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MENINGITIS CAUSED BY *STREPTOCOCCUS PNEUMONIAE*: A REVIEW

Sawati Sharma*, Shubham Goyal, Narinder Pal Kaur and Akhilesh Vats

Department of Pharmacology, School of Pharmacy & Emerging Sciences, Baddi University of Emerging Sciences and Technology Makhnumajra, Baddi, Distt. Solan-173205, Himachal Pradesh, India

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Correspondence to Author:

Sawati Sharma

Assistant Professor, Department of Pharmacology, School of Pharmacy & Emerging Sciences, Baddi University of Emerging Sciences and Technology, Makhnumajra, Baddi, Distt. Solan-173205, H.P, India.

E-mail: swatisharma713@gmail.com

ABSTRACT: Meningitis is a condition whereby the protective membranes covering the central nervous system (or meninges) become inflamed. Infections of the central nervous system are still considered to be among the most debilitating diseases in the 21st century. The mortality from this infection ranges from 15% in industrialized to 40% in developing countries. *Streptococcus Pneumoniae* infections, including pneumococcal meningitis, are therefore likely to remain an important health issue. Pneumococcal meningitis in human beings is associated with long-term sequelae including sensory-motor deficits, seizures, and impairments of learning and memory. Neurological sequelae occur in up to half of the survivors of pneumococcal meningitis. Meningitis is manifested as severe headache, occurring in almost 90% of cases of bacterial meningitis, followed by nuchal rigidity. Meningitis is a potentially serious condition due to the proximity of the inflammation to the brain and spinal cord. The potential for serious neurological damage or even death causes meningitis to need immediate medical attention and evaluation.

INTRODUCTION: Meningitis is a condition whereby the protective membranes covering the central nervous system (or meninges) become inflamed. Infections of the central nervous system are still considered to be among the most debilitating diseases in the 21st century [1]. The mortality from this infection ranges from 15% in industrialized to 40% in developing countries.

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Despite improvement in the anti-microbial therapy bacterial meningitis is still associated with a surprisingly high mortality of 28% and 50% of the survivors suffer from neurological sequel. Even though some forms of meningitis are mild and resolve on their own, meningitis is a potentially serious condition due to the proximity of the inflammation to the brain and spinal cord.

The potential for serious neurological damage or even death causes meningitis to need immediate medical attention and evaluation [2].

Acute bacterial meningitis is a medical emergency which warrants early diagnosis and aggressive therapy. Most often therapy for bacterial meningitis has to be started before the etiology is known.

The choice of anti-microbial therapy is based on the most common pathogen prevalent in a particular geographical area and age group and their antibiotic susceptibility pattern. Though the common pathogens associated with bacterial meningitis in the west are *H. influenzae, N. meningitidis, S. pneumoniae and Listeria monocytogenes* [3].

S. pneumoniae infections, including pneumococcal meningitis, are therefore likely to remain an important health issue. Pneumococcal meningitis in human beings is associated with long-term sequelae including sensory-motor deficits, seizures, and impairments of learning and memory. Neurological sequelae occur in up to half of the survivors of pneumococcal meningitis [4]. Meningitis is manifested as severe headache, occurring in almost 90% of cases of bacterial meningitis, followed by nuchal rigidity (inability to flex the neck forward passively due to increased neck muscle tone and stiffness). The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever and altered mental status; however, all three features are present in only 44-46% of all cases of bacterial meningitis. Other signs commonly associated with meningitis include photophobia (intolerance to bright light) and phonophobia (intolerance to loud noises) [5].

Animal experimentation is an essential tool to study the pathogenesis of infectious diseases and test novel drugs and vaccines. The development of animal models mimicking the human disease is the cornerstone for the studies of mechanisms of infection, pathogenesis and immunity, efficacies of anti-microbials and screening of vaccine candidates. Even though patient studies have provided insight into disease pathology as well as the prognostic significance of clinical and paraclinical parameters, animal models have substantially contributed to the disclosure of the pathophysiological mechanisms, despite obvious flaws in the animal models used especially with respect to pathogen sensitivity and infectious dose and modality [1].

Before the introduction of antibiotics (sulphonamides in the 1930's and penicillin 1940's), meningitis due to *Streptococcus pneumoniae* ended without exception in the death of the patients [6, 7]. Several desperate therapeutic attempts such as drainage of cerebrospinal fluid (CSF) and treatment with optochin, bile salt or pneumococcal antiserum were performed on experimental basis during the pre-antibiotic period, but without clinical success [8]. Although treatment with antibiotics made *S. pneumoniae* meningitis a curable disease [9, 10] the morbidity and mortality from the disease have not changed significantly over decades and remain unacceptably high, despite continuous improvements in intensive care technology and the introduction of new more potent antibiotics [11].

