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REVIEW

Optimal antibiotic therapy for bacterial central nervous system infections in adults

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ABSTRACT

Introduction: Central nervous system (CNS) infections are a health concern, leading to high morbidity and mortality. Community-acquired and nosocomial meningitis are distinct entities with potentially different pathogens involved. Prompt antibiotic therapy is crucial. However, challenges arise due to the emergence of multidrug-resistant bacteria and the poor CNS penetration of most antibiotics.

Areas covered: This review summarizes the pathogenesis of bacterial CNS infections, the pharmacokinetics, and pharmacodynamics of several classes of antibiotics within the cerebrospinal fluid (CSF) and the optimal treatment of these infections in adults. A literature search was performed in PubMed and Embase including all available articles up to February 2025.

Expert opinion: The selection of antibiotics with proven CNS penetration and activity against the suspected or confirmed pathogens is essential, particularly in the context of emerging resistance. Higher daily doses and continuous or extended infusions (CI/EI) help maintain therapeutic concentrations in critically ill patients, while intrathecal (IT) administration of antibiotics should be considered when systemic therapy alone is insufficient. Therapeutic drug monitoring (TDM) is crucial for optimizing dosing, especially for drugs with narrow therapeutic indices. Although CSF TDM remains uncommon and challenging, it should be performed in specialized centers with experience in antibiotic pharmacokinetics.

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Antibiotics; central nervous system infections; pharmacokinetics; pharmacodynamics; therapeutic drug monitoring

1. Introduction

Central nervous system (CNS) bacterial infections are a significant source of morbidity and mortality worldwide [1,2]. CNS bacterial infections include meningitis, encephalitis, and intracranial suppuration complications (e.g. brain abscesses). These infections can be subdivided in community-acquired and nosocomial bacterial CNS infections, which can occur after invasive procedures (e.g. external devices or shunt insertions, craniotomy, or lumbar puncture) or after head trauma, with potentially different organisms involved. The main bacterial pathogens responsible for community-acquired meningitis in adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*. *Listeria monocytogenes* is an important cause of meningitis in immunocompromised patients and in older adults (above 60 years of age) [3,4]. In contrast, nosocomial bacterial meningitis is most commonly caused by *Streptococcus spp., Staphyloccocus spp*. and Gram-negative bacilli [5,6]. However, the epidemiology of bacterial meningitis varies substantially across different regions of the world. Bacterial CNS infections are medical emergencies requiring early and appropriate antibiotic treatment, which can be difficult to administer given the emergence of multidrug-resistant bacteria [7]. This review focuses on acute bacterial CNS infections in adults, with an emphasis on the most common pathogens and resistance patterns in Europe and North America. We summarized the pathogenesis of bacterial CNS infections, the pharmacokinetics, and pharmacodynamics of several classes of antibiotics within the cerebrospinal fluid (CSF) and optimal treatment strategies. Mycobacterial CNS infections and brain abscesses were excluded from the scope of this review. A comprehensive literature search was performed in PubMed and Embase, including all available articles up to February 2025. The search strategy included the following keywords and their combination: 'bacterial meningitis,' 'central nervous system infections,' 'pathogenesis,' 'pharmacokinetics,' 'pharmacodynamics,' 'antibiotic therapy', and 'intrathecal administration.' Only articles published in English were considered.

2. Pathogenesis of CNS infection

The CNS is protected by the skull and enveloped by the meninges. The blood–brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) separate the CNS from the systemic circulation and one of their roles is to protect the brain against microbial invasion. The BBB, the largest interface between brain and the systemic circulation, is composed of endothelial cells connected by tight junctions, astrocytes, and pericytes to form a contiguous membrane barrier [3,8]. The BCSFB is composed of epithelial cells and tight junctions located at the choroid plexus and endothelial cells within the subarachnoid space [9]. Pathogens may enter the CNS by direct invasion through the external barrier or through the bloodstream in association with breaches in the BBB. Several transport mechanisms can explain the passage of pathogens across the BBB, such as the paracellular, the transcellular, and the Trojan-Horse mechanisms [10]. Transcellular traversal occurs when

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Article highlights

- The main bacterial pathogens responsible for community-acquired meningitis in adults are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, while *Streptococcus* spp., *Staphylococcus* spp., and Gram-negative bacilli are the predominant pathogens in nosocomial bacterial meningitis.
- The diffusion of antibiotics into the CSF and brain extracellular space is influenced by factors such as molecular size, lipophilicity, ionization, plasma protein binding, active transport, and barrier integrity.
- Due to antibiotic resistance and difficulties with penetration into the CSF, higher doses of antibiotics, prolonged infusions, or continuous and intrathecal administration may be considered.
- Intrathecal administration may be considered for antibiotics with poor CSF penetration and/or significant systemic toxicity, which limits higher daily doses, especially in patients with multi-resistant pathogens or treatment failure with systemic antimicrobial alone.
- Empirical treatment for community-acquired meningitis in areas of the world with low prevalence of cephalosporin resistance to *Streptococcus pneumoniae*, includes a third-generation cephalosporin, with amoxicillin or ampicillin added for suspected neurolisteriosis, and for nosocomial bacterial meningitis, vancomycin plus an anti-pseudomonal beta-lactam based on local susceptibility patterns is the recommended treatment. However, antibiotic regimens should always be adapted to local epidemiology, particularly in settings with a high prevalence of multidrug-resistant pathogens.

microbes penetrate through brain microvascular endothelial cells (BMECs), paracellular traversal mechanism occurs when pathogens penetrate between BMECs and the Trojan-horse mechanism occurs when phagocytes carry intracellular microbes across the BBB. The method of penetration across the BBB, and consequently the way CNS infections occur, varies depending on the type of pathogen. For example, *Neisseria meningitidis* uses transcellular and paracellular traversal and does not require Trojan horse transit, in contrast with *Listeria monocytogenes* [11].

3. Penetration of anti-infective drugs within the CNS

Molecular size, lipophilicity, degree of ionization, plasma protein binding, active transport, and barrier integrity are factors influencing the diffusion of antibiotics into the CSF and extracellular space of the brain [12], as described in Figure 1. Lipophilic agents, with low molecular weight, can penetrate easily into the CNS, in contrast with large hydrophilic agents, which have decreased CSF penetration [12]. Concerning ionization, antibiotics with high ionization, such as aminoglycosides, have poor CSF penetration. Protein binding is also an important factor influencing the entry of antibiotics into the CSF, with only the unbound fraction that can penetrate the cerebral tissue. Penetration of antibiotics depends also on their affinity to transport systems, such as the P-glycoprotein (P-gp), the organic anion transporter 3 (Oat3) and the peptide transporter 2 (PEPT2) [13]. All are expressed in the BBB to limit CNS entry of many drugs, affecting their efficacy and toxicity. For example, in Pgp-deficient mice, the brain penetration of Pgp substrate drugs, such as ivermectin, can increase up to 100-fold, increasing the toxicity compared to wild-type control mice with intact P-gp transporters [14]. The presence of meningeal inflammation will also influence the degree of penetration into the CSF. Indeed, in bacterial meningitis, the activity of these transport systems can be inhibited by pro-inflammatory cytokines. Furthermore, these pro-inflammatory

