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REVIEW

Treatment of Ventriculitis and Meningitis After Neurosurgery Caused by Carbapenem-Resistant *Enterobacteriaceae* (CRE): A Challenging Topic

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Abstract: Post-neurosurgical infection is a common complication of neurosurgery, and serious infection can threaten the life of patients. In recent years, the increase in multidrug-resistant bacteria, especially carbapenem-resistant *Enterobacteriaceae* (CRE), has proved fatal to patients. Although there are a few cases of CRE meningitis and few clinical trials have been carried out, it has attracted increasing attention with the increasing probability of its occurrence, especially considering that there are few successful cases. An increasing number of studies are also looking for the risk factors and clinical symptoms of CRE intracranial infection. In terms of treatment, some new antibiotics are gradually being used in the clinic, but due to the complicated drug-resistant mechanism of CRE and the obstruction of the blood–brain barrier (BBB), the therapeutic effect is still very poor. In addition, obstructive hydrocephalus and brain abscess caused by CRE meningitis are still important causes of patient death and are also difficult to treat.

Keywords: CRE, ventriculitis and meningitis, polymyxin, ceftazidime-avibactam, cefiderocol

Introduction

Post-neurosurgical infection is very harmful, which can not only prolong the length of stay of patients, consume medical resources and increase medical costs but also lead to poor prognosis of patients, including increased disability and mortality.[1–3] Due to different surgical methods, the infection rate after neurosurgery is also different. In general, the infection rate after external ventricular drainage (EVD) is approximately 10%,[4,5] also reported to be approximately 0–22% in the literature,[6–8] and even 45% in individual reports, which has the highest infectious rate.[9] However, it has been pointed out that the infection rate of EVD can be reduced to 0.80%[4,10] under the use of strict disinfection skin preparation and strict aseptic operations, including subcutaneous tunnels and disinfection films. However, these surgical methods are very difficult to carry out in every clinical work, especially in emergency surgery. The infection rate of ordinary craniotomy, including resection of brain tumours, clearance of intracerebral haematoma, brain trauma surgery, cranioplasty, and microvascular decompression, is approximately 2.2–19.8%.[11–13] The infection rate of shunt surgery represented by ventriculoperitoneal shunt (V-P shunt) is approximately 5–12%.[14] Because this kind of operation is also common in children, many studies have reported that the infection rate in children is approximately 3–15%.[15] Postoperative intracranial infection, especially the infection of implant surgery, has brought great harm to patients, and some severe infections can lead to death.[16,17]

For the types of bacteria infected after neurosurgery, most studies have noted that coagulase-negative staphylococci are the main genus of infection,[18] but in recent years, an increasing number of studies have reported that the infection rate of gram-negative bacilli is increasing.[17,19–21] In particular, *A. baumannii* has a particularly high mortality rate because of its multiple drug resistance.[17,20] Because the majority of antibiotics cannot pass through the blood–brain barrier or the blood–brain barrier permeation rate is very low and unable to achieve effective bacteriostatic or bactericidal

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concentrations, intracranial infections caused by drug-resistant gram-negative bacilli have very serious consequences; these bacteria mainly include multidrug resistant (MDR), extensively drug resistant (XDR) or even pandrug resistant (PDR) *A. baumannii, Pseudomonas aeruginosa* and *Enterobacteriaceae*.[22–24]

Carbapenem-resistant *Enterobacteriaceae* (CRE) mainly refers to *Enterobacteriaceae* that is resistant to any kind of carbapenem and it is usually MDR, XDR or even PDR bacteria. CRE mainly includes *Klebsiella pneumoniae* and *Escherichia coli* which are also the top two CRE in China.[25] More and more CRE meningitis has been reported in recent years, but few cases have been successfully cured. Briefly, CRE meningitis is one of the most difficult infection to cure because the bacteria have high drug resistance, greater toxicity, and severe systemic reactions, and it is easier to form obstructive hydrocephalus, leading to the death of patients. Our article mainly reviews the risk factors, diagnosis and treatment of CRE ventriculitis and meningitis after neurosurgery.

