



# Pharmacokinetics and pharmacodynamics of antibiotics in central nervous system infections

Roland Nau<sup>a,b</sup>, Jana Seele<sup>a,b</sup>, Marija Djukic<sup>a,b</sup>, and Helmut Eiffert<sup>c</sup>

## Purpose of review

The barriers surrounding the central nervous system (CNS) together with the emergence of multiresistant pathogens pose a therapeutic challenge for the effective treatment of CNS infections.

## Recent findings

In addition to vancomycin, colistin and aminoglycosides, classically used for intrathecal injection, drug concentrations in cerebrospinal fluid after intrathecal injection of daptomycin and tigecyclin were recently studied.

## Summary

The entry of anti-infectives into the CNS compartments is determined by the physicochemical properties of the drug and by conditions in the host. The most important drug properties are lipophilicity at a neutral pH, molecular mass and drug binding to serum proteins. In clinical practice, active transport is of importance only for some drugs. In recent years, intrathecal injection of anti-infectives in addition to systemic therapy has regained attention as a means to achieve high cerebrospinal fluid concentrations. The classification of antibacterials and antifungals into time-dependent and concentration-dependent compounds is also valid for the CNