Chapter

Infections in CSF Shunts and External Ventricular Drainage

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Abstract

Infection in those with hydrocephalus shunts or external drains (EVDs) can cause serious central nervous system damage with lasting sequelae. The infections usually involve bacterial colonisation and biofilm formation in the catheters. The nature and sources of pathogens and preventive measures are discussed. The risks of infection in shunts and EVDs is different. Infection in shunts is almost always initiated at their insertion or revision (exceptions are described). In contrast, in EVDs, the risk of infection persists throughout their use. The pathogen profile is also different. These factors are important considerations when planning preventive measures. Newer strategies such as antimicrobial catheters are discussed. Diagnosis of EVD infections in an already ill patient is difficult but guidelines can be useful. Treatment of the shunt and EVD infections are also addressed, with reference to modes and routes of antibiotic administration.

Keywords: Hydrocephalus, shunt, external ventricular drain, infection, biofilm, diagnosis, treatment, prevention, prophylactic antibiotics, antimicrobial catheters

1. Introduction

Though several historical attempts had been made to drain excess cerebrospinal fluid (CSF) in cases of hydrocephalus, this remained largely unsuccessful until the advent of valved shunting devices in the 1950's in USA. More recently endoscopic third ventriculostomy has been used in selected patients, but shunting is still the usual method of treatment of hydrocephalus. In patients with raised intracranial pressure due to trauma, malignancy or haemorrhage, where it is hoped the situation is temporary, external ventricular drainage (EVD) is often used. This temporary method of control of intracranial pressure is also used after shunt removal for infection, before insertion of a new shunt. The risks for infection in the two modes of treatment are different.

Infection in shunts appeared soon after they became more widely used [1], though for some time their cause and treatment remained poorly understood, until it was realised in the early 1970's that most were caused by a bacterium, *Staphylococcus epidermidis*, that hitherto had been considered a harmless commensal and common culture contaminant [2]. The mechanisms of infection and reasons for difficulty in treatment have been clarified over the subsequent decades.

EVD has a very long history, but infection remained a major problem until the introduction of sterile closed systems of drainage in 1941 [3]. It is still a matter of

concern and more recent increases in infections due to multi-drug-resistant (MDR) bacteria have exacerbated this.

Infections in shunts lead to repeated operations and courses of antibiotics and can lead to further cognitive impairment. Infections in EVDs lead to longer hospital stay, courses of antibiotics, and worse overall neurosurgical outcomes. In both cases death can result. Prompt diagnosis and appropriate treatment are essential, and prevention should be the primary goal. These can be achieved best with an understanding of the underlying science.

2. Aetiology and incidence

Infection rates have fallen in both shunting and EVD since the 1970's when up to 23% of shunts were reported as becoming infected [4, 5]. More recent rates for shunt infection have been below 10%, with 6% reported in a clinical trial [6]. However, it has been clear for some time that the infection rate in infants shunted when less than 6 months of age is significantly higher [7, 8] sometimes approaching 15–20% of operations [9].

The reported infection rate in EVDs is very variable, mainly due to difficulties in diagnosis, diagnostic criteria used and significant differences in underlying pathologies between patient groups studied. Earlier studies reported higher rates, 15–23% [10, 11] while slightly later studies reported 7.5% more in keeping with our own observations [12, 13].

2.1 Causative organisms in shunt infection

Since the first reports of shunt infection, staphylococci have predominated in shunt infection, with the majority being coagulase – negative staphylococci (CoNS). Of these, most are *Staphylococcus epidermidis*. A minority of staphylococci are *Staphylococcus aureus*. The proportion of these that are methicillin- resistant (MRSA) varies between countries according to national MRSA epidemiology [14], but in most countries especially The Netherlands, Scandinavia and United Kingdom, the proportion of MRSA in shunt infections is low [15]. However, methicillin resistance in CoNS is now common [16, 17]. Another important shunt pathogen is *Cutibacterium* (*Propionibacterium*) *acnes* [18, 19], found mainly in adolescents and adults. This bacterium is under-reported and probably accounts for some of the "culture-negative" shunt infections, as it is anaerobic and slow-growing, taking up to 14 days to appear in culture. Infection with gram negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* is less common [15, 16, 20] and probably occurs more commonly in shunted infants than in adults [21].

2.2 Causative organisms in EVD infection

Most cases of ventriculitis associated with EVD use are caused by staphylococci [13, 22, 23] but there is evidence that the proportion of gram negative bacteria might be increasing. Chatzi et al. [24] reported 81% of their EVD infections were due to MDR gram negative bacteria, mainly *Acinetobacter baumannii*; similar proportions were reported by others [25, 26]. Another matter of concern is the increase in enterococcal infections, reflecting the rise of this MDR gram positive bacterium in general surgical site infections. Notable differences between pathogens in shunts and EVDs are the increasing proportion of MDR gram negative bacteria and the occurrence of polymicrobial infections in EVD, uncommon in shunts.

