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Ventricular shunt infections: Immunopathogenesis and clinical management

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Abstract

Ventricular shunts are the most common neurosurgical procedure performed in the United States. This hydrocephalus treatment is often complicated by infection of the device with biofilm-forming bacteria. In this review, we discuss the pathogenesis of shunt infection, as well as the implications of the biofilm formation on treatment and prevention of these infections. Many questions remain, including the contribution of glia and the impact of inflammation on developmental outcomes following infection. Immune responses within the CNS must be carefully regulated to contain infection while minimizing bystander damage; further study is needed to design optimal treatment strategies for these patients.

Keywords

Shunt infection; biofilm; catheter; central nervous system

1. Introduction

Hydrocephalus is defined as the pathological increase in intracranial cerebrospinal fluid (CSF) volume and can be either congenital or acquired following brain injury, tumor or infection. Normal production of CSF occurs in the ventricles; however, it can accumulate due to overproduction or decreased circulation to other brain compartments. The accumulation leads to swelling of the ventricular system and ultimately to brain damage due to decreased blood flow and altered metabolism in the compressed tissues (Del Bigio 1998).

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The primary neurosurgical treatment of hydrocephalus involves the surgical insertion of a shunt system which drains the excessive fluid into other body cavities where it can be reabsorbed. Since its introduction in the 1950's, placement of ventriculoperitoneal (VP) shunts has provided a highly efficacious treatment for thousands of hydrocephalus patients annually. Nevertheless, its effectiveness has been overshadowed by complications such as infection and mechanical malfunction (Barton, Campbell & Piatt 2013).

Biofilm forming bacteria such as *Staphylococcus epidermidis* and *S. aureus* attach to the surface of implanted devices to cause shunt infections. Shunt infection is generally defined as the identification of a bacterial pathogen from the CSF both by gram stain and culture, in conjunction with CSF pleocytosis, fever, neurologic symptoms, and signs of shunt malfunction (Odio, McCracken & Nelson 1984, Gathura et al. 2010, Younger, Simmons & Barrett 1987, Bruinsma et al. 2000). The clinical symptoms associated with SI can vary due to the organism involved and can be initially blunted in biofilm infections, leading to delayed diagnosis and treatment in some cases (Fleisher, Ludwig 2010). Shunt infections are associated with higher rates of revision, recurrence of infection, ventriculitis, meningitis, and encephalitis, and often with greater mortality rates (Winston, Ho & Dolan 2013). Complications include loss of intelligence quotient (IQ) and increased seizure risk, both of which occur via mechanisms that have yet to be defined (Vinchon, Dhellemmes 2006, Sato et al. 2001, Stellman, Bannister & Hillier 1986, Chadduck, Adametz 1988). This may be due to neuronal death as a direct result of infection or may be a consequence of inflammation within the central nervous system (CNS) due to the infection.

Shunt infection rates per patient range from 10% to 22% and around 6.0% per procedure, with 90% of infections occurring within 30 days of surgery (Vinchon, Dhellemmes 2006, Duhaime 2006, Vinchon et al. 2003). These events are mostly attributable to normal skin flora such as coagulase-negative staphylococci, *S. aureus* and *Propionibacter acnes*, which are thought to be introduced at the time of surgery although gram-negative organisms and *Candida* species have also been reported (Choksey, Malik 2004, Vinchon et al. 2002, McGirt et al. 2003, Ersahin, Mutluer & Guzelbag 1994, Piatt 1995). Risk factors for infection include young age, frequent revisions and causes of hydrocephalus such as post-infectious hydrocephalus, posthemorrhagic hydrocephalus or hydrocephalus due to spina bifida or other neurologic defects resulting in communication of the CSF with skin (Kebriaei et al. 2013, Davis et al. 1999, Duhaime 2006, Pople, Bayston & Hayward 1992, McGirt et al. 2002, Simon et al. 2012, Warf et al. 2011).

Rates of shunt infection have also been reported to be influenced by potentially modifiable factors, including length of hospital stay, number of revisions per patient, surgeon's experience, surgical technique, duration of procedure, manipulation of the indwelling device during surgery, and health insurance (Simon et al. 2012, Simon et al. 2009). Kestle et al. and Choux et al. found that after the implementation of a standardized protocol for shunt implantation, there was a significant lowering in shunt infection occurrence (Choux et al. 1992, Kestle et al. 2011). Similar results were found by Pirotte et al. following the implementation of a stringent protocol for sterile shunt placement (Pirotte et al. 2007). However, despite these advances, shunt infections remain the most significant complication associated with hydrocephalus treatment.

