Cerebrospinal fluid shunt infection: Microbiological basis

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Abstract

Shunt infection rates have fallen in recent decades but are still too high, especially when infants under 6 months of age are shunted. The causative bacteria are mainly staphylococci derived from the patient's skin during operation. Bacteria develop biofilms inside the shunt and this has important implications for treatment. The protective effect of perioperative antibiotic prophylaxis is weak, leading to increased use of antimicrobial shunt catheters, though greater attention to operating room asepsis and antisepsis are at least as important.

Introduction

Until the development of successful shunting devices for the treatment of hydrocephalus in the 1950s, little could be done to control the increasing intracranial pressure and many infants and adults either lived a miserable life or died of their condition. The valve mechanisms, and particularly the materials, were improved and eventually a silicone shunt became available that was biocompatible and could be safely sterilized. Gradually shunting became the

treatment of choice for hydrocephalus. However, as early as 1959, Andersen, Carrington, and others were reporting feverish illness and bacteraemia in shunted children. Of course, these early shunts were ventriculoatrial (VA). Cohen and Callaghan (1961) reported that most of these bacteraemias were due to staphylococci, yet they were rarely treatable with antistaphylococcal antibiotics. Reports of infection continued throughout the 1960s, with little progress in identifying the cause or in developing a successful treatment. Only in the 1970s was progress made towards understanding these infections and their cause, yet infection rates remain unacceptably high in many settings. However, much of the new knowledge obtained from the study of shunt infections applies to other infections occurring in implantable devices such as hip and knee replacements.

Aetiology of shunt infections

Incidence of infection

There has always been considerable variation in reported shunt infection rates, due partly to different standards of investigation and diagnostic criteria, but generally the incidence has fallen over the last 25 years from the 14-23% reported by Shurtleff et al (1971) and Schoenbaum et al (1975). The usual rate reported in the recent literature is around 10% (Kulkani et al 2001; Simon et al 2009; Lee et al 2012). However, it has been clear for some time that the infection rate in infants shunted before the age of six months is significantly higher that that for other age groups (Renier et al 1984; Pople et al 1992; Kulkani et al 2001), and can reach 15-20% of operations (Kulkani et al 2001). Most studies have not found a significant difference in shunt infection rate between the atrial and peritoneal routes (Puca et al 1991; Borgbjerg et al 1995).

Causative bacteria, their habitats and sources

Staphylococci are the commonest bacteria causing shunt infection, with the coagulase – negative group (CoNS) represented by *Staphylococcus epidermidis* in the majority (Desai et al 2009). Propionibacteria form a smaller but important proportion especially in adults (Desai et al 2009; Portillo et al 2013). Other bacteria and fungi are seen in smaller proportions but in shunted neonates the gram negative bacteria such as *Escherichia coli* are important, especially in those with congenital anomalies such as meningomyelocele (Stamos et al 1993). In well – run institutions, outbreaks of shunt infection due to a particular bacterium are rare but they do occur and when temporally related cases due to the same organism are found, then a point source should be sought. This might be a member of staff who is carrying a particularly virulent strain such as MRSA, or it might be an engineering problem in the operating suite, or a breach of aseptic protocol. Apart from such instances, most shunt infections are considered to be due to normal skin inhabitants (Bayston and Lari 1974;) though this is difficult to demonstrate because of low infection rates, and the concept has been challenged (Thompson et al 2007). The skin flora can be transient, arising from recent contamination of the skin from the environment or from faeces, or they can be the more common resident flora that is relatively stable. At this point, it is useful to consider the extremely valuable data from the Human Microbiome Project (Grice and Segre 2011). To a large extent the different physiology of the skin in various body sites determines the bacterial flora. Sebaceous and moist areas such as the upper face, scalp, external ear canal and retroauricular crease harbour most staphylococci and they are also the sites where most

