

Neisseria gonorrhoeae

as *gonococci* (plural), or *gonococcus* (singular), is a species of Gram-negative coffeebean-shaped diplococci bacteria responsible for the sexually transmitted infection gonorrhea. *N. gonorrhoea* was first described by Albert Neisser in 1879.

Microbiology

Neisseria are fastidious Gram-negative cocci that require nutrient supplementation to grow in laboratory cultures. Specifically, they grow on chocolate agar with carbon dioxide. These cocci are facultatively intracellular and typically appear in pairs (diplococci), in the shape of coffee beans. Of the eleven species of *Neisseria* that colonize humans, only two are pathogens. *N. gonorrhoeae* is the causative agent of gonorrhea (also called "The Clap," which is derived from the French word "clapier," meaning "brothel") and is transmitted via sexual contact.

Neisseria is usually isolated on Thayer-Martin agar (or VPN agar)—an agar plate containing antibiotics (vancomycin, colistin, nystatin, and TMP-SMX) and nutrients that facilitate the growth of *Neisseria* species while inhibiting the growth of contaminating bacteria and fungi. Further testing to differentiate the species includes testing for oxidase (all clinically relevant *Neisseria* show a positive reaction) and the carbohydrates maltose, sucrose, and glucose test in which *N. gonorrhoeae* will only oxidize (that is, utilize) the glucose.

N. gonorrhoeae are motile (twitching motility) and possess type IV pili to adhere to surfaces. The type IV pili operate mechanistically similar to a grappling hook. Pili extend and attach to a substrate which signals the pilus to retract, dragging the cell forward. *N. gonorrhoeae* are able to pull 100,000 times their own weight and it has been claimed that the pili used to do so are the strongest biological motor known to date, exerting one nanonewton.

N. gonorrhoeae has surface proteins called Opa proteins, which bind to receptors on immune cells. In so doing, *N. gonorrhoeae* is able to prevent an immune response. The host is also unable to develop an immunological memory against *N. gonorrhoeae* – which means that future reinfection is possible. *N. gonorrhoeae* can also evade the immune

system through a process called antigenic variation, in which the *N. gonorrhoeae* bacterium is able to alter the antigenic determinants (sites where antibodies bind) such as the Opa proteins^[4] and Type IV pili that adorn its surface. The many permutations of surface proteins make it more difficult for immune cells to recognize *N. gonorrhoeae* and mount a defense

N. gonorrhoeae is naturally competent for DNA transformation as well as being capable of conjugation. Both of these concepts allow for the DNA of *N. gonorrhoeae* the ability to undergo conformational changes. Especially dangerous to the health industry is the ability to conjugate since this can lead to antibiotic resistance.

In 2011, researchers at Northwestern University found evidence of a human DNA fragment in a *Neisseria gonorrhoeae* genome, the first example of horizontal gene transfer from humans to a bacterial pathogen

Genome structure

Neisseria gonorrhoeae have a circular DNA genome. *N. gonorrhoeae* strain 1090 genome was sequenced by the University of Oklahoma. The genome length is 2,153,922 nt and contains 2069 genes and 67 structural RNAs. It also has 2002 protein genes. This includes the opacity (Opa) proteins which are responsible for the opaque colony phenotype caused by tight junctions between adjacent *Neisseria*, and are also responsible for tight adherence to host cells. This organism is also naturally competent for the update of DNA.

Neisseria gonorrhoeae can produce one or several Opa proteins. These proteins are subject to phase variation and are usually found on cells from colonies possessing a unique opaque phenotype called O+. At any particular time, the bacterium can express zero, one, or several different Opa proteins, and each strain has 10 or more genes for different Opas.

More specifically, during infection, *N. gonorrhoeae* is like to encounter hydrogen peroxide, which inhibits growth. Since it is an obligate human pathogen, it would not be exposed to typical environmental stress such as UV light, ionizing radiation, or chemical mutagens. The type of DNA damage *N. gonorrhoeae* would come across is oxidative.

