonorrhoeae* to Zoliflodacin has been tested extensively, using strain collections from Europe, China USA, Thailand, and South Africa,143 and global reference and defined multidrug-resistant strains, and all studies resulted in MIC90 values of 0.06–0.25mg/L. Importantly, no cross-resistance was observed with ciprofloxacin-resistant isolates, but Zoliflodacin-resistant derivatives were readily acquired on antibiotic plates and generally contained gyrB mutations at position 429 and 450. it appears that Zoliflodacin provides good activity for treatment of uncomplicated urogenital gonorrhea, but not for infections of the pharynx. Gepotidacin (GSK2140944) is a novel triazaacenaphthylene antimicrobial agent that inhibits DNA topoisomerase IV and DNA gyrase through a distinct mechanism from fluoroquinolones and therefore remains active against ciprofloxacin-resistant *N. gonorrhoeae*, although specific parC mutations have been identified that reduced susceptibility.148,149 Studies on antimicrobial susceptibility using collections of clinical isolates and international reference strains, including multidrug- and ciprofloxacin-resistant isolates, reported MIC90 values of 0.25–1mg/L [2].

A. Uncomplicated gonococcal infections

Ceftriaxone has been shown to cure 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections in published clinical trials while a dose of 125 mg was recommended until recently for lower genital and anorectal infection, a doubling of the dose is recommended to reduce development of resistance and to cover unrecognized oropharyngeal infection. Other injectable cephalosporins recommended for gonococcal treatment include ceftizoxime, cefoxitin, and cefotaxime. None of these offers any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain. The only recommended oral choice for gonorrhoea is cefixime, which has a lower cure rate at 97.5% for uncomplicated urogenital and anorectal and 92.3% of pharyngeal gonococcal infections. The 2 g dose of azithromycin should be used only in limited circumstances because of concerns about resistance development to macrolides. The 1 g dose is not recommended because of documented treatment failures, and concerns about rapid emergence of antimicrobial resistance are even greater than with the 2 g dose.All alternative regimens for gonorrhea are considered inferior to ceftriaxone, because of lower efficacy in urogenital and rectal infection and unacceptably low cure rates for oropharyngeal infection. Cure of gonococcal infection may become increasingly elusive, given growing clinical and in vitro resistance patterns. Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites, leaving ceftriaxone 250 mg intramuscularly as the single drug of choice. Two treatment failures have been reported and sensitivity of gonococcal isolates to ceftriaxone has been steadily declining.53,61 This trend is expected to continue. Women diagnosed with gonococcal conjunctivitis should undergo saline lavage of the infected eye and be treated with high-dose ceftriaxone.

B. Complicated gonococcal infections

Disseminated gonococcal infection is a serious infection, for which hospitalization is recommended in consultation with an infectious disease specialist, both for initiation of treatment as well as for completion of a diagnostic evaluation for endocarditis and meningitis. Parenteral therapy should be continued for 24–48 hours after improvement begins, at which time therapy can be switched to oral therapy to complete at least 1 week of antimicrobial therapy. Prolonged duration of therapy is required for other complicated infections as well, including 10–14 days for meningitis, and at least 4 weeks for endocarditis.

C. Pelvic inflammatory disease

Given the asymptomatic nature of lower genital tract gonococcal infection, nearly one in five women who do not receive treatment will develop pelvic inflammatory disease. Women diagnosed with pelvic inflammatory disease may have lower and or upper genital tract evidence of a number of microbes, including *N. gonorrhoeae* and *C. trachomatis*, and a large number of Gram-negative and anaerobic bacteria. Treatment may be administered in inpatient or outpatient settings, and there are regimens that are primarily parenteral and others that are primarily oral, choices which should be undertaken based on the severity of the infection.

D. Cotreatment for *C. trachomatis*

Because women with gonorrhea are frequently coinfected with chlamydia, treatment for gonococcal infection at all sites and of all levels of severity should include antibiotics that eradicate both *N. gonorrhoeae* and C. trachomatis.65 because most gonococci in the US are susceptible to doxycycline and azithromycin, routine Cotreatment might also hinder the development of antimicrobial-resistant *N. gonorrhoeae*. Limited data suggest that dual treatment with

azithromycin might enhance treatment efficacy for pharyngeal infection when using oral cephalosporins.