Risk Factors of Carbapenem-Resistant *Enterobacteriaceae* (CRE) Ventriculitis and Meningitis

Postsurgery infection is a common complication. Due to different surgical methods in neurosurgery, the infection rate is also different, and the risk factors for surgical infection are not the same. Many literatures from 2016 to 2022 have pointed out the risk factors for infection after EVD, including CSF leak, insertion site dehiscence, catheterization time and many other factors.[5,8,21,26–35] We summarized the literature in recent years in Table 1. For craniotomy, we also

Table 1 Risk Factors of EVD Infections in Previous Literatures

Study	No. of Patients	Infection Rate%	Risk Factors	Comment
Mehreen et al[21]	192	19.4	Longer duration of catheter Higher frequency of CSF[a] sampling	214 EVDs
Walek et al[8]	409	2.2%	Prior brain surgery CSF leak Insertion site dehiscence	479 EVDs; NS[b]: duration of EVD placement
Khalaveh et al[26]	396	8.1%	EVD from another hospital Multiple EVDs Mean CSF sampling frequency Mean duration of catheterization in days Reinsertion frequency after first EVD	NS: surgeon's experience, the setting of EVD insertion, the operating time
Dakson et al[27]	348	12.2%	Catheters inserted at the bedside Smaller incisions (≤ 1 cm)	NS: antibiotic prophylaxis, catheter replacement and catheter tunneling length
Zhu et al[28]	284	12.7%	Longer ICU stay Lower GCS[c] Longer drainage duration CSF sampling Artificial airway status Intracranial hemorrhage diagnosis	IRFs[d]: Longer ICU stay; CSF sampling counts; EVD duration; Artificial airway status
Sweid et al[29]	389	3.1%	EVD replacement Bilateral EVDs Duration of EVD Increased CSF output/day CSF leak Longer hospital stay	IRFs: Female sex; EVD replacement; Increased CSF output/day; CSF leak

(*Continued*)

Table 1 (Continued).

Study	No. of Patients	Infection Rate%	Risk Factors	Comment
Kim et al[30]	247	10%	Multiple EVD insertions EVD duration Hospital length of stay	VCTH[e] is a potentially significant risk factor.
Sam et al[31]	714	6.3%	Use of steroid *Pseudomonas aeruginosa* infection Multiple organism infection Lower GCS Longer duration the EVD was in place before the diagnosis	
Hussein et al[32]	155	18.7%	Diabetes mellitus Drain number Drain insertion in the first three hospitalization days Drain opening Drain days	212 EVDs IRFs: Drain days
Kohli et al[33]	163	6.13%	No significant risk factor	NS: Initial diagnosis, Drain replacement Duration of drain placement
Jamjoom et al[5]	452	9.3%	EVD placement for ≥8 days Regular sampling (daily sampling and alternate day sampling)	495 EVDs NS: Catheter type (antibiotic-impregnated) Tunneling distance
Phan et al[34]	110	11.5%	Multiple drains	Antibiotic prophylaxis associated with decreased rates of infections
Atkinson et al[35]	263	5.7%	EVD replacement Bilateral EVDs CSF leak	362 EVDs IRFs: EVD replacement
Corsini Campioli et al[36]	94	34	EVD in place >10 days	For spontaneous intracranial hemorrhage

Notes: [a]Cerebrospinal Fluid. [b]No Significance. [c]Glasgow Coma Scale. [d]Independent Risk Factors. [e]Ventriculostomy-related Catheter Tract Hemorrhage.

summarized many studies. The risk factors for postoperative infection include the length of operation, reoperation, external drainage and other risk factors.[18,36–44] We have also summarized the literature in recent years in Table 2.