N. gonorrhoeae genome contains many genes that are predicted to be involved several DNA repair pathways. Recombinational DNA repair has been studied in *N. gonorrhoeae* and requires the *recA* and *recX* genes, which act with either the RecBCD pathway (*recB*, *recC*, and *recD* genes) or the RecF-like pathway (*recO*, *recQ*, *recR*, and *recJ* genes). Also, contributing to the recombinational DNA repair pathway is the Holliday

junction processing enzymes encoded by *recG*, *ruvA*, *ruvB*, and *ruvC*. *N. gonorrhoeae* seems to use both DNA recombinational repair pathways simultaneously. This is in contrast to *Escherichia coli*, where mutants in the RecF pathway generally show phenotypes only in the context of *recBC sbcBC* mutations. This leads to the conclusion that recombinational DNA repair is especially important for the repair of damaged DNA in *N. gonorrhoeae*.

During repair of oxidatively damaged DNA in *E. coli*, *recA* and other recombinational repair genes have been shown to be important. *E. coli recA* is important for both functions in DNA repair and its role in the induction of the SOS response of DNA repair. But because *N. gonorrhoeae* does not have SOS response, it does not use *recA* for the repair of oxidatively damaged DNA.

Analysis has shown that only *recN*, a single known DNA repair and recombination gene is upregulated after hydrogen peroxide treatment. It is unclear as to what the exact role of this gene is, but it seems to function in the repair of DNA double strand breaks. In addition, an *N. gonorrhoeae recN* mutant displays decreased survival to nalidixic acid and hydrogen peroxide, both of which can result in DNA double-strand breaks.

Although several gonococcal genes have been identified that protect against oxidative damage, few of them are predicted to function in the repair of DNA. To date, only two genes that are involved in DNA repair and recombination have been found to protect against oxidative damage in *N. gonorrhoeae*. Both the *N. gonorrhoeae recN* mutant and a mutant inactivated in *priA*, which is involved in replication restart, show decreased resistance to oxidative damaging agents. In contrast to *E. coli recA*, *N. gonorrhoeae recA* was reported to not protect against oxidative damage caused by H₂O₂. This suggests that DNA repair and recombination enzymes may differ between *N. gonorrhoeae* and *E. coli* in their importance to the repair of oxidatively damaged DNA.

RecA, genes of the RecBCD and RecF-like recombination pathways, and genes whose products are involved in Holliday junction processing are all important for mediating repair of oxidative damage. Furthermore, data suggest that these genes are expressed at basal levels sufficient to mediate repair and do not need to be upregulated upon encountering DNA damage in order to function in *N. gonorrhoeae*.

The recent demonstration that *N. gonorrhoeae* is polyploid suggests that, in the event of chromosomal damage, these additional copies of the chromosome could provide the genetic information present on the damaged copy, perhaps anticipating the necessity of recombinational

repair. Therefore, of the many mechanisms of resistance used by *N. gonorrhoeae* to combat oxidative insult, recombinational DNA repair appears to be one layer of resistance.

Cell structure and metabolism

Neisseria gonorrhoeae possesses a typical gram negative outer membrane that is composed of proteins, phospholipids, and lipopolysaccharide (LPS). Neisserial LPS is unique in that it has highly-branched basal oligosaccharide structure and the absence of repeating O-antigen subunits. Thus, they are referred to as lipooligosaccharide (LOS). During growth, the bacterium releases outer membrane fragments called "blebs". These contain LOS and may have a role in the pathogenesis if they are distributed during the course of an infection.

The bacterium has fimbriae, which is a proteinaceous appendage that is thinner than a flagellum. They play a major role in adherence and extend several micrometers from its cell surface. There are four types of *N. gonorrhoeae* based on the presence of fimbriae and they are called T1, T2, T3, and T4.

In vitro studies show that these piliated cells bind more efficiently to eukaryotic cells than non-piliated cells, which suggests that the pilus structure plays an important role in this interaction.

N. gonorrhoeae also can move in a jerky fashion across solid surfaces. This type of motility is called twitching, which depends on type IV pili and takes place by a "grappling hook" mechanism, which is the extension of the pilus, its attachment, and its retraction back into the cell. Twitching motility also contributes to the formation of biofilms. During growth, *Neisseria gonorrhoeae* releases soluble fragments of peptidoglycan. These molecules are implicated in the pathogenesis of different forms of gonococcal infection. A major peptidoglycan fragment released by *N. gonorrhoeae* is identical to the tracheal cytotoxin of *Bordetella pertussis* and has been shown to kill ciliated fallopian tube cells in organ culture. In the examination of the role of other putative lytic transglycosylases in peptidoglycan-derived cytotoxin (PGCT) production, results suggest that this gonococcal gene (ltgA) encodes a lytic peptidoglycan transglycosylase and that it is responsible for a significant proportion of the PGCT released by *N. gonorrhoeae*.

