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Current Understanding on the Virulence and Immune Response of Streptococcus Pneumoniae: A Critical Appraisal

Mahendra Pal[1,*], Adugna Girma Lema[2], Mati Roba Bulcha[3], Getahun Duguma Jeto[3]

[1]Narayan Consultancy on Veterinary Public Health and Microbiology, Anand, Gujarat, India
[2]Wolmera Woreda Animal Health Profession, West Shoa, Oromia, Ethiopia
[3]Yemalog Walal Woreda Livestock and Fishery Development and Resource Office, Kellem Wollega Zone, Oromia, Ethiopia
*Corresponding author: palmahendra2@gmail.com

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Abstract Infectious diseases present a significant health burden affecting the immunocompromised as well as immunocompetent subjects throughout the world. Most of these diseases are due to the invasion of the host cells and organs by the microorganisms. Common widespread diseases of the respiratory system occur when the organisms invade the respiratory tract of the host. The infectious respiratory diseases are globally observed as a major health concern because they can rapidly become severe and lead to death. *Streptococcus pneumoniae* is a medically important bacterium that has been commonly linked to causing respiratory infections in individuals with a weakened immune system. *Streptococcus pneumoniae*, also known as pneumococcus, can survive in both aerobic and anaerobic conditions. The organism has the potential to produce pneumonia, bacteremia, meningitis, acute otitis media, and sinusitis. It colonizes the upper respiratory tract particularly the nasopharynx. *Streptococcus pneumoniae*, like many other bacterial species, produce toxins that are harmful to its host, has several surface proteins and physical structures, which play a very crucial role in its pathogenesis.

Keywords: *bacterium, immune response, infection, meningitis, pneumonia, streptococcus pneumoniae, virulence*

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1. Introduction

Infectious diseases that involve varied etiologies, such as virus, bacterium, fungus, and protozoa, are a major health burden affecting the people of the developing as well as developed countries of the world. Most of those diseases measure high due to the invasion of host cells and organs by the microorganisms [1]. These pathogens disrupt the conventional performance of the body by impeding the immune responses and producing harmful toxins. Commonly prevalent diseases of the system occur once the microbes invade the respiratory tract. The infectious respiratory disease is seen as a serious health hazards as it may quickly happen to be severe and result in death.

A host with a healthy and well-developed immune system can clear the pathogens before they can become infectious and cause diseases. The ability to clear the organisms before they can become infectious depends on the quality of the immune system and its effectiveness, which is linked strongly to age of the host [2]. *Streptococcus pneumoniae* is a medically significant bacterium that has been commonly associated in respiratory infections of the individuals with the compromised immune system [3]. The bacterium invades the host by colonizing the nasopharynx asymptomatically, as it is a part of the commensal microbiota of the upper respiratory tract [1].

The pathogen has several properties, which allow it to go unnoticed by the host immune system, and defend against the resident flora within the nasopharynx that would try to clear the bacteria [4]. Thus, decreasing the burden of this bacterium and preventing further infections is very important to promote the healthcare. Furthermore, *S pneumoniae* is an opportunistic pathogen that takes advantage of hosts with underdeveloped, weakened, and or deteriorating immune systems [5]. The primary objectives of this review are to provide a concise introduction to the expanding literature on *S. pneumonia*, and also to focus on exploring the characteristics of *S. pneumonia*, and its virulence factors.

2. Streptococcus Pneumonia

Streptococcus pneumoniae, a Gram-positive, bacterium additionally called pneumococcus, has the ability to survive both in aerobic and anaerobic conditions. It is a

facultative organism that is usually found as diplococci. Pasteur and Sternberg are credited who initially isolated *Streptococcus pneumoniae* from the saliva in 1881 [6]. Currently, there are varied reports on the number of known serotypes of *S. pneumoniae*. However, a minimum of 97 serotypes of *Streptococcus pneumoniae* are known and characterized so far; and the host independently recognizes all of those serotypes. Pneumococcal diseases have been reported from many countries of the world [7].

Streptococcus pneumoniae causes bronchopneuomia, pneumonia, bacteremia, meningitis, otitis media, conjunctivitis, sinusitis, peritonitis, percarditis, and empyema. The bacterium colonizes the upper respiratory tract; and is in a position to asymptomatically reside within the upper respiratory tract and thus this can be called as the carriage [6]. Biofilms are formed within the nasopharynx during the colonization. *Streptococcus pneumoniae* has several virulence factors that yield adherence to the host cells, scale back the host's immune system's ability to clear the bacteria, and promote the invasion of animal tissue cells [8].

