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Streptococcus pneumoniae

Streptococcus pneumoniae, or **pneumococcus**, is a Grampositive, alpha-hemolytic, aerotolerant, anaerobic member of the genus*Streptococcus*. A significant human pathogenic bacterium, *S. pneumoniae* was recognized as a major cause of pneumonia in the late 19th century, and is the subject of many humoral immunity studies.

S. pneumoniae resides asymptomatically in the nasopharynx of healthy carriers. However, in susceptible individuals, such as elderly and immunocompromised people and children, the pathogen can spread to other locations and cause disease. *S. pneumoniae* is the main cause ofcommunity acquired pneumonia and meningitis in children and the elderly, and of septicemia in HIV-infected persons.

Despite the name, the organism causes many types of pneumococcal infections other than pneumonia. These invasive pneumococcal diseases include acute sinusitis, otitis media, conjunctivitis, meningitis, bacteremia, sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis,pericarditis, cellulitis, and brain abscess.

S. pneumoniae is one of the most common causes of bacterial meningitis in adults and young adults, along with *Neisseria meningitidis*, and is the leading cause of bacterial meningitis in adults in the USA. It is also one of the top two isolates found in ear infection, otitis media. Pneumococcal pneumonia is more common in the very young and the very old.

S. pneumoniae can be differentiated from *Streptococcus viridans*, some of which are also alpha-hemolytic, using an optochin test, as *S. Pneu - moniae*is optochin-sensitive. *S. pneumoniae* can also be distinguished based on its sensitivity to lysis by bile, the so-called "bile solubility test". Theencapsulated, Gram-positive coccoid bacteria have a distinctive morphology on Gram stain, lancet-shaped diplococci. They have a polysaccharidecapsule that acts as a virulence factor for the organism; more than 90 different serotypes are known, and these types differ in virulence, prevalence, and extent of drug resistance.

Genetics

The genome of *S. pneumoniae* is a closed, circular DNA structure that contains between 2.0 and 2.1 million base pairs, depending on the strain.

It has a core set of 1553 genes, plus 154 genes in its virulome, which contribute to virulence, and 176 genes that maintain a noninva sive phenotype. Genetic information can vary up to 10% between strains.

Virulence factors

S. pneumoniae expresses different virulence factors on its cell surface and inside the organism. These virulence factors contribute to some of the clinical manifestations during infection with *S. pneumoniae*.

- **Polysaccharide capsule**—prevents phagocytosis by host immune cells by inhibiting C3b opsonization of the bacterial cells
- **Pneumolysin** (Ply)—a 53-kDa pore-forming protein that can cause lysis of host cells and activate complement
- **Autolysin** (LytA)—activation of this protein lyses the bacteria releasing its internal contents (i.e., pneumolysin)
- **Hydrogen peroxide**—causes damage to host cells (can cause apoptosis in neuronal cells during meningitis) and has bactericidal effects against competing bacteria (Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus)
- **Pili**—hair-like structures that extend from the surface of many strains of *S. pneumoniae*. They contribute to colonization of upper respiratory tract and increase the formation of large amounts of TNF by the immune system during sepsis, raising the possibility of septic shock
- **Choline binding protein A/Pneumococcal surface protein A** (CbpA/PspA)—an adhesin that can interact with carbohydrates on the cell surface of pulmonary epithelial cells and can inhibit complement-mediated opsonization of pneumococci .

Transformation in *S. Pneumoniae*

Natural bacterial transformation involves the transfer of DNA from one bacterium to another through the surrounding medium. Transformation is a complex, developmental process requiring energy, dependent on expression of numerous genes. In *S. pneumoniae* at least 23 genes are required. In order for a bacterium to bind, take up and recombine exogenous DNA into its chromosome it must enter a special physio - logical state, called competence.

Competence, in *S. pneumoniae,* is induced by DNA-damaging agents such as mitomycin C, a DNA inter-strand cross-linking agent, and the fluoroquinolone antibiotics norfloxacin, levofloxacinand moxifloxaci n, topoisomerase inhibitors that cause double-strand breaks.