Bacterial Meningitis: Bacterial meningitis is among the most feared of human infectious diseases because of its possible seriousness, its rapid progression, its potential for causing severe brain damage and its frequency of occurrence. Most types of acute bacterial meningitis are septic-borne in that they originate when bacteria in the bloodstream (bacteremia, septicemia) gain entrance into the CSF. Meningitis arising by this route is called primary bacterial meningitis. Secondary meningitis is that which develops following direct entry of bacteria into the central nervous system (CNS), which can occur at the time of neurosurgery, in association with trauma or through an abnormal communication between the external environment and the CSF [12].

Basic anatomy of the Brain: The brain is covered by three protective coverings known as meninges, which are dura mater, the toughest and the outermost layer, in intermediate contact with the inside of the skull. The middle layer, arachnoid membrane, is important because of its involvement in the normal flow of the CSF, a lubricating and nutritive fluid that bathes both the brain and spinal cord. The innermost layer, the pia mater connects blood vessels to the brain. The space between the arachnoid membrane and the pia mater contains CSF, which help in insulating the brain from stress [13]. As the brain is enclosed in the hard, bony case of the skull, any disease that produces swelling will damage the brain. The cells of the brain require a very well-regulated environment. Optimum balance of oxygen, carbon dioxide, glucose, sodium, calcium, potassium and other substances must be maintained in order to avoid damage to brain tissue.

An infection upsets this balance and brain damage occur when the cells of the brain are either deprived of important nutrients or exposed to toxic levels of particular substances such as pathogens, reactive oxygen species (ROS), allergens and inflammatory precursors. The Blood Brain Barrier (BBB) prevents various substances that could be poisonous to brain tissue, as well as many agents of infection, from crossing from the blood stream into the brain tissue. The BBB also serves to complicate treatment in the case of an infection by making it difficult for medications to pass out of the blood and into the brain tissue where the infection is located [12,13].

Pathogenesis of Bacterial Meningitis: *Streptococcus pneumoniae* cause bacterial (also known as pneumococcal) meningitis, which for a long time was considered to be a strictly fatal disease. Due to advances with antibiotic research, penicillin specifically, the mortality levels of meningitis have decreased, but these mortality levels are still too high [14]. In fact, *S. pneumoniae* presents the greatest risk of death with bacterial meningitis [15]. Furthermore, fatality is not the only major devastating result from pneumococcal meningitis, because nearly half of the survivors of the disease have been reported to have neurological and neuropsychological sequelae [15]. Many of the deleterious effects of meningitis are caused by the host defense mechanisms, such as inflammatory reaction [16].

Therefore, rather than most of the damage being inflicted by *S. pneumoniae*, the host is injuring itself in an attempt to stop the infection. So, mediating the host's defense mechanisms may be the key to limiting the detrimental effects of meningitis [17].The infection of the brain and spinal fluid by *S. pneumoniae* is both difficult and complicated due to the complex defenses that protect the brain, including the BBB [17]. The process is demonstrated in **Figure 1**.