Streptococcus pneumoniae when colonizes the upper respiratory tract, the bacterium multiplies, disrupts the regular non-pathogenic flora of the respiratory system [9], and is ready to migrate to the tissues and organs of the body and thus causes the infection. The migration of the organism to the sterile tissues and organs is that the main reason of pneumococcus diseases for instance, once the tissue layer, the protecting membranes encompassing the spinal cord and brain, become inflamed because of *S. pneumoniae* infection, this can be referred to as bacterial meningitis disease. It is pertinent to mention that bacterial meningitis is predominantly noticed in young children and is generally caused by *S. pneumoniae* [10]

2.1. Clinical signs

Streptococcus pneumoniae, which at the start inhabits the membrane surfaces of the nasopharynx in its hosts, will migrate to the lungs, and causes pneumonia. This can be an infection of the lungs that results in the inflammation of the air sacs inflicting them to fill with fluid, and creating it difficult to breathe [9]. People who have respiratory disease sometimes suffer from high heart rates, shortness of breath, frequent coughing, and high fever; despite *S. pneumoniae* well colonization of the nasopharynx, having a poor immune response, and lack of clearance, could turn out to be pneumonia, which may be a significant health risk for those with reduced host defenses [11].

2.2. Transmission

The severity of pnemunococcal diseases have led to multiple studies to investigate how *S. pneumoniae* is transmitted. The nasopharynx has been mentioned as the main reservoir of *S. pneumoniae*. This is often due to the nasopharynx of hosts being settled with no symptoms. Following colonization, the spreading of the disease depends on carriers coming back into close contact with healthy people inside the population. The transmission of *S. pneumoniae* occurs mostly by direct contact with secretions of the respiratory system of a carrier [4].

Streptococcus pneumoniae additionally produce toxin substance, pneumolysin, which promotes shedding and successively enhances the transmission of the organism [12]. Pneumolysin induces inflammation in the hosts throughout colonization and this promotes shedding of the bacteria. Transmission via co-infection with *S. pneumoniae* is usually seen throughout the viral infections. Co-infections by infective bacterium like *Streptococcus pneumoniae* increases the severity and mortality rates of the infections [13]. It is reported that co-infection is feasible due to the pre-existing injury on the epithelia of the tract that promotes the colonization of the microorganism. Accumulated host colonization and microorganism cell density of *S. pneumoniae* throughout the infections promote transmission [14].

2.3. Virulence Factor

Streptococcus pneumoniae, like several different bacterial species, produces toxins that are harmful to its host; and has many surface proteins and physical structures, which play an important role in its pathogenesis [5]. *Streptococcus pneumoniae* virulence thrives owing to the ability of the microbes to acquire new genetic material via transformation and recombination. About 4,000 *Streptococcus pneumoniae* genomes have already been sequenced, more than 2000 genes are annotated, however, novel genes are still frequently discovered as additional sequences become on the market [4].

2.4. Major Virulence Factor

2.4.1. Polysaccharide Capsule

The extracellular polysaccharide capsule, the foremost important virulence factor, helps to initiate the infection by permitting the bacteria to stick to the host cells and cause inflammation, whereas conjointly protecting the host's system [4]. The capsule inhibits the body process by innate immune cells, prevents the popularity of the bacteria by host receptors and enhances factors, and conjointly avoids neutrophils traps. The roles of the capsule in pathogenesis are delineated to result in its charge. The capsule includes a negative web charge that is partly because of the acidic polysaccharides and phosphates that frame this layer [15].

2.4.2. Streptococcus Pneumoniae's Plasma Membrane Elements

Streptococcus pneumoniae is a non-sporulated, Gram-positive bacterium with a thick cell wall. The cell wall is vital as it provides protection and shapes the cell. Peptidoglycan, wall teichoic acid (WTA), and lipoteichoic acids (LTAs) are the main elements of *S. pneumoniae's* plasma membrane [16]. Wall teichoic acid are covalently connected to peptidoglycan wherever as lipoteichoic acids are non-covalently connected to the protoplasm membrane with a lipid anchor. The capsular and cell-surface proteins all joined to the peptidoglycan [17].

Alternating glycan chains of N-acetylglucosamine (GlcNac) and N-acetylmuramic (MurNac) acids are cross-linked by peptides frame peptidoglycan. These glycan chains

bear secondary modifications like deacetylation of GlcNac and O-acetylation of MurNac. These modifications aid in *S. pneumoniae's* virulence by creating the cell resistant muramidase [18].