3. Mechanisms of infection

3.1 Shunts

The main source of pathogens in shunts is the patient's skin [8, 27]. Skin commensals such as CoNS and *C acnes* cannot be eradicated by skin preparation, and they easily enter the incision where they are able to gain access to the shunt and possibly the ventricular system during shunt insertion. Once inside the shunt tubing, they attach to the surface of the silicone, after which they begin to proliferate. This proliferation is slow, because the carbon and nitrogen sources in CSF are insufficient to support vigorous bacterial growth, and in particular it has a very low iron content [28]. However, the plaques of bacteria eventually develop into a biofilm. Biofilms are communities of micro-organisms usually attached to a surface, and they are very common in device infections and in the environment. They are also the preferred mode of growth, rather than the very artificial growth conditions applied in the laboratory. It is interesting that the first report of a biofilm in a medical device was from a shunt infection [29]. This early report was produced in response to the need to explain why antibiotic treatment, shown to be effective against shunt pathogens in the laboratory, was ineffective in treating shunt infections. It is now generally accepted that biofilms explain this difficulty, which is found in infections in other implants. The early report postulated that the biofilm structure was maintained by a glycosaminoglycan produced by the bacteria, and that antibiotics were unable to penetrate this effectively. Further research has confirmed the chemistry of the biofilm matrix (though it is now accepted that other components are present). Later studies have confirmed the presence of bacterial biofilms in infected shunts [30, 31]. It is now realised that most antibiotics can penetrate bacterial biofilms effectively [32], but that they fail to kill the constituent bacteria [33–35]. This is because, when bacteria attach to a surface and develop a biofilm, they change their metabolism in order to conserve energy, and this involves downregulating all inessential functions such as cell wall synthesis, most protein synthesis and DNA replication. All these are target sites for common antibiotics, and the concentration of antibiotic needed to even reduce the numbers of biofilm bacteria is 500 to 1000 fold higher than that found in the laboratory [32]. This explains why antibiotic treatment alone is usually ineffective against biofilm infections.

Bacteria are shed from biofilms and this is one way in which they might reach the ventricular system, but bacteria also spread along the inside surfaces of the tubing, and they might also be introduced from the incision during shunt insertion.

3.2 EVD

EVD infections also involve biofilm formation inside the tubing as well as externally to it in the subcutaneous tunnel, and all shunt and EVD pathogens including *C acnes* and *Acinetobacter baumannii* produce biofilms [36, 37].

3.3 Periods of risk for infection

Generally shunts are at risk of infection only at insertion or revision, but exceptions are postoperative CSF leak from the incision, and later skin erosion over the shunt or perforation of abdominal viscus. Skin erosion might be due to pressure in a debilitated patient, or to poor tissue coverage and skin health in premature infants, or to malnutrition. The viscus most often perforated by the lower catheter is the

intestine. Reports in the literature often concern children and surprisingly, many are brought to the emergency room by parents worried that they have a parasitic infection, based on the lower catheter protruding from the anus [38]. Unlikely though this may seem, we have also seen two similar cases. There are often several bacteria of enteric origin, including anaerobes, in the CSF but the patients are often not as ill as might be expected.

It is generally agreed that the risk to shunts from bacteraemia during dental treatment is extremely small and does not warrant antibiotic prophylaxis. Haematogenous infection in both VP and VA shunts is very uncommon.

The period of risk for EVDs is very different. Access by skin bacteria is possible during insertion of the EVD, but the main risk extends for the time the EVD is in place, and is from skin bacteria that migrate from the exit site, from interventions such as CSF sampling and drug administration, flushing for blockage and changes of collection system.

4. Diagnosis

4.1 Shunt infections

The features of infection are different in VP and VA shunts. The discharge of bacteria and inflammatory products from an infected VP shunt into the peritoneal cavity triggers a local inflammatory response that often results in obstruction of the outflow of CSF. Sometimes this involves the greater omentum, and a CSF-filled cyst is formed around the end of the shunt [39]. This inflammatory response causes distal-end blockage of the shunt and return of the symptoms of hydrocephalus. This is the main reason for the important difference in time of presentation between infected VP and VA shunts: VP shunt infections usually present within months of operation, while VA shunt infections can present years later. However, CSF pseudocysts can present many years after shunt insertion with no evidence of infection [40].

In view of the presenting symptoms in VP shunt infection being those of raised intracranial pressure, it is important to distinguish between a non-infected blockage and one arising from shunt infection. Features of VP shunt infection include fever, headache, vomiting and irritability, though all of these are variable in consistency and can be due to non-infective obstruction. If the symptoms appear within 6–8 months of insertion or revision, this increases the likelihood of infection. If there is erythema over the catheter track then this is an important sign, but it is not always present. Abdominal ultrasound may show adhesions or cyst formation. Shunt aspiration will reveal bacteria on gram film and/or culture, but will not always show raised white cell count or other CSF abnormalities. In the absence of clear indications, there is often reluctance to aspirate the shunt due to concern for introduction of infection, but this risk is slight. Blood culture is usually negative. Blood C-reactive protein (CRP) is useful as it is often raised as part of the tissue inflammatory response. The features of VP shunt infection therefore include:

Presentation <6-8 months of operation
Symptoms of shunt obstruction
Erythema over the catheter track
Raised C-reactive protein
Pyrexia
Bacteria in gram stain and culture of aspirated CSF

Gram film examination is useful even if the CSF appears to be clear to the naked eye, as if bacteria can be seen it can make an early diagnosis irrespective of culture results. If culture is negative in the presence of a positive gram film then further measures can be taken such as extended anaerobic culture.

