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

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SUMMARY

Gonorrhea 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 gonorrhea 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”. Gonorrhea 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. Gonorrhea 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 gonorrhea, which is currently the main reason for public concern 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 gonorrhea 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 gonorrhea.

In this paper we investigated the remedies and treatments employed against gonorrhea during the 19th century in Ferrara, referring to Campana’s Pharmacopoeia and unpublished manuscripts concerning the treatment of this disease in medical practice.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 gonorrhea 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: gonorrhea, 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 discharge, the discharge is unclean,” it gives reason to believe that gonorrhea 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 gonorrhea; 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 gonorrhea were suggested to be treated with “endourethral instillations of oil of sandalwood”.

The term gonorrhea 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 gonorrhea (from the Greek gonos=semen and rhoia=flow) in the chapter “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 gonorrhea as “sperm sine voluntary concupiscencia est” (sperm flow without sexual desire) [1].

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

In the United States, gonorrhea 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 gonorrhea control program but remained stable since that time.

In 2013, the CDC reported that there were more than 330,000 new cases of gonorrhea, 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 gonorrhea 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 gonorrhea 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 gonococcemia and disseminated gonococcal afflication 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. Gonorrhea 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 gonorrhea 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 gonorrhea 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 gonorrhea was found among female adult and adolescent sexual assault survivors [12].

Gonorrhea is a debilitating disease, which was responsible for an estimated 445,000 years lived with disability (YLD) in 2015 [13]. As gonorrhea 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 gonorrhea, 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 gonorrhea 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 gonorrhea 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 gonorrhea (blennorrhagia) 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 gonorrhea (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 - Gonorrhea patients hospitalized in St. Anna Hospital (Statistical Report, 1871) |
|-------------------------------------------------|----------------|----------------|----------------|
| Month/Year                                      | M  | F  | M  | F  |
| Jan-June                                       |    |    |    |    |
| Blenorragia                                     | 3  | 1  |    |    |
| Orchite blenorragica                            | 4  | 5  |    |    |
| Blenorragia uretrale                            | 1  |    |    |    |
| Blenorragia vaginale                            | 4  | 2  |    |    |
| Total 1871                                     | 20 |    |    |    |
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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 *sublimate corrosivo* (mercuric chloride) led to the clinical improvement in cases of chronic gonorrhea.

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 gonorrhea 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 (*empiastr i 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)**

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

BO, Blenorragic Orchitis; UB, Uretral 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 gonorrhea and 4 females with vaginal gonorrhea were hospitalized. The patient suffering from urethral gonorrhea was discharged from the hospital after 12 days, healed with pills made of Balsamo del Coppaibe and pepe Cubeba, local bath of Acqua vegetominerale, uretral injections with zincum sulphate solution. Of the four females affected by vaginal gonorrhea, one completely healed in three weeks after treatment with bibite gommose (mucillaginous 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 gonorrhea 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 empiastri (poultice) on the belly, with semicupi (baths), with purganti oleosi (purgative), orally or as a suppository, with bibite di Senata e di gomma (drinks) or tamarind drinks, or with graminacce (grasses). Coppaibe pills and acqua vegeto-minerale injections were used against gonorrhea.

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

In July-December, two females affected from acute and subacute vaginal gonorrhea, 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 Coppaiba, trementina e tannino.

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

<table>
<thead>
<tr>
<th></th>
<th>Jan-Apr</th>
<th>May-Aug</th>
<th>Sep- Dec</th>
<th>Total 1876</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Blerorragia</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Orchite blenorragica</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Total 1876</td>
<td>15</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 gonorrhea 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 gonorrhea, in May-August, 14 males with orchite blenorragica, in September-December, 4 males and 2 females with orchite blenorragica and gonorrhea (Table 3).

General remedies for venereal diseases are reported, not specifically related to gonorrhea 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 Copaiba

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

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

![Figure 3 - Campana A. Farmacopea ferrarese (Silvestro Gnoato) 1805. Venezia.](image-url)
Mercurial pills were made of Mercurio dolce, guaiac extract, scraped camphor and Balsam di Copaiba [19] (1808). In the edition (1841) updated by Michelotti after his death, new galenic preparations appear as Elixir antivenereo di Lemort, made of Balsamo del copaiba, Resina di guaiaco, legno sassafras polv., Alcool di vino [20]. The Elixir must be taken with mucilage of gum arabic or decoction of Altea. Balsamo del Copaibe solido combined with Magnesia calcinata has shown to be an excellent remedy for gonorrhea. Calcined magnesia determines the hardening of the balm so that it can be reduced in pills without the need for other powders. Elettuario per la gonorrea was made of Balsamo di Copaibe seeds of fellandrio acquatico, Spirito di nitro dolce, white sugar and arabic gum. Effectiveness is praised: Questo elettuario è attivissimo. In 1858, it was suggested to administer sotto-nitrato di Bismuto in order to avoid flatulence and diarrhea caused by the use of Balsam copaibe and Pepe cubebe [21]. In 1860, the Capsule d’Emilio made of Balsamo Copaibe were promoted in the newspapers. They were approved by the Protomedicato Regio in Naples, in preference to those that so far, the foreigner gave us at a very expensive price (Figure 4-6) [22].
**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 gonorrhea.

Copaiba oleoresin continues to be widely used as a popular medicine for the treatment of leukorrhea and gonorrhea 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*) bitno 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. reticulate* [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 gonorrhea**

*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 gonorrhea even if from 2011, resistance to it has been noted in Japan and now in Europe [35].
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 his 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 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.

**REFERENCES**