Propionibacterium acnes are found. It is no coincidence that the most common shunt pathogens are found in sites adjacent to the incision sites. While the environment and particularly the operating room air have been held to be sources of shunt pathogens, they represent a minor source in modern operating environments, and evidence points clearly to the patient's skin as the main source. Evidence in support of this was found several decades ago (Bayston and Lari 1974). A consecutive series of 100 shunt insertions was studied by sampling the patient's skin before incision, and sampling the incision just before placement of the shunt. All bacterial isolates were saved and compared with those from shunt infections that presented over the following two months. Nine shunt infections occurred, and the causative strains of *S epidermidis* in seven of these were found to be indistinguishable from those found in the incision and on the patients' skin at operation. The remaining two isolates were a coryneform and a viridans streptococcus, neither of which could be typed for comparison. Rather surprisingly, 58 of the incisions showed contamination with skin bacteria at the time of shunt placement, and the majority appeared to have originated on the patients' skin; all of the shunt infections were caused by these isolates, and not by any of those from elsewhere. In addition, the non-patient-derived isolates were represented by significantly lower numbers in the incision. Peri-operative contamination of the incision was also confirmed by Rahaave et al (1976) and a similar finding was reported in a study of incision contamination in spine surgery (McLorinan et al 2005). In a study of sources of infection in shunted neonates, Pople et al (1992) also found a high rate in incision contamination from the patient's skin, and also linked the high rate in this group to statistically significantly heavier bacterial skin colonisation with highly adherent strains.

This could be because premature infants often spend much of their early lives in hospital, and this has been shown to lead to colonisation of their skin by adherent, multiresistant "hospital" strains.

Conventional patient skin antisepsis is not as effective as many believe at removing bacteria from the skin. Many studies have been carried out to compare the two main agents, chlorhexidine (CHD) and povidone iodine (PVPI), but conflicting results have appeared, mainly because of poor trial design such as comparison of aqueous PVPI with alcoholic CHD (Darouiche et al), and one study showed that alcohol alone was just as effective (Maiwald and Chan 2012). However, almost all studies have used skin surface swabs to assess bacteria eradication, and it has been known for some time that none of the available skin antisepsis regimens penetrates well enough to kill bacteria in the dermis, particularly in the sebaceous glands, and these survive to enter the incision during the procedure.

Access to the device

In view of the above studies, one can see the ease with which skin bacteria can access the incision and then can access the shunt as it is placed. Bacteria can be pushed into the ventricular system or the peritoneal cavity along with the catheters, and they can also enter the shunt tubing when connections are made. The most important mode of transfer from incision to shunt is probably by means of the surgeon's gloves, which become contaminated with skin bacteria early in the procedure (Sørensen et al 2008). This has led to the use of double gloving, which was originally introduced to protect the surgeon from blood – borne infection. The rationale is probably that the outer (contaminated) pair is

removed before handling the shunt. A study by Tulipan et al (2006) suggested that double gloving reduced shunt infection, though in that study the gloves were not changed.

Mechanisms of shunt colonisation and infection

Once the bacteria are inside the shunt tubing they have the opportunity to adhere to the silicone shunt material. This is hydrophobic and most bacteria readily attach. Once attached, the bacteria modify their metabolism under genetic regulatory control, down-regulating cellular metabolic activity associated with synthesis of haemolysins, toxins etc in favour of developing a sessile lifestyle. This also results in significant increases in concentrations of antibiotic needed to kill them (Williams et al 1997). Eventually (usually after a few weeks) they develop a biofilm inside the shunt (Figs 1 and 2). It is of interest to note that the first biofilm affecting a medical device was found in a CSF shunt (Bayston and Penny 1972). A biofilm is a functional community of bacteria attached to a surface. The term "functional" is important as it is not merely a passive heap of bacteria. As the biofilm develops, the bacteria in the deeper layers become depleted of energy (Proctor 1998) and the metabolic down-regulation continues until the bacteria become dormant. In this state, most synthetic processes of cell wall, proteins and DNA replication are severely reduced, and these are the targets for the most common groups of antibiotics: penicillins and cephalosporins, vancomycin, aminoglycosides and quinolones. The dormant state is therefore responsible for persistence of low grade infection and failure of systemic antibiotic therapy (Tuomanen 1986; Brown et al 1988; Hoiby et al 2010).

Other sources of shunt infection

It is likely that almost all shunt infections begin at insertion or revision surgery, and haematogenous seeding appears to be rare. However, infection can occur as a result of erosion of skin over the shunt, if it is unwisely positioned, if the skin is fragile as in an infant, or if a debilitated patient lies on it for long periods. Other rare causes are reported in the literature and some have been seen by this author. Perforation of an abdominal viscus leads to contamination of the distal catheter and can progress to ventriculitis, and this is often due to a mixture of enteric bacteria including anaerobes (Brook et al 1977). Such cases sometimes present as protrusion of the distal catheter through the anus or vulva (Ghritlaharey et al 2007).

