GONORRHOEA - CONTEMPORARY REVIEW OF THE DISEASE AND NEW TREATMENT AGENTS

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Abstract

The increasing antimicrobial resistance in *Neisseria gonorrhoeae* observed worldwide, combined with the increasing incidence of gonococcal infections, is a serious public health concern. Although the disease is curable, the choice of antimicrobials used to treat gonorrhoea is very limited and cases continue to rise internationally. The World Health Organization reports millions cases of infection each year because of indiscriminate sexual activity, reduced condom use, increased urbanization and travel, low infection detection rates, and inadequate or failed treatment. The purpose of this review is to provide up-to-date information on gonorrhoea disease, antimicrobial resistance of *Neisseria gonorrhoeae* and the latest treatment agents for the infection. Materials and methods: review of scientific literature, research and international experience that provide information about gonorrhoea disease. Conclusion: Continuous monitoring of antibiotic resistance in *Neisseria gonorrhoeae* and promotion of research and development of new treatment regimens is crucial. Joint efforts between clinicians and public health professionals at the local, national and global levels are needed to effectively prevent, identify, treat and monitor cases of gonococcal infection, and especially those resistant to antimicrobials.

Key words: *gonorrhea, antimicrobial resistant, new treatment agents.*

Introduction

Gonorrhoea is one of the most common sexually transmitted bacterial infections in modern society. It remains a major public health challenge due to the increasing incidence of the infection worldwide, as well as the increasing gonococci antimicrobial resistance and results in substantial morbidity and economic cost internationally. The limited choice of antimicrobials used to treat gonorrhoea, together with indiscriminate unprotected sexual activity, growing urbanization and travel, low infection detection rates, and inadequate or failed treatment, increase cases worldwide [1].

The purpose of this review is to provide up-to-date information on gonorrhoea disease, antimicrobial resistance of *Neisseria gonorrhoeae* and the latest treatment agents for the infection.

Materials and methods: review of scientific literature, research and international experience that provide information about gonorrhoea disease.

History - The gonorrhoea has been known in medicine since the Middle Ages, although it is named by different terms. It was originally called "The Clap" before the causative agent was found. The current name was first used by the Greek physician Galen before 200 CE who referred to it as "an unwanted discharge of semen" [2]. The earliest known records date back to around 1611, when the English Parliament passed a law in order to ensure that the disease would be eradicated from all society strata [3]. In 1256, King Louis IX of France passed a similar law in an attempt to control the disease and stop the spread of gonorrhoea among French society [4]. It has

been more than 200 years since Albert Neisser isolated *Neisseria gonorrhoeae* - the causative agent of gonorrhoea, in 1879.

Causative agent - *N. gonorrhoeae* (gonococci) belong to the family *Neisseriaceae*, genus *Neisseria*. They are Gram-negative diplococci, facultative intracellular bacteria [5].

Epidemiology - Gonorrhoea is a sexually transmitted disease. The infection is usually easy spread from one person to another through vaginal, oral, or anal sex [6,7]. Men have a 20% risk of getting the infection from a single act of vaginal intercourse with an infected woman and the risk for men that have sex with men (MSM) is higher [8]. Women have a 60–80% risk of getting the infection from a single act of vaginal intercourse with an infected man [9]. Another possible gonorrhoea spread mechanism is vertically transmission from infected mother to a newborn during childbirth [6].

Clinical findings - The incubation period of the disease is two to 14 days. The infection is often asymptomatic, especially in women, or minor symptoms are presented [10]. The combination of a highly infectious organism together with absence of symptoms results in a high rate of onward transmission. Urogenital gonococcal infection in men is usually symptomatic, but extra-genital (rectal, pharyngeal) infections in either sex are usually asymptomatic and often remain untreated, despite their key role in disease transmission. [11]. In men infection manifests most commonly as urethritis with feeling of pain and burning sensation during urination and purulent genital discharge with different color (white, yellowish or greenish) [6]. The most common complication in men is epididymitis and the gonorrhoea is also associated with an increased risk of prostate cancer [12]. In women, gonococcal infection can occur as cervicitis with pain or burning sensation during urination, pain during sexual intercourse, abnormal vaginal discharge, vaginal bleeding between the menstruation and lower abdominal and pelvic pain [6, 13]. In addition to adverse effects on joints, skin, and the cardiovascular system, untreated gonorrhoea can cause serious and permanent complications in both men and women - pelvic inflammatory disease and ectopic pregnancy, spontaneous abortions in women, infertility in either sex [14]. Infants born to women with gonorrhoea develop neonatal conjunctivitis (gonococcal ophthalmia neonatorum), characterized by marked bilateral local inflammation and purulent secretions. Co-infections with other major causative agents of sexually transmitted diseases (*Human Immunodeficiency Virus, Herpes simplex virus, Chlamydia trachomatis, Mycoplasma genitalium, Treponema pallidum*) are common and may result in synergistic effects on incidence and disease severity [15]. Patients with a proven gonococcal infection have been found to have a fivefold increased risk of *HIV* infection [16].