Among these postoperative infections, we found that the proportion of gram-negative bacilli is increasing, and there are increasingly more reports of *Enterobacteriaceae* ventriculitis and meningitis. Shi et al[45] analysed 2416 patients with postoperative craniocerebral infection from 2014 to 2019 and found that *Enterobacteriaceae* infection accounted for 7.3%. A total of 164 cases had a statistical prognosis, including 77 patients with *Klebsiella pneumoniae* infection, accounting for 47%. The risk factors for death caused by *Enterobacteriaceae* meningitis/encephalitis infection include comorbidities, Glasgow Coma Scale (GCS) score, sepsis, intensive care unit (ICU) admission, extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, and ventilation. An updated literature counted 90 patients with iatrogenic meningitis caused by multidrug-resistant *Enterobacteriaceae* after neurosurgery, of which 46 were *Klebsiella pneumoniae*, and 40 of them were resistant to carbapenem. In this paper, univariate analysis showed that the rates of EVD, assisted mechanical ventilation (AMV), GCS scores ≤ 8, ICU admission, sepsis, and hospital-acquired pneumonia (HAP) were significantly different between patients in the survival and nonsurvival groups, and Multivariate Cox survival analysis showed that EVD and a GCS score ≤ 8 were independent mortality risk factors for patients with

Table 2 Risk Factors of Postcraniotomy Infection in Previous Literature

Study	No. of Patients	Infection Rate%	Risk Factors	Comment
Corsini Campioli et al[36]	5328	1.1%	Emergency surgery Dirty surgery Antibiotic prophylaxis (ABP)	Cefazolin and vancomycin for ABP
Jiménez-Martínez et al[37]	595	15.3%	ASA[a] score > 2 Extrinsic tumors Re-intervention	IRF[b] ASA score > 2 Re-intervention
Chen et al[18]	755	8.60%	Male patients GCS[c] under 12 External ventricular drainage Lumbar drainage Enteral nutrition Surgery duration > 4.5 hours Repeat operations Antibiotic prophylaxis Concurrent infection	IRF Diabetes mellitus External ventricular drainage Lumbar drainage
Wang et al[38]	2174	9.0%	Male patients Age≤45 Hypertension Tumor surgery Surgery in autumn (compared with spring) Surgical duration ≥4 hr Blood loss≥400 mL Postoperative oral infection Coma Serum RBC > normal value	Trauma surgery is an independent protective factor
Kuwano et al[39]	1012	3.1%	Three or more surgeries Radiation therapy	NS[d]: intraoperative MRI[e] IRF: Three or more surgeries Only for glioma surgery.
Maye et al[40]	267	4.5%	–	NS: Intraoperative monitoring and 5-ALA[f] Only for neuro-oncology surgery.
Caruso et al[41]	71	4.2%	–	NS: Postoperative drain placement; Administration of intrawound vancomycin powder; Prophylactic preoperative IV vancomycin is a protective factor; For autologous cranioplasty after decompressive craniectomy in TBI[g].
Alkhaibary et al[42]	103	15.7%	Blood glucose levels Skull defect size	For Autologous Cranioplasty
Valentini et al[43]	6359	1.7%	Younger patients (≤14 years) The number of surgeries Surgeries lasting longer than 3 hours Two or more surgeries with prosthetic implants	ABP prolongation showed limited efficacy for wound complication.

(*Continued*)

Table 2 (Continued).

Study	No. of Patients	Infection Rate%	Risk Factors	Comment
Shi et al[44]	5723	6.8%	Patients ≤ 45 years old Recurrent tumors Preoperative hospital length of stay Duration of craniotomy Preoperative V-P shunt[h] Postoperative administration of antibiotics External CSF drainage / monitoring devices placement Postoperative leakage of CSF Postoperative intracranial hemorrhage Surgical wound classification Metastatic tumors Intraventricular tumor	IRFs: Clean-contaminated craniotomy; Prolonged operation (>7h); external CSF drainage / monitoring device placement; Postoperative CSF leakage; For brain tumors surgery.

Notes: [a]American Society of Anesthesiologists. [b]Independent Risk Factors. [c]Glasgow Coma Scale. [d]No Significance. [e]Magnetic Resonance Imaging. [f]5-aminolevulinic acid. [g]Traumatic Brain Injury. [h]Ventriculoperitoneal Shunt.

MDR *Enterobacteriaceae* meningitis.[46] In addition, the literature also suggested that the risk factors for CRE infection were surgical wound classification, ventilation rate, craniotomy, bacteraemia, ICU admission, hospital-acquired pneumonia and mortality attributed to infection. Among them, hospital-acquired pneumonia and mortality attributed to infection were identified as independent risk factors for CRE meningitis/encephalitis.[47] We summarize these studies in Table 3.