N. gonorrhoeae genome contains homologues of enzymes involved in PG recycling, and the levels of turnover are consistent with a certain level of recycling occurring in gonococci. It is unknown if *N. gonorrhoeae* have cytoplasmic proteins for sensing PG fragments; but, this would be a favorable mechanism for controlling cell processes, including autolysis.

The presence of two, maybe more enzymes with potentially redundant functions either indicates that gonococci have an elaborate backup system for cell wall processes or may suggest that the enzymes have different functions or are differently regulated or localized. AtlA is encoded in a group of type IV secretion genes in the gonococcal genetic island, and recent evidence suggests that AtlA may have a role in assembly of the type IV secretion system.

PGCT is expected to be released during infection, due to the extensive turnover and release of PG fragments in vitro.

Although many lytic transglycosylases were characterized in *E. coli*, the genes for PGCT production have not been previously characterized in bacteria in which PGCT is thought to act in infection.

These organisms are aerobic, strongly oxidase-positive, have an oxidative metabolism, are susceptible to drying and are fastidious (growth is inhibited by free fatty acids).

Pathogenesis

Neisseria gonorrhoeae infections are acquired by sexual contact and usually affect the mucous membranes of the urethra in males and the endocervix and urethra in females. The pathogenic mechanism involves the attachment of the bacterium to nonciliated epithelial cells through pili (fimbriae) and the production of lipopolysaccharide endotoxin. *Neisseria gonorrhoeae* is only found after sexual contact with an infected person (or in the case of infections in the newborn, direct contact).

Adherence is mainly done through fimbriae and opa (P.II) protein although nonspecific factors such as surface charge and hydrophobicity may play a role. The bacteria only attach to microvilli of nonciliated columnar epithelial cells and not ciliated cells.

After the bacteria attach to the nonciliated epithelial cells of the fallopian tube, they are surrounded by the microvilli that draw them to the surface of the mucosal cell. Then the bacteria enter the epithelial cells by a process called parasite-directed endocytosis. During this process, the membrane of the mucosal cell retracts and pinches off a membrane-bound vacuole that contains the bacteria. The vacuole is transported to the base of the cell, where the bacteria are released by exocytosis into the subepithelial tissue.

During infection, bacterial lipooligosaccharide (LOS) and peptidoglycan are released by autolysis of cells. Both bacterial polysaccharides activate the host's alternative complement pathway, while LOS stimulates the production of tumor necrosis factor (TNF) which causes cell damage. Neutrophils are then attracted to the site and feed on the bacteria. For

reasons not known, many gonococci are able to survive inside of the phagocytes. [8] Gonococcal LOS produces mucosal damage in fallopian tube organ cultures and brings about the release of enzymes, such as proteases and phospholipases. Thus, gonococcal LOS seems to have an indirect role in mediating tissue damage.

Sometimes *Neisseria gonorrhoeae* can enter the bloodstream causing a Gram-negative bacteremia which may lead to a disseminated bacterial infection. Strains of *N. gonorrhoeae* that cause disseminated infections are usually resistant to complement and the serum bactericidal reaction. This accounts for their ability to persist in the bacteria infected blood. Gram-negative bacteremias of this kind can be aggravated by the lysing of bacterial cells which may simply liberate soluble LPS.

Virulence Factors

Although it does not produce any exotoxins, *Neisseria gonorrhoeae* has a wide range of virulence determinants. The first stages of infection, which includes adherence and invasion, are mediated by surface components. The bacterium first attaches to epithelial cells by means of its fimbriae, specifically N-methylphenylalanine (Type IV) pili, with the main subunit Pile. After initial attachment, the bacteria enter a second stage of binding mediated by the outer membrane protein P.II (also known as Opa) which is needed for tight binding and invasion of epithelial cells. Also, P.II from one bacterium will bind to LOS of an adjacent bacterium, which allows for the construction of a small colony that may function similarly to a biofilm. *Neisseria gonorrhoeae* also produces an IgA1 protease that may take part in the colonization stage.

