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Editorial

CNS infections in patients with temporary CSF shunts: Diagnostic, preventive and therapeutic approach

Infecciones del SNC en pacientes con drenaje ventricular externo: aproximación diagnóstica, preventiva y terapéutica

External ventricular drainage (EVD) is one of the most commonly performed neurosurgical procedures: more than 25,000 EVD are inserted annually in USA alone.

EVD are placed for treatment of hydrocephalus and management of different neurosurgical pathologies such as craniocerebral trauma, shunt malfunction or infection, cerebrospinal fluid leaks, intraventricular, subarachnoid and intracerebral hemorrhages, tumor related hydrocephalus, and for the intracranial pressure monitoring.

The placement of EVD, a lifesaving intervention but a relatively easy neurosurgical procedure, however have in some occasions very important complications, procedural and catheter related, as malposition, hemorrhage, and EVD infection.

Infection of the EVD is a devastating event, with dramatic clinical consequences for the patient and family, and a significant increase in intensive care unit (ICU) and hospital stays, prolonged antibiotic therapy, morbility and mortality. Treatment need catheter replacement surgeries and, in many cases, permanent ventrículo-peritoneal shunt, and worse prognosis. In a multicenter and prospective study,[1] the death rate was 25.2% within 30 days after EVD-insertion. The outcome was poor in 38.5% and only 36.3% of the patients was good. In addition to this, the economic cost of an EVD infection is estimated at 35,000 €.

The published infection rates of EVD are very variable (10–45%), and this is due to several factors: differences in the definition criteria for EVD infection, methodology, monitoring and draining time, surgical protocols, etc. Recent reports publish rates from 6.1% to 11%, or 11.4–17 per 1000 catheter-days.[1,4]

Diagnostic approach

The first problem is the definition of EVD infection. There is no unanimity in the infection criteria.[2] EVD infection studies show, on many occasions, discordant data due to study design, integrated hospitals, population age, infection criteria, risk factors considered, etiological agents and antimicrobial sensitivities, study and follow-up time, different types of EVD, etc.

The CDC criteria for EVD infection is based on clinical symptoms (new or worsening altered mental status), laboratory findings (increased CSF leucocytes) and positive cultures in CSF.[3]

Other criteria are more restrictive and only consider EVD infection when there is culture in CSF, because patients who require EVD usually have altered level of consciousness or other symptoms by underlying disease. Fever may also be from other infections or in the context of subarachnoidal or ventricular hemorrhages. In addition, prior neurosurgery, catheter placement, hemorrhages, or other underlying neurological diseases can cause inflammatory changes in the CSF without infection and that may be confounding factors. Ventricular CSF has lower leucocytes tan lumbar CSF. Peripheral leukocyte count and CSF glucosa and protein levels are no predictors for incipient EVD infection. Even, when there is evident infection, some of the most frequent etiological agents (*Cutibacterium acnes* and *Staphylococcus* spp.) are clinically indolent with no significant meningeal inflammation and cause little or no changes in CSF.

On the other hand, anaerobic CSF cultures should be carried out with prolonged incubation (at least 10–14 days) in order to isolate microorganisms such as *C. acnes*. A negative CSF Gram stain or CSF culture does not exclude completely EVD infection. CSF cultures may be negative if the patient has received or receives antimicrobial treatment. Finally, the use of antibiotic impregnated EVD (AI-EVD) o silver-coated EVD (SI-EVD) can interfere in obtaining positive cultures. Some of these problems could be avoided using a broad-range 16S rRNA polymerase chain reaction or broad-range real-time PCR, that increase the ability to identify bacteria by 25%.

Preventive approach

Multiple risk factors that influence the occurrence of infections in EVD have been identified such as age, sex, underlying disease and clinical severity of the patient, intracranial pressure maintained above 20 mmHg, previous EVD replacement, neurosurgical procedures or intraoperative endoscope, previous or concomitant extracranial infections, CSF leakage, previous shunts or EVD infection, type of cleansing or dressings, duration of the insertion and manipulations of the EVD as CSF sampling, intraventricular or antibiotics or plasminogen instillation.

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In recent years, numerous strategies have been developed to reduce this infection rate: use of EVD care bundles, antibiotic prophylaxis, impregnated-catheters, used of closed systems, shaving only areas of puncture and insertion and exit with electric razor and immediately before surgery, insertion of the EVD in conditions of asepsis and sterility, subcutaneous tunneling, avoiding of unnecessary manipulations, etc.

