Chapter

Infections in Intracranial Pressure Management: Impact of New Technologies on Infection Rates

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Abstract

It is now recognised that infections in CSF shunts and external ventricular drains (EVDs) are biofilm infections, and the scientific basis of these infections is better understood. Infection rates in shunts have now fallen but remain unacceptably high. There is an increase in infections due to multi-drug-resistant bacteria in EVDs. Reliance on antimicrobial prophylaxis has potential lifethreatening consequences and safer more effective measures are available. These consist of well-founded "bundles" or surgical protocols that have been shown to reduce infection by application of well known but not universally applied principles. New developments in antimicrobial technology have now been shown to be clinically effective and have reduced healthcare costs. The reduction in antibiotic use has led to fewer adverse effects. Problems with multidrug resistance in EVD infections remain and technology to address these has been developed but is not yet clinically available.

Keywords: CSF shunt, external ventricular drainage, antimicrobial prophylaxis, antimicrobial catheters

1. Introduction

Intracranial pressure needs to be controlled in cases of hydrocephalus, or after cranial trauma, or cerebral oedema due to, for example, tumour. In hydrocephalus, the most common treatment involves placement of a shunt to drain cerebrospinal fluid (CSF) from the cerebral ventricles to a body cavity such as the peritoneum (ventriculoperitoneal, VP, shunt) or the right cardiac atrium (ventriculaoatrial, VA shunt). Sometimes other sites are used, such as the pleural space. Where there is free communication with the spinal theca and the ventricular system, a lumbar-peritoneal (LP) shunt can be used. Shunts are totally internal and are intended to be in place permanently, though they often require revision due to obstruction. In cases where the need for control of intracranial pressure is temporary, such as following cranial trauma or haemorrhage, or as part of the management of a shunt infection, an external ventricular drain (EVD) is used. This drains CSF from the cerebral ventricles, exiting through a burr hole to an external collecting system. It might be in place for a few days or a few weeks depending on the patient's condition. The collecting bag is changed when approximately 75% full. Another temporary means of controlling CSF pressure is insertion of a reservoir,

typically Ommaya or Rickham. As these are "blind" with no drainage tube, it is necessary to aspirate CSF percutaneously, typically daily. Reservoirs are also commonly used as access ports for administration of drugs to the ventricular system.

2. Infections in CSF drainage devices

All surgical procedures carry a risk of infection, and the presence of a biomaterial significantly increases the risk [1, 2]. The insertion of silicone CSF drainage devices is no exception to this, and infection poses a real clinical problem. Hydrocephalus shunts are at risk of infection almost exclusively at the time of insertion or revision, and not thereafter. The main pathogen is coagulase negative staphylococci (CoNS) derived mainly from the patient's skin [3, 4], and entering the operative field during the procedure. Other bacteria are also involved, including *Cutibacterium acnes* [5, 6], also a skin commensal, and less often gram negative bacteria such as *Escherichia coli*. Infection rates have fallen in recent years, but still remain high in infants less than 6 months old [3, 7], and less so in adults [8]. The microbiology and pathology have been elucidated in previous publications [9, 10]. As EVD is by its nature an external device which also connects with other tissues and the central nervous system, it is perhaps not surprising that the infection rate is higher than in shunts. While many large institutions report rates of 8–10% [11], some recent studies have reported rates in excess of 20% [12]. Again the most common EVD pathogen is CoNS, but there is a higher proportion of gram negative bacteria, and particularly multi-drug-resistant strains including *Acinetobacter baumannii* [13]. The sources of EVD pathogens are the patient's skin and mucous membranes, staff managing the EVD, and the hospital environment. Ventricular access reservoirs are at risk at the time of insertion, but mainly during use, as with EVD. Infection rates are 5–8%, with ventriculitis/meningitis accounting for most cases but cellulitis around the reservoir occurs in 20% of cases. Most pathogens are derived from the skin, and include CoNS (56%) and *C acnes* (24%) [14, 15].

Infected shunts and EVDs should be removed a soon as possible and systemic antibiotics given, often for several weeks, but relapses are common [16]. In the case of infected reservoirs, successful treatment has been achieved with systemic and intra-reservoir antibiotics without device removal [17, 18].