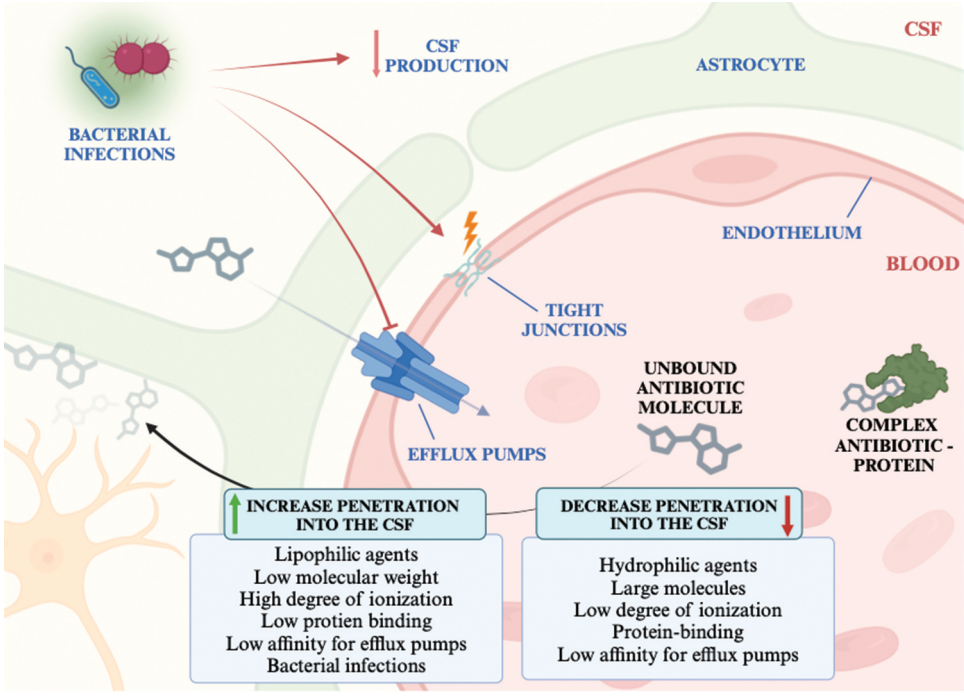

Figure 1. Penetration of anti-infectives within the CNS. This figure depicts the dynamics influencing the penetration of antibiotics into the cerebrospinal fluid (CSF) and the central nervous system (CNS). *Created with biorender.com.*

cytokines can also increase the permeability of the BBB by opening intracellular tight junctions and reducing CSF production and absorption rates, thus resulting in increased antibiotic concentrations in the CSF.

4. Pharmacokinetic and pharmacodynamic properties of antibiotics within CSF

The clinical efficacy of antibiotic treatment in CNS infections depends on the drug tissue concentrations and its bactericidal activity against causative bacteria [12]. Antibiotics can be divided into two categories based on their antibacterial efficacy: time-dependent or concentration-dependent [15]. The efficacy of time-dependent antibiotics (e.g. beta-lactams, glycopeptides) depends on the percentage of the time that the free drug concentration remains above the minimal inhibitory concentration (MIC – i.e. %fT > MIC) between two administrations. The efficacy of concentration-dependent antibiotics (e.g. aminoglycosides, fluoroquinolones) depends on the maximum unbound concentration above the MIC. As tissue concentration is extremely difficult to obtain, most of the data on antibiotic concentrations within the CNS are related to measurements performed from CSF samples.

In critically ill patients, several factors can significantly alter the pharmacokinetics (PK) and consequently the pharmacodynamics (PD) of antibiotics, necessitating careful management to ensure therapeutic efficacy. Acute kidney injury, a common complication in critically ill patients, can profoundly impact drug elimination and distribution, increasing the risk of toxicity. Additionally, sepsis increases capillary permeability, which expands the volume of distribution for hydrophilic antibiotics, potentially lowering their plasma concentrations and reducing their efficacy [16]. Moreover, in CNS infections, the permeability of the BBB is often compromised, leading to variations in antibiotic penetration into the CSF [12]. Furthermore, intensive care units face a higher prevalence of infections caused by antibiotic-resistant microorganisms, complicating empirical and targeted therapies. Another key consideration in critically ill patients is augmented renal clearance (ARC), which may lead to subtherapeutic antibiotic levels and insufficient tissue penetration, thereby increasing the risk of treatment failure [17]. In patients with external ventricular drains, the CSF drainage volume can also alter the concentration of antibiotics in the CSF [18,19]. To counter these challenges, dose adjustments are often necessary for CNS infections, including higher daily regimens, continuous/extended infusions (CI/EI) or intrathecal administration (IT) [20–25]. To optimize antibiotic therapy, therapeutic drug monitoring (TDM) is a crucial tool. By individualizing dosing regimens based on measured drug levels and patient-specific factors, TDM theoretically ensures optimal efficacy while minimizing toxicity risks.

A summary of drug concentrations in the CSF is reported in Table 1.

4.1. Beta-lactams

Beta-lactams are hydrophilic agents with low molecular weight, which may limit their penetration into the CSF. However, their penetration is enhanced in the presence of inflammation. Increasing the daily dose of many beta-lactam antibiotics, as well as prolonged or continuous infusions, can also ensure higher CSF concentrations [26]. Indeed, PK/PD studies and case reports have shown higher meropenem concentrations in the CSF with CI in CNS infections compared to intermittent infusion [27]; however, whether these findings translate into improved clinical cure rates in bacterial meningitis remains to be established.

4.1.1. Cephalosporins

Third and fourth-generation cephalosporins are highly active against pathogens causing community-acquired meningitis (*Streptococcus pneumoniae*, and *Neisseria meningitidis*) and are also effective in meningitis caused by Gram-negative bacilli [28]. Ceftriaxone and cefotaxime have almost similar

Table 1. Antimicrobial drugs and their main relevant variables for daily regimens.

Drug	CSF/Serum ratio (%)	Serum Protein binding	Total IV dosing daily	Reference(s)
Cefotaxime	3–48	31–50%	2 g q6h	[11]
Ceftriaxone	0.6–94	83–96%	2 g q12h	[11,28]
Ceftazidime	2.7–15	<10%	2 g q8h	[11]
Cefepime	10	20%	2 g q8h	[11]
Meropenem	10.7–21	2%	2 g q8h	[11,18]
Ciprofloxacin	10–50	20–40%	400 mg q8h	[11,39]
Moxifloxacin	30–70	32%	400 mg q24h	[11,39]
Amikacin	10–22	<10%	15 mg/kg of total body weight q24h	[11,60]
Gentamicin	7.4–57.6	<30%	3–5 mg/kg q24h	[11]
Doxycycline	11–56	93%	200 mg q24h	[11,62]
Metronidazole	18–86	<20%	500 mg q6h	[11,63]
TMP-SMX		TMP 44% - SMX70%	8-12 mg/kg divided q6h (TMP component)	[11,64]
Vancomycin	15.1–80	50%	30-60 mg/kg divided q12h or loading dose followed by continuous infusion adapted to renal function	[11,43]
Colistin	5–25	50%	Loading dose of 9 MIU followed by 4.5MIU q12h	[11,53]
Linezolid	66–77	31%	600 mg q12h	[11,118–120]
Tazobactam	3–74	30%	0,5 g q8h	[71]
Avibactam	38	5.7–8.2%	0,5 g q8h	[68]
Cefiderocol	10	58%	2 g q8h	[74–77]

CSF = cerebrospinal fluid ; TMP-SMX = Trimethoprim-sulfamethoxazole; MIU = million international units.