Undoubtedly, the first and most efficient strategy to prevent infection of the EVD is to avoid its implantation; stating if its placement is strictly necessary. In certain circumstances, the placement of an EVD is done for theoretical reasons of safety, such as after successful endoscopic surgery, ventricular surgery without evidence of obstruction of CSF pathways or in patients with ventriculomegaly, subarachnoid hemorrhage or chronic hydrocephalus. In many patients who theoretically would need an EVD, if they are treated by expert neurosurgeons, with intense neurological surveillance, and quick access to insertion of an EVD if necessary, it is possible to avoid an EVD, and its complications.

Once it is decided that the EVD is necessary, the next issue is where and under what conditions it should be implanted. There are protocols to minimize the risk of infection, through preoperative preparation, antibiotic prophylaxis, and meticulous sterile technique (sterile gowns, gloves and masks; sterile adhesive cloths, etc.) and aseptic EVD manipulation.[6,7] Unfortunately, protocols are highly variable among hospitals, as is adherence to them.

In general, it is desirable that the EVD be inserted in the operating room if the patient's clinical situation allows it. In neurocritical patients, many of them clinically unstable, the transfer to the operating room is an additional risk. However, an increased risk of complications has been observed is EVD is placed at ICU (21.5%) compared to those inserted in the operating room (6.7%): greater risk of hemorrhage (15.1% vs 4.4%), infections (4.3% vs 0%), and non-functional drains (5.4% vs 2.2%).[8] A 4-fold increased risk of infection has been proven when the placement of catheters is made outside the operation rooms.

Antisepsis of the skin before insertion of EVD is essential. The sequential use of chlorhexidine and povidone-iodine gets a greater reduction of the skin bacterial flora and lower risk of intravascular catheter colonization, and risk of surgical site infection, compared to use of either agent alone.[9] The protection of the surgical site with chlorhexidine discs or antibiotic-impregnated disk seems to reduce the risk of EVD infection (from 6.3% to 0.8%/1000 catheter days). Also, cyanoacrilate at the catheter exit site is used with good results. Benzoil-peroxide is a promising agent that penetrate deeper layers of the skin and is very active against *C. acnes*, one of the most frequent germs in neurosurgical infections in our hospital.

The techniques of EVD insertion through the trephine or twist drill have not shown differences. Although less aggressive percutaneous techniques reduce surgical time, the implantation of an EDV through a very narrow hole requires an expert neurosurgeon. It has also been studied if the experience of the neurosurgeon influences the onset of EVD infection. Previous data suggested that more experienced neurosurgeons and those who had placed a greater number of EVD had more placement accuracy and fewer EVD infections. More recent studies do not demonstrate these differences.[1]

The prophylactic antibiotic administration is another prophylactic measure. Recent data demonstrate its effectiveness, reducing EVD infections from 27% to 9%.[3] Although, it is not a universal measure: in the USA, only 69% of the centers perform its.[6]

There is controversy about the duration of antibiotic administration: from a unique preoperative intravenous dose in anesthetic induction, up to 24 h, several days, or until discharge. Rodriguez-Lucas[10] use prophylaxis for 24 h (cefazolin 1 g/8 h). Some authors recommend prolonged antimicrobial prophylaxis, but their works or reviews have important methodological failures.[3] In patients with AI-EVD no additional protection is observed with prolonged systemic prophylaxis. The current trend recommend use of shorter prophylaxis: one periprocedural dose of antimicrobial. So, in our hospital we administer a single dose periprocedural (cefazolin 1 g iv). Antibiotic prophylaxis must be chosen by each hospital based on the etiological agents that cause neurosurgical and EVD-infections, resistance profile, and CSF penetration. Against extended prophylaxis it is argued: more incidence of diarrhea due to *Clostridium difficile*, selection of antibiotic-resistant microorganisms,[2] greater toxicity and economic cost.

EVDs become infected by three mechanisms or routes: (1) inoculation of skin flora during surgery, (2) ascending migration of skin bacteria through the catheter, and (3) obtaining CSF samples, from the EVD. Once the ventricle is cannulated and CSF flows, it is very important to tunnel the catheter as far as possible from the drill and exit through a narrow cutaneous stoma. A direct relationship between infection and length of EVD tunneling (distance between burr hole and skin stoma) has been proven: higher infection rate in short-tunneled EDVs, with more complications like CSF leak (16% vs 2%), infection (19.6% vs 4%), blockage, misplacement or migration of intraventricular catheter, longer stay in ICU (10.27 vs 6.26 days) and hospital stay (17.18 vs 12.2 days).[4,11] Surprisingly, Jamjoom et al.[1] found no relationship between tunneling distance and infection risk. Other authors perform a longer tunneling to the upper thorax, and report a lower infection rate (0–10%) and lower morbidity, and they conclude that it is an effective method for patients who need a prolonged temporary CSF diversion.[12]