Transformation protects *S. pneumoniae* against the bactericidal effect of mitomycin C. Michod et al. summarized evidence that induction of competence in *S. pneumoniae* is associated with increased resistance to oxidative stress and increased expression of the RecA protein, a key component of the recombinational repair machinery for removing DNA damages. On the basis of these findings, they suggested that trans - formation is an adaptation for repairing oxidative DNA damages. *S. pneumoniae* infection stimulates polymorphonuclear leukocytes (granulocyte) to produce an oxidative burst that is potentially lethal to the bacteria. The ability of *S. pneumoniae* to repair the oxidative DNA damages in its genome, caused by this host defense, likely contributes to this pathogen's virulence.

Pathogenesis

S. pneumoniae is normally found in the nasopharynx of 5–10% of healthy adults, and 20–40% of healthy children.[2] It can be found in higher amounts in certain environments, especially those where people are spending a great deal of time in close proximity to each other (day care centers, military barracks). It attaches to nasopharyngeal cells through interaction of bacterial surfaceadhesins. This normal colonization can become infectious if the organisms are carried into areas such as the Eustachian tube or nasal sinuses where it can cause otitis media and sinusitis, respectively. Pneumonia occurs if the organisms are inhaled into the lungs and not cleared (again, viral infection, or smoking-induced ciliary paralysis might be contributing factors). The organism's polysaccharide capsule makes it resistant to phagocytosis, and if there is no pre-existing anticapsular antibody, alveolar macrophages cannot adequately kill the pneumococci. The organism spreads to the blood stream (where it can cause bacteremia) and is carried to the meninges, joint spaces, bones, and peritoneal cavity, and may result in meningitis, brain abscess,septic arthritis, or osteomyelitis.

S. pneumoniae has several virulence factors, including the polysaccharide capsule mentioned earlier, that help it evade a host's immune system. It has pneumococcal surface proteins that inhibit complement-mediated opsonization, and it secretes IgA1 protease that will destroy secretory IgA produced by the body and mediates its attachment to respiratory mucosa.

The risk of pneumococcal infection is much increased in persons with impaired IgG synthesis, impaired phagocytosis, or defective clearance of pneumococci. In particular, the absence of a functional spleen, through congenital asplenia, splenectomy, or sickle-cell disease predisposes one

to a more severe course of infection (Overwhelming post-splenectomy infection) and prevention measures are indicated (see asplenia).

People whose immune system is compromised, such as those living with HIV, are also at higher risk of pneumococcal disease. In HIV patients with access to treatment, the risk of invasive pneumoccal disease is 0.2–1% per year and has a fatality rate of 8%.

There is an association between pneumococcal pneumonia and influenza.[4] Damage to the lining of the airways (respiratory epithelium) and upper respiratory system caused by influenza may facilitate pneumococcal entry and infection. Other risk factors include smoking, injection drug use, Hepatitis C, and COPD*S. pneumoniae* is part of the normal upper respiratory tract flora, but, as with many natural flora, it can become pathogenic under the right conditions, like if the immune system of the host issuppressed. Invasins, such as pneumolysin, an anti-phagocytic capsule, various adhesins and immunogenic cell wall components are all major virulence factors.

Types of infection caused

S. pneumoniae is responsible for 15–50% of all episodes of community acquired pneumonia, 30–50% of all cases of acute otitis media and a significant proportion of bacteremia and bacterialmeningitis. It kills at least one million children under the age of five every year: >70% of these deaths are in developing countries. This total is greater than that due to malaria, AIDS andmeasles combined.

In the 19th century, it was demonstrated that immunization of rabbits with killed pneumococci protected them against subsequent challenge with viable pneumococci. Serum from immunized rabbits or from humans who had recovered from pneumococcal pneumonia also conferred protection. In the 20th century, the efficacy of immunization was demonstrated in South African miners.