2.4.3. Pneumolysin

Pneumolysin is the toxin that is capable of forming pores in cell membranes. It is found within the living substance of *S. pneumoniae* and alternative Gram-positive microorganisms [19]. Pneumolysin is discharged as a result of cell lysis, and is toxic to the host cells. Pneumolysin binds to membranes containing cholesterol and forms pores that later results in host cell lysis [20]. They showed that the poisons will dysregulate the assembly of reactive oxygen species (ROS) intracellularlly. This is often attainable due to pneumolysin's pore-forming properties. Further, it creates particle channel that disrupts the cell calcium levels, which results in overrun of ROS, and then causes damage to DNA [21].

2.4.4. Autolysin

Autolysin enzyme is involved in the autolysis of bacteria, which results in the release of pneumolysin, teichoic acid, and other components from within the cell [1].

2.4.5. Pneumococcal Surface Proteins

Streptococcus pneumoniae has a large variety of surface-exposed proteins [1] that aids in its pathogenesis by acting as adhesins to the host cells and hindering the host's immune system, specifically the complement system [22]. Pneumococcal surface proteins are categorized into four groups:

Choline binding proteins, lipoproteins, non-classical proteins: CBPs, lipoproteins, non-classical proteins and proteins that have an LPXTG motif (x represents any amino acid) and can be covalently bound through sortase cleavage of the motif [20].

Choline binding proteins (CBPs): Many surface proteins of *Streptococcus pneumoniae* are classed as CBPs [24]. These proteins are known for binding to PCho on *S. pneumoniae's* cell wall, and are necessary for the adhesion to the host cells [23].

Lipoproteins: Lipoproteins are necessary for transport of the substrate. There are approximately 50 lipoproteins that have been characterized. The four main lipoproteins are the pneumococcal surface adhesion A (PsaA), pneumococcal iron acquisition A (PiaA), pneumococcal iron uptake A (PiuA), and pneumococcal iron transporter (PitA) [23]. They are all metal-binding proteins that combine with ATP-binding cassette (ABC) transporter complexes. ABC transporters carry the substrates across the membranes by utilizing the energy generated from ATP binding and hydrolysis [25].

LPXTG: The cell wall-bound proteins are recognized by sortase of the cell wall. Sortase recognizes the LPXTG sequence, cleaves at this site, and anchors the proteins to the cell wall [26].

Non-classical surface proteins (NCSPs): Non-classical surface proteins are found on *S. pneumoniae's* surface but do not have a membrane-anchoring motif or a leader peptide. They are also known as moonlighting proteins for having multiple functions [27].

2.4.6. Pili

These hair-like structures are located on the cell surface of *S. pneumoniae* and many other bacteria. They assist with *S. pneumoniae's* attachment and colonization of the epithelial cells within the nasopharynx and lungs of the hosts [28]. These pili also help the bacteria to avoid phagocytosis by the host immune cells [27].

2.4.7. Immunoglobulin A1 (IgA1) Protease

This enzyme is produced by *S. pneumoniae* and it works by cleaving IgA1 into fragments [29]. The IgA1 represents an isotype of immunoglobulin A (IgA), which has two isotypes: IgA1 and IgA2. These two isotypes differ in hinge regions. IgA1 has an extended hinge region because of insertion into this region of a set of duplicated amino acids [30]. IgA1 proteases reduce the binding IgA's effector region of the heavy chain, and hinder the killing of the bacterium by these antibodies [29].

2.4.8. Hydrogen Peroxide

Streptococcus pneumoniae secretes hydrogen peroxide (H_2O_2) which causes damage to the host DNA. H_2O_2 production also has bactericidal effects. *Streptococcus pneumoniae* uses this to reduce the growth of bacteria it may be competing with [31].

2.4.9. Pathogenicity Islands (PAIs)

These are parts of pathogenic bacteria genomes that are acquired via horizontal gene transfer [32]. The genes on PAIs aid in the virulence of the pathogen. PAIs can code for iron-uptake systems and proteins involved in the cell attachment [33].

2.4.10. Biofilms

Biofilms are structured communities that consist of aggregated microbial cells surrounded by an extracellular matrix of polysaccharides that attach to the surfaces [34]. The extracellular matrix provides protection and enhances *S. pneumoniae's* virulence [35]. Biofilms are formed in response to stress and harsh conditions to promote bacterial survival [34]. To promote biofilm formation and competence, *S. pneumoniae* down-regulates the expression of capsular proteins. Within biofilms, horizontal gene transfer rates increase due to the close cell proximity [33].

