REVIEW

Current Perspectives on the Diagnosis and Management of Healthcare-Associated Ventriculitis and Meningitis

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Abstract: Ventriculitis or post-neurosurgical meningitis or healthcare-associated ventriculitis and meningitis (VM) is a severe infection that complicates central nervous system operations or is related to the use of neurosurgical devices or drainage catheters. It can further deteriorate patients who have already presented significant neurologic injury and is associated with high morbidity, mortality, and poor functional outcome. VM can be difficult to distinguish from aseptic meningitis, inflammation that follows hemorrhagic strokes and neurosurgical operations. The associated microorganisms can be either skin flora or nosocomial pathogens, most commonly, Gram-negative bacteria. Classical microbiology can fail to isolate the culprit pathogen. Novel cerebrospinal fluid (CSF) biomarkers and molecular microbiology can fill the diagnostic gap and expedite pathogen identification and treatment. The pathogens may demonstrate significant resistant patterns and their antibiotic treatment can be difficult, as many important drug classes, including the beta-lactams and the glycopeptides, hardly penetrate to the CSF, and do not achieve therapeutic levels at the site of the infection. Treatment modifications, such as higher daily dose and prolonged or continuous administration, might increase antibiotic levels in the site of infection and facilitate pathogens clearance. However, in the case of therapeutic failure or infection due to difficult-to-treat bacteria, the direct antibiotic instillation into the CSF, in addition to the intravenous antibiotic delivery, may help in the resolution of infection. However, intraventricular antibiotic therapy may result in aseptic meningitis and seizures, concerning the administration of aminoglycosides, polymyxins, and vancomycin. Meanwhile, bacteria form biofilms on the catheter or the device that should routinely be removed. Novel neurosurgical treatment modalities comprise endoscopic evacuation of debris and irrigation of the ventricles. VM prevention includes perioperative antibiotics, antimicrobial impregnated catheters, and the implementation of standardized protocols, regarding catheter insertion and manipulation.

Keywords: ventriculitis, cerebrospinal fluid, external ventricular drain, molecular diagnostics, antibiotic penetration, intraventricular treatment

Introduction

Ventriculitis or post-neurosurgical meningitis or healthcare-associated ventriculitis and meningitis (VM) is a severe disease of diverse etiology, following central nervous system (CNS) operation or trauma or the insertion of central nervous system (CNS) device.[1,2] In the post-neurosurgical setting, this infection presents at a rate of less than 1% to as high as 8.6%.[3,4] Rates vary between studies using different definitions of meningitis. Moreover, diverse implantable devices are used for the diagnosis and treatment of numerous neurological disorders. These devices might be inserted temporarily, like external ventricular (EVD) and lumbar drains for measuring the intracranial pressure and cerebrospinal fluid (CSF) diversion. The reported VM incidence varies widely between 2% and 22%. In addition, the pooled incidence rate of EVD-associated ventriculitis was estimated at 11.4 per 1000 catheter-days (95% CI, 9.3–13.5) and in a recent

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study, the mean rate was 3.96/1000 catheter-days.[5–7] On the other hand, ventriculoperitoneal (VP) and ventriculoatrial shunts to the peritoneal cavity and the right atrium, respectively, provide more permanent CSF diversion alternatives. The VP shunts are used more often, having an infection rate of 11.7% (range 4.1–20.5%).[8] Finally, several cranial or spinal neurostimulators and baclofen infusion pumps are implanted to manage various conditions, from Parkinson's disease and obsessive-compulsive disorders to spasticity and morbid obesity. However, the latter interventions carry only a small (much less than 1%) risk for a device-associated VM.[9–11]

Ventriculitis is associated with high mortality in the range of 15% to 23% which can be improved with adequate initial treatment.[12,13] EVD infection can double the length of catheterization, the intensive care unit (ICU) stay, and the total health-care costs.[14]

Another issue of growing importance is the shift in microbiology during the last decade towards Gram-negative (GN) infection, notably with *Acinetobacter baumannii*, becoming more common.[1,15] This emergence of difficult-to-treat-resistant GN pathogens[16] can lead to inappropriate, discordant antibiotic treatment which may adversely affect the outcome.[17]

The literature search shows a lack of standardized diagnostic and treatment protocols as neurosurgical centers deal with variable pathologies, local flora, and infection control policies. Therefore, they can hardly perform high-quality, multi-center, controlled studies, and the available recommendations are based on weak evidence and heterogeneous reports.[1,15]

In this review, we aim to identify current perspectives and discuss controversies and challenges on the diagnosis and management of VM.

Risk Factors

VM following neurosurgical operations seemed to be associated with the extent of dural opening during the procedure.[12] Craniotomy predisposed the infection more than shunt insertion while spinal fusion has been even less associated with VM.[12] Despite its value, EVD is a foreign body with an inherent risk of infection. The insertion technique and venue, the catheterization duration, the presence of blood in the CSF, the presence of CSF leak, and regular catheter sampling and manipulation, including EVD exchange, have been all associated with increased risk for VM.[18,19] Of interest, the use of bilateral catheters might elevate the risk of VM.[20] The average time from the operation to the diagnosis of VM was 10.3 days analogous to the EVD-related infection, which peaked at about 10 days post-insertion.[12,19] Regarding VP shunts, device revision due to prior shunt infection or malfunction, and post-neurosurgical leak, increase the infection risk the most.[21,22]

Pathogenesis-Microbiology

The microorganisms responsible for VM, which reside in the patient's skin flora (*Staphylococcus* spp., *Cutibacterium acnes*) or the hospital environment (various pathogens including GN bacilli), gain direct access to the subarachnoid space and/or the cerebral ventricles following craniotomy or the external diversion of the CSF. Overall, colonization precedes infection;[23] the catheter is colonized directly during its entry from a failure of the sterile technique or intraluminally following CSF sampling or by the microorganisms extraluminally migrating down the drain tract. Rarely, the drain can be hematogenously colonized.[22]

Bacteria frequently form biofilms, colonies growing within a polysaccharide matrix upon the device surface, protecting the microorganisms from the host's immune system and the administered antibiotics.[22] Regarding EVDs, most drains develop biofilm after day 7 post-insertion.[24] Apart from GP bacteria, GN pathogens, particularly *A. baumannii*, are linked to biofilm-associated nosocomial infections.[25,26] In the early stages of the infection and up to 6 weeks, the biofilm is usually "immature" and amenable to rigorous surgical debridement and antimicrobial therapy, and possibly device removal can be avoided. However, in later stages, the "mature" biofilm requires device removal and prolonged antibiotic administration.[22]

The relative frequency of the causative agents varies between different countries or different hospitals.[1] In a recent multicenter study, both GP and GN pathogens were equally isolated.[27] However, there has been a steady increase in the prevalence of DTR-GN isolates in many centers around the globe, including multidrug-resistant *Pseudomonas aeruginosa*, and the carbapenemase-resistant *A. baumannii* and *Klebsiella pneumoniae*.[28–30] It should be highlighted that,

although GN-VM patients were sicker compared to GP-VM-affected individuals, there were no consistent differences regarding outcomes.[31,32]

Although bacteria are the predominant CSF isolates, Candida species can rarely cause VM, which is a late occurrence, associated with the use of CSF-diversion devices, and follows prolonged antibiotic treatments for nosocomial infections. Of note, the antecedent infection is a previous bacterial VM, while there is a paucity of data regarding any characteristics that differentiate this entity from the bacterial one.[33,34] The mortality can be as high as 27%.[34]

Diagnosis
Non-Microbiological Diagnosis
The clinical presentation of VM varies according to the patient's age, primary neurological disease, the underlying pathogen, and the critical care status of the individual.[6,35,36]