Laboratory diagnosis

Though they are often done, blood cultures are not usually positive in VP shunt infections. Inflammatory markers, especially C-reactive protein (CRP), are usually raised because of the inflammatory response in the abdomen and around the distal catheter. If there is clinical suspicion of shunt infection, if the CRP is raised and especially if no more that 6-8 months have elapsed since operation, then aspiration of CSF from the shunt reservoir should be carried out. The CSF should be examined according to routine protocols for meningitis, with cell count, protein and glucose estimations. Agar media should be inoculated and incubated aerobically for 48-72 hours, and anaerobically for 10-14 days (Desai et al 2009). If the latter media are discarded before this, *P acnes* will not be detected. The use of liquid cultures is debated: they are more sensitive than solid

media but are prone to contamination. Again, the dormant biofilm phenotype described above often gives rise to very small colonies (small colony variants, SCV) which can remain undetected or can be dismissed as contaminants, especially if mixed with the larger parent colonies (Proctor et al 2006 Nature; Spanu et al 2005; Johns et al 2015) (Fig 3). SCV usually revert to large colonies on repeated subculture, and are otherwise phenotypically and genetically identical to the parent forms. A direct gram film of the CSF is valuable as, if no bacteria are seen on reasonable search, any isolate is very likely to be a contaminant, and if bacteria are seen but not grown then further extended culture is prompted. Antibiotic susceptibility tests should be carried out according to national guidelines.

Blood cultures from patients with VA shunts are usually positive, except in delayed presentation when several pairs of cultures might be needed to yield the causative bacteria, and again they might appear as SCV (Ben – Ami et al 2003). Aspner et al (2000) have suggested massaging the scalp over the shunt before withdrawing blood for culture, and where possible the valve chamber can be depressed a few times, but practitioners should be aware that rigors could be precipitated. Contamination of blood samples is always a possibility where the pathogens sought are also common skin bacteria such as *S epidermidis*, and repeat cultures might be needed to confirm. The clinical presentation of VA shunt infection is so variable (Bayston et al; Legoupil et al 2003; Rames et al 1970) that further confirmation might be needed, and a simple serological test, the ASET or anti-*Staphylococcus epidermidis* titre, can be very useful (Bayston 1979). Where VA shunt infections present as immune complex disease, with potentially misleading features such as skin rash, cough, haematuria or joint

swelling, the ASET can be useful to confirm or even suggest the diagnosis (Clayton et al 2005). Serum complement (C3, C4) levels will be depressed in most cases of immune complex disease due to late-presenting VA shunt infection. If shunt nephritis is suspected, ASET, blood culture, complement levels and any renal function anomalies should be sufficient to make a diagnosis and renal biopsy is not necessary (Bayston and Rodgers 1994). Culture procedures and microscopy for aspirated CSF should be the same as those for VP shunts.

When a shunt is removed because of suspected infection, it should always be sent to the laboratory for examination (Bayston et al 1983). Microbiologists need to be familiar with shunt anatomy, and samples of fluid should be withdrawn with strict aseptic precautions from the shunt tubing and cultured as for CSF. Again, gram film is essential. Simply immersing tubing in liquid medium for culture is not advisable as it often gives rise to positive cultures that are contaminants from the outer surfaces of the tubing, and for the same reason ventricular catheter tip cultures tend to over-diagnose infection. Sonication of the tubing may yield more bacteria from the inside so long as the ends of the tubing are not immersed in the sonicator, but simply squeezing the tubing by hand before aspirating it usually suffices. In a colonized shunt, it is not unusual to find milky fluid containing millions of bacteria per mL.

Pathogenesis of shunt infection

Though most shunt infections give rise to a degree of ventricular inflammation, in the case of *S epidermidis*, *P acnes* and other "low grade" pathogens this is not great, and this has therapeutic implications. However, even these organisms are capable of causing ventricular loculation where the diagnosis is delayed or

treatment is suboptimal (Jamjoom et al 1996). It is also important to appreciate that in some cases the ventricular CSF is normal and yields no growth on culture, and a negative aspiration does not necessarily rule out shunt infection. In VP shunts the bacteria and their products are discharged into the peritoneal cavity, which reacts by sealing off the distal catheter by adhesions or omentum. This has two results: it obstructs free drainage of CSF precipitating return of symptoms of raised intracranial hypertension, and it often causes reflux up the catheter track, showing as erythema over the distal catheter. Severe infection of the omentum can present as acute abdomen (Reynolds et al 1983; Patrick et al 1990; Worley et al 2001). While cystic obstruction of the distal catheter can occur in the absence of evidence of infection, if it appears within 6-8 months of shunt surgery it strongly suggests shunt infection. The inflammatory response in the abdomen and the catheter track accounts for the rise in inflammatory markers such as CRP.