Both the antibiotic resistant properties of biofilms and the anatomic difficulties with antibiotic penetration into the brain make treatment of these infections difficult. Thus, shunt infections can increase the morbidity and mortality of neurosurgery patients and leads to disproportionate use of hospital days and healthcare dollars (Simon et al. 2008). In this review, we discuss the pathogenesis of shunt infection, immune response to infection and the implications of biofilm formation on treatment and prevention of shunt infection.

2. Pathogenesis

Biofilms are protected communities of bacteria or fungi capable of attaching to surfaces by forming a heterogeneous structure composed of cellular elements and a complex selfproduced matrix (Scherr et al. 2014, Braxton, Ernest E., Jr et al. 2005). Biofilms have increased in relevance in recent years because of the widespread use of implanted medical devices. This is a significant problem because biofilms are able to evade the host immune defense and are more resistant to antimicrobial treatment than planktonic forms of bacteria (Hess, Henry-Stanley & Wells 2012).

Development of biofilm comprises a sequence of events characterized by the initial adherence of an organism to an artificial or host surface (Figure 1). Following attachment, the bacteria accumulate and proliferate on the bacterial device or host surface. *In vitro* studies suggest that different events may provide the initial signal for biofilm development, including environmental stresses like high temperature, high osmolarity or the presence of ethanol or antibiotics although the relevance of these factors *in vivo* is unknown (Lavery, Gorman & Gilmore 2013, Götz 2002). Several genes and molecules have been identified that participate in attachment and serve as significant virulence factors, particularly among staphylococcal strains (Yao et al. 2006). Polysaccharide intercellular adhesion (PIA) is one of the best characterized of these molecules, rendering staphylococcal strains better able to form biofilms and more resistant to phagocytosis by neutrophils and antibacterial peptides (Rohde et al. 2010, Vuong et al. 2004, Cheung et al. 2010). It is a significant factor in staphylococcal pathogenesis, particularly in *S. epidermidis* strains where PIA is present in approximately 85% of strains from positive blood cultures (Mack et al. 1996). Many other molecules have been identified, including Embp (fibronectin-binding protein) and accumulation associated protein (Aap), and are under investigation to determine their importance in human disease and their impact on the immune response to these infections (Christner et al. 2010, Rohde et al. 2010, Schommer et al. 2011, Rohde et al. 2005). Many of these molecules are under evaluation as drug targets for biofilm dispersal, although this has not yet been explored in the CNS.

Once the bacteria attach and proliferate on the medical device, maturation and detachment occur to establish and spread biofilm-related infections and sepsis (Fey, Olson 2010). Biofilm maturation implies physiological and metabolic changes in the cells living within the biofilm. It has been hypothesized that those altered metabolic states are partially responsible for biofilm's tolerance to antibiotics. Cells within the biofilm are under the influence of a heterogeneous environment in terms of nutrients and oxygen supply, and cell-cell contact. This variability fosters changes in bacterial physiologic states, which are mainly controlled by the *agr* master regulator (Yao et al. 2006). Recent publications have provided

evidence that *S. epidermidis* β -subclass of phenol-soluble modulins (PSMs) are key factors to promote biofilm structuring and detachment as well (Wang et al. 2011). Studies are ongoing to further explore the signals triggering release of bacteria from the biofilm structure, which leads to spread of infection and worsened morbidity and mortality.

3. Immune response to biofilms

CNS resident immune defenses

Recognition of infection and other threats in the CNS is primarily mediated by glial cells, such as microglia and astrocytes. Microglia have macrophage-like function and are responsible for surveying the CNS by means of a wide array of receptors such as Toll-like receptors (TLR) 1-9, TREM-2 and P2Y6 (Hanke, Kielian 2011, Fu et al. 2014). Sensing of foreign antigens causes microglial activation and the secretion of proinflammatory mediators such as TNF- α , IL-1 β , nitric oxide and superoxide free radicals (Liu, Hong 2003). Microglia play an important role in responding to parenchymal brain infection, with studies in a staphylococcal brain abscess model showing that microglia produce pro-inflammatory chemokines and cytokines in response to *S. aureus* and its components, as well as displaying bactericidal activity (Kielian, Mayes & Kielian 2002). Additionally, microglia appear to have a greater contribution to the overall immune response to parenchymal staphylococcal infection than infiltrating peripheral immune response, based on studies using bone marrow chimeras to evaluate the relative contribution of these two cell types (Garg et al. 2009). Experiments evaluating the response of microglia to staphylococcal biofilms *in vitro* are currently underway in our laboratory to define the contributions of this essential first responder.