3. Non-technological prevention measures

In view of the morbidity, costs and difficulty in successful treatment of infected shunts and EVDs, prevention is a major goal. Great success has been achieved by institution of care "bundles," packages of procedures included in written protocols to which all personnel contribute and with which there is general consensus [19–21]. Infection rates usually fall, and spikes of infection can usually be attributed to a protocol violation [20]. The disadvantage of this approach is that infection rates tend to rise again due to habituation, or if the protocol lead moves on. More specific measures include reducing the duration of EVD use where possible, and tunneling the ventricular catheter a few centimetres away from the burr hole (or in some cases down to the abdominal wall [22].) Another innovation is the placement of a port in the subclavian region and the ventricular catheter tunnelled to connect with it [23]. The use of prophylactic antibiotics is controversial. They are used almost universally in shunt placement, but the evidence for their effectiveness is weak. In EVD, two regimens are used. One consists of a single

dose of antibiotic given just before EVD insertion, and the IDSA Guidelines recommend this [24]. However, in some institutions the systemic antibiotics are continued throughout the duration of EVD use. While there is some evidence that the long regimen can reduce EVD infection, it is clearly associated with higher healthcare costs [25] and with severe, often lifethreatening infection with *Clostridioides difficile* [26, 27].

4. New technology for infection prevention

4.1 Types of technology and modes of action

The technologies aimed at reducing infection in neurosurgical devices must satisfy basic criteria: biocompatibility in tissues of the central nervous system and elsewhere; activity against at least the most common pathogens involved; sufficient duration of activity to cover the period of risk; and ability to be sterilized without significant loss of activity or adverse mechanical changes. These criteria are difficult to achieve.

4.2 Laboratory testing of antimicrobial technologies

All materials and devices for use in neurosurgery must undergo testing for mechanical properties (to ensure their robustness and suitability for use, including in the case of catheters, measurement of the force needed to disconnect (pull-off), tensile strength and other properties. They also undergo tests for toxicology of component materials, biocompatibility using international standard tests [28, 29], and certification of sterility and shelflife. Any modification of the materials or device has potential to affect all of these and antimicrobial processes such as coatings will require significant further testing. The processing might affect the mechanical properties and this might affect the likelihood of disconnection during use. Biocompatibility of the antimicrobials or the coating material will need to be determined, and this must include the possible chemical effects of sterilization which can give rise to toxic degradation products. Any claim for reduction in infection, at this stage usually expressed as reduction in bacterial attachment, or killing of test bacterial in vitro, will need to be determined, and animal implantation and challenge is often undertaken. However, while all potential neurosurgical implants must pass these tests, the current standards are not sufficiently meshed to the intended use. An example is testing for antimicrobial activity by immersing the processed material in a liquid culture of bacteria and measuring reduction in viability. This rarely has any relevance to the intended use of the material or device, and merely "ticks the box" for regulatory purposes. Another example is implantation subcutaneously into the flank of a rodent of material intended for use as a catheter, again bearing no relevance to intended use or anatomical site, yet giving information for regulatory purposes. For the purposes of this paper, test methods for antimicrobial activity will be discussed.

4.3 Laboratory testing for antimicrobial activity of processed neurosurgical devices

4.3.1 Surface modification

Modification of catheter surfaces can take the form of biomaterial modification, coating with a secondary material, or application of an antimicrobial coating.

Application of a material intended to reduce or inhibit bacterial attachment, by changing the hydrophobicity or charge of the surface, can be tested by a variety of means including those of surface physics and microbiology. For the latter, simple immersion into a suspension of bacteria followed by counting of attached bacteria might give interesting data, but unless a conditioning film consisting of extracellular matrix proteins similar to that occurring in vivo is applied to the modified surface, the data will be potentially misleading. Such a conditioning film is deposited rapidly on all biomaterials after implantation, and the modified surface is easily obliterated. The conditioning film is the surface that potential device pathogens usually attach to and this must not be omitted. This is also true of antimicrobial coatings, intended to kill bacteria that attach to the material. Test results that do not include a conditioning film are unreliable. A polyvinylpyrrolidone (PVP)—coated shunt catheter was tested without a conditioning film after soaking in antimicrobial [30]. Here they found that the PVP coating reduced bacterial attachment irrespective of any antimicrobial soaking. They also carried out an in vivo study by inserting a coated, inoculated catheter intraventricularly in a rat model. After removal of the catheters 7 days later, they found that both coated and uncoated catheters were colonised. They concluded that, even if attached bacterial numbers were reduced, full colonisation would eventually occur unless bacterial attachment was totally prevented. The PVP-coated catheter was tested with a serum conditioning film after it had been rehydrated in a solution of rifampicin [31], and the deposited serum proteins significantly reduced the antimicrobial activity. The same coated catheter was tested by Bayston et al. [32] who also applied a plasma conditioning film. They also found that the conditioning film further reduced bacterial numbers attached to the catheter even in the absence of antimicrobial. However, they also found that, contrary to claims, the lumen surface of the catheters was uncoated and became fully colonised by bacteria. This is important as most shunt and EVD catheters are, at least initially, colonised on the lumen surface. A rather concerning observation was also made in an animal implantation study [33] that even dead bacteria were able to induce abscess formation around the PVP-coated catheter, suggesting that the PVP coating might modify the local cellular immune response. A heparin-coated catheter was investigated by Nomura et al. [34] with the intention of producing a hydrophilic silicone surface. They soaked their coated catheters in CSF and found that the conditioning film consisting of CSF proteins also reduced bacterial adhesion. CSF protein is mainly albumen, and this has been shown to reduce bacterial attachment to shunt catheter material [35]. Plasma also contains fibrinogen and fibronectin, and these are known to favour bacterial attachment [36, 37], so the choice of conditioning film for in vitro testing is important.