As not all VP shunt infections are contracted at operation, there will be some resulting from skin erosion over the valve or perforation of abdominal viscus but these are uncommon and the diagnosis is usually obvious. Haematogenous shunt infections are extremely rare. "Late" infections sometimes occur, due especially to *C acnes*, but those due to *Streptococcus pneumoniae*, *Neisseria meningitidis* or *Haemophilus influenzae* are almost always community-acquired meningitis in a person with a shunt, not a shunt infection, and this has important implications for treatment.

Presentation of VA shunt infection is often also within a few months of operation but in this case it can extend to several years later, leading to the unfounded suspicion that these infections are not contracted at surgery. Those VA shunt infections that present after more than 1–2 years are sometimes associated with immune complex disease. Here, the bacterial antigen discharging from the shunt into the bloodstream provokes an antibody response, and eventually the concentrations of circulating antigen and antibody combine into insoluble complexes that are deposited mainly on basement membranes [41, 42]. The skin, lungs, joints and renal glomerulae are particularly affected [43]. VA shunt infections can therefore present as chronic skin lesions (some haemorrhagic), chronic non-productive cough, swollen painful joints or haematuria. This often leads to initial referral to dermatology, respiratory medicine, rheumatology [44], orthopaedics and nephrology [45], and the diagnosis of shunt infection is sometimes missed or delayed. The causative bacteria in such cases are usually either CoNS or *C acnes*. Immune complex disease usually resolves on shunt removal.

Again aspiration of CSF from the shunt reservoir usually reveals the infecting bacterium. Blood cultures are usually positive but in very longstanding cases the pathogen might be non-culturable, or might appear as the biofilm phenotype known as small colony variants (SCV) which can be difficult to identify in the clinical laboratory [46, 47]. Iron-unresponsive anaemia is often a feature, and complement C3 and C4 levels are usually low due to complement consumption. CRP is often normal. An antibody assay has been used to diagnose late-presenting VA shunt infection [48, 49].

4.2 EVD infection

Diagnosis of infection in EVDs is often difficult. Features consistent with a diagnosis of ventriculitis are often present in patients with traumatic brain injury or stroke, and fever, with raised CSF white cell count, raised CSF protein level, disturbance of consciousness, Glasgow Coma Score, and inflammatory markers such as CRP are not helpful [50, 51]. In order to overcome the problem of raised white blood cell counts in patients with blood in the CSF, an index has been proposed, based on comparison of white cells and red cells in CSF and blood [52] but the number of patients in their study was small. A raised level of soluble Triggering Receptor Expressed on Myeloid cells (s-TREM) in CSF has been reported to be a reliable marker of ventriculitis even in the presence of haemorrhage [53] and this merits further investigation.

However, a positive culture result from CSF has been held to be the "gold standard," yet this is fraught with problems. Many isolates are skin commensals, and might be either pathogens or contaminants, or might be colonising the distal parts of the ventricular catheter but absent from the ventricles. If a recognised pathogen

such as *S aureus* or *A baumannii* is isolated then this is generally taken as a reason to begin definitive treatment, but more than a single isolate of the same strain of CoNS is usually required. Isolates from broth cultures alone should usually be disregarded as likely contaminants, and broth cultures are generally unhelpful. Some have advocated daily CSF aspiration and examination [54] but this has not been found to be reliable in diagnosing or predicting ventriculitis [55], and has been identified as a risk factor for EVD infection. Therefore, in addition to a positive CSF culture, the Infectious Diseases Society of America (IDSA) recommendation is: "*New* headache, fever, evidence of meningeal irritation, seizures, and/or *worsening* mental status are suggestive of ventriculitis or meningitis in the setting of recent trauma or neurosurgery (strong, moderate evidence)" [56]. This guidance applies the need for the feature to be "new" and this is an important consideration in those patients already showing non-specific symptoms due to their underlying pathology.