The outer membrane porin of *N. gonorrhoeae* P.I (also known as Por) is equivalent to the ompC and ompF porins of *E. coli*. They are involved in the passage of solutes through the outer membrane. However, P.I apparently has a role in virulence that allows the gonococci to survive inside of phagocytes. Purified P.I has also been shown to inhibit the ability of phagocytes to kill ingested bacteria. The lipooligosaccharide (LOS) is thought to be responsible for most of the symptoms of gonorrhea. Gonococcal LOS triggers an intense inflammatory response. The activation of complement, attraction and feeding by phagocytes, and the lysing of the phagocytes themselves, contributes to the purulent discharge. The local production of TNF is thought to be the main cause of damage to the fallopian tubes. In addition, in strains that cause systemic infection, LOS binds sialic acid from the serum forming a microcapsule of sialylated LOS, which allows the gonococci to resist the host immune response and serum bactericidal reaction.

Nonsialyated LOS and P.I (Por) on the bacterial surface are known to be effective targets for bactericidal antibodies. However, if antibodies produced against P.III (also known as Rmp) react with their antigenic site on the gonococcal surface, the effect is to block bactericidal antibodies against LOS and P.I and to protect the bacterium from complement-mediated lysis.

Neisseria gonorrhoeae also have a well-developed iron acquisition system that allows it to extract iron from its host during growth, which is necessary to support bacterial invasion. The bacterium is able to form two transferrin receptors (Tbp1 and Tbp2) and one lactoferrin receptor (Lbp) in its outer membrane, which are stimulated under low-iron conditions, and are able to directly extract iron from transferrin and lactoferrin. These proteins can also extract iron from heme and hemoglobin.

Neisseria gonorrhoeae usually infects the mucous membranes causing infections such as urethritis, cervicitis, salpingitis, pelvic inflammatory disease, proctitis, conjunctivitis and pharyngitis.

Disease

Symptoms of infection with *N. gonorrhoeae* differ depending on the site of infection. Note also that 10% of infected males and 80% of infected females are asymptomatic. Infection of the genitals can result in a purulent (or pus-like) discharge from the genitals which may be foul smelling. Symptoms may include inflammation, redness, swelling, and dysuria. *N. gonorrhoeae* can also cause conjunctivitis, pharyngitis, proctitis or urethritis, prostatitis and orchitis.

Conjunctivitis is common in neonates (newborns), and silver nitrate or antibiotics are often applied to their eyes as a preventive measure against gonorrhoea. Neonatal gonorrheal conjunctivitis is contracted when the infant is exposed to *N. gonorrhoeae* in the birth canal and can lead to corneal scarring or perforation, resulting in blindness in the neonate.

Disseminated *N. gonorrhoeae* infections can occur, resulting in endocarditis, meningitis or gonococcal dermatitis-arthritis syndrome. Dermatitis-arthritis syndrome presents with arthralgia, tenosynovitis and painless non-pruritic (non-itchy) dermatitis.

Infection of the genitals in females with *N. gonorrhoeae* can result in pelvic inflammatory disease if left untreated, which can result in infertility. Pelvic inflammatory disease results if *N. gonorrhoeae* travels

into the pelvic peritoneum (via the cervix, endometrium and fallopian tubes). Infertility is caused by inflammation and scarring of the fallopian tube. Infertility is a risk to 10 to 20% of the females infected with *N. gonorrhoeae*.

Treatment and prevention

If *N. gonorrhoeae* is resistant to the penicillin family of antibiotics, then ceftriaxone (a third-generation cephalosporin) is often used. Sexual partners should also be notified and treated.

Antibiotic-resistant gonorrhea has been noted by epidemiologists; beginning in the 1940s gonorrhea was treated with penicillin, but doses had to be continually increased in order to remain effective, and by the '70s, penicillin- and tetracycline-resistant gonorrhea emerged in the Pacific Basin. These resistant strains then spread to Hawaii, California, the rest of the United States, and Europe. Fluoroquinolones were the next line of defense, but soon resistance to this antibiotic emerged as well. Since 2007, standard treatment has been third-generation cephalosporins, such as ceftriaxone, which are considered to be our "last line of defense."

