

Gonorrhoea, a current disease with ancient roots: from the remedies of the past to future perspectives

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SUMMARY

Gonorrhoea can be traced back to the earliest records of the human race even if Albert Neisser first described gonococcus in 1879. The Romans, Jews and Arabs all have documents referring to gonorrhoea and each society had their own description of symptoms and treatment. The Roman physician Galen in 130 AD described the disease as an “involuntary escape of semen”. The word itself derives from the Greek, meaning “the flow of seed”. Gonorrhoea is currently the second most commonly notifiable sexually transmitted infection (STI) reported to Centers for Disease Control and Prevention (CDC), second only to chlamydial infection. Gonorrhoea notifications have been on the rise all over the world and in several European countries since the early 2000s, particularly in populations with higher frequency of spread of STIs, such as men who have sex with men and young heterosexual individuals of both sexes.

Having been recognized at least 3500 years ago, the fight against the disease began infinitely before the antibiotic era, using healing compounds. In the absence of an ideal vaccine, the most important challenge today is the emergence of the multidrug-resistant gonorrhoea, which is currently the main reason for public con-

cern responsible for the evolution of *N. gonorrhoeae* into a superbug. *N. gonorrhoeae* strains resistant to extended spectrum cephalosporin (ESC) form a threat to effective control of gonorrhoea for which there are currently ongoing clinical trials to evaluate the efficacy and safety profile of old and new antimicrobial molecules for monotherapy and as dual therapy of gonorrhoea.

In this paper we investigated the remedies and treatments employed against gonorrhoea during the 19th century in Ferrara, referring to Campana’s Pharmacopoeia and unpublished manuscripts concerning the treatment of this disease in medical practice. The remedies for gonorrhoea adopted in the city were in line with those utilized in other countries. Among these, copaiba oleoresins have been demonstrated to have been efficacious in the past against gonococcal disease in popular medical use and, recently, against a large number of bacteria, fungi and protozoa, which will call for more *in vitro* and clinical studies to evaluate their real effectiveness on the *N. gonorrhoeae* bacterium.

Keywords: gonorrhoea, blenorrhagia, *Neisseria gonorrhoeae*, sexually transmitted infection.

INTRODUCTION

Historical accounts and descriptions of the disease *Blenorrhagia*, date back to the third book of Moses in the Bible. In this respect, a passage in the Old Testament (Leviticus, Chap. XV:1-3), warns that “When any man has a bodily dis-

charge, the discharge is unclean,” it gives reason to believe that gonorrhoea is an ancient disease and has successfully adapted itself to existing with *Homo sapiens*. Sarah, the wife of Abraham, probably had the inability to conceive until advanced age for having contracted gonorrhoea; Leviticus (Chap. XV and XXII), denounces the contagiousness of an affection characterized by continuous emission of semen and painful erection (Genesis, Chapter XII).

Numbers (Bible, Chap. XXV) write of a similar illness that had struck by divine punishment

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thousands of Jews after the trade with Moabite maiden worshipers of the god Baal-Fegor (the Greek-Latin Priapus).

Subsequently, the disease is reported in numerous testimonies, from the ancient Greeks philosopher Aristotle (384-322, BC) to Plato (437-347, BC) and many others.

In the Papyrus of the XVIII Dynasty (1500 BC) found in 1862 in Luxor by Georg Moritz Ebers (1837-1898), the symptoms of an acute urethritis referable to gonorrhoea were suggested to be treated with "endourethral instillations of oil of sandalwood".

The term gonorrhoea can be firstly attributed to Greek physician Galen from Pergamon (131-200 CE) in the 2nd century AD who coined the disease "as flow of seed", even if, Lucio Celio Aureliano (3rd - 4th century AD) from Sicca, in Numidia (today, Algeria), reports the discharge from the urethra as a unwanted excretion without erection, for which introduced the name gonorrhoea (from the Greek gonos=semen and rhoia=flow) in the chap-

ter "De debilitate seminalium viarum" of his most famous book translated from Greek to Latin from a work of the Methodist Soranus of Ephesus, (2nd century AD, Alexandria and Rome) and entitled "De morbis acutis et chronicis" (Figure 1).