antimicrobial spectrum of activity [29]. To maintain its therapeutic efficacy and considering its rapid elimination, cefotaxime administration intervals should not exceed every 8 h; ceftriaxone is usually prescribed at higher daily doses than the standard dosage regimen (2 g q12h) [30]. In a recent observational cohort study on patients with pneumococcal meningitis, it was observed that infections due to strains resistant to penicillin (MIC > 0.06 mg/L) and third-generation cephalosporines (MIC > 0.5 mg/L) were associated with therapeutic failure, as was treatment with vancomycin alone [31], while high dose of cefotaxime (300 mg/kg per day) appeared to prevent therapeutic failure. The authors therefore suggest using higher than standard recommended cephalosporin doses as empirical therapy in all cases until the MIC is known and to continue this therapy for strains with MICs up to 2 mg/L for either penicillin or third-generation cephalosporins [31]. Although a maximum daily dose of 4 g per day of ceftriaxone has been recommended by the manufacturer, high-dose ceftriaxone (daily dosage ≥4 g per day or ≥75 mg/kg per day) has been evaluated for CNS infections in a multicenter prospective cohort study [32]. The study demonstrated that this dosing regimen was generally well tolerated, with ceftriaxone-related adverse drug reactions being infrequent and mostly mild or harmless. A population PK study was also conducted in patients with suspected or confirmed bacterial meningitis to develop a dosing nomogram for ceftriaxone. The authors concluded that the high-dose ceftriaxone (75–100 mg/kg per day, ranging from 4 to 8 g per day, without fixed upper limit) dosage regimen should be adjusted based on the patient's estimated glomerular filtration rate (eGFR) and body weight to ensure optimal efficacy and safety [30]. Further clinical trials to confirm these findings are also required. Ceftazidime, a third-generation cephalosporin, is effective in treating meningitis caused by susceptible *Pseudomonas aeruginosa* strains [33]. Cefepime, a fourth-generation cephalosporin, has *in vitro* activity against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [34]. Cefepime was more active than ceftazidime against *Escherichia coli, Staphylococcus aureus* and *Streptococcus pneumoniae* in experimental CNS infection models [34]. However, cefepime may not be the first choice for CNS infections due to its relatively frequent association with encephalopathy [35].

4.1.2. Monobactams

Aztreonam penetrates well into the CSF and demonstrates significant activity against common Gram-negative meningitis pathogens, including *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Escherichia coli,* and *Neisseria meningitidis*, while showing poor activity against Gram-positive and anaerobic organisms [36].

4.1.3. Carbapenems

Meropenem is effective against most bacteria causing community-acquired meningitis and hospital-associated meningitis [37], although carbapenem resistant infections are increasing over time, as will be discussed more in detail further on [38]. The area under the curve (AUC) CSF/AUC free serum ratio of carbapenems is close to the ratio observed for other beta-lactams [12]. The recommended dosage of meropenem for CNS bacterial infections is 2 g every 8 h. A pharmacokinetic study involving patients with meningitis showed that a dose of 2 g every 8 h administered as a 4 h prolonged infusion with CSF drainage of less than 150 ml per day achieved more than 90% probability of success for strains with MICs ≤ 0.5 mg/L [19]. In contrast, a prospective observational pharmacokinetic study conducted in neurocritical care patients with confirmed or suspected ventriculitis receiving 2 g administered every 8 h as a 4 h prolonged infusion of meropenem, demonstrated that only 54% of patients achieved a minimum meropenem CSF trough concentration of 2 mg/L, which is insufficient to treat resistant pathogens [20]. A Monte Carlo simulation identified a regimen of 5 g every 6 h to allow 95% of patients to achieve these target drug levels. However, this approach still requires validation through clinical studies and its safety has not been adequately evaluated. In one study [39], a nomogram based on renal function was established to achieve effective meropenem concentrations during continuous infusion while minimizing the risk of adverse effects. For example, to achieve a target concentration of 8 mg/L, the required daily doses ranged from 910 mg (for an estimated creatinine clearance according to Cockcroft-Gault of 20 mL/min) to 3940 mg (for an estimated creatinine clearance according to Cockcroft-Gault of 180 mL/min), with a very low risk of adverse effects at these doses. Konig et al. [40] developed, in a retrospective study, a nomogram to predict effective meropenem doses based on protein levels in the CSF and estimated clearance, which depends on the estimated glomerular filtration rate, in patients with nosocomial ventriculitis treated with continuous infusion of meropenem. A daily dose of 6 g achieved therapeutic targets (2x MIC for 100% of the dosing interval) in only 80% of patients with preserved renal function (eGFR >50 mL/min/1.73 m^2) and low protein levels in the CSF (<500 mg/L). However, further studies are needed to confirm the applicability and effectiveness of nomograms in clinical practice. Regarding imipenem and doripenem, they have poorer CSF penetration compared to meropenem, with a higher risk of seizures.

4.2. Fluoroquinolones

Fluoroquinolones are lipophilic agents with low binding to plasma proteins, and most agents are unionized [41]; therefore, they penetrate adequately into the CSF. They have good activity against Gram-negative bacilli and poor activity against enterococci and streptococci, except moxifloxacin [42,43]. Indeed, moxifloxacin has been shown to be as effective as ceftriaxone in bacterial meningitis caused by *Streptoccocus pneumoni*ae penicillin-susceptible strains and as effective as vancomycin and ceftriaxone against penicillin-resistant *Streptococcus pneumoniae* strains [44]. However, due to the limited published literature and the rapid emergence of resistance to this class of antibiotics, fluoroquinolones should only be used as an alternative for bacterial meningitis in case of resistance or contraindications to other agents [28].

4.3. Glycopeptides

Glycopeptides are large hydrophilic antibiotics with a protein binding rate ranging from 50% for vancomycin to 90% for teicoplanin [45]. For these reasons, teicoplanin has poor CSF penetration and is rarely used to treat CNS infections. Moreover, concomitant administration of steroids can further reduce vancomycin CSF penetration [46]. This effect can be circumvented by the systemic administration of high doses of vancomycin [47,48] and by co-administration with rifampicin [49]. Standard dosing regimen of 2 g every 12 h of vancomycin may be insufficient to maintain adequate CSF concentrations for infections caused by pathogens with an MIC ≥1 mg/L [50]. Doses of at least 30–60 mg/kg every 12 h for intermittent administration and 60 mg/kg per day for continuous infusion after a loading dose of vancomycin for CNS infections, targeting an optimal serum trough concentration of 15–20 mg/L for intermittent administration and 20–25 mg/L for continuous infusion are recommended [2]. Recently, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS), and the Society of Infectious Diseases Pharmacists (SIDP) recommended monitoring vancomycin exposure using the area under the curve to minimum inhibitory concentration ratio (AUC/MIC), targeting a range of 400–600, rather than relying on trough concentrations. This approach aims to reduce the risk of nephrotoxicity while maintaining clinical efficacy in patients with severe Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections. However, CNS infections are not specifically addressed in these recommendations [51]. In addition, TDM is not universally available, limiting the use of AUC/MIC-guided dosing in many centers. A case report describes the successful treatment of a patient with methicillin-resistant *Staphylococcus aureus* meningitis using an AUC/MIC target of 600 [52]; however, further studies are needed to assess the efficacy of targeting higher AUC/MIC values. Regarding the mode of administration, Taheri et al. [53], in a randomized clinical trial involving patients with post-neurosurgical meningitis, showed that continuous infusion (loading dose of 25 mg/kg over 2 h followed by 50 mg/kg/day) achieved more stable serum vancomycin concentrations and significantly higher mean CSF vancomycin concentrations compared to the intermittent infusion group (loading dose of 25 mg/kg over 2 h followed by 25 mg/kg infusions every 12 h). However, no difference was observed in the CSF/serum ratios between the two groups. Vancomycin can be administered in monotherapy or combination therapy with beta-lactams in cases of meningitis caused by Gram-positive pathogens.

4.4. Polymyxins

Polymyxins are large hydrophilic agents with poor penetration into CSF and can cause severe nephrotoxicity and neurotoxicity [54]. Colistin (or polymyxin E) can be administered to patients with CNS infections due to multi-drug resistant (MDR) Gram-negative bacteria [54]; moreover, the current polymyxin resistance rate is low. However, available data in humans have shown that IV administration of colistin provides only a minimal contribution to the levels of colistin needed in the CSF, hence the need of simultaneous IT administration of polymyxins when systemic therapy alone is insufficient [55].