While the primary role of astrocytes is in supporting normal CNS homeostatic functions, they can also play a role in the response to infection. Astrocytes express pattern recognition receptors, such as Toll-like receptors, and can produce a wide array of chemokines and cytokines in response to infectious stimuli (Dong, Benveniste 2001, Liu, Kielian 2011). They have been shown to play important roles in the response to gram-negative bacteria, such as *Citrobacter koserii*, as well as gram-positive bacteria such as *S. aureus* in parenchymal CNS infections through their control of gap junction communications and production of proinflammatory mediators (Liu, Kielian 2011, Karpuk et al. 2011, Holm, Draeby & Owens 2012). While the role of astrocytes *in vivo* in response to biofilm infections has yet to be defined, *in vitro* studies by Stevens et al demonstrated the ability of these cells to recognize and respond to PIA from *S. epidermidis*, suggesting that these cells may play a role in recognizing biofilm components in the CNS (Stevens et al. 2009).

Proinflammatory mediators are necessary to control infection, but they can also cause neuronal damage. Chronic inflammation has been associated with neurodegeneration, behavioral disorders, seizures, and cognitive impairment (Barichello et al. 2013, Zhao et al. 2013, Hagberg, Gressens & Mallard 2012). Of particular relevance to the neonates and infants who are at highest risk of SI, the effect of CNS inflammation in the perinatal period on long term outcomes has been repeatedly noted in neonatal animal infection models (Kosmac et al. 2013, Meyer, Feldon & Fatemi 2009, Nelson, Willoughby 2000, Chen et al. 2011, Bilbo, Schwarz 2009). The widespread effects of inflammation on neurologic function

may explain the IQ loss and increased seizure risk observed in patients with shunt infections. Interestingly, in our own CNS catheter infection model in the mouse, we have observed seizure activity following infection in mice infected with *S. aureus* but not in mice infected with *S. epidermidis* (Snowden et al. 2012). This may be due to the increased inflammatory response observed in response to the more virulent *S. aureus* strain or greater tissue damage as a result of its broader array of toxins and other virulence factors. Immune responses within the CNS must be carefully regulated to maximally contain infection while minimizing bystander damage and thus further study is needed to design optimal treatment strategies for these patients.

Peripheral immune responses to biofilm infections

The recognition of a biofilm as non-self is the initial step of host innate defense. In addition to the resident microglia in the brain, innate immune cells such as macrophages and neutrophils detect conserved molecular patterns in bacteria through membrane or cytoplasmic pattern recognition receptors such as TLRs and NOD-like receptors (NLRs), respectively (Savva, Roger 2013, Suresh, Mosser 2013, Hanke, Kielian 2011, Akira, Uematsu & Takeuchi 2006). In the case of gram-positive bacteria, TLR2 is considered the cognate receptor for peptidoglycan, teichoic acids (TA) and lipoproteins (Lpp) (Akira, Uematsu & Takeuchi 2006, Hussain, Hastings & White 1992, Jabbouri, Sadovskaya 2010). Notably, even though PIA, peptidoglycan, lipoteichoic acid (LTA), lipoproteins, and e-DNA found in the biofilm's external matrix are capable of engaging innate immune cells receptors TLR2 and TLR9 *in vitro*, there no apparent role in responding to biofilm infections *in vivo* (Thurlow et al. 2011, Stevens et al. 2009). A study using TLR2 and TLR9 knock out mice found no difference in the inflammatory mediator expression compared to the wild type, suggesting that the ligands for the TLRs may not be readily accessible to the innate immune cells or that these TLR may not be relevant for the immune response against the biofilm *in vivo* (Thurlow et al. 2011). Also noteworthy is the fact that inflammatory mediators such as IL-1 β , TNF- α , CXCL2, and CCL2 were reduced in biofilm infected mice compared to uninfected controls (Thurlow et al. 2011). Conforming to the above results, an *in vitro* study by Cerca et al. found that biofilm growth triggered less death and lower pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) when cultured with bone marrow derived macrophages in comparison to macrophages cultured with planktonic bacteria (Cerca et al. 2011). Similar responses have also been reported in the CNS. A study from our laboratory using a CNS catheter model found that a *S. aureus* *sar A* mutant, which exhibits reduced biofilm forming ability, induces a more inflammatory profile compared to the strong biofilm forming wild type isogenic strain, supporting the idea that response to planktonic bacteria is more inflammatory than to biofilms (Snowden et al. 2013).