It was discovered that the pneumococcus's capsule made it resistant to phagocytosis, and in the 1920s it was shown that an antibody specific for capsular polysaccharide aided the killing of *S. pneumoniae*. In 1936, a pneumococcal capsular polysaccharide vaccine was used to abort an epidemic of pneumococcal pneumonia. In the 1940s, experiments on capsular transformation by pneumococci first identified DNA as the material that carries genetic information.

In 1900, it was recognized that different serovars of pneumococci exist, and that immunization with a given serovar did not protect against

infection with other serovars. Since then over ninety serovars have been discovered, each with a unique polysaccharide capsule that can be identified by the quellung reaction. Because some of these serovars cause disease more commonly than others, it is possible to provide reasonable protection by immunizing with less than 90 serovars; the current vaccine contains 23 serovars (i.e., it is "23-valent").

The serovars are numbered according to two systems: the American system, which numbers them in the order in which they were discovered, and the Danish system, which groups them according to antigenic similarities.

Pneumococcal vaccine

A **pneumococcal vaccine** is a vaccine against *Streptococcus pneumoniae*.

Types include:

- **Pneumococcal polysaccharide vaccine**
- **Pneumococcal conjugate vaccine**

Mechanism

Polysaccharide vaccine

The polysaccharide vaccine most commonly used today consists of purified polysaccharides from 23 serotypes (1, 2, 3, 4, 5, 6b, 7F, 8,9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F). Immunity is induced primarily through stimulation of B-cells which release IgM without the assistance of T cells.

This immune response is less robust than the response provoked by conjugated vaccines, which has several consequences. The vaccine is ineffective in children less than two years old, presumably due to their less mature immune systems. Non-responders are also common amongst older adults Immunization is not lifelong, so individuals must be re-vaccinated every 5–6 years. Since no mucosal immunity is provoked, the vaccine does not affect carrier rates, promote herd immunity, or protect from upper or lower respiratory tract infections. Finally, provoking immune responses using unconjugated polysaccharides from the capsules of other bacteria, such as H. influenzae, have proven significantly more difficult.

Conjugated Vaccine

The conjugated vaccine consists of capsular polysaccharides covalently bound to the diphtheria toxoid CRM197, which is highly immunogenic but non-toxic. This combination provokes a significantly more robust immune response by recruiting CRM197-specific type 2 helper T cells, which allow for immunoglobulin type switching (to produce non-IgM immunoglobulin) and production of memory B cells. Among other things, this results in mucosal immunity and eventual establishment of lifelong immunity after several exposures. The main drawbacks to conjugated vaccines are that they only provide protection against a subset of the serotypes covered by the polysaccharide vaccines.

Vaccination in the USA

In the USA, a heptavalent pneumococcal conjugate vaccine (PCV 7) (e.g. Prevenar) was recommended for all children aged 2–23 months and for at-risk children aged 24–59 months in 2000. The normal 4-dose series is given at 2, 4, 6 & 12–14 months of age. In February 2010, a pneumococcal congugate vaccine which protects against an additional 6 serotypes was introduced (PCV 13 / brand name: Prevnar 13) and can be given instead of the original Prevnar. Similar 9-, and 10-valent vaccines have been tested. Protection is good against deep pneumococcal infections (especially septicemia and meningitis). However, if a child is exposed to a serotype of pneumococcus that is not contained in the vaccine, he/she is not afforded any protection. This limitation, and the ability of capsular-polysaccharide conjugate vaccines to promote the spread of non-covered serotypes, has led to research into vaccines that would provide species-wide protection.

Pneumococcal polysaccharide vaccine (Pneumovax is one brand) gives at least 85% protection in those under 55 years of age for five years or longer. Immunization is suggested for those at highest risk of infection, including those 65 years or older; generally the vaccine should be a single lifetime dose, as there is a high risk of side effects if repeated. The standard 23-valent vaccines are ineffective for children under two years old.

