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Gonorrhea

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10.1   Introduction

Gonorrhea is a sexually transmitted disease (STD) caused by the obligate human pathogen *Neisseria gonorrhoeae* or gonococcus. This Gram-negative bacteria is highly infective due to its virulence factors: pili, Por proteins, Opa proteins, Rmp proteins, lipooligosaccharides, and IgA protease. The most common form of presentation in men is acute anterior urethritis, while gonococcal infection in women does not have specific symptoms. More than 106 million new cases of gonorrhea are estimated to occur yearly worldwide. The highest incidence areas include Africa and the Western Pacific regions. Gonorrhea is primarily transmitted from an infected individual by direct human-to-human contact between the mucosal membranes of the urogenital tract, anal canal, and the oropharynx, usually during sexual activities. Ever since sulphonamides were introduced to treat gonorrhea in the 1930s, gonococci have continuously shown an extraordinary ability to develop resistance to any antimicrobial introduced for treatment. Treatment is currently given empirically, without performing antimicrobial susceptibility tests. However, the increasing issue of drug-resistant gonococci led the scientific community to focus research in new drugs and alternative treatments, having obtained encouraging results. The diagnosis of gonorrhea is established by identification of *N. gonorrhoeae* in genital, rectal, pharyngeal, or ocular secretions. *N. gonorrhoeae* can be detected by culture or nucleic acid amplification tests and, in some cases, Gram staining. Seeing as all attempts to develop a vaccine against gonococci have been unsuccessful, prevention, and control of the disease relies completely on early diagnosis, accurate treatment and public health education.

This disease can be traced back to ancient Egyptian literature; the George Ebers papyrus describes a vulvovaginal inflammation that could be gonorrhea (Bingham 2014). It was not until 1879 when Albert Neisser described the

gonococcus as the pathogen responsible of the disease from exudate from patients with urethritis and neonatal (Neisser 1911). In 1884, the Danish bacteriologist Hans Gram identified it using Gram staining, and in 1885, Ernest Bum finally isolated it in an artificial medium.

Currently, gonorrhea is a community disease with a high morbidity burden. In fact, more than 106 million new cases are estimated to occur yearly worldwide (World Health Organization (WHO) 2012a). Furthermore, incidence is rising due to the prevalence of multidrug-resistant strains of *N. gonorrhoeae* (Suay-Garcia and Perez-Gracia 2017). The increase is so alarming that *N. gonorrhoeae* was classified as a "Priority 2" microorganism in the recently published WHO *Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics* (World Health Organization (WHO) 2017). This document reported the existence of *N. gonorrhoeae* strains resistant to third-generation cephalosporins and fluoroquinolones and stressed the importance of developing new antibiotics for oral formulations in order to treat the disease.

Seeing as there currently is no gonococcal vaccine, prevention and control of gonorrhea rely on sexual education and contact notification, epidemiological surveillance, diagnosis and, especially, effective antibiotic treatment. In fact, finding new effective antibiotic treatments is a major concern because *N. gonorrhoeae* has an extraordinary ability to develop resistance to all antimicrobials introduced for its treatment (World Health Organization (WHO) 2012a) has led to the Centers for Disease Control and Prevention (CDC) to classify it as a *superbug*, alerting the medical community about the prospect of untreatable gonorrhea in the near future (Centers for Disease Control and Prevention (CDC) 2012).

10.2   Pathogen

10.2.1   Morphology

Neisseria gonorrhoeae is a Gram-negative coccus with a size oscillating between 0.6 and 1 μm in diameter, with 0.8 μm its mean size. It presents itself in pairs (diplococci), the adjacent faces are flattened (similar to coffee grains). These microorganisms are visualized under optic microscope as extracellular and intracellular diplococci, inside neutrophils (Figure 10.1).

This bacterium lacks a capsule; however, it produces a polyphosphate that could have a function similar to that of the capsule, seeing as it creates a hydrophilic surface with a negative charge.

The structure of *N. gonorrhoeae* is the typical for Gram-negative bacteria, with a thin layer of peptidoglycan between the inner and outer cytoplasmic membranes. It has pili, Por proteins, Opa proteins, and Rmp proteins in the outer membrane as well as lipooligosaccharides (LOS). Moreover, three groups of proteins have been identified in the outer membrane, and they act as mediators in the acquisition of iron by binding to transferrin, lactoferrin, and hemoglobin. All of these structures can act as antigens and virulence factors.
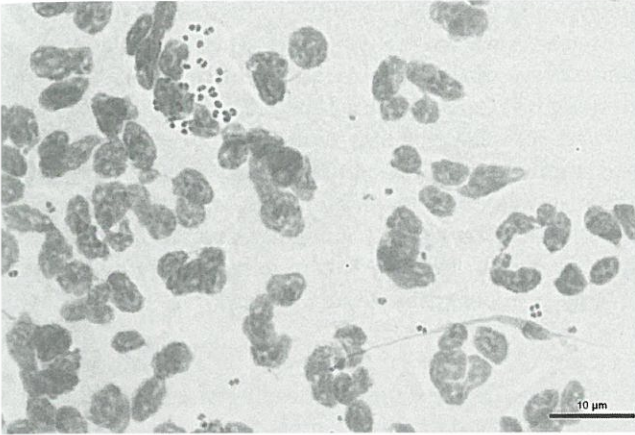
Figure 10.1 Gram stain of *Neisseria gonorrhoeae* in urethral sample. (*See color plate section for the color representation of this figure.*)

10.2.2 Virulence Factors

10.2.2.1 Type IV Pili (Tfp)

Clinical isolates of *N. gonorrhoeae* present pili or fimbria, which extend from the cytoplasmic membrane through the outer membrane. These pili are composed of repeated protein subunits (pilins), whose expression is controlled by the group of genes *pilE* (Swanson et al. 1971). Pili expression is associated with virulence, partly because these structures play a part in the adhesion to nonciliated epithelial cells, while providing a resistance mechanism to neutrophil phagocytosis. Gonococcal pili are classified as type IV, seeing as the polypeptide PilE is initially synthesized with a short (7 amino acids) leader N-terminal peptide that is later endo-proteolytically cleaved (Freitag et al. 1995). Pilin proteins have a preserved region in the amino-terminal end, which is very little immunogenic, and a very immunogenic hyper-variable region in the carboxi-terminal end. This region presents antigenic variations, allowing the classification of these bacteria in more than 50 serotypes and, therefore, avoiding recognition by immune cells of the human host (Hill and Davies 2009). It has been observed that a single strain is capable of presenting more than one type of fimbria and that these variations also occur *in vivo*, when the same strain is isolated from different locations within the patient. The absence of immunity after reinfection by *N. gonorrhoeae* is partly the result of the antigenic variation among pilins and, partly due to the variation in the expression phase of pilins. Both factors have truncated the attempts made to develop an effective vaccine using these structures (Boslego et al. 1991).