E. Allergic reactions

Up to 10% of individuals with a history of penicillin allergy develop an adverse reaction to first-generation cephalosporins, and fewer react to third-generation cephalosporins.67 Cephalosporin use should be avoided only in those with a history of a severe reaction to penicillin (e.g., anaphylaxis, *Stevens Johnson syndrome*, and toxic epidermal necrolysis), and further treatment decisions should be made in consultation with an infectious disease specialist [6:7:8:9].

F. Gonococcal Infections of the Pharynx

Gonococcal infections of the pharynx are generally asymptomatic. Several recent studies have identified a high prevalence of asymptomatic gonococcal infections of the pharynx in specific populations, such as MSM, STD clinic patients, and HIV-positive patients. These studies highlight the importance of having patients who report a history of unprotected oral sex undergo testing for gonococcal infections of the pharynx. On the basis of available data, it is recommended that heterosexual patients be treated with ceftriaxone (125 mg im) for gonococcal infections of the pharynx MSM and patients with a history of recent travel who are being treated for gonococcal infections of the pharynx should receive ceftriaxone (125 mg im) because of the high prevalence of QRNG in this population. As was noted above, spectinomycin does not adequately treat gonococcal infections of the pharynx and should not be used if pharyngeal gonorrhea is likely. Limited data suggest that 2g of azithromycin may also be an option for treatment of gonococcal infections of the pharynx.Although chlamydial coinfection of the pharynx is unusual, coinfection at genital sites sometimes occurs. Therefore, treatment for both gonorrhea and chlamydia is recommended.

G. Gonococcal Infections of the Rectum

Anogenital gonorrhea is frequently asymptomatic but may pre-send with a wide range of symptoms, from mild pruritis ortenesmus to overt proctitis.

H. Special Situations

Pregnancy: Pregnant women should not be treated with quinolones or tetracyclines. As was discussed above, because of high levels of resistance to penicillin, this drug is no longer recommended for the treatment of gonorrhea in any patient. Two clinical trials among pregnant women have been conducted since 2000.Women who cannot tolerate a cephalosporin should be treated with spectinomycin, if available, or desensitized for cephalosporins.

Allergy, intolerance, and adverse reactions

Persons who cannot tolerate cephalosporins or quinolones should be treated with spectinomycin, if available. Because spectinomycin is not adequately effective against pharyngeal infections, patients who have suspected or known pharyngeal infection should have a pharyngeal culture evaluated 3–5 days after treatment, to verify eradication of infection. An additional treatment option for patients, including pregnant women, with a documented history of severe allergic reaction to penicillins or cephalosporins is 2 g of azithromycin.

Adolescents

Fluoroquinolones have not been recommended for persons! 18 years of age because studies have indicated that they can damage articular cartilage in some young animals. However, no joint damage attributable to quinolone therapy has been observed in children treated with prolonged ciprofloxacin regimens.Thus, children who weigh 145 kg can be treated with any regimen recommended for adults.

HIV infection: Little has been published in recent years

about the presentation or response to treatment of gonorrhea in patients with HIV infection. There are no data to suggest that complications of gonorrhea are more common among patients with HIV infection than among those without HIV infection. Patients who have gonococcal infection and also are HIV positive should, therefore, receive the same treatment regimen as those who are HIV negative [14:15:16:17:18:19:20].

Ceftriaxone: According to summed data from clinical trials published in the 1980s and early 1990s, the effectiveness of ceftriaxone 250 mg for uncomplicated urethral, cervical, and rectal gonococcal infections is 99.2% (95% CI, 98.8%–99.5%) .There are no new clinical trial data on the efficacy of ceftriaxone 250 mg. The evaluation of ceftriaxone 500 mg reported a cure rate of 90% in 100 patients with urethral or cervical infection.