Earlier studies indicated that *S. pneumoniae* biofilms are not effectively cleared during antimicrobial treatments due to increased antimicrobial resistance. Also, *S. pneumoniae* biofilms can escape the host immune responses, such as mucociliary clearance [36].

2.5. Host Immune System Response to *S.pnemoniae*

The protection from *S. pneumoniae* is dependent on the state of the host's immune system [37].

2.5.1. Innate immune Responses

Innate immunity involves non-specific immune responses cells and receptors acknowledge the foreign particles and elicit immune responses to eliminate the invaders, which will be harmful to the host [38]. Cell related

innate immune responses against diplococcus infection include-

I. Tissue layer and metabolism animal tissue cells: Animal tissue cells offer a protecting barrier for tissues and organs [39]. During this case, they line the tract and shield against *S.pneumoniae*. There are animal tissues cells referred to as goblet cells, which secrete secretion [38]. The charged secretion is important for maintaining wetness and tack foreign particles and pathogens. Additionally, rough animal tissue cells operate at the same time with the secretion to clear the pathogens. This method is thought of as mucociliary clearance [20].

II. Phagocytes: The neutrophils are found in larger concentrations compared to the other white blood cells (WBC), and they are usually the primary travel to the infection. The neutrophils are vegetative cells that conjointly produce granules that break down the cell walls of the pathogens ultimately killing them [40]. There are two main varieties of granules made by the neutrophils: primary and secondary, that dissent supported the maturity of the WBC [41].

Primary granules embrace defenses whereas secondary granules embrace enzymes necessary for digestion, like lysosomes. The neutrophils also can lure *S. pneumoniae* living thing by victimization, and living thing extracellular created from deoxyribonucleic acid. The macrophages are derived from the monocytes and performance as vegetative cells that engulf and directly kill *S. pneumoniae* [42].

2.5.2. Adaptive immune Responses (B and T Cells)

Adaptive immune responses appear in exceedingly few too many days post-infection. The cells concerned with adaptive immune responses reply to the specific antigens from the pathogens. Adaptive immunity also can be diminished into two varieties of responses: humoral and cell-mediated [43]. Humoral immunity involves B cells that are activated by antigens, and the production of antibodies that are specific to antigens. Cell-mediated immunity conjointly involves T cells, together with lymph cell activation and T cell-mediated accomplishment that involves the activation of alternative immune cells, which directly kill the pathogenic cells [44]. These immune cells are shaped within the bone marrow B cells mature within the bone marrow into plasma cells that create substance-specific antibodies [38].

Chemokines and cytokines are signed molecules free by innate and adaptive immune cells, and receptors to direct alternative immune cells to the infected tissues. Chemokines are samples of cytokines that attract cells to the infected site. Additionally to recruiting cells, they promote the inflammation [45].

2.6. Prevention, Antibiotic Response of *Streptococcus pneumoniae*

The two main modes of preventing pnemococcal infections are victimization antibiotics and vaccinations against *S. pneumoniae* [46]. Antibiotics are essential in reducing the load of microorganisms. Such treatment will work by killing the organisms inhibiting their growth [47].

3. Conclusion and Recommendations

Streptocoocus pneumonia is an important bacterial pathogen that causes life threatening infection in humans worldwide. In this review, abundant progress is being made in our understanding of *S. pneumoniae* and pneumococcal infections. The true burden of disease is now better recognized. Different kinds of virulence of *S. pnemoniae* help them to overcome the immune system of the host and aspects of more optimal treatment, both with antibiotics and with adjunctive therapies, are being delineated. It is hoped that all these advances in our understanding of the disease will ultimately lead to a better outcome and prevent *S. pneumoniae* infection. Based on the above conclusion, the following recommendations are forwarded:-

Serotype independent vaccines should be included in the vaccination in all ages.

Treatment may be complicated by antibiotic resistance so that focusing on the prevention is the best choice of managing *S. pneumoniae* infection.

There should be strict nursing care for the children, and vaccination of *S. pnemoniae* should be done on time.

Further work on the pathogenicity, immunology, and molecular epidemiology of *S. pnemoniae* should be conducted.

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Contribution of Authors

All the authors contributed equally. They read the final version, and approved it for the publication.

Conflict of Interest

The authors declare that they do not have conflict of interest.

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