Bolt EVDs avoid the need for tunneling and reduce the incidence of complications (17.6% vs. 59.4%), such as CSF leak, infection and catheter migration. Bolt EVD can be placed outside the operating rooms (at emergency or in the ICU bedsides) with the same safety and accuracy and with a decrease in costs (335 $ vs 1.698 $). A disadvantage: the burr hole determines the trajectory of the EVD, and if the ventricle is not punctured in the first passage, the burr hole and trajectory must be changed.[13]

The stabilization and fixation of the EVD to the scalp is very important. An easily mobilized EVD facilitates the opening of the cutaneous stoma and fluid outflow accelerating bacterial colonization. Additionally, accidental explantation is more likely, with the consequent need for new neurosurgery. Our group published an extremely simple technique to fix catheters between two hydrocolloid dressings, securing it with staples, that collects the exudation through the cutaneous stoma and critically reduces explantations.[14]

Type choice of catheter is a matter of debate. There are three types of catheter: standard (non-impregnated with rifampin 0.054% plus clindamycin 0.1% (for example Bactiseal^{TM}) (AI-EVD), and impregnated-catheter with silver nanoparticles and an insoluble silver salt (Silverline^{TM}) (SI-EVD).

AI-EVDs do not reduce bacterial adhesion, although they are able to lyse adhered bacteria within 48–52 h, both intra and extraluminally, even in the presence of biofilms. AI-EVD shows only protection against gram-positive germs. Several studies have demonstrated that the use of AI-EVD reduces colonization and EVD-associated infection rate: from 24.5 to 4.4 per 1000 devices-days. The absolute risk decreased by 19.2%. In children, a significant decrease in EVD infections has been demonstrated from 6% (8.6 per 1000 catheter days) with standard EVD to 0.9% (0.99 per 1000 catheter days) with AI-EVD. However, in the USA, AI-EVDs are only used in 53% of hospitals. The time interval between EVD insertion and EVD infection is longer in AI-EVD than in standard EVD (15 ± 4 vs 4 ± 2 days).

SI-EVD decreases also bacterial growth. Due to its antiseptic characteristics, its preventive activity against gram-positive and gram-negative bacteria, fungi and virus. SI-EVD reduce the risk of infections related to EVDs (21.4% plain vs. 12.3% SI-EVD), allow a longer catheterization time, and are clinically safe. Although more

recent studies question this data: SI-EVD have the same incidence as the plain-EVD, and more than the AI-EVD.[1] Other authors have observed non-significant tendency to decrease infection with SI-EVD (from 18.9% to 15.5%), without reducing the subsequent need for shunt placement, days of EVD, or days of stay in the ICU, or of antimicrobial therapy. Finally, an increase in infections due to gram-negative rods has been reported; although other authors observe that SI-EVD infection are caused by similar microorganisms to those collected in standard catheters. Recently, BASICS[15] show no significant difference between plain and SI-catheters (6% of infections in each).

AI-EVD and SI-EVD have a higher cost than noncoated-EVDs, although by reducing the rate of infections, their use is cost-effective. Use of coated EVDs are recommended to prevent ventriculitis by the IDSA guideline[3] and the American Neurocritical Care Society[2] in order to reduce infections related to EVD.

A meta-analysis of 5.242 cases demonstrates the effectiveness of combined iv. antimicrobial prophylaxis and AI-EVDs: incidence of 13–38% with no prophylaxis, 7–18% with perioperative iv. prophylaxis, 3–9% with either extended iv. prophylaxis or AI-EVD as monotherapies, and as low as 0.8–2% with extended iv. prophylaxis and AI-EVD dual prophylaxis.[16]

Recently, articles and meta-analyses have been published in which the utility of AI-EVD is questioned, indicating that they do not reduce the rate of infections. This may be due to the low rate of infections observed in these articles, and so difficult to prove an AI-EVD-related reduction.

The risk of false negative CSF sampling extracted through coated-catheters should also be considered, as well as an increase in infections by microorganisms not sensitive to antibiotics included in these catheters.

Systemic complications or allergies related to antibiotics present in coated-EVDs are very rare.

