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Pathogenesis of Various Bacterial Agents in CSF during Meningitis

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Abstract

The human central nervous system (CNS) infections remain the leading cause of intensified morbidity and mortality rates around the world. Vanquish the barriers that protect the brain from pathogens is a prerequisite to develop meningitis. The commonest pathogens, pneumococcus, meningococcus, *E. coli, H. influenzae* are main causative agents in children and adults; are associated with high morbidity and mortality. Bacteria have evolved a variety of different strategies for breaching the blood–brain barrier (BBB), evade the immune system and enter CNS. For this purpose, they use a variety of different virulence factors, allowing them to adhere to and overcome these barriers. These virulence factors arbitrate adhesion host cell invasion, intracellular survival, host cell signaling and induction of inflammation. The CNS will ultimately be invaded by the bacteria, causing inflammation of meninges, increased permeability of BBB, and pleocytosis in cerebrospinal fluid (CSF) as well as nervous tissue infiltration. Some of these mechanisms are different, but others are shared by some pathogens. Supplementary understanding of these processes, especially, differences between the blood-brain barrier and the blood-cerebrospinal fluid barrier, and Virulence factors used by pathogens are still required.

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Introduction

Various meningeal pathogens have the ability to colonize skin as well as various mucosal surfaces of individuals who are otherwise healthy. In different cases, host cellular barriers are penetrated by the bacteria for initiation of local infection which causes a systemic spread. A relation between high grade bacteraemia and meningitis development has been indicated for some of the bacteria (Moxon & Ostrow, 1977; Rosenstein *et al.*, 2001). This infers that survival of the bacteria in blood is a crucial trait of virulence for meningeal pathogens. Upon surviving in bloodstream or by spreading via infectious foci in surroundings of the brain (sinusitis, mastoiditis), central nervous system (CNS) will ultimately be invaded by the bacteria, causing inflammation of meninges, increased permeability of blood–brain barrier (BBB), pleocytosis in cerebrospinal fluid (CSF) as well as nervous tissue infiltration. Consequent injury of the CNS tissue is resulted by cerebral ischemia, hydrocephalus, apoptotic neuronal injury, increased intracranial pressure and edema (Petersdorf *et al.,* 1962) and is resulted due to toxic products made by the bacteria as well as initiation of host inflammatory pathways for the clearing of infection. Particularly, the uncontrolled inflammatory response exhibited by neutrophils (PMNs) has shown to be linked with elevated injury to the CNS (Koedel *et al.,* 2009). Recently made progress regarding the understanding of interactions between host and pathogen during bacterial meningitis has been summarized in this review, showed by four commonest pathogens, *S. pneumoniae*, Meningococcus, *E. coli, H. influenza* and the very rarely meningitis causing *S. aureus* and *K. pneumoniae*. Common mechanisms as well as steps involved in bacterial meningitis pathogenesis are as follows, Pathogens that cause meningitis are often found colonizing mucosal surfaces as well as exhibit similar patterns for the progression of disease. Hence, it is logical to think that common strategies are followed for advancing from mucosa in bloodstream moving further into brain (Quagliarello & Scheld, 1992). Many bacteria use extracellular matrix proteins for binding, such as laminin, fibronectin or collagen, to mediate primary attachment followed by invasion (Vercellotti *et al.,* 1985). Additionally, some of the bacterial adhesins, like that of *N. meningitidis*, also show binding to carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family members of the molecules for cell adhesion *(Hauck et al.,* 2006), others, such as *E. coli* K1 OmpA, identify particular glycoproteins in lectin-like manner (Prasadarao *et al.,* 1996). Bacterial adhesins binding to particular receptors of host cell might lead towards signal transduction causing tight attachment of bacteria to the host cells or their internalization. One of the common entry mechanism is known as “innate invasion” which counteracts mechanisms of the innate immune system and uses molecular mimicry such as mimicking of chemokine platelet activating factor (PAF) by the Phosphorylcholine (PCho) (Cundell *et al.,* 1995; Gratz *et al.,* 2015). The characteristic feature of different bacteria that infect the CNS is the ability required for their survival in the bloodstream by protecting or all together avoiding phagocytosis such as by capsule expression by *K. pneumoniae* (Wu *et al.,* 2011) or by gaining entry in the macrophages or Polymorphonuclear leukocytes (PMNs) and persisting there as in *E. coli* K1 (Kim *et al.,* 1992). Nonetheless, prolonged bacteraemia sometimes may not be a prerequisite for entrance of the bacteria in the CNS, as meningitis can also be resulted due to direct invasion by infected tissue located in the surrounding. However, there are certain barriers to be breached by the bacteria, like BBB and blood–CSF barrier (B-CSFB), to acquire entrance to brain. They translocate over these barriers through a paracellular or intracellular process that is dependent on virulence traits specific to the pathogen. Cytolytic toxins such as the ones expressed by *E. coli,* GBS, *S. pneumoniae* and *S. suis* can cause damage to the host cells thus causing barrier disruption as well as facilitation of paracellular invasion. Barrier breaching in a transcellular manner has its basis on the intracellular invasion, that often includes bacterial “hijacking” or exploitation of pathways and signal platforms as shown by *N. meningitidis* (Coureuil *et al.,* 2009; Schubert-Unkmeir *et al.,* 2010). After pathogen

reaches brain, bacterial components, or bacteria itself are identified by the immune cells residing there like astrocytes and microglia, which leads them to get activated. Moreover, maven immune cells in the circulation like monocytes/ macrophages and granulocytes are attracted followed by subsequent infiltration of the infected parenchyma of the brain. Particularly in the neonates, the immune response generated as a result might prove overwhelming and disorganized, causing prominent neuronal damage and sometimes even death. If infection is survived by the host, post-infectious sequelae that are specific to the pathogen like blindness, deafness or different kinds of mental retardations might take place (Edwards *et al.,* 1985).

Pathogenesis of streptococcus pneumoniae

S. pneumoniae is a pathogenic gram positive microbe and is a primary causative agent of bacterial meningitis in developing countries (Scarborough & Thwaites, 2008). *Streptococcus Pneumoniae* has huge genetic diversity as a bacterial species and usually carried asymptomatically by infants in their nasopharynx region, these individuals are at an age where strong adaptive immune responses are absent against capsule comprising of polysaccharide which encapsulates majority of the pneumococcal cells (Weintraub, 2003). System invasion is done following colonization in the nasopharyngeal region which allows bloodstream access to the bacteria. Primary cause of meningitis is CNS invasion through the barriers present for the brain (Iovino *et al.,* 2013).

Majority of findings concerning pneumococcal meningitis pathophysiology are derived from the autopsies of the brain that only represents cases where fatality has occurred or otherwise using animal models which objectively have the capability of mimicking clinical features of the disease affecting humans, as closely as possible. The well-known models that are used include rat, mouse, and rabbit. Using the knockout technology has made mouse to be used a model animal for studying responses of the host towards pneumococcus during the meningitis (Paul *et al.,* 2003). Also, by using this model, we have made observations about cortical brain damage (Klein *et al.,* 2006) as well as hippocampal neuronal apoptosis (Mitchell *et al.*, 2004). For studying processes happening in the CSF related to the meningitis such as growth of the bacteria, penetration of the antibiotic as well as immune response components, rabbit has been used as a model animal (Dacey & Sande, 1974; Østergaard *et al.,* 1999).

Nasopharynx colonization by Streptococcus pneumoniae

A prerequisite regarding the bacterial meningitis development is the adherence of the microbe to the nasopharynx as well its colonization. Numerous surface proteins are exhibited by the all the bacterial pathogens responsible for causing meningitis and these proteins provides interaction between pathogen and the host cell. As per an estimate, pneumococci has around 500 surface proteins (Wizemann *et al.,* 2001). Studies conducted previously have reported initial binding of S pneumoniae to the carbohydrates present on cells of epithelium like GalNAc(β1–4)Gal, GalNAc(β1–3)Gal as well to the sialic acid (Andersson *et al.,* 1983; Idänpään-Heikkilä *et al.,* 1997). Phosphorylcholine seems a primary structure of the surface of pneumococci. It has two variants that are chemically distinct, one among them has choline binding proteins (Cbps) attached to it while the other one is free. The most abundant Cbp is Cbp A, which serves as one of the important factors of adherence for *S. pneumoniae*. Absence of this protein in the mutant variants renders them unable to colonize the nasopharyngeal region in the model of an infant rat (Rosenow *et al.,* 1997). Cbp D and E are some other Cbp family members that are thought to play some role in bacterial adherence and Cbp G is supposedly a serine protease that might potentially serve two roles i.e., serving as a virulence factor in the sepsis and as an adherence factor (Gosink *et al.,* 2000). Other pneumococcal proteins like IgAl protease and neuraminidase NanA further support nasopharyngeal colonization. NanA enzymatically results in the cleaving of N-acetylneuraminic acid from oligosaccharides, glycolipids, mucin and glycoproteins that decreases the mucus viscosity to

enhance colonization or through exposure of the receptors present on the surface of pneumococcus cells (Tong *et al.,* 2000). Pneumococcus protein called IgAl protease results in inactivation of the of human IgA thorough cleaving immunoglobulin molecule located at hinge region of the heavy chain, providing pneumococcus with a counter against defenses of the host (Reinholdt & Kilian, 1997).

Invasion of Streptococcus pneumoniae and its dissemination

To result in a CNS infection, entry of the pneumococcus to the respiratory tract following its escape from the mucous defenses is important while translocating either to the blood stream which will result in invasive disease caused by pneumococci or IPD or causing sinusitis or alternatively mastoiditis and locally dispersing through the defects in the skull or through the vessels that penetrate the skull. It uses a whole arsenal of virulence factors to enter into the bloodstream including proteins located on its surface, capsule made up of polysaccharides and its cell wall. The innate invasion mechanism acts against mechanisms for innate immune responses and implements molecular mimicry for the promotion of invasion (Thornton *et al.,* 2010).