Later, over time, lay medical schools also developed in Italy. In particular, in Salerno, the first lay medical school (schola) was founded where Costantin Africano (1020-1087) taught and translated many important medical manuscripts from Arabic to Latin (the books of Hippocrates, Galen and some Arab doctors). He also described gonorrhoea as "sperm sine voluntary concupiscentia est" (sperm flow without sexual desire) [1].

It was not until 1879 that Albert Ludwig Sigismund Neisser described the Gram-negative bacterium diplococcus *Neisseria gonorrhoeae*, the etiologic agent of the sexually transmitted infection (STI) gonorrhoea which etiological relationship with humans was established in 1885 and which has become a growing global public health problem [2].

In the United States, gonorrhoea is the second most commonly notifiable disease reported to the Centers for Disease Control and Prevention (CDC) and second to the chlamydial infection [3]. Rates of gonococcal infection steadily declined from 1975 to 1997 after implementation of a national gonorrhoea control program but remained stable since that time.

In 2013, the CDC reported that there were more than 330.000 new cases of gonorrhoea, with an incidence of 106.1 cases per 100,000 population [4]. The World Health Organization (WHO) estimates that, worldwide, there are over 106 million new cases of gonorrhoea annually [5]. However, incidence is expected to continue to rise with the increasing reports of treatment failures, particularly because of increasing levels of untreatable multi-drug-resistant *N. gonorrhoeae* strains. The African region has the highest rates of gonococcal infections worldwide, with about 50 and 100 new infections per 1,000 women and men, respectively, every year [6].

In Europe, more than 31,983 cases of gonorrhoea were registered by European Centre for Disease Prevention and Control (ECDC) in 2010 and a quarter of these cases was in men who have sex with men (MSM) and more than 40% in those under 25 years old [7, 8].

In most cases, the disease is a non-complicated

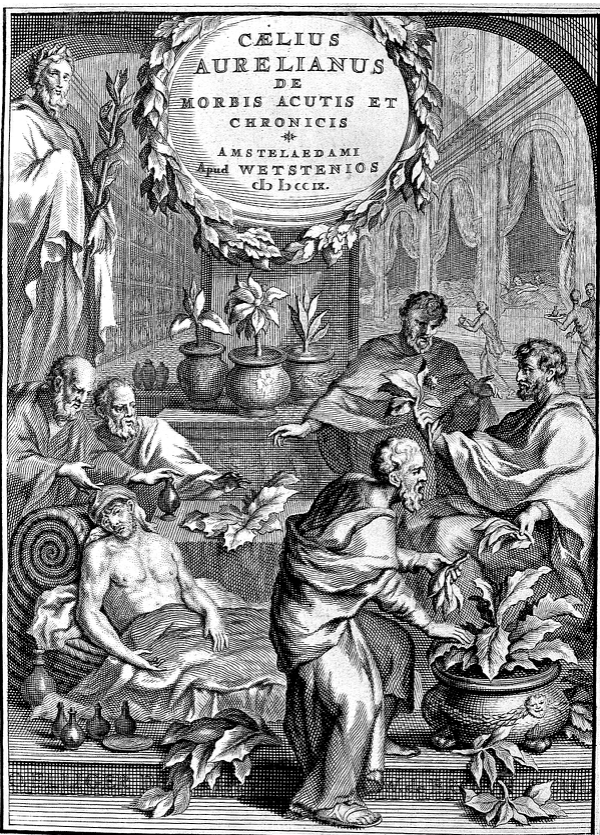


Figure 1 - Caelius Aurelianus, *De morbis acutis & chronicis* [...] Amstelaedami, ex officina Wetsteniana, 1709.