Different studies have reported that bacterial biofilms are able to recruit macrophages and neutrophils to the site of infection, albeit not to the extent of the planktonic form (Thurlow et al. 2011, Meyle et al. 2012, Cerca et al. 2011, Snowden et al. 2012, Snowden et al. 2013). Macrophages responding to the infection display dysfunctional phagocytic activity by a still unknown mechanism (Thurlow et al. 2011). Some *in vitro* studies have explored the hypothesis that inhibition of NF- κ B activation and IL-1 β production may be related to this effect (Park, Bryers 2012, Schommer et al. 2011, Prosser et al. 2013). *In vitro* studies with

murine macrophages found a higher proportion of non-activated macrophages and lower proportion of activated macrophages in the peritoneum of mice challenged with biofilm (Cerca et al. 2011). Furthermore, Thurlow et al. found that biofilm effectively elicits macrophage influx during early infection but limits invasion, function and viability of these cells (Thurlow et al. 2011). This study suggests a skewing of the immune response toward an alternatively activated M2 macrophage phenotype, demonstrated by attenuated iNOS expression and increased arginase-1 (Thurlow et al. 2011). The mechanism that biofilm uses to re-direct macrophage response to the less inflammatory M2 phenotype has yet to be determined, but this skewed response likely mediates the immune evasion observed in biofilm infections (Thurlow et al. 2011).

Neutrophils have also been found to be relevant for the containment of biofilm infections (Meyle et al. 2012). Neutrophil presence at the site of infection was found to be dependent on IL-1 β secretion and both components appeared to have a protective role in a post arthroplasty model (Meyle et al. 2012, Bernthal et al. 2011). Nonetheless, neutrophils are not capable of overcoming the infection even when present as their action can be hampered by bacterial production of poly-N-acetylglucosamine and poly-D-glutamic acid (PGA), which prevent bacterial engulfment by neutrophil and antibody mediated phagocytosis. The latter is possibly explained by inhibition of antibody binding directly to the surface of the bacteria due to the large amount of extracellular matrix produced (Cheung et al. 2010, Cerca et al. 2006). Neutrophils appear to be able to respond in some ways to biofilm components, but effective killing is limited by the decreased C3b and IgG deposition, leading to ineffective opsonization (Meyle et al. 2012, Kristian et al. 2008, Guenther et al. 2009). Additionally, studies utilizing adoptive transfer of neutrophils into sites of *S. aureus* biofilm infection demonstrated no effect on bacterial burden (Hanke et al. 2013). In contrast, adoptive transfer of classically activated macrophages did significantly reduce biofilm (Hanke et al. 2013). This corresponds with other studies showing a shift in *S. aureus* biofilm gene expression on microarray when exposed to macrophages, but not neutrophils (Scherr et al. 2013). Cumulatively, these studies suggest that although the function of macrophages is limited in terms of interaction with biofilm, macrophages are more involved in the immune response to biofilms than are neutrophils. In PIA-independent biofilm forming strains, anti-phagocytic properties appear to be attributable to a 20-kDa polysaccharide currently under study as a possible vaccine component (Spiliopoulou et al. 2012). This molecule is mainly composed of glucose, N-acetylglucosamine, and it is partially sulfated. Interestingly, 20-kDa PS antiserum limits adhesion of *S. epidermidis* on endothelial cells and development of keratitis in rabbits. Therefore, it is currently under investigation as a potential conjugate vaccine to enhance phagocytic potential of monocytes and macrophages (Spiliopoulou et al. 2012).