Initiation of the innate invasion is carried out by bacterial binding to the epithelial layer of the respiratory tract. Polymeric immunoglobin receptor (pIgR) is bound by choline binding protein A, and absorption of the transcytosis machinery for pIgR can be done by *S pneumoniae* which can aid in the transversion of the mucosal barrier thus translocation of the bacteria is initiated which helps it transverse across epithelium of the nasopharynx (Zhang *et al.,* 2000). Bacteremia of advanced grade then leads towards the promotion of meningitis development by interactions of host at the blood brain barrier (BBB). Binding of the laminin receptor also called LR is done by CbpA at cerebrovascular endothelium (Orihuela *et al.*, 2009). Other than laminin receptors, platelet endothelial cell adhesion molecule-1 (PECAM-1) also called as CD31 as well as NanA domain similar to lectin have been reported to be a contributing factor for the attachment of the pneumococcus to the endothelial cells of the blood brain barrier (Iovino *et al.,* 2014; Uchiyama *et al.,* 2009).

Translocation of Streptococcus pneumoniae into the CNS

Advanced grade bacteremia also known as sustained bacteremia is considered necessary but insufficient for entry of the microbe in the subarachnoid space (Tuomanen, 1996). For the invasion of the meninges, crossing of the physiological barriers located between the CNS and the bloodstream is mandatory by blood borne pathogen. There are two distinct structures separating CNS from the bloodstream: blood-CSF barrier and BBB.

After the attachment of bacteria to the cells of endothelium or epithelium, process of innate invasion again mediates the translocation of the pathogens across barriers. Phosphorylcholine (PCho) is exhibited by almost every respiratory pathogen on its surface and mimicry of PAF chemokine mediates it to bind to receptor for platelet activating factor (PAFr) in humans (Cundell *et al.,* 1995). In cases pertaining to the pneumococcus, addition of phosphorylcholine is done to the teichoic acid of the cell wall and to the lipoteichoic acid in variable phase manner (Cundell *et al.,* 1995). Binding of PCho to PAFr leads towards the bacterial uptake mediated via clathrin into vacuole, thus providing facilitation to the intracellular translocation of the bacteria from bloodstream to the brain (Radin *et al.,* 2005). There are also reports of vitronectin-αvβ3 integrin complex usage by pneumococcus to invade endothelium and epithelium(Bergmann *et al.,* 2009).

Other than opting for uptake by receptor meditated method to enter in the host cells, pneumococcus also acquire access to CNS paracellularly through disruption of the integrity of blood brain barrier. Cytolysin pneumolysin, a cholesterol dependent virulence factor mediates this process (Zysk *et al.,* 2001) as well as α-glycerophosphate oxidase GlpO (Mahdi *et al.,* 2012) by creating H_2O_2 that causes apoptosis of the microvascular endothelium of the

brain. Hyaluronidase may also play its role in meningitis by degrading the components of extracellular matrix (Kostyukova *et al.,* 1995).

Pathogenesis of Streptococcus pneumoniae in the brain (CSF)

Upon gaining access to CNS, pneumococcus gains advantage of limited defense mechanisms of the host in this region and multiplies rapidly inside the CSF. Once it reaches CSF, it becomes more likely that the pathogen will survive as the defenses located in the CSF of the host are not effective against pathogens that have a capsule around them like *S pneumoniae.* Prior to the infection, dominating mechanisms of the host such as, immunoglobulins, polymorphonuclear leucocytes and components of the complement system, are practically absent in cerebrospinal fluid (Simberkoff *et al.,* 1980; Smith *et al.,* 1973; Stahel & Nadal, 1997). Transmigration of the leucocyte in the CSF results due to multiplication of the bacterial and/or release of the components by the bacteria. But leucocytes fail to phagocytize and kill *S. pneumoniae* in CSF. There is a partial understanding of this discrepancy in the functionality. One of them is having insufficient concentrations of the complement for achieving opsonic activity (Simberkoff *et al.,* 1980). Concentrations of other crucial bacterial opsonin, and particular antibodies for the capsule are also found to be lower in normal CSF than a CSF IgG/ blood ratio about 1/800. Even though the concentrations of IgG in CSF observes an increase while bacterial meningitis is present, they correspondingly have concentrations below optimal levels for achieving opsonic activity (Smith *et al.,* 1973). Hence, it can be conceived that CSF is a localized region found in the humans with host immunodeficiency that facilitates pneumococci to proliferate in an unrestrained manner, which if left untreated can lead towards the death of the host. Thus, the CSF can be conceptualised as a localised area of host immunodeficiency facilitating unrestrained proliferation of pneumococci which, if untreated, overwhelms the host until death. While its multiplying, release of the numerous highly immunogenic components is done by pneumococcus which are identified by receptors located on the surface of cells responsible for the presentation of the antigen that are found in lower quantity in cerebrospinal fluid. These receptors are called as pattern recognition receptors or PRRs. Recognition of these components released by the pathogen via the immune system creates a strong inflammatory response that leads to impairment of the blood brain barrier due to occlusion of the vessels, leukocyte recruitment, vasculitis, and vascular deregulation that results in aggravated intracranial pressure. Exhilaratingly, inflammation present in CNS remains detectable when there is sustained bacteremia even before the crossing of BBB by the bacteria (Iovino *et al.,* 2013).

Intracisternal inoculation of the bacterial cell wall components in the animals are enough to trigger the whole complex of symptoms associated with meningitis, even when the live bacteria is completely absent (Tuomanen *et al.,* 1985). It is an important observation in clinical settings since lysis of the bacteria resulted by treatment through the antibiotics causes explosive release due to the cell wall rupturing which in turn causes elevated responses from the host, adding to the severity of the disease (Nau & Brück, 2002).

Pattern recognition receptors

Pneumococcal meningitis triggers a wide range of pathways of PRR which have an influence on not just the outcomes by anti-bacterial responses from the host but also by associated CNS function disruption. The primary PRRs which are responsible for detecting pneumococcus in central nervous system are the members which belong to Toll-like receptors family that includes TLR4, TLR9 and TLR2, and are located on the glial cells (Vijay, 2018) as well as NOD2 belonging to NOD like receptors family also called as NLRs (Mook-Kanamori *et al.,* 2011). Cell wall of pneumococcus is recognized by TLR2 along with lipoteichoic acid and lipoproteins, while TLR9 is responsible for sensing DNA of bacteria which releases during the autolysis and detection of pneumolysin is carried out by TLR4 (Koppe *et al.,*

2012). Additionally, intracellular NOD2 recognize muramyl peptides from the peptidoglycan of the pneumococcus (Liu *et al.,* 2010) and binding of PAFr to the teichoic acids bearing PCho takes place (Cundell *et al.*, 1995). Recognition of the pneumococcus mediated by the inflammasome also plays its role in the innate immune response of the host. NALP3, the component of inflammasome has been described for playing a crucial role in that process (Hoegen *et al.,* 2011).

Infiltration of leukocyte and the Cytokine Storm

Following the activation of the microglial cells mediated by the PRRs, proinflammatory responses related to the pneumococcal meningitis is driven by infiltration of the leukocytes initiated by glia. Inflammatory response engagement results in activation of numerous signaling cascades causing pro-inflammatory mediator production which orchestrates an effective immune response. Patients affected with pneumococcal meningitis demonstrate in their CSF elevated levels of pro-inflammatory cytokines such as interleukin-1β, interferon- γ, tumor necrosis factor- α, interleukin 2, 6 and 12, as well as some anti-inflammatory cytokines such as interleukin-10 including tumor growth factor- β and some chemokines like CCL2, CCL3, and CXCL8 (Coutinho *et al.,* 2013). A characteristic of PM is chemokines being upregulated in CNS and these secreted chemokines work together with additional chemoattractants such as ROS, reactive nitrogen specie and PAF and also with complement system and results in attraction of highly active PMNs towards the brain. These PMNs cross the blood brain barrier by the tightly knit junctions of the endothelium forming the barrier in a process involving multiple steps that includes selectins and integrins, leading towards the pleocytosis of CSF *(Mook-Kanamori et al.,* 2011).

The existence of leukocytes inside CNS contributes further towards the establishment of cytokine environment by the residing CNS cells, leading towards the formation of "cytokine storm". Levels of archetypal inflammatory cytokines including tumor necrosis factor, interleukins-1β, interleukin-6 and interferon-γ remains constantly noticeable in clinical pneumococcus meningitis (Barichello *et al.,* 2010; Mook-Kanamori *et al.,* 2012; Yau *et al.,* 2016) and has correlation with mortality of meningitis (Grandgirard *et al.,* 2013).

Matrix metalloproteinases

Activated leukocytes secrete matrix metalloproteinases or MMPs, which are endopeptidases that are dependent on zinc (Könnecke & Bechmann, 2013) and are thought to be specifically damaging the blood brain barrier during meningitis. MMPs cause degradation of extracellular matrix (Leib *et al.,* 2000) while increase in the concentrations of MMP9 and MMP8 has been observed in CSF of patients present with meningitis (Leppert *et al.,* 2000), whereas MMP9 is associated with dysfunction of the blood brain barrier as well as with neuronal apoptosis (Grandgirard *et al.,* 2013; Liechti *et al.,* 2014).

Disruption of blood brain barrier as a result of pathogenesis of S. pneumoniae

By evading the physiological and immunological barriers of the host, pneumococcus gain access to the CNS and triggers various inflammatory response cascades while recruiting cells of the immune system to this site. This process causes the blood brain barrier to become permeable allowing *S. pneumoniae* as well as leukocytes to additionally augment the immune response of the host through numerous positive feedback loops. During the general *S. pneumoniae* pathogenesis in CSF, dysregulation of the immune responses can take place in many cases of pneumococcal meningitis, contributing to a wide range of neurological complications which can cause disabilities for a life time, such as disorders associated with behaviors, impairments in the cognitive abilities, and hearing arrears (Klein *et al.,* 2017).

The pathogenesis of *S. pneumoniae* is driven by the pathological proportion of inflammatory cytokines exposure which might also play role in cellular genetic modifications that are irreversible via epigenetic

processes, hence serving as a contributing factor for the altered functions of neurological behavior (Roth, 2013).

Pathogenesis of Neisseria meningitidis

Meningococcal sepsis as well as meningococcal meningitis both are devastating diseases that affects people with a varying incidence ranging from 0.5 cases per 100 000 to 1000 cases per 100 000, that is dependent on epidemiological area. A gram-negative bacteria called *Neisseria Meningitidis* is the etiological agent which is also an obligate pathogen affecting humans. Nasopharyngeal cavity is colonized by meningococcus and 10% people carry this asymptomatically at any period in time (Caugant & Maiden, 2009).

A prerequisite required for meningitis development is interaction between the endothelial cells of the human body which form lining of the blood vessels of blood-cerebrospinal fluid barrier (B-CSFB) and *N. meningitidis*.