mucosal infection. However, in a few patients, especially women, more serious sequelae can occur and include salpingitis, pelvic inflammatory disease (PID; an infection in the upper part of the female reproductive system), ectopic pregnancy, infertility and rarely, a bloodstream infection resulting in gonococemia and disseminated gonococcal affliction of the joints (especially knees), cardiovascular system, and skin [9]. If left untreated, these serious complications can result in sterility, ectopic pregnancy, septic arthritis, and occasionally death. Approximately 3% of women presenting with a urogenital infection develop the most severe forms of the disease. Other (than lower genital tract mucosa) possible ports of entry of *N. gonorrhoeae* are oral, anal and conjunctival mucosa, making this infection a bit more complex than usually expected. Gonorrhoea also increases HIV transmission [5]. In 2015, the prevalence of HIV among people with a confirmed STI was about 60 times higher than that estimated in the Italian general population [10].

Increases in oropharyngeal gonorrhoea have been noted recently among MSM and certain populations of women. This form is vastly asymptomatic and thus is often not screened and remains un-diagnosed. The CDC has recommended routine screening of MSM for pharyngeal gonorrhoea since 2002 using nucleic acid amplification testing (NAAT) which is more sensitive than culture [11]. In men, the risk for infection after a single exposure to an infected person is around 20%, increasing to 60% to 80% after four or more exposures [8]. Transmission is more efficient from men to women than from women to men, particularly when men with symptomatic urethritis continue to have unprotected sex.

Infection in children is considered a marker for child sexual abuse. In this setting, a high prevalence of pharyngeal gonorrhoea was found among female adult and adolescent sexual assault survivors [12].

Gonorrhoea is a debilitating disease, which was responsible for an estimated 445,000 years lived with disability (YLD) in 2015 [13].

As gonorrhoea is a disease recognized for at least 3500 years, the fight against it began infinitely before the antibiotic era using healing compounds, some of which have recently been shown to be effective *in vitro* against Gram-negative and Gram-positive bacteria.

Herein, we have investigated the remedies and the treatments employed against gonorrhoea, an illness of great concern for the public health of the 19th century.

We have chosen Campana's Pharmacopoeia as a good example to help us understand how the treatments, remedies and cures improved over the century. Antonio Campana (1751-1833), professor of Pharmaceutical Chemistry and Botany, wrote a successful pharmacopoeia for the apothecaries in Ferrara that was also used in several Italian editions and abroad from 1798 to 1851. The remedies for gonorrhoea adopted in the city were in line with those utilized in other countries.

The Statistical Report from St. Anna Hospital, compiled by Alessandro Bennati in 1871 and 1876, provides detailed and complete information about the treatments for gonorrhoea in Ferrara [14, 15].

Alessandro Bennati's Case Reports of the St Anna Hospital (1871, 1876)

In 1871, St. Anna Hospital Medical and Surgical Division contained rooms with 400-500 beds. *Sala Nuova* also called the *Sala Chirurgica* (new room, surgical room), was next to the hall of the hospital and it was reserved for critically ill patients and those unhealthy with fetid exhalations.

In the *Comparto delle Malattie Veneree e Sifilitiche*, 20 patients affected from gonorrhoea (*blenorragia*) were hospitalized (7 males and 5 females in January-June and 6 males and 2 females) in July-December (Table 1).

Alessandro Bennati states that in January-June, 3 males with acute and chronic gonorrhoea (one and two cases, respectively), were admitted; in one case, the sites were the prepuce and the urethra, in the others, simply urethral (Figure 2). Injections with *acqua vegeto-minerale* (made of lead acetate and lead oxide) or silver nitrate and frozen,

Table 1 - Gonorrhoea patients hospitalized in St. Anna Hospital (Statistical Report, 1871)

| | Jan-June | | July-Dec | |
|-----------------------------|----------|---|----------|---|
| | M | F | M | F |
| <i>Blenorragia</i> | 3 | | 1 | |
| <i>Orchite blenorragica</i> | 4 | | 5 | |
| <i>Blenorragia uretrale</i> | | 1 | | |
| <i>Blenorragia vaginale</i> | | 4 | | 2 |
| Total 1871 | 20 | | | |