Recent data from Heim et al demonstrated that myeloid-derived suppressor cells represented the primary cellular infiltrate in the tissue surrounding *S. aureus* biofilm infected orthopedic implants, which may explain the paucity of T lymphocytes present at the infection site in that model (Heim et al. 2014). Studies examining human tissue samples from patients with chronic rhinosinusitis have reported the presence of small numbers of CD4⁺ and CD8⁺ lymphocytes in those tissues, suggesting that the T lymphocyte response to biofilm infection may depend of the location of the infection (Wang, Du & Zhao 2014). Our own unpublished

data has not identified a significant T lymphocyte infiltrate into the brain in response to CNS catheter infection, although these cells are known to play a role in parenchymal *S. aureus* infections in the brain (Nichols et al. 2009, Holley, Kielian 2012).

Immune evasion by biofilms

Biofilm structures also produce molecules that directly lyse and inhibit immune function, such as phenol soluble modulins (PSMs). PSMs are synthesized by staphylococcal strains and have lytic activity against leukocytes and red blood cells (Wang et al. 2007). They may play a role as defense mechanism against the immune system, in addition to their role in the structure and development of the biofilm (Otto 2012). Studies have also reported that PSMs trigger chemotaxis and priming of human neutrophils and cytokine expression, so their role in promoting or inhibiting an effective inflammatory response is still under investigation and may vary depending on the type of infection (Wang et al. 2007, Queck et al. 2009, Vuong et al. 2004). *S. aureus* has wide array of toxins produced against innate immune cells, such as leukocidin A/B (LukA/B) which is sufficient to kill macrophages, dendritic cells and neutrophils (Dumont et al. 2011, DuMont et al. 2013). Alpha-toxin is a pore forming toxin capable of destroying many host cells and has been reported in community-acquired methicillin resistant *S. aureus* strains (Hanamsagar, Torres & Kielian 2011). Pantone-Valentine leukocidin (PVL) is another pore-forming toxin reported in staphylococcal strains that is thought to increase virulence by lysing host cells to limit the immune response (Cheung et al. 2010). Furthermore a recent surface proteome study of USA300, a clinically significant methicillin resistant staphylococcal strain, identified a leukotoxin, LukGH, localized on the cell surface which also has cytolytic activity against neutrophils and a synergistic effect with PVL to lyse PMN *in vitro* (Rigby, DeLeo 2012).

4. Treatment

Treatment of shunt infections currently includes shunt removal and systemic or intraventricular antibiotic therapy. A study on the pediatric population found that shunt removal in addition to antibiotic treatment and external ventricular drainage is the most effective approach to eradicate shunt infection (Schreffler, Schreffler & Wittler 2002). Empiric antibiotics recommended by the Infectious Diseases Society of America are vancomycin, for broad spectrum coverage of staphylococci and other gram-positive organisms, and ceftazidime, cefepime or meropenem to provide coverage against gram-negative bacteria (Prusseit et al. 2009). However, the impact of antibiotic therapy alone is limited by pharmacokinetic factors such as drug solubility, pH gradient between the CSF and blood, ionization, protein binding ability, molecular size, drug configuration and the extent of meningeal inflammation, which all limit the ability to reach therapeutic concentrations of antibiotics in the CNS (Nau, Sorgel & Eiffert 2010). Administering antibiotics intra-ventricularly may bypass some of the pharmacokinetic barriers to effective treatment in the CNS and is sometimes used (McGirt et al. 2002, Simon et al. 2012, Kebriaei et al. 2013).

The metabolic and structural characteristics of biofilms also make these infections less susceptible to antibiotic treatment (Hess, Henry-Stanley & Wells 2012, Mah 2001). The extracellular matrix characteristic of biofilm growth can limit antibiotic treatment by binding

the antimicrobial compounds or by degradation of the antimicrobial compounds by enzymes and other by-products. The growth and nutrient adaptations that the biofilm undergoes as a part of metabolic maturation also limit the efficacy of many antibiotics, as their mechanism of action targets growth of the organism (Mah 2001). The multiple mechanisms of antibiotic evasion employed by the biofilm are undergoing extensive study so that more effective treatments can be designed for biofilm infections.

Recently, other approaches dealing with the disruption of the biofilm have been explored. Hydrogels are compounds with antimicrobial activity capable of eradicating the biomass and reducing microbe viability of the biofilm. These antimicrobial polycarbonates do not induce significant cytotoxicity towards human dermal fibroblasts *in vitro* (Lee A. L. Z. et al. 2013). Thus, they may be used either to prevent or to eradicate biofilms but these have yet to be studied *in vivo*.