Invasion and dissemination of N. meningitidis

Binding of the bacteria to the endothelial cells of the brain is rudimentary for bacteria to successfully enter the CSF. Huge colonies of *N. meningitidis* have reportedly been located in parenchyma, subarachnoid space capillaries as well as in choroid plexus in histological samples of the brain sections during postmortem (Pron *et al.,* 1997). To bind to the host cells, *N. meningitidis* carries is dependent on numerous determinants which play their roles in making these interactions possible and include a type IV pili, two proteins located on the outer membrane called Opc and Opa, as well as various newly reported minor adhesion proteins or adhesion like proteins like autotransporter meningococcal serine protease A (MspA) or adhesin complex protein (ACP) (Virji, 2009).

Type IV pili or Tfp are exhibited by various gram-negative bacteria and are polymeric filaments. They facilitate in establishing the primary contact of *N. meningitidis* to the surface of eukaryotic cells and play their role in aggregation of the bacteria, migration of the bacteria, natural bacterial transformation and twitching motility of the bacteria (Carbonnelle *et al.,* 2006). These proteins are multimeric, where pilin E acts as pilus scaffold spanning both the inner membrane and the outer membrane extruding through pore, which PilQ forms (Pelicic, 2008). There is the requirement of more than 20 proteins so that a functional and correctly assembled Type IV pilus can be made (Brown *et al.,* 2010). Both PilV and PilE play their role in adhering to the host cells are have been recently observed to result in the activation of β2-adrenergic receptor (β2-AR), that promotes signaling events of endothelial cells which in turn enables translocation of *Neisseria* through endothelium of the brain (Coureuil *et al.,* 2014; Lécuyer *et al.*, 2012).

Significant efforts for the determination of Tfp binding receptors on the eukaryotic cells have been made. Membrane co-factor protein or CD46 has been proposed as the Tfp receptor by the host cell (Källström *et al.,* 1997), but there are controversies surrounding the role played by CD46 as being the host cell receptor. Moreover, PAFr or platelet activating factor has been defined as pilus receptor that is targeted on the epithelial cells of the airway (Jen *et al.,* 2013). Bernard *et al.* (2014) demonstrated in their study that CD147 that is one of the members of immunoglobulin family is used by *N. meningitidis* for adhering to the endothelial cells in a Tfp dependent manner as well as showed the primary role played by CD147 for meningococcal vascular colonization. Facilitated adhesion by Tfp to the CD147 have been depicted to be involving minor pilin PilV and PilE both.

Curiously, both of these pilins reportedly lead towards the activation of G protein-coupled β2-adrenergic receptor (β2-AR) which plays the role of signaling receptor primarily (Coureuil *et al.,* 2010). As a response to adhesion of the bacteria and microcolonies formation of meningococcus, recruitment of β2-AR is done to endothelial cell apical surface underneath microcolonies. Interaction

between extracellular N-terminal domain of β2-AR with PilV and PilE is highly likely to modify the receptor conformation which results in activation of signaling pathways facilitated by β-arrestin (Coureuil *et al.,* 2010). Nevertheless, signal transduction mediated by G protein is not induced by β2-AR activation that is elicited by *N. meningitidis*. β-arrestin pathway is given biasness when meningococci activate the receptor. Non-receptor kinase (RTK) c-Src that causes phosphorylation of cortactin and ezrin are recruited by the trapped β-arrestin. Furthermore, β-arrestin-interacting proteins accumulation is carried out by β-arrestin like p120-catenin as well as VE-cadherin allegedly called 'cortical plaques' under the bacterial microcolonies. The accumulation of these proteins has been demonstrated to cause intercellular junctions to deplete.

Proteins of the outer membrane makes up opacity associated proteins Opa and Opc. Though a polysaccharide capsule partially masks the proteins of the outer membrane, their role in adhesion as well as invasion into the eukaryotic cells is efficient (Bradley *et al*., 2005). Majority of the Opa proteins have been found to bind with carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family members of humans located on epithelial cells (Sadarangani *et al.,* 2011). Other than that, binding of some Opa proteins with the heparan sulfate proteoglycans (HSPG) and to the integrins through proteins found in extracellular matrix fibronectin and vitronectin or through the saccharides has been demonstrated (Van Putten & Paul, 1995).

The Opc protein of the outer membrane is specially implicated in the invasion of the host endothelial cells, as well as with endothelial cells of the brain (Virji, 2009). Opc, a beta barrel protein has five surface loops that has antigenic stability and a single gene called opcA encodes it (Sarkari *et al.,* 1994). Numerous virulent lineages of *N. meningitidis* express Opc while specific epidemic clones such as ET-37/ST-11 clonal complex as well as some random endemic isolates have reported it to be absent (Sarkari *et al.,* 1994).

Binding of Opc proteins with the extracellular matrix components as well as with serum proteins like fibronectin and vitronectin is direct (Sa E Cunha *et al.,* 2010; Unkmeir *et al.,* 2002). Additionally, via heparin, there may be indirect binding of Opc with vitronectin and fibronectin. Bacterial adhesins after binding with vitronectin and fibronectin can target proteoglycans as well. Tight association of Opc with vitronectin or fibronectin or both facilitates meningococcal binding to the cognate receptor called endothelial αVβ3 integrin (Sa E Cunha *et al.,* 2010) or/and α5β1-integrin (fibronectin receptor) (Unkmeir *et al.,* 2002) on to the brain vessel cells.

Furthermore, Opc protein of meningococci grants tight association of fibronectin and vitronectin with the bacteria facilitating binding with endothelial integrins. This interaction causes non- receptor tyrosine kinases such as focal adhesion kinase (FAK) and Proto-oncogene tyrosine-protein kinase c-Src as well as receptor tyrosine kinases (ErbB2) activation, which in turn causes phosphorylation and causes cytoskeletal rearrangement and cortactin to activate.
Even though pili Opa and Opc represent most crucial and extensively studied meningococcus adhesins, there are descriptions of various other adhesins like NhhA (Neisseria homologue of hsf/hia) which is a trimeric autotransporter that shares homology with Hsf and Hia *Haemophilus influenzae* adhesins that binds with proteins of extracellular matrix laminin and heparan sulfate and aids in providing attachment to the cells of the host (Scarselli *et al.,* 2006; Sjölinder *et al.,* 2008) App protein (adhesion and penetration protein) that shares homology with the Haemophilus Hap (Hadi *et al.,* 2001; Serruto *et al.,* 2003) and as well as NadA (Neisseria adhesin A), a trimeric autotransporter that belongs to Oca family (oligomeric coiled-coil adhesins) (Comanducci *et al.,* 2002). Stable trimers are formed by NadA on the surface of the bacteria that facilitates in binding with epithelial cells by interacting with protein receptor molecule distinctively expressed by different epithelial cells lines (Capecchi *et al.,* 2005).

The presence of multiple adhesins in meningococci with various receptor specificnesses indicates that they can possibly cooperatively interact with various receptors on the same cell under target or might act along the different stages of the infection, facilitating adhesion of Neisseria to the different types of the cell at their different sites.

Tight interactions between invasins and adhesins of the bacteria to the receptors of endothelial cells of the brain as well as subsequent uptake of induction supports the transcellular pathway strategy for traversing meningococcus across tight B-CSFB. Opening of these tight junctions is a requirement for paracellular pathway. Recently published data have shed a light on mechanisms facilitating paracellular route for the translocation of *N. meningitidis* in the central nervous system (Coureuil *et al.,* 2009; Schubert-Unkmeir *et al.,* 2010). Local elongation of cells is induced by *N. meningitidis* when they adhere to the endothelial cells that resembles structures of epithelial microvilli (Eugène *et al.,* 2002). Bacteria gets surrounded by these structures resembling microvilli and their internalization inside the vacuole is initiated (Eugène *et al.,* 2002). They increase the surface area of the cell which facilitates adhesion of the bacteria while also contributing in resisting against the shear stresses imparted by bloodstream (Mairey *et al.,* 2006). These protrusions have high amounts of moesin and ezrin which belong to ezrin–radixin–moesin (ERM) family of proteins, as well as some transmembrane proteins such as CD44, ICAM-1, and ICAM-2 (Eugène *et al.*, 2002). Adapter proteins and recruited integral membrane proteins along with actin cytoskeleton give rise to particular molecular complexes called as cortical plaques. As a matter of interest, cortical plaque formation leads to the localized replacement of proteins at intercellular junctions. Particularly, recruitment of PAR3/PAR6/αPKC proteins polarity complex at site of adhesion for meningococci (Coureuil *et al.,* 2009) with cell to cell interface depletion and intercellular junction opening of brain-endothelial interface. Mislocated adherence junction formation might lead towards a paracellular route to open up for the transversal of *N. meningitidis* into CNS (Coureuil *et al.,* 2009). Further alteration of proteins for cellular junction in vitro has depicted for occludin, which is a protein of tight junction, by using HBMEC cell line as performed in in vitro model. Long time infection caused occludin to be proteolytically cleaved by matrix-metalloproteinase MMP-8. Disappearance of occludin from cell periphery consequently results and causes it to be cleaved into 50-kDA protein of smaller size in the infected cells causing detachment of the endothelial cells and elevated paracellular permeability (Schubert-Unkmeir *et al.,* 2010).

Studies conducted in the previous years demonstrated cell membrane lipids to have a non-random but rather organized distribution. The most prevalent sphingolipid is sphingomyelin, which is localized predominantly in anti-cytoplasmatic leaflet of the cell membranes as well as intracellular vesicles. The structure comprises of extremely hydrophobic ceramide moiety as well as headgroup having hydrophilic phosphorylcholine. Sphingomyelin hydrolysis causes the ceramide release that leads towards biophysical properties of membrane to be altered. There is spontaneous interaction between ceramide molecules that leads to the formation of domains that are enriched in ceramide and because of biophysical properties they have, membranes enriched in these ceramide domains then fuse together and result in the formation extended platforms spanning from few hundred nanometers to many micrometers. Other than causing alteration in the rigidity and fluidity of the membrane, platforms enriched with ceramide play their role in sorting and eventually concentrating membrane receptors as well as components of membrane proximal signalling, thus causing signal transduction as well as cellular responses to be amplified. Platforms enriched in ceramide have been implied in internalization of various bacteria (Grassmé & Becker, 2013).