5. Treatment

5.1 Shunt infections

There are several obstacles in the way of successful treatment of shunt infections. Though in most institutions, MRSA is not a common shunt pathogen, many CoNS are multi-resistant including to methicillin and other beta-lactam antibiotics. Another problem is the poor CSF penetration of most antibiotics given intravenously [57] so CSF levels are below the minimum bactericidal concentration (MBC). A third problem is the presence of shunt pathogens as biofilms in the catheter, as eradication of these requires up to 1000 times more antibiotic than the MBC measured in the laboratory [32]. The best chance of successful treatment of shunt infection is therefore shunt removal followed by a course of antibiotics and usually EVD before replacement with a new shunt if required [58]. This topic has been further confirmed by a review by James et al. [59]. A study in children showed 88% first-time cure using shunt removal, antibiotics and EVD, a lower success rate with an immediate shunt replacement protocol, but only 33% success with antibiotics and no shunt removal [60]. In many such studies there is also a disturbingly high mortality rate in those managed with shunt retention. Once the shunt is removed, this leaves a residue of infection in the ventricular system, and as it has arisen from the biofilm in the catheters it is likely to exhibit the biofilm phenotype and have a raised MBC. However, the problem of CSF penetration now becomes paramount. Ventriculitis caused by CoNS or *C acnes* does not give rise to vigorous inflammatory response [61], and this limits access of antibiotics to the CSF. Several factors apart from inflammation also influence the penetration of antibiotics into CSF [57]. Many antibiotics that could be used to treat ventriculitis fail to achieve sufficient concentrations in the CSF [62–64], and this has led to consideration of additional intraventricular administration via EVD [65]. Such a protocol was recommended by the British Society for Antimicrobial Chemotherapy [66] for staphylococcal infections, consisting of intraventricular vancomycin 20 mg daily, and oral or intravenous (IV) rifampicin 300 mg twice daily (15 mg/kg daily for children). The protocol has been shown to reduce the risk of relapse and to shorten the course of treatment needed [67, 68]. However, the association of variable to low antibiotic penetration with clinical failure has been questioned [69], but much of the information on antibiotic penetration into the CSF comes from patients with meningitis, and it is accepted that in ventriculitis the penetration is lower, especially when staphylococci are involved. A general principle is that if CSF antibiotic levels that reach the MIC can be achieved by intravenous administration, then this is sufficient, but the MBC is

probably more important and this needs to be 5–8 times the MIC to ensure clinical success [70]. It is generally agreed that intraventricular administration of vancomycin is safe, irrespective of CSF levels, which can reach 100 mg/L, though some have advocated monitoring of CSF levels and dosage adjustment [68], which we have not found necessary. This is not necessarily true of all antibiotics: gentamicin CSF trough levels must be maintained below 5–20 mg/L [71], and betalactams should not be given by the intraventricular route due to neurotoxicity [72].

Though the general principle is that successful management of shunt infection can be best achieved by shunt removal, linezolid, an oxazolidinone antibiotic, might offer some prospect of retaining an infected functioning shunt due to its excellent CSF penetration and its anti-biofilm activity. An in vitro study has shown that linezolid in concentrations achievable in CSF can eradicate staphylococcal biofilms, including those of MRSA, from shunt catheters [73]. Linezolid gives high CSF levels even after oral administration [74, 75] and it has been used successfully in a small number of cases of shunt infection. Success has been achieved against vancomycin partially – resistant MRSA in shunt infection with shunt removal [76, 77]. In some cases it has been used without shunt removal. One case due to meticillin-resistant CoNS responded to oral linezolid without shunt removal after failed therapy with IV vancomycin and cefotaxime [78], and a further two, one due to MRSA and the other to meticillin-resistant CoNS, were initially unsuccessfully treated with IV vancomycin and ceftriaxone, but responded without shunt removal after IV linezolid. Further trials of this mode of management are urgently needed.

An exception to the rule that shunt removal should be the management of choice applies to those with a shunt who contract community-acquired meningitis, due to *S pneumoniae*, *H influenzae* or *N meningitidis*. As noted above, these are not true shunt infections, and the bacteria appear unable to colonise the shunt in the same way as other organisms. Clinical experience has shown that a conservative approach consisting of usual treatment for meningitis is almost always successful, and the patients usually recover quickly [79–83].

5.2 EVD infections

The general principles of treatment of shunt infections apply to EVD-associated ventriculitis, in that bacterial biofilms are involved and there may be difficulty in achieving sufficiently high CSF antibiotic levels during IV administration. An important difference from shunt infections is the much higher proportion of infections caused by gram negative bacteria, many of which are multi – drug - resistant. These include *K pneumoniae*, *A baumannii* and *Pseudomonas aeruginosa*, though the last are less common.

As soon as a diagnosis of certain or probable ventriculitis is made the EVD catheter should be removed. Failure to remove the infected EVD catheter was identified as a significant risk for treatment failure and mortality [84]. Once a new EVD catheter has been placed, appropriate antibiotic treatment should begin, and this should be guided by laboratory identification and antibiotic susceptibilities. IV colistin does not reliably result in sufficient CSF levels [85]. Again the question of IV or intraventricular administration or both arises, but the EVD makes intraventricular administration (IVT) easier. Recent guidelines from the Neurocritical Care Society [86] recommend the use of IVT "…in patients who fail to respond to IV antimicrobials alone or when organisms have high MICs to antimicrobials that do not achieve high CSF concentrations, especially MDR organisms." In a study of 31 cases, caused mainly by *Enterobacter* spp., *Ps aeruginosa* or *Stenotrophomonas* (*Xanthomonas*) *maltophilia*, the 13 cases which received IVT gentamicin as well as IV antibiotics had a higher cure rate and a lower relapse rate (0/13 vs. 6/18) [71]. None of these cases