Patients with VM may present fever >38.0°C, meningeal irritation, and cranial nerve palsies.[37] Although fever can be the primary sign of VM, it is non-specific.[38,39] On the other hand, the clinical presentation of shunt infections is more obscure and, usually, includes headache, malaise, and altered consciousness. Hydrocephalus might occur as well due to shunt malfunction.[40] In addition, the drainage tubing course is frequently hard, red, and tender. Depending on the location of the distal end, an infected shunt could also manifest as peritonitis, pleuritis, bacteremia, and endocarditis or immune complex glomerulonephritis.[41,42]

Serum markers, notably procalcitonin and not C-reactive protein, might point to the presence of VM in EVD-treated trauma patients after excluding other infection sites.[43] Regarding CSF, its composition in VM patients is altered, exhibiting increased leucocyte (WBC) and protein values, with decreased glucose levels.[37] Admittedly, the differentiation of VM from postoperative aseptic meningitis (AM) is challenging due to the intraoperative CSF contamination with blood, including leucocytes, and the inflammatory reaction to heme metabolism byproducts.[44,45] Nowadays, it is common to adjust the CSF cell count for red blood cells (RBC), using the cell index (CI), a ratio of the WBC to RBC in the CSF divided by the ratio of WBC to RBC in the blood.[41] It assumes that the CSF WBC to RBC ratio is roughly proportional to peripheral blood in patients with intracranial hemorrhage. Any deviation to this general rule, which may occur during infection can impact the CI. The diagnostic accuracy of CI differed according to the population under study.[45,46] Indeed, Liew et al studied the diagnostic value of the CI in EVD-treated, predominantly intracerebral hemorrhage patients. The peak CI of VM patients, sampled within 72 hours preceding the diagnosis, significantly differed from the highest value, at any given day, of non-VM individuals and exhibited a cut-off value of 10.4 that was associated with sensitivity and specificity rates as high as 80.5% and 70.5%, respectively.[46] Montes et al studied a patient cohort of intracranial hemorrhage only and reported that CI had the best diagnostic accuracy among various indices, with a corresponding area under the receiver operating curve (AUC) of 0.825, outperforming the corrected CSF WBC count (0.770) and uncorrected CSF WBC count (0.652).[45]

Researchers have targeted several CSF biomarkers with interesting results. CSF lactate can be valuable for differentiating bacterial from aseptic meningitis.[47] A meta-analysis of 404 post-neurosurgical patients, using a lactate cut-off of 4.41 ± 0.85 mmol/L demonstrated a pooled sensitivity and specificity as high as 92% and 88%, respectively.[47] Notwithstanding, CSF lactate may also increase in several other intracranial pathologies like ischemia, subarachnoid vasospasm, seizures, and trauma, while it might decrease following antimicrobial administration.[39,47,48]

In a study of 239 post-neurosurgical patients, Abudeev et al focused on presepsin, a biomarker produced by the microglial cells and unaffected by the presence of blood in the CSF. The optimal threshold concentration for diagnosing culture-positive VM was 1257.5 pg/mL with moderate diagnostic accuracy (AUC 0.725).[49] However, when combined with CSF lactate, the diagnostic efficiency was boosted (AUC, 0.856 with a sensitivity of 82.8% and specificity of 73.5%).[50]

Lenski et al retrospectively studied 40 EVD-treated traumatic brain injury patients for markers of inflammation. CSF interleukin-6, at a cutoff of 4064pg/mL, detected VM better than CSF's WBC and protein, with a sensitivity and specificity of 100% and 92.3% for early diagnosis.[51] The same group investigated 63 individuals with subarachnoid hemorrhage (SAH) for the potential of CSF IL-6 to discriminate VM from vasospasm and sole SAH. The respective AUCs were 0.757 and 1.0 and a cutoff value of more than 3081pg/mL probably presented VM.[52] This population was

further examined for increased inflammatory markers (neutrophil percentage, total cell count, glucose, protein in the CSF, and the CSF to blood glucose ratio) to discriminate infection from AM. The neutrophil percentage AUC prevailed with a value of 0.900 and the total cell count followed with 0.841.[53]

Regarding the combination of CSF diagnostic markers, Zhang et al studied 112 neurosurgical patients with suspected CNS infection. The AUC for differentiating VM from aseptic inflammation was 0.936 (0.895–0.977) for lactate, 0.803 (0.724–0.883) for procalcitonin, 0.860 (0.797–0.929) for interleukin-10, and 0.771 (0.683–0.860) for interleukin-8. However, the composite AUC for all the parameters was 0.954 (0.922–0.989).[54] The AUC of IL-1β, another cytokine, for detecting VP-shunt associated VM at a cutoff value of 4pg/mL was 0.927.[55] Liu et al investigated 32 post-neurosurgical feverish patients for the CSF cytokine and procalcitonin kinetics on days −4, −2, 0, 2, and 4 days concerning the fever onset. The proinflammatory cytokines assessed were tumor necrosis factor-α, interleukin-1β, interleukin-6, and interleukin-8, which were significantly increased, starting 4 days before fever commencement, in the bacterial VM group compared to the AM group patients who in turn had higher values than their non-meningitis counterparts. Contrary to that, procalcitonin levels elevated late, on day 4 post-fever onset.[56]

The potential of CSF cytokine profile for diagnosing VM was examined in a recent study with a two-step process: in the first step, patients with neuroinflammation, in general, were identified via the biomarker signature of raised IL-6, oncostatin M and C-X-C motif chemokine 8, while in the second step the additionally increased IL-17, IL-12p40/p70, and IL-23 levels signified a bacterial-associated inflammation pattern.[57] Moreover, the discriminative accuracy for VM of a new CSF biomarker the high-mobility group box 1 protein was studied in 29 EVD-treated neurosurgical patients and performed better than CSF lactate, leucocytes, protein, and glucose with an AUC of 0.83.[58]

Regarding diagnostic modeling, Zheng et al constructed a model-algorithm using routine CSF examinations.[59] They selected five variables (CSF WBC count, CSF glucose, blood glucose, CSF lactate, and CSF-to-blood glucose ratio) through multivariate analysis. They developed and verified a fitted variable, which excellent performance, an AUC 0.907, at a cut-off value of 0.505, and an overall concordance rate of 88.6%.[59]

A prediction score was developed in a cross-sectional study for discriminating VM from AM. Their final model comprised of six variables: aneurysmal SAH as primary diagnosis, C-reactive protein >6mg/dL, CSF-to-blood glucose ratio <0.4, CSF leak status, CSF neutrophil percentage >50%, CSF lactate > 4mmol/L while the respective variable contribution was 1, 1, 1, 1.5, 1.5 and 4 points. If the sum of the points was equal to or higher than 6, the discrimination was excellent (AUC 0.94).[60]

Finally, the CSF proteome was studied in a rat model of CSF drainage catheter experimental *C. acnes* infection. The proteome of C. acnes infected rats differed from the aseptic inflammation of the control animals both on day 1 post-insertion and later it evolved differently.[61]

Regarding the sampling site, CSF is regularly drawn via the catheter, if present. Of interest, in a recent study, 141 paired samples were collected, via the EVD and lumbar puncture. The CSF collected from lumbar puncture was twice more likely to fulfill infection criteria (WBC, protein, and lactate were raised and glucose CSF/blood glucose decreased) compared to the EVD sample; this increased LP sensitivity might aid in the exclusion of VM. However, LP collection isolated fewer bacteria.[62]

To conclude, common CSF measurements, ie, WBC count, glucose, and their ratios relative to the corresponding blood values, can often guide diagnosis. However, novel biomarkers and cytokines emerge and hold promise for the future.