Infection in VA shunts has very different pathology. The infected CSF discharges directly into the bloodstream, causing pyrexia and sometimes rigors, and giving rise to increasing antibody production. The amount of bacterial antigen in the blood is often high, and when the immune complexes of antibody and antigen reach a certain concentration they precipitate on basement membranes, particularly in the lungs, joints, glomeruli and skin (Haffner et al 1997; Kauffman et al 1971). As VA shunts do not usually obstruct due to infection, the immunization process can continue for months or years before the immune complex disease shows itself as skin rash, arthropathy or haematuria. Once the correct diagnosis is made and effective treatment instituted, these features

usually subside, and even renal function usually improves to near normal. Endocarditis in VA shunt infection is rare.

Treatment of shunt infection

The two main therapeutic problems in antibiotic treatment of shunt infection are poor penetration of most systemically administered antibiotics into the CSF, and reduced susceptibility of biofilm bacteria to almost all antibiotics (Hoiby et al 2010). As the degree of ventricular inflammation in most shunt infections is low (Lutsar et al 1998; Sullins et al 2013), only a few antibiotics are able to penetrate into the CSF in therapeutic quantities, and even these are not capable of eradicating biofilm bacteria in the shunt catheters. The nature of shunt infection as a biofilm disease therefore explains the need in most cases for shunt (and therefore biofilm) removal. As an example, an isolate of *S epidermidis* from a shunt infection patient will show a Minimum Inhibitory Concentration (MIC) of 1mg/L of vancomycin in laboratory testing, but the same bacteria growing as a biofilm in the shunt are up to 1000 times less susceptible, giving an MIC of 1000mg/L. This concentration is not achievable by systemic administration of vancomycin or other antibiotics. Even with continuous intravenous infusion, when plasma levels are maintained at 20-30mg/L to avoid toxicity, the CSF levels range from 2-5mg/L. Even after the shunt is removed, the same bacteria in the ventricular system retain reduced susceptibility, and this along with the poor penetration suggest that intrathecal administration might be more successful. Guidelines were introduced in UK in 1995 (Working Party on the Use of Antibiotics in Neurosurgery of the British Society for Antimicrobial Chemotherapy) that included intraventricular administration of 20mg/day

vancomycin and oral or intravenous administration of rifampicin 300mg twice daily or 15mg/Kg/day for children). Use of this regimen has given good results in terms of first – time success without relapse (Bayston et al 1987), and a much shorter course of antibiotics before re-shunting. CSF vancomycin levels can reach 200-250mg/L on this regimen (Pfausler et al 1997; Al Jeraisy et al 2004) but they are administered for only 7-10 days and have proved to be safe and effective (Thompson et al 2005). A few reports have appeared of CSF eosinophilia associated with intraventricular vancomycin use (Al Jeraisy et al 2004) but CSF eosinophilia can be associated with infection and shunt malfunction as well as other factors and the reported cases were not necessarily caused by vancomycin (Bezerra et al 2011). In one case, the eosinophilia was probably secondary to shunt obstruction and latex allergy. The CSF eosinophilia was successfully treated with pulsed methylprednisolone (Tangsinmankong et al 1999). The intraventricular route has also been shown to be both safe and effective for other agents such as aminoglycosides and colistin for treatment of ventriculitis caused by gram negative bacilli (Tängden et al 2011; Bargiacchi et al 2014). CSF colistin levels after intravenous administration do not reach sufficiently high concentrations (Antachopoulos et al 2010), and toxicity is a concern, but as with vancomycin, higher concentrations can be achieved safely with intraventricular administration. The efficacy of colistin against multi-resistant gram negative bacteria such as *Acinetobacter baumannii* can be enhanced by the addition of intravenous rifampicin (Bargiacchi et al 2014). Recently linezolid, an oxazolidinone antibiotic, has been shown to give very high CSF concentrations on oral and intravenous administration (Diekma and Jones 2000; Gill et al 2002) and its safety and CSF pharmacokinetics have been