Microbiological diagnosis of gonorrhoea - *N. gonorrhoeae* can be diagnosed by culture or nucleic acid amplification tests and, in some instances, Gram stain. Samples for microbiological culture of suspected gonorrhoea include ejaculate, cervical, urethral, anal, throat and eye swabs and urine only when highly sensitive methods are used. Optimal isolation of *N. gonorrhoeae* requires good specimen collection, timely inoculation into adequate and appropriate culture media, proper transportation and appropriate incubation [14]. Gram-stained microscopy is used to reveal morphology of gonococci. No further testing is required to establish the diagnosis gonorrhoea if characteristic morphology of gonococci is visualized on direct Gram stain of male genital system samples (Gram-negative diplococci located inside or outside the leukocytes) [17, 18]. However, if gonococcal infection is suspected in women, a culture is required because it is difficult to distinguish *N. gonorrhoeae* from other Gram-negative diplococci, native to the normal vaginal flora on direct Gram stain of cervical swabs. Modern, highly sensitive and specific diagnostic

method that can be conducted on a wide range of samples is polymerase chain reaction (PCR). Culture remains the preferred testing method for diagnosis of extra-genital infections, which are often asymptomatic [19]. It is also useful for antimicrobial susceptibility testing of gonococci, detecting multiple and widely antibiotic-resistant isolates, and formulating treatment guidelines [18]. However, the recent use of molecular genetic methods to diagnose gonorrhea, compared to culture, has made the treatment of the disease a serious challenge.

World data - There are many reasons why the number of gonorrhoea cases reported in Europe and the United States varies - different testing policies and methods, health systems and access to services, reporting and surveillance structures, easy infection, sexual contact during travel, frequent asymptomatic infections, undiagnosed cases, self-medication or changing treatment recommendations [20]. According to Annual Epidemiological Report of European Centre for Disease Prevention and Control (ECDC), based on data for 2018 and retrieved from The European Surveillance System (TESSy) on 9 December 2019, 100 673 confirmed gonorrhoea cases were reported in 28 countries, an increase of 12% compared with 2017, as 61% of all cases reported were announced in the United Kingdom [20]. The highest notification rates in 2018 (>30/100 000 population) were observed in the United Kingdom (93 per 100 000), Ireland (50), Denmark (38) and Norway (31) [21]. The lowest rates (<1 per 100 000) were observed in Bulgaria, Croatia, Cyprus, Poland and Romania [20]. The reported higher number of cases over time may be due to improved national monitoring systems and use of more sensitive tests. The male-to-female ratio in 2018 was 3.2:1 [20]. Male-to-female ratios below 2 were reported by Denmark (1.6) and Estonia (0.5) and the highest male-to-female ratios were reported by Romania (14), Poland (11) and Portugal (10) [20]. The growing trend in the number of reported gonorrhoea cases in many countries continues to be mainly driven by increasing cases in MSM, but the number of cases among women has also been continuously increasing since 2009 [20]. In 2018, for the first time since reporting of gonorrhea in the countries of the European Union and the European Economic Area (EU/EEA) started, cases in women outnumbered those in heterosexual men among countries consistently reporting data on mode of transmission [20]. The largest proportion of cases reported in countries of the EU/EEA in 2018, was among the age groups 25–34 (37% of cases) and 15–24 years (34% of cases) [20]. In countries with comprehensive surveillance systems, age-specific rates of reported cases in 2018 were highest among the age group 20–24 years (112 per 100 000 population) [20].