However, this study did not use standard bacteriologic criteria to confirm gonococcal infection and treatment failure, and these results should be interpreted with caution. The evaluation

Of ceftriaxone 1 g demonstrated a cure rate of 100% in 48 patients with urethral or cervical gonococcal infection. A pharmacodynamics modeling study published in 2010 predicted that treatment failures with ceftriaxone 250 mg would be likely at ceftriaxone MICs of 0.125–0.25 µg/mL. However, clinical data on the ceftriaxone MIC breakpoint that is correlated with treatment failure for urethral, cervical, or rectal infection are lacking. The available clinical data indicate that ceftriaxone 250 mg is effective in approximately 99% of uncomplicated urethral, cervical, and rectal gonococcal infections. There are no clinical data to support the administration of ceftriaxone at higher doses than 250 mg. Therefore, dual treatment for gonorrhea that includes ceftriaxone at the 250-mg dose is recommended for the treatment of uncomplicated urethral, cervical, and rectal gonococcal infections.

Azithromycin: Based on summed data from clinical trials, monotherapy with azithromycin 1 g cures 97.6% of uncomplicated gonococcal infections of the urethra, cervix, or rectum (95% CI, 95.7%–98.9%), and monotherapy with azithromycin 2 g cures 99.2% of these infections (95% CI, 97.3%–99.9%). For urethral and cervical infections, a more recent review estimated that the clinical effectiveness of azithromycin 1 g was 96.5% (95% CI, 94.3%–97.6%) if retrospective studies were excluded and 97.0% (95%CI, 95.2%–97.9%) if retrospective studies were included. The same review estimated that azithromycin 2 g cured 99.0% (95% CI, 97.5%–99.6%) of urethral or cervical infections. When azithromycin 1 g is given as part of a dual treatment regimen with ceftriaxone, development and subsequent transmission of azithromycin resistance is unlikely. Therefore, based on the effectiveness of azithromycin 1 g and the increased adverse effects associated with the 2 g dose, azithromycin 1 g should be used when given as part of a dual treatment regimen with ceftriaxone. The recommended regimen for uncomplicated urethral, cervical, or rectal gonococcal infection is dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and azithromycin 1 g orally as a single dose.

Cefixime: Based on summed data from clinical trials published in the 1980s and 1990s, the effectiveness of cefixime 400 mg for urethral, cervical, and rectal gonococcal infections is 97.5% (95% CI, 95.4%–98.8%)the only recent data on cefixime effectiveness come from a retrospective analysis of gonococcal infections at any anatomic site. Overall, in this analysis cefixime-based regimens cured 93.2% of gonococcal infections among patients who returned for test of cure, but cefixime effectiveness varied depending on cefixime MIC. Among patients who returned for test of cure, cefixime-based regimens successfully cured 98.1% of infections associated with a cefixime MIC<0.12 µg/mL, but only 75.0% of infections associated with a cefixime MIC ≥0.12 µg/mL

(relative risk of treatment failure, [95% CI, 2.9–59.7]). Clinical data from a recent retrospective analysis and from documented cefixime treatment failures suggest that gonococcal infections with cefixime MICs ≥0.125 µg/mL are associated with a higher risk of treatment failure compared to those with MICs<0.125 µg/mL. Given the increase in cefixime MICs observed in the last decade, ceftriaxone is clearly preferable to cefixime for the treatment of gonococcal infections. However, there are no data to suggest that the clinical effectiveness of dual treatment with cefixime and azithromycin for urethral, cervical, and rectal gonococcal infections is <95% in the United States. Recognizing that there are circumstances where ceftriaxone is not available or where an injection is not possible, and that treatment with a cefixime-based dual treatment regimen is preferable to no treatment, dual treatment with cefixime 400 mg orally as a single dose and azithromycin 1 g orally as a single dose will continue to be an alternative regimen for the treatment of uncomplicated urethral, cervical, and rectal gonococcal infections when ceftriaxone is not available [10:11:12:13].