4.5. Rifampicin

Rifampicin is a lipophilic agent with good penetration into the CSF in the presence of meningeal inflammation and demonstrates high *in vitro* activity against common pathogens responsible for community-acquired bacterial meningitis. However, in tuberculous meningitis, CSF penetration is limited and higher doses may be required to achieve therapeutic concentrations [56]. Most studies of rifampicin in bacterial meningitis have investigated its use in combination therapy because on the rapid emergence of bacterial resistance that is observed when rifampicin is administered in monotherapy [57]. Rifampicin has also shown bacteriological efficacy in methicillin-resistant *Staphylococcus aureus* infections [58].

4.6. Linezolid

Due to its good CSF penetration, linezolid is an alternative to vancomycin for CNS infections caused by multi-resistant Gram-positive pathogens [59]. It has been reported to be effective in meningitis caused by methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin-resistant streptococci [59,60]. Although linezolid resistance is less common than vancomycin resistance, it is emerging in certain regions of the world [61]. Despite this, current guidelines continue to recommend vancomycin as the first-line empirical treatment, with linezolid reserved as an alternative in cases of vancomycin resistance or intolerance [2]. Moreover, prolonged administration of linezolid has been linked to hematologic toxicity, most notably myelosuppression with thrombocytopenia, as well as an increased risk of optic neuropathy [62]. Therefore, its use in CNS infections should be carefully individualized, balancing the potential benefits against these risks, in particular for longer duration of therapy.

4.7. Other drugs

Aminoglycosides are hydrophilic agents with low plasma protein binding, resulting in poor CSF penetration [63]. Therefore, they are not recommended as IV monotherapy for CNS infections. They can be administered in combination (e.g. ampicillin plus gentamicin for *Listeria monocytogenes* meningitis) or as adjunctive IT administration when systemic therapy alone is insufficient [28]. Macrolides are large lipophilic agents with a high affinity for P-gp [64]. Therefore, the diffusion into the CSF is poor and their role in the treatment of CNS infections is limited. Doxycycline, the most studied tetracycline, and tigecycline, a glycylcycline, are lipophilic drugs with high protein binding and, therefore, penetrate poorly into the CNS [65]. However, doxycycline remains the drug of choice for CNS infections caused by *Rickettsia spp*. with tigecycline representing a potential alternative in cases where doxycycline is contraindicated or unavailable [66,67]. Metronidazole is a small lipophilic agent that is active against most anaerobic bacteria, and penetrates well into CSF and brain abscesses [68]. Therefore, metronidazole is part of the standard therapy for

bacterial brain abscesses. In contrast, clindamycin is strongly bound to plasma proteins and, therefore, has poor penetration into the CNS [12]. Sulfonamides and trimethoprim are small lipophilic agents with good CSF penetration [69]. Trimethoprim-sulfamethoxazole (TMP-SMX) has a high *in vitro* activity against the three most frequent meningeal pathogens (*Streptococcus pneumoniae*, *Neisseria meningitidis,* and *Listeria monocytogenes*), staphylococci, and several Enterobacteriaceae [70]. TMP-SMX may be a therapeutic option for bacterial meningitis caused by pathogens resistant or only moderately susceptible to beta-lactam antibiotic agents, yet susceptible to TMP-SMX.

4.8. Newer antibiotics

Data relating to CSF penetration and the efficacy of new antibiotics in CNS infections are limited to few case reports. In one case report, a patient with nosocomial extended-spectrum beta-lactamase (ESBL-) and OXA-48-producing *Klebsiella pneumoniae* meningitis related to an external lumbar drainage was treated with intravenous ceftazidime-avibactam in combination with intrathecal amikacin and withdrawal of the external lumbar drainage, resulting in clinical cure [71]. Other case reports showed similar positive outcomes [72–75]. Ceftazidime-avibactam has also shown efficacy, as monotherapy or in combination with an intrathecal administration, to treat hospital associated meningitis caused by carbapenem-resistant *Enterobaceriaceae spp*. (CRE) and *Pseudomonas aeruginosa* [73]. Standard doses (2.5 g q8h) seemed to achieve adequate CSF concentrations [73].

In one study, Sime et al. demonstrated that ceftolozane/tazobactam inadequately penetrates the CSF and that if given as monotherapy at a dosage of 3 g q8h, it could be effective to treat only very susceptible pathogens (e.g. MIC ≤ 0.25 mg/L) in the CNS [76]. However, ceftolozane/tazobactam in combination with amikacin and meropenem demonstrated a favorable outcome in a patient with meningitis caused by an extensively drug-resistant *Pseudomonas aeruginosa (XDR-PA)* [77]. The same favorable outcome was reported in another patient with meningitis caused by an XDR-PA treated with ceftolozane/tazobactam and fosfomycin [78].

Several case reports have reported successful treatment of carbapenemase producing *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii,* or carbapenem-resistant *Pseudomonas aeruginosa* nosocomial meningitis using cefiderocol in combination therapy [79–82].

5. Intrathecal administration

Although IV administration is the most common route for antibiotic administration, direct administration of the drug into the CSF may be a possible option for certain antimicrobials, especially when the drug of choice is not expected to efficiently cross the BBB. Indeed, IT administration, including both intraventricular and intralumbar administration, in addition to IV drug administration, has been shown to be an effective method to optimize antimicrobial concentrations within the CNS and to successfully treat nosocomial CNS infections in case series and case reports [83–87]. This method can be considered for antibiotics with poor penetration into the CSF (e.g. aminoglycosides, vancomycin, colistin, and tigecycline) and/or a significant systemic toxicity (e.g. nephrotoxicity of aminoglycosides) that limit the possibility to increase daily doses in patients with multi-resistant pathogens refractory to systemic treatment.

Nevertheless, it must be noted that IT administration of antimicrobials is an off-label use, except for colistin. Several studies, including a meta-analysis, regarding Gram-negative CNS infections caused by resistant pathogens, have shown that the combination of IV and IT antibiotic therapy was superior to IV therapy alone [88]. This approach resulted in greater eradication of pathogens, better improvement in clinical symptoms and lower mortality rates, without increased severe adverse reactions [89–91]. The antibiotics most often administered IT, their dosage regimens and associated side effects are summarized in Table 2. To administer an antibiotic intrathecally into the CNS, it is required to withdraw 5 mL of CSF followed by the administration of the antibiotic in a 5-mL sterile saline solution through the most proximal tap of an external ventricular drain (e.g. external ventricular or lumbar drainage). To slow elimination and increase half-life ($t_{1/2}$), the external ventricular catheter should be clamped after the administration for a duration ranging from 1 to 3 h depending on intracranial pressure and tolerance.

Beta-lactams should never be administered intrathecally because intrathecal administration can rapidly induce seizures [92]. Intrathecal administration of tigecycline has been reported, but due to its neurotoxic effects, it is not recommended as a first-line agent [93]. If tigecycline is the only therapeutic option, a low dose of less than 5 mg q12h could be considered. In a systematic review, IT administration of vancomycin is reported to be safe and effective [94], while IT administration of teicoplanin has been rarely reported. IT doses of 10 to 20 mg vancomycin every 24 h ensure

Table 2. Antibiotics often administered intrathecally, their dosage regimens and associated side effects.