Type IV pili, besides promoting binding to host cells, are also involved in bacterial spasmodic motility, biofilm formation, and DNA transformation (Heckels 1989).

10.2.2.2 Por Proteins

These proteins are porins that form pores or channels and are present in the outer membrane. They represent 60% of the total proteins. Two types of Por proteins have been identified (PorA and PorB), each with diverse antigenic

variations. The strains expressing PorA are resistant to the bactericidal action of serum and are consequently associated to the disseminated disease, more complicated. On the other hand, those expressing PorB are associated with uncomplicated mucosal infection (Cannon et al. 1983). The antigenic variation of Por proteins has been used in the serotype classification of *N. gonorrhoeae*.

Porins allow the transport of ions and nutrients through the outer membrane and also contribute to the survival of bacteria in host cells (Judd 1989). Por proteins also modulate maturation of phagosomes, changing their protein composition through an increase in early endocytic makers and a decrease of late endocytic markers, which results in a delay in phagosomal maturation (Mosleh et al. 1998).

10.2.2.3   Opacity Proteins (Opa)

Opa proteins are a family of integral proteins in the outer membrane, which cause the opaque aspect of colonies when seen under phase-contrast microscope due to intergonococcal aggregation (Swanson 1982). These proteins contribute to the binding with epithelial cells and enable the adherence of bacteria among themselves and with other eukaryotic cells.

Unlike pili, the expression of Opa proteins is not required for the initial fixing of gonococci to the host. However, as infection progresses, expression of these proteins varies (Swanson et al. 1992) and bacteria expressing Opa can be observed in epithelial cells and neutrophils of infected voluntaries (Jerse et al. 1994). The invasive ability of *N. gonorrhoeae* is determined by the differential expression of Opa. Individual Opa proteins bind to a variety of receptors in human cells through their hyper-variable regions. The binding specificity for human receptors is divided in two groups: OpaHS, which recognize heparin sulphate proteoglycans; and OpaCEA, which recognize the family of carcino-embryonic antigen-like cellular adhesion molecules (CEACAMs), formed by several CD66 molecules. CEACAMs are the main receptors for Opa proteins and are expressed in many different cell types including epithelial cells, neutrophils, lymphocytes, and endothelial cells (Sadarangani et al. 2011).

10.2.2.4   Rmp Proteins

Rmp proteins (reduction modifiable) constitute the third group of proteins present in the outer membrane of gonococci. These proteins are not modified with heat, do not suffer antigenic variations, and are common to all strains. They stimulate antibodies that block the serum bactericidal activity of *N. gonorrhoeae* (Li et al. 2014).

10.2.2.5   Lipooligosaccharide (LOS)

Another important antigen in the cell wall is the LOS. This antigen is formed by the lipid A and an oligosaccharide nucleus, similar to the lipopolysaccharide (LPS) of Gram-negative bacteria, but lacking the repetitive O antigens of LPS. It has endotoxin activity and is toxic for the mucosa in the fallopian tubes, causing detachment of ciliated cells. Moreover, gonococcal LOS can also be sialylated, making bacteria resistant to serum (Ram et al. 2017). Therefore, this structure contributes to gonococcal pathogenicity, enabling bacterial translocation through the mucosal barrier and providing resistance against human serum.

10.2.2.6 IgA Protease

Immunoglobulin A protease (IgA) is another virulence factor of *N. gonorrhoeae* (Hill et al. 2016). This protease experiments several endo-proteolitic divisions when liberated, resulting in its maturation. During infection, the mature protease is directed specifically towards IgA1, exactly toward the region situated within the hinge region rich in proline. IgA2 is not split by this protease, seeing as it lacks the proline-rich region. IgA protease is also capable of dividing the lysosomal-associated membrane protein 1 (LAMP-1) gene, which results in lysosome modification and, therefore, bacterial survival (Ayala et al. 2002).

10.2.3 Physiology

Like all bacteria, *N. gonorrhoeae* reproduces asexually by binary division, originating two daughter cells of approximately the same size from the mother cell. This division is not complete, seeing as the septum does not divide completely because they are arranged in pairs (diplococci). Gonococci are immobile, aerobic, and nutritionally fastidious and grow best at a temperature range of 35–37 °C, in an atmosphere of 3–5% CO_2 and a pH of 7.2–7.6. Autolysis occurs when it is exposed to room air, desiccation, ultraviolet light, silver salts, phenol, and humid heat at 55 °C. They differ from other species of *Neisseria* in their ability to transform glucose but not maltose, sucrose, lactose, fructose, and mannose. They are catalase and oxidase positive.

10.2.4 Genome

Gonococci have a circular genome, formed by a DNA molecule of 980 megadaltons (MDa) and approximately 2154 Mb. *Neisseria gonorrhoeae* can acquire genetic information through transformation and conjugation, more frequent in strains with pili.

    N. gonorrhoeae has several mobile genetic elements (MGEs). MGEs such as transposable elements control intra-chromosomal rearrangements, while plasmids and the gonococcal genetic island are involved in inter-chromosomal gene transfer. Moreover, gonococcal MGEs act as hotspots for recombination and integration of other genetic elements such as bacteriophages, contribute to gene regulation or spread genes through gonococcal populations by horizontal gene transfer (Cehovin and Lewis 2017).

10.3 Pathogenesis and Immunity

Gonococcal infection is highly infective. The risk of a woman acquiring the disease after sexual contact with a man is of an estimated 50–70% and of a man from a woman 20–30%.

    Gonococci adhere to mucosal membranes, especially columnar squamous epithelium from urethra and cervix, and can infect the Bartholino glands, the conjunctive, and the rectum (Cornelissen 2011). Furthermore, they affect soft stratified epithelium in young women, while the vagina and vulva of adult women

is less susceptible. In the mucosa of the vaginal tract, eyes, rectum, and throat, they produce acute suppuration and tissue invasion, causing chronic inflammation and fibrosis.

Once adhered to mucosal membranes, they penetrate epithelial cells by endocytosis and multiply to later pass through the cells into the sub-epithelial space, where infection occurs. The presence of pili is important for the initial adherence. Cells without pili are not virulent. After initial adhesion, Opa proteins control a stronger union with the surface of host cells and the migration of bacteria within epithelial cells (Martin et al. 2016). At this point, Por proteins act to protect phagocytized bacteria from intracellular death by inhibiting phagolysosome fusion. The gonococcal LOS stimulates inflammatory response and liberation of tumor necrosis factor-α (TNF-α), responsible for most symptoms associated to the gonococcal disease.