were due to *A baumannii*, which is often susceptible only to colistin. In a small study of two groups of nine patients with ventriculitis due to *A baumannii*, one group had both IV and IVT colistin while the other had IV only [87]. CSF sterilisation was achieved in 100% of those having IVT therapy (vs 33%) and the five deaths due to ventriculitis occurred in the IV - only group but none in the IV + IVT group. Cure is also reported when IVT colistin is used without IV colistin [88], so avoiding some of the systemic toxicity. Some strains of *A baumannii* are now resistant to colistin, but there is in vitro evidence of useful synergy with rifampicin, which suppressed emergence of colistin resistance as well as killing of a colistin-resistant strain. A combination of colistin and rifampicin was effective against colistin – resistant strains of *K pneumoniae* in vitro [89]. There are a few clinical reports of synergy with rifampicin, and especially if the mutual protection against resistance can be confirmed, this might improve prospects of treatment.

6. Risk factors and prevention

6.1 Shunts

Most analyses of risks for shunt infection identify shunting below the age of 1 year as a factor [8, 14, 90]. Young age or prematurity at shunting and intraventricular haemorrhage have been identified on univariate analysis but only young age on multivariate analysis, suggesting that age was the factor and the other two were dependent factors [91]. Why this should be has been debated. The main source of shunt pathogens being the patient's skin, any factor that influences this adversely might be expected to increase the risk. Premature infants have a high risk of intraventricular haemorrhage, and they often have been in hospital separated from their mothers before shunting, and it has been found that their skin bacterial densities were significantly higher, and that their skin bacteria were more likely to be able to adhere to silicone [8]. Loss of close maternal contact means that the babies become colonised with hospital strains of staphylococci that appear to be more virulent as shunt pathogens.

CSF protein content at the time of shunt insertion has been suspected to be a risk factor for infection, but this has been discounted [92, 93] though it may indicate a higher risk of re-infection after treatment of an initial shunt infection [94], possibly suggesting an incomplete eradication of the initial infection.

Intra-operative interventions to reduce the risk of shunt infection include "bundles" which are widely recognised in infection control and prevention to be effective if correctly applied. Choux et al. [95] introduced a protocol consisting of a range of sixteen measures such as restricting the number of people in the operating theatre to four, shunt insertion first thing in the morning, neonates before older children, limiting duration of surgery to 20–40 minutes, as well as technical surgical stipulations regarding a no-touch technique for the shunt, haemostasis and wound closure. On applying this to 1197 procedures he reduced the infection rate to 0.17%. Similar measures have been introduced such as use of a dedicated neurosurgical theatre, all passage into and out of the theatre prohibited, and no more than seven people present. Skin preparation used two separate applications, and both drapes and the peritoneal catheter introducers were smeared with povidone iodine which was also used to irrigate the incision and the surgeon's gloves. Using this protocol the infection rate was 0.57% [96]. The Hydrocephalus Clinical Research Network has also published protocols aimed at reducing shunt infection [97]. The refined protocol has eight essential steps, reduced from eleven in earlier versions. Results of 1935 procedures at eight centres showed an overall infection

rate of 6% with 77% compliance with the protocol. Infection rates differed significantly between centres in full compliance and those which were not (5% vs. 8.7%, p = 0.005). Others have used similar protocols [98, 99]. One problem with these protocols is that they are difficult to compare, and almost none of the measures are evidence-based. However, this is considered acceptable in view of the usual fall in infection rate when they are introduced. An important aspect of bundles is mentioned by Choux [95] and emphasised by Choksey [96]: to be fully effective they must be made compulsory and violations must be detected and remedied. Though many components of the protocols are "common sense" measures such as rigorous asepsis, their main mechanism might be behavioural change in personnel, and this is not necessarily teachable and exportable to other institutions. Interestingly, few "bundles" mention the possible use of laminar flow ventilation in the OR. Choksey [96] used a laminar flow hood, while Pirotte [98] did not: both reduced their shunt infection rate to <1%. Though laminar flow ventilation was recommended for arthroplasty, recently several centres have reported either no benefit, or in some cases a small but significant increase in infection rate [100, 101].

However, certain constituent measures deserve attention. Many use antiseptics to either irrigate the incision or to isolate the wound skin edges [102], a measure suggested some time ago [103–105]. It is clear that skin bacteria enter the incision from this source [27, 106]. It is important that the contribution of patient skin bacteria is minimised by avoiding contact with skin edges by gloves, instruments or shunt components, and measures to isolate them might be helpful in this regard. Surgeons' gloves become contaminated early in the operation and double – gloving is recommended so that the contaminated outer pair can be discarded before the shunt is handled. At this point it is advisable to rinse the gloved hands in antiseptic before touching the shunt, or to use a "no - touch" technique. Double gloving was introduced in a sequential study but without removal of the outer pair, as the presumption was that the source of shunt pathogens was glove perforation [107]. However, the diagnostic criteria in this study are in doubt as most of the "infections" were culture-negative, and the change of outer glove remains the most important measure.