4.3.2 Antimicrobial coatings

Shunt or EVD catheters can be coated with antimicrobial substances, and the most common is some form of silver. In 1997 Guggenbichler et al. developed a new technique for mixing nanoparticulate silver with polyurethane, the water porosity of which was claimed to ensure release of antimicrobial silver ions for long periods [38]. This was not strictly a coating as the silver was dispersed throughout the polymer, but it was not an impregnation technique. Several publications followed, with variable results in laboratory studies [39, 40]. An explanation of why silver-processed catheters might not be effective has been offered by Schierholz et al. [41] More complex silver-processed catheters have shown reduction in bacterial attachment and biofilm formation in the laboratory [42, 43].

4.3.3 Antimicrobial impregnation

A technique for post-manufacture impregnation of silicone materials with antimicrobials has been developed [44]. This process allows even dispersion of molecules of certain antimicrobials throughout the silicone material, and ensures that they are able to migrate freely even in the absence of water. Molecules of antimicrobials removed from the surface by fluid flow are replenished by those migrating from the catheter material. In turn, this gives a long duration of activity. Laboratory testing on shunt and EVD catheters processed by this method have shown that bacterial colonisation and biofilm development can be prevented even with high-number bacterial challenges in flow conditions [44, 45]. The test catheters were perfused for up to 4 weeks with repeated weekly challenges, and were shown to be free of colonisation at the end of this period. Further studies have shown that the antimicrobial material does not prevent bacterial attachment, but that attached bacteria are all killed within 48 hr. (the tK100 test) [45]. The antimicrobials were chosen partly for their known spectrum of activity against common shunt pathogens (mainly staphylococci) and because of their compatibility with the impregnation process and to give the required post-impregnation performance. The two antimicrobials chosen were rifampicin and clindamycin hydrochloride (Bactiseal, Codman, Integra Life Sciences), and the processed catheters have no activity against gram negative bacteria.

Using the same impregnation process, a shunt catheter containing rifampicin alone has been investigated. A very high concentration of rifampicin was used, resulting in visible crystal formation on the catheter surface, and change in mechanical properties, tensile strength reducing by 27% and elasticity by 45% [46]. However, the catheter showed antistaphylococcal activity in vitro for more than 60 days, and protected shunts from bacterial colonisation in a rabbit model [47]. In a later study in two patients with existing shunt infections the rifampicin- impregnated shunt catheters replaced the infected shunts, and the two patients remained free of infection thereafter [48]. However, the shunt catheter was never commercialised, possibly because of the deleterious effect on mechanical properties, and possibly because of the well-known risk of resistance when rifampicin is used alone in any context. Using the same impregnation method, an experimental catheter containing rifampicin, mupirocin and fusidic acid was tested in vitro against *S epidermidis* and gave protective activity for at least 20 days [49]. A catheter containing rifampicin and trimethoprim was tested in vitro against *S aureus* and gave strong killing effect over the short period tested [50]. The same group used the same process to test a catheter impregnated with rifampicin and sparfloxacin against *S epidermidis* and showed prolonged drug release and protection against colonisation for 1 year, after static soaking [51]. A process for coating polyurethane catheters with rifampicin and minocycline was investigated in vitro [52]. The process was then revised to make it suitable for silicone. Though the nature of the process was very different from the impregnation process above [44], an antimicrobial EVD catheter using this process containing rifampicin and minocycline has been described (Ventriclear, Cook Inc) [53]. A legitimate concern has been voiced that antimicrobial devices might lead to increased bacterial resistance. A long-known but not widely recognised principle for avoidance of resistance is the use of two or more antimicrobials, each of which is active against a different bacterial target site, such as RNA polymerase (rifampicin) and DNA gyrase (sparfloxacin) or protein synthesis (clindamycin). This principle was introduced by Ehrlich [54] and has been extended by Zhao and Drlica [55] as the Dual Drug Principle. Experimental studies show clearly that exposure of bacteria

to a single antimicrobial usually results in resistant mutants arising whereas when exposed to dual or triple drugs, this does not happen. Some authors have emphasised this important principle when designing antimicrobial materials [44, 49, 51].

5. Interference of released antimicrobials with diagnostic tests

Concern has been raised that release of antimicrobials into the lumen of the catheter might interfere with diagnosis of ventriculitis by inhibiting or killing any bacteria before they can be grown on culture. This concern was reinforced by a study by Stevens et al. [56] who suggested, on the basis of in vitro studies, that it might be justified. However, the methods used did not simulate events encountered in practice, and the issue was revisited [57]. In this study, both the commercially available antimicrobially impregnated catheters (Bactiseal and Ventriclear) were included, and the methods were designed to mimic their use in an EVD system, with bacterial challenge and CSF sampling modelled on clinical events and procedures. The study found that, in samples taken on Day 1 of "EVD" bacterial viability was significantly reduced by the antimicrobial release, which occurred as a burst effect only in the first 24 hr. After this, no reduction was seen. It is unlikely that CSF sampling would be required as early as the first 24 hr. of EVD, and the conclusion was that no clinically relevant interference with diagnosis was found.

6. Activity of impregnated EVD catheters against multi-drug-resistant pathogens

Though the Ventriclear EVD catheter contains minocycline, neither this nor Bactiseal catheters are likely to have any useful effect against gram negative EVD pathogens. These include not only *E coli* and *Klebsiella pneumoniae*, but multi-drug-resistant (MDR) strains of these as well as intrinsically MDR bacteria such as *A baumannii*. A catheter with activity against these pathogens is badly needed. The catheter containing trimethoprim developed by Kohnen et al. [50] might have some activity against *E coli* and *K pneumoniae* (unless MDR) but these were not tested. A later development by the same authors, containing sparfloxacin, would probably show better anti-gram negative activity, but again they did not test this [51]. An EVD catheter impregnated with rifampicin, trimethoprim and triclosan, using the impregnation method previously described [44] has been tested in vitro [58]. The antimicrobials were again chosen to provide broad spectrum of activity against EVD pathogens, to reduce the risk of resistance developing (Dual Drug Principle) and for compatibility with the impregnation technology. The impregnated catheters were installed in a modular longterm flow apparatus and perfused constantly with nutrient medium. Both plain and impregnated catheters were challenged weekly with suspensions of test bacteria (10^5cfu/mL) and monitored for colonisation. Plain catheters all colonised within 24-48 hr., but none of the impregnated catheters colonised. The 17 test bacteria consisted of clinical isolates of *E coli* (including ESBL and NDM-1 producers), *Enterobacter cloacae*, *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *S epidermidis* (MRSE), and *A baumannii*. Also included was a series of 5 isolates of *S epidermidis* from Bactiseal shunt infections due to intrinsic resistance to either rifampicin or clindamycin, or both. Catheter segments were inserted stereotactically into the frontal lobes of rats

and the brains examined after either 1 week or 4 weeks for signs of neurotoxicity. Behavioural changes and weight gain in the rats was also monitored. All rats gained weight normally and did not show any behavioural anomalies. Neurohistochemical examination showed significant glial response in both control and impregnated segments after 1 week, considered to be due to surgical trauma, and this had subsided by week 4. The findings suggest that this EVD catheter might address the remaining problem of antimicrobial activity against MDR EVD pathogens including *A baumannii*. The catheter has not yet been commercialised. The same impregnation method was used to produce an EVD catheter containing rifampicin, clindamycin and trimethoprim [59]. The catheters were tested by the Serial Plate Transfer test (SPTT) [44, 60], which is useful as a screening test but does not dispense with the need for more rigorous clinically predictive tests. As expected, the catheter showed prolonged activity against *S epidermidis*, but not MRSA, in the SPTT. Animal inoculation was carried out by subcutaneous implantation to test for biocompatibility, but no implantation into the central nervous system was done.

7. Clinical studies

7.1 Surface-modified neurosurgical materials and devices

A silicone shunt catheter made from expanded polytetrafluoroethylene (e-PTFE) has been evaluated but failed due to its porosity allowing tissue ingrowth [61].