The recent studies has revealed the capability of *N. meningitidis* in activating acid sphingomyelinase (ASM) in micro vessels of the brain therefore causing formation of ceramide as well as generation of

platforms enriched with ceramide (Simonis *et al.,* 2014). Mechanistically speaking, activation of ASM is dependent on *N. meningitidis* binding to HSPG, its attachment receptor, accompanied by phosphatidylcholine-specific phospholipase activation. The data acquired suggests ceramide system/ASM activation by *N. meningitidis* species concluding their invasiveness into the endothelial cells of the brain.

Activation of immune system and inflammatory response generated by N. meningitidis in the brain

Activation of cytokines is one of the crucial events meningococcal disease pathogenesis (Waage *et al.,* 1989). Compartmentalization of acute inflammatory response is inside subarachnoid space and release of IL-6, G-CSF, MIP-α, tumor necrosis factor α (TNF-α), IL-1β, MCP-1 and IL-8 is their characterizing feature (Waage *et al.,* 1989). Intriguingly, on the basis of the experiments conducted on meningioma cells, induction of high levels of cytokine is carried out by the *N. meningitidis* compared to similar number of the E. coli K1, S. pneumoniae or influenzae (Humphries *et al.,* 2005). The main inflammatory modulin created by *N. meningitidis* is LPS but numerous studies have demonstrated some non-LPS to be also a contributing factor for secretion of the cytokines (Humphries *et al.,* 2005; Sprong *et al.,* 2004; Sprong *et al.,* 2001; van der Ley & Steeghs, 2003). Alteration in meninges vasculature is resulted due to the cytokines release, and upregulation of various adhesins on endothelial cells is also altered that includes intercellular adhesion molecules (ICAMs), vascular endothelial adhesion molecules (VECAMs) and selectins (Dixon, 2000; Drevets & Leenen, 2000). IL-8 attract leukocytes in circulation, mainly neutrophils, which pass between activated endothelial cells and enter subarachnoid space. At the same time, immunoglobulins, complement factors, and proteins (usually albumin) leak in the CSF. Production of IL-1β and TNF-α happens at a really earlier stage which in fifty percent of admitted patients can be detected in its bioactive form. IL-8, MIP-α, IL-6 and MCP-1 are continually released for longer periods of time or their upregulation takes place and their detection can be done in larger number of patients while they are admitted in the hospital (Dixon, 2000).

Pathogenesis of Haemophilus influenzae

Pfeiffer in 1892 first described *Haemophilus influenzae* bacteria, which stains negatively during gram staining (Pfeiffer, 1892). It is ubiquitous in nature and being distinct to humans, was first considered as being etiologic agent behind "influenza". But isolation of *H. influenzae* was not consistent via the autopsy of patient's lungs who died in 1918 during influenza pandemic. The confusion surrounding the relationship between *H. influenzae* prevalence and illness of humans was mitigated by Pittman who discovered that strains of the bacterium can be separated into two distinct groups i.e., strains that are nonencapsulated (nontypeable) and strains that are encapsulated (typeable) (Pittman, 1931). Pittman additionally determined six encapsulated types of *H. influenzae* and named them from a to f by their capsular polysaccharide serological specificities (Pittman, 1931).

Primarily type b (Hib) strains result in serious invasive illnesses such as septicemia and meningitis including pneumonia, cellulitis, empyema, epiglottitis, and septic arthritis (Alexander, 1965; Turk & May, 1967).

In USA, *Haemophilus influenzae* type b (Hib) strain causes nearly 10, 000 cases annually of meningitis in the children aged younger than 5 years as well as infants. Even though the disease proves fatal in only around 5% cases, permanent neurological sequelae is reported in nearly half or more than half of the survivors, these include severe deficiencies in behavior and learning, cerebral palsy or deafness (Peltola, 2000). Investigation of *H. influenzae pathogenesis* has been done using animal models, by case studies and in vitro infection models. *H. influenzae* investigation has been paragoned to understand bacterial meningitis pathogenesis generally. A number of different stages during invasion of Haemophilus have been identified.

Colonization of nasopharynx by H. influenzae

Upper respiratory tract is the place of *H. influenzae acquisition*. Practically every child carries *H. influenzae* in their nasopharynx reaching 3 months in age but larger number of these bacteria do not have a capsule with only 5% of them being type b (Smith *et al.,* 1985).

For the nasopharyngeal colonization of Hib, adherence of the bacteria to the nasopharyngeal cells in mandatory. In animal model experimentations, observation of colonization has been made after Hib inoculation (Moxon *et al.,* 1974).

H. influenzae strains expresses around 10 to 20 OMPs (Murphy *et al.,* 1983) that range from 16-kDa to 98-kDa in size. Different strains express different combinations of proteins (Loeb *et al.,* 1981). P2 porin protein is the OMP of Hib that is found in the highest quantity (Coulton & Wan, 1983; Loeb *et al.,* 1981). Cope along with his colleagues reported in their study the contribution of P2 in Hib virulence as virulent strain of Hib isogenic mutant, unable to produce P2, was reportedly avirulent in infant rat (Cope *et al.,* 1990). Interaction of this protein is with LPS (Gulig & Hansen, 1985). P5 protein is thought to play role in mucosal epithelium invasion (Chanyangam *et al.,* 1991).

Pili apparently facilitate in the adherence of the bacteria to the mucosal surfaces thus facilitating colonization of the respiratory tract. Anderson along with co-workers noted piliated *H. influenzae* exhibiting solider adherence to the buccal epithelial cells as well as noted them to be more efficient in rat colonization after intranasal inoculation compared to the nonpiliated variants (Anderson *et al.,* 1985). Moreover, stimulation of phagocytosis with neutrophils that is dependent on enhanced opsonization has been noted in piliated *H. influenzae* (Tosi *et al.,* 1985). Apparently, pili expression is of importance in colonization stage during pathogenesis but during systemic stages, its rather detrimental. Pili expressions in *H. influenzae* variable by the phases, as in different other organisms (Krogfelt, 1991). Single pilin locus copy consisting of hifA to hifE has been identified in majority of the Haemophilus strains that have been studies so far (Fleischmann *et al.,* 1995).

IgAl proteases of Haemophilus are serine type enzymatic molecules which are made as 169-kDa proteins (Klauser *et al.,* 1993; Pohlner *et al.,* 1987). IgA1 protease activity in the inactivation and cleaving of human IgA1, a secretory antibody predominantly located in upper respiratory tract (Kilian *et al.,* 1996) is thought to provide facilitation in the colonization (Plaut, 1983). Particularly one out of the four peptide bonds are cleaved by IgA1 protease which are found inside the limited α chain hinge region sequences of amino acids of the human IgA1 as well as its secretory form (S-IgAl). As a result, antibody molecules become intact fragments of Fab where Fc portion is missing, which is predominantly responsible for shielding properties presented by particularly this immune factor (Kilian *et al.,* 1988). After cleaving, IgA1 protease C-terminal domain with a molecular mass of 50-kDa rests in outer membrane of the bacteria whereas N terminus that is proteolytically active, is secreted. Two IgA1 classes of *H. influenzae* on the basis of them cleaving at the prolyl-seryl (designated type 1) or on a site four amino acids away at a prolylthreoryl bond (type 2) have been described (Bricker *et al.,* 1985; Bricker *et al.,* 1983; Grundy *et al.,* 1990).

A virulence factor implied in *H. influenzae* pathogenesis and colonization are appendages made up of proteins called as fimbriae. Four different families of fimbriae have been identified, but long thick hemagglutination (HA)-positive (LKP) family of the fimbriae have been observed to provide facilitation adhering to the human mucosal cells (Brinton Jr *et al.,* 1989). Furthermore, fimbriae of this type grants mucosal binding (Read *et al.,* 1991) causing human erythrocytes agglutination through AnWj blood group antigen (van Alphen *et al.,* 1986). Lactosylceramide eukaryotic receptor containing sialic acid is involved in adherence to the epithelial cells (van Alphen *et al.,* 1991).

Type b polysaccharide capsule is the most significant *H. influenzae* virulence factor. Considering the description of Pittman of six capsular serotypes of *H. influenzae* given in 1931(Pittman, 1931), that are designated as types a, b, c, d, e, and f, recognition of strains belonging to type b was done as being the commonest causative agent behind invasive diseases, particularly in the children (Dajani *et al.,* 1979; Fraser, 1982; Turk, 1982). A wide variety of epidemiological and experimental data validates the type b virulence strains. Capsule of type b strains comprises of ribitol phosphate and ribosyl repeating units is an antiphagocytic (Moxon, 1997; Ward & Zangwill, 1998).

Translocation of H. influenzae into the CNS and associated pathology

Akin to the other pathogens described before, it is crucial for the *H. influenzae* to cross upper respiratory tract epithelial barrier and after survival following its dissemination in the blood stream, it crosses the brain barriers and enter into the CNS (Doran *et al.,* 2013). Traversing both BCSFB and BBB has been showed for *H. influenzae*(Al-Obaidi & Desa, 2018; Häuser *et al.,* 2018).

Strategy of *H. influenzae* for entering in endothelial cells is similar to that of *N. meningitidis* and *S. pneumoniae*, involving binding to PAFR which is facilitated by phosphorylcholine (ChoP) (Cundell *et al.,* 1995; Swords *et al.,* 2001). Due to this interaction pathogens gain entry in the BBB by β-arrestin facilitated uptake activation (Radin *et al.,* 2005). PAFR binding by lipooligosaccharide (LOS) glycoforms that contains phosphorylcholine has also been shown during the invasion. Host cell signaling activation is resulted due to this binding as coupling of protein complexes, pertussis toxin sensitive (PTX) heterotrimeric G happens, and pathogen invades. Additionally, this mechanism was indicated to be more effective compared to micropinocytosis (Swords *et al.,* 2001). Binding to the receptor of laminin, is another mechanism shared by these pathogens, is started by OmpP2, that facilitates brain endothelium interaction by *H. influenzae* (Orihuela *et al.,* 2009).

In BCSFB in vitro model, adherence, and invasion of HIBCPP cells was shown by Hib along with Hib clinical isolates as well as *H. influenzae* serotype f (Hif) acting as intracellular bacterial pathogens. Attenuated invasion were due to capsule and fimbriae (Häuser *et al.,* 2018). Also, in a study that used a co-culture of pericytes and HBMECs and *H. influenzae* serotype a (Hia) noted stimulated A2B and A2A adenosine receptors activation following an infection. That resulted in Vascular Endothelial Growth Factor (VEGF) released by pericytes causing detachment of pericytes as well as proliferation of endothelial cell leading to overall impairment of BBB (Caporarello *et al.,* 2018).