In 2018, a total of 583,405 cases of gonorrhoea were reported in the United States (a rate of 179.1 cases per 100,000 population) [21]. During 2017–2018, the rate of reported cases increased 5.0%, and increased 82.6% since the historic low in 2009 [21]. During 2014–2018, the rate of reported gonorrhoea cases increased 78.7% among males (119.1 to 212.8 cases per 100,000 males) and increased 45.2% among females (100.4 to 145.8 cases per 100,000 females) [21]. In 2018, in the United States, the highest rates among females were observed among those aged 20–24 years (702.6 cases per 100,000 females) and 15–19 years (548.1 cases per 100,000 females) [21]. Among males, the rate was highest among those aged 20–24 years (720.9 cases per 100,000 males) and 25–29 years (674.0 cases per 100,000 males) [21].

Treatment - Gonorrhoea treatment is empirical (based on the symptoms, without identifying the causative agent and without antimicrobial susceptibility profile of the isolate) in accordance with the guidelines of the World Health Organization (WHO) [22]. Treatment is complicated, as *N. gonorrhoeae* have acquired various resistance mechanisms (mutations, plasmids) to many of the antimicrobials used over the years [23]. The resistance is documented by surveillance

programs, which are used to support appropriate treatment recommendations [24]. Widespread antimicrobial resistance (AMR) in *N. gonorrhoeae* strains continuously compromise the management and control of gonorrhoea. Reliable and quality-guaranteed monitoring is essential for detecting emerging and increasing AMR and providing qualitative data on gonorrhoea treatment guidelines. In 1986, in order to monitor trends in antimicrobial susceptibility of *N. gonorrhoeae* strains and to select evidence-based appropriate gonococcal therapies, the Gonococcal Isolate Surveillance Project (GISP) was established in the United States. The GISP facts directly contribute to the guidelines for the treatment of sexually transmitted diseases, including gonorrhoea in 1993, 1998, 2002, 2006, 2010 and 2015 and the updates in 2000, 2004, 2007 and 2012 [25]. In the countries of the EU/EEA, the antimicrobial susceptibility of gonococci is monitored by the European Gonococcal Antimicrobial Surveillance Program (Euro-GASP), launched in 2004 and coordinated with the ECDC since 2009 [26].

The first antimicrobial gonorrhea treatment was performed with sulfonamides, discovered in 1935. Soon after its introduction, penicillin became the preferred treatment for the disease, including due to resistance to sulfonamides in the early 1940s but only a few years later, (in 1946), high penicillin resistance began to be noticed [27]. In 1972, spectinomycin was used almost exclusively for gonorrhoea treatment (its only main indication) even its limited efficacy in gonococcal pharyngeal infections [28]. It was widely used in cases where penicillin and related drugs have not been available for use. Supply interruption and limited availability led to the cessation of its use in the 1990s [29]. Any subsequent treatment - tetracyclines, fluoroquinolones, macrolides, after initial success and several years of efficacy, was followed by progressively increasing resistance [30]. According to WHO data, resistance to extended-spectrum cephalosporins (the latest option for first-line gonorrhoea monotherapy), is reported worldwide [1, 31, 32]. Therefore, dual therapy option with azithromycin added has been accepted and preferred option for treatment [33]. Gonococcal strains resistant to both antibiotics have been reported in the United Kingdom and Australia, some of which are related to travel in Southeast Asia [34]. It is well documented that travel is associated with sexual risk-taking [35]. In some regions of Africa and Latin America, fluoroquinolones are still recommended for the empirical treatment, although they were removed from the WHO guidelines as early as 2007 due to the reported high level of resistance [36].

Effective treatment of pharyngeal (regardless of resistance) is more difficult than treatment of urogenital infections - while the average cure for urogenital infection is 96%, the rates drop to 79% and 84% (men and women, respectively) for pharyngeal infections [37]. Possible reason is insufficient exposure to antibiotics at the site of infection. Furthermore, the pharynx acts as a reservoir of the causative agent, which threatens global efforts to slow the spread of resistant strains and is considered a favorable site for the emergence of resistance due to horizontal genetic exchanges and the acquisition of resistant traits by commensal *Neisseria* species [38].