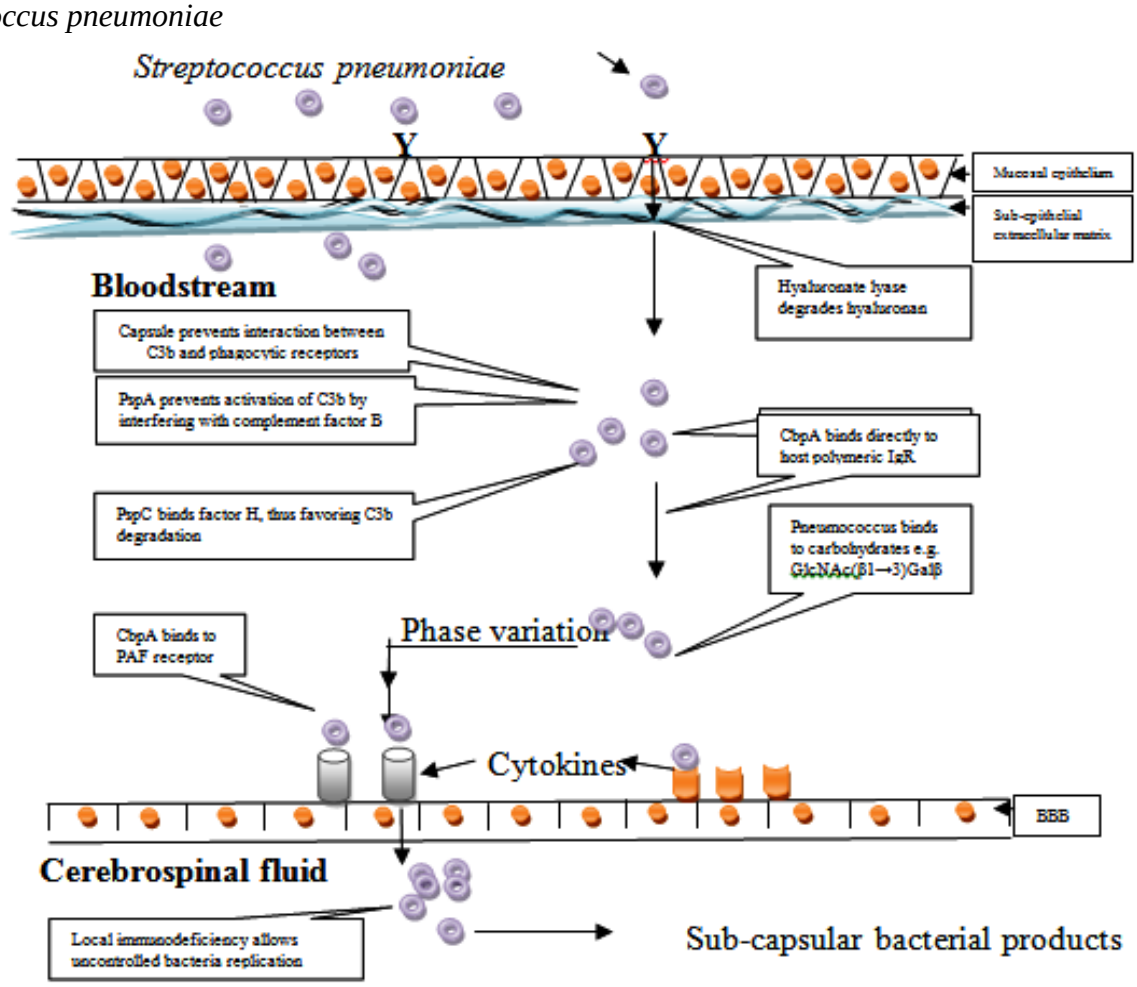

FIGURE 1: PATHOGENIC STEPS LEADING TO THE INITIATION OF *PNEUMOCOCCAL* MENINGITIS

Adhesion: The first step in the process of initiating pneumococcal meningitis is *S. pneumoniae* must adhere to the mucosal epithelium of the nasopharynx. The bacteria that cause meningitis make possible the interaction with the host cell via their own bacterial surface proteins [17]. It was stated that *Streptococcus pneumoniae* possess over 500 surface proteins, which are used to attach to the nasopharynx mucosal epithelium [18]. Epithelial cells express carbohydrates, and *Streptococcus pneumoniae* binds to these surface sugars, specifically GlcNAc (β1→3)Galβ, in order to adhere to pharyngeal epithelial cells [19]. The most important protein on the *S. pneumoniae* cell membrane surface may be the phosphorylcholines, because they are an important pneumococcal adherence factor. Of these phosphorylcholines, there is a group with proteins that attach to it, called choline binding proteins (Cbp's). The most abundant choline binding protein is Cbp A, which is a critical element in pneumococcal adherence [17].

The human brain has specialized cells capable of combating pneumococcal infection while the bacteria is adhering to and colonizing epithelial cells. The antibody Immunoglobulin A (IgA) can uptake and destroy *S. pneumoniae* by means of phagocytosis [20]. However, *Streptococcus pneumoniae* express a protein called IgA1 protease, which allows the bacteria to cleave and inactivate the antibody and escape phagocytosis [17].

Bacteremic spread: Once the bacteria have adhered to the epithelial cells, the *Streptococcus pneumoniae* invades the mucous and move into the bloodstream, which is termed bacteremic spread [17]. The next challenge facing the pneumococcal invasion is surviving in the blood stream. *Streptococcus pneumoniae* have a capsular polysaccharide, which has strong anti-phagocytic properties, surrounding the entire organism, and this sugar covering is considered integral for the survival of *S. pneumoniae* in the bloodstream. All of the *Streptococcus pneumoniae* isolates that were taken from people with pneumococcal infections had the capsular polysaccharide surrounding the bacteria [21].

CNS invasion: The next step in the pneumococcal infection is crossing the BBB and infecting the normally sterile CNS. Infection of the sterile bloodstream (bacteremia) is necessary for *Streptococcus pneumoniae*, but other events and processes must accompany [22], such as the BBB separates the CNS and the bloodstream, and the BBB prevents crossing of pathogens and non-specific transport of ions, proteins, cells, and pathogens into the CNS [23]. *Streptococcus pneumoniae* may enter primarily into the CNS through the brain endothelium. In order to move through the BBB, S. *pneumoniae* has to adhere to the surface of the brain endothelial cells, attaching to the carbohydrates on the surface of the endothelial cells [17]. *Streptococcus pneumoniae* activates the endothelial cells, which increases their production of surface-expressed platelet activating factor (PAF) receptor, which binds the phosphorylcholine that the *S. pneumoniae* expresses on their cell walls [24]. PAF receptors are quickly internalized after interaction with a ligand, *S. pneumoniae* infest the endothelial cells in vacuoles along with the PAF receptors [17].

Neuronal injury: *S. pneumoniae* induce the inflammatory defenses of the host inside the central nervous system **(Figure 2)**. Autolysis is one pneumococcal process that can initiate host defense. Autolysis involves the bacteria digesting itself by means of autolysins, which are peptidoglycan hydrolases that break down their own cell walls [25]. Host immune activation during acute meningitis can occur as a result of interaction with the DNA released from *S. pneumoniae* upon autolysis. Additionally, products from pneumococcal cell wall trigger an inflammatory response in the host [17].