It is important to remember that, irrespective of the antiseptic used, pre-operative skin preparation does not sterilise the skin. Much of the literature discusses the merits of various antiseptics but relies on skin swabs for evaluation, though most of the skin flora reside in the glands and follicles in the dermis [108]. When full thickness skin biopsies have been used they have shown that, irrespective of the agent used, while the numbers of bacteria can be reduced they cannot be eradicated, and they will re-emerge during surgery. The numbers of bacteria required to cause an infection in the presence of a biomaterial such as a shunt are at least ten thousand – fold fewer that those needed in its absence [109]. While there is little evidence that chlorhexidine is better than povidone iodine it is clear that the alcohol version of either is superior to the aqueous version, and it is possible that the alcohol component is the major antiseptic factor [110].

Adhesive drapes are not of proven benefit in preventing the skin bacteria from entering the incision, even when iodine-treated. They are, however, useful in covering the cloth drapes and providing a dry aseptic surface. Shaving of head hair is now accepted as unnecessary and possible a risk for infection [111], and clipping should be carried out with scissors if necessary, and the hair prepared as for the skin.

The use of pre-operative prophylactic antibiotics is controversial [112]. Most of the reports, including where infection rates are considered unacceptably high, are from centres using antibiotic prophylaxis. Again the issue of timely penetration of IV antibiotics into the CSF is important, and most studies have found ineffective peri-operative levels. They also do not act rapidly enough to affect the numbers

of skin bacteria in the incision during shunt insertion, and while this remains as a risk to the shunt, they might act to reduce postoperative wound infection. Intraoperative IVT vancomycin has not been shown to reduce shunt infection rate, probably due to the slow kill rate, but an interesting finding has been reported [113]. In this study, when only IV antibiotics were used, the infection rate was 6.74%; when IVT gentamicin was added, the infection rate was similar at 5.45%; when both IVT gentamicin and IVT vancomycin were used together, the infection rate fell to 0.41%. This interesting observation needs to be confirmed.

Another approach is the use of triclosan - coated sutures [114]. Though numbers of patients were small, when triclosan - coated sutures were compared with plain sutures in a randomised controlled trial, there was a reduction in shunt infection rate from 21% to 4.3%. Some, but not all, infections were postoperative wound suppurations.

There is increasing use of topical application of vancomycin powder before fascial closure in spinal surgery with significant infection reduction and low toxicity compared to IV vancomycin prophylaxis. The same approach has been used in a small uncontrolled series of shunt insertions with a reduction of shunt infection from 5.8% to 0% though the postoperative revision rate was unaltered [115]. The diagnostic criteria for shunt infection were not clear but this use of vancomycin is safe and effective in spine surgery and might be useful in shunt surgery.

It appears that attempts to prevent skin bacteria from accessing the shunt during surgery are only partly successful, and further measures are needed. Systemic prophylactic antibiotics are well researched but an unacceptably high infection rate remains. This has led to development of shunt materials intended to reduce bacterial colonisation of the catheters and therefore shunt infection.

Antimicrobial shunt catheters have been available for some time. Coating the shunt surface with a hydrophilic material as in the Bioglide catheter is intended to reduce bacterial attachment, and if the catheter is soaked in a solution of antibiotic then this has been claimed to add to the effect. The catheters have been evaluated in vitro using rigorous clinically predictive tests and though they did reduce bacterial attachment they were found not to be effective in preventing colonisation by staphylococci [116] even when soaked in gentamicin or vancomycin [117]. Clinical assessment [118, 119] has confirmed this. Silver in various forms has been promoted as a useful antimicrobial for implantable devices, but variable results have been reported. Shunt catheters impregnated with nanoparticulate silver, a particularly active form, have been marketed. Again an in vitro evaluation has found that they failed to prevent colonisation by staphylococci, *C acnes* or *E coli*, and this has been confirmed in a large randomised controlled clinical trial [6]. Silver undoubtedly has antibacterial activity, but the concentrations of silver ions needed are also cytotoxic, and silver ions combine avidly with chloride and protein. As it is likely that a prolonged duration of antimicrobial activity of at least a few days is required to prevent survival and regrowth of bacteria in shunt catheters, and as antimicrobial coatings are easily removed by CSF flow and obliterated by protein deposition, a system is needed that maintains an antimicrobial surface. One such system distributes molecules of antimicrobials throughout the silicone matrix, allowing them to migrate freely to replenish the surface when CSF removes molecules from there, so maintaining an antimicrobial surface for sufficient time, in this case for over 40 days [120]. This system is unaffected by protein. When the clinically predictive tests are applied in vitro, the antimicrobial catheters remain free of bacterial colonisation even after serial high - dose bacterial challenge. Clinical studies have demonstrated reduction in shunt infection [121] and considerable cost savings [122] as well as reduction in systemic antibiotic use. A large randomised controlled trial comparing antimicrobial, silver and plain shunts found that the antimicrobial

shunts gave a statistically significant reduction in shunt infections while results for silver-processed shunts were indistinguishable from those of plain catheters [6].