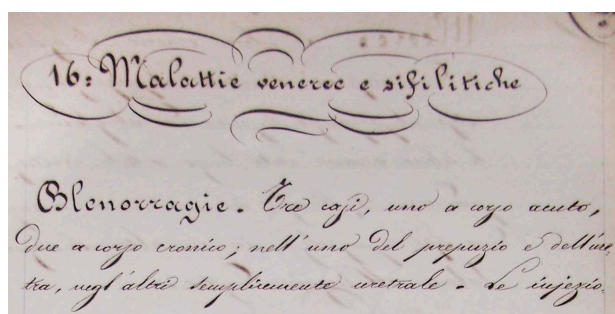


Figure 2 - Bennati A., *Resoconto statistico Sanitario dell'Arcispedale per l'anno 1871*.

mucilaginous, *gramigna* drinks (*bibite di semifreddi, gommose, di gramigna*) led to the recovery of acute blennorrhagia in 25 days.

Treatments with potassium iodide (internal use), with injections of silver nitrate or *sublimato corrosivo* (mercuric chloride) led to the clinical improvement in cases of chronic gonorrhoea.

Four males were affected by right and left (two cases, respectively) gonococcal orchitis (*orchite*

blenorragica), healed in 12 or 15 days, with the usual anti-inflammatory care, and particularly with the leeches on the sperm cord pattern corresponding to the inflamed testis.

In July-December, 1 male with urethral gonorrhoea and 5 males with gonococcal orchitis were hospitalized. Inflammation of the urethra was treated with leeches applied to the perineum, injections of frozen water and *bibite di semifreddi stibiate* (frozen drinks of antimony potassium tartrate). Later, *Balsamo del Copaibe* pills and injections of silver nitrate were effective against the *scolo blenorragico*.

The five males with gonococcal orchitis were affected by left and right gonococcal orchitis and healed in 2-3 weeks, with leeches on the sperm cord pattern corresponding to the inflamed testis, poultices (*empiastru ammollienti*), ointments (*Unguento mercuriale* also with Belladonna extract); in some cases by compression, by surrounding the scrotum with patches of *cerotto mercuriale*, made of wax (*cera bianca*), oil, mercury oxide.

Table 2 - St. Anna Hospital Statistical Report (1871)

| Remedies employed for the 30 hospital patients | M | M BO | F UB | F VB |
|---|-----|---------|---------|---------|
| <i>Acqua vegetominerale</i> , local bath (<i>lavacri</i>) | | | x | x |
| <i>Acqua vegetominerale</i> (injections) | x | | | xx |
| Silver nitrate, injections | xxx | | | x |
| Cold water, injections | x | | | |
| Mercuric chloride, injections (<i>sublimato corrosivo</i>) | x | | | |
| Zincum sulphate, injections | | | x | |
| Ointments (<i>Unguento mercuriale</i> and extract of Belladonna) | | x | | |
| Poultices (<i>empiastru ammollienti</i>) | | x | | |
| Antimonial frozen drinks (<i>bibite di semifreddi stibiate</i>) | x | | | |
| Frozen and mucilaginous drinks (<i>bibite di semifreddi, bibite gommose, bibite di gramigna e semata</i>) | x | x | | xx |
| Anti-inflammatory care | x | | | |
| Leeches (<i>mignatte</i>) | x | xx | | |
| Bath (<i>semicupi</i>) | x | | | x |
| Purgatives (<i>purganti oleosi</i>) | | x | | x |
| <i>Balsamo del Copaibe</i> pills | x | | | x |
| <i>Balsamo del Coppaiibe</i> and <i>pepe Cubeba</i> pills | | | x | |
| <i>coppaiba/trementina/tannino</i> pills | | | | x |
| Frank's Resolvent Powders | | x | | |
| Potassium iodide (internal use) | x | x | | |

BO, Blenorragic Orchitis; UB, Urethral blenorragia; VB, Vaginal Blenorragia.