The brain damage that occurs during meningitis is mostly attributable to the side effects of the host's own inflammatory response. When leucocytes are activated by *Streptococcus pneumoniae* they release proteolytic enzymes and reactive oxygen species, and both of these can potentially damage host tissue **(Figure 3)** [26]. Matrix metallo proteinases (MMPs) are one of the proteolytic enzymes released by the leucocytes, and MMPs have been found to disrupt the BBB [27]. ROS produced by leucocytes may contribute to brain damage incurred during meningitis, and this can occur via reactive oxygen species (O_2^-) attacking polyunsaturated fatty acids, which can damage cell membranes and lead to loss of membrane function [28].

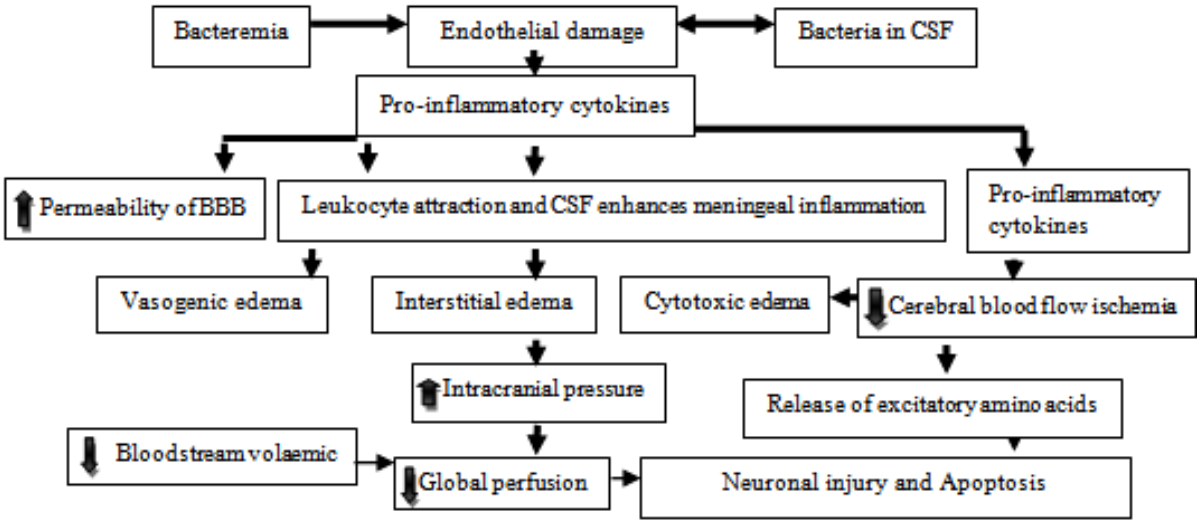

FIGURE 2: LEADING TO NEURONAL INJURY DURING BACTERIAL MENINGITIS

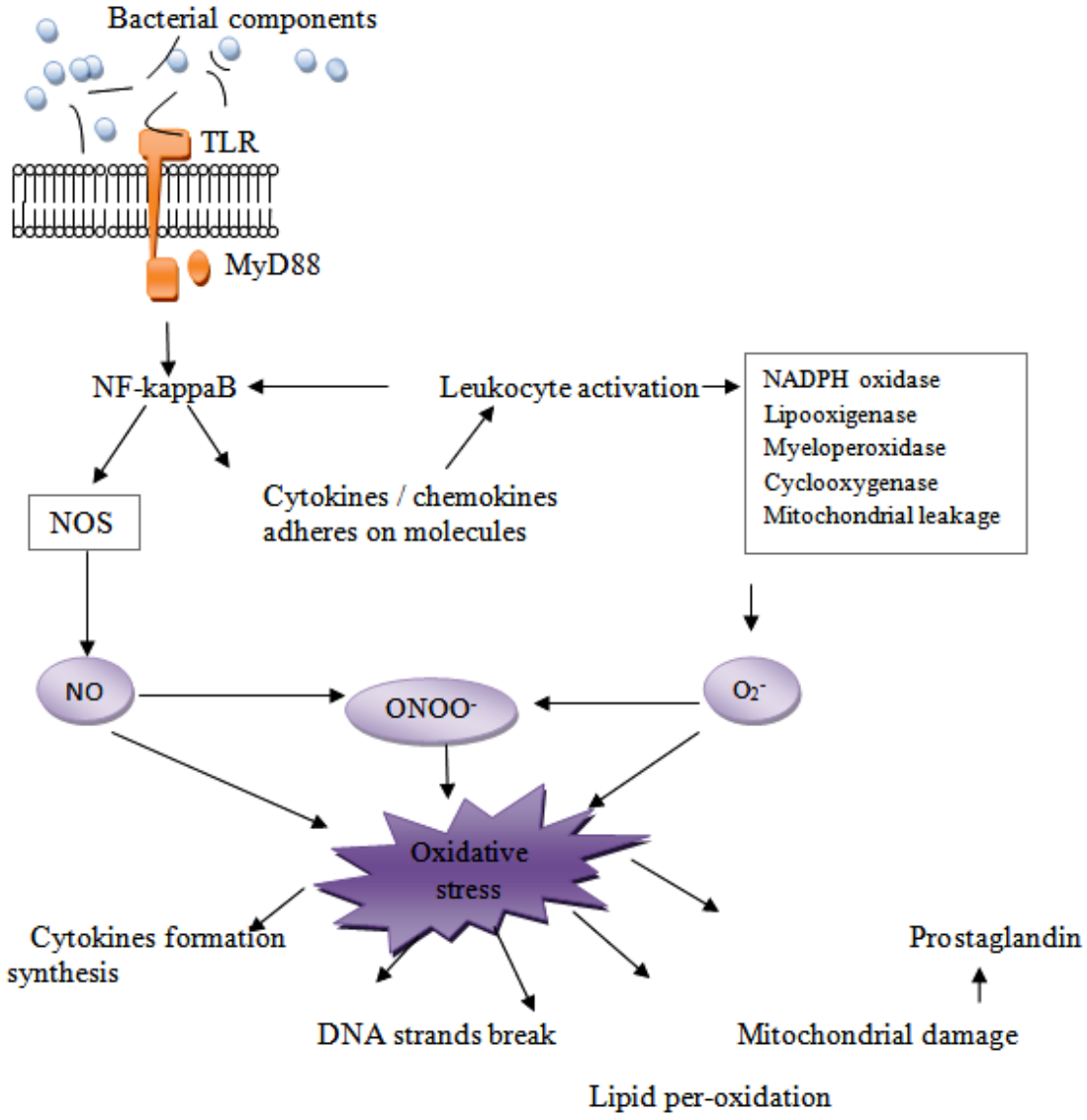

FIGURE 3: OVERVIEW OF MECHANISM OF OXIDATIVE STRESS

Models of experimental bacterial meningitis: Animal experimentation is an essential tool for the study of infectious diseases. Numerous animal models of diseases caused by *S. pneumoniae* are currently available for clarifying mechanisms of disease pathogenesis, testing novel drugs and vaccine candidates and characterizing the role of bacterial and host factors. The choice of both animal and bacterial strains should be carefully considered before approaching the study of pneumococcal disease *in vivo*. Several animal species, ranging from dogs to mice have been used in experimental meningitis research. However, none of the model has been shown to be superior and more closely resemble meningitis in humans. Since the majority of experimental research is performed using rabbits, rats or mice, these models appear more refined and versatile. Ultimately, the selection of the model has depended on the experimental aim and ethical guidelines [29].

Rabbit model of meningitis: The rabbit model of meningitis is used primarily for short-term studies (24 to 36 hours after pneumococcal inoculation) of inflammatory kinetics and in-vivo trials of antibiotic efficacy since CSF and blood samples can be obtained in greater volumes and on several occasions The study of meningitis related pathophysiology such as brain edema and alterations in cerebral blood flow have been investigated using this model [1].