Recently, a high-level ceftriaxone-resistant strain of gonorrhea, called H041, was discovered in Japan. Lab tests found it to be resistant to high concentrations of ceftriaxone, as well as most of the other antibiotics tested. Within *N. gonorrhoeae*, there are genes that confer resistance to every single antibiotic used to cure gonorrhea, but thus far they do not coexist within a single gonococcus. Because of *N. gonorrhoeae*'s high affinity for horizontal gene transfer, however, antibiotic-resistant gonorrhea is seen as an emerging public health threat. Patients should also be tested for other sexually transmitted infections, especially *Chlamydia* infections, since co-infection is frequent (up to 50% of cases). Antibacterial coverage is often included for *Chlamydia* because of this.

Transmission can be reduced by the usage of latex barriers, such as condoms or dental dams, during intercourse, oral and anal sex, and by limiting sexual partners.

Vaccine

Due to the relative frequency of infection and the emerging development of antibiotic resistance in strains of *N. gonorrhoeae*, vaccines are thought to be an important goal in the prevention of infection. However, there

have been a relatively low emphasis on research to such a vaccine in the medical literature and few human clinical trials for prospective vaccines. The ability to develop an effective vaccine has been limited by the lack of acquired immunity to infection to model a vaccine after and the current lack of commitment in effort and resources.

Survival of gonococci

The exudates from infected individuals contain many polymorphonuclear leukocytes (PMN) with ingested *gonococci*. These *gonococci* stimulate the PMN to release an internal oxidative burst involving reactive oxygen species in order to kill the *gonococci*. However, a significant fraction of the *gonococci* can resist killing and are able to reproduce within the PMN phagosomes.

Stohl and Seifert showed that the bacterial RecA protein, that mediates recombinational repair of DNA damage, plays an important role in *gonococcal* survival. The protection afforded by RecA protein may be linked to transformation, the process by which recipient *gonococci* take up DNA from neighboring *gonococci* and integrate this DNA into the recipient genome through recombination. Michod et al. have suggested that an important benefit of transformation in *N. gonorrhoeae* may be recombinational repair of oxidative DNA damages caused by oxidative attack by the hosts phagocytic cells.

Gonorrhea

Gonorrhea (colloquially known as **the clap**) is a common human sexually transmitted infection caused by the bacterium *Neisseria gonorrhoeae*. The usual symptoms in men are burning with urination and penile discharge. Women, on the other hand, are asymptomatic half the time or have vaginal discharge and pelvic pain. In both men and women if gonorrhea is left untreated, it may spread locally causing epididymitis or pelvic inflammatory disease or throughout the body, affecting joints and heart valves.

Treatment is commonly with ceftriaxone (Rocephin) as antibiotic resistance has developed to many previously used medications. This is typically given in combination with either azithromycin or doxycycline, as gonorrhea infections may occur along with chlamydia, an infection which ceftriaxone does not cover. Some strains of gonorrhea have begun

showing resistance to this treatment, which will make infection more difficult to treat.

Signs and symptoms

Half of women with gonorrhea are asymptomatic while others have vaginal discharge, lower abdominal pain or pain with intercourse. Most men who are infected have symptoms such as urethritis associated with burning with urination and discharge from the penis.^[4] Either sex may also acquire gonorrhea of the throat from performing oral sex on an infected partner, usually a male partner. Such infection is asymptomatic in 90% of cases, and produces a sore throat in the remaining 10%.^[5] The incubation period is 2 to 14 days with most of these symptoms occurring between 4–6 days after being infected. Rarely, gonorrhea may cause skin lesions and joint infection (pain and swelling in the joints) after traveling through the blood stream (see below). Very rarely it may settle in the heart causing endocarditis or in the spinal column causing meningitis (both are more likely among individuals with suppressed immune systems, however).

Cause

Gonorrhea is caused by the bacterium *Neisseria gonorrhoeae*. The infection is transmitted from one person to another through vaginal, oral, or anal sex. Men have a 20% risk of getting the infection from a single act of vaginal intercourse with an infected woman. The risk for men who have sex with men is higher. Women have a 60–80% risk of getting the infection from a single act of vaginal intercourse with an infected man. A mother may transmit gonorrhea to her newborn during childbirth; when affecting the infant's eyes, it is referred to as ophthalmia neonatorum. It cannot be spread by toilets or bathrooms.