Imaging

Imaging's role for VM diagnosis is mainly limited to exclusion of other pathologies like abscesses. Gadolinium contrast-enhanced T1-weighted images can demonstrate ependymal enhancement, whereas diffusion-weighted imaging can show pus collection in the ventricular system.[2]

Microbiological Diagnosis

Microbiological diagnosis is routinely based on CSF Gram stain and culture. However, their respective sensitivity may be as low as 20% and 50%, and the administration of antibiotics before CSF sampling may further decrease their diagnostic

yield.[32,35,41] Regarding *C. acnes* that is difficult to isolate, the use of anaerobic culturing and the regular prolongation of the culture observation period to 10 days can improve its isolation rate.[63,64]

Various molecular methods, either commercial or in-house, such as nucleic acid amplification tests (NAATs), have been studied and compared with the gold standard, ie, CSF culturing.[65–71] Compared to the classical microbiology assays, they return positive results sooner, they are less prone to false-negative results as prior antimicrobial therapy minimally affects pathogen recovery, and might reveal novel etiologic microorganisms. However, it should be noted that microorganisms of questionable clinical significance may be identified, as well.[70,71] Modern NAAT methods have played a supplementary role in CSF microbial culture.[68,69] The turnaround time varied between the techniques; overall, real-time and next-generation sequencing PCR take less than 24 up to 48 hours to give results.[67–71] Notably, in a recent study of metagenomic next-generation sequencing of 102 CSF samples, the assay missed 15 culture isolates; however, it identified 22 pathogens, all from suspected VM cases, not detected in culture. Eventually, 10 of these 22 patients had their treatment favorably adjusted. Sequencing also reported coinfections, unidentified by conventional microbiology.[71]

Currently, the only NAAT with FDA clearance for CSF testing (ie, Xpert EV, Cepheid; is the novel syndromic FilmArray meningitis/encephalitis [ME] panel, BioFire Diagnostics, Salt Lake City, UT).[72] The FilmArray ME directly examines the CSF, without prior handling; however, it mostly targets community pathogens and is not suitable for the detection of the nosocomial pathogens causing VM.[72] On the other hand, the bacteremia FilmArray panel (Biofire blood panel [BCID]) can identify both skin GP and aerobic GN microorganisms, including nosocomial ones, that are frequently responsible for VM.[73] A recent study analyzed CSF samples of patients with CNS infections using the BCID panel and reported promising results.[74] Ninety CSF samples were analyzed with the BCID panel achieving a sensitivity of 77.4% and specificity of 100%, while the use of lower cut-offs, improved the sensitivity to 83.9% without any significant impact on a specificity that remained high (98.3%).[74] The turnaround time of both ME and BCID panels is much faster than conventional cultures, approximately 1 hour.[72,73]

An alternative technique for the molecular identification of the pathogen is to process an aliquot of a positive CSF culture into a micro/nanofluidic chip platform that contains many genetic targets, species-specific or resistance determinants. The pathogen and resistance pattern detection was expedited by a day and was highly concordant to the phenotype identification through conventional microbiology.[75]

A matrix-assisted laser desorption/ionization time-of-flight mass spectrometry assay was directly applied to Gram smear-positive CSF of meningitis patients. Regarding the post-neurosurgical meningitis group, the GN pathogen was correctly identified in 17/21 specimens compared to the implicated GP microbe detected in just 1/11 samples.[76]

Regarding VPS, the infection frequently escapes the diagnosis based on the classical infection criteria.[40] Sonication utilizes focal ultrasound to dislodge biofilm bacteria from the surface of explanted materials before prolonged cultures, such as explanted orthopedic and neurosurgical hardware.[77–79] A recent meta-analysis showed that the sensitivity and specificity of sonication were as high as 87% and 57%, respectively.[80] Moreover, sonication was superior to conventional techniques, particularly in coagulase-negative staphylococci infections.[81]

Diagnostic Criteria

The diagnostic criteria in the literature vary. Apart from the Infectious Diseases Society of America (IDSA) guideline definition,[2] many authors adopt the nosocomial infections surveillance definition,[37] which delineate VM as fulfilling, in any case, at least one of the two criteria below: 1) A performed CSF culture or another method, not part of active surveillance testing, has identified a microorganism, 2) The patient presents *two* of the ensuing a) fever or headache (if they coexist, they count as one element only), b) meningeal signs, c) cranial nerve signs (b and c, not attributed to other causes) *and* at all events, *one* of the following: i) Pleocytosis, raised protein, decreased glucose in the CSF, ii) a microorganism distinguished on the CSF Gram stain, iii) a microorganism is identified in the blood by either culture or non-culture testing, iv) serologic diagnosis for the microorganism with single IgM titer or 4-fold raise in dual sera.

There is an array of definitions with a variety of diagnostic items, different laboratory thresholds, and a lack of an objective gold standard for diagnosis.[2,19,37,82–84] An overview of the diagnostic elements is displayed in Table 1.

Prevention

Prevention strategies include a wide spectrum of interventions that are designed to cope with various risk factors of VM.[19,85,86] Although most of these prevention aspects are recommended and well studied, some are weakly supported by limited or controversial evidence.

Recommendations for the Prevention of VM in Patients with CSF Shunts or Drains
Periprocedural Chemoprophylaxis

Although antimicrobial prophylaxis peri-insertion might favor the selection of resistant pathogens,[87,88] their administration before the device placement or for a limited period post-insertion (for up to 24–48 hours) is considered, nowadays, as the standard of care in patients undergoing CFS shunt insertion and placement of EVD catheters.[2] A current Cochrane database review demonstrated that periprocedural prophylactic antimicrobial administration decreased VM rates by approximately 50%.[89] Of note, in most of the included studies, the prophylactic antibiotics target GP pathogens, although GN bacteria account for about 50% of the culprit microorganisms.[89] Moreover, the protracted use of systemic prophylactic antimicrobials is a controversial issue. Leading societies recommend against the prolonged, for the entire duration of catheter placement, administration of antimicrobial prophylaxis due to resistance,[88] and cost concerns.[85] Thus, they advocate that a single dose of an antibiotic, selected following local antimicrobial resistance patterns, would suffice.[90]

Silver and Antimicrobial-Impregnated Catheters

Antimicrobial-impregnated catheters for CSF shunts and drains are typically impregnated with rifampicin combined with either minocycline or clindamycin. Silver-impregnated catheters contain silver as an antimicrobial substance. They were designed to impede colonization of the catheter during placement and were soon found to be effective in decreasing colonization rates.[91] The efficacy of antimicrobial-impregnated catheters to reduce post-intervention infection rate compared to plain catheters, regarding both CSF shunts and external ventricular drains, is currently supported by the literature.[92–94] In addition, it seems that this strategy results in significant hospital cost reduction.[95] Of interest, the available antimicrobial-impregnated catheters contain chemotherapeutics active against GP pathogens, including the commonly occurring coagulase-negative *Staphylococcus*. Thus, their use tends to decrease the GP-VM events and not the GN ones, which might cause more severe infection.[31,93,94] Of note, a catheter targeting GP and GN bacteria and containing rifampicin, trimethoprim, and triclosan was not toxic to the rats tested while in vitro mitigated colonization.[96]

Standardized Protocols and Bundles of Care

Protocolized care (or bundled care) uses a group of applied preventive measures related to the placement and maintenance of EVDs with promising results. In a pilot study, Korinek et al reported that the adoption of a strict, written protocol for EVD insertion, nursing, and surveillance was associated with a significant decrease in the incidence of patient-related ventriculitis and demonstrated the value of proper hand hygiene and limited system manipulation for prolonging drainage duration.[86]