The study of desquamated cells from the urethra of males with symptoms of early infection reveals that gonococci are present in the interior of cellular cytoplasm. Cells start to be destroyed four hours after infection and bacteria remain inside a matrix with cellular wastes that protect them from external aggressions.

The rates of disseminated infection, 1–3% of the cases, could be higher among patients with asymptomatic local infection, partly due to the fact that the microorganism has more time to penetrate the circulatory system. In men, this is the primary risk factor; in women there is also the presence of intrauterine devices and cellular changes in the endometrium during menstruation, which reduce local barriers and enable the access of bacteria to blood vessels (Edwards and Apicella 2004). It has been observed that people with hereditary alterations of the complement have a considerably higher risk of systemic disease (Davido et al. 2014).

Gonococcal infection does not provoke a protective immune response or immune memory. Consequently, individuals can be repeatedly infected. However, specific antibodies are produced inside the genital tract, inhibiting the adherence to epithelial cells in the mucosa, albeit their short persistence. Generally, immune response to an uncomplicated genital infection is still modest (Hedges et al. 1999). The IgG is the main antibody produced as a response to gonococcal infection. Although the response of antibodies to Por is minimal, antibodies against pili, Opa proteins, and LOS are easily detected in serum. Antibodies against LOS can activate the complement, liberating the component C5a of the complement, which has a chemo-attractant effect on neutrophils. Nevertheless, antibodies IgG and IgA aimed against the Rmp protein can block the bactericidal response of antibodies.

10.4 Epidemiology

More than 106 million new cases of gonorrhea are estimated to occur yearly worldwide (World Health Organization (WHO) 2012a). The highest incidence areas include Africa and the Western Pacific regions. The burden is such that a review regarding infections during pregnancy in sub-Saharan Africa revealed the

prevalence of sexually transmitted and reproductive tract infections to be comparable with that of malaria (Chico et al. 2012). However, gonorrhea is not a problem limited to developing countries. In fact, it is the second most frequently reported notifiable disease in the United States, with about 820 000 new gonorrhea infections occurring yearly (Centers for Disease Control and Prevention (CDC) 2016a). Similarly, the latest report of the European Center for Disease Prevention and Control (ECDC) showed a 25% increase in the number of reported cases between 2013 and 2014 (European Centre for Disease Prevention and Control (ECDC) 2016b).

Gonorrhea is primarily transmitted from an infected individual by direct human-to-human contact between the mucosal membranes of the urogenital tract, anal canal, and the oropharynx, usually during sexual activities. These infections are most frequently identified in men who have sex with men (MSM), but can be encountered in both genders in many settings (sex workers, sex tourists, etc.) (Unemo et al. 2016).

Ever since sulfonamides were introduced to treat gonorrhea in the 1930s, gonococci have continuously shown an extraordinary ability to develop resistance to any antimicrobial introduced for treatment (World Health Organization (WHO) 2012a). Such is the case that the recent emergence of strains resistant to third-generation extended-spectrum cephalosporins (ESCs) (cefixime and ceftriaxone), combined with resistance to most available treatment options, has turned *N. gonorrhoeae* infection into a great public health issue (Bolan et al. 2012).

The first gonorrhea superbug, H041, was isolated in Japan in 2011 (Ohnishi et al. 2011). This strain exhibited extremely high resistance levels to all ESCs, including cefixime (MIC $8 \, mg \, L^{-1}$) and ceftriaxone (MIC $2-4 \, mg \, L^{-1}$), as well as to most of the other available treatments. Since H041 was isolated, other multidrug-resistant strains have also been isolated in France, F89 strain (Unemo et al. 2011a), and Spain (Camara et al. 2012), proving that the rapid spread of drug-resistant strains is a major public health concern (Unemo and Nicholas 2012). Moreover, the fact that MDR strains have been isolated from commercial sex workers, homosexual men, sex tourists, truck drivers, and people undergoing forced migration suggests that these strains have the potential to spread globally.

The issue with resistant gonococci is such that the first case of failure to the standard dual antimicrobial treatment of gonorrhea was recently reported in the United Kingdom (Fifer et al. 2016). Antibiogram results showed that the strain was resistant to ceftriaxone, azithromycin, cefixime, cefoxatime, penicillin, tetracycline, and ciprofloxacin, only being susceptible to spectinomycin.

The detection of these strains in Japan, Spain, France, and the United Kingdom proves that the treatment for gonococcal infection is being seriously threatened by the emergence of antimicrobial resistance. With this in mind, governments worldwide have created programs to collect data in order to study the evolution of this species in developing resistances and presenting itself at the community level (Ohnishi et al. 2011; Unemo et al. 2011a; Bolan et al. 2012; Camara et al. 2012; Unemo and Nicholas 2012; Fifer et al. 2016; Public Health England 2016; Unemo et al. 2016; Centers for Disease Control and Prevention (CDC) 2016a, 2016b; European Centre for Disease Prevention and Control (ECDC) 2016a, 2016b).

10.5   Clinical Features

10.5.1   Gonococcal Infection in Men

The most common form of presentation is acute anterior urethritis. The incubation period is of two to six days. It is characterized by the appearance of abundant purulent urethral exudate and dysuria. Balanopostitis may appear in noncircumcised men. Without treatment, 95% of cases are resolved within eight weeks and symptoms disappear after six months, even though complications such as abscesses, fistulas, and urethral stenosis may occur.

In 3–12% of men, urethral infection is present without symptoms, representing an important group in the transmission of the microorganism (Hill et al. 2016).

10.5.2   Gonococcal Infection in Women

Infection in women presents two features responsible for the prolonged period between acquiring the disease and its treatment, which increases the possibility of complications and determines the important epidemiological role they play in transmitting the disease. These features are the absence of specific symptoms and a more difficult diagnosis than that for male urethritis.

The columnar epithelium of the endocervix is the first site of urogenital infection in women (endocervicitis). Unlike men, women do not have properly defined signs and symptoms of genital infection. The most frequent are leukorrhea, dysuria, and pruritus, but 50% of the cases are asymptomatic.

Ascending infection in a woman constitutes a serious complication, seeing as 10–20% female gonococcal infection develop acute salpingitis, tube-ovarian abscesses, and pelvic inflammatory disease (PID), and of these cases, 20% will present fertility problems. The term *PID* includes endometritis, salpingitis, and pelvic linfagitis or peritonitis, seeing as it is difficult to set them apart clinically and they can occur simultaneously. Different pathogens may be involved in the etiology of PID, such as *Chlamydia trachomatis, Mycoplasma,* and aerobic and anaerobic bacteria.

10.5.3   Extragenital Locations

Disseminated infections with septicemia or skin and joint infections are observed in 1–3% of infected women, and in a much lower percentage of infected men. Most disseminated infections in women are due to the numerous asymptomatic infections that remain untreated. Clinical manifestations of the disseminated disease are fever, migratory arthralgia, suppurative arthritis in wrists, knees, and ankles, and a pustular exanthema on an erythematous base in limbs but not in head or torso.

The anorectal form is caused by direct inoculation; its frequency is linked to sexual practices. Clinic of this infection is variable. It may present itself in a silent form, unapparent but biologically active, which is the most common; in a

subacute way with essentially endoscopic expression; or in the most striking but exceptional way, as gonococcal proctitis. Up to 40% of women with genital infection and homosexual men present gonococci in the rectum.

Pharyngeal gonococcal infection is asymptomatic in 80% of the cases, presents mild symptoms in 15%, and in the remaining 5% presents febrile angina. This form, along with the rectal presentation, is defined as location more than infection, seeing as both are generally asymptomatic.

Newborns of infected mothers can acquire the infection in their eyes, which produces conjunctivitis (*ophtalmia neonatorum*), characterized by a bilateral purulent exudate that sometimes leaves severe consequences such as corneal opacification and blindness.

10.6 Diagnosis

The diagnosis of uncomplicated gonorrhea is established by identification of *N. gonorrhoeae* in genital, rectal, pharyngeal, or ocular secretions. *N. gonorrhoeae* can be detected by culture or nucleic acid amplification tests (NAATs) and, in some cases, Gram stain. Culture detection of *N. gonorrhoeae* has long been available for the detection of rectal and oropharyngeal gonococcal infection (Centers for Disease Control and Prevention 2015) but implementation of NAATs for this pathogen has been reported to double its detection from rectal samples and increase its detection from pharyngeal samples fivefold (Cornelisse et al. 2017). A drawback of currently available commercial NAATs is their inability to provide information on antimicrobial susceptibility. Cultures should be done in parallel with NAATs to allow for susceptibility testing. Samples from all cases of suspected gonococcal infection should be collected for microbiological culture and antimicrobial susceptibility testing, to the extent possible, considering local availability of resources. No test offers 100% sensitivity and specificity (Table 10.1). Since laboratory diagnostic tests are not available in most countries, diagnosis is often made clinically, based on the presence of symptoms such as vaginal and urethral discharge.

10.6.1 Samples

The sampling site in gonorrhea diagnosis depends on age, gender, sexual habits of the individual, and the features of the infection (Table 10.2). Samples must be taken using swabs, and sowing must be done immediately. Two different swabs must be taken, one for culture and another one for Gram staining (Aznar et al. 2007).

Gonococci are very sensible to adverse conditions in the environment and, generally, the number of microorganisms in the samples is small. The highest positivity index is obtained when samples are inoculated directly in a culture medium that will be incubated at 35 °C with 5% CO_2. In cases where the sample is not inoculated directly, a transport medium is used (Stuart-Amies, Transgrow, or Jembec) (Table 10.3).

Table 10.1 Sensibility and specificity of several tests for *Neisseria gonorrhoeae* according to sample type.

Test used	Sample type	Sensitivity (%)	Specificity (%)
Gram stain	Endocervical swabs	45–65	90–99
	Symptomatic: urethral swabs	85–98	95–99
	Asymptomatic: urethral swabs	45–70	85–87
BioStar OIA GC Test (Immunoassay)	Endocervical swabs; urine	60; 100	89.9; 93–98
ACON Duo (duplex for *Chlamydia trachomatis* and *N. gonorrhoeae*) (Immunoassay)	Endocervical swabs	12.5	99.8
GeneXpert (duplex for *C. trachomatis* and *N. gonorrhoeae*) (NAAT)	Endocervical swabs; vaginal swabs; female urine; male urine	100; 100; 95.6; 98.9	100; 99.9; 99.9; 99.9
Aptima COMBO 2 assay Aptima CT assay Aptima GC assay (Hologic/Gen-Probe Inc., San Diego, CA)	Multitest Swab (Clinician-Collected Vaginal Sample); Multitest Swab (Patient-Collected Vaginal Sample); endocervical swab; ThinPrep Liquid; male urethral swab; male urine	98.5; 100; 99.2; 92.3; 99.1; 98.5	99.6; 99.5; 98.7; 99.8; 97.8; 99.6
Abbott RealTime CT/NG (Abbott Molecular Inc., Des Plaines, IL)	Symptomatic: Multitest Swab (Clinician-Collected Vaginal sample); Multitest Swab (Patient-Collected Vaginal Sample); endocervical swab; female urine; male urethral swab; male urine	96.3; 96.2; 88; 93.8; 99.5;98.7	99.7; 100; 99.6; 99.8; 99.5; 99; 99.2
	Asymptomatic: Multitest Swab (Clinician-Collected Vaginal Sample); Multitest Swab (Patient-Collected Vaginal Sample); female urine; male urine	100;100; 82.6; 100	100; 100; 99.5; 100
BD ProbeTec Q^{X}GC Amplified DNA assay (Becton Dickinson and Company, Sparks, MD)	Symptomatic: endocervical swabs; urethral male; female urine; male urine	100; 98.9; 94.7; 98	99.4; 98.6; 99.6; 98.7
	Asymptomatic: endocervical swabs; urethral male; female urine; male urine	92.9; 100; 82.1; 92.3	99.3; 100; 99.5; 99.8
cobas CT/NG test (Roche Diagnostics, Indianapolis, IN)	Endocervical swabs; Multitest swab (Clinician-collected Vaginal sample); Multitest swab (Patient-collected Vaginal sample); female urine; male urine	96.6; 100; 96.7; 95.6; 100	99.9; 99.7; 100; 99.7; 99.3

Table 10.2 Clinical samples for the diagnosis of gonorrhea.

Patient	Sample of choice	Secondary sample
Women	Endocervix	Rectum[c], urethra, pharynx[a]
Heterosexual men	Urethra	
Homosexual men	Urethra, rectum[c], pharynx	
Disseminated gonococcal infection		
Women	Blood, endocervix, joint blood	Pharynx[a], skin lesions[b], rectum[c]
Men	Blood, urethra, joint liquid, rectum[c]	Pharynx[a], skin lesions[b]

[a]If there has been orogenital contact;
[b]If existing;
[c]If there has been anogenital contact.

