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History

Gonorrhea: Historical outlook

Predesh Parasseril Jose[1], Vatsan Vivekanandan[1], Kunjumani Sobhanakumari[1]

[1]Department of Dermatology, Venereology and Leprology, Government T.D. Medical College, Alappuzha, Kerala, India.

***Corresponding author:**
Predesh Parasseril Jose, Department of Dermatology, Venereology and Leprology, Government T.D. Medical College, Alappuzha, Kerala, India.

prej69@gmail.com

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GONORRHEA: HISTORICAL OUTLOOK

History of gonorrhea dates back to the history of mankind. In this review, we have attempted to provide an overview of the historical aspects of the disease.

Gonorrhea is one of the oldest sexually transmitted infections (STIs) known to humankind. There is some conflict of opinion regarding its exact origin, but according to the general consensus, the disease has been present from the ancient times.[1] A disease resembling gonorrhea was described by the Chinese emperor, Huang Ti (2600 BC) in his textbook.[2] It is believed that the mention of "an issue of seed" in the Book of Leviticus in the Old Testament and the precautions suggested refers to this disease.[1] Gonorrhea was termed "strangury" by Hippocrates (460–375 BC) who claimed that it resulted from the "pleasures of Venus."[3] Celsus (25 BC–50 AD) was well aware of gonorrhea and its complications. He used to catheterize patients with urethral strictures.[4] The Greek physician, Galen (131–200 AD) coined the term "gonorrhea" and he referred to it as "an unwanted discharge of semen" (gono: seed, rhea: flow).[5]

The disease was also referred to as "The Clap," referring to the "clapping" sensation experienced by the infected person during urination. Others believe that the name is derived from the ancient treatment of "clapping" an infected penis on either side with a big book to remove pus. Some others are of the opinion that the word "The Clap" is derived from French brothels, known as "Les Clapiers," where the disease was quite rampant.[6] This name translates as "rabbit huts," referring to the small huts in which the prostitutes lived. In those days, men were considered as victims and women as the cause. The basic biology of the female reproductive tract was mistakenly thought to breed diseases since it was believed to provide adequate warmth and moisture for microbial growth.[6]

Throughout the history, wars were associated with outbreaks of STIs. Historical evidence suggest that the Roman soldiers fighting with Julius Caesar (100–40 B.C) suffered from gonorrhea. STIs including gonorrhea had caused many deaths during the Crimean war (A.D 1854–1856).[7]

Although the actual cause remained obscure, English parliament passed a law to halt the spread of "the perilous infirmity of burning" so as to ensure that gonorrhea was brought to a decline and ultimately removed from the society.[8] This remains the earliest known legal records of the disease and dates back to around 1161 AD.

The French king Louis IX passed a similar law in 1256 AD.[9]

Confusion regarding the relation between gonorrhea and syphilis arose with the arrival of syphilis in Europe in the late 15th century. Great surgeons such as Ambroise Pare and John Hunter considered gonorrhea and syphilis to be manifestations of the same disease. Hunter

drew conclusions from a famous experiment in which he inoculated himself with the material from a patient with gonorrhea and acquired syphilis. There were discordant views, suggesting that the inoculation was done on another patient and not on Hunter himself and that the patient had syphilis before the inoculation.[10] The confusion existed till 1838 when Phillippe Ricord after studying 2500 patients, categorically proved the existence of two different entities – syphilis and gonorrhea.[1]

Albert Ludwig Sigesmund Neisser in 1879 discovered the causative organism, *Neisseria gonorrhoeae*. His results were published in 1882.[11] Leistikow and Bumm in 1882 and 1885, respectively, were successful in growing the organism in culture media. The latter was able to produce characteristic symptoms and signs of the infection by inoculating the organism into the male urethra.[12] Another achievement was the introduction of the gonococcal complement fixation test in 1906 by Muller and Oppenheim.[1]