New catheters with activity against multi-drug resistant (MDR) or extensive-drug resistant (XDR) bacteria are being developed. An impregnated EVD with rifampicin, trimethoprim and triclosan has demonstrated, in Wistar rats, activity against MDR gram-negative bacteria and no evidence of neurotoxicity.[17]

Another point of debate is the duration of the antimicrobial activity of AI-EVD. Protection for up to 50 days was reported for Bactiseal™. Mounier et al.[18] observe a shorter duration of protection (inner and outer lumens) than expected: <20% of the initial concentration of clindamycin on the 5th day. For rifampicin they verify a decrease correlated with the duration of catheterization (>10 days) and volume of CSF drained (>1500 cc). They conclude that Bactiseal™ activity decreases rapidly to approximately 50% at 11th day.

The duration of the insertion of the EVD should be as short as possible and be removed as early as clinical situation allows. There is a greater probability of EVD infection with longer insertion times,[7,11] greatest in the 7–12 days following insertion. EVD placement for ≥8 days is an independent risk factor.[1] Bacteria may progress around the catheter, and penetrate the CSF and cause infection, especially in very long-term catheters. Gradual removal of the DVE for several days, raising the height of the drain, until clamping, increases the drainage time by 3–4 days, and the risk of DVE infection. A rapid weaning (24 h) can be carried out safely, more efficiently with the aid two pressure continuous monitoring, reducing the stay in ICU an average of 2.8 days.

Mayhall[19] proposed the routine change of the EVD and the insertion site every 5 days. Current data does not support this practice. In fact, there is a higher infection rate (32% vs. 8%), longer stay in the ICU (30.5 vs. 17 days) and hospital (33 vs. 24 days) in patients in whom the EVD is replacement every 5 days, than those who are replaced only if it is clinically indicated.[20] The placement and removal of EVD carries a risk of bleeding (20%) due to direct trauma, adherence of the EVD to choroid plexus or cerebral parenchyma, that is under-estimated. Ventriculostomy-related catheter tract hemorrhage is a factor for EVD infection. The placement of multiple catheters is another independent risk factor[20]: each additional EVD increase the risk of infection by 4-fold.[5] Therefore, the routine change of EVD might be harmful, so it is not recommended. In addition, with the use of AI-VED, the current trend is to maintain the AI-EVD as long as there is no clinical cause that justifies its withdrawal or replacement.

Another substantial aspect is the minimization of unnecessary opening and manipulation of the derivative system. Routine sampling of CSF samples may result in contamination of the EVD, with unnecessary clinical and economic costs; and an increased risk of EVD infection: each CSF sample increased the likelihood of ventriculitis by 8.3%. CSF samplings every day is an independent risk factor for EVD infection, when compared with sampling 1–2 times per week.[5] Additionally, when the CSF samples are reduced to two per week, an important cost reduction is obtained: $ 175 per patient per day.

When several measures are implemented at the same time, the reduction in EVD infections is 75%: 3.3 infections per 1000 devices day with EVD standard, 1.6 infections per 1000 devices day with AI-EVD, and 0.8 with AI-EVD plus reduced CSF sampling. In our hospital, the application of a minimal manipulation protocol of derivative systems plus AI-EVD have shown a significant and substantial reduction in infection rates: 85.8%.[21] Applying strict EVD care protocols, reductions of EVD infections from 10% to 3% and even lower have been reported.[6]

Before requesting a CSF study, we must ask ourselves if the results will have an impact on the clinical management of the patient, and if they will change our therapeutic decision. CSF samples should be performed only when there is clinical suspicion of infection, changes in the appearance of the CSF or in neurologic status or patient's clinical condition, fever without apparent focus, and 1–2 days before placement of a ventriculoperitoneal shunt. Manipulation must be carried out by expert personnel, taking extreme measures of asepsis.[6] The system should be closed a few minutes before, and, if possible, avoid active CSF aspiration, to prevent that EVD being attached to the walls of the ventricular system and clogged by ependymal tissue. Also, frequent changes of the drainage set are not recommended, since the sterility of a closed system is broken and risk of EVD infection increased. The drainage system should be manipulated as little as possible.[2]

Surprisingly, there is no consensus on protocols to prevent EVD infections. Ideally, a protocol should include all the measures and interventions analyzed plus a care bundle. We are convinced that the application of this protocol, with adherence and compliance in 100% of the cases, would result in a near zero infection EVD rate. Implementing a 11-steps bundle managed decrease EVD infections from 16 per 1000 EVD days to 1.3 per 1000 catheter days. Protocol compliance was 75%, and 20% did 10 of the 11 steps.[3]