Purgatives (*purganti oleosi*) and Frank's Resolvent Powders were useful. In case of fever, *bibite di gramigna* (drinks), *Semata* (drink made of melon seeds or almond) [16] and potassium iodide were effective.

In 1871, Frank's Resolvent Powders (*Polveri risolventi del Frank*) were first employed in Ferrara. The so called *Pillole di Sanità* or *Grani di Salute del Dott. Frank*, as Campana stated in *Farmacopea ferrarese*. They are made up of Socotrine aloes (*Aloe squarrosa di Socotora*), colocynth and spirits, enough to create pills.

In January-June, 1 female with urethral gonorrhoea and 4 females with vaginal gonorrhoea were hospitalized. The patient suffering from urethral gonorrhoea was discharged from the hospital after 12 days, healed with pills made of *Balsamo del Coppaiibe* and *pepe Cubeba*, local bath of *Acqua vegetominerale*, urethral injections with zincum sulphate solution.

Of the four females affected by vaginal gonorrhoea, one completely healed in three weeks after treatment with *bibite gommose* (mucilaginous drinks) and *acqua vegeto-minerale* injections, another one, after four days of decubitus, came out of the hospital in the same condition, forced by family needs. Two other patients affected by vaginal gonorrhoea had infection associated to metritis or intestinal catarrh.

The flogistic states of the uterus and intestines resolved with *mignatte* (leeches) applied to the groin and to the *vasi sedali*; with *empiastris* (poultice) on the belly, with *semicupi* (baths), with *purganti oleosi* (purgative), orally or as a suppository, with *bibite di Semata e di gomma* (drinks) or tamarind drinks, or with *graminacee* (grasses). *Coppaiibe* pills and *acqua vegeto-minerale* injections were used against gonorrhoea.

The patient affected by gonorrhoea associated to metritis recovered in five weeks. The other, healed from the intestinal catarrh and improved the gonorrhoea; one-month after, she was discharged for insubordination.

In July-December, two females affected from acute and subacute vaginal gonorrhoea, were hospitalized.

The first, healed in 12 days with injections of silver nitrate, *semicupi* (baths), *purganti oleosi* (purgatives), *bibite di gramigna* (drinks); the second, in 18 days with the same injections, local bath of *Acqua vegetominerale* and internally, with pills made of *Balsamo di Coppaiiba*, *trementina e tannino*.

Table 3 - Patients with Gonorrhoea hospitalized in St. Anna Hospital (Statistical Report, 1876).

| | Jan-Apr | | May-Aug | | Sep-Dec | | Total 1876 |
|----------------------|---------|---|---------|---|---------|---|------------|
| | M | F | M | F | M | F | |
| Blenorrhagia | 3 | 1 | 7 | - | 2 | 2 | 15 |
| Orchite blenorragica | 6 | | 7 | | 2 | | 15 |
| Total 1876 | | | | | | | 30 |

Alessandro Bennati's Case Reports cited in Rendiconto (1876) of St. Anna Hospital

The *Rendiconto*, a concise report of Alessandro Bennati, states that in 1876, 30 patients affected from gonorrhoea were recovered at the St. Anna Hospital between January and December. In January-April, 9 males and 1 female with gonococcal orchitis - *orchite blenorragica* - and gonorrhoea, in May-August, 14 males with *orchite blenorragica*, in September-December, 4 males and 2 females with *orchite blenorragica* and gonorrhoea (Table 3).

General remedies for venereal diseases are reported, not specifically related to gonorrhoea such as: potassium iodide, mercurials (*protoioduro e deutocloruro di mercurio*), *Decotto del Salvatori* and *Decotto del Pollini* (made of *sarsaparilla* and *mercurio dolce*).