Spectinomycin: Spectinomycin (2 g) has long been recognized as a safe and effective option for treating infection with N. gonorrhoeae and has been found to cure 98.2% (95% CI, 97.6%–98.9%) of uncomplicated urogenital and anorectal infections .However, it must be given as an intramuscular injection, can be expensive or difficult to obtain, and has poor efficacy against pharyngeal infection (effectiveness in published trials, 51.8%; 95% CI, 38.7%–64.9%). Spectinomycin is currently not manufactured in the United States or elsewhere in the world. The CDC plans to post updates on the Availability of spectinomycin in the United States on its Website as information becomes available.

The possible emergence of widespread resistance to spectinomycin is another significant consideration when evaluating

The use of spectinomycin for the treatment of gonorrhea. High-level resistance to spectinomycin can be the result of a single-step mutation. Resistance to spectinomycin has been rare in the United States (only 5 isolates were ever identified in GISP through 2004), but the use of spectinomycin is also relatively uncommon (1% of patients in GISP were treated with spectinomycin in 2004) However, in the mid-1980s, high levels of spectinomycin resistance were documented among US servicemen in Korea, in a setting in which this antimicrobial was widely used. Once widespread use of spectinomycin was discontinued, levels of resistance decreased. In recent years, only occasional isolates resistant to spectinomycin have been identified from any country in the Western Pacific Region. As a result of these considerations, the CDC recommends

Spectinomycin, if available, as an alternative regimen for the treatment of uncomplicated urogenital or anorectal gonorrhea. Spectinomycin is useful for the treatment of patients who cannot tolerate cephalosporins and for whom quinolones are not appropriate therapy.

Penicillin/tetracycline: Although penicillin was the mainstay of gonorrhea treatment for years, the emergence of PPNG in 1976 and subsequent widespread dissemination of PPNG and chromosomally mediated penicillin resistance has made penicillin an unacceptable treatment for gonorrhea. Tetracycline resistance emerged ~10 years later than penicillin resistance, but it also became widespread enough to prohibit the use of tetracycline for the treatment of gonorrhea. Although resistance to penicillin and tetracycline has decreased from a peak in 1992, overall, ~16% of GISP isolates 2004 were resistant to penicillin, tetracycline, or both.

Other drugs: Despite increasing concerns about gonococcal resistance to all classes of antimicrobials used to treat infections with N. gonorrhoeae, very little clinical research has been published in recent years. This literature

review identified only 4 prospective clinical trials of antimicrobial therapy for gonorrhea since 2000. The therapies evaluated were as follows: cefixime (400 mg) in pregnant women, gatifloxacin (400 mg and 600 mg; currently unavailable in the United States; for information on availability, see nonoxynol-9 gel, and cefodizime (1.0g intravenously). Only 1 retrospective clinical study of azithromycin (1 g) was performed. In vitro evaluations were published for the following new regimens: cefodizime (1 g), chlorhexidine in vaginal lubricants, ertapenem, faropenem, garenoxacin, gemifloxacin, LBM415 (peptide de-formylase inhibitor), plant extracts (Terminalia macroptera, Ocimum sanctum, Drynaria quercifolia, and Annona squamosa), porphyrins, metalloporphyrins, sitafloxacin, olamufloxacin, tel-ithromycin, tigecycline, and an array of topical microbicides.The small number of published clinical studies and the limited number of in vitro evaluations of antimicrobials outside of the current classes used to treat gonorrhea suggest that inadequate attention is being directed toward the development of new antimicrobials for the treatment of gonorrhea, especially in light of emerging antimicrobial resistance [14, 15,16,17,18,19,20].

Research Priorities

Further research is needed to inform future recommendations for the optimal management of gonorrhea. Research priorities identified at the 2013 meeting included (1) evaluation of novel oral antimicrobials or novel combinations of antimicrobials for treatment of gonorrhea; (2) pharmacokinetic models for ceftriaxone and azithromycin in the treatment of gonorrhea at urethral, cervical, rectal, and pharyngeal sites; and (3) evaluation of transport media for gonococcal culture, to facilitate access to gonococcal culture and antimicrobial susceptibility testing [10:11:12:13].

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