Treatment approach

Gram-positive skin germs are traditionally considered to be responsible for EVD infections (*Staphylococcus* spp and *C. acnes*). Currently, a progressive increase in gram-negative bacilli is described (50–70.5%).[7] Many of them are MDR or XDR nosocomial bacteria, mainly *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[20] A germ infrequently described in EVD infections is *P. aeruginosa* (3.4%),[1] although appears to be increasing. Rodriguez-Lucas describes a series of 51 EDV-infections caused by *P. aeruginosa*.[10] The emergence of gram-negative bacteria has been tried to explain for several reasons: (1) greater hospital stay, which entails a higher risk of nosocomial infections; (2)

use of gram-positive antimicrobial prophylaxis, sometimes very prolonged; (3) patients with greater clinical and neurosurgical complexity, who require longer stays in the ICU; (4) use of AI-EDV or SI-EVD.

Antimicrobial treatment of post-neurosurgical meningitis/ventriculitis are limited due to low penetration in CSF, which is influenced by drug lipophilicity and degree of ionization, protein binding, meningeal inflammation and active transport system through the blood-brain barrier.

The treatment of EVD-infection by gram-negative bacteria has important complexity. And it becomes extremely difficult due to the emergence of MDR and XDR germs, to the limited number de antibiotics with activity against them and/or their low penetration in CSF. Recommended treatment for infections caused by *Pseudomonas* spp. is ceftazidime, cefepime or meropenem. Extended-spectrum-beta-lactamase producing gram-negative bacilli may be treated with intravenous meropenem.

Ventriculitis caused by MDR/XDR gram-negative bacteria show higher morbi-mortality (33–58%) due to antimicrobial resistance and poor penetration of antibiotics in CSF when administered only intravenously. There are studies that show that higher doses or expanded perfusion of meropenem or cefepime, or the combination of antimicrobials (carbapenem plus rifampicin or colistin) can improve the results of conventional systemic monotherapy.

The main objective of antibiotic treatment is to achieve rapid sterilization of the CSF, as quickly as possible. When systemic treatment is ineffective, intraventricular antimicrobial treatment (IVT) may get adequate CSF concentrations, since bypass the blood-brain barrier and achieve higher concentrations in CSF. Systemic and IVT antimicrobial treatment has been used as a last resort for the treatment of meningitis/ventriculitis caused by MDR/XDR bacteria; observing a faster sterility and normalization of the CSF.

On the other hand, IVT may have several problems: (1) more frequent manipulation of the EVD favoring the appearance of re-infections; (2) non always uniform distribution of antibiotics in different CNS compartments; (3) MIC of causative microorganism; (4) different degrees of meningeal inflammation; (5) variable doses administered; (6) different concentrations in CSF of antibiotics according to the neurological/neurosurgical pathology of the patient; (7) varying concentrations of antibiotic due to the volume, circulation and drainage of CSF; (8) metabolism, and clearance rates within the CSF differ from that in serum; (9) local toxicity (meningeal irritation, seizures, anorexia, eosinophilia, leg pain, sensorineural hearing damage, seizures, eosinophilic granulocytosis or aseptic meningitis); and (10) influence on ventricular compliance.

IVT antimicrobial treatment is not approved by the US Food and Drug Administration, and there is no sufficient evidence to recommend their general use. However, it is widely used in special clinical situations (contraindication of systemic antimicrobial treatment, clinical status of the patient, need to use systemic drugs with low CSF penetration, AI-EVD infection, when the patient is unable to undergo new neurosurgery, etc.) and clinical or microbiological failure of systemic antimicrobial treatment. For the treatment of meningitis/ventriculitis caused by MDR/XDR gram-negative bacteria IVT plus systemic treatments are recommended per 2017 IDSA's Clinical Practice Guidelines for Healthcare-associated Ventriculitis and Meningitis[3] and per American Neurocritical Care Society.[2] Theoretically, IVT treatment achieve higher concentrations in CSF, without the need to reach very high plasma concentrations, and with less systemic toxicity. It is recommended to clamp the EVD for 15–60 min to achieve a more uniform distribution of the antibiotic in CSF.