Controversial Topic: External Ventricular Drain Exchange

External ventricular drains are often colonized after the first seven drainage days.[24] Moreover, the risk of infection is reported to rise with the increased duration of drainage for the first 7–10 days and afterward plateaued or became less likely.[97,98] An older study suggested that the scheduled EVD exchange every 5 days decreased the infection rate.[99] However, Holloway et al reported that if catheters were replaced before 5 days the patients had not presented a lower infection rate compared to the individuals whose catheters were exchanged at more than 5-day intervals.[97] Indeed, Wong et al reported, in a randomized controlled trial examining catheter exchange, that the infection rates for the change vs the control group were 7.8% vs 3.8%, respectively.[100] In a before-after study, a bundle that successfully decreased the VM infection rate included scheduled catheter exchange among other interventions; however, it was uncertain which bundle element made the difference in the outcome.[101]

Summarizing the evidence, prophylactic catheter exchange at a set interval is not recommended, since it can be used for as long as clinically indicated. In contrast, prophylactic antimicrobial chemotherapy of limited duration, the

maintenance of a sterile protocol, the meticulous intraventricular catheter handling, the cerebrospinal fluid sampling only when clinically necessary, and the prompt removal of the catheter when no longer needed may all lower the infection risk. Of note, an EVD insertion checklist is, at present, a recommended clinical performance measure.[102] An overview of prevention studies of the last decade is displayed in Table 2.[28,85,101,103–119]

Treatment
Pharmacokinetic/Pharmacodynamic Considerations

Neurosurgical patients who suffer a CNS infection are often critically ill and the hydrophilic antibiotics' pharmacokinetics (such as beta-lactams, aminoglycosides, vancomycin, and daptomycin) is altered compared to general ward patients.[120] Thus, critically ill patients may warrant loading doses and a higher daily antibiotic dose with therapeutic drug monitoring, which, however, is not widely available for many commonly used antibiotics as yet.[121]

Apart from the dosage, impediments to the entry of the antimicrobials into the CNS are the barriers that shelter the brain and the spinal cord, the blood-brain, blood-spinal cord, and blood-CSF barriers that separate the CNS compartments from the central, blood, compartment.[122] The degree of antibiotic penetration into the CSF is influenced by both antibiotic physicochemical factors and patient factors.[123] Unionized, non-protein bound antibiotics with low molecular weight and lipophilic antibiotics (such as quinolones, rifampicin) have enhanced penetration into the CSF which is not inflammation dependent.[124] CNS inflammation facilitates antibiotic diffusion into CSF due to the opening of the tight junctions of the blood-brain-barrier cells.[123] However, intense meningeal inflammation that enables elevated CSF antibiotic concentrations is not regularly present in VM; thus, the disease is associated with low drug levels.[125,126] Among the antimicrobial classes commonly used, the glycopeptides and the beta-lactam are both hydrophilic and ionized.[125] The glycopeptides, such as vancomycin, due to their hydrophilicity and large molecular size, were considered as having very poor CSF penetration. However, the penetration of vancomycin is not universally low, but variable and unpredictable, and does not correlate with the clinical outcome.[127] Furthermore, the CSF half-lives of beta-lactams may be prolonged and variable, depending on several factors, such as the rate of CSF production and the CSF volume (including ventricle size), the integrity of blood-barrier, and in case of drainage, the EVD drainage pressure scale and alternations.[128]

In terms of pharmacokinetics (PK), there is a delay in drug entry into the CSF compared to other body compartments, and thus, there is a time lag between the respective peak levels between the blood and the CSF (hysteresis phenomenon), while the CSF to plasma ratio is expected to increase following the initiation of the antibiotic infusion.[128] Therefore, the best PK parameter, for the assessment of antibiotic penetration into the CSF, is the ratio of the area under the antibiotic concentration curve of the CSF to that of the serum.[122,124]

There are older antibiotics with favorable CSF penetration profiles. Chloramphenicol (penetration of approximately 50%) presented treatment results comparable to beta-lactams in meningitis studies.[129] Intravenous fosfomycin, virtually always combined with other antimicrobials, presents acceptable penetration into the CSF compartment.[130] Fosfomycin's antimicrobial spectrum covers multidrug-resistant GP and GN bacteria while the cure rate was excellent.[131] If the intravenous formulation is available, as in many European countries, it might provide a valuable treatment option.[132]

In contrast, the intravenous high 10mg/Kg dosing of daptomycin for VM, and a mean of 5.6 days hardly penetrated the CSF compartment.[133] In addition, a single-dose ceftaroline pharmacokinetic model displayed low drug concentrations, below 0.5ng/μL, and the MIC of most clinically relevant isolates.[134]

Not only is the antimicrobial transfer altered in comparison with the central blood compartment, but the CSF milieu also differs from that of the extracellular space. The CSF has a pH of 7.28–7.32, low sugar and protein content impending the bacterial growth, but, on the other hand, hindering the action of many antibiotics. The former combined with the minimal immune response of the CSF denotes the need for high antimicrobial levels above the minimum inhibitory concentration (MIC) of the pathogen.[124,135] There are no well-established optimal pharmacodynamic (PD) targets for CNS infections that maximize bacterial killing.[123]

Although the scarcely available data has not pointed to an association between the CSF drug levels and clinical cure or microbial eradication, high antibiotic levels, often >10 × MIC, may be needed to enable fast bacterial killing.[127,136]

Finally, it should be noted that CSF concentrations are just an estimate, a surrogate marker, of the active unbound antibiotic concentration beyond the blood-brain barrier. Studies in animal brain biopsies have shown, despite undetectable CSF levels, levels in brain tissue 10–20% of the serum levels.[137]

Systemic Treatment-Empirical Therapy

The initial, empirical treatment of VM has to cover the most common etiological microorganisms considering the local epidemiology. The recent guidelines recommend a combination regimen of vancomycin and an antipseudomonal beta-lactam (meropenem or cefepime or ceftazidime).[2] If the patient has a severe beta-lactam allergy, they suggest either meropenem or aztreonam, or ciprofloxacin for GN coverage.[2] Meropenem is the preferred option in a setting of infections by extended-spectrum beta-lactamase-producing *Enterobacterales*.[138] Resistant non-fermenting GN pathogens may need the administration of alternative antimicrobial agents, such as colistin, tigecycline, and novel beta-lactam/beta-lactamase inhibitors.[16] The evidence, however, regarding the efficacy of novel beta-lactam/beta-lactamase inhibitors in the setting of CNS infection is yet limited.[139,140] Moreover, the beta-lactam antimicrobials could be given in much higher doses than those recommended to facilitate their transfer to the CSF.[141] Parallel to the initiation of empirical antibiotic therapy, prompt removal of the relevant CNS device should regularly be performed.[2] It should be highlighted that the current recommendation on antimicrobial dosing for CNS infections may lead to subtherapeutic exposures.[123]

Systemic Treatment-Targeted Therapy

Gram-Positive Bacteria

Staphylococcal penicillin, either alone or in combination with another antimicrobial drug, such as rifampicin or fosfomycin, is recommended for the treatment of methicillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci.[132] Of note, one cannot solely administer either of the latter two drugs to avert the emergence of resistance.[131] Rifampicin, in particular, is valuable for the treatment of device-associated infections due to its biofilm activity.[22]