Under the public health regulations, ophthalmia neonatorum was made a notifiable disease in England and Wales in 1914. Crede's method, the time tested procedure for the prevention of ophthalmia neonatorum, is still in practice in some parts of the world with apparent success.[13] Stuart's medium, a transport medium for gonococci, was devised in 1946 by Stuart *et al.*[14] Chacko and Nair, in the late 1960s, developed the Chacko Nair medium for culturing gonococci.[15] Nowadays, nucleic acid amplification test remains the gold standard for the diagnosis of gonorrhea.[16]

TREATMENT

The treatment of gonorrhea dates back to the 16th century when mercury was injected into the urethra of crewmen suffering from the infection.[17]

In the 18th century, quantity and quality of pus from urethra determined the choice of treatment. Those with mild symptoms received bland fluids while extreme measures such as bloodletting and urethral lavage were adopted for patients with severe symptoms. Urethral lavage, a painful procedure involved introduction of a catheter through the urethra and flushing the urethra with water at 46–50°C. The quantity of water used was the maximum the patient could tolerate. It was believed that the success of the treatment was directly proportional to the discomfort experienced by the patient during the procedure. The treatment was repeated for 2–3 consecutive days.[18]

In the 19th century, an Indonesian type of pepper (cubebs) and balsam extracted from a South American tree (copaiba) were used in treatment with variable results.[19]

Mercurochrome, a derivative of fluorescein with bromine and mercury, was prepared by Young *et al.*, a Urology professor at John Hopkins Hospital, which was considered as an effective remedy. Three to six infusions of 1% mercurochrome solution were injected intravenously, at an increasing dose, a few days apart.[20] The injection, when given in 50% glucose solution, was more effective. Bactericidal action of mercury and the direct stimulation of antibacterial substances were thought to play a role.[21] Young *et al*. found that this treatment did not sterilize the urethra. According to Young *et al*., in addition to the intravenous mercurochrome, instillation of mercurochrome into the urethra or instillation of mercurochrome into the urethra and potassium permanganate into the seminal vesicle yielded satisfactory results.[22]

Heat therapy was advocated as an effective treatment for gonorrhea in 1913. Initially, limited to gonococcal arthritis; later, it found a place in the management of genital disease as well.[23] In 1932, investigators in the University of Rochester, New York, discovered that 99% of a gonococcal culture was killed by 2 h of exposure to heat at 41.5–42°C *in vitro*.[24] A fever cabinet which enclosed the whole body of the patient except the head was used to provide heat therapy. The temperature of 41°C was maintained for 4–6 h. Five to six such sittings at an interval of 3 days were given.[25] Mayo Clinic treated patients with intravenous infusion of mercurochrome in hypertonic glucose followed by hyperthermia.[26] Some investigators suggested that the curative effect may be facilitated by pelvic heating since the infection was focused there. Heating elements were inserted in the vagina and rectum to maintain temperature at about 44°C for about 2 h.[27] Heat therapy became obsolete with the introduction of sulfonamides.

Silver nitrate, one of the widely used drugs in the 19th century, was replaced by protargol (silver proteinate), invented by Arthur Eichengrun. From 1897, this was marketed by Bayer. The silver-based treatment was in use till the first antibiotics arrived in the 1940s.[28]

From the killed gonococci taken from Neisser's laboratory, the first vaccine was prepared in 1890, which was introduced in 1909.[29] It had a low efficacy and did not propagate extensively.

In 1937, Dees and Colston introduced sulfonamides in the treatment of gonorrhea.[30] As per John Hopkins University clinic protocol, gonorrhea patients received sulfonamides at a dose of 4.8 grams initially, tapered to 1.2 g/day for 4 weeks.[31] Best results were obtained when the treatment was initiated in the second rather than the 1st week of symptoms. This was explained by "Ehrlich hypothesis" – sulfanilamide, being bacteriostatic agents require immune mechanisms for effective action.[32] While symptoms cleared in a week, 80% of patients achieved a cure after 3 weeks of treatment.[32] Sulfapyridine followed by sulfathiazole became available in 1940–1941.[33] By 1944, Campbell noted failure of treatment

and relapses among troops fighting in the Italian campaign.[34] By late 1940s, >90% gonococcal isolates showed resistance to sulfonamides *in vitro*.[35]