IVT with vancomycin, teicoplanin and daptomycin are currently used for infections caused by gram-positive bacteria; and aminoglycosides (gentamicin, amikacin, tobramycin) and polymyxins B and E against gram-negative bacillus infections. The dosages used and duration of treatment are very different, based on expert opinion or clinical experience, which makes it difficult to draw conclusions.[2,22]

A meta-analysis study,[23] which includes 296 patients, compares systemic plus IVT antimicrobial treatment with intravenous monotherapy in meningitis/ventriculitis caused by MDR/XDR gram-negative bacteria. Polymyxins and aminoglycosides were the main antibiotics used intraventricularly. There was higher mortality and a slower microbiological clearance in CSF in the monotherapy group. Also, shorter treatments (less than 7 days) correlated with higher mortality. Another study of 33 patients with meningitis caused by carbapenem-resistant *A. baumannii* showed that patients who received intravenous plus IVT colistin showed a not significantly statistical tendency to lower mortality than those who received only intravenous treatment. Likewise, they had significantly lower hospital cost, shorter lengths of hospital and ICU stay and less ventilator days. Rodríguez-Lucas[10] obtains also a tendency (not statistically significant) to present lower mortality with systemic treatment plus IVT.

it is necessary to perform antibacterial activity test; as well as pre and post dose levels, and adjust the dosage. Dosages and interval of IVT therapy is controversial, and this must be adjusted to the CSF drainage volume, ventricular size and MIC of causative bacteria, in order to achieve a trough CSF concentrations (CSF concentration immediately before the next IVT dose) of 10–20 times the MIC of the etiologic agent; or greater than 10–20 mg/L the CMI of causative microorganism.

IVT aminoglycosides have been used in combination with intravenous treatment with aminoglycosides or other antimicrobials, successfully. For meningitis/ventriculitis caused by MDR gram-negative bacilli, the recommended dosage of colistin would be 5–10 mg/day for 21 days. However, in different studies colistin has been administered from 2 to 40 mg/day for 2 to 28 days, even longer (144 days). The same applies to aminoglycosides: 1–10 mg of gentamicin for 3–35 days (more frequently 4–10 mg/d); 2–100 mg of amikacin for 2–42 days (more frequently 5–50 mg/d), and 2–10 mg of tobramycin for 7–40 days (more frequently 5–10 mg/d).[22]

Another point of conflict is the duration of antimicrobial treatment. For infections caused by gram-negative bacilli, IDSA guidelines recommend 21 days of antimicrobial treatment, although it should be adjusted according to the patient's clinical response. Other authors recommend continuing antimicrobial treatment for 10 or 21 after obtaining a negative CSF culture; or even less (2–3 days). We agree more with the IDSA guidelines.

We believe that the duration of treatment should be individualized, based on obtaining negative cultures, normalization of CSF, removal of infected EVD, underlying pathology and clinical response.

We believe that IVT and systemic treatment with colistin should be reserved, as a last option in the treatment of MDR/XDR infections of gram-negative bacilli.

Recently, Zhang et al.[24] have performed systemic treatment in 86 patients with post-neurosurgical infections with vancomycin (1 g/12 h) and meropenem (2 g/8 h). Forty-three of them also administered IVT treatment with 20 mg/24 h of vancomycin and 20 mg/12 h of meropenem. This second group has a higher cure rate in less time, and with less sequelae and complications, and economic costs. They conclude that IVT plus intravenous treatment is more effective and safer than systemic treatment alone; although they do not specify the etiologic agents of their infections.

The side effects are frequent (up to 66%, mainly seizures, worsening GCS, and chemical meningitis), of medium intensity and generally reversible, although sometimes they require discontinuation of IVT treatment. This side effects are dose-independent and may be under-estimated, since in neurosurgical patients, the assessment of neurotoxicity can be difficult. Preservative-free

formulations should be utilized to minimize adverse drug reactions, for example diluting the aminoglycosides in normal saline.

On the other hand, the infected EVD must be removed and insert a new EVD. In the article by Rodríguez-Lucas et al., the withdrawal of the EVD was shown as an independent factor with a better prognosis.[10] After the placement of the new EVD, it is recommended to perform CSF cultures until its negativity is verified.