Using rat meningitis models, increase in the permeability of BBB dependent on dose was noted following Hib LPS inoculation (Wispelwey *et al.,* 1988). Studies conducted later on demonstrated increase in the BBB permeability in the rats following outer membrane vesicles (OMV) inoculation of *H. influenzae*, proposing the role of these vesicles during meningitis in Hib LPS transportation to CSF (Wispelwey *et al.,* 1989). Moreover, a cytoskeletal protein called zyxin was noted to be implied in TJs protection in BBB, is crucial for BBB integrity and consequently for providing protection against a pathogenic invasion by different pathogens like *H. influenzae* (Parisi & Martinez, 2014). Generally, determination of inflammatory response exhibited by patients while being infected with *H. influenzae* is by numerous virulence factors such as adhesion proteins, outer membrane proteins, capsule and pili along with IgA1 protease and LPS (Kostyanev & Sechanova, 2012).

Pathogenesis of E. coli

Most commonly found gram-negative bacteria is *Escherichia coli* which causes meningitis, especially in neonatal period. Majority of cases of meningitis caused by *Escherichia coli* happen due to hematogenous spread (Dietzman *et al.,* 1974; Kim *et al.,* 1992) but there is lack of understanding as to how *Escherichia coli* circulation transverses BBB. Considering *Escherichia coli* has a plethora of serotypes, it is a surprising finding that stains of *E.*

coli having K1 capsular polysaccharide are found predominantly (nearly 80%) than the other strains isolated from the *E. coli* meningitis in neonates (Gross *et al.,* 1983; Korhonen *et al.,* 1985; Ropes, 1958), and majority of the K1 isolated are linked to a limited to O serotypes such as O16, O45, O7, O1, O18 (Bonacorsi *et al.,* 2003; Kim *et al.,* 1992; Kim *et al.,* 1988; Sarff *et al.,* 1975). Even though rate of the mortality has seen a 30% drop from 1970 to 20% nowadays, the rate of morbidity remains unchanged even following the introduction of efficient antibiotics as well as supportive care (Furyk *et al.,* 2011). The number of *E. coli* strains resistant to the antibiotics is at a constant rise which has made the situation alarming. A staggering 30% to 58% of the survivors encumber significant neurological complications like loss of hearing, cortical blindness, and mental retardation (Furyk *et al.,* 2011).

Even though the bacteria are removed from circulation by the use of antibiotics, endotoxins released in larger quantities from the lysed bacteria sets in motion huge inflammatory responses that cause septic shock. Using corticosteroids for the reduction of these inflammatory responses proves inefficient in relieving neurological deficits linked with the disease. Thus, there is a dire need of understating the pathogenesis behind *E. coli* meningitis comprehensively so that advanced therapeutic strategies can be developed.

Among *E. coli* strains decorated with K1-CPS, sialic acid residue polymer is predominantly responsible for neonatal meningitis (Kim *et al.,* 1992). Other than K1 CPS, there are several other surface structures exhibited by *E. coli* like lipopolysaccharide, pili as well as proteins of the outer membrane which has potential interactions with the tissues of the host while meningitis is being established. OmpA or outer membrane protein A is a structurally conserved and the primary *E. coli* protein (Pautsch & Schulz, 2000). But, studies conducted recently demonstrated pathogenic *E. coli* exhibiting minor distinctions in extracellular OmpA loops in comparison to the strains that are non-pathogenic (Smith *et al.,* 2007). Numerous studies demonstrate OmpA to be playing a crucial role in pathogenesis of different diseases (Krishnan & Prasadarao, 2012).

For the purpose of gaining as insight into pathophysiology of diseases caused by bacteria, it is required that animal models be carefully selected and used. Use of newborn mouse and rat models is done routinely for studying *E. coli* pathogenesis. These models share similarities with human disease as in both of them infection is dependent on the age and the disease is resulted due to hematogenous spread. Mouse and rat brain pathology is the same as infected humans exhibiting neutrophil infiltration, meningeal damage, edema and neuronal apoptosis (Mittal *et al.,* 2010). Thus, studies noted here are based on in vitro experimentations or are relevant in terms of being based on newborn mouse and rat models.

Pathogens that cause meningitis cross the BBB paracellularly, transcellularly or by infected phagocytic cells also known as Trojan horse" mechanism or by all of these means (Kim, 2001; Kim, 2002; Kim, 2003; Kim, 2008; Kim, 2014).

Invasion of E. coli and its dissemination

Mucosal colonization by *E. coli* takes place that is followed up by invasion of the epithelial surfaces as well as crossing which is a crucial step following which it eventually spreads to the intravascular space. *E. coli* express Hek protein that facilitates adherence to the epithelial cells as well as their invasion by heparin sulfate glycosaminoglycans binding (Fagan *et al.,* 2008). Successfully invading the mucosal surfaces permits the *E. coli* to propagate through hematogenous spread. During this stage the bacteria has to avoid initial bactericidal activity of the serum. Bacterial opsonization takes place as a result of complete activation that leads to the membrane attack complex formation or surface of the pathogen that facilitates bacteriolysis. Opsonization of bacteria with the complement proteins makes presentation of bacteria to the immune cells of the host for the purpose of phagocytosis. *E. coli* K1 CPS has been demonstrated crucial for the bacterial survival in

blood (Kim *et al.,* 1992). Similar studies based on *E. coli* OmpA further revealed OmpA absence of OmpA leaves the bacteria to be sensitive to serum (Prasadarao *et al.,* 2002). The classical complement pathway facilitates the bactericidal serum activity against *E. coli* OmpA. Studies following up demonstrated *E. coli* OmpA to be binding to the C4-binding protein (C4 bp) that is a regulator for classical complement pathway for blockage of complement cascade reaction hence bacteriolysis is avoided as well as immune cell recognition (Prasadarao *et al.*, 2002). C4 bp bound with OmpA allows it to act as Factor I co-factor that cleaves both C4b and C3b, that are crucial to the presentation of bacteria to the phagocytes (Wooster *et al.,* 2006).

E. coli survival in the PMNs is apparently the primary step in the pathogenic procedure as depletion of PMN inhibits meningitis onset in the newly born mice (Mittal & Prasadarao, 2011). OmpA expression is crucial for the survival of the bacteria inside the PMNs following their phagocytosis as *E. coli* having no OmpA did not survive. *E. coli* OmpA phagocytosis by the PMNs creates a huge amount of reactive oxygen species also called ROS (Shanmuganathan *et al.,* 2014). Compared to that *E. coli* having OmpA suppress the ROS release even while external stimuli like LPS are present suggesting that PMN machinery is overridden by *E. coli* so that antimicrobial activity can be prevented. Absence of several other factors responsible for virulence like type-1 fimbriae, S-fimbriae, CNF-1 and, IbeA bear no effect in suppressing production of ROS. Gp91Phox, rac1 and rac2 are NADPH oxidase components which is a complex of enzyme needed for ROS production, K1 *E. coli* suppresses these at the level of transcription in PMNs (Mittal *et al.,* 2011).

Analysis of different receptors present on the surface like TLRs, complement receptors and Fc-gamma receptors on PMNs following the *E. coli* infection showed increased expression of gp96 by the bacteria, which is a β-form of Hsp90 but other structures on the surface showed no effect (Mittal *et al.,* 2011). Again, interaction of gp96 with the *E. coli* OmpA happens that bacteria can enter as well as survive in the PMNs, while on the other hand, gp96 expression being absent, bacteria that were phagocytosed where effectively killed. Furthermore, *E. coli* entry facilitated by the interaction of gp96 with OmpA which is needed for causing ROS levels to reduce. Corroborating the role played by gp96 in meningitis induced by *E. coli*, suppressing gp96 by in vivo single stranded RNA in mice that were three days old, made them resistant to the infection as well as preventing damage to the brain. Mice having gp96 knocked out failed to develop level of bacteremia needed for crossing the BBB, indicating survival of *E. coli* in the PMNs to be a crucial stage amidst the primary phases of the infection.

PMNs have a short life which die by apoptosis predominantly, there must be alternative routes used by *E. coli* for their survival followed by their multiplication in the neonates so that a high-grade bacteremia can be reached. Phagocytosis assay by primary macrophages and RAW 264.7 demonstrated entry, survival and multiplication of the *E. coli* happening in the cells, while *E. coli* lacking OmpA were immediately killed by the cells (Sukumaran *et al.,* 2003). Notably, newborn mice having depleted levels of macrophage turned resistant to infection of the *E. coli* even after PMNs being present, indicating macrophages to be also providing a niche for the multiplication of the bacteria. *E. coli* OmpA binds with Fc-gamma receptor I (CD64) alpha chain in the macrophages, that is a IgG binding receptor having high affinity through N-glycosylation sites (Krishnan *et al.,* 2014).

Immune cells having an infection are killed by the apoptosis serves as a limiting factor for the intracellular pathogen dissemination hence preventing bacterial spread in host. Nonetheless, numerous strategies are developed by the pathogens for the manipulation of apoptotic mechanism inside the macrophages. A strategy used by the *E. coli* against apoptotic mechanism in the macrophages was increasing Bcl-XL expression which is an anti-apoptotic protein (Sukumaran *et al.,* 2004). Whereas

E. coli absent with OmpA, caused enhancement of Caspase 6 and Bax expression in macrophages with infection, that eventually have to go through apoptosis. Infection of monocytes by *E. coli* does not only allow the survival of bacteria but also prevents various chemokines as well as cytokines by the cells from being produced (Selvaraj & Prasadarao, 2005). IκB degradation following NF-κB activity inhibition causes the pro-inflammatory cytokines blocking effect by the *E. coli*. Moreover, p38 MAP kinases and ERK1/2 are controlled by *E. coli* by the modulation of their phosphorylation status hence IκB degradation is regulated. Keeping that in mind, three-day-old mice infection resulted in triggering Il-10 production at the early infection stage, pointing that pro-inflammatory response suppression in the stage of replication serves an advantage to the *E. coli* in establishing meningitis (Mittal *et al.,* 2010).