reported (Boak et al 2014). The drug has been shown in vitro to eradicate *S aureus* (including MRSA) and *S epidermidis* biofilms from shunt catheters without regrowth (Bayston et al 2012). Earlier in vitro investigation suggested that addition of rifampicin might be necessary for eradication of *P acnes* biofilms (Bayston et al 2007). Three cases of staphylococcal shunt infection have now been treated successfully with linezolid without recourse to shunt removal (Castro et al 2005, Yilmaz et al 2010). If confirmed, this regimen would offer treatment of staphylococcal shunt infection without surgical removal and without intraventricular administration of antibiotics. A multicentre trial has begun in UK to evaluate this novel treatment approach.

Another exception to the principle that the shunt must be removed is in cases of community-acquired meningitis in a shunted patient. The bacteria involved, *Streptococcus pneumoniae, Haemophilus influenzae* or *Neisseria meningitidis*, do not colonise the shunt catheters and shunt removal in such a case is unnecessary and often detrimental (O'Keefe et al 1991; Stern et al 1988; Rennals et al 1980).

<u>Prevention</u>

As we have now established the source of most shunt pathogens and the means by which they access the shunt, we can apply the information to attempts at prevention, or at least reduction of risk. Even though most bacteria causing shunt infection originate with the patient, other factors such as attention to operating theatre discipline are important. Though most operating theatre practices are "rituals" (Humphreys JHI 2009) and have little or no evidence base, this is not a reason for their abandonment (Smith BMJ Parachute paper 2003). The introduction of a practice protocol consisting of "common sense" activities

and emphasising aseptic technique, agreed upon by all surgical staff including nursing and technical, and regularly reviewed and reinforced, has been found frequently to be beneficial in reducing infection rates (Choux et al 1992; Choksey and Malik 2004), and breaches of the protocol have been associated with increased infection risk (Kestle et al 2011). This might be thought of as exploitation of the Hawthorne Effect (McCambridge et al 2014).

Operating room ventilation

However, more specific measures are also available. The quality of air and ventilation in the operating theatre is very important, but there is no requirement for ultra-clean laminar flow, and in recent years the desirability of this mode of ventilation has been reassessed and brought into question. Current evidence from arthroplasty surgery shows that laminar flow ventilation either makes no difference to infection rates, or in some cases is associated with a statistically significant increase (Brandt et al 2008; Hooper et al 2010). The reasons for this are two-fold. In a modern operating theatre, standards of general hygiene are such that almost all shunt pathogens arise from the patient, and this would not be affected; and laminar flow operates efficiently only when the theatre is not in use. Interference with the laminar air flow by lights, surgeons' heads and hands, and other obstructions causes flow to become turbulent. Another factor is that the high frequency of air changes causes dehydration of tissues, and means that the patient must be kept warm by equipment that causes back-flow of heated air into the operation field (Gastmeier et al 2012).

Shaving

Traditionally, the head was shaved before neurosurgery, but this has now been shown to damage the skin and increase the risk of infection (Broekman ML et al

2011; Ross 2013). Hair can be clipped shorter over the planned incision site though this is not necessary. The whole of the head hair should be shampooed with an antiseptic such as aqueous povidone iodine just prior to surgery, and then prepared again in the operating suite in the same way as the skin, using an alcoholic preparation. It is important to ensure that the hair is dry before applying adhesive drapes.

Drapes and skin edge barriers

The use of impervious adhesive drapes does not in itself reduce infection rates, even when iodine – impregnated ones are used (Webster and Alghamdi 2015). However, if the adhesive drapes are applied over the cloth drapes, which often become wet and therefore contaminated during surgery, they provide a clean, dry, uncontaminated field immediately around the incision.

As bacteria resident in the skin are known to enter the incision from the cut skin edges (Bayston and Lari 1974; Rahaave 1974), the application of gauze barriers soaked in bacitracin solution or aqueous antiseptic such as povidone iodine around the edges of the incision has been suggested (Thompson et al 2007). Irrigation of the incision at intervals during shunt surgery, usually with povidone iodine (Choux et al 1992) or bacitracin solution, has been widely used, but in a recent study (Hayashi et al 2010) irrigation with saline alone was found to be equally effective as with amikacin solution.