10.6.2 Staining

Bacteria can also be visualized on microscopy of stained genital tract smear to facilitate rapid diagnosis in symptomatic men with urethritis (Figure 10.1). In low-income settings, Gram stains may provide a less-expensive alternative to NAATs for symptomatic men. Microscopy (×1000) using Gram or methylene blue staining for identification of diplococci within polymorphonuclear leukocytes offers good sensitivity (≥95%) and specificity as a rapid diagnostic test in symptomatic men with urethral discharge (Taylor et al. 2011). However, results in endocervical samples of women present a sensibility of 45–65%, which could be an indication of the lower number of gonococci in them. Moreover, false positives may appear, and the specificity (90–99%) will depend on the experience of the microscopist. Microscopy has poor sensitivity (≤55%) in asymptomatic men and in identifying rectal infection (≤40%) and cannot be recommended as a test of exclusion in these situations (Table 10.4). Microscopy is not recommended for identification of pharyngeal infection due to poor specificity as well as low sensitivity (Hughes et al. 2014).

10.6.3 Culture

For decades, cultures of *N. gonorrhoeae* have been considered the reference method for the diagnosis of both genital and extragenital gonorrhea. Cultures offer a specific and cheap diagnostic test that allows for rapid confirmatory identification (Figure 10.2). It is the only diagnostic test that enables antimicrobial susceptibility testing, and the capacity to perform culture remains essential for detecting and monitoring evolving antimicrobial resistance. The antimicrobial resistance of gonococci is a serious problem worldwide, seeing as culture is the only method that allows for sensibility testing; it is essential to maintain and strengthen the capability of all countries to work with cultures.

Selective culture media (agar modified Thayer-Martin (TMM), Martín-Lewis (ML), or New York City (NYC)) containing antimicrobials are recommended (Jephcott 1997). Nonselective media (agar chocolate) can be beneficial in

Table 10.3 Characteristics of Gram-negative, oxidase-positive *Neisseria*, and related species of human origin.

Species	Acid from					Superoxol	Reduction of nitrate	Polysaccharide from sucrose	Tributyrin hydrolysis	ONPG	GGT	PIP
	Glucose	Maltose	Lactose	Sucrose	Fructose							
Neisseria gonorrhoeae	+	–	–	–	–	+	–	–	–	–	–	V
Neisseria meningitidis	+	+	–	–	–	+	–	–	–	–	V	V
N. lactamica[a]	+	+	+	–	–	+	–	–	–	+	–	+
N. cinérea[a]	–	–	–	–	–	+	–	–	–	–	–	+
N. polysaccharea[a]	+	+	–	–	–	+	–	–	–	–	–	+
N. subflava[a]	+	+	–	V	V	+	–	V	–	–	–	+
N. sicca	+	+	–	+	+	+	–	+	–	–	–	+
N. mucosa	+	+	–	+	+	+	+	+	–	–	–	+
N. flavescens	–	–	–	–	–	+	–	+	–	–	–	+
N. elongata	–	–	–	–	–	–	–	–	–	–	–	+
Branhamella catarrhalis	–	–	–	–	–	+	+	–	+	–	–	V
Kingella denitrificans	+	–	–	–	–	–	+	–	–	–	–	+

Abbreviations: + = positive; – = negative; V = variable. ONPG = o-nitrophenyl-b-galactoside; GGT = γ-glutamilaminopeptidase; PIP = proliliminopeptidase.
[a]Certain strains grow on selective media for the isolation of *N. gonorrhoeae*.

addition to the selective media for urogenital and conjunctival samples if afford-able. Culture is appropriate for endocervical, urethral, rectal, pharyngeal, and conjunctival specimens but not for urine samples. The sensitivity of culture is high (85–95%) for urethral and endocervical samples providing that specimen collection, transport, storage, and isolation procedures are optimized. An appro-priate quality assurance is needed for the gonorrhea culture system, since com-mercial media and culture procedures vary in their selectivity and sensitivity.

Culture (ideally supplemented with a NAAT for optimal diagnostic sensitivity) should be performed for antimicrobial sensitivity testing in patients with persist-ing infection or symptoms following treatment or if treatment failure is sus-pected (Unemo et al. 2011b; Whiley et al. 2012). Cultures should be incubated in a humid environment with 5% CO_2 at 35–37 °C. The cultures must be examined every 24 hours for at least 72 hours.

Surveillance of antimicrobial sensitivity is an essential part in controlling gonococcal infection, seeing as treatment generally consists of a single dose that cures 95% of the cases. In the last few years, a change in treatment has been sug-gested when more than 5% of the isolates become resistant to an antibiotic. In order to determine MICs, the method of the Clinical Laboratory Standards Institute (CLSI) is suggested; however, simpler methods such as the E-test are also valid.

10.6.4   Identification

The finding of Gram-negative, oxidase, and superoxol positive diplococci on selective media allows for the presumptive identification as gonococci (Table 10.3). Definitive identification is carried out by means of the sugar degradation test or serologic methods, such as indirect immunofluorescence and coaglutina-tion. There are three available methods for the epidemiologic identification of *N. gonorrhoeae*: auxotyping, serotyping, and genotyping methods: pulsed-field gel electrophoresis (PFGE), amplified fragment length polymorphism (AFLP), and sequencing. Beta-lactamase production must be studied in all strains to avoid treatment failure, and epidemiological surveillance of antibiotic resist-ance must be carried out.

10.6.5   *Neisseria gonorrhoeae* Genotyping

Understanding clonal relationships among *N. gonorrhoeae*-resistant isolates is an important strategy to controlling the spread and increase of resistance. There are two main DNA sequence-based typing methods performed in gonococcus with data stored on public websites. The *N. gonorrhoeae* multi-antigen sequence type (NG-MAST) is specific to this species and analysis of two variable *loci, porB*, and *tbpB*, which encode one of the two porins expressed by *N. gonorrhoeae* (PIB porin) and the B subunit of binding transferrin protein, respectively (NG-Mast n.d.). NG-MAST is a convenient tool for micro-epidemiological studies due to its discriminatory property (Ilina et al. 2010). The other method is multilocus sequence typing (MLST), available for the gender *Neisseria*. This approach is based on the analysis of seven housekeeping genes, and is appropriate to track

Table 10.4 Summary of commercially available FDA-approved gonorrhea NAAT platforms.