PVP-coated catheters have been commercialised (Bioglide, Medtronic, USA). They need to be handled carefully when dry to prevent cracking of the coating, and must be soaked and rehydrated for use. This gives the opportunity for the surgeon to add antibiotics such as vancomycin or bacitracin to the soak saline, with the intention that it will add antimicrobial activity to the hydrophilic anti-attachment surface. Kaufmann et al. [62] carried out a clinical trial of commercially available PVP-coated shunts pre-soaked in bacitracin and found no effect on infection rates ($p > 0.24$). According to the authors, the concentration of bacitracin was not expected to be sufficient to affect infection risk, and reliance was mainly on the hydrogel, but is has been common practice to soak shunt and EVD catheters in antibiotic solution. However, in vitro studies have not shown an advantage of antibiotic soaking of PVP catheters [30, 31] and this was the case even when high concentrations of various antibiotics were tested [32]. An increase in shunt infection when PVP catheters were used was observed in another study by Kestle et al. [63] though no details were given on antibiotic soaking. In this study, a clearly higher infection risk was seen with PVP catheters (OR 1.91, CI 1.19–3.05, $p = 0.007$). While the lack of PVP coating in the catheter lumen might have been a factor in failure to prevent infection, the higher risk of infection in PVP-coated catheters compared to plain catheters remains unexplained.

7.2 Antimicrobial coatings

Silver-processed shunt and EVD catheters have been the subject of several clinical studies. An insignificant reduction (2.7% vs. 4.7%) was reported by Fichtner et al. [64] from a retrospective cohort study, while Lackner et al. [65] reported a statistically significant reduction in EVD infections (25–0%) in a mixed retrospective/prospective cohort study with small numbers. A retrospective study comparing three

different types of polyurethane catheters, one of which was silver-processed, found a significant difference in infection rates between two non-silver catheters, both from different manufacturers, for unexplained reasons, but there was no significant difference in infection rates between the two polyurethane catheters (one containing silver) each from the same manufacturer [66]. This study would seem to indicate a difference in infection risk between two types of polyurethane catheter rather than any effect of silver, contrary to the claim in the title. A meta-analysis [67] found no significant overall reduction in EVD infection rate when silver-processed catheters were used, but they commented that their effect may be selective: a significantly lower rate of infection due to gram positive, but not gram negative, bacteria was found in the silver catheter groups. However, despite this, a large randomised controlled clinical trial of silver-processed EVD found a reduction in infection rate from 21.4 to 12.3% (13). The very high rate of infection in the plain catheter arm is unusual in UK, and the rate of 12.3% is still much higher than the 9.3% in most UK and Irish centres [68], though the authors state that they chose high-risk patients for their trial. A multicentre survey of EVD infections in UK and Ireland [68] found a higher infection rate (13.7%) in silver -processed catheters than in plain catheters (7.4%) but this did not reach statistical significance. Another randomised controlled trial of silver-processed catheters in CSF shunting failed to find any difference between plain and silver-processed arms [69] and this is consistent with studies of such catheters in other fields [70–72]. It is important to note that the precise nature of the silver -processing differs between studies, and this might affect the results.

7.3 Antimicrobial impregnation

The first technology for impregnation of silicone catheters with antimicrobials was published in 1989 [44]. This technology, resulting in a CSF shunt containing relatively small concentrations of rifampicin and clindamycin, was the subject of numerous clinical studies. The first was a prospective randomised study of 110 patients [73]. The infection rates were 6% in the impregnated group and 17% in the plain control group. Importantly all the infections were due to staphylococci in the control group, and there were no staphylococcal infections in the impregnated group. Of the three infected patients in the "impregnated" group, all had gram negative infections and one was also infected with HIV. In another study with historical controls, there were seven infections (15%) in the plain catheter group, and one (3%) in the "impregnated" group [74]. This was a child who scratched open the abdominal wound in the postoperative period, and contaminated the shunt with *S aureus*. In another study, again with historical controls, there were three shunt infections (1.2%) in the antimicrobial catheter group and 36 (6.5%) in the preceding plain catheter group ($p = 0.0015$) [75]. Of the three infections in the "impregnated" group, two were due to *S epidermidis*, both susceptible to rifampicin and clindamycin, and in one case the clinical course was complicated by EVD, reservoir placement and shunt revision for intraventricular haemorrage before the infection occurred. The third case was due to *Haemophilus influenzae* 8 months postoperatively. *H influenzae* was, at the time, a common cause of childhood community—acquired meningitis. The antimicrobial activity of the shunt would probably have declined by that time and in any case would not have been very effective against this bacterium. A retrospective study in children, again with historical controls, showed a statistically non-significant reduction in shunt infection (7 vs. 4 infections, $p = 0.534$). Two of the 4 infections in the antimicrobial catheter group were due to gram negative bacilli and only one was