Table 3 The Risk Factors of *Enterobacteriaceae* Meningitis in Previous Studies

Study	No of Postoperative Infection in Neurosurgery	Enteroba-Cteriaceae Meningitis Rate %[a]	CRE Infection Rate %[b]	Risk Factors	Comment
Shi et al[45]	2416	7.3%	14.6%	Comorbidities; GCS[c] score; Sepsis; ICU admission; ESBL[d]-producing *Enterobacteriaceae*; Ventilation;	IRF[e]: GCS score ≤8
Guanghui et al[47]	2947	6.3%	19.5%	Ventilator; Bacteremia; ICU admission; HAP[f]; Mortality attribute to infection	IRF: HAP; Mortality attribute to infection
Zheng et al[46]	3570	6.8%	16.5%	EVD[g]; ICU admission; GCS score ≤8; HAP; Ventilation; Sepsis;	IRF: EVD; GCS score ≤8

(*Continued*)

Table 3 (Continued).

Study	No of Postoperative Infection in Neurosurgery	Enteroba-Cteriaceae Meningitis Rate %[a]	CRE Infection Rate %[b]	Risk Factors	Comment
Zheng et al[78]	4198	6.5%	15%	Ventilation; Surgical wound classification; Craniotomy; Malignancy	IRF: Craniotomy; Malignancy

Notes: [a]Account for Postoperative infection in neurosurgery. [b]Account for *Enterobacteriaceae* Meningitis. [c]Glasgow Coma Scale. [d]Extended Spectrum β-Lactamase. [e]Independent Risk Factors. [f]Hospital-Acquired Pneumonia. [g]External Ventricular Drainage.

Diagnosis of Iatrogenic Ventriculitis and Meningitis

There are a variety of clinical manifestations of postoperative intracranial infection, and sometimes it is challenging to diagnose the infection, especially in patients after craniocerebral surgery. The majority of patients have clear clinical signs and laboratory changes, such as new headache, nausea, fever, somnolence, and decreased GCS score. In particular, fever, in the absence of another clear source of infection, indicates central nervous system (CNS) infection during recent head trauma or neurosurgery. Of course, the emergence of new meningeal irritation signs after neurosurgery also suggests the possibility of infection. During shunt surgery, erythema tenderness in the subcutaneous shunt and new abdominal tenderness in peritonitis indicate the possibility of infection.Laboratory examination is also an important index for the diagnosis of iatrogenic ventriculitis and meningitis, especially cerebrospinal fluid (CSF) examination, which plays an important role in the diagnosis of meningitis. Cerebrospinal fluid culture is the most important index, and it also provides a basis for further targeted treatment. However, cerebrospinal fluid culture and smears do not have positive results in most cases. Therefore, the number of leukocytes in cerebrospinal fluid and changes in sugar and protein play an important role in the diagnosis of meningitis. However, low glucose, elevated neutrophils and protein changes in cerebrospinal fluid tests cannot determine intracranial bacterial infections. Similarly, a normal cerebrospinal fluid test cannot rule out intracranial bacterial infections. In addition, positive blood culture can also indicate the types of bacteria in intracranial infections.Imaging examination is necessary for patients with suspected intracranial infection, and contrast-enhanced MRI and diffusion weighted imaging (DWI) are necessary for patients with abscess. MRI can not only make a definite diagnosis of hydrocephalus caused by severe infection, especially obstructive hydrocephalus but also provide a basis for further operation.

In recent years, some new specific tests have been incorporated into the diagnosis of iatrogenic ventriculitis and meningitis, such as CSF lactate[48] or CSF procalcitonin[49] for the diagnosis of bacterial intracranial infection, but its clinical application is not clear. In addition, nucleic acid amplification detection of infected CSF using polymerase chain reaction (PCR), which is used to determine pathogenic bacteria, is also widely used in clinics, but its accuracy is worth deliberating. The pathogens detected need to be consistent with the clinic before further treatment can be carried out.