NAAT	Amplification technology	Sample types	Specimen transport and storage conditions	Target
Abbott RealTime CT/NG (Abbott Molecular Inc., Des Plaines, IL)	Real-Time PCR	Asymptomatic women: clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, and urine. Asymptomatic men: urine. Symptomatic women: endocervical swab, clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, and urine. Symptomatic men: urethral swab and urine.	14 days at 2°–30°C 90 days at −10°C or lower Thaw frozen specimens at 2°–30°C Specimens must not undergo more than four freeze/thaw cycles	48 base pair sequence within the *Opa* gene of *Neisseria gonorrhoeae*.
Aptima COMBO 2 assay Aptima CT assay	Transcription mediated amplification (TMA)	Asymptomatic women: endocervical swab, clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, gynecologic specimens collected in PreservCyt solution and urine. Asymptomatic men: urethral swab and urine.	24 hours at 2–30 °C (urine specimen in primary cup) 30 days at 2–30 °C (urine specimen in Aptima urine transport tube)	Specific region within the 16S rRNA from *N. gonorrhoeae* (Aptima COMBO 2 assay).
Aptima GC assay (Hologic/Gen-Probe Inc., San Diego, CA)		Symptomatic women: endocervical swab, clinician-collected vaginal swab, patient-collected vaginal swab in a clinical setting, gynecologic specimens collected in PreservCyt solution and urine. Symptomatic men: urethral swab and urine.	60 days at 2–30 °C (swab in Aptima swab transport tube) 12 months at −20° to −70°C (urine specimen and swab specimens in respective Aptima transport tubes)	Specific region with the 16S rRNA from *N. gonorrhoeae* that is distinct from the Aptima COMBO 2 assay target (Aptima GC assay).

| BD ProbeTec CT/GC Amplified DNA assay (Becton Dickinson and Company, Sparks, MD) | Strand displacement amplification (SDA) | Asymptomatic women: endocervical swab and urine.

Asymptomatic men: urethral swab and urine.

Symptomatic women: endocervical swab and urine.

Symptomatic men: urethral swab and urine. | 30 hours at 2°–30°C (urine specimen in primary cup)

7 days at 2°–8°C (urine specimen in primary cup)

30 days at 2°–30°C (urine specimen in urine processing tube)

60 days at −20°C or lower (neat urine specimen or urine in urine processing tube)

6 days at 2°–27°C (swab specimens)

30 days at 2°–8°C (swab specimens) | Chromosomal pilin gene-inverting protein homologue. |
| BD ProbeTec Q^XGC Amplified DNA assay (Becton Dickinson and Company, Sparks, MD) | Strand displacement amplification (SDA) | Asymptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, gynecologic specimens collected in BDSurePath or PreservCyt solution and urine.

Asymptomatic men: urethral swab and urine.

Symptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, gynecologic specimens collected in BDSurePath or PreservCyt solution and urine.

Symptomatic men: urethral swab and urine. | 30 hours at 2°–30°C (urine specimen in primary cup).

7 days at 2°–8°C (urine specimen in primary cup)

30 days at 2°–30°C (urine specimen in urine processing tube)

180 days at −20°C or lower (neat urine specimen or urine in urine processing tube)

30 days at 2°–30°C (endocervical and urethral swab specimens)

180 days at −20°C or lower (endocervical and urethral swab specimens)

14 days at 2°–30°C (dry vaginal swab specimens)

30 days at 2°–30°C (expressed vaginal swab specimens)

180 days at −20°C or lower (dry or expressed vaginal swab specimens) | Chromosomal pilin gene-inverting protein homologue. |

Table 10.4 (Continued)

| NAAT	Amplification technology	Sample types	Specimen transport and storage conditions	Target
Xpert CT/NG assay (Cepheid, Sunnyvale, CA)	Real-Time PCR	Asymptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, and urine. Asymptomatic men: urine. Symptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, and urine. Symptomatic men: urine.	24 hours at room temperature (female urine specimen in primary cup) 3 days at room temperature (male urine specimen in primary cup) 8 days at 4 °C (female and male urine specimen in primary cup) 3 days at 15°–30 °C (female urine specimen in Xpert CT/NG Urine Transport Reagent tube) 45 days at 2–15 °C (female urine specimen in Xpert CT/NG Urine Transport Reagent tube) 45 days at 2–30 °C (male urine specimen in Xpert CT/NG Urine Transport Reagent tube) 45 days at 2–30 °C (swab in Xpert CT/NG Swab Transport Reagent tube)	Two distinct chromosomal sequences each with a different reporter. Both sequences have to be detected to obtain a positive *N. gonorrhoeae* result.
Cobas CT/NG test (Roche Diagnostics, Indianapolis, IN)	Real-Time PCR	Asymptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, clinician-collected vaginal swab, gynecologic specimens collected in PreservCyt solution and urine. Asymptomatic men: urine. Symptomatic women: endocervical swab, patient-collected vaginal swab in a clinical setting, clinician-collected vaginal swab, gynecologic specimens collected in PreservCyt solution and urine. Symptomatic men: urine.	≤1 year at 2–30 °C (swab or urine specimen in cobas PCR media) 24 hours at 2–30 °C (Neat male urine specimen prior to addition to cobas PCR media) Cervical specimens collected in PreservCyt Solution may be stored at 2–30 °C for up to 12 months. Aliquots (≥1 ml) of cervical specimens collected in PreservCyt Solution may be stored in 13 ml round-based Sarstedt tubes for up to 4 weeks at 2–30 °C.	NG primers NG514 and NG519 to define a sequence of approximately 190 nucleotides (DR-9A) from the direct repeat (DR-9) region. NG primers, NG552 and NG579, to define a second sequence of approximately 215 nucleotides (DR-9B) from the DR-9 region.
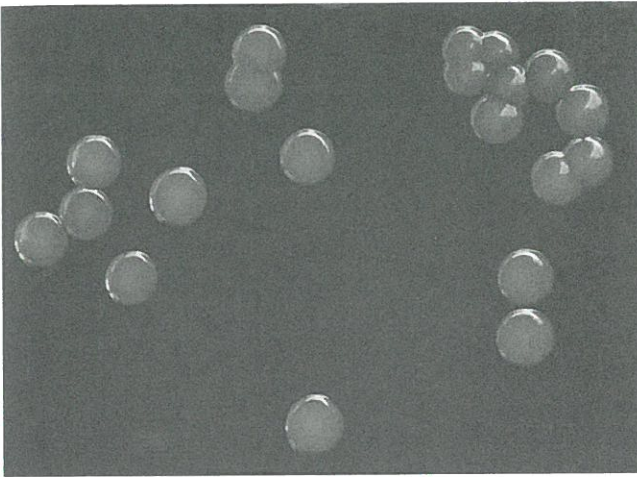
Figure 10.2 Typical colonies of *Neisseria gonorrhoeae* in modified Thayer Martin culture medium. (*See color plate section for the color representation of this figure.*)

the spread of international clones (Neisseria Sequence Typing Home Page, n.d.). Both typing tools have demonstrated that infections may occur in clusters, and resistant clones may spread across continents (Unemo and Dillon 2011). In addition to those methods, whole genome sequencing has brought new epidemiologic information in studies of transmission pathways (Vidovic et al. 2014).