Drug	IT dosing (daily)*	Side effects	Reference(s)
Amikacin	20-50 mg	Neurotoxicity (Radicular pain, epileptic seizures, aseptic meningitis), transient vomiting, hearing loss	[27,49]
Gentamicin	5-10 mg	Neurotoxicity (epileptic seizures, aseptic meningitis and CSF eosinophilia), hearing loss	[27,49]
Tigecycline	5 mg q12h	Neurotoxicity (epileptic seizures)	[27,49,88]
Vancomycin	10-20 mg	Neurotoxicity (epileptic seizures, increased CSF leukocyte count, headache), red man syndrome, hearing loss	[27,49,89]
Colistin	0.125 MIU	Neurotoxicity (epileptic seizures, aseptic meningitis, peripheral neuropathy, agitation), muscle weakness, diaphragmatic paralysis	[26,27,49,91,92]

*Higher doses have been administered in case reports and were well tolerated.
CSF = cerebrospinal fluid.

concentrations above the MIC of susceptible pathogens and were well tolerated [29]. Combined IT and IV administration of colistin (polymyxin E) resulted in higher CSF levels of the drug compared to IV administration alone [55,95]; IT dosages of colistin have been chosen empirically and range between 0.02 and 0.5 millions international units [96]. Nevertheless, guidelines recommend a daily dose of 0.125 millions units with concomitant IV polymyxin for ventriculitis or meningitis caused by MDR or extensively drug-resistant (XDR) Gram-negative pathogens [28,97]. Neurotoxicity has been reported with IT administration of colistin and the use of IT polymyxin B is less common than IT colistin.

6. Treatment of CNS infections

Delay in appropriate antibiotic treatment of bacterial meningitis is associated with adverse clinical outcomes [98,99]. Therefore, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend the administration of antibiotics as soon as possible, within 1 h from hospital presentation [7]. The choice of empiric antibiotic treatment depends on the patient's age, the presence of risk factors, and local epidemiology. Empirical treatment for community-acquired meningitis includes administration of a third-generation cephalosporin, with the addition of amoxicillin or ampicillin if neurolisteriosis is suspected. A large prospective study comparing treatment with meropenem versus cefotaxime plus ampicillin for empirical therapy of community-acquired bacterial meningitis demonstrated that there was no statistically significant difference in 30-day or 90-day mortality rates or in the likelihood of an unfavorable outcome between the two study treatments [100]. However, to preserve carbapenems and reduce the risk of resistance development, it is preferable to adhere to current guidelines, which recommend the use of a third-generation cephalosporin combined with ampicillin for empirical treatment of community-acquired bacterial meningitis. In patients with a beta-lactam allergy, moxifloxacin can be used as an alternative, with or without vancomycin, while TMP-SMX should be added if neurolisteriosis is suspected.

Initial empirical treatment for hospital-associated bacterial meningitis recommended by the IDSA and ESCMID guidelines includes vancomycin as well as an anti-pseudomonal beta-lactam such as cefepime, ceftazidime, or meropenem, based on the local antimicrobial-susceptibility and the pathogenesis of the infection [2]. In case of allergy or contraindication to beta-lactam antibiotics, guidelines recommend aztreonam or ciprofloxacin as an alternative [2]. Even if linezolid and daptomycin have been successfully used to treat staphylococcal meningitis, vancomycin is recommended as the first-line therapy for the empirical treatment of nosocomial bacterial meningitis [2]. After identification of the causative pathogen, specific antibiotic treatments can be initiated depending on the results of *in vitro* susceptibility testing. The following sections review the treatment of the most common bacteria in patients with CNS infections. This approach is summarized in Table 3.

6.1. *Streptococcus pneumoniae*

In meningitis due to *Streptococcus pneumoniae* susceptible to penicillin (MIC ≤ 0.06 mg/L), amoxicillin or ampicillin is the standard treatment, while a third-generation cephalosporin is the standard treatment for meningitis due to *Streptococcus pneumoniae* resistant to penicillin (MIC > 0.06 mg/L) [7]. In patients with *Streptococcus pneumoniae* meningitis at risk of penicillin and cephalosporin-resistant strains (MIC ≥ 0.5 mg/L), vancomycin should be added to a third-generation cephalosporin (either cefotaxime or ceftriaxone) [7]. Rifampicin is an alternative agent in the setting of reduced pneumococcal susceptibility rates in combination with cefotaxime or

Table 3. Recommended antimicrobial therapy based on isolated pathogen.

Pathogen	First line treatment	Alternative	Reference(s)
Streptococcus pneumoniae			
Penicillin MIC ≤0.06 mg/L	Amoxicillin or ampicillin	Third-generation cephalosporin or penicillin G	[6]
Penicillin MIC > 0.06 mg/L			
Cefotaxime or ceftriaxone MIC ≤0.5 mg/L	Third-generation cephalosporin	Cefepime or meropenem	[6,95–97]
Cefotaxime or ceftriaxone MIC > 0.5 mg/L	Vancomycin plus a third-generation cephalosporin	Fluoroquinolone or rifampicin + vancomycin	[6,29,95–98]
Neisseria meningitidis	Amoxicillin or ampicillin	Third-generation cephalosporin, meropenem, fluoroquinolone or aztreonam	[6,26,101,103]
Listeria monocytogenes	Amoxicillin or ampicillin ± gentamicin	TMP-SMX or meropenem	[6,104–107]
Staphyloccoci spp.			
Methicillin susceptible	Oxacillin or flucloxacillin ± IT vancomycin**	Cefazoline, Vancomycin ± IT vancomycin**	[49,113–115]
Methicillin resistant	Vancomycin ± IT vancomycin	Linezolid, rifampicin in combination, daptomycin or TMP-SMX	[49,112,118–122]
Gram-negative bacteria			
Pseudomonas aeruginosa	Ceftazidime or cefepime ± IT*,**	Aztreonam, meropenem, ceftolozane-tazobactam or fluoroquinolones	[26,49]
Acinetobacter baumannii	Meropenem ± IT*, **	Colistin or polymycin B IV + IT* ± rifampicin IV or PO	[49,124]
Klebsiella pneumoniae	Third-generation cephalosporin ± IT*,**	Meropenem, cefepime, aztreonam, TMP-SMX, ceftazidime-avibactam or fluoroquinolones	[40,41,49]
Escherichia coli	Third-generation cephalosporin ± IT*,**	Cefepime, meropenem, aztreonam, fluoroquinolone or TMP-SMX	[40,41,49]

IT = intrathecal; IV = intravenous; TMP-SMX = Trimethoprim-sulfamethoxazole.
*aminoglycosides, or colistin or polymycin B or tigecycline.
**based on expert opinion.

ceftriaxone [7] or with vancomycin [31]. Higher doses of cefotaxime (300 mg/Kg/day) can be administered in cases of strains with MICs of 1 or 2 mg/L [31]. Meropenem represents another effective therapeutic option for the treatment of meningitis caused by *Streptococcus pneumoniae* strains resistant to penicillin and third-generation cephalosporins. Cefepime and moxifloxacin have also demonstrated efficacy in the management of streptococcal meningitis [100–102]. Given that some experimental studies have demonstrated a risk of worsening brain injury with the use of beta-lactams in *Streptococcus pneumoniae* meningitis due to the release of pro-inflammatory toxins during bacterial cell lysis, experimental studies have been conducted on the use of non-bacteriolytic antibiotics, such as clindamycin, rifampin, and daptomycin, and showed more rapid bacterial killing, reduced inflammation, and less brain damage compared to beta-lactams [103–105]. Grandgirard et al. demonstrated, in an experimental study, that combining daptomycin with ceftriaxone may improve outcome in *Streptococcus pneumoniae* meningitis by reducing apoptosis and enhancing hearing capacity [104]. However, Maldiney et al. did not demonstrate any synergy of the combination of daptomycin with rifampicin on *Streptococcus pneumoniae* infections [105]. A multicenter phase II study is ongoing to assess the efficacy and safety of adding daptomycin (10 mg/kg/day for 8 days) to the recommended treatment regimen (corticosteroids + third-generation cephalosporin) in adults with confirmed pneumococcal meningitis (NCT03480191).