Bacterial translocation into the CNS

BBB is formed by BMEC which prevents harmful substances from being transported as well as stops transport of pathogenic microbes from blood to brain. High grade bacteremia is prerequisite for the interaction between *E. coli* and the BBB. All surface structures of K1 *E. coli* have the potential for interaction with the BMEC for the invasion as well as entry to CNS. Among the surface appendages of *E. coli*, one is S-fimbriae (Sfa) which particularly have interactions with epitopes of 3GlcNAc, NeuAcα2, and 3Gal1 located on glycoproteins is demonstrated as being responsible for BMEC binding through SfaS adhesin located at Sfa tip (Stins *et al.*, 1994). Nevertheless, there is no significant role played by Sfa in HBMEC invasion. Subsequently conducted studies demonstrate type-1 fimbriae that binds with glycoproteins mannose residues to be a contributing factor in the invasion of HBMEC by the *E. coli* (Teng *et al.*, 2005). But invasion by the bacterium could not take place by the OmpA⁻ *E. coli* where the expression of type-1 fimbriae was found to be similar to the wild type *E. coli* in which *fimH* operon was kept, that encodes type-1 fimbriae tip. Moreover, pretreating *E. coli* by α-methyl mannoside (an inhibitor that inhibits type-1 fimbriae) yielded no differences in invasion, suggesting OmpA to be the primary determinant in the invasion of HBMEC by *E. coli* (Krishnan & Prasadarao, 2014). Binding of OmpA has been shown with HBMEC for the invasion through activity similar to lectin particular to epitopes of 4GlcNAc (chitobiose) and GlcNAc1that are attached to the glycoproteins linked with asparagine (Prasadarao *et al.,* 1996).

Ratifying the need of chitobiose moieties for pathogenesis, treating *E. coli* with chitooligomers before infecting newborn rats resulted in prevention of meningitis. In subsequently conducted studies a heat-shock protein called as β-form of gp96 have been identified and be found in HBMEC (designated as Ecgp96), that serves as an OmpA receptor for cellular binding and invasion. Ecgp96 comprises of 803 amino acid having a poor transmembrane domain (Prasadarao *et al.*, 2003). The interaction between *E. coli* OmpA and two sites of N-glycosylation of Ecgp96 leads towards further enhancement of receptor expression which subsequently leads towards more bacterial bindings and furthers the invasion of HBMEC (Krishnan *et al.,* 2014). Moreover, Ecgp96 C-terminal domains are needed to induce signaling network for entering the HBMEC (Maruvada *et al.,* 2008). Expression of TLR2 is also triggered by interaction of *E. coli* with HBMEC at the surface, that leads to formation of a complex with Ecgp96 whereas *E. coli* having no OmpA⁻ enhance TLR4 expression, does not link up with receptor (Krishnan *et al.,* 2013).

Actin cytoskeletal rearrangements are induced by the *E. coli* for the internalization that triggers mechanism similar to the zipper, in HBMEC that causes engulfment of the bacteria in the cell. Other than actin microfilaments, K1 *E. coli* also need microtubules to invade, which in HBMEC, provide pulling force presumably, for the internalization of the bacteria. Entrance of *E. coli* causes induction of tyrosine residues of the focal adhesion kinase (FAK) to phosphorylate, that is not dependent on the activity of Src kinase (Reddy *et al.,* 2000). Activity of PI3-kinase is also crucial for the invasion of HBMEC by *E.*

coli that consequently causes PLCγ activation for extracellular calcium influx as well as for intracellular calcium mobilization (Reddy *et al.,* 2000; Sukumaran *et al.,* 2003). PKC-α is activated by calcium mobilization, that has interaction with the caveolin-1, which is 22 kDa protein found in the plasma membrane caveolae and induces *E. coli* ingestion by the HBMEC (Sukumaran *et al.,* 2002). Activated PKC-α links with VE-cadherin that is a molecule for adherens junction and β-catenin is released from junction, as a result HBMEC monolayer permeability is increased (Sukumaran & Prasadarao, 2003). Pre-incubating *E. coli* by anti-OmpA antibodies or doing same with HBMEC by anti-Ecgp96 antibodies resulted in reduction of permeability induced by *E. coli* validating that interaction of OmpA-Ecgp96 is crucial for the disruption of tight junctions.There is enough evidence suggesting role of nitric oxide (NO) as antimicrobial molecule as well as facilitator of the cerebral vascular permeability. Upon the invasion of HBMEC, NO is produced in high amounts by the *E. coli* by activation of inducible nitric oxide synthase (iNOS) and cyclic GMP (cGMP) is also generated which is a critical NO downstream target (Mittal *et al.,* 2010).

Furthermore, increased cGMP production causes PKC-α activation, suggesting two pools of PKC-α, whereas one of them under regulation of Ecgp96 and other one under modulation of NO that causes HBMEC monolayers permeability to enhance. It has been demonstrated by further studies that GTP cyclohydrolase (GCH1) which is a enzyme that limits the rate and causes production of co-factor tetrahydrobiopterin needed for the activation of iNOS, is related to intracellular Ecgp96 (Shanmuganathan *et al*., 2013). Other than that, small molecule library screening by HBMEC invasion assays lead to the recognition of Telmisartan which is a blocker for angiotensin II receptor 1 (AT1R), as having potential for inhibiting the invasion (Krishnan *et al.,* 2014). Follow-up experimentation revealed AT1R to be forming a complex with the Ecgp96 while HBMEC is being invaded by *E. coli*. Pre-treatment of the mice with the TS made them resistant to bacteremia development as well as entrance of the bacteria in the brain. These experimentations evidently demonstrated that for the aversion of meningitis induced by *E. coli* Ecgp96 can be targeted and would prove beneficial.

Immune activation by E. coli and the inflammatory response generated by it in the brain

Multiplication as well as survival of *E. coli* inside the PMNs along with macrophages causes pro-inflammatory cytokines production in blood that results in upregulation of intracellular adhesion molecule 1 (ICAM-1) expression on BBB. Additionally, interaction between *E. coli* OmpA and Ecgp96 located on HBMEC leads towards induction of ICAM-1 expression which as a result cause THP-1 cells binding in the culture to be enhanced (Selvaraj *et al.,* 2007). ICAM-1 expression upregulation helps PMNs to be infiltrated in the duration of meningitis onset. Moreover, neuronal apoptosis as well as gliosis in hippocampus and cortex both and IL1β and TNF-α production in great amounts have been noted in newborn mice brain upon *E. coli* infection (Mittal *et al.,* 2010). However, *E. coli* interaction with the glial cells as well as with neuronal cells is not studied properly. There is a need for further studies so a better understanding about if the bacteria directly inflict damage to the brain or that the damage is resulted due to the causal effects of pro-inflammatory responses.

Pathogenesis of Klebsiella pneumoniae

Klebsiella pneumoniae, is a pathogenic gram-negative bacillus bacteria bearing a capsule, which over the last 30 years has acquired a progressively crucial role in causing adult meningitis in community-acquired settings as well as in hospital-acquired settings (Cherubin *et al.,* 1981; Durand *et al.,* 1993; Mangi *et al.,* 1975). A number of patients show susceptibility to *K. pneumoniae* meningitis, such as patients present with extrameningeal *K. pneumoniae* infections, debilitating diseases, *K. pneumoniae* bacteraemia, patients who underwent some neurosurgical procedures where leakage of CSF was involved or not or diabetic patients (Liu *et al.,* 1991; Mombelli *et al.,*

1983; Spivack *et al.,* 1957; Thompson *et al.,* 1952). *K. pneumoniae* in Taiwan serves as being the commonest pathogens causing bacterial meningitis acquired from the community (Fang *et al.,* 2000).

Among other gram-negative bacterial pathogens, *Klebsiella pneumoniae* remains commonest in Taiwan as well in numerous other countries in the South Asian region (Chang *et al.,* 2012; Chang *et al.,* 2008; Moon *et al.,* 2010). Meningitis caused by *K. pneumoniae in these regions was linked to a novel variant called as* hypervirulent *K. pneumoniae* (hvKP) in the last decades, and the mortality reported ranged from 33.3% to 48.5% (Fang *et al.*, 2007; Lu *et al.,* 2000).

Designated as hvKP, hypermucoviscosity (HM) phenotype was shown by the newly associated variant which shows frequent associations with particular sequence types (STs) primarily including ST86, ST23 and ST65 (Bialek-Davenet *et al.,* 2014). Upon their description in 1986, pyogenic liver abscesses (PLA) were resulted increasingly by hvKP that was complicated due to catastrophic metastatic infections like necrotizing fasciitis, meningitis in healthy young individuals and endophthalmitis (Fang *et al.,* 2007; Fazili *et al.,* 2016; Shon *et al.,* 2013). Nonetheless, hvKP pathogenesis resulting in metastatic infections is yet not properly understood so far, and no particular advancements have yet been made for describing the pathogenesis resulting in meningitis. As of now, some of the details of hvKP pathogenesis are described. Hypervirulence of the strains of hvKp has its foundation on virulence factors owned by the cKp strains. Reports and review of these factors are done elsewhere (Bachman *et al.,* 2015; Hsieh *et al.,* 2010; Martin & Bachman, 2018; Martin *et al.,* 2018; Mills *et al.,* 2017; Paczosa & Mecsas, 2016; Pan *et al.,* 2011; Podschun & Ullmann, 1998). In the current section, our primary focus is on the factors which are particular to hvKp.

Colonization by hvKP

Probably the initial step required for the subsequent endogenous infection of hvKP is acquisition that causes colonization (Montgomerie, 1979). Human mucosal surfaces are readily colonized by the *K. pneumoniae* such as oropharynx as well as gastrointestinal (GI) tract, in there, colonization effects appear benign (Bagley, 1985; Dao *et al.,* 2014; Rock *et al.,* 2014). Strains of, *K. pneumoniae* acquire entrance into the other tissues from those sites and results in severe human infections. It is noteworthy that factors should be delineated, and mechanisms should be defined which enables successful colonization of hvKP to various mucosal and epidermal surfaces since those represent potential intervention points for decreasing infection incidence. Up until now, majority of the studies had their focus on colonization of the gastrointestinal tract.