Treatment of Carbapenem-Resistant *Enterobacteriaceae* (CRE) Ventriculitis and Meningitis

The treatment of carbapenem-resistant *Enterobacteriaceae* is very difficult, with a poor prognosis and high mortality of patients.[50] Particularly in CRE ventriculitis and meningitis, most antibiotics cannot reach their bacteriostatic concentration in CSF due to the blood–brain barrier (BBB). Carbapenem-resistant *Enterobacteriaceae* are generally extensively drug resistant (XDR) or pandrug resistant (PDR), and consequently, it is very difficult to treat CRE ventriculitis and meningitis. Next, we will review the treatment of CRE meningitis drugs and surgical selection.

Drug Therapy

Since the first case of CRE infection was reported, researchers have studies the mechanism of drug resistance, which is very complicated.[51,52] The main reason is the production of carbapenemase, which is a class of β-lactamase that can hydrolyse carbapenem drugs and mainly includes three types of enzymes according to the Ambler molecular classification: Class A enzymes, mainly *Klebsiella pneumonia* carbapenemase (KPC); Class B metal enzymes, including IPM, VIM and New Delhi metallo-β-lactamase (NDM); and Class C enzymes, mainly OXA-23 and OXA-48. These drug resistance genes are mainly carried on the plasmid. The main reason for the drug resistance of CRE in China is the production of KPC, followed by NDM, and these bacteria can carry other drug resistance genes at the same time, such as qnr, OXA, ESBLs, and AmpC, thus forming XDR or PDR to all conventional antibiotics.[25]

Due to the extensive drug resistance of CRE, few therapeutic drugs are available in the clinic. Currently, these medications mainly comprise polymyxin, tigecycline, ceftazidime-avibactam and the new antibiotics meropenem/vaborbactam, cefiderocol, plazomicin, and eravacycline. Previous studies evaluated more than 1800 patients with CRE infection in China from 2012 to 2016 and found that the sensitivity rate of polymyxin was 96.9% and that of tigecycline was 89.7%.[25] For CRE ventriculitis and meningitis, Shi et al[45] reported 164 cases of intracranial *Enterobacteriaceae* meningitis from 2014 to 2019, of which 25 cases were CRE, which is sensitive to polymyxin, and most cases were sensitive to chloramphenicol and amikacin. Similarly, Zheng et al[46] counted 90 patients with multidrug resistant *Enterobacteriaceae* meningitis, of which 40 were CRE. These cases were also all sensitive to polymyxin, and most were sensitive to trimethoprim/sulfamethoxazole and amikacin. Another report[47] counted 133 cases of *Enterobacter* meningitis after neurosurgery, including 26 cases of CRE. These CRE cases were all sensitive to polymyxin; therefore, polymyxin + meropenem or polymyxin + meropenem + tigecycline was used in the follow-up treatment of patients, of whom 8 survived and 18 died. Through the report of *Enterobacteriaceae* meningitis after neurosurgery, we can conclude that CRE accounts for approximately 15% and 25% of intracranial *Enterobacteriaceae* infections, which is higher than that of other infections.[53] All intracranial CRE are highly sensitive to polymyxin but not sensitive to tigecycline (the resistance rates are 35%, 60%, and 34.1% according to the three studies above); consequently, we still use polymyxin as an important drug in the treatment of CRE ventriculitis and meningitis. Some case reports have also shown that polymyxin is effective in the treatment of CRE ventriculitis and meningitis.[54,55] In addition, some intracranial infections caused by CRE are sensitive to certain traditional antibiotics, such as amikacin[56,57] and gentamicin,[58] which have successfully saved the lives of some patients. According to retrospective studies, single use of tigecycline or polymyxin did not significantly increase mortality from pulmonary infection caused by CRE, while combination of drugs (carbapenem combined with polymyxin or tigecycline or gentamicin) reduced mortality.[52,59] Similar studies have not been carried out in cases of intracranial CRE infection. But most cured intracranial CRE infection cases were used by multiple antibiotics.[55–57,60]