The current guidelines of the American College of Physicians call for administration of the immunization between ages 2 and 65 when

indicated, or at age 65. If someone received the immunization before age 60, the guidelines call for a one-time revaccination.

Revaccination at periodic intervals is also indicated for those with other conditions such as asplenia or nephrotic syndrome.

Vaccination in the UK

It was announced in February 2006 that the UK government would introduce vaccination with the conjugate vaccine in children aged 2, 4 and 13 months. This is expected to start on September 4, 2006 and is to include changes to the immunisation programme in general In 2009, the European Medicines Agency approved the use of a 10-valent pneumcoccal conjugate vaccine for use in Europe The 13 valent pneumococcal vaccine has been introduced in the routine immunisation schedule of the UK in April 2010.

Vaccination in South Africa

Pneumovax 23 is used, and according to the enclosed patient information leaflet, has a reported 76% to 92% protective efficacy (pneumococcal types 1, 2, 3, 4, 5, 6B**, 7F, 8, 9N, 9V**, 10A, 11A, 12F, 14**, 15B, 17F, 18C, 19A**, 19F**, 20, 22F, 23F** and 33F** are included, where ** indicates drug resistant pneumococcal infections; these are the 23 most prevalent or invasive pneumococcal types of Streptococcus pneumoniae).

Vaccination worldwide

Pneumococcal vaccines Accelerated Development and Introduction Plan (PnemoADIP) is a program to accelerate the evaluation and access to new pneumococcal vaccines in the developing world. PneumoADIP is funded by the Global Alliance for Vaccines and Immunization (GAVI). Thirty GAVI countries have expressed interest in participating by 2010. PneumoADIP aims to save 5.4 million children by 2030

A pilot Advance Market Commitment (AMC) to develop a vaccine against pneumococcus was launched in June 2009 as a strategy to address two of the major policy challenges to vaccine introduction: a lack of affordable vaccines on the market, and insufficient commercial incentives to develop vaccines for diseases concentrated in developing countries. Under the terms of an AMC, donors make a legally binding guarantee that,if a future vaccine is developed against a particular disease, they will purchase a predetermined amount at an agreed-upon price. The guarantee

is linked to safety and efficacy standards that the vaccine must meet and is structured in a way to allow several firms to compete to develop and produce the best possible new product. AMCs reduce risk to donor governments by eliminating the need to fund individual research and development projects that may never produce a vaccine. If no company produces a vaccine that meets the predetermined standards, governments (and thus their taxpayers) spend nothing. For the bio-pharmaceutical industry, AMCs create a guaranteed market, with a promise of returns that would not normally exist. For developing countries, AMCs provide funding to ensure that those vaccines will be affordable once they have been developed. It is estimated that the pneumococcal AMC could prevent more than 1.5 million childhood deaths by 2020.

Interaction with *Haemophilus influenzae*

Both *Haemophilus influenzae* (H. influenzae) and *S. pneumoniae* can be found in the human upper respiratory system. A study of competition *in vitro* revealed *S. pneumoniae* overpowered *H. influenzae* by attacking it with hydrogen peroxide.

When both bacteria are placed together into the nasal cavity of a mouse, within 2 weeks, only *H. influenzae* survives. When both are placed separately into a nasal cavity, each one survives. Upon examining the upper respiratory tissue from mice exposed to both bacteria, an extraordinarily large number of neutrophil immune cells were found. In mice exposed to only one bacterium, the cells were not present.

Lab tests show neutrophils that were exposed to already-dead *H. influenzae* were more aggressive in attacking *S. pneumoniae* than unexposed neutrophils. Exposure to killed *H. influenzae* had no effect on live *H. influenzae*.

Two scenarios may be responsible for this response:

1. When *H. influenzae* is attacked by *S. pneumoniae*, it signals the immune system to attack the *S. pneumoniae*
2. The combination of the two species sets off an immune system alarm that is not set off by either species individually.

It is unclear why *H. influenzae* is not affected by the immune system response.