The Balsamo di Coppaiiba

In the numerous editions of the Ferrara Pharmacopoeia of Antonio Campana, two remedies of plant origin appear with the specific indication against gonorrhoea, *Lonicera diervilla* W., *sommità fiorite* (*In America it is estimated to be an excellent remedy for gonorrhoea*) and *Coppaifera officinalis* L.

The *Balsamo di Coppaiiba* (*Resina fluida*, *C. officinalis*) already appears from the first edition (1798) of *Pharmacopoeia ferrarese* of Antonio Campana, as a vulnerary, astringent and healing compound (Figure 3) [17,18].

Balsamo di Coppaiiba. of. Resina fluida.
Coppaifera officinalis. L.
 È di colore giallo chiaro, ed ha odore di trementina tendente alla lavandula, e sapore amaro.
 Si adopra come vulnerario, astringente, cicatrizzante.
 Dose: da mezzo scropolo a uno scropolo.

Figure 3 - Campana A. *Farmacopea ferrarese* (Silvestro Gnoato) 1805. Venezia.

Antimicrobial activity of Copaiba oils

Copaifera genus grows in tropical areas, in particular in the Amazon region. The healing properties of Copaiba oil are known since thousands of years. In general, Copaiba has various ethnopharmacological indications, including bronchitis, pains in general, back pain, injury and blennorrhagia. The indigenous people from northwest Amazonia have used the oleoresins produced by the plant for medicinal purposes to wounds healer, to stop bleeding, for skin sores and psoriasis, and to treat gonorrhoea.

Copaiba oleoresin continues to be widely used as a popular medicine for the treatment of leukorrhoea and gonorrhoea topically (vaginal capsules) and orally, as the oil is eliminated through the kidney and has urethral transit [23].

Recently, copaiba oleoresin has been studied in depth arousing the interest of researchers for the possible antibacterial and antifungal activities [24]. In particular, oils obtained from *C. officinalis* were demonstrated to be active against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, and *Enterococcus faecalis*. Copaiba oil has shown to effectively inhibit *S. aureus* growth and to be a promising adjuvant for wound and scar healing [25]. This oil also showed a bacteriostatic activity against *Streptococcus mutans* and at low concentrations it could be an option of phytotherapeutic agent to be used against cariogenic bacteria in the prevention of caries disease [26]. A moderate activity was observed against dermatophyte fungi (*Trichophyton rubrum* and *Microsporum canis*) but no activity against Gram-negative bacteria and yeast [27].

Copaifera reticulata oil showed bactericidal activity against the causative agents of tooth decay and periodontitis, *Fusobacterium nucleatum*, *Streptococcus mitis*, *Prevotella nigrescens*, *Porphyromonas gingivalis*, *Lactobacillus casei*, *Streptococcus salivarius*, *Streptococcus mutans*. β -bisabolene, trans- α -bergamotene, β -selinene, α -selinene, and the terpene acids ent-agathic-15-methyl ester, ent-copalic acid, and ent-polyalthic acid are the major constituents of oil [28].

The copaiba oleoresins are also used in the suppository form for gynecological infections. The effects of vaginal cream of copaiba oleoresin (*Copaifera duckei*, Dwyer) have been evaluated on the reproductive performance of female Wistar rats [29].

The oleoresins produced by several members of the genus *Copaifera* were also employed in the Amazon region for the treatment of cutaneous ulcerations due to leishmaniasis particularly against *Leishmania amazonensis*. The most active oil was that from *C. reticulata* [30]. Although the mechanism of action of the oleoresin is still unclear, these findings indicate that copaiba oil is a possible new drug, which would provide a safer, shorter, less-expensive, and more easily treatment for leishmaniasis [31]. *C. officinalis* has also shown to exhibit activity against *Trypanosoma cruzi* [32]. A recent study allowed the development of low-cost ecofriendly green natural-based nano-formulations (of Copaiba, *C. duckei*, oleoresin) with potential larvicidal activity against *Aedes aegypti*, using a nanobiotechnology approach [33].