Diagnosis

Traditionally, gonorrhea was diagnosed with gram stain and culture; however, newer polymerase chain reaction (PCR) based testing methods are becoming more common. In those who fail initial treatment culture should be done to determine sensitivity to antibiotics. All people who test positive for gonorrhea should be tested for other sexually transmitted diseases such as chlamydia, syphilis and human immunodeficiency virus.

Prevention

The risk of infection can be reduced significantly by using condoms correctly and by having a mutually monogamous relationship with an uninfected person. It may also be reduced by avoiding sexual intercourse.

Management

Penicillin entered mass production in 1944 and revolutionized the treatment of several venereal diseases.

As of 2010, injectable ceftriaxone appears to be one of the few effective antibiotics. This is typically given in combination with either azithromycin or doxycycline. Because of increasing rates of antibiotic resistance local susceptibility patterns need to be taken into account when deciding on treatment. Many antibiotics that were once effective including penicillin, tetracycline and fluoroquinolones are no longer recommended because of high rates of resistance. Resistance to cefixime have reached a level such that it is no longer recommended as a first line agent in the United States and if it is used a person should be tested again after a week to determine if the infection still persists. Cases of resistance to ceftriaxone have been reported but are still rare, though public health officials are concerned that an emerging pattern of resistance may predict a global epidemic.

The UK's Health Protection Agency reported that 2011 saw a slight drop in gonorrhoea antibiotic resistance, the first in 5 years.

It is recommended that sexual partners be tested and potentially treated. One option for treating sexual partners of people infected is patient-delivered partner therapy (PDPT) which involves providing prescriptions or medications to the person to take to their partner without the health care provider first examining them.

Prognosis

If not treated gonococcal ophthalmia neonatorum will develop in 28% of infants born to women with gonorrhea. Gonorrhea if left untreated may last for weeks or months with higher risks of complications. One of the complications of gonorrhea is systemic dissemination resulting in skin pustules or petechia, septic arthritis, meningitis or endocarditis. This occurs in between 0.6 and 3.0% of women and 0.4 and 0.7% of men.

In men, inflammation of the epididymis (epididymitis); prostate gland (prostatitis) and urethral stricture (urethritis) can result from untreated gonorrhea. In women, the most common result of untreated gonorrhea is pelvic inflammatory disease. Other complications include perihepatitis, a rare complication associated with Fitz-Hugh-Curtis syndrome; septic arthritis in the fingers, wrists, toes, and ankles; septic abortion; chorioamnionitis during pregnancy; neonatal or adult blindness from conjunctivitis; and infertility.

Neonates coming through the birth canal are given erythromycin ointment in the eyes to prevent blindness from infection. The underlying gonorrhea should be treated; if this is done then usually a good prognosis will follow.

Among persons in the United States between 14 and 39 years of age, 46% of people with gonorrheal infection also have chlamydial infection.^[20]

Symptoms

In males there is an approximate 2-3 day incubation period after which a purulent discharge from the urethra and dysuria develops. Around 95% of infected males are symptomatic. Rare complications include prostatitis, epididymitis, and periurethral abscesses.

In women, *Neisseria gonorrhoeae* primarily infects the cervix in women. The symptoms of gonorrhea are often mild and most women who are infected do not have symptoms. Even when a woman has symptoms, they can be so non-specific and can be mistaken for a bladder or vaginal infection. Symptoms include vaginal discharge, dysuria, and abdominal pain. Around 10%-20% of infected women develop these complications. In 1%-3% of infected women and a lower percentage of infected men the bacterium disseminates via the blood causing bacteremia and arthritis.

Neisseria meningitidis

Neisseria meningitidis, often referred to as *meningococcus*, is a bacterium that can cause meningitis and other forms of meningococcal disease such as meningococcemia, a life-threatening sepsis. *N. meningitidis* is a major cause of morbidity and mortality during childhood in industrialized countries and has been responsible for epidemics in Africa and in Asia. Upon Gram staining, it appears as a Gram-negative diplococcus and cultures of the bacteria test positive for the enzyme cytochrome c oxidase.