Diagnosis

Diagnosis is generally made based on clinical suspicion along with a positive culture from a sample from virtually any place in the body. An ASO Titre of >200 units is significant. *S. pneumoniae* is, in general , optochin sensitive, although optochin resistance has been observed. Atromentin and leucomelone possess antibacterial activity, inhibiting the enzyme enoyl-acyl carrier protein reductase, essential for the biosynthesis of fatty acids) in *S. pneumoniae*.

Depending on the nature of infection, an appropriate sample is collected for laboratory identification. Pneumococci are typically gram-positive, cocci, seen in pairs or chains. When cultured onblood agar plates with added optochin antibiotic disk, they show alpha-hemolytic colonies and a clear zone of inhibition around the disk meaning they're sensitive to the antibiotic. Pneumococci are also bile soluble. Just like other streptococci, they are catalase-negative. A Quellung test can identify specific capsular polysaccharides.

Pneumococcal antigen (cell wall C polysaccharide) may be detected in various body fluids. Older detection kits, based on latex agglutination, added little value above Gram staining and were occasionally false-positive. Better results are achieved with rapid immunochromatography, which has a sensitivity (identifies the cause) of 70–80% and >90% specificity (when positive identifies the actual cause) in pneumococcal infections. The test was initially validated on urine samples, but has been applied successfully to other body fluids Chest X-rays can also be conducted to confirm an infection.

Treatment

Throughout history, treatment relied primarily on β-lactam antibiotics. In the 1960s, nearly all strains of *S. pneumoniae* were susceptible to penicillin, but, since that time, there has been an increasing prevalence of penicillin resistance, especially in areas of high antibiotic use. A varying proportion of strains may also be resistant to cephalosporins, macrolides (such as erythromycin), tetracycline, clindamycin and the quinolones. Penicillin-resistant strains are more likely to be resistant to other antibiotics. Most isolates remain susceptible to vancomycin, though its use in a β-lactam-susceptible isolate is less desirable because of tissue distribution of the drug and concerns of development of vancomycin resistance. More advanced beta-lactam antibiotics (cephalosporins) are commonly used in combination with other drugs to treat meningitis and community-acquired pneumonia. In adults, recently developed fluoroquinolones such as levofloxacinand moxifloxacin are often used to

provide empiric coverage for patients with pneumonia, but, in parts of the world where these drugs are used to treat tuberculosis, resistance has been described. Susceptibility testing should be routine, with empiric antibiotic treatment guided by resistance patterns in the community in which the organism was acquired, pending the results. There is currently debate as to how relevant the results of susceptibility testing are to clinical outcome. There is slight clinical evidence that penicillins may act s

What is Pneumococcal Disease?

Pneumococcal disease is an infection caused by the*Streptococcus pneumoniae* (*S. pneumoniae*) bacterium, also known as pneumococcus. Infection can result in pneumonia, infection of the blood (bacteremia/sepsis), middle-ear infection (otitis media), or bacterial meningitis.

The World Health Organization (WHO) says that pneumococcal disease is the world's number 1 vaccine-preventable cause of death among infants and children younger than 5 years of age.

There are two main types of pneumococcal diseases:

1) Non-invasive pneumococcal diseases

These may be less serious than invasive pneumococcal disease and occur outside the major organs or the blood. *S. pneumoniae*can spread from the nasopharynx (nose and throat) to the upper and lower respiratory tract and can cause:

- Otitis media - middle ear infection. Inflammation of the middle ear, typically with accumulation of fluid in the middle ear, swelling of the eardrum, earache. If the eardrum is perforated drainage of pus into the ear canal.
- Non-bacteremic pneumonia - infection of the lower respiratory tract without detectable spread of organisms to the blood stream

2) Invasive pneumococcal diseases (IPD)

These tend to be more serious and occur inside a major organ, or in the blood. Examples of IPDs include:

- Bacteremia (sepsis) - bacterial infection of the blood. Bacteremia refers to the presence of live bacteria in the blood, while sepsis means a blood infection which is associated with capillary leak, shock and an increased risk of mortality.