Prophylactic antibiotics

Prophylactic antibiotics are widely used in most types of surgery, yet there are different factors to consider in neurosurgery. One must consider in the light of our knowledge of the mechanisms of shunt infection whether antibiotics are required in the tissue or in the CSF, or both. As skin bacteria easily enter the

incision during surgery, antibiotics in the tissue might appear to be desirable, yet one can find antibiotic concentrations and susceptible bacteria co-existing in the incision (Bayston 1975). The explanation for this is that antibiotics are very slow to act on bacteria. In addition, most shunt infections are due to bacteria gaining access to the inside of the shunt catheters and to the ventricle, and prophylactic antibiotics are most likely to be effective if they are present in the CSF. However, as is found in treatment of shunt infection, most intravenous antibiotics do not reach therapeutic concentrations in the CSF in the absence of significant inflammation (Arnell et al 2007), suggesting that intraventricular administration might be needed. Unfortunately, a small trial of intraventricular vancomycin (Bayston et al 1990) failed to reduce the shunt infection rate, probably because of the slow action of vancomycin and its progressive dilution in the CSF after administration. Interestingly, a sequential study has been reported in which intravenous cefazolin plus intraventricular gentamicin gave an infection rate of 5.5% and the addition to this regimen of intraventricular vancomycin reduced this to 0.4% (Ragel et al 2006). This synergy has been noted previously in clinical studies on endocarditis, and has been explained by Cottagnoud et al (2003) by significantly greater penetration of bacterial cells by gentamicin in the presence of vancomycin. A randomised controlled trial would be useful to confirm Ragel's findings. The conventional systemic prophylaxis has been studied numerous times with variable results, and meta-analyses have tended to support its use, but more analytical studies have found that a beneficial effect on infection rate can be expected only if the base infection rate exceeds 15% (Infection in Neurosurgery Working Party of the British Society for Antimicrobial

Chemotherapy: Antimicrobial prophylaxis in Neurosurgery and after Head Injury 1994).

Local administration of antiseptics and antibiotics

The Listerian principle of placing the antimicrobial where the bacteria are located, and by implication not elsewhere, supports local antibiotic prophylaxis such as perioperative irrigation. Recently there has been increasing interest, especially in spinal instrumentation, in the peri-operative use of antibiotic powder, and both bacitracin and vancomycin have been used. Bacitracin has been widely used in USA for irrigation of shunts before implantation, but the powder has also been used directly into the incision before closure. This has been reported to be both safe and effective (Beckman et al 2015a, Beckman et al 2015b). However, the authors also changed several aspects of their practice during this sequential study, including the use in some patients of intrathecal prophylactic antibiotics, and impregnated catheters. All patients received peri-operative wound irrigation with bacitracin solution. While the authors carried out rigorous multivariate analysis that clearly identified the application of bacitracin powder as the main factor in reducing shunt infection rate, the sequential nature of the trial and the changes in practice indicate the need for confirmation using a randomised controlled trial model. It is also difficult to understand how application of antibiotic powder to the extracranial surfaces just before closure could influence intracranial of intrashunt events. Vancomycin powder has also been used in craniotomies (Abdullah et al 2015), where the aim is to reduce infection in bone and soft tissue, and this rationale is easier to accept.

Antimicrobial catheters

The Listerian principle also underlies the use of antimicrobial –impregnated shunt catheters. We must accept that, while the risk might be reduced, shunt pathogens will gain access to the shunt catheters in some cases. Once bacteria attach to a surface, and even before they have begun to form a biofilm, they change their metabolism to become significantly less susceptible to antibiotics, and they take longer to kill. For a given antibiotic, a bacterium might take 6hours to kill in suspension in a laboratory culture, yet it might take several days for 100% kill when attached to a catheter surface (Bayston et al 2004). Antimicrobial catheters must therefore present a surface that has sufficient antimicrobial activity that persists in flow conditions for at least several days. In addition to the outer surface, the activity must exist on the inner surface of the catheter as this is where most shunt infections begin.