Colibactin, a peptide-polyketide which is produced through nonribosomal synthesis. Genes responsible for its biosynthesis (PKSs) are found inside ICEKp10, that is a mobile genetic element in strains of hvKp that usually also has genes for synthesis of microcin E492 and yersiniabactin (Lam *et al.,* 2018; Struve *et al.,* 2015). CG23 strains of hvKP mostly have this element but its less common in other strains of hvKP, it is absent (Chen *et al.,* 2017; Lai *et al.,* 2014; Lam *et al.,* 2018).

Colonization of E.coli (Raisch *et al.,* 2014) as well as of 1084 strain of hvKP (Lu *et al.,* 2017) has been demonstrated to be promoted by the colibactin. Microcin E492 is 8-kDa which activates against Enterobacteriaceae (de Lorenzo, 1984). Salmochelin attachment is required for the activity, that enables microcin uptake by bacteria (Lagos *et al.,* 2001). Thus, strains of hvKP which produce microcin E492, salmochelin and colibactin in combination would presumably have significant advantage in the colonization in the colonic environment where there is a tough competition.

There have been identification of numerous genes through mutagenesis tagged with a signature which apparently play some role in intestinal colonization or/and mucosal barrier invasion following an intragastric (i.g.) challenge in the mice (Tu *et al.,*

2009). Transcriptional regulator of LuxR family (kva15), monamine regulon positive regulator (moaR), a putative type III fimbrial usher protein (mrkC), a regulator system based on two components (kvgA-kvgS that are demonstrated to be playing role in the production of the capsule) (Lin *et al.,* 2006), 2 hypothetical proteins (kva7 and kva21) or uracil permease (kva28), play a significant role for those factors in colonization of intestine and/or mucosal invasion. Kfu, a facilitator involved in the uptake of iron, is found to be more prevalent in the strains of hvKP. Kfu has been demonstrated to play a contributing role in the viriulence following i.g., but intraperitoneal challenges in mice (Hsieh *et al.,* 2008; Ma *et al.,* 2005).

Role related to intestinal invasion or/and colonization is supported by this data. Nonetheless, considering its role in the acquisition of free iron that is found in gastrointestinal tract, it seemingly become more likely that it contributes to the colonization. Colonic colonization has seen an increase by the undefined strain of K. pneumoniae Ca0437 due to the antimicrobial peptides (SAP) sensitivity in mice model with i.g. challenge (Hsu *et al.,* 2019). Adherence was also enhanced by the SAP transporter in vitro to the epithelial cells of intestine.

Both of the adhesins i.e., hvKP and cKP have type 1 (sensitive to mannose) and a type 3 (resistant to mannose) fimbriae. In the cKP strains, adherence of these fimbriae has been demonstrated to occur with the epithelial cells of the host from the urinary or the respiratory tract which adds to the infection (Hornick *et al.,* 1992; Rosen *et al.,* 2008). Even though there is a lack of work on hvKP, a study conducted recently examined type 3 fimbriae regulation in the CG43 hvKP strain (Wu *et al.,* 2012). This study validated observations of the contribution of type 3 fimbriae in the formation of the biofilm and exhibited that concentration of iron and expression have a positive correlation. Even though there was no reference to the in vivo virulence, it was suggested by the data that role of type 3 fimbriae in humans where there is a limit of free iron, is may of no importance. Finally, NTUH-K2044 strain of hvKp, treC disruption, the product of which enables utilization of trehalose, causes decrease in the colonization of intestine in the mice where the strain competed against the wild type of parental organism. Some of the additional effects were also observed including decrease in the production of capsule and formation of biofilm, indicating potential mechanisms (Wu *et al.,* 2011). In a similar way, celB loss, the product of which is required for transporting cellobiose in the cytoplasm, led towards decrease in the formation of the biofilm, lethality in i.g. challenged mice and intestinal colonization (Wu *et al.,* 2012). Even though there is no discrimination regarding which step or steps during the pathogenesis were affected, this data consistently points towards role of capsule or/and formation of the biofilm to serve as facilitators for the colonization of the intestine, a primary and necessary step in the pathogenesis of Klebsiella (Wu *et al.,* 2012; Wu *et al.,* 2011).

Entry in the host

In settings of healthcare, epithelial or mucosal barrier disruptions e.g., surgical incisions, catheters and endotracheal tubes might make entry possible (Gu *et al.,* 2018). But, for majority of the patients in whom hvKP infection develop, the primary entry site is not clear. Up till now, majority of the hvKP infections are acquired through the community which are often found occurring in the healthy hosts in whom no epithelial or mucosal barrier disruption is present.

It is uncertain that hvKP uses what kind of mechanism that enables it to cross epithelial or/and mucosal barriers in humans. Occult disruptions of skin might provide the bacteria with an entry point resulting in the subsequent bacteremia as well spread to other distant sites, similar to the mechanism used by the Staphylococcus aureus.

Studies based on 52145 strain of hvKP showed entry impeded by the capsule into the A549 epithelial cells (de Astorza *et al.,* 2004), as well as where undefined strains of K. pneumoniae were used, it was shown that invasion impeded by the capsule of cell line of

ileocecal epithelial cells, has at least in some way decreased adherence (Sahly *et al.,* 2000), is paradoxical. More studies conducted on effects of capsule production being increased which occur in hvKP strains on the cellular adhesion and invasion would be interesting.

Growth and Survival of hvKp in the host

It has been demonstrated that hvKP strains have higher resistance against neutrophil extracellular traps (NETs), activity mediated by complement and neutrophils and phagocytosis compared to cKP strains (Fang *et al.,* 2004; Fang *et al.,* 2007; Pomakova *et al.,* 2012; Wang *et al.,* 2017). hvKP strains enhance production of the fluids in humans ex vivo as well increase in the virulence in a number of different infection models than the cKP strains (Pomakova *et al.,* 2012; Yu *et al.,* 2007). Discussion of factors specific to the hvKP recognized up till now which facilitates these phenotypes as well as the clinical manifestations is done in following section.

RmpA, RmpA2, and capsule production

A critical factor contributing to phenotype of hvKp is its ability that enables the production of capsular polysaccharides in high amounts. RmpA2 or/and RmpA maybe in part, at least facilitate this, and are factors specific to the hvKP found on virulence plasmid of hvKP (Chen *et al.,* 2004; Lai *et al.,* 2003; Russo *et al.,* 2018). An environmental signal showing increased production of capsule is presence of glucose (Lai *et al.,* 2003; Lin *et al.,* 2013). Ferric regulator for its uptake (Fur) has been demonstrated to suppress the production of the capsule in CG43 strain of hvKP through suppressing rmpA2 and rmpA expression (Cheng *et al.,* 2010; Lin *et al.,* 2011). Thus, production of capsule in the hvKP strains is presumed to be elevated in environments where iron is limited, as inside human hosts.

Studies conducted on hvKP strains showed their capsular polysaccharide to provide protection against phagocytosis (Cortés *et al.,* 2002; March *et al.,* 2013; Pan *et al.,* 2011) as well as bactericidal activity mediated by human defensins (Moranta *et al.,* 2010), and human defensins production was attenuated in vitro (Moranta *et al.,* 2010).

Capsule type

There have been numerous investigations examining that whether K2 or/and K1 types of the capsule cause enhancement of the virulence than the nonK2/K1 types (Fang *et al.,* 2007; Yu *et al.,* 2007). It was reported by these studies that K2/K1 groups show metastatic spread more commonly.

Colibactin

Besides playing a potential role in colonizing, is it also shown that colibactin plays a contributing role in the survival of the bacteria in bloodstream of the infected mice intravenously or intranasally (Lu *et al.,* 2017). The mechanism involved is not clear.

LPS

LPS has been demonstrated to provide protection against phagocytosis, bactericidal activity mediated by the complement, antimicrobial peptides and causes enhancement of virulence in the systemic infection. (Hsieh *et al.,* 2012; Kidd *et al.,* 2017; Llobet *et al.,* 2015; March *et al.,* 2013; Mills *et al.,* 2017; Pan *et al.,* 2011).

Metastatic Spread

Multiple infection sites as well as metastatic spread are commonly observed more with hvKp strains compared to the cKp strains in the humans (Russo *et al.,* 2018; Yu *et al.,* 2007). cKp along with other Enterobacteriaceae family members hardly ever cause infection in the secondary sites due to bacteremia, with the exception of settings where the host is immunocompromised e.g., neutropenia. hvKp strains cause infection of multiple sites through bloodstream. This occur either at the time of the bacterial entry or after infecting a primary infection site such as meningitis that in turn provides subsequent source of bacteremia and further spread is not clear. It seems that both of these mechanisms are operational. Regardless of the ability to enter bloodstream and surviving the resident factors of host defenses is the initial necessary step. Resistance to complement's

bactericidal activity of the hvKp strains that is facilitated partially by the capsule is required to achieve that as well as it contributes to the step in this process (Fang *et al.,* 2007).

This indicate hvKP to be more efficient in invading the host tissue via bloodstream. There is lack of knowledge regarding the mechanism involved. Even though measurement of bacteremia as well as its consequent spread to the various sites and organs can be done using the animal models that are used for studying hvKP, model which provide direct measurement of tissue invasion by hvKP via bloodstream at the level of cells can potentially provide assistance in identification of potential factors which enables systemic invasion of the tissues. It is postulated that it uses "Trojan horse" mechanism with the neutrophils suggesting them being used as potential vehicles (Lin *et al.,* 2010). hvKp strains have been demonstrated to have the ability enabling them to survive inside the neutrophils (Lee *et al.,* 2017; Lin *et al.,* 2010) as well as delaying apoptosis process for nearly 24 hours (Lee *et al.,* 2017), whereas intraperitoneal injection containing infected neutrophils caused dissemination of the infection: but it was not clear if infected neutrophil integrity was conserved post injection (Lin *et al.,* 2010).

In majority of the infections that are complicated because of bacteremia, 1 CFU/ml to 102 CFU/ml titers are seem commonly (Yagupsky & Nolte, 1990). A titer of hvKP that is quantitatively higher during bacteremia maybe responsible or maybe contributory. There is little evidence supporting this hypothesis (Lu *et al.,* 2017; Russo *et al.,* 2011).

One other possibility is that the increased production of capsule by hvKP drives the spread. Even though its speculative, this phenotype perhaps causes increased bacterial in vivo clumping that as a result cause enhancement of survival with the hematogenous dissemination.