The question of whether to use prophylactic antibiotics for people with shunts who undergo dental treatment has been raised frequently. Studies have shown that the risk is negligible, and there is no evidence that bacteria of oral origin have caused shunt infections, whether VP or VA, after dental treatment [123]. It is likely that antibiotic prophylaxis used in this way treats the dental practitioner but is of no benefit to the patient.

6.2 EVDs

Whether risks of infection are different if the EVD is inserted in the intensive care unit or the operating room (OR) is debatable. In one study there were fewer infections in those inserted in the OR but this difference was not statistically significant [124]. While the OR might offer a more controllable aseptic environment, transfer of acutely ill patients to the OR for this purpose might pose additional risks [125].

Periprocedural prophylactic antibiotics are commonly used. However, many centres use prolonged antibiotic prophylaxis throughout the EVD use. Flibotte et al. [126] used either nafcillin or vancomycin but noted that most infections were still due to gram positive pathogens, and that their use of prolonged nafcillin appeared to lead to an increase in resistance to this antibiotic. Wong and Poon [127] reported a comparison of two regimens for prolonged prophylaxis but did not comment on the influence on resistance, but a later study by the same authors [128] using the same regimen found three cases of pseudomembranous colitis due to *Clostridioides difficile*, one of whom required total colectomy. A similar experience was reported [129] reducing the number of *C difficile* infections in the ICU from 19 to 5 by changing the antibiotic prophylaxis regimen from prolonged to peri-procedural with no change in ventriculitis rate. Antimicrobial impregnated EVD catheters were used in both phases of both these studies [128, 129]. In another study comparing prolonged and peri-procedural antibiotics there was no difference in infection rate, the difference being a saving of $80,000 a year in drug costs [130]. Murphy et al. [131] also compared a period when prolonged antibiotics were used with a period where only periprocedural antibiotics were given; in both periods antimicrobial EVD catheters were used. The infection rate in the periprocedural-only period actually fell from 1.35/1000 catheter days to 0.54/1000 catheter days, though this was not statistically significant. Remarkably, there was a significantly higher rate of bloodstream infections (BSI) and pneumonia (VAP) in the prolonged – antibiotics period, and the drug cost for treating these infections were $155,253 but there were no cases of BSI or VAP in the second periprocedural - only period.

Antimicrobial catheters have been developed for EVDs as for shunts, though there have been fewer clinical trials. The hydrophilic-coated catheters intended to reduce infection by preventing bacterial attachment have already been discussed; these have not been successful. Silver-processed catheters have shown non-significant results in some clinical studies [132–135]. One three-phase retrospective/ sequential study showed that introduction of silver-processed catheters reduced the infection rate from 3.8% to zero, though due to small numbers this was not statistically significant [136]. A randomised prospective controlled trial comparing silver-processed with plain catheters has reported a significant reduction in ventriculitis from a very high rate of 21.4% to 12.3%, a fall that just met statistical significance $p = 0.0427$ [137]. A thorough assessment of the value of silver-processed EVD catheters [138] has found no significant overall difference in infection rate in a meta-analysis but did identify a statistically significant reduction

in infection due to gram positive bacteria (6.7–2%, p = 0.002). The conclusion was that silver-processed catheters require further evaluation, and that they have no activity against gram negative bacteria. This was confirmed in vitro using the same rigorous clinically – predictive testing used for shunts, when silver-processed EVD catheters were found to show a weak activity against *S epidermidis* but none against gram negative bacteria [139].