10.6.6 Nucleic Acid Amplification Tests (NAATs)

Throughout the last two decades, nucleic acid amplification tests (NAATs) have been developed and introduced for the specific detection of DNA or rRNA of *N. gonorrhoeae*. These techniques are characterized by their promptness and are generally more sensible than cultures in diagnosing gonorrhea, especially in pharyngeal and rectal samples (Mimiaga et al. 2009; Bachmann et al. 2010). Table 10.4 shows the characteristics of the NAATs authorized by the Food and Drug Administration (FDA). NAATs offer testing on a wider range of sample types and are less demanding in sample quality, transportation, and storage (Van der Pol et al. 2001; Van Dyck et al. 2001; Moncada et al. 2004; Chernesky et al. 2005; Schachter et al. 2005; Ison 2006; Whiley et al. 2008; Harryman et al. 2012). They show high sensitivity (>96%) in both symptomatic and asymptomatic infection, equivalent sensitivity in urine and urethral swab specimens from men (Chernesky et al. 2005), and equivalent sensitivity in clinician-taken or self-taken vulvovaginal and endocervical swabs from women (Schachter et al. 2005). NAATs significantly outperform transported samples for culture and are the test of choice for testing individuals who are asymptomatic (Whiley et al. 2008). In women, urine samples offer a lower sensitivity than swabs from the genital tract and are not the optimal sample for testing (Van der Pol et al. 2001; Van Dyck et al. 2001; Ison 2006). The performance characteristics of different commercially available or in-house gonococcal NAATs differ substantially, particularly in regard to specificity.

When using NAATs to detect *N. gonorrhoeae*, the positive predictive value (PPV) of the testing protocol used should exceed 90%. The main factors influencing the PPV are the prevalence of gonorrhea in the population tested and variation in the specificity of available NAATs, particularly at nongenital sites. If the used diagnostic NAAT does not display a PPV exceeding 90%, positive samples are recommended to be subjected to confirmatory testing, i.e. repeated with a NAAT targeting another sequence (Smith et al. 2005; Hughes et al. 2014). NAATs are significantly more sensitive than culture for detecting pharyngeal and rectal infection (McNally et al. 2008; Schachter et al. 2008; Alexander 2009; Ota et al. 2009; Mimiaga et al. 2009; Bachmann et al. 2010) and are the test of choice for screening for rectal and pharyngeal gonococcal infection. However, commercially available NAATs are not licensed for testing samples from these sites, and they differ significantly in their specificity (Palmer et al. 2003; Tabrizi et al. 2011), particularly at the pharynx due to the frequent presence of other *Neisseria* species. It is recommended that strict local evaluation is performed before introducing a NAAT to test rectal and pharyngeal samples. When used after evaluation, confirmatory testing is recommended, i.e. repeated with a NAAT targeting another sequence (58, 66).

Women may have genital tract infection localized to the endocervix or urethra. In the current era of NAAT testing, asymptomatic women are commonly offered screening for gonorrhea and chlamydial infection by a single vulvovaginal or endocervical test (Lavelle et al. 2006). This pragmatic approach is endorsed even though evidence is still lacking regarding its effectiveness in excluding gonorrhea. The additional contribution of routinely testing rectal and pharyngeal sites when screening women for gonorrhea is poorly defined in Europe, although sampling these sites should be considered when there is a history of direct exposure (Cortina et al. 2016; Unemo et al. 2017). Evidence on the minimum incubation period necessary before testing is lacking, although clinical experience suggests that positive NAAT results may be observed within one to two days of infection.

A minority of MSM with gonorrhea (20–30%) have infection at multiple sites. Tests should be taken from the urethra/urine, rectum, and pharynx as directed by sexual practices.

10.7 Treatment

Neisseria gonorrhoeae is rapidly evolving, having developed resistance to all previous and current antimicrobials. In fact, the increasing detection of gonococcal strains resistant to ESCs and azithromycin may lead to a situation where gonorrhea becomes untreatable.

Currently, treatment for gonococcal infection is given empirically at the first clinical visit, meaning that antimicrobial susceptibility is rarely performed prior to prescription. According to WHO guidelines (World Health Organization (WHO) 2012b), first-line antimicrobial therapy should be highly effective, widely available and affordable, lack toxicity, be a single dose, and – rapidly – cure at least >95% of infected patients. Bearing these premises in mind, different health

associations worldwide have established treatment guidelines (Table 10.5), mostly consisting of dual therapy with a single oral or intramuscular dose (Bignell et al. 2011, 2013; Public Health Agency of Canada 2013; Australasia Sexual Health Alliance 2014; variation in Neisseria gonorrhoeae: reassessing the old paradigms 2014; Centers for Disease Control and Prevention (CDC) 2015; World Health Organization (WHO) 2016).

However, gonococci have been shown to have the ability to acquire different types of antimicrobial resistance (AMR), which include drug inactivation, modification of drug targets, changing bacterial permeability, and increasing efflux properties (Unemo and Shafer 2011, 2014). Most resistance determinants are a consequence of chromosomal mutations, with only two known plasmid-borne genes having been described: *bla*TEM plasmid (Ashford et al. 1976), responsible for penicillin resistance, and *tetM* (Morse et al. 1986), which causes tetracycline resistance. The issue with resistance determinants is that, once acquired, they are stably carried within gonococci populations even after antibiotic treatment is withdrawn from treatment regimens (Unemo and Shafer 2014). Furthermore, antibiotic resistance not only decreases susceptibility to current treatment but

Table 10.5 Treatment Guidelines of Different Health Associations Worldwide.

Guidelines	Geographical Area	Treatment
Australian STI Management Guidelines for Use in Primary Care (Australasia Sexual Health Alliance 2014)	Australia	Ceftriaxone 500 mg IM + azithromycin 1 g PO
Canadian Guidelines on Sexually Transmitted Infections (Public Health Agency of Canada 2013)	Canada	Ceftriaxone 250 mg IM *or* cefixime 800 mg PO + azithromycin 1 g PO
European Guideline on the Diagnosis and Treatment of Gonorrhea in Adults (Bignell et al. 2013)	Europe	Ceftriaxone 500 mg IM + azithromycin 2 g PO
Sexually Transmitted Diseases Treatment Guidelines (Centers for Disease Control and Prevention (CDC) 2015)	USA	Ceftriaxone 250 mg IM + azithromycin 1 g PO
UK National Guideline for the Management of Gonorrhea in Adults (Bignell et al. 2011)	UK	Ceftriaxone 500 mg IM + azithromycin 1 g PO
New Zealand Guideline for the Management of Gonorrhea (The New Zealand Sexual Health Society 2014)	New Zealand	Ceftriaxone 500 mg IM + azithromycin 1 g PO
WHO Guidelines for the Treatment of *Neisseria gonorrhoeae* (World Health Organization (WHO) 2016)	International	*Dual therapy:* ceftriaxone 250 mg IM *or* cefixime 400 mg PO + azithromycin 1 g PO *Single therapy:* ceftriaxone 250 mg IM

also enhances bacterial fitness (Warner et al. 2007), further complicating treatment options.