due to *S epidermidis*. In the control group, four infections were due to *S epidermidis*. The authors concluded on this basis that there was no evidence of efficacy of antimicrobial shunt catheters [76]. A multicentre study in children, again with historical controls, had considerable problems with differences in results between centres, but concluded that antimicrobial shunt catheters might significantly reduce infection rates in paediatrics, but that a randomised controlled trial was needed [77]. An observational study [78] found no significant difference in shunt infection rates between antimicrobial and plain catheters. However, there were additional postoperative risk factors, such as further neurosurgical intervention, and the diagnostic criteria included late ulceration over the shunt in three of the five infections in the antimicrobial catheter group, leading to non-surgical shunt infection which, as the authors say, the antimicrobial shunt could not be expected to prevent. A systematic review found a significant reduction in shunt infection rate for antimicrobial catheters (RR 0.42, 95% CI 0.32–0.55) [79]. A retrospective review of VP shunts in high-risk children, defined as premature when shunted, post-meningitic, post shunt infection, or having undergone EVD, found a statistically significant reduction in infection in all these groups [80]. The reduction from 20 to 5.5% in the high-risk neonate group was also found by Hayhurst et al. [81] Parker also recorded the lack of adverse effects in this vulnerable group [81]. Their finding of a reduction in the group where EVD had been used was interesting, as others had suggested that this might have increased the risk of failure of the antimicrobial catheters. All of these studies used the rifampicin + clindamycin impregnated shunt. None of them was a randomised controlled trial and in many cases such a study was called for in the conclusions. There is a formal registry of CSF shunting in UK, based in Cambridge, and a report issued in 2009 on almost 2000 matched impregnated / plain cases showed a reduction from 4.7 to 3%, which just reached statistical significance ($p = 0.048$) [82]. However, there were limitations such as reporting bias, and use of an intention—to—treat analysis as well as very different rates and criteria from contributing institutions. Eventually, a formal multicentre randomised controlled trial, the BASICS study, was carried out, comparing plain shunts with silver-processed and antimicrobial impregnated ones in 1594 patients [69]. After a median follow-up of 22 months (IQR 10–24), the infection rates were 6% in both plain and silver-processed groups, and 2% in the antimicrobial impregnated group ($p = 0.0038$). This finding confirmed most of the previous retrospective or historically-controlled studies. Even before this definitive study, there had been a steady increase in uptake of antimicrobial-impregnated shunts in UK, so that since their introduction in 2001 they were used in approximately 70% of shunt surgeries in 2014 [83]. This seems to have been matched by a steady decline in shunt infection rates over this period.

7.4 Cost-effectiveness studies

The BASICS study raised the issue of healthcare cost savings based on reduction of treatment costs for infection. This had been addressed by Sciubba et al. who speculated that shorter hospital stay (30 vs. 17 days) and reduced adverse events due to treatment of shunt infection might lead to significant cost savings [84]. A German study found a cost saving of $17,300 in children and $13,000 in adults in those receiving antimicrobial -impregnated shunts compared to plain shunts [85]. An American study found that the hospital cost per 100 patients shunted was $151,582 and $593,715 for antimicrobial and plain shunts respectively, due to reduction in costs of treatment of infection [86]. In a meta-analysis and cost study, it was found

that, assuming 200 shunt operations per year, annual costs savings would range from $90,000 to $1.3 M in American centres [87]. The use of shunt catheters impregnated with rifampicin and clindamycin appears to reduce the incidence of shunt infection and by so doing, reduce healthcare costs very significantly. The benefit for patients and their relatives is also therefore obvious, with less morbidity, fewer shunt revisions for infection, and less time spent in hospital.

7.5 Impregnated EVD catheters

Two antimicrobial-impregnated EVD catheters have been commercialised and approved for human clinical use. A catheter impregnated with two antimicrobials, rifampicin and minocycline, has been the subject of a prospective randomised controlled trial [53]. They found a significant reduction in ventriculitis (from 36.7 to 17.9%) from plain EVD catheters to impregnated catheters respectively ($p = 0.00095$). EVD pathogens were mainly *S epidermidis* in the plain catheter group, with gram negative bacteria found in both groups. A study from USA considered the question of whether clinical trial results for this catheter translated into real-life clinical practice. In 113 consecutive patients who received the rifampicin-minocycline impregnated EVD, only one confirmed case of ventriculitis was seen, and this was due to *Enterobacter aerogenes*, against which the catheter offered no protection [88]. The same impregnated catheter was compared with the rifampicin-clindamycin impregnated catheter for EVD in another study but there were no infections in either group [89]. An interesting study comparing rifampicin—clindamycin and rifampicin- minocycline impregnated EVD catheter with plain controls in a sequence of five periods found an infection rate in Period 1 (plain catheters) of 6.7%, Period 2 (plain catheters with procedural changes) 8.2%, Period 3 (rifampicin-clindamycin catheters) 1%, and Period 4 (return to plain catheters) 7.6%, and Period 5 (rifampicin -minocycline catheters) 0.9% [90]. This showed clearly the advantage of both of the commercially available impregnated EVD catheters.