The irrigation is a risk factor for EVD infection, due the manipulation of the catheter system. However, lately a preliminary work shows that IVT lavage with colistin solutions followed by IVT colistin treatment, is superior a IVT colistin for treatment of MDR/XDR gram-negative bacteria: earlier CSF sterilization, and lower morbidity and mortality when compared with IVT colistin administration.[25]

In conclusion, due to the heterogeneity observed between the studies, we believe that it is necessary to establish criteria for EVD-infection that are generally accepted. There should be consensus protocols, which avoid inserting EVDs when they are not absolutely necessary, with strict application of EVD care bundles, periprocedural prophylaxis antibiotic (with a single dose), use of AI-EVD and closed systems, insertion of the EVD in the operating room, with meticulous sterile technique, antisepsis of the skin with chlorhexidine and povidone-iodine, subcutaneous tunneling as far as possible, stabilization and fixation of the EVD to the scalp, avoiding of unnecessary manipulations and routine change of the EVD and reducing CSF samples (1–2 per week); and insertion duration as short as possible. The antimicrobial treatment of EVD-infections should be intravenously. Systemic and ITV treatments should be reserved when there is clinical or microbiological failure of intravenous antibiotic treatment or in specific clinical situations. It is necessary to achieve an antibiotic concentration in CSF 10–20 times the MIC of the germ, for which it is necessary to carry out determinations of antibiotic levels in CSF pre and post-dose, and adjust dosage.