In 2009, definitions of multidrug-resistant (MDR-GC) and extensively drug-resistant gonococci (XDR-GC) were established [39]. MDR-GCs are strains with reduced susceptibility/resistance to a current guideline treatment including cephalosporin plus resistance to at least two or more of other antimicrobial agents (penicillin, tetracycline, macrolides, fluoroquinolones, aminoglycosides, carbapenems) [39]. XDR-GCs are strains with reduced susceptibility/resistance to two currently recommended therapies including cephalosporin plus resistance to at least three other antimicrobial agents (macrolides, fluoroquinolones, penicillins, tetracycline, aminoglycosides and carbapenems) [39]. In 2012, ECDC published a Response Plan

for the control and management of multidrug-resistant gonorrhoea treatment, outlining recommendations and possible strategies for controlling the threat across Europe [40]. While nosocomial pathogens are at the top of this list, due to the high mortality rate they cause, *N. gonorrhoeae* is specifically included because infections are extremely widespread, cause significant morbidity with significant healthcare costs for countries, can affect pregnant women and their newborns and develop antimicrobial resistance at a particularly rapid rate. The World Health Organization classifies *N. gonorrhoeae* as a priority bacterial pathogen, due to the high global burden of infection combined with evolution and global spread of resistance to every antibiotic historically used against it [41]. Gonorrhoea is included in the at the top of the Centers for Disease Control and Prevention (CDC) Emergency Threat category list among 18 other drug-resistant pathogens and in similar priority lists of antimicrobial resistance in the United Kingdom and Canada.

New treatment agents - The prevalence and incidence of gonococcal AMR is of great concern and outrun the development of new drugs, raising the prospect of untreatable gonorrhoea [42]. The emergence of untreatable strains of *N. gonorrhoeae* combined with the limited pipeline of novel anti-gonococcal agents, underscores the urgent need to update global treatment recommendations to effectively respond to the changing AMR patterns of *N. gonorrhoeae* and to discover new antibacterial agents [43]. Currently, the gonorrhoea treatment is severely depleted, with only three new chemical substances in various stages of a clinical trial as two of these are being developed for other indications. Solithromycin (Cempra Inc.) is an oral fluoroketolide with target prokaryotic ribosomes and activity against Gram-positive and fastidious Gram-negative bacteria, including *N. gonorrhoeae, M. genitalium*, and *C. trachomatis* [44]. It has shown good efficacy in a phase II clinical trial, with 100% effectiveness for genital, pharyngeal and rectal gonococcal infection in both men and women [45]. Phase III of a clinical trial has also been completed. Zoliflodacin (Entasis Therapeutics) is a first-class spiropyrimidinetrione topoisomerase II inhibitor with activity against several pathogens and highly effective in vitro against a large collection of geographically and genetically diverse *N. gonorrhoeae* isolates [46]. Phase II clinical trial results showed high efficacy against urogenital infections (98%–100% microbiological cure rate, depending on the dose; ClinicalTrials.gov number NCT02257918). Over 90% of the participants in the study were male. Gepotidacin (GlaxoSmithKline) is another bacterial topoisomerase II inhibitor, a novel triazaacenaphthylene with good in vitro activity against a wide range of resistant bacteria, including methicillin-resistant *Staphylococcus aureus*), ESBL (extended-spectrum β-lactamases)-producing *Enterobacteriaceae*, and *N. gonorrhoeae* [47]. A Phase II clinical trial completed with 96.7% and 94.8% cure rates achieved with doses of 1500 mg and 3000 mg, respectively (ClinicalTrials.gov number NCT02294682) [47]. Over 90% of the participants were male. Phase III clinical trial is upcoming.

Conclusion

Gonorrhoea is the second most common sexually transmitted bacterial infection and a major public health problem worldwide, affecting quality of life and with direct impact on reproductive and child health through infertility, cancers and pregnancy complications. The number of gonococcal infections is increasing rapidly worldwide. The limited number of anti-gonococcal agents currently in clinical trials and the growing antimicrobial resistance in *N. gonorrhoeae*, including extended-spectrum cephalosporins, raise concerns that the disease may become untreatable. Surveillance of antimicrobial resistance of gonococci, which is essential for

optimizing standard treatment, is often lacking or of poor quality in countries with a high incidence of the disease. Enhanced cooperation between clinicians, microbiologists, epidemiologists and public health authorities at national and international level is needed. Prevention efforts against increasing AMR in *N. gonorrhoeae* strains and increasing gonorrhea cases worldwide should rely on effective preventive measures, regular screening, rapid diagnosis, provision of effective therapy, new therapeutic treatment strategies, encouraging research and development of novel therapeutic agents.

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