Penicillin became the mainstay of treatment for gonorrhea since the 1940s.[35] However, by 1946 itself, four cases of penicillin-resistant gonorrhea were reported.[1] In 1963, Willcox introduced ampicillin to treat gonorrhea and observed a cure rate of 98%.[36] However, resistance due to beta-lactamase and chromosomal (plasmid mediated) mutation was detected in 1976 and 1980, respectively.[37] Mutations in penicillin-binding protein and alterations in efflux-influx systems are also cited as the causes of resistance to penicillin.[37]

Csonka and Knight introduced cotrimoxazole for the treatment of gonorrhea in 1967.[38] Cross-resistance between penicillin and cotrimoxazole was reported by Rodin and Seth, in 1972, thus making it a less attractive choice in areas with high prevalence of penicillin-resistant strains.[39]

In 1949, chlortetracycline was found to be effective with the added advantages of oral administration and efficacy against penicillin-resistant gonococcal strains.[39-41] However, the emergence of tetM determinant (causing high-level plasmid-mediated tetracycline resistance) in the mid-1980s brought its use to a halt in many countries worldwide.[42] Spectinomycin, introduced in 1967, substituted tetracycline as the alternative to penicillin.[42] It showed high cure rates in uncomplicated anorectal and urogenital disease, but has poor efficacy in pharyngeal infections.[43] It is still effective in gonorrhea, though inferior to cephalosporins.

In 1977, erythromycin was introduced in the management of gonorrhea (Brown *et al.*), especially in pregnant women with a history of penicillin allergy.[44] At present, due to the development of resistant strains, its use is limited to ophthalmia neonatorum.

Ceftriaxone was recommended as the first-line anti-gonococcal therapy in 1989.[45] Other cephalosporins including cefixime, cefazolin, cefuroxime, and cephalexin also showed excellent cure rates. However, in the past few decades, there are emergences of cephalosporin-resistant strains.

Aminoglycosides such as kanamycin and gentamicin were shown to be highly effective against gonococci. They are non-treponemicidal, hence do not mask syphilis so that a coexisting infection with *Treponema pallidum* does not go undetected.[46,47]

Although norfloxacin and ciprofloxacin were used during the 1980s and 90s, the WHO and centers for disease control (CDC) no longer recommend fluoroquinolones for the treatment of gonorrhea due to drug resistance.[48]

The WHO introduced the syndromic approach for the management of STIs in 1991 which was adopted by National AIDS Control Organisation in 1992.[49,50] The recommended drugs for gonococci were single dose of 400 mg cefixime or 500 mg ciprofloxacin or 125 mg of ceftriaxone (intramuscular) or 500 mg of erythromycin 6th hourly for 7 days. Along with these, single dose of azithromycin 1 g was advised. The current recommendation prescribes single dose of 1 g azithromycin with either 400 mg cefixime or 250 mg ceftriaxone.

The CDC recommendations vary according to the sensitivity patterns of the pathogens. The latest CDC guidelines recommend dual therapy for uncomplicated gonorrhea with single dose each of intramuscular ceftriaxone (250 mg) and 1 gram azithromycin per orally.[51] Patients with suspected treatment failure receive retreatment with the same regimen, as reinfection is more likely than treatment failure. Dual treatment with oral gemifloxacin 320 mg or intramuscular gentamicin 240 mg plus azithromycin 2 g single dose is recommended in those who do not respond to retreatment.[52] The recommended treatment for disseminated gonococcal infection includes ceftriaxone 1 g intravenously or intramuscularly every 24 h for 7 days with azithromycin 1 g single dose per orally.[51]

CONCLUSION

Gonorrhea, one of the oldest known STIs, has witnessed drastic changes in the diagnosis and management over the centuries. Even though there had been a decline, we are facing a resurgence of the infection during the past few decades. Emergence of drug-resistant strains and promiscuous sexual behavior could have contributed to this resurgence. Safe sex practices, sex education, especially among teenagers, and timely modifications in the treatment regimens to overcome the resistant strains may go a long way in preventing the spread of gonorrhea.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

Dr Kunjumani Sobhanakumary is on the editorial board of the Journal.

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