It exists as normal flora (nonpathogenic) in the nasopharynx of up to 5–15% of adults.^[4] It causes the only form of bacterial meningitis known to occur epidemically. *Streptococcus pneumoniae* (aka *pneumococcus*) is the most common bacterial etiology of meningitis in children beyond 2 months of age (1–3 per 100,000). Meningococci only infect humans and have never been isolated from animals because the bacterium cannot get iron other than from human sources (transferrin and lactoferrin). Meningococcus is spread through the exchange of saliva and other respiratory secretions during activities like coughing, sneezing, kissing, and chewing on toys. It infects the host cell by sticking to it using Trimeric Autotransporter Adhesins (TAA). Though it initially produces general symptoms like fatigue, it can rapidly progress from fever, headache and neck stiffness to coma and death. The symptoms of meningitis are easily confused with those caused by other organisms such as *Hemophilus influenzae* and *Streptococcus pneumoniae*. Death occurs in approximately 10% of cases.^[5] Those with impaired immunity may be at particular risk of meningococcus (e.g. those with nephrotic syndrome or splenectomy; vaccines are given in cases of removed or non-functioning spleens).

Subtypes

These are classified according to the antigenic structure of their polysaccharide capsule. Serotype distribution varies markedly around the world,^[8] with type A being most prevalent in Africa and Asia but practically absent in North America hindered development of a universal vaccine for meningococcal disease. Groups of *N. meningitidis* have been identified, six of these (A, B, C, W135, X, and Y) are able to cause epidemics

Epidemiology

Approximately 2500 to 3500 cases of *N. meningitidis* infection occur annually in the United States, with a case rate of about 1 in 100,000. Children younger than 5 years are at greatest risk, followed by teenagers of high school age. Rates in sub-Saharan Africa can be as high as 1 in 1000 to 1 in 100.

Virulence

Lipooligosaccharide (LOS) is a component of the outer membrane of *N. meningitidis* which acts as an endotoxin which is responsible for septic shock and hemorrhage due to the destruction of red blood cells. Other virulence factors include a polysaccharide capsule which prevents host phagocytosis and aids in evasion of the host immune response; and fimbriae which mediate attachment of the bacterium to the epithelial cells of the nasopharynx.

Recently a hypervirulent strain was discovered in China. Its impact is yet to be determined.

Mechanisms of cellular invasion

N. meningitidis is an intracellular human-specific pathogen responsible for septicemia and meningitis. Like most bacterial intracellular pathogens, *N. meningitidis* exploits host cell signaling pathways to promote its uptake by host cells. The signaling leading to bacterial internalization is induced by the type IV pili, which are the main means of meningococcal adhesion onto host cells. The signaling induced following Type IV pilus-mediated adhesion is responsible for the formation of microvilli-like structures at the site of the bacterial-cell interaction.^[11] These microvilli trigger the internalization of the bacteria into host cells. A major consequence of these signaling events is a reorganization of the actin cytoskeleton, which leads to the formation of membrane protrusions, engulfing bacterial pathogens into intracellular vacuoles. Efficient internalization of *N. meningitidis* also requires the activation of an alternative signaling pathway coupled with the activation of the tyrosine kinase receptor ErbB2. Beside Type IV pili, other outer membrane proteins may be involved in other mechanisms of bacteria internalization into cells.

Signs and symptoms

Suspicion of meningitis is a medical emergency and immediate medical assessment is recommended. Current guidance in the United Kingdom is that if a case of meningococcal meningitis or septicemia (infection of the blood) is suspected intravenous antibiotics should be given and the ill person admitted to the hospital.^[14] This means that laboratory tests may be less likely to confirm the presence of *Neisseria meningitidis* as the antibiotics will dramatically lower the number of bacteria in the body.

The UK guidance is based on the idea that the reduced ability to identify the bacteria is outweighed by reduced chance of death.