7.6 Does the use of antimicrobial devices increase the risk of resistant infections?

Concern has been expressed that antimicrobial shunt and EVD catheters might give rise to increased antimicrobial resistance. This has been investigated in vitro [91]. A central venous catheter impregnated in the same way and with the same antimicrobials as the rifampicin-minocycline EVD was serially exposed to bacteria in vitro for 21 days without any resistance, again due to the Dual Drug Principle. These in vitro findings confirmed an earlier study by Munson et al. [92] A clinical study of the rifampicin-clindamycin shunt showed that the overall infection rate fell and there was no increase in gram negative bacteria following its use [93]. However, in a systematic review of rifampicin-minocycline and rifampicin-clindamycin impregnated shunts and EVDs it was claimed that the use of these devices ran the risk of increase in more virulent and drug-resistant infections [79]. The evidence for this, cited by the authors, was a large study of over 2000 paediatric shunt placements using either plain catheters or the rifampicin-clindamycin shunts [94]. The authors found a statistically significant reduction in infection in the antimicrobial shunt group ($p < 0.005$). They also noted a change in the proportions of shunt pathogens. The proportions of *S aureus* infection in each group were approximately the same, whereas the proportions of *S epidermidis* infections fell from 52 to 16% in the

antimicrobial shunt group. Moreover, the proportions of shunt infections due to gram negative bacilli were identical. The authors stated that no unusually resistant bacteria were isolated in either group. The only significant change was the rate of *C acnes* infection: 2.2% in the control group and 16% in the antimicrobial shunt group. This was a sequential study with a historical control group, and the authors considered that the apparent proportional increase in *C acnes* infections was due to the introduction during the period that the antimicrobial shunt was used of extended culture times, which are essential for isolation of this organism. The statement by Konstantelias et al. [79] is therefore based on a misunderstanding of the source data cited. Increased rifampicin resistance was claimed to be due to the use of rifampicin-clindamycin impregnated shunts [95]. This study concerned the consecutive use of these shunts in all cases for 52 months, during which there were only 4 shunt infections (3.2%), all due to rifampicin—resistant *S epidermidis*. The authors felt that this had revealed a threat of selection of rifampicin resistance due to the use of these shunts. However, 4 shunt infections in 4.3 years equates to a shunt infection rate of 0.92%. Also, it is recognised that a very small proportion of *S epidermidis* strains are resistant to rifampicin, and an encounter with such a resistant strain by a patient with a rifampicin—impregnated shunt would be as likely to result in a shunt infection as if a plain catheter were used. There was no evidence in this study that the use of rifampicin-impregnated shunts had caused the rifampicin resistance.

Bacterial resistance due to drug exposure can arise in other ways than genetic mutation. One important example is the consequence of antibiotic exposure in "normal flora" sites such as the skin, intestine or mucous membranes. Here the maintenance of the balance of many different bacteria and fungi is important. The commensal bacteria at these sites are largely beneficial, but if the balance is disturbed so that one organism is allowed to predominate, then a disease state can result. A common example of this is the overgrowth of *Candida albicans*, a commensal yeast, that is a cause of thrush after a course of antibiotics. In the context of EVD management, prophylactic antibiotics are used either as one dose at insertion, or continued systemic administration throughout the use of EVD. These two regimens have been considered in terms of their potential to reduce EVD infection. A study of antibiotic prophylaxis for 24 hr. compared to an extended regimen for the duration of EVD found no significant difference in EVD infection but there was a statistically significant fall in the number of cases of *Clostridioides difficile* infection in patients with EVD [96]. *C difficil*e can cause life-threatening colitis that may require colectomy. The bacterium is a normal commensal of the colon in small numbers, but if the ecological balance of the colonic microbiome is disturbed by antibiotics, *C difficile* numbers rise and the toxin produced causes necrosis of the colonic epithelium and severe inflammation. Another study has confirmed this, with statistically significant falls in both *C difficile* infection and antibiotic use [26]. A similar result has been reported in the context of intracranial pressure monitoring, where there was difference in infection (0.7 vs. 1.4 per patient, ($p = 0.05$) and particularly in the number of multidrug resistant bacteria isolated per patient (0.03 vs. 0.33. $p < 0.01$) indicating no advantage in extended prophylaxis but a significant increase in infections due to resistant bacteria. This pattern was also seen in the ventilator-associated pneumonia (VAP) and septicaemia cases [97]. Prolonged antibiotic use has also been identified as a key factor in the increase in *A baumannii* infections in ventilated trauma patients [98]. Others have now questioned the use of extended duration antibiotic prophylaxis for EVD, on the grounds of both lack of benefit and risk of drug resistant infections and *C difficile* disease.