The recent IDSA guidelines recommend vancomycin for the treatment of methicillin-resistant staphylococci, while its trough levels should be kept at 15–20μg/mL;[2] however, they suggest a second-line drug if the microorganism's minimal inhibitory concentration is ≥1ng/μL. Of the available other options, daptomycin, even at high, doses can fail and ceftaroline, a novel cephalosporin, which is active against methicillin-resistant *S. aureus*, at the double recommended dosing (600mg QDS), might eradicate a susceptible isolate in the CSF and needs further investigation.[142] However, linezolid presents an advantageous CSF penetration profile and was a reasonable alternative whenever a patient was allergic to vancomycin or the latter had failed.[143] Although linezolid had not demonstrated mortality benefit compared to vancomycin, it was associated with better microbiological and clinical outcomes.[144] Considering the vancomycin's limitations some investigators have questioned its value as the first-line drug for staphylococcal VM treatment.[145]

Regarding the antimicrobial chemotherapy of *C. acnes*, the recent guidelines recommend penicillin G.[2]

Gram-Negative Bacteria

An antipseudomonal beta-lactam is suggested for the treatment of a susceptible isolate. However, the high prevalence of DTR-GN isolates in many centers around the world has complicated antibiotic choice.[16] Available intravenous options for these pathogens include aminoglycosides, polymyxins, and tigecycline.[16] The aminoglycoside and colistin dosing can only be increased by a limited amount due to their narrow therapeutic index.[146,147] From a practical standpoint, one often adds colistin on meropenem pending the culture results.[1] Colistin's in vitro efficacy against *A. baumannii*, at regular dosing, might be augmented by the addition of either fosfomycin or sulbactam.[148] Moreover, fosfomycin in tandem with either aminoglycosides or colistin or tigecycline presented synergistic effects against DTR *A. baumannii*.[149] However, the clinical potential of those combinations for the treatment of the infection due to DTR-GN pathogens remains unknown.

Duration of Systemic Antibiotics

The antimicrobial chemotherapy duration should last for 10–14 days for coagulase-negative staphylococci or *C. acnes* infection while this timespan could extend up to 21 days for *S. aureus*- or GN-VM. Whenever the cultures continue to be positive, it is suggested that patients should continue treatment for 10–14 days following the last pathogen isolation.[2]

Infusion Strategy

A possible way to improve the CSF levels of antibiotics with time-dependent killing, such as beta-lactams, could be via dose optimization using continuous or prolonged antimicrobial infusion. At present, there is only preliminary evidence for the benefit of administering continuous or prolonged over intermittent antibiotic infusion for the treatment of VM,[150] while this practice has been studied for the management of sepsis.[151,152] The prolonged, over 4 hours, meropenem infusion of 2g TDS in neurocritical patients with suspected VM resulted in CSF levels of <2ng/μL, which are insufficient to cover marginally sensitive pathogens.[153] The continuous infusion of ceftolozane-tazobactam has been recently evaluated and enabled high drug levels in the CSF.[140] Similar to the above, the administration of higher than the recommended dose of cefazolin by continuous delivery resulted in free medicine's CSF levels always superior to MIC.[154] In a recent study, authors have administered cloxacillin or cefazolin via CI to the majority of 17 staphylococcal meningitis patients and only two cloxacillin-treated individuals stopped the drug due to clinical failure.[150] Indeed, the continuous infusion of cefazolin achieved high enough CSF levels that regularly exceed the epidemiological cut-off values.[150] Contrary to the above, the continuous infusion of both meropenem and vancomycin resulted in low CSF levels.[155] Finally, therapeutic drug monitoring during the continuous infusion may facilitate the achievement of higher serum drug concentrations while likely mitigating antibiotic toxicity.[152,156] For an overview of systemic therapy, we refer the reader to Table S1.[2, 22, 129, 131, 139, 146, 150, 157–164]

Intraventricular/Intrathecal Therapy

Generally, beta-lactams have a wide therapeutic index that allows aggressive dosing to be implemented, however, other antimicrobials, such as colistin and aminoglycosides, have a more narrow therapeutic index.[146,147] An alternative to high intravenous dosing administration that bypasses the blood-brain and blood-CSF barriers and may overcome the limited penetration of the antibiotics into the CSF and raise the respective drug concentrations is the direct instillation of antimicrobials into the CSF compartment, added on the intravenously administered drug.[136] The antibiotics regularly administered through the IVT (or IT) route are vancomycin, polymyxin B, colistin, aminoglycosides, and, more recently, daptomycin and tigecycline.[136] The drug is administered either through the intraventricular route (IVT) or the lumbar sac, the intrathecal route (IT).[15] Indeed, IVT(IT) antibiotic administration adjunct to the intravenous one resulted in therapeutic CSF drug levels.[126,165] Of note, the CSF space demonstrates a concentration gradient between the ventricles and the lumbar subarachnoid fluid and, therefore, the direct IVT delivery differs from the direct IT administration.[166]

The current IDSA guidelines suggest using adjunct IVT(IT) to IV antimicrobial administration if the patient did not clinically improve on solely systemic treatment or the disease was caused by a DTR microorganism, notably *A. baumannii*.[2,90] IVT(IT) salvage therapy, for clinical or bacteriological failure after a mean of seven days IV-only treatment, was successful in expediting microbial eradication.[167] Regarding the management of DTR pathogens, carbapenem-resistance status seemed to justify IVT(IT) treatment for both the CSF sterilization and mortality outcomes; however, the quality of data was very low.[15] Direct comparison between combined IVT/IV and IV only therapy favored the joint delivery in terms of faster bacterial eradication, better CSF microscopy recovery, and shorter hospital length of stay; however, the results were from a retrospective single-center study and need further evaluation.[168]

IVT vancomycin had been investigated in a case series of 45 CSF shunt- and 5 EVD-treated patients. Despite the inconsistent CSF levels measured after the regular, non-infant, dose of 20mg, the treatment cured the infection in all EVD- and the vast majority of shunt-associated cases.[169] IVT daptomycin has been used to complement the IV administration as the latter often failed to clear the CSF.[164,170]

Adjunct IVT gentamicin has been retrospectively examined in 31 post-neurosurgery patients.[171] The participants had received a variety of IV antimicrobials and were separated into two groups: the one had been administered solely IV

treatment while the other IV plus IVT gentamicin. The majority of the latter group received the drug late for failure to sterilize the CSF. The addition of IVT gentamicin cured all the patients with no relapses.[171] This sequential addition of IVT was evident in another study where the authors used amikacin or gentamicin or colistin after a time lag of 5–63 days from the initial pathogen isolation.[172] Combined IVT(IT) to IV colistin can cure VM over 80% of the times delivered, at a regular dose of 125000iu QD for a median of 18 days.[173] Of note, the European Medicines Agency, stating poor penetration, has approved colistin at a dose of 10mg (125000i.u.) for IVT(IT) use. Up to this date, colistin remains the solely approved drug for the IVT treatment of VM.[174] In a retrospective study, adjunct IVT(IT) to IV polymyxin B was compared to routine just IV drug for DTR *A. baumannii* and resulted in a 91.3% to 18.4% eradication rate and improved mortality (8.7% vs 55.3%).[175] Tigecycline has been recently introduced as adjunct IVT to IV tigecycline therapy;[176,177] in a recent case series the antimicrobial combined with IVT colistin often sterilized the CSF while the treatment lasted for 9–45 days; however, this is preliminary data.[176]