Mouse model of meningitis: The mouse model of meningitis and especially genetically engineered mice are used for the investigation of basic studies of host pathogen recognition and subsequent inflammatory response. Also mice are used to study survival outcome, memory function and brain injury even though brain pathology appear limited in this model. CSF infection and sampling is more delicate in mice and sample amount naturally limited. Since mice are not continuously anaesthetized, clinical observation and basic disease scores are commonly used [1].

Rat model of meningitis: The rat model of meningitis is versatile combining the advantages of the models described above and therefore suitable for the study of many aspects of the disease. The rat model allows for a refined assessment of clinical and neurological symptoms due to the nature of rat handling and the calm nature of the rat. The rat has also been exploited for studying invasive pneumococcal disease and otitis media. Other advantages of the rat model include inoculation and CSF sampling. Out bred strains, including Wistar and Sprague-Dawley have been extensively utilized as experimental models [29].

Modes of infection:

Directly into CSF: The injection of large numbers of viable pneumococci directly into the CSF may well be subject to due criticism since disease development and inflammatory reaction is unlikely to closely follow the initial stages of the human disease due to the relatively high number of bacteria injected. However, this methodology remains the most commonly used because of its ability to induce reproducible infection and disease.

Nasal route (*i.n.*): Another way of induction is through intra nasal route i.e. intra-nasal (*i.n.*) where bacterial instillation is done into the nostrils of the animal, this model displays reduced homogeneity and significantly lowere rates of developing meningitis in animals.

Intra-cisternal (*i.c.*): Intra-cisternal (*i.c.*) infection is the one where the suspended micro-organisms are injected directly into the cisterna magna [1].

Change in the biochemical parameters: Once the infection is established, a number of biochemical factors needs attention for estimation, such as C Reactive protein (CRP), Lactate dehydrogenase (LDH), Glucose, Total leukocyte count (TLC), Malondialdehyde (MDA), Adenosine deaminase (ADA), Total proteins, Sodium, Potassium and Cytokines (TNF-α and IL-6) to understand the progression of cerebral meningitis.