Types of catheter available for use in shunting

One approach to reducing shunt infection risk is to make the catheter surface "non-stick". Bacteria adhere more readily to hydrophobic surfaces such as silicone, and if the silicone were to be coated with a hydrophilic surface then the numbers of bacteria attaching might be reduced (Bridgett et al 1993). Whether this reduction would translate into a reduction in infection is unknown. Hydrophilic coatings need to be rehydrated by soaking in sterile water before use, and addition of antibiotics to the water is often recommended. It is also difficult to coat the inside surface by such processes. An example of such a catheter is Bioglide. After soaking the catheters in solutions of several antibiotics, the internal surfaces of the catheters still became colonized in vitro because they were treated only on the outside. Even on the outside, antibacterial activity was short-lived (Bayston et al 2005). A clinical study of the same

catheters used in external ventricular drainage (EVD) confirmed their lack of protection against infection (Kaufmann et al 2004), and this was also noted by Kestle et al (2011).

Antibiotic-coated catheters lack the necessary duration of activity and a different approach is needed. A process has been devised in which antimicrobials in molecular form are introduced throughout the catheter material, and are able to migrate through the material so that as antimicrobial molecules are removed from the surface by fluid flow they are replenished from the material itself (Bayston et al 1989). This can provide protective antimicrobial activity for about 50 days (Bayston et al 1997). This duration is suitable for use in EVD as well as in shunts. Several clinical studies of the antimicrobial catheters (Bactiseal, Johnson & Johnson Inc, USA) have been carried out, and though they vary considerably in quality, most indicate significantly reduced shunt infection rates. A meta-analysis (Thomas et al 2012) confirmed a significant benefit, as did a UK National Registry report (Pickard et al 2015).

Silver-processed catheters have been used in various clinical settings for several years. Silver can be bactericidal with a broad spectrum of activity, but only under certain defined conditions. Metallic silver has minimal antibacterial activity, and the metal must ionise in order to be bactericidal. Its use as a coating on shunt material often means that the duration of activity is short. However, silver can be used as nanoparticles which have very different physicochemical behaviour from the bulk metal. When nanoparticulate silver is incorporated throughout polyurethane catheters, the absorption of water by the catheters apparently leads to release of silver ions that migrate to the surface (Guggenbichler et al 1999) in a similar way to that in which antibiotics migrate in Bactiseal catheters.

When nanoparticulate silver- processed silicone shunt catheters of the same manufacture were evaluated in vitro they failed to prevent bacterial colonization (Bayston, Vera et al 2009), introducing doubt that the mechanism of silver ion migration identified in polyurethane catheters applied to silicone.
Commercial EVD catheters employing this technology (Silverline, Spiegelberg GmbH, Germany) have been available for some time and several clinical studies have reported mixed results (Lajcak et al 2010, Fichtner et al 2010, Keong et al 2012), very like those for nanoparticulate silver catheters in other settings (Kalfon et al 2007, Crabtree et al 2003, Pickard et al 2012). A review has compared antimicrobial- impregnated with silver-processed catheters in external ventricular drainage and found evidence to support effectiveness of the former but not the latter (Wang et al 2013). A systematic review of Bactiseal, Silverline and hydrogel-coated catheters for shunts and EVD has suggested that there may be some selection of more resistant bacteria such as MRSA or gram negative bacilli (Konstantelias et al 2015), though this might be a phenomenon of proportionality where the gram positive bacteria are "removed" from the profile by the antimicrobial catheters, leaving an apparently increased number of those insusceptible to them. Certainly, a large study of Bactiseal shunts has revealed no such increase in multiresistant bacteria including gram negative bacilli (James et al 2014). Silverline shunt catheters are now also available and are currently being compared to Bactiseal shunts and plain catheters in the UK randomised controlled multicentre BASICS trial.

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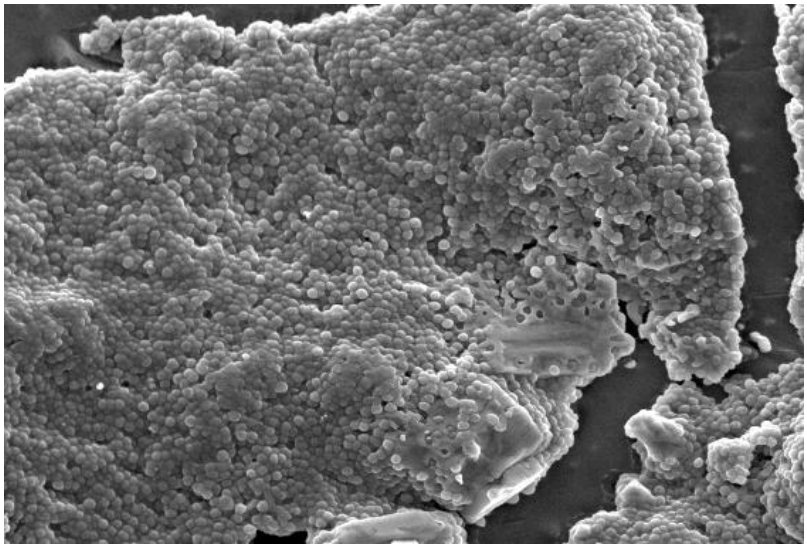