References

1. Jamjoom AAB, Joannides AJ, Poon MT, Chari A, Zaben M, Abdulla MAH, et al. Prospective, multicentre study of external ventricular drainage-related infections in the UK and Ireland. J Neurol Neurosurg Psychiatry. 2018;89:120–6, http://dx.doi.org/10.1136/jnnp-2017-316415.
2. Fried HI, Nathan BR, Rowe AH, Zabramski JM, Andaluz N, Bhimraj A, et al. The insertion and management of external ventricular drains: an evidence-based consensus statement. A statement for healthcare professionals from the neurocritical care society. Neurocrit Care. 2016;24:61–81, http://dx.doi.org/10.1007/s12028-015-0224-8.
3. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld WM, et al. 2017 infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis. 2017;64:e34–65, http://dx.doi.org/10.1093/cid/ciw861.
4. Chau CYC, Craven CL, Rubiano AM, Adams H, Tülü S, Czosnyka, et al. The evolution of the role of external ventricular drainage in traumatic brain injury. J Clin Med. 2019;8(9.):E1422, http://dx.doi.org/10.3390/jcm8091422.
5. Sorinola A, Buki A, Sandor J, Czeiter E. Risk factors of external ventricular drain infection: proposing a model for future studies. Front Neurol. 2019;10:226, http://dx.doi.org/10.3389/fneur.2019.00226.
6. Catapano JS, Rubel NC, Veljanoski D, Farber SH, Whiting AC, Morgan CD, et al. Standardized ventriculostomy protocol without an occlusive dressing: results of an observational study in patients with aneurysmal subarachnoid hemorrhage. World Neurosurg. 2019;131:e433–40, http://dx.doi.org/10.1016/j.wneu.2019.07.183.
7. Hussein K, Rabino G, Feder O, Eghbaryeh H, Zayyad H, Sviri G, et al. Risk factors for meningitis in neurosurgical patients with cerebrospinal fluid drains: prospective observational cohort study. Acta Neurochir (Wien). 2019;161:517–24, http://dx.doi.org/10.1007/s00701-019-03801-y.
8. Foreman PM, Hendrix P, Griessenauer CJ, Schmalz PG, Harrigan MR. External ventricular drain placement in the intensive care unit versus operating room: evaluation of complications and accuracy. Clin Neurol Neurosurg. 2015;128:94–100, http://dx.doi.org/10.1016/j.clineuro.2014.09.026.
9. Mermel LA. Sequential use of povidone-iodine and chlorhexidine for cutaneous antisepsis: a systematic review. Infect Control Hosp Epidemiol. 2019, http://dx.doi.org/10.1017/ice.2019.287 [Epub ahead of print].
10. Rodríguez-Lucas C, Fernández J, Martínez-Sela M, Álvarez-Vega M, Moran N, Garcia A, et al. Pseudomonas aeruginosa nosocomial meningitis in neurosurgical patients with intraventricular catheters: therapeutic approach and review of the literature. Enferm Infecc Microbiol Clin. 2020;38:49–53.
11. Zhou YJ, Wu JN, Chen LJ, Zhao HY. Comparison of infection rate with tunneled vs standard external ventricular drainage: a prospective, randomized controlled trial. Clin Neurol Neurosurg. 2019;184:105416, http://dx.doi.org/10.1016/j.clineuro.2019.105416.
12. George T, Moorthy RK, Rajshekhar V. Long tunnel external ventricular drain: an adjunct in the management of patients with infection associated hydrocephalus. Br J Neurosurg. 2019, http://dx.doi.org/10.1080/02688697.2019.1667483 [Epub ahead of print].
13. Roach J, Gaastra B, Bulters D, Shtaya A. Safety accuracy, and cost effectiveness of bedside bolt external ventricular drains (EVDs) in comparison with tunneled EVDs inserted in theaters. World Neurosurg. 2019;125:e473–8, http://dx.doi.org/10.1016/j.wneu.2019.01.106.
14. Velásquez C, Rivero-Garvía M, Mayorga-Buiza MJ, Cañizares-Méndez ML, Jiménez-Mejías ME, Márquez-Rivas J. Avoiding pullout complications in external ventricular drains: technical note. J Neurosurg. 2017;126:1003–5, http://dx.doi.org/10.3171/2016.2.JNS1678.
15. Mallucci CL, Jenkinson MD, Conroy EJ, Hartley JC, Brown M, Dalton J, et al. Antibiotic or silver versus standard ventriculoperitoneal shunts (BASICS): a multicentre, single-blinded, randomised trial and economic evaluation. Lancet. 2019;394:1530–9, http://dx.doi.org/10.1016/S0140-6736(19)31603-4.
16. Sheppard JP, Ong V, Lagman C, Udawatta M, Doung C, Nguyen T, et al. Systemic antimicrobial prophylaxis and antimicrobial-coated external ventricular drain catheters for preventing ventriculostomy-related infections: a meta-analysis of 5242 cases. Neurosurgery. 2018, http://dx.doi.org/10.1093/neuros/nyy522 [Epub ahead of print].
17. Bayston R, Ashraf W, Pelegrin I, Fowkes K, Bienemann AS, Singleton WGB, et al. An external ventricular drainage catheter impregnated with rifampicin, trimethoprim and triclosan, with extended activity against MDR Gram-negative bacteria: an in vitro and in vivo study. J Antimicrob Chemother. 2019;74:2959–64, http://dx.doi.org/10.1093/jac/dkz293.
18. Mounier R, Lang E, Hulin A, Woerther PL, Lobo D, Martin M, et al. Durability of antimicrobial activity of antibiotic-impregnated external ventricular drains: a prospective study. J Antimicrob Chemother. 2019;74:3328–36, http://dx.doi.org/10.1093/jac/dkz335.
19. Mayhall CG, Archer NH, Lamb VA, Spadora AC, Baggett JW, Ward JD, et al. Ventriculostomy-related infections. A prospective epidemiologic study. N Engl J Med. 1984;310:553–9, http://dx.doi.org/10.1056/NEJM198403013100903.
20. Katzir M, Lefkowitz JJ, Ben-Reuven D, Fuchs SJ, Hussein K, Sviri GE. Decreasing external ventricular drain-related infection rates with duration-independent clinically indicated criteria for drain revision: a retrospective study. World Neurosurg. 2019;131:e474–81, http://dx.doi.org/10.1016/j.wneu.2019.07.205.
21. Rivero-Garvía M, Márquez-Rivas J, Jiménez-Mejías ME, Neth O, Rueda-Torres AB. Reduction in external ventricular drain infection rate. Impact of a minimal handling protocol and antibiotic-impregnated catheters. Acta Neurochir (Wien). 2011;153:647–51, http://dx.doi.org/10.1007/s00701-010-0905-1.
22. Mrowczynski OD, Langan ST, Rizk EB. Intra-cerebrospinal fluid antibiotics to treat central nervous system infections: a review and update. Clin Neurol Neurosurg. 2018;170:140–58, http://dx.doi.org/10.1016/j.clineuro.2018.05.007.
23. Hu Y, He W, Yao D, Dai H. Intrathecal or intraventricular antimicrobial therapy for post-neurosurgical intracranial infection due to multidrug-resistant and extensively drug-resistant Gram-negative bacteria: a systematic review and meta-analysis. Int J Antimicrob Agents. 2019;54:556–61, http://dx.doi.org/10.1016/j.ijantimicag.2019.08.002.
24. Zhang Q, Chen H, Zhu C, Chen F, Sun S, Liang N, et al. Efficacy and safety of intrathecal meropenem and vancomycin in the treatment of postoperative intracranial infection in patients with severe traumatic brain injury. Exp Ther Med. 2019;17:4605–9, http://dx.doi.org/10.3892/etm.2019.7503.
25. Pandey S, Li L, Deng XY, Cui DM, Gao L. Outcome following the treatment of ventriculitis caused by multi/extensive drug resistance gram negative *Bacilli*; *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Front Neurol. 2019;9:1174, http://dx.doi.org/10.3389/fneur.2018.01174.

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