Pro-inflammatory cytokines TNF-α and IL-6: After invasion of *S. pneumoniae*, the sub-arachnoidal space (SAS), leukocytes, endothelial cells and other cells in the central nervous system (CNS) are stimulated to produce pro-inflammatory mediators such as cytokines and prostaglandins, which leads to an increased permeability of the BBB, this effect enhances the migration of leukocytes i.e. granulocytes and monocytes, which can eliminate the bacteria in the SAS but can also harm the CNS.

The increased permeability of the BBB also promotes leakage of plasma into the CNS, with development of an inflammatory exudates, cerebral edema, elevation of intra-cranial pressure, and alteration of cerebral blood flow [30].

The early appearance of tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), IL-6, and IL-8 in CSF prior to the increase of leukocytes shows that these cytokines are released from cells normally present in the CNS, such as endothelial cells, microglial, cerebral endothelial cells and astrocytes, which indicates that they play a role in the initial phase of the local inflammatory reaction. TNF-α is formed by a wide variety of cells, such as monocytes, macrophages, microglial cells, astrocytes and endothelial cells. During bacterial meningitis, TNF-α is predominantly found in CSF and its high level has been found to be implicated in precipitation of seizures, whereas, high levels of TNF-α in serum has been demonstrated to cause high mortality. TNF-α *in vitro* promotes inflammation in the SAS and can cause tissue damage of oligodendrocytes, astrocytes, neuronal cells and myelin [30, 31].

IL-1 is formed by many kinds of cells, e.g. monocytes, macrophages, granulocytes, endothelial cells, microglial cells, and astrocytes. IL-1 stimulates the production of other cytokines such as IL-6 and TNF-α. In patients with bacterial meningitis IL-1 is present in the CSF, but not in the circulation and high levels correlate with the development of neurological complications. IL-1 enhances BBB permeability for leukocytes and plasma, thus contributing to the development of inflammatory exudates. IL-6 is formed by monocytes, macrophages, endothelial cells, T lymphocytes and fibroblasts. The production of this cytokine is stimulated by IL-1 and TNF-α. The levels of IL-6 in the circulation and CSF are elevated during meningitis and very high levels are associated with a fatal outcome [30, 32].

Adenosine deaminase (ADA): The isoenzymes ADA_1 and ADA_2 of the enzyme adenosine deaminase, deaminates mainly two nucleosides: adenosine and 2'-deoxyadenosine, producing inosine and 2'-deoxyinosine respectively. The isoenzyme ADA_1 is also present in red cells, which are equipped with an efficient mechanism to capture and internal 2'-deoxyadenosine (2'-deoxyadenosine is deleterious for nucleic acid). The isoenzyme ADA_2 is not ubiquitous, but coexists with ADA_1 only in monocytes and macrophages. ADA_1 and ADA_2 act as a system which acts to guarantee the homeostasis of adenosine and 2'-deoxyadenosine in monocytes and macrophages.

This homeostatic mechanism involves two substrates and two isoenzymes. Both isoenzymes have similar affinity for the substrate adenosine, whilst ADA_2 has a different affinity (very weak) for the substrate 2'-deoxyadenosine. Increase of ADA_2 in monocytes and macrophages occurs when these cells are infected by intracellular micro-organisms and whilst the parasite is still alive and the fact that, monocytes and macrophages, especially in an activated state, tolerate high levels of 2'-deoxyadenosine and ADA_1-ADA_2 homeostatic system may be a tool in the production of a "weapon" (2'-deoxyadenosine) of monocytes-macrophages against offending microorganism [33].

Malondialdehyde (MDA): Upon activation, cells of the immune system can produce a range of free radicals, such as reactive oxygen species (ROS), which can contribute to tissue damage. Free radicals are defined as ions with an electron that possess unusual chemical reactivity, including an ability to alter and to fragment membrane lipids In healthy conditions, the constantly produced oxygen derived free radicals are scavenged by endogenous antioxidants such as, e.g. superoxide dismutase and glutathione peroxidase.

During pathological conditions, such as ischemia and inflammation, however, this defense mechanism is perturbed and results in the over production of oxygen-derived free radicals ROS can cause considerable damage to the membrane lipids in the CNS. The polyunsaturated fatty acids after reacting with ROS can become peroxidated, destroying the structure of myelin and cell membranes. ROS degrade polyunsaturated lipids, forming MDA. This compound is a reactive aldehyde and is one of the many *reactive electrophile species* that cause toxic stress in cells and form covalent protein adducts referred to as advanced lipoxidation end-products (ALE), in analogy to advanced glycation end-products

(AGE). The production of this aldehyde is used as a biomarker to measure the level of oxidative stress in an organism [34].

Changes in Biochemical parameters: During meningitis it has been observed that the levels of CRP, Glucose, LDH and Total proteins in the CSF have been modulated.