Anti-biofilm catheter lock therapies have also been used in animal models and human studies, in which high concentrations of bactericidal antibiotic and/or other anti-biofilm compounds are instilled in the lumen of indwelling vascular catheters (Raad et al. 2013, Rosenblatt et al. 2013, Meije et al. 2014, Estes et al. 2013). This approach allows for increased penetration of the biomass and higher levels of local drug delivery to potentially overcome some of the inherent antibiotic resistance seen in biofilm infections. In addition to antibiotics such as daptomycin, ethanol, glyceryl trinitrate and iron chelating agents have been used with preliminary success (Estes et al. 2013, Meije et al. 2014, Raad et al. 2013, Rosenblatt et al. 2013). Other targets of potential anti-biofilm therapy include disruption of the quorum sensing system, dispersion enhancing molecules such as nitric oxide, classically activated macrophages delivered to the site of infection and the use of bacteriophages to lyse bacteria and deliver enzymes that degrade biofilm components (Yu et al. 2012, Jardeleza et al. 2011, Sillankorva, Azeredo 2014, Hanke et al. 2013, Jardeleza et al. 2011, Sillankorva, Azeredo 2014). While these treatment modalities are currently under investigation for the treatment of biofilm infections in the periphery, they have not yet been utilized in CNS catheters.

5. Prevention

Ventriculoperitoneal shunt infection is an undesirable outcome in neurosurgery and as such, preventative strategies are being explored as well as new treatment options. Risk factors associated with the perioperative and operative period are of critical importance so that we can see reductions in the infection rate. Simple measures such as hand washing and reducing the bacterial load from patient's skin, double gloving or changing the gloves during surgery, and minimizing the handling of shunt have proven to be effective and efficient techniques against shunt infections (Prusseit et al. 2009, Pirotte et al. 2007, Kestle et al. 2011). Peri-operative antibiotics are also helpful in reducing the risk of infection, but the optimal antibiotic for this purpose is not clear, as resistance patterns may limit the effectiveness of beta-lactam antibiotics and pharmacokinetic factors and the concern for increasing resistance rates may limit the efficacy of vancomycin (O'GARA, HUMPHREYS 2001, Sieradzki et al. 1999). Kestle, et al, evaluated a surgical protocol for the purpose of decreasing the shunt infections including intraventricular antibiotics at the time of surgery,

in attempt to overcome the pharmacokinetic limitations of perioperative antibiotics in this setting; while the protocol did result in a decrease in the infection rates observed, no decrease was specifically attributable to the intra-ventricular antibiotics (Kestle et al. 2011).

Antibiotic impregnated shunts, including devices with added rifampicin or clindamycin, have also been studied as a means of preventing shunt infection (Gutierrez-Gonzalez et al. 2008). Bayston et al used an *in vitro* model to test the ability of antibiotic impregnated catheters to effectively control bacterial infection (Bayston, Ashraf & Bhundia 2004). They found that antibiotic impregnated catheters do not prevent microbial adherence but do kill 100% of attached cells in 48–52 hours, even in the presence of a biofilm (Bayston, Ashraf & Bhundia 2004). Despite the efficacy of antibiotic impregnated catheters in *in vitro* models, retrospective studies and clinical trials have not found significant reduction in the rate of infection between patients with conventional versus antibiotic impregnated devices (Ritz et al. 2007, Kan, Kestle 2007). Antibiotic impregnated shunts are promising, but further studies are needed regarding the risks of antimicrobial resistance and the cost benefits of these devices (Stevens et al. 2012, Gutierrez-Gonzalez et al. 2010). Other biomaterials under investigation include silverimpregnated catheters, which may prevent the initial adherence of bacteria to the catheter at the time of implantation (Lorente et al. 2014). These have been shown to be well tolerated in the periphery and associated with decreased rates of infection, as well in the CNS when used as external ventricular drains (Keong et al. 2012, Winkler et al. 2013).