It has been indicated that colibactin plays a role on meningeal spread (Lu *et al.,* 2017). It is not clear as if this is a directly facilitated by the colibactin or by increased bacteremia magnitude. Isolation of NTUH-K2044 strain of hvKP was done from the patient present with meningitis, with the isolate being unable to produce colibactin, should be noted (Lin *et al.,* 2008).

Tissue damage

Until now, there is lack of insight regarding the host or bacterial factors that are responsible. Colibactin among the others is the best one defined yet, that is genotoxic, resulting in damage to the DNA as well as cell death (Lai *et al.,* 2014; Lu *et al.,* 2017). Nonetheless, strains of hvKP not producing colibactin such as non-CG23-K1 capsule type, also resulted in causing abscesses on multiple sites. This indicates towards the possibility that there are some hvKp factors that are yet unrecognized which may play a contributory role. Without a doubt, a response from the host that is unregulated also play some contributory role in damage to some extent.

Pathogenesis of Staphylococcus aureus

Staphylococcus aureus is a pathogenic microbes that stains positive during gram staining and causes a diversified disease pathologies range starting from the dermal lesions that are relatively minor to the sepsis disorders with severe invasiveness, abscesses of the deep tissues and pneumonia (Decker, 2008; Gordon & Lowy, 2008; Lowy, 1998). Majority of the bacterial infections acquired in the hospitals are caused by S. aureus in the developed regions (Diep & Otto, 2008; Jacobsson *et al.,* 2008), whereas in USA, the leading causative bacterial agent causing deaths is now community-acquired methicillin-resistant S. aureus (CA-MRSA) (Otto, 2010).

S. aureus is a very persistent commensal microbe in nearly 20% of population and in about further 60% intermittently; mainly in anterior nares and also the groin, GI tract and axillae, that contributes to its widespread pathogenesis (Lindsay & Holden, 2004). Due to it being ubiquitously present, breaching the defenses of the host could lead towards an invasive and may be a fatal infection of *S. aureus* (Lowy,

1998). Majority of the *S. aureus* clinical isolates exhibit an array of factors responsible for its virulence that enables it to invade and disseminate in the bloodstream even when tissue trauma is significantly absent (Naber, 2009). *S. aureus* bacteremia incidence has seen a considerable rise since CA-MRSA has emerged as well as *S. aureus* infection prevalence in the environment of the hospitals (Saginur & Suh, 2008). Abscesses of deep tissue, endocarditis and vertebral osteomyelitis makes up for more than half of the secondary infections caused by *S. aureus* (Rubinstein, 2008).

S. aureus is most commonly related to the brain abscesses caused by the bacteria (Bloch *et al.,* 2005). Head injury, inadequate treatment of meningitis or sepsis caused by *S. aureus* and surgery may give rise to the complication known as brain abscesses (Bloch *et al.,* 2005). Even though it is considered that meningitis is rarely occurring complication of an infection of *S. aureus*, there are numerous clinical reports describing meningitis caused due to infection of *S. aureus* from a source that is not known (Pedersen *et al.,* 2006; Vartzelis *et al.,* 2005).

In such cases, spread of bacteria via bloodstream from the initial infection site implicates the ability of *S. aureus* to the cross BBB and penetrate into the CNS. While numerous pathogens that stain positive during gram-staining such as *group B Streptococcus (GBS), S pneumoniae* (SPN) and Streptococcus agalactiae are all well known for having the ability to acquire access to CNS, penetration of BBB by Staphylococcus was not well studied until this point.

Mechanisms of Pathogenicity of Staphylococcus aureus

Up-regulation of the virulence factors in the presence of stressful stimuli such as circulating antibiotics or immune response of the host, serves as an important factor which *enables S. aureus* to survive in bloodstream, seed into deep tissues and formation of a secondary hub for infection. Strains of *S. aureus* have been able to efficiently adhere to the skin followed by its colonization as well as of the nares mucosa, for bloodstream invasion and evasion of the immunological responses of the host, formation of the protective biofilms as well as development of resistance to different antibiotics. As a result, even after having a plethora of antibiotics showing activity towards wild-type strains, *S. aureus* remain a very successful as well as gram-positive bacteria with increasing clinical importance

Adhesion and colonization

Various virulence factors can be upregulated by the S. aureus, enables its adherence and colonization of nares as well as damaged surfaces or skin where devices had been implanted or prostheses and cause severe bloodstream infections. Teichoic acid is a polymer located on the *S. aureus* surface is crucial for that purpose *(Weidenmaier et al.,* 2004).

The cell wall pf gram-positive bacteria comprise of thick peptidoglycan along with teichoic acids that are linked by the lipids, called as lipoteichoic acids (LTA). LTA is polymer of glycerol phosphate extending through cell wall peptidoglycan and is considered to play a role in attachment to the host cell by different pathogens (Courtney *et al.*, 1992; Jonquieres *et al.,* 1999).

Staphylococci have LTA that is attached to cytoplasmic membrane through an anchor of glycolipid; particularly β-gentiobiosyldiacylglycerol (diglucosyl-diacylglycerol [DGlcDAG]) (Fedtke *et al.,* 2007; Gründling & Schneewind, 2007). For the synthesis of DGlcDAG, *S. aureus* requires YpfP which is a glycosyltransferase (Gründling *et al.,* 2007).

Invasion

Can causes disruption of skin barrier due to the secretion of exfoliative toxins (Amagai *et al.,* 2000), hemolysins such as α-hemolysin α-toxin, that causes pore formation in cell membranes of skin, along with different enzymes which causes tissue destruction (Lowy, 1998). Immune system getting compromised triggers invasion as well as physical integument getting broken or the presence of localized inflammation (Otto, 2004).

Evasion

Evasion of immune responses of the host by the S. aureus is achieved by secretion of anti-opsonizing proteins such as proteins inhibiting chemotaxis that prevents phagocytosis by the neutrophils (Haas *et al.,* 2004). Protein located on the S. aureus surface called protein A also exhibits antiphagocytic properties. Moreover, leukotoxins such as Panton-Valentine leukocidin is secreted by the *S. aureus* that causes leukocytes to lyse (Lowy, 1998), and superantigens are expressed such as toxin 1 which is responsible for toxic shock syndrome as well as some enterotoxins (McCormick *et al.,* 2001), that deposes normal immune response and induce intense, polyclonal stimulation as well as T cell receptor, Vβ-specific T cells expansion that is followed by suppression or deletion of the said T cells to anergic state (Wang *et al.,* 1998).

Biofilms

Quorum sensing of *S. aureus* might regulate expression of genes for the formation of slimy biofilms on top of fitted medical devices, damaged or healthy heart valves and on top of damaged skin. Depletion of oxygen and nutrients enable the bacteria to acquire a nongrowing state where they show less susceptibility to some of the antibiotics. Specially, *S. aureus* variants from small colony, when adhered to and are in stationary phase show nearly a complete resistance to the antimicrobial agents (Proctor *et al.,* 1998). The matrix of the biofilm provides protective covering against immune cells and might restrict some antibiotics from penetrating (Patel, 2005).

Mechanisms of disruption of blood brain barrier by s. aureus

It is thought to be an opportunistic pathogenic bacterium having the highest prevalence and is considered responsible for hospital as well as community acquired infections around the whole world. Rate of mortality of mmeningitis and sepsis facilitated by the *S. aureus* is 36% (Aguilar *et al.,* 2010). The variable protein range on the surface of *S. aureus,* serve as factors for virulence which provide assistance to the bacterium in adhesion as well invasion of the host cells, such as vascular endothelial cells. (Foster *et al., 2014*). McLoughlin *et al.* (2017), in their study showed permeability of BMEC to be induced by infection of *S. aureus* by reducing VEC, ZO-1 and claudin-5 in manner dependent on dose. The primary mechanism behind the disruption of BBB because of the disruption of junctional protein is associated with signalling of pro-inflammatory cytokines, that is related to production of ROS (Rochfort *et al.,* 2016; Rochfort & Cummins, 2015). There is noticeable correlation between ROS signalling and levels of ZO-1. It is noted that disruption of ZO-1 happens in the murine cells upon their exposure to the hypoxia by reoxygenation (MHR) because of the activation of Nicotinamide adenine dinucleotide phosphate (NADPH). It is documented that expression of mRNA levels of different cytokines such as MCP-1, macrophage inflammatory proteins-1 alpha (MIP1α), IL-1α, TNF-α, IL-6 and IL-1β in higher levels in the rat brain abscess model infected by *S. aureus* causes disruption of the BBB (Kielian & Hickey, 2000). Furthermore, production of IL-6 induced by the infection of *S. aureus* in HUVEC (Park *et al.,* 2007). Observation of ROS generation has also been made in infection by *S. aureus* particularly in the resident stems cells in the bone marrow, monocytes, neutrophils and macrophages (Nandi *et al.,* 2015), causing enhancement of inflammatory response. Moreover, adhesin protein (SpA) expression has been noted to increase permeability of BMEC, accompanying reduction of VEC protein as well as activation of NF-κB/p65 by this bacteria (McLoughlin *et al.,* 2017). Consequently, disruption in the integrity of the barrier might be because of BMECs infection via pro-inflammatory cytokines induction, activation of NF-κB, reduction in the expression of TJ protein and oxidative stress. From a therapeutic point of view, a study conducted previously showed role of lipoteichoic acid (LTA) anchored to the membrane facilitating in the adhesion as well as with the cellular invasion in the immortalized BMECs of the humans, causing penetration of the BBB (Sheen *et al.,* 2010).It has also been reported by a previous study that host defence circuit enchantment by IL-17 might provide

basis for novel therapeutic approaches for the treatment of infectious diseases caused by *S. aureus* (Cho *et al.,* 2010).

Conclusion

Noteworthy advances have been made recently to identify pathophysiological mechanisms contributing to host–bacterial interactions amid bacterial meningitis. Those incorporate the characterisation of pathways utilized by these pathogens to cross mucosa, survive in the blood and encourage innate immune response, and/or immune escape, together with the recognition of ligand or receptor interactions used by these bacterial species to interweave the brain barriers. These findings have already made a difference in the advancement of viable treatments. Taking into consideration the low efficacy of present vaccines and antibiotic resistance aiming bacterial adhesions or their host receptors and corresponding signaling events demonstrate curative strategies to lessen the effect of bacterial meningitis. Although considerable development has been made in figuring out mechanisms of host–pathogen interactions at some stage in bacterial meningitis, extra efforts are required to evaluate bacterial and host cell targets.

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