The emergence of multidrug-resistant gonorrhoea

N. gonorrhoeae has developed multiple immunological mechanisms to escape the immunity system (innate and adaptive immunity) of the host [24]. This ability to escape host's defensive systems allows us to understand the evolutionary processes used by gonococci to resist the inestimable number of antibiotics used to treat infections for the past 70 years (Table 4).

Gonococcus has cleverly developed resistance to all first-line antimicrobials since the arrival of the first antimicrobials in the '30, the sulfonamides and subsequently developed resistance to penicillins, introduced in the mid-1940s a "new miracle drug" and then to tetracyclines, spectinomycin, macrolides and fluoroquinolones. In fact, *in vitro* studies have shown that, after introducing a new antimicrobial drug, strains resistant to these alternative antibiotics emerged due to chromosomal mutations and gonococci become resistant and replace sensitive bacterial population within two decades. In this way, gonococci have evolved and acquired or developed all known physiological resistance mechanisms to all antimicrobials used for treatment such as: enzymatic antimicrobial destruction or modification; target modification or protection reducing affinity for the antimicrobials; decreased or increased efflux of antimicrobials [34].

Ceftriaxone (an injectable cephalosporin) has been chosen as the latest drug option available to treat gonorrhoea even if from 2011, resistance to it has been noted in Japan and now in Europe [35].

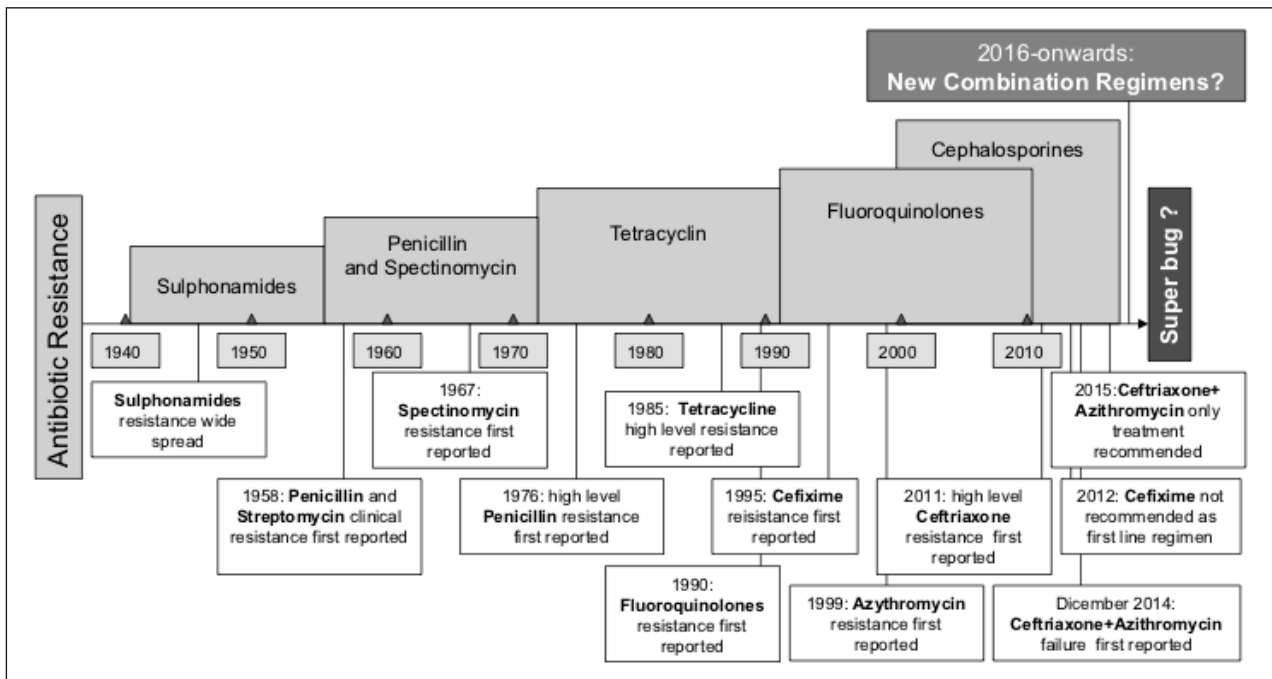


Table 4 - Evolution of antibiotic resistance against *N. gonorrhoeae* (Modified and adapted from Unemo M. et al. Antibiotic resistance in *Neisseria gonorrhoeae*: origin, evolution, and lessons learned for the future [34].