7.7 Antimicrobial devices and antibiotic prophylaxis

The role of antimicrobial EVD catheters in reducing the need for prophylactic antibiotics has also received attention. One sequential study compared ventriculitis rates between a group receiving a rifampicin+clindamycin EVD and single dose antibiotic prophylaxis with a second group that had extended antibiotics with plain EVD catheters. There was a non-statistically significant reduction in ventriculitis in the antimicrobial catheter group, indicating that the extended duration antibiotic regimen did not add any benefit over antimicrobial EVD catheters. However, an important finding was that there were 3 cases of serious *C difficile* disease in the group without antimicrobial catheters, one patient requiring a colectomy [27]. The authors concluded that the antimicrobial catheters were as effective in preventing EVD infections as extended antibiotic prophylaxis, but safer. Another sequential study with 545 EVD placements, all using the rifampicin+clindamycin catheter, showed that there was a statistically non-significant fall in ventriculitis rates after switch from extended antibiotic prophylaxis to single dose, but a statistically significant fall in nosocomial infections such as VAP. The authors concluded that there was no need for an extended prophylaxis regimen if antimicrobial EVD catheters were used [99].

8. Surgical bundles with antimicrobial devices

Despite the very positive findings showing the effectiveness of antimicrobial catheters in prevention of infection in both shunts and EVDs, it would be wrong to assume that other aspects of surgical procedures can be relaxed. The best approach would be to ensure that a robust surgical bundle was instituted along with adoption of an antimicrobial catheter. This was clearly illustrated by a study in which, after a preliminary period to establish a baseline, a completely new surgical bundle was introduced, that included rigorous aseptic technique and intensive staff training, and an antimicrobial EVD catheter [100]. The infection rate fell sequentially each quarter, from baseline of 9.2 to 2.6%, then to 0% over 4 years. In such a study, it is impossible to say whether the antimicrobial catheter alone, or the bundle alone, was responsible but it is likely that a combination of the two brought about the dramatic and sustained fall in infection rates.

9. Recommendations in international guidelines

The Infectious Diseases Society of America (IDSA) have issued guidelines for clinicians on reducing infections in patients with neurosurgical devices [24]. They say that "Use of antimicrobial-impregnated CSF shunts and CSF drains is recommended (strong recommendation, moderate confidence rating)." Similarly the Neurocritical Care Society published their guidelines for insertion and management of EVDs [101] and stated "We recommend using antimicrobial-impregnated catheters as part of a comprehensive management protocol to reduce the rate of VRI (strong recommendation; moderate-quality evidence)" These recommendations, and the quality-of-evidence assessments, were made before the latest RCT results were published in 2019 [69].

10. Reservoirs and intracranial pressure monitors

Infection in ventricular access reservoirs is rare, but when it occurs it can result in ventriculitis [15]. However, direct ventricular access is available for administration of antimicrobials. There is no current antimicrobial materials approach to reservoir infections. Techniques for measurement and monitoring of intracranial pressure vary and again, those not dependent on EVD have a low infection rate [102, 103].

11. Conclusions

There has been a dramatic fall in the rate of infections associated with CSF shunts and EVDs over the past two decades. This has been due to a much greater understanding amongst clinicians of the underlying science and the causes of the infections, and has led to well-thought-out non-technological approaches such as care bundles. However, these need to be more widely adopted. Their effect has been enhanced by improvements in anti-infective technology that has centred on development of coated and impregnated devices, and certainly the latter have been shown to be highly effective in reducing further the infection rates as well as healthcare costs. An additional benefit to this approach has been the reduction in antibiotic use, leading to less drug resistance and adverse effects. The use of antimicrobial shunts and EVDs has now been recommended as the standard of care in neurosurgery. Problems remain, especially in EVD where increase in infections due to highly drug-resistant bacteria is seen, and these are not currently preventable by the impregnation technology. New formulations that have been shown to have activity against even the most drug-resistant EVD pathogens have been thoroughly evaluated in the laboratory, but as yet they have not been commercial adopted.

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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