IVT Dosing

IVT(IT) dosing varies with the ventricle size and the CSF output; however, once-daily dosing, at the suggested drug doses, usually suffices.[1,2,136] Meanwhile, the current IDSA guidelines suggest drug CSF levels 10-fold to 20-fold the MIC of the isolate. For a CSF volume of approximately 250 mL, the IVT administration of 5mg of gentamicin or tobramycin and 30–50 mg of amikacin, is expected to attain a CSF Cmax/MIC >10 for susceptible pathogens and, regardless of the averse acidic CSF milieu, to achieve maximal killing.[123] Regarding the IVT administration of colistin, the attainment of AUC/MIC >50 that has been related to maximal antibacterial activity against susceptible isolates (MIC, 2 mg/L), is most probable after the delivery of 10mg, in a single or divided dose.[178] Concerning tigecycline, it should be noted that to date, there are no available data from PD studies in patients with CNS infections.[123] IVT administration of tigecycline has been reported in case reports or small case series with doses up to 8 mg/day, but not based on PK/PD target attainment.[123,176]

Notably, the antimicrobial CSF concentrations are not certainly associated with outcome or toxicity.[179] Therefore, therapeutic drug monitoring might be a useful practice whenever there is a failure of IVT(IT) treatment to sterilize the CSF or a need for prolonged therapy or suspicion of toxicity.[2,136,179] However, in a small care series, an IVT colistin load of 40mg followed by de-escalation to the recommended 10mg dose QD or every 48 hours always sterilized the CSF in 1–5 days.[180]

Duration of IVT Antibiotic Treatment

The length of IVT delivery varied between the available studies (mostly case reports of individualized, and not protocolized treatment) while the total treatment duration has often not been specified.[15] The suggested minimum installation duration was 2–3 days after CSF sterility although the overall treatment may last for up to 3 weeks following culture negativity.[179] In a retrospective cohort study, although the 105 patients received IVT for a total of 5–6 days, they had their CSF sterilized at a rate of 88.4% and a positive culture persistence/recurrence rate at 9.5%.[181]

Side Effects

From a technical standpoint, the clamping of the drain for 15–60 minutes ensures the delivery and the equilibration of the antimicrobial dose.[2] Regarding the antibiotic instilled, it should be sterile, single-dose, free of preservatives to mitigate toxicity, although in many of the literature reports there is no data about the presence of any preservatives in the antibiotic formulation delivered.[136,182] The IVT therapeutic modality is linked to side effects. It requires catheter handling with the inherent risk of secondary infections from the daily manipulation of the catheter.[1] Moreover, in a recent meta-analysis, 223 patients with GN-VM treated with IVT(IT) demonstrated a high local complication rate, of 13%; the prime concerns comprise chemical meningitis [11% (95% CI 7–17%)] and seizures [7% (95% CI 4–12%)].[182] However, many patients were either comatose or sedated and the clinical signs of toxicity might have been unnoticed.

The above side effects suggest that IVT antibiotic delivery should be reserved for treating DTR-GN pathogens, where it might improve the outcome.[15]

An overview of IVT(IT) is displayed in Table 3.

Neurosurgical Perspective

Although the optimal antimicrobial scheme and the duration of treatment remain to be identified, the management frequently involves neurosurgical interventions. To begin with, EVDs frequently fail in patients with ventricular empyema due to drain malfunction from tissue membrane-like debris and high fluid viscosity of fibrin. In these cases, endoscopic evacuation using a side-cutting aspiration device could be of help.[183] The technique can be supplemented by a septostomy using biopsy forceps, ventricular lavage with saline, and intraventricular antibiotic administration.[184] Endoscopic evacuation and lavage advantages are safe debris removal, targeted high-flow irrigation and tissue sampling, and microabscess destruction.[184] Endoscopic evacuation and irrigation indications are not clear, and currently, neuroendoscopy has been used to treat primarily purulent meningitis when intravenous antibiotics and EVDs fail.[184] The results are frequently encouraging, with a good outcome in most of the cases and moderate results regarding shunt dependence.[185,186] However, further high-quality research is required to elucidate the role of neuroendoscopy in managing post-neurosurgical infections. About DTR *A. baumannii*, the combined use of IVT irrigation with colistin solution, up to clear return, and IVT colistin resulted in negligible infection relapse and an 80% success rate.[187]

In cases of implants, eradication of VM is unlikely without implant removal.[1,2,22] Notwithstanding, a significant problem that should be considered in managing post-neurosurgical ventriculitis is that neurosurgical patients are frequently device-dependent. Permanent devices could be re-implanted after a variable period and negative serial cultures in a one- or two-stage process.[1,2,22] The one-stage process involves device removal and implantation of a new one at a single operation.[1,2,22] In the two-stage process, the device removal is followed by a device-free period before device re-implantation.[1,2,22] There is plenty of controversy regarding the optimal timing of re-implantation, but the new device could be safely re-implanted 10 to 15 days after the infection eradication based on negative cultures and without antibiotic cessation.[1,2,22]

Prognosis

The prognosis can be dismal; the in-hospital mortality burden is increased and varies from 9.3% to as high as 40.3%.[35,188] Settings with resistant GN bacteria are associated with higher mortality[15,187] compared with settings of less resistant pathogens;[35] however, direct comparison is lacking. Apart from mortality and regardless of the causative agent, adverse neurological outcome (dependent daily living, vegetative state, and death) was evident in about 60% of the patients assessed.[35,101] The factors independently implicated with mortality were unhealthy neurological examination, admission Glasgow Coma Scale <8, age older than 40 years of age, coexisting diseases, CSF pleocytosis over 200 cells/μL, the presence of EVD, and failure to sterilize the CSF.[35,188–190] Of interest, mortality following postoperative VM in a DTR setting was independently associated with the isolation of *A. baumannii* and the administration of inappropriate empirical treatment.[17]

In a cohort of patients with intracranial hemorrhage, the development of VM presented an additional and independent factor that further worsened their prognosis.[191,192] VM patients compared with non-VM individuals had higher mortality and doubled both the hospital length of stay (median stay of 31 vs 16 days) and cost of care.[191] Moreover, good neurological recovery occurred significantly less often, in VM patients compared to their non-VM counterparts (17.5% vs 71%).[192]

Expert Opinion

The presence of VM can lead to daunting sequelae as the patients suffer increased mortality and functional compromise. Diagnosis might be elusive whenever no pathogen is isolated from the CSF, often due to prior administration of antimicrobial chemotherapy or infections with slow-growing, biofilm-forming microorganisms, such as *S. epidermidis* or *C. acnes*. There is no diagnostic gold standard and the current criteria do not confidently differentiate VM from aseptic inflammation (Table 1). Novel experimental diagnostic methods, such as proteomics, which exploit the synthesis and the daily evolution of CSF proteins can improve diagnostic accuracy. Meanwhile, the expansion of molecular libraries and the technical refinements of novel microbiological assays gradually replace conventional microbiology, although they still warrant further validation. The molecular identification of the pathogens themselves, and their relevant resistance

Table 1 Diagnostic Criteria for External Ventricular Drain-Associated Ventriculomeningitis

Considerations	IDSA[2]	CDC[37]	Lozier[§19]	Mounier[82]	Gozal[§83]	Honda[84]
Fever*	Yes	Yes	Yes	No	Yes	No
Clinical meningitis symptoms and signs [#]	Yes	Yes	Yes	No	No	No
Suggestive CSF profile	Yes	No/yes[¶]	Yes	No	Yes[##]	Yes[¶¶]
CSF culture required for diagnosis	Yes	Yes/no[¶]	Yes (or Gram stain)	Yes**	Yes	Yes
Quantity of microorganism growth required	Any	Any	Any	Any	Any	Any
Aseptic meningitis excluded	Yes	No	Yes	Yes	Yes	Yes
Antibiotic pretreatment considered	No	Yes	No	No	No	No
Antimicrobials targeting CNS	No	No	No	Yes	No	No
Time required after EVD insertion	No	No	No	No	No	>48-hours
Interval from catheter removal for a valid diagnosis	No	No	No	No	Up to 72 hours	Up to 5 days

Note: *May represent other focus of infection. [#]Can be absent due to severity of the primary disease. [¶]By the criterion 1 of the definition/by the criterion 2. [§]Definitions of ventriculitis. **Two CSF samples necessary for skin flora microorganisms. [##]CSF glucose <50mg/dL or CSF glucose to same-day serum glucose ratio < 50%. [¶¶]Required only to consider skin flora.
Abbreviations: CDC, Center for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; EVD, external ventricular drain; IDSA, Infectious Diseases Society of America.