In recent years, a new antibiotic ceftazidime-avibactam has been used in the clinical treatment of patients with CRE infection. Avibactam is a novel synthetic β-lactamase inhibitor that inhibits a wide range of β-lactamases, including Class A (KPC), and some Class D (OXA-48) β-lactamases and it does not inhibit Class B (IMP, VIM, VEB, and NDM) β-lactamases. Since 2016, a series of cases have been reported that ceftazidime-avibactam alone or in combination with intraventricular administration of other drugs has achieved partial success in the treatment of CRE meningitis.[60–66] We have summarized the reports in Table 4 and ceftazidime-avibactam is an important choice for the treatment of intracranial CRE producing KPC or OXA-48 β-lactamase. What's more, Gatti et al[66] has shown that ceftazidime-avibactam can penetrate BBB and reach an effective bactericidal concentration by increasing drug dosage (up to 2.5g q6h). In addition, ceftazidime -avibactam has no bactericidal activity against carbapenem-resistant *A. baumannii*, which is more common than CRE in intracranial infections.

A new drug Meropenem/Vaborbactam is approved in August 2017 by the United States Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis. Vaborbactam is a new type of β-lactamase inhibitor that mainly acts on class A carbapenemases, such as KPC, to fight CRE. In many studies, it can also be seen that its antibacterial effect is similar to that of ceftazidime-avibactam.[67] However, its application in intracranial CRE infection is not clear because meropenem can partially pass through the blood–brain barrier in the case of intracranial

Table 4 Ceftazidime-Avibactam Treatment for CRE Ventriculitis and Meningitis

Study	Case Characteristics	Pathogen	Dose and Duration	Other Therapy	Prognosis
Pektezel et al[61]	A 62 man with ICH[a], treated with EVD[b].	OXA-48 CRKP[c]	2.5g q8h IV[d]	SMZ-TMP[e]; Amikacin ICV[f]	Clinical cure
Holyk et al[62]	An elderly patient with SAH[g] treated with EVD.	CRKP	2.5g q8h IV	Gentamicin 8mg/day ICV	Clinical cure
Gofman et al[63]	A 32 man with TBI[h] treated with craniotomy	CRKP PA[i]	2.5g q8h IV	Amikacin 30mg/day ICV	Clinical cure
Yasmin et al[64]	A 38 man with TBI treated with craniotomy	KPC-CRKP	2.5g q8h IV	Amikacin ICV	Clinical improvement
De Santis et al[65]	A 50 man with TBI treated with craniotomy	OXA-48 CRKP	2.5g q6h IV	Amikacin ICV	Clinical improvement
Gatti et al[66]	A 52 man with TBI treated with V-P shunt	CRKP	2.5g q6h IV	EVD	CSF Sterilization Dead

Notes: [a]Intracerebral Hemorrhage. [b]External Ventricular Drainage. [c]Carbapenem-Resistant *Klebsiella pneumoniae*. [d]Intravenous Injection. [e]Sulfamethoxazole-Trimethoprim. [f]Intra-Cerebro Ventricular Injection. [g]Subarachnoid Haemorrhage. [h]Traumatic Brain Injury. [i]*Pseudomonas aeruginosa*.

infection, but the distribution of vaborbactam in the brain is unknown. Whether it can pass through the BBB needs further study. In addition, it also had no killing activity against carbapenem-resistant *A. baumannii*.

Plazomicin is a new generation of semisynthetic aminoglycoside antibiotics and a structural derivative of sisomicin.[68] It has antibacterial activity against CRE, which produces Class A and Class D β-lactamases. However, its antibacterial activity against Class B, especially NDM, is very poor, mainly because most NDM CRE carry 16S rRNA methyltransferase, which methylates nucleotides G1405 and A1408 on the 16S site of the ribosomal RNA 30S subunit, resulting in a significant decrease in drug affinity for the A site.[68] Plazomicin was approved in June 2018 by the FDA for the treatment of adults with cUTIs, including pyelonephritis. However, its application in CRE meningitis has not been reported. Considering that most aminoglycosides cannot easily pass through the BBB, it is unlikely that plazomicin can do so.