Another prophylactic approach being currently explored is the use of immunotherapy or vaccines against *S. epidermidis* biofilms (Van Mellaert et al. 2012). Development of a staphylococcal vaccine is difficult, particularly given the lack of protective immunity after natural staphylococcal infection (Harro et al. 2010). Current vaccine targets include secreted and cell surface associated virulence factors from planktonic and biofilm growth modalities, as well as other protective antigens identified after vaccination with attenuated staphylococcal strains (Kim et al. 2014, Stranger-Jones, Bae & Schneewind 2006, Brady et al. 2011, Anderson et al. 2012). Greater understanding of immunological interactions between the host and the biofilm is required for the selection of effective targets for optimal vaccine design.

6. Conclusions and Outstanding Questions

Shunt infections can complicate otherwise successful treatment of hydrocephalus, leading to increased healthcare costs and patient morbidity. Great strides have been made in recent years regarding the pathogenesis of biofilms and their role in these device infections, as well as the role of the host immune response to this infection. However, limited data is available regarding the immune response to biofilm infections in the CNS. Given the unique and complex inflammatory milieu in the CNS, it is reasonable to assume that the immune response will be distinct from that observed in the periphery. The relative contribution of resident glia such as microglia, versus the innate immune cells such as macrophages, which have been shown to be skewed in response to biofilm infection, needs to be better defined. The homeostatic activities of microglia and other resident CNS cells, as well as their somewhat anti-inflammatory profile at baseline, may alter the immune response in the CNS in

comparison to peripheral sites. For example, microglial production of IL-10, which has been demonstrated to be neuroprotective and important in neuronal synapse formation, may play a significant role in the skewed immune response to a biofilm infection in the brain (Lim et al. 2013). These factors unique to the CNS may provide therapeutic targets specifically tailored for treatment of these infections in such a privileged site.

The relative contribution of direct bacterial damage versus the effect of the immune response to biofilm in the brain on neurologic development also remains unknown. This is of particular interest given the high incidence of these biofilm infections in neonates and young infants, where infection and inflammation could have profound impact on developmental outcomes. Infants less than 6 months of age, particularly those who are premature or had low birth weights, are at particularly high risk for shunt infection and complications (Pople, Bayston & Hayward 1992, Duhaime 2006) (McGirt et al. 2002). This may be related to immaturity of the neonatal immune system, poor skin barrier protections, altered skin bacterial density and other comorbidities and procedures (Pople, Bayston & Hayward 1992).

Strategies to modify the immune response to minimize damage secondary to inflammatory mediators while preserving the protective mechanisms inherent to the CNS are needed to optimize treatment of SI. It is imperative to combine clinical and laboratory research efforts to overcome this problem, by finding new methods to treat and prevent biofilm formation using infection resistant shunts, anti-biofilm compounds, adjunctive immunotherapies or immune screening to identify high risk patients. Further exploration of these issues is ongoing to devise strategies that will translate from the laboratory to patient care, to assist in the prevention and treatment of these infections.

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Abbreviations

CSF	cerebrospinal fluid
VP	ventriculoperitoneal
SI	shunt infection
CNS	central nervous system
IQ	intelligence quotient
PIA	polysaccharide intercellular adhesion

Embp	fibronectin-binding protein
Aap	accumulation-associated protein
PSM	phenol-soluble modulin
TLR	Toll-like receptor
NLR	Nod-like receptor
TA	teichoic acids
Lpp	lipoproteins
LTA	lipoteichoic acid
LukA/B	leukocidin A/B
PVL	Panton-Valentine leukocidin.

Highlights

- Infection often complicates shunt placement, causing long term neurologic problems.
- These infections are caused by biofilms which are antibiotic resistant.
- The immune response to biofilm infection is skewed, allowing bacterial persistence.
- Understanding the neuroimmune response to biofilm is needed to improve outcomes.

Figure 1. Overview of biofilm pathogenesis, immune responses and prevention/treatment options Biofilm development occurs in three stages, with attachment followed by proliferation and then dispersal. Prevention strategies, such as antimicrobial and antibiofilm materials, decrease initial attachment. The proliferation phase is marked by a skewed immune response, with decreased inflammation. Strategies currently under investigation for treatment of proliferating biofilm include dispersal agents, classically activated macrophages and lock therapy with antibiotic or other antibiofilm agents. Patients typically become symptomatic during the dispersal phase, with release of planktonic bacteria prompting a more inflammatory immune response. During the dispersal phase, systemic and intra-ventricular antibiotics can be used to treat the planktonic bacteria but device removal is still needed because of residual biofilm.