Septicaemia caused by *Neisseria meningitidis* has received much less public attention than meningococcal meningitis even though septicaemia has been linked to infant deaths. Meningococcal septicaemia typically causes a purpuric rash that does not lose its color when pressed with a glass ("non-blanching") and does not cause the classical symptoms of meningitis. This means the condition may be ignored by those not aware of the significance of the rash. Septicaemia carries an approximate 50% mortality rate over a few hours from initial onset. Many health organizations advise anyone with a non-blanching rash to go to a hospital as soon as possible. Note that not all cases of a purpura-like rash are due to meningococcal septicaemia; however, other possible causes need prompt investigation as well (e.g. ITP a platelet disorder or Henoch-Schönlein purpura).

Other severe complications include *Waterhouse-Friderichsen syndrome* (a massive, usually bilateral, hemorrhage into the adrenal glands caused by fulminant meningococemia), adrenal insufficiency, and disseminated intravascular coagulation

Diagnosis

The gold standard of diagnosis is isolation of *N. meningitidis* from sterile body fluid. A cerebrospinal fluid (CSF) specimen is sent to the laboratory immediately for identification of the organism. Diagnosis relies on culturing the organism on a chocolate agar plate. Further testing to differentiate the species includes testing for oxidase, catalase (all clinically relevant *Neisseria* show a positive reaction) and the carbohydrates maltose, sucrose, and glucose test in which *N. meningitidis* will ferment (that is, utilize) the glucose and maltose. Serology determines the subgroup of the organism.

If the bacteria reach the circulation, then blood cultures should be drawn and processed accordingly.

Clinical tests that are used currently for the diagnosis of meningococcal disease take between 2 and 48 hours and often rely on the culturing of bacteria from either blood or CSF samples. However, polymerase chain reaction tests can be used to identify the organism even after antibiotics have begun to reduce the infection. As the disease has a fatality risk

approaching 15% within 12 hours of infection, it is crucial to initiate testing as quickly as possible but not to wait for the results before initiating antibiotic therapy.

Treatment

Persons with confirmed *N. meningitidis* infection should be hospitalized immediately for treatment with antibiotics. Indeed, because meningococcal disease can disseminate very rapidly, a single dose of intramuscular antibiotic is often given at the earliest possible opportunity, even before hospitalization, if disease symptoms look suspicious enough. Third-generation cephalosporin antibiotics (i.e. cefotaxime, ceftriaxone) should be used to treat a suspected or culture-proven meningococcal infection before antibiotic susceptibility results are available. Empirical treatment should also be considered if a lumbar puncture, to collect CSF for laboratory testing, cannot be done within 30 minutes of admission to hospital. Antibiotic treatment may affect the results of microbiology tests, but a diagnosis may be made on the basis of blood-cultures and clinical examination

Prevention

All recent contacts of the infected patient over the 7 days before onset should receive medication to prevent them from contracting the infection. This especially includes young children and their child caregivers or nursery-school contacts, as well as anyone who had direct exposure to the patient through kissing, sharing utensils, or medical interventions such as mouth-to-mouth resuscitation. Anyone who frequently ate, slept or stayed at the patient's home during the 7 days before the onset of symptom, or those who sat beside the patient on an airplane flight or classroom for 8 hours or longer, should also receive chemoprophylaxis (the agent of choice is usually oral rifampicin for a few days).

Vaccination

There are currently three vaccines available in the U.S. to prevent meningococcal disease for people aged 2 or older. All three vaccines are effective against the same serogroups: A, C, Y, and W-135. Two meningococcal conjugate vaccines (MCV4) are licensed for use in the U.S. The first conjugate vaccine was licensed in 2005, the second in 2010. Conjugate vaccines are the preferred vaccine for people 2 through

55 years of age. A meningococcal polysaccharide vaccine (MPSV4) has been available since the 1970s and is the only meningococcal vaccine licensed for people older than 55. MPSV4 may be used in people 2–55 years old if the MCV4 vaccines are not available or contraindicated. Information about who should receive the meningococcal vaccine is available from the Centers for Disease Control and Prevention (CDC).

On June 14, 2012, the U.S. Food and Drug Administration (FDA) approved a new combination vaccine against two types of meningococcal diseases and Hib disease for infants and children 6 weeks to 18 months old. The vaccine, Menhibrix, will prevent disease caused by *Neisseria meningitidis* serogroups C and Y, and *Haemophilus influenzae* type b. This is the first meningococcal vaccine that can be given to infants as young as six weeks old