C Reactive Protein (CRP): CRP is an acute phase reactant protein synthesized by the liver in response to diseased state, including trauma, infectious neoplasm and collagen vascular disease, the CRP synthesis is attenuated.

Glucose: Decreased CSF glucose results from change in the physiological function of the choroid epithelium as well as from consumption by bacterial pathogens and leukocytes.

Total proteins: CSF protein increase is associated with increased permeability of the BBB, vasogenic brain edema, hyper-cellularity and release of brain specific protein during cell death.

Lactate dehydrogenase: Lactate dehydrogenase is an intracellular enzyme that catalyzes the final step of anaerobic glycolysis and it serves as a useful CSF analyte for detecting bacterial meningitis, the concentration are higher in patients with disease [35].

Mechanism of resistance: The genetic basis of resistance plays a key role in determining how resistance develops and spreads within communities. A number of biological features distinguish pneumococci from other pathogens with acquired drug resistance:

Resistance in pneumococcal isolates is rarely due to single-point mutations alone or due to plasmid carriage. Transformation (the uptake and chromosomal exchange of free DNA from closely related strains or species), and conjugative transposons (transfer and genetic incorporation of small segments of DNA during bacterial fusion events) are the most common mode for pneumococci to acquire resistance genes. Pneumococci are commonly carried asymptomatically in the nasopharynx, which is also the cause of person-to- person transmission. Resistant strains can differ in their degree of resistance to a particular drug, measured as the minimum inhibitory concentration of a particular antibiotic [36].

Pneumococcal resistance to β-lactam agents like penicillin and cephalosporins is due to change in the target sites of the enzymes called penicillin binding proteins (PBP). These high molecular weight proteins are believed to catalyze the terminal stage in peptidoglycan (murein) synthesis. There are 6 PBP found in susceptible strains of *S. pneumoniae* viz. PBP 1a, 1b, 2a, 2x, 2b, and 3.

The altered PBP's in pneumococcus have low affinity for penicillin and related β-lactam compounds. Pneumococcal isolates with high penicillin MIC seems to be entirely due to expression of low affinity form of PBP 1a, 2a, 2b, 2x and 1b. High level resistance to cephalosporin requires reduction in the affinity of only PBP 2x and 1b [37].

TABLE 1: GENETIC MECHANISMS OF PNEUMOCOCCAL ANTIBIOTIC RESISTANCE

Phenotype	Genetic basis of resistance	Origin	References
Intermediate β-lactam resistance	Penicillin binding protein (PBP) gene alteration	Transformation with PBP genes from resistant species	38, 39
High level resistance to extended spectrum cephalosporins (e.g. cefotaxime)	PBP gene mosaic involving *pbp1a* and *pbp*2	Transformation which can happen by a single transformation event.	40
Intermediate and high level trimethoprim/ sulfamethoxazole resistance	Dihydrofolate reductase (DHF) gene mosaics and point mutation alleles	Transformation or spontaneous mutation	41,42,43
High level chloramphenicol resistance	*cat* gene	Conjugative transfer of transposons (Tn5253).	44
Low and high level fluoroquinolone resistance	*parC* mutations and *parC* and *gyrA* double mutants respectively	Transformation and point mutation	43,45

Management of meningitis: Management of pneumococcal infections used to be relatively straightforward, and penicillin generally was the antibiotic of choice. However, the worldwide emergence of antibiotic resistance among *S. pneumoniae* isolates has changed this approach.
Since the degree of antibiotic resistance continues to change and increase, the approach to managing these infections must be modified in response to these changes [46].

The most important step in the treatment of bacterial meningitis is the prompt initiation of antibiotic therapy [47]. The choice of antibiotic therapy for treatment of bacterial meningitis depends primarily on local susceptibility patterns for meningeal pathogens, the age of the patient and on considerations of CSF pharmacokinetic (PK) and pharmacodynamic (PD) properties of antibiotics. Such PK/PD data have predominantly been obtained from experimental studies using the rabbit meningitis model. Empiric therapy with a third generation cephalosporin in combination with penicillin covers most meningeal pathogens in Denmark [48], whereas in countries with high penicillin and cephalosporin resistance, recommended therapy includes the addition of Vancomycin and/or Rifampicin [49].

Treatment regimens: The pharmacokinetic and bacteriological efficacies of penicillin (50mg/Kg), Ceftriaxone (25mg/Kg), Vancomycin (15mg/Kg) and Imipenem (24 mg/Kg) using a penicillin susceptible strain. Both Imipenem and Vancomycin were effective as single dose and continuous infusion as compared to Penicillin and Ceftriaxone [50].

Vancomycin has been evaluated in the therapy of bacterial meningitis caused by penicillin-resistant pneumococci. In a study of 11 adult patients with pneumococcal meningitis caused by strains with intermediate resistance to penicillin, Vancomycin therapy was associated with clinical failure in 4 patients; however, the dosage of Vancomycin used (15 mg/Kg daily) was below standard recommendations. There were no failures in 14 subsequent patients treated with Ceftriaxone in this study [51].