Table 2 Prevention Studies Reporting Incidence

First Author, Year; Study; Period; Country; Reference	Device	Catheter Type	Hand Hygiene Enhanced; Hand Hygiene Compliance Monitoring; Educational Program and/or Checklist	Item(s) Related to Insertion				Items Related to Manipulation				Routine Catheter Exchange; Catheter Removal	VM Rate Before/ CG	VM Rate After/ IG
				Antibiotic Prophylaxis; Patient Skin Antisepsis	Head Hair Management	SC Tunneling; Length	Other	Aseptic Management	Dressing Change; Type	CSF Sampling Frequency	Other			
Walek; 2021; Retrospective; 2007-2019; USA;[103]	EVD	Plain; AIC only after suspected or proven VM	Yes; yes; yes	No; yes	Clipping	Yes; NA	Sterile implantation; all OR doors closed strategy	Yes	No dressing, unless oozing from site	Only if suspected VM	Aseptic management of unintended disconnection; aseptic change of full collection reservoir	No; as soon as possible	6.7 / 1000 EVD days	2/ 1000 EVD days*
Thien; 2019; Prospective, following retrospective audit; 2014-16; USA;[104]	EVD	Plain, SIC, and AIC	NS; no; no	Single dose before; scrub with Hexodane followed by Cetrimide 1% and povidone iodine	At least ¼ head shave	Yes; ≥5cm	Double gloves and change outer glove before handling EVD	Yes	Elective change at 4 days; plain	According to the level of suspicion	EVD clamped when handled or patient is mobilized; drainage bag changed when ¾ full	Optional if colonized or after 21 days; within 10 days if feasible	4.8%	2%
Yang Li; 2019; prospective; 2016-18 China;[105]	EVD	NS	Yes; no; yes	Single dose before; CHX antisepsis	NS	NS	–	Yes	Changed every 2 days; NA	Every 2 days for culturing	Daily drainage bag emptying	NS	5.48%	2.62%*
Ates; 2020; before-after; 2011-13; Turkey;[106]	VPS	AIC	Yes; yes; yes	Yes; CHX antisepsis	Shave	By definition; NA	OR doors closed	Yes	Changed 48 hours later; NS	NA	NA	NA	6.8%	2,6%*
Whyte; 2020; before-after; 2014-15 and 2017; USA;[107]	EVD, SGD, SDD	NA	NS; NS; yes	Started before, <48-hour prophylaxis;	Clipping	NS	–	Yes	When loose or soiled; CHX- eluting	NS	–	NS	5.5%	5.6%
Hussein; 2019; before-after; 2014-17; Israel;[28]	EVD, LD, ICP	NA	Yes; yes; yes	Yes, unspecified timing; NS	NS	NS	OR insertion for EVD, ICP	Yes	NS	Only if VM suspected	MDR-carriers' cohorting; Daily catheter assessment	No; as soon as possible	17.3/ 1000 catheter days	9.2/ 1000

(*Continued*)

Table 2 (Continued).

First Author, Year; Study; Period; Country; Reference	Device	Catheter Type	Hand Hygiene Enhanced; Hand Hygiene Compliance Monitoring; Educational Program and/or Checklist	Item(s) Related to Insertion				Items Related to Manipulation				Routine Catheter Exchange; Catheter Removal	VM Rate Before/ CG	VM Rate After/ IG
				Antibiotic Prophylaxis; Patient Skin Antisepsis	Head Hair Management	SC Tunneling; Length	Other	Aseptic Management	Dressing Change; Type	CSF Sampling Frequency	Other			
Sweeny; 2019; Retrospective cohort; 2012-18; USA;[108]	VPS	Plain	NS; NS; yes	Before and up to 24 hours; CHX antisepsis	NS	By definition; NA	CHX antisepsis 12h before operation; Limited traffic in OR Double gloves and change outer glove before handling hardware	NS	NS	NA	NA	NA	8.8%	5.6%
Katzir; 2019; retrospective cohort; 2010-15; Israel;[109]	EVD	AIC	NS; NS; NS	Single dose before; NS	NS	Yes; ≥5cm	OR insertion	Yes	Every 2 days; semi-occlusive adhesive	NA	NA	Every 5 days vs clinically indicated; NS	32%	8%
Mallucci; 2019; Single blinded RCT; 2013-17; UK/Ireland;[85]	VP shunt	Plain vs AIC vs SIC	NS; NS; NS	Before was standard, further NS; NS	NS	NS	NS	NS	NS	NA	NA	NA	6%	2%* AIC/ IG vs 6% SIC/IG
Roethlisberger; 2018; Single-blinded RCT Trial; 2013-16; Switzerland;[110]	EVD	SIC	NS; NS; NS	Single-dose, before skin incision; yes	Hemicranial clipping	5cm	OR indertion	NS	If bleeding 12hs post-operation or every 5 days; non-CHX-adhesive (CG) vs CHX-containing (IG)	NS	Dressing edges secured by surgical stapler	NS	26%	14%#

Omrani; 2018; Retrospective cohort; 2009-15; UK;[111]	VPS, VAS, VpS	AIC	NS; NS; Yes	Yes; Povidone iodine scrub	Clipping	By definition; NA	OR insertion; Restricted access; Double glove changed before assembling shunt and inserting ventricular catheter	NS	NS	NA	NS	NA	5.43%	3.27%
Ershova;, 2018; Prospective; 2011-16; Russia;[112]	EVD	NS	Yes; yes; yes	Single anesthesia induction dose; CHX antisepsis	NS	NS	Sterile implantation, only by clear indications	Yes	NS	NS	Minimization of disconnections	No; as soon as possible	22.2 cases per 1000 EVD days	13.5 cases per 1000 EVD days
Bashir; 2016; Retrospective; 2003-9; Denmark;[113]	VPS	Plain	NS; NS; NS	Vancomycin, 980mg IV and 20mg IVT before; CHX antisepsis	Shaving	By definition; NA	Limited traffic in the OR; Glove change before shunt handling	NS	NS	NA	NA	NA	11.8%	9.8%
Chatzi; 2014; before-after; Greece;[101]	EVD	Plain	Yes; yes; yes	30 minutes prior to and 6–8 hr after insertion	Shaving	Yes; ≥5cm	OR insertion	Yes	Daily; plain	If clinically indicated	EVD unblocking was avoided or, otherwise, performed distally	Aiming at 7th drainage day; as soon as possible	28%	10.5%*
Camacho; 2013; before-after; 2007-10; Brasil;[114]	EVD	NA	Yes; yes; yes	Before and up to 24 hours post-insertion; CHX antisepsis	Whole scalp clipping	5cm	OR insertion; semirecumbent position;	Yes	Daily dressing changes and head wrapping by neurosurgery residents	Only when infection is suspected	Avoidance of catheter unblocking	No; If the system integrity is violated or as soon as possible	9.5%	4.8%

(*Continued*)

Table 2 (Continued).