- Meningitis - inflammation of the meninges. The meninges are the three membranes that cover the brain and the spinal cord.
- Bacteremic pneumonia - inflammation of one or both lungs, with pneumococcus in the bloodstream.

Synergistically with macrolides to improve outcome

Who is at Risk of Pneumococcal Disease?

Anybody can get pneumococcal disease. However, some groups are at a significantly higher risk for pneumococcal disease or its complications.

People at higher risk include:

- Infants and children younger than two years of age.
- Children who have an underlying medical condition which predisposes them to invasive pneumococcal disease.
- People over 65 years of age.
- Children in poor areas of developing countries.
- People with weakened immune systems, such as those with immunosuppression (e.g. high-dose steroids, chemotherapy), HIV, or AIDS.
- Patients with chronic diseases, such as:
  - Diabetes
  - Lung disease
  - Heart disease
  - Cancer
  - Kidney disease
  - Sickle cell disease
  - Alcoholism
- Residents of chronic (long-term) care facilities.
- Patients who have a history of spleen dysfunction or spleen disease.
- Tobacco smokers.
- People who have a cochlear implant (a type of hearing aid).
- Patients with cerebrospinal fluid leak (e.g. due to fractured base of skull)

What are the Signs and Symptoms of Pneumococcal Disease?

Signs and symptoms of pneumococcal infection depend on the type of infection the patient has.

A symptom is something the patient feels, while a sign is something other people, such as the doctor or family members see. An example of a symptom may be a headache, and an example of a sign might be a rash.

The signs and symptoms of pneumococcal disease may be non-specific.

The most common signs and symptoms include:

- An elevated body temperature (fever)
- Chills
- Sweat
- Aches and pains
- Headache
- Malaise (generally feeling unwell)

Pneumococcal bacteremia - signs and symptoms of may include:

- An elevated body temperature (fever)
- Headache
- Muscular aches and pains
- Rapid heart rate
- Rapid breathing

Pneumococcal meningitis - signs and symptoms of may include:

- An elevated body temperature (fever)
- Headache
- Nausea
- Vomiting
- Sleepiness
- Irritability
- Stiff neck
- Seizures
- Sometimes coma

Pneumococcal pneumonia - signs and symptoms of may include:

- Cough
- An elevated body temperature (fever)
- Breathing problems, such as shortness of breath (rapid breathing)
- Chest pain

Other symptoms may include:

- Nausea
- Vomiting
- Headache
- Fatigue (tiredness)
- Muscle aches

Pneumococcal acute otitis media - signs and symptoms of may include:

- Earache
- An elevated body temperature (fever)
- Vomiting
- Diarrhea
- Temporary hearing loss
- Ear discharge

Non-invasive infections

Laboratory tests are not usually ordered if the patient has conjunctivitis, or otitis media, unless they have an unusually high fever or appear to be extremely ill.

What are the Treatment Options for Pneumococcal Disease?

Despite early and adequate treatment, there can still be serious and potentially life-threatening complications arising from pneumococcal infection.

Otitis media

May need to be treated with antibiotics.

Bacterial pneumonia

Needs to be treated with antibiotics.

Invasive pneumococcal infections

Doctors will usually prescribe antibiotics for invasive pneumococcal infections. If the infection is mild the patient will take oral antibiotics. Serious infections will require intravenous administration - a solution containing antibiotics will be administered directly into the venous circulation via a syringe or intravenous catheter (tube).

Doctors may recommend administering a combination of different antibiotics, in case the *S. pneumoniae* has developed resistance. The emergence of resistant pneumococcal strains over the last few years is making treatment more difficult, extending the period of many hospitalizations, as well as increasing the likelihood of more expensive alternative therapy.

Patients with very serious infection will be hospitalized so that they can be supported.

Experts say that the growing problem of antibiotic resistance places further emphasis on the need for preventing pneumococcal disease through vaccination.