6.2. Neisseria meningitidis

In the past, standard therapy for meningococcal meningitis was ampicillin or amoxicillin [7,28,106]. However, due to the increase in meningococcal strains with reduced susceptibility to penicillin [107], patients with suspected meningococcal meningitis should receive a third-generation cephalosporin empirically, until antibiotic susceptibility results are obtained [7]. Chloramphenicol, which has good penetration into the CSF, was also used in the past as the treatment of meningitis due to *Neisseria meningitidis*, but it is no longer recommended because of its toxicity and the emergence of resistance [108]. Meropenem, fluoroquinolones, and aztreonam have also been effective in the treatment of meningococcal meningitis [109].

6.3. Listeria monocytogenes

Immunosuppressed (e.g. malignancies, Human Immunodeficiency Virus (HIV) infection, cirrhosis, diabetes mellitus, alcoholism, or immunosuppressive therapies) and/or patients older than 50 years are at risk of meningitis due to *Listeria monocytogenes* [4]. However, cases of *Listeria monocytogenes* meningitis in patients under 50 years old without risk factors have also been reported. In the case of suspected *Listeria monocytogenes* meningitis, empirical treatment should include amoxicillin or ampicillin because second- and third-generation cephalosporins are not effective against this pathogen. If this pathogen is identified to be the cause of the infection, treatment with amoxicillin should be continued at a dosage of 2 g q4h for at least 21 days [110]. Even though current guidelines recommend the combination of amoxicillin and gentamicin in this context [7], this approach remains a topic of debate in the literature. However, a recent retrospective study demonstrated a reduced 90-day mortality rate with the addition of gentamicin to amoxicillin in patients with invasive *Listeria* infections [111]. TMP-SMX, fluoroquinolones, rifampicin, meropenem, and linezolid have also demonstrated activity against *Listeria monocytogenes* [112,113]. TMP-SMX is an alternative in case of allergy to penicillin [114,115]. Concerning linezolid, a patient with a brain abscess caused by *Listeria monocytogenes* with an allergy to both ampicillin and TMP-SMX, was successfully treated with a combination of linezolid and rifampicin in a case report [116]. However, data are limited to support the use of linezolid in neurolisteriosis.

6.4. Staphylococcus aureus

Staphylococcus aureus meningitis occurs predominantly after neurosurgical procedures [117] but may also be acquired in the community setting in patients with predispositions (e.g. endocarditis, intra-venous drug users). Empirical treatment should depend on the local prevalence of drug resistance. Even if some penicillins (e.g. flucloxacillin, oxacillin) are more effective than vancomycin for the treatment of methicillin-susceptible *Staphylococcus aureus* meningitis, empirical vancomycin should be used until susceptibility testing results are available, if there is a risk of methicillin-resistant strains [118]. Flucloxacillin and oxacillin are the recommended antibiotics for patients with methicillin-susceptible staphylococcal meningitis and vancomycin is the first-line recommended treatment for methicillin-resistant staphylococcal meningitis [2]. Cefazolin has demonstrated non-inferiority to anti-staphylococcal penicillin for the treatment of methicillin-susceptible *Staphylococcus aureus* infections, including meningitis and bacteriemia, with lower associated nephrotoxicity [119–121]. Although cefazolin may be considered a potential alternative for methicillin-susceptible *Staphylococcus aureus* CNS infections, further studies are needed, including investigations to determine the optimal dosing regimens for this indication. Indeed, various daily doses have been used, ranging from 2 g every 6 or 8 h via intermittent infusion to 8–10 g per day via continuous infusion [122,123]. For resistant strains (MIC > 2 mg/L) or contraindications to vancomycin, linezolid (600 mg q12h), a bacteriostatic antibiotic with good CSF penetration, is a safe and effective alternative [124–126]. In a retrospective multicenter cohort study of patients treated with linezolid for *Staphylococcus aureus* meningitis, mortality rates did not differ significantly between those receiving linezolid and those treated with vancomycin for MRSA meningitis [126]. Rifampicin in combination therapy, TMP-SMX or daptomycin may also be treatment options [127,128]. IT vancomycin in combination with IV administration should also be considered.

6.5. Enterococcus

Enterococcal meningitis most frequently arises as a complication of neurosurgical interventions or in patients with indwelling CSF devices. Management is particularly

challenging given the intrinsic and acquired resistance of enterococci to many antimicrobial agents. For susceptible *Enterococcus faecalis*, high-dose intravenous ampicillin remains the treatment of choice, typically in combination with an aminoglycoside to achieve synergistic bactericidal activity [129,130]. In the presence of aminoglycoside resistance, the combination of ampicillin with ceftriaxone has been reported as an effective alternative [129]. For ampicillin-resistant *E. faecalis* or *E. faecium*, vancomycin is generally recommended, while linezolid represents the first-line option for vancomycin-resistant enterococci (VRE) [131]. Other agents, including daptomycin, fosfomycin, rifampicin, and chloramphenicol, generally used in combination, may offer additional therapeutic options; however, supporting evidence is limited to case reports and small case series [132–134].

6.6. Gram-negative bacilli

Gram-negative bacilli, such as *Klebsiella spp.*, *Acinetobacter baumannii*, *Escherichia coli*, and *Pseudomonas aeruginosa*, can cause bacterial meningitis after head trauma or neurosurgical procedures [83,135]. Ceftriaxone or cefotaxime is recommended for the treatment of nosocomial meningitis caused by Gram-negative bacteria susceptible to third-generation cephalosporins [2]. Ceftazidime or cefepime is the standard treatment for *Pseudomonas spp*. CNS infections. Aztreonam and fluoroquinolones are alternatives in case of contraindications to beta-lactams and meropenem [28]. The first-line treatment for Gram-negative bacteria producing ESBL is high-dose meropenem. However, the emergence of multidrug-resistant Gram-negative bacilli is problematic in hospital-associated meningitis, with a reduced range of antibiotic options available. Indeed, resistance to third- and fourth-generation cephalosporins as well as to carbapenems have been reported and is a major public health issue. For example, the mortality rate for *Acinetobacter baumannii* meningitis ranges from 20% to 38.9% in various studies, with mortality rates reaching up to 70% in regions where carbapenem-resistant strains are prevalent [136,137]. A study suggests that mortality due to *Acinetobacter baumannii* meningitis is associated with carbapenem resistance [136]. A combination of IV and IT antibiotic administration may be considered in this setting of resistance. Indeed, in patients with *Acinetobacter baumannii* meningitis, IV meropenem, in combination or not with colistin or polymyxin B administered either IV or IT, depending on whether or not the infection is due to a carbapenem-resistant strains, is the treatment recommended [2]. In a retrospective study, the use of colistin and the combination of IV and IT treatment were significantly associated with clinical cure in patients with carbapenem-resistant *Acinetobacter baumanii* meningitis [136]. A 16-year retrospective cohort study in China [138] comparing carbapenem-non-susceptible (Carba-NS) and carbapenem-susceptible (Carba-S) Gram-negative bacterial meningitis found significantly higher in-hospital mortality in the Carba-NS group compared to the Carba-S group (18.8% vs. 7.4%; $p = 0.005$). Aminoglycoside-based combination (primarily with carbapenems) therapy achieved higher efficacy compared to non-aminoglycoside regimens (69% vs 38.7%; $p = 0.019$) in Carba-NS *Enterobacterales* meningitis. Treatment with aminoglycosides were an independent factor for improved survival (Hazard Ratio (HR): 0.371; $p = 0.039$). Higher doses or prolonged infusion of beta-lactam antibiotics and the use of novel antibiotics are also available options when faced with infections due to resistant strains [79–82].