The increasing issue of drug-resistant bacteria has led the scientific community to focus research on new drugs and alternative treatments (Suay-Garcia and Perez-Gracia 2014). Along these lines, new antimicrobials have been developed to treat gonorrhea. New broad-spectrum fluoroquinolones avarofloxacin (Biedenbach et al. 2012), delafloxacin, sitafloxacin (Hamasuna et al. 2015), and WQ-3810 (Kazamori et al. 2014) have displayed high activity against MDR gonococci *in vitro*, including ciprofloxacin-resistant strains. Other antimicrobials with proven *in vitro* activity include the novel macrolide modithromycin (Jacobsson et al. 2014), tetracycline derivatives tigecycline, and eravacycline (Nix and Matthias 2010), the lipoglycopeptide dalvabancin and 2-acyl carbapenems (Fujimoto et al. 2012). Novel antimicrobials designed to inhibit new targets have also been developed and tested *in vitro*. These include protein inhibitors (pleuromutilin BC-3781), boron-containing inhibitors (AN3365) (Mendes et al. 2013), efflux pump inhibitors that increase susceptibility to antimicrobials (Lomovskaya and Watkins 2001), host innate defense components and toxic metabolites, non-cytotoxic nanomaterial (Li et al. 2013), host defense peptides (Bucki et al. 2010), LpxC inhibitors (Zhou and Barb 2008), species-specific Fab1 inhibitors (MUT056399) (Escaich et al. 2011), and inhibitors of bacterial topoisomerases (VT12–008911 and AZD0914) with different targets to those of fluoroquinolones (Jeverica et al. 2014).

Ideally, future treatment of gonorrhea will consist on rapid characterization of clinical isolates (phenotypic AMR tests and genetic antimicrobial resistance profiling), followed by an individually tailored drug regime.

10.8   Prevention and Control

Preventing the transmission of gonorrhea is key to controlling the spread of the disease and, therefore, the increasing resistance rates. WHO established a global action plan (World Health Organization (WHO) 2012a) to control the spread and impact of antimicrobial resistant *N. gonorrhoeae*. Its key points at the community level include the following:

- Improving sexual education and systematic monitoring
- Increasing awareness of appropriate use of antimicrobials
- Improving diagnosis and treatment of gonorrhea
- Improving early detection and follow-up of clinical treatment failures
- Establishing effective drug regulation and prescription policies
- Encouraging consistent and correct use of condoms for anyone having sex with new or casual sex partners
- Conducting regular testing for sexually transmitted diseases

  Research-wise, the plan suggested:

- Strengthening quality-assured antimicrobial susceptibility surveillance
- Establishing regional networks of laboratories to perform quality-assured gonococcal culture antimicrobial susceptibility testing

- Conducting research to identify novel molecular methods to detect and monitor antibiotic resistance
- Developing new treatments as well as a vaccine

Regardless of the prevention measures previously described, developing an effective vaccine against *N. gonorrhoeae* would be a turning point in preventing gonorrhea and controlling the development of antibiotic resistant strains. Historically, the development of vaccines for STDs has always been a goal for the scientific community (Russel et al. 1999). However, most attempts have turned out to be unsuccessful due to the extensive antigenic variation of gonococci and their ability to suppress and manipulate the host immune response. Research suggests two proteins as possible vaccine components: pilus constituents and Por, the major outer membrane protein. The detection of anti-pili antibodies in vaginal secretion after infection suggested this protein as a candidate for vaccine development (Tramont et al. 1980). However, administration of this vaccine resulted in partial protection only against homologous strains. Moreover, it showed poor immunogenicity and an ineffective antibody response at the site of infection (Tramont and Boslego 1985; Boslego et al. 1991).

Por proteins are an interesting vaccine candidate because they have been found to serve as adjuvants to B-cells and, more importantly, stimulate Por-specific circulating Th2-cells that migrate to mucosal surfaces (Massari et al. 2003). Por proteins are also capable of stimulating dendritic cells where activation depends on toll-like receptor 2 (Singleton et al. 2005).

Interestingly, a mouse infection model (Jerse et al. 2014) showed that if Th1 responses can be induced, infection will clear and immune memory will be established. This fact, along with the relatively stable composition of Por proteins, suggests that a vaccine containing Por proteins, Th1-inducing adjuvants and toll-like 2-inducing adjuvants could be crucial in achieving a successful combination. However promising these findings were, only four vaccines have ever progressed to clinical trials, and none provided protection against gonococcal infection (Edwards et al. 2016).

The first step in the right direction appears to come from recently published research by Petousis-Harris and colleagues (2017). Their study concluded that the *Neisseria meningitidis* serogroup B vaccine MeNZB was associated with decreased rates of gonorrhea. In their retrospective case–control study of data from 15- to 30-year-old patients, individuals who had been vaccinated during the serogroup B meningococcal epidemic between 2004 and 2008 were significantly less likely to have gonorrhea. In fact, the estimated effectiveness of MeNZB against gonorrhea was 31%. This vaccine is no longer available; however, Bexero contains the same outer membrane vesicle antigen as MeZNB in addition to three recombinant proteins (NHBA, fHbp, and NadA) (Toneatto et al. 2017). This means that the administration of Bexero to adolescents could also result in a decline in gonorrhea as a result of cross-protection.

These are encouraging results (Craig et al. 2015), seeing as mathematical models show that even a vaccine of moderate efficacy could have a substantial effect on the transmission and prevalence of gonorrhea. For this reason, further investigation of the antigens and mechanisms responsible for the MeNZB-mediated protection will provide crucial information in guiding future vaccine development.

10.9 Conclusion

Gonorrhea can be prevented by practicing safer sex and, particularly, with the correct and systematic use of condoms. Proper information, education, and communication can encourage and allow for safer sexual practices, improve the ability of people to recognize symptoms of gonorrhea and other STI, and increase the probability of them seeking healthcare.

There are no affordable, fast, and in-clinic diagnostic tests for gonorrhea. Many gonorrhea cases are asymptomatic, thus, are not diagnosed and remain untreated. In those cases that present symptoms, such as urethral or vaginal secretion, doctors generally assume it is gonorrhea and prescribe antibiotics, when in fact it could be another type of infection. The inappropriate use of antibiotics increases the appearance of resistances, for gonorrhea as well as for other bacterial diseases.

Therefore, in order to control gonorrhea in the short term, instruments and systems that improve prevention, treatment, and early diagnosis – as well as follow-up and notification of new infections, antibiotic use, resistances, and therapeutic failures – are required. Development of a vaccine will be necessary to prevent gonorrhea in the long term.

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