Figure 1. Biofilm of Staphylococcus epidermidis, scanning electron micrograph x 5000.

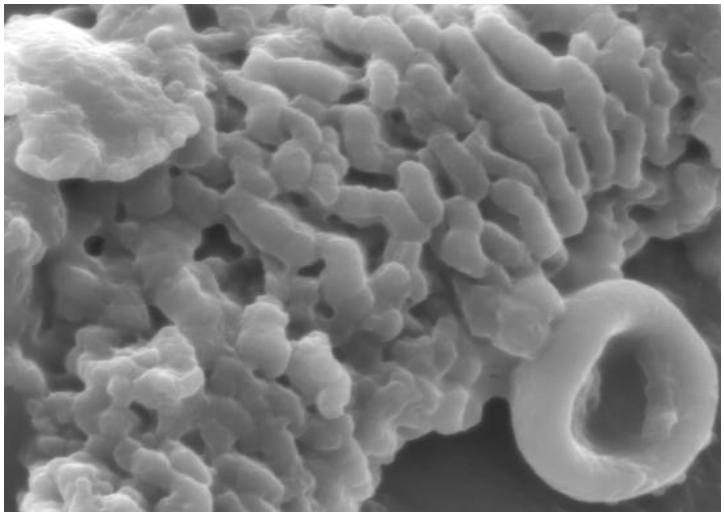

Figure 2: Biofilm of *Propionibacterium acnes* with a red blood cell. Electron micrograph x 5000.

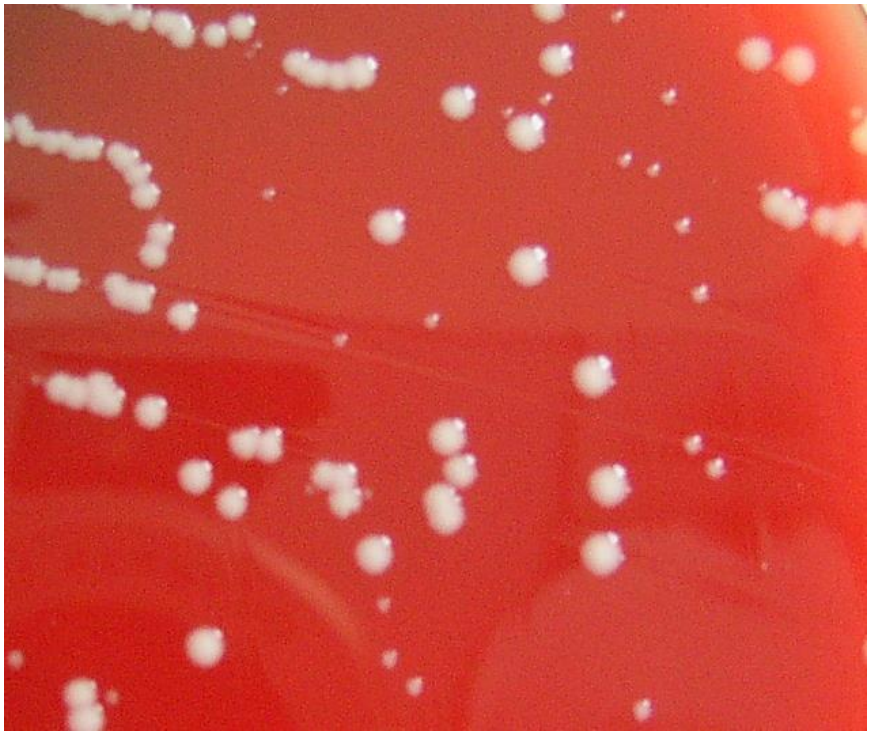

Figure 3: Normal sized *Staphylococcus aureus* colonies with their small colony variants (SCV) on blood agar.