First Author, Year; Study; Period; Country; Reference	Device	Catheter Type	Hand Hygiene Enhanced; Hand Hygiene Compliance Monitoring; Educational Program and/or Checklist	Item(s) Related to Insertion				Items Related to Manipulation				Routine Catheter Exchange; Catheter Removal	VM Rate Before/ CG	VM Rate After/ IG
				Antibiotic Prophylaxis; Patient Skin Antisepsis	Head Hair Management	SC Tunneling; Length	Other	Aseptic Management	Dressing Change; Type	CSF Sampling Frequency	Other			
Flint; 2013; retrospective before-after; 2005-7 and 2009-11; USA;[115]	EVD	Plain (before), AIC (after)	Yes;NS; yes	Single dose before; CHX antisepsis	Broad clipping	3–5cm	ICU insertion; all staff in room wore mask and cap; full draping of patient's head and body;	Yes, strict technique	No routine change; adherent transparent dressing	On clinical indication	Manipulation steps: a) all staff in room wore mask and cap; b) 3-way stopcock positioned at 45°, b) stopcock and adjacent tubing submerged into isopropyl alcohol, c) the physician wears sterile gloves and gown, d) rubbed with CHX, e) port opened and cap discarded, f) inner port repeatedly rubbed with CHX, g) saline rinsing, h) CSF sampling or flush, i) new, sterile cap placed	No; NS	6.3%	0.8%*
Kubilay; 2013; prospective; 2006-12; USA;[116]	EVD	AIC	Yes; no; yes (nurse monitoring at bedside)	Before and up to 24 hours; iodine povacrylex and isopropyl alcohol antisepsis	Clipping	NS	Compliance monitoring by the patient's bedside nurse	Yes	NS	N	NA	NS	9.2%	0%

Lwin; 2012; Prospective, 3-phased audit; 2007-8; Singapore;[117]	EVD	Plain initially and SIC during the last phase	Yes; yes; yes	NS; NS	NS	NS	Limiting the number of personnel in the OR and minimising the duration of the operation	Yes	NS	When VM was suspected	–	Within 10 days; as soon as possible	6.1%	0%
Kestle; 2011; Prospective; 2007-9; USA;[118]	VPS, VAS, VpS	Non-AIC	Yes; yes; yes	A dose before and a second dose following operation; CHX antisepsis	Clipping	By definition; NA	Limited traffic in the OR; Patient position of the OR site away from door	NS	NS	NA	–	NA	8.8%	5.7%*
Williams; 2011; before-after; 2005-7; Australia;[119]	EVD	NS	NS; NS; NS	NS; CHX antisepsis	Clipped or shaved only around bur hole	No	–	Yes	Every 3 days; plain transparent	Daily vs every 3 days	Unblocking by saline with sterile gloves and aseptic technique	NS	17%	10.8%*

Notes: *denotes significant reduction; #denotes nonsignificant VM reduction ; however, the bacterialregrowth at the catheter exit site was significantly decreased.
Abbreviations: AIC, antibiotic-impregnated catheter; CG, control group; CHX, chlorhexidine; CSF, cerebrospinal fluid; EVD, external ventricular drain; ICP, intracranial pressure; ICU, intensive care unit; IG, intervention group; IV, intravenous; IVT, intraventricular; NA, not applicable; NS, not specified; OR, operating room; SIC, silver-impregnated catheter; UK, United Kingdom; USA, United States of America; VAS, ventriculoatrial shunt; VP, ventriculoperitoneal shunt; VpS, ventriculopleural shunt; VM, ventriculitis or postoperative meningitis or healthcare-associated ventriculitis and meningitis.

Table 3 Common Intraventricular/Intrathecal Treatment Options

Drug	Recommended Adult Daily Dose[#2]	Loading Dose Suggested	Adverse Events Reported[136]	Targeted Pathogens[2,136]
Amikacin	5–50mg	–	Transient hearing loss, seizures, chemical meningitis, radiculopathy (IT)	DTR Gram-negatives
Colistin	10mg	40mg	Chemical meningitis, seizures	DTR Gram-negatives
Daptomycin	5mg	–	Limited data available	Gram-positives non-responding to systemic treatment
Gentamycin	4–8mg	–	Equivalent to amikacin	DTR Gram-negatives
Polymyxin B	5mg	–	Equivalent to colistin	DTR Gram-negatives
Tigecycline*[176]	4–8mg	–	None attributed to the drug	DTR Gram-negatives, especially if colistin-resistant as well; potentially VRE[177]
Tobramycin	5–20mg	–	Equivalent to amikacin	DTR Gram-negatives
Vancomycin	5–20mg	–	CSF pleocytosis, headache	Gram-positives non-responding to systemic treatment

Notes: *Limited data available. #Apart from tigecycline, according to Infectious Disease Society of America recommendations.[2]
Abbreviations: CSF, cerebrospinal fluid; DTR, difficult-to-treat resistant; IT, intrathecal; VRE, vancomycin-resistant enterococci.

genes can identify the culprit pathogens faster. Better diagnostics should exclude AM and limit empirical treatment of VM (and, therefore, limit unnecessary resistant selection pressure).

Preemptive or earlier targeted treatment of the disease should commence instead, following the paradigm of Candida infections. Regarding IV antimicrobial chemotherapy, most available PK/PD studies are not robust enough to clearly define therapeutic targets. Meanwhile, CSF therapeutic drug monitoring is usually not available for many antibiotics in use for VM. The implementation of such monitoring will enable increasingly higher doses or more frequent dosing of IV antimicrobials with a broad therapeutic index, such as beta-lactam-antibiotics, to achieve therapeutic levels in the CSF.

The medical literature on intraventricular antibiotics has been fraught with case series and reports, and low-quality evidence. However, it describes the valuable experience to manage this demanding infection. Notably, IVT remains a last resort targeted therapy of VM due to DTR-GN isolates. The molecular identification of either a DTR-GN pathogen or a relevant resistance phenotype might expedite the initiation of this adjunct treatment to improve outcomes. Endoscopic treatment has recently supplemented antimicrobial chemotherapy; it comprises the evacuation of debris and ventricular lavage. Preliminary data on lavage preceding IVT colistin treatment demonstrated promising results for the treatment of VM due to multi-resistant *A. baumannii* and *K. pneumoniae*.

Regarding prevention, the use of bundles for infection prevention can be indispensable in the era of DTR bacteria and their corresponding "hard to handle" infections. Indeed, the Neurocritical society has recently published a set of suggested clinical performance measures which include a documented EVD insertion bundle. Novel antimicrobial combinations, active against Gram-negative pathogens and ventriculostomy catheters impregnated with these drugs, are needed.

To conclude, the recent advances in diagnosis, management, and prevention might help mitigate the devastating sequelae of this critical infection.

Abbreviations

AUC, area under the receiver operating curve; BCID, Biofire blood panel; CI, cell index; CNS, central nervous system; CSF, cerebrospinal fluid; DTR, difficult-to-treat resistant; EVD, external ventricular drain; GN, Gram-negative; GP, Gram-positive; IDSA, Infectious Diseases Society of America; IT, intrathecal; IVT, intraventricular; ME, meningitis/

encephalitis; MIC, minimal inhibitory concentration; NAAT, nucleic acid amplification test; PK, pharmacokinetics; PD, pharmacodynamics; RBC, red blood cell count; SAH, subarachnoid hemorrhage; VM, ventriculitis or postoperative meningitis or healthcare-associated ventriculitis and meningitis; VP, ventriculoperitoneal shunt; WBC, white blood cell count.

Disclosure

The authors declare no conflicts of interest in this work.

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