Between 2006 and 2011, there has been a rapid increase in the percentage of isolates in the United States with a minimum inhibitory concentration (MIC) (the amount of an antimicrobial needed to inhibit the growth of an *in vitro* bacterium) to cefixime, the oral third generation of extended spectrum cephalosporins (ESCs). Following the increasing number of reports on the increase in resistance to ESCs, cefixime and ceftriaxone combined with resistance to practically all other available gonorrhea antimicrobials, the threat of resistant antimicrobial gonorrhea (AMR) has become a major public health concern. Reports of therapeutic failures both in cefixime and ceftriaxone in Japan and Europe, pushed the head of the Sexually Transmission Division of the CDC to “give the alarm”.

In response to increasing cefixime MICs in the United States (the evolution of resistance in *N. gonorrhoeae* in the United States is highly influenced from other geographic regions, especially through the import of resistant strains from Asia), CDC recently updated its treatment recommendations for gonococcal infections.

In 2016, two new dual antimicrobial therapies were recently proposed and evaluated: gentamicin intramuscularly plus azithromycin orally

and gemifloxacin plus azithromycin, both orally. These combinations were effective in 100 and 99.5%, respectively, thus proving that any of these two regimes is suitable as alternative treatment options in the presence of ceftriaxone resistance, treatment failure with the recommended regimen, or ESC allergy [36]. To implement action plans at global and national levels, especially enhancing surveillance of gonococcal AMR (phenotypic and genetic) and treatment failures and improve early diagnosis and prevention, would be mandatory. In this setting, specific programs exist to monitor resistance data and to detect the emergence of any AMR which could threaten the effectiveness of current first-line treatments in Europe and in United States [37, 38].

CONCLUSIONS

Many centuries before the discovery of *N. gonorrhoeae*, already Roman, Hebrew and Arabic had papers related to gonorrhea. Each society had its own description of the symptoms and treatment. The Greek Galen in 130 AD, described the disease as an “involuntary escape of the sperm” (the flow of seeds). The evolution of the disease and its complications have had such an impact in the

human societies that over the centuries more and more compounds against gonorrhea were tested. Among them, Copaiba oleoresins, widely used as popular medicine through topical and oral administration, have been shown to be effective against gonorrhea in the past in popular medical use and recently against a large number of bacteria, fungi and protozoa. However, they will require more *in vitro* and clinical studies to assess their actual efficacy on the *N. gonorrhoeae* bacterium.

Due to its significant ability to cause repeated infections in the same host and its tendency to develop resistance to all clinically useful antibiotics tested so far, *N. gonorrhoeae* has proved to be an ideal STI pathogen on which to study the evolution of bacterial pathogenesis and AMR within the host, during the infection. Up to now, gonorrhea is the second most commonly notifiable disease reported to the Centers for Disease Control and Prevention (CDC) and second to the chlamydia. The number of gonococcal infections is rapidly rising worldwide, and *N. gonorrhoeae* seems to be evolving into a true "superbug" as new treatment options for multidrug-resistant gonorrhea and established programs for gonococcal surveillance are yet lacking.

In the absence of new antibiotics against gonorrhea and given the speed with which resistance has emerged to all previously used antibiotics, development of a vaccine would be the ideal solution to this public health emergency. Presently, many biological challenges exist to gonococcal vaccine development and there is no naturally acquired immunity to the infection. A vaccine with high coverage and lasting protection could have a substantial impact on gonococcal prevalence and on disease sequelae especially among young people and some risk categories including MSM.

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