Different anti-microbial regimens were assessed for their therapeutic response in conventional animal model of meningitis caused by penicillin resistant strains. The anti-microbial agents used in the study were Ceftriaxone (125mg/Kg), Cefpirome (100mg/Kg), Vancomycin (20mg/Kg), Meropenem (125mg/Kg), Rifampin (15mg/Kg), Ceftriaxone (125mg/Kg) + Vancomycin (20mg/Kg), Ceftriaxone (125mg/Kg) + Rifampin (15mg/Kg) and Vancomycin (20mg/Kg) + Rifampin (15mg/Kg). Ceftriaxone alone did not produce significant results and thus it was anticipated that Ceftriaxone alone was ineffective for treating resistant strains. The combination of Rifampin showed neither additive effect nor synergism. The synergism of Ceftriaxone + Vancomycin was confirmed in this study. Thus it was conferred that the combination of an extended spectrum cephalosporin and Vancomycin would be appropriate for the initial treatment of pneumococcal meningitis especially for resistant strains [52].

Penicillin resistance to multiple antibiotics is an increasing challenge, the efficacy of Rifampin (5mg/Kg), Ofloxacin (10mg/Kg), Rifampin (5mg/Kg) + Ofloxacin (10mg/Kg), Rifampin (10mg/Kg) + Ofloxacin (40mg/Kg), Ofloxacin (10mg/Kg), Ofloxacin (40mg/Kg) and Ceftriaxone (10mg/Kg) in meningitis due to resistant strains. The results from the study suggested that addition of Rifampin did not improve the bactericidal effect of other antibiotic in the treatment of pneumococcal meningitis. Against pneumococci that are susceptible to β-lactam Rifampin appeared to be considerably less active than Ceftriaxone [53].

The above results were confirmed by *in vitro* studies in which the Minimum inhibitory concentration (MIC) of Penicillin G, Meropenem, Imipenem, Ceftriaxone and Vancomycin was determined. The best killing activity against resistant strains was that of Ceftriaxone + Vancomycin on the other hand Imipenem and Ceftriaxone were less active alone. Changes in β-lactam susceptibility among *S. pneumoniae* isolates have led to recommendation that high dose Ceftriaxone combined with Vancomycin be used to treat meningitis [54].

Broad spectrum cephalosporin especially Cefotaxime and Ceftriaxone are widely used in the treatment of pneumococcal meningitis caused by partially resistant strain, thus high dose of cephalosporin may be administered in combination with Vancomycin.

Clinical failure and delayed sterilization of CSF is reported due to extended spectrum cephalosporin resistance strain. The MIC of Penicillin, Meropenem, Imipenem and Ceftriaxone + Vancomycin was determined. The best killing activity against resistant strains was that of Ceftriaxone + Vancomycin and Imipenem and Ceftriaxone were less active alone. Changes in β-lactam susceptibility among *S. pneumoniae* isolates have led to recommendation that high dose Ceftriaxone combined with Vancomycin be used to treat meningitis [55].

Experimental data indicate that the combination of Vancomycin and Ceftriaxone induces more rapid killing of pneumococci than is achieved by either agent alone [56]. Efficacy study *in vivo* and *in vitro* of Ceftriaxone (100mg/Kg), Vancomycin (15mg/Kg) and Rifampicin (15mg/Kg) alone and in combination against a highly cephalosporin resistant strain was assessed. The study provided an experimental basis for using combination as empirical therapy for pneumococcal meningitis regardless of the degree of cephalosporin resistance. The combination of Ceftriaxone + Vancomycin and Ceftriaxone + Rifampicin was significant when compared to that of Ceftriaxone monotherapy, an additive effect was observed when Ceftriaxone + Vancomycin were used. On the other hand Rifampicin + Vancomycin did not produce noticeable variation in the activity as compared to either drug alone [57].

Once the diagnosis of bacterial meningitis is established by CSF analysis, the combination of Vancomycin and a third generation cephalosporin (Ceftriaxone and Cefotaxime) is the recommended drug combination of choice [58].

The American Academy of Pediatrics Committee on Infectious Diseases recommended that patients with "definite or probable bacterial meningitis" should empirically receive combination therapy with Vancomycin plus either Cefotaxime or Ceftriaxone. The rationale for the inclusion of Vancomycin in initial therapy was based on the known association between delayed CSF sterilization and neurologic sequelae in children with bacterial meningitis [59].

CONCLUSION: Pneumococcal meningitis in human beings is associated with long-term sequelae including sensory-motor deficits, seizures, and impairments of learning and memory. *S. pneumoniae* infections, including pneumococcal meningitis, are therefore likely to remain an important health issue. Acute bacterial meningitis is a medical emergency which warrants early diagnosis and aggressive therapy. Most often therapy for bacterial meningitis has to be started before the etiology is known. The choice of anti-microbial therapy is based on the most common pathogen prevalent in a particular geographical area and age group and their antibiotic susceptibility pattern.

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