6.7. Adjunctive corticosteroids treatment

Corticosteroids have been shown to reduce neurological sequelae, hearing loss and improve clinical outcomes in community-acquired bacterial meningitis in studies performed in high-income countries [1,139]. International guidelines recommend intravenous dexamethasone 10 mg q6h, before or together with the administration of the first dose of antibiotic, in case of community-acquired bacterial meningitis. Treatment should be pursued for 4 days only in case of meningitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae* [7]. In *Listeria monocytogenes* meningitis, the evidence regarding adjunctive corticosteroid therapy is more conflicting. A prospective observational cohort study showed an excess of mortality in patients receiving adjunctive dexamethasone (adjusted odds ratio (OR) 4.58; 95% CI 1,50–13.98; $p = 0.008$) [140], whereas a nationwide cohort study found that adjunctive dexamethasone was associated with a reduced risk of poor outcome (adjusted OR 0.40; 95% CI 0.19–0.81; $p = 0.017$) [141]. Dexamethasone is not recommended in the treatment of meningitis due to Gram-negative bacilli (except for *H. influenzae* type B) and in nosocomial-acquired meningitis either.

6.8. Infections of devices in the CNS

If an external ventricular catheter-associated infection is suspected, in addition to IV antibiotics, removal of the external catheter is recommended to avoid treatment failure [2,142,143]. If a drain-free interval is not possible, a new external ventricular catheter can be placed with a daily monitoring of CSF cultures. In the case of an infected CSF shunt, antibiotics, complete removal of this infected CSF shunt, and placement of an external ventricular catheter appear to be the most effective treatment [2]. The optimal timing for the replacement of the shunt is unclear. However, the IDSA guidelines recommend a delay, before placement of a new shunt, of: 7 to 10 days in patients with shunt infections that are caused by Gram-positive bacteria excluding *Staphylococcus aureus* with associated CSF abnormalities but negative repeat CSF cultures; at least 10 days of consecutive negative CSF cultures in the case of shunt infections caused by *Staphylococcus aureus* or Gram-negative bacilli [2].

6.9. Influence of regional antibiotic resistance on the choice of empirical treatment

Resistance profiles differ across countries and even within different regions. Most available data on antimicrobial susceptibility derive from Europe and North America, whereas surveillance in many low- and middle-income countries

remains limited [144]. Knowledge of these local resistance patterns is essential to guide empirical antibiotic treatment. For example, in countries with high penicillin resistance in *Streptococcus pneumoniae* (≥25%), such as Belarus, France, Romania, Serbia, and Turkey, third-generation cephalosporin is the standard empirical treatment, combined with ampicillin to cover *Listeria monocytogenes* if required [7]. To be noted, even in countries where penicillin resistance in *Streptococcus pneumoniae* is minimal, third-generation cephalosporins are recommended as empirical treatment due to the potential for penicillin resistance in *Neisseria meningitidis*. In areas where the prevalence of ceftriaxone-resistant pneumococci reaches or exceeds 1%, such as in Eastern, and Southern Europe, vancomycin should be included in the empirical regimen to ensure adequate coverage [7].

Regarding methicillin-resistant *Staphylococcus aureus*, a north–south gradient is observed in Europe, with a resistance prevalence of less than 1% in Scandinavian countries, contrasting with southern European countries, especially in Portugal and Italy, where methicillin-resistant *Staphylococcus aureus* rates vary between 25% and 50% in several regions. Outside Europe, high prevalence rates have been reported in certain Asian countries, such as China, where the rate is >50% as well as in North America (World Health Organization (WHO) 2021). Vancomycin is the first-line recommended treatment in this situation [7].

Regarding Gram-negative bacilli, resistance to carbapenems has increased alarmingly between 1990 and 2021, with *Klebsiella pneumoniae* exhibiting the most significant rise [145]. Carbapenem resistance in *Klebsiella pneumoniae* was generally low in Northern and Western Europe (<1%). However, resistance rates equal to or above 50% have been reported in Belarus, Georgia, Greece, Moldova, Romania, Russia, Serbia, and Ukraine. Resistance of *Klebsiella pneumoniae* to third-generation cephalosporins is widespread, with rates exceeding 50%, primarily in Southern and Eastern Europe. In North America, it is also widely reported. The percentages of carbapenem-resistant *Acinetobacter* vary widely from <1% in Norway, Sweden, and the Netherlands to ≥50% in Southern and Eastern Europe. In North America, carbapenem-resistant *Acinetobacter* shows substantial geographic heterogeneity. The percentages of carbapenem-resistant *Pseudomonas aeruginosa* are less than 5% in Denmark and Finland and 50% or higher in Belarus, Georgia, Russia, Serbia, and Ukraine. In North America, average rates are generally lower. The emergence of carbapenem-resistant *Escherichia. coli* has been reported, with 1% or higher percentages in Belarus, Cyprus, Georgia, Greece, Russia, Serbia, Turkey, and Ukraine. In North America, carbapenem-resistant *Escherichia coli* remains uncommon overall but is increasing. For third-generation cephalosporin resistance in *Escherichia coli*, a rate greater than 50% is observed in North Macedonia, Russia, Turkey, and Ukraine. In North America, rates are generally lower. The ESCMID and the IDSA provide guidelines for the treatment of infections caused by these MDR Gram-negative bacilli [146,147].

7. Therapeutic drug monitoring in CSF

Doses of antimicrobial agents and frequency of administration for intraventricular use have been determined empirically, with adjustments made based on the agent's ability to achieve sufficient CSF concentrations. However, CSF concentrations observed for the same intraventricular dose in pharmacokinetic studies have shown considerable variability, likely attributable to differences among patients in factors such as volume of distribution, ventricular size, or variable CSF clearance due to drainage. An interesting method for adjusting doses, to ensure efficacy while minimizing toxicity, involves monitoring CSF drug concentrations. Nevertheless, currently, very few studies have evaluated drug dosage regimens based on CSF TDM. Moreover, TDM in the CSF has certain limitations, such as CSF samples may be difficult to obtain, precise thresholds for CSF TDM are not well established, drug concentrations measured in the CSF do not always accurately reflect those within the brain parenchyma, where the infection may be localized, and TDM may not be available in all health-care facilities. Together, these factors represent limitations to the implementation of CSF TDM in the clinical setting. Performing TDM in plasma for CNS infections also has certain limitations. Indeed, since the BBB restricts the passage of antibiotics from the blood into the CSF, plasma concentrations of an antibiotic do not always accurately reflect its concentration in the CSF, especially because BBB inflammation varies. As a result, the antibiotic's effective concentration in plasma may be insufficient to achieve therapeutic levels in the CSF.

8. Expert opinion

CNS infections present a significant clinical challenge due to the difficulty of achieving effective antimicrobial concentrations at the site of infection. Therefore, the selection of antimicrobial agents with proven CNS penetration and efficacy against the suspected or confirmed pathogens is crucial. As such, the authors propose an algorithm to manage CNS infections, based largely on expert opinion. However, this approach requires further validation through clinical studies to confirm its effectiveness.

In line with the WHO 2025, IDSA, and ESCMID guidelines, empirical treatment of community-acquired bacterial CNS infections, should target the common pathogens involved, such as *Streptococcus pneumoniae*, *Neisseria meningitidis and Listeria monocytogenes* [7,28,148]. Recommended regimens often involve higher-than-standard doses to ensure adequate penetration into the CNS, e.g. ceftriaxone 2 g every 12 h [30]. Additionally, antibiotics should be administered promptly in combination with IV steroids to reduce inflammatory responses and prevent neurological sequelae. The use of steroids should be continued in pneumococcal infections, as evidence suggests improved outcomes in this subgroup of patients [7]. In nosocomial or device-associated CNS infections, additional therapeutic strategies are required due to the frequent involvement of resistant organisms. When external material, such as external ventricular drains or implantable devices, is present, removal should be performed whenever feasible to reduce the local inoculum, as emphasized by the IDSA guidelines. Empirical antibiotic regimens should combine vancomycin with an antipseudomonal beta-lactam, tailored to local epidemiology and susceptibility patterns.