An antibiotic-impregnated catheter containing rifampicin and minocycline (VentriClear, Cook Inc) is available in USA, and Bactiseal (Codman Integra Life Sciences) that contains rifampicin and clindamycin, produced by a different process, is available worldwide. A significant (p = 0.002) reduction in ventriculitis has been reported when VentriClear catheters were used, from 9.4% to 1.3% [140]. Harrop et al. [12] carried out a five -phase prospective cohort study. Phase I, the baseline, showed a rate of 6.7%, and the introduction of a standardised protocol in Phase II did not reduce this (8.2%). However, in Phase III the Bactiseal catheter was included, and the infection rate fell to 1% (p = 0.0005). This catheter gave an unacceptable rate of occlusion and its use was discontinued, and reversion to the Phase II protocol showed a return to a 7.6% rate. In Phase V, the VentriClear catheter was introduced and the ventriculitis rate again fell to 0.9% (p = 0.0001). Though a sequential cohort study, this provided strong evidence that both antimicrobial catheters were effective. This was confirmed by a comparison of VentriClear with Bactiseal [141] using alternating 3-month periods when 129 patients received either a VentriClear or a Bactiseal catheter. No cases of ventriculitis were recorded in the study, showing that both were equally effective in this study. No excess of occlusion was recorded with either catheter. A series involving historical controls found a reduction of ventriculitis from 15% in plain catheters to 5% in Bactiseal catheters but this failed to reach statistical significance [142]. Bactiseal was compared with plain EVD catheters in an interesting study in which CSF samples were taken every 2 days, and if culture-positive, irrespective of clinical evidence, the catheter was changed and 10 days of intraventricular antibiotics were given [143]. In this study there were no cases of clinical infection in either group. As with shunts, there is no evidence that antimicrobial-impregnated EVD catheters increase the risk of bacterial resistance, and in reducing the need for systemic antibiotics for prophylaxis and treatment of infections they are likely to contribute to reduction of antimicrobial resistance generally. This has been underlined by three studies in which prolonged systemic antibiotic prophylaxis for EVD has been compared with use of the Bactiseal catheter. In two studies the antimicrobial catheter gave equivalent protection against ventriculitis but avoided the serious risk of *C difficile* infection [128, 129], a known consequence of over-use of antibiotics. In the third study [131] the Bactiseal EVD catheter was used but in one group, prolonged antibiotic prophylaxis were added. There was no difference in ventriculitis rate between the two groups, but there was a significantly higher rate of BSI and VAP, requiring further courses of antibiotics for treatment, again contributing to antimicrobial resistance. While good quality randomised controlled trials are needed for antimicrobial - impregnated EVD catheters, the studies so far strongly suggest that they can reduce the incidence of ventriculitis by gram positive bacteria, but there is currently no EVD catheter available that protects against gram negative bacteria, which are increasing in frequency and importance. An experimental antimicrobial EVD catheter that can protect against colonisation by MDR gram negative bacteria including *A baumannii* has been developed but is not yet clinically available [144].

There is general agreement that the EVD catheter must be tunnelled subcutaneously for approximately 5 cm away from the burr hole, but some prefer to tunnel for much longer. When the exit site was placed in the lower chest or upper abdomen, no infections were reported in the first 16 days. In those 45 requiring EVD for longer,

four developed ventriculitis [145]. In a study using a long tunnel of at least 20 cm an infection rate significantly lower than those reported in the literature using conventional tunnels was noted, though an antimicrobial EVD catheter was also used [146]. However, Leung et al. [147] found no advantage in a longer tunnel.

The infection rate for EVDs is said to rise with duration of use, though this is sometimes contested. The duration of EVD use has frequently been identified as a risk factor for infection. As the increase in infection appears to begin after about 5 days, suggestions have been made that changing the EVD catheter at this stage might avoid the subsequent rise in infection rate [148]. However, this practice has been shown not to help [149, 150] and might increase the risk [151]. The risk for ventriculitis increases in most studies until about 10–12 days then levels off. The message is that the EVD should be removed as soon as possible when no longer needed.

EVD pathogens are more varied, and more likely to be MDR gram negative bacteria than those found in shunts. They might originate on the patient's body surfaces, ears and respiratory tract as broad-spectrum antibiotics given for chest infections and other purposes promote colonisation of these sites with such organisms. The intensive care environment is often a source of such bacteria due to the throughput of very sick patients and heavy use of antibiotics. This environment includes all inanimate surfaces, textiles and water sources [152, 153]. The EVD must be managed with careful attention to aseptic technique, and breaches of the system should be avoided unless absolutely necessary. This includes CSF sampling for monitoring purposes. The practice of daily CSF sampling is said to enable early diagnosis of infection [154, 155], but represents a risk for introduction of infection, and CSF sampling is best confined to cases where there is a suspicion of infection [155].

As with shunts, the introduction of "bundles" has usually been associated with a reduction in infection rate. Korinek et al. [156] developed a bundle protocol and introduced a violation score to monitor it. Their ventriculitis rate fell from 9.9% to 4.6%, and the most significant factors in infected patients were CSF leak and protocol violation, which in the infected cases was 4 times higher $p < 0.0001$. The value of this approach was also demonstrated by others with a significant fall in infection rate [155, 157]. Importantly, the bundle approach should include full involvement of all personnel involved and should be monitored and regular feedback given on violations and infection rates. Again, not all of the constituents of the bundle are evidence – based and they vary between reports, but the behaviour change brought about by this approach is the most important factor.

7. Conclusions

Infection in shunting and EVD is often devastating. Prevention is paramount and a greater understanding of the science and the risk factors should inform more effective measures including surgical practice and OR discipline. Antimicrobial catheters are useful in reducing infection in shunts and EVDs, but the problem of gram negative infection needs to be addressed. There should be no delay in instituting effective treatment, including removal of hardware and ensuring adequate levels of antibiotics. Successful first pass treatment should be the goal. Treatment without hardware removal, using relatively new antibiotics, should be thoroughly investigated in view of the potential benefits.

Importantly, the contribution of overuse or misuse of antibiotics to the increasing problem of antimicrobial resistance both locally and globally should be kept in mind.

Conflict of interest

The author is the inventor of the "Bactiseal" antimicrobial catheter, but he has not and does not receive any royalties or other payment. He receives speaker fees from Codman Inc., but not for personal gain and these are paid to his University.

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