Eravacycline is a newly synthesized tetracycline antibiotic with a wide antibacterial spectrum. Similar to tigecycline, it has no antibacterial activity against *P. aeruginosa*.[69] It was approved by the FDA in August 2018 for the treatment of complicated intra-abdominal infections (cIAIs). Eravacycline has broad-spectrum antibacterial activity against Class A and B and D β-lactamases and thus has certain bactericidal activity against CRE. However, the application of eravacycline in intracranial CRE infection lacks clinical experience, and its BBB permeability is still unclear.

Cefiderocol is a novel siderophore cephalosporin that has a unique antibacterial mechanism in which it forms a bactericidal complex that is transported into bacteria via iron transporters.[70] In addition, it can also resist carbapenemase and therefore has broad-spectrum antibacterial activity against Class A, B and D β-lactamases.[71] In addition, many case reports also show that it has good bactericidal activity against intracranial CRE infection,[72] but also has good effect on carbapenem-resistant *A. baumannii* (CRAB)[73] and carbapenem-resistant *P. aeruginosa* (CRPA)[74] meningitis. Considering that most cases are cured intravenously, cefiderocol should partially pass through the inflammatory blood–brain barrier, but its effect still needs to be supported by further clinical trials.[74]

Surgical Treatment

EVD and lumbar drainage (LD) are important methods for the treatment of CRE ventriculitis and meningitis. On the one hand, EVD can drain infected cerebrospinal fluid and treat hydrocephalus. On the other hand many antibiotics, such as polymyxin, tigecycline, amikacin, and gentamicin, cannot pass through the BBB, whereas antibiotics that pass through the BBB are not effective against CRE. Therefore, it is necessary to inject antibiotics through EVD or LD. The dosages of intraventricular antimicrobial drugs should be selected based on CSF concentrations to 10–20 times the MIC of the

pathogenic bacteria, ventricular volume, and daily drainage volume of CSF. When antibiotics are administered by intracerebroventricular injection, the drain is clamped for 15–60 minutes to allow the agent to equilibrate throughout the CSF.[75] Of course, intrathecal injection of antibiotics has a serious of side effects, which mainly depends on the type of antibiotic used. For example, polymyxin can lead to chemical meningitis, seizures, and cauda equina syndrome.[76] While aminoglycosides can cause transient hearing loss, seizures, chemical meningitis, and radiculopathy.[24,77] In addition, there are few studies on whether EVD or LD is more suitable for intracranial drug injection, but there is no doubt that EVD is better than LD for postinfection obstructive hydrocephalus.

The treatment of obstructive hydrocephalus caused by CRE infection is extremely complex and difficult. Because one or two tubes of EVD cannot make CSF aseptic and isolated ventricles without drainage are the medium for bacterial reproduction, this results in poor infection control. Therefore, antibiotics with high BBB permeability are needed to control CRE ventriculitis and meningitis. However, in many cases, although ceftazidime-avibactam and cefiderocol can be used intravenously to control intracranial infection, they most often need to be combined with other antibiotics (such as polymyxin) via intraventricular injection. The treatment of obstructive hydrocephalus sometimes requires ventriculoscopy to turn obstructive hydrocephalus into communicating hydrocephalus, and then aseptic treatment of CSF is needed. However, the operation is sometimes very difficult, there are many serious postoperative complications, and the survival rate of the patients is not high. Sometimes craniotomy is needed to remove brain abscesses and subdural abscesses, which is undoubtedly another fatal blow to certain patients under the circumstances of poor infection control.

Conclusion

Infection after neurosurgery is still an important cause of death and disability in patients. Among the intracranial infections caused by various bacteria, although the incidence of CRE meningitis is low, it is difficult to treat and has high mortality, which has posed difficulties in the treatment of NICU patients. Considering that the mechanism of CRE resistance is complex, it is easy to form XDR and PDR pathogens, and most antibiotics have low capacity to pass through the BBB, it is difficult to control intracranial CRE infection by intravenous administration alone. There is an urgent need for new antibiotics with good blood–brain barrier permeability and good antibacterial activity against CRE. In addition, obstructive hydrocephalus caused by CRE remains a difficult problem in the field of neurosurgery.

Data Sharing Statement

All data generated or analyzed in this study are included in this published article.

Disclosure

The authors declare no conflicts of interest in this work.

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