In our view, several challenges remain unresolved. First, in situations where pathogens show reduced susceptibility or when adequate drug concentrations cannot be achieved with systemic therapy alone, IT or IV administration and/or CI may be considered. However, robust clinical data supporting their routine use are lacking. Although this strategy is not included in current international guidelines, we propose that in methicillin-resistant *Staphylococcus aureus* (MRSA) infections, IT administration, and CI of vancomycin (targeting serum concentrations of 20–25 mg/L) may represent a therapeutic option. A similar approach may be considered for other methicillin-resistant *Staphylococcus spp.*, although the optimal vancomycin levels for such infections remain undetermined. In methicillin-susceptible *Staphylococcus* infections, IT vancomycin may also be considered as a therapeutic option to ensure adequate concentrations of antibiotics in the CSF, in combination with intravenous flucloxacillin or oxacillin given that this is a severe infection and that IT administration of vancomycin has shown its efficacy without being associated with severe or irreversible toxicity. However, there is currently a lack of robust clinical data to recommend it as a routine clinical practice. For Gram-negative infections, it is essential to identify risk factors for therapeutic failure. One major factor is augmented renal clearance (ARC) [149], which can significantly enhance beta-lactam antibiotic elimination, leading to subtherapeutic circulating drug levels and insufficient tissue penetration [150]. Risk factors for ARC include younger age, trauma, burn injuries, and low disease severity; in such patients, daily urinary creatinine clearance measurements are warranted to detect ARC [151]. Another critical risk factor is the presence of pathogens with decreased susceptibility (e.g. elevated MICs) to the selected antibiotics, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* or multi-drug-resistant organisms. In these cases, although not formally recommended in guidelines, in our expert opinion, IT administration of aminoglycosides, colistin or tigecycline, combined with CI of beta-lactams, may be necessary to achieve adequate drug concentrations in the CNS. This latter approach, utilizing higher doses of beta-lactams through continuous or extended infusions, is gaining recognition as an effective strategy for optimizing pharmacokinetic/pharmacodynamic (PK/PD) target attainment, particularly in critically ill patients [152]. In patients without ARC or in the absence of difficult-to-treat pathogens, standard daily drug regimens without IT administration may be sufficient. Based on these considerations, we propose an algorithm to treat bacterial CNS infections, which is summarized in Figure 2.

Second, therapeutic drug monitoring (TDM) is a vital tool in optimizing antibiotic dosing, particularly in critically ill patients with CNS infections, but its application in CSF is technically difficult and restricted to specialized centers. TDM ensures that therapeutic drug concentrations are achieved in the CSF, thereby maximizing the effectiveness of the treatment while minimizing the risk of systemic toxicity. This is particularly important for antibiotics with narrow therapeutic indices, such as aminoglycosides, colistin, and vancomycin, as well as for managing infections caused by multidrug-resistant (MDR) organisms. Routine TDM of plasma levels should be performed in centers equipped with the necessary resources and expertise to interpret results effectively and adjust dosing. Monitoring drug levels in the CSF may also be useful to guide antibiotic dosage regimens, but it is both rarely implemented and technically challenging. This is primarily due to the difficulty of obtaining CSF samples and the limited availability of standardized assays for measuring antibiotic

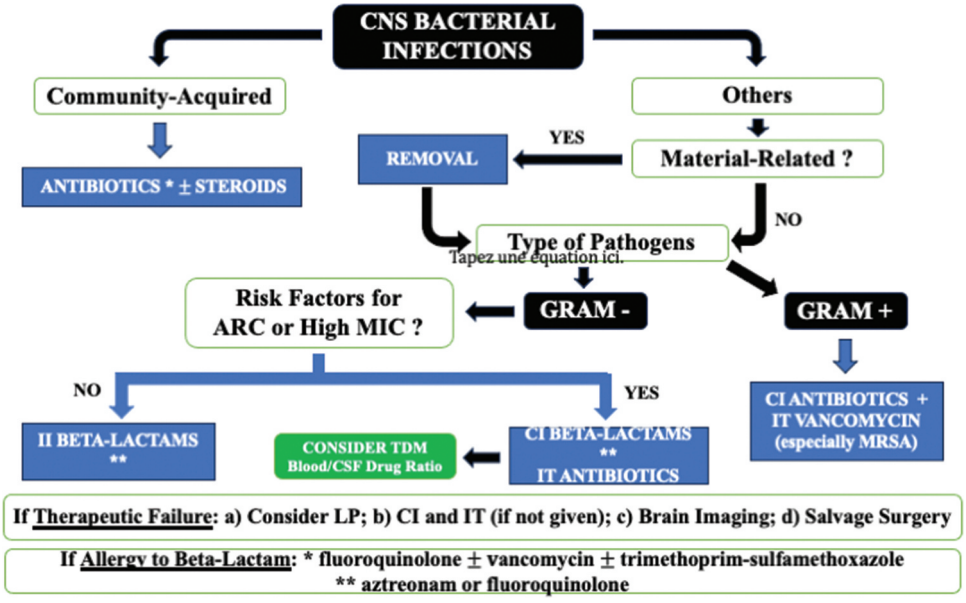

Figure 2. Proposed algorithm for the management of bacterial central nervous system infections in adult patients in Europe and North America. Proposed algorithm to manage central nervous system infections, according to the type of infection (community-acquired vs. others), the presence of infected material, the type of pathogen and the presence of risk-factors for augmented renal clearance (ARC) or for less susceptible strains (with high minimal inhibitory concentrations for the selected drug). Intrathecal administration (IT) or continuous infusion (CI) administrations are also considered. Therapeutic drug monitoring (TDM), including also drug levels measurement in the cerebrospinal fluid (CSF), are proposed for selected cases. In patients with beta-lactam allergy, additional therapeutic alternatives are discussed in the text. Abbreviations: LP = lumbar puncture; IT = intrathecal; CI = continuous infusion; ARC = augmented renal clearance; TDM = therapeutic drug monitoring; CSF = cerebrospinal fluid.

concentrations in this compartment. Consequently, CSF-level TDM is typically reserved for specialized centers with clinicians who are highly experienced in antimicrobial pharmacokinetics and pharmacodynamics. In such cases, CSF TDM can provide valuable insights for refining dosing regimens, particularly in complex cases where plasma levels may not accurately reflect therapeutic concentrations at the infection site. Given the challenges and limitations of CSF TDM, its application in clinical practice remains limited, but ongoing research is essential to expand its utility. Future studies should focus on developing standardized methods for CSF drug level measurement and identifying the clinical scenarios where CSF TDM could significantly impact patient outcomes. In the meantime, TDM should continue to be used as part of a comprehensive approach to antibiotic stewardship, ensuring optimal dosing in critically ill patients while mitigating the risks of under- or overtreatment.

9. Conclusions

Bacterial infections of the CNS in the adult, whether community-acquired or nosocomial, are associated with substantial morbidity and mortality. The widespread use of broad-spectrum antimicrobials has contributed to an increased incidence of infections caused by MDR pathogens, further complicating the management. Intrathecal antibiotic administration allows for higher therapeutic drug concentration directly at the site of infection and may provide more rapid bactericidal activity compared with intravenous therapy alone. Accordingly, combined IT and IV administration has emerged as a potential therapeutic option for CNS infections caused by resistant organisms. However, robust evidence remains limited, and further research is urgently needed to establish clinical guidelines. Key priorities include defining optimal dosing regimens for CNS infections, evaluating the efficacy of IT and continuous infusion strategies to maximize CNS drug exposure, and clarifying the role of therapeutic drug monitoring in both plasma and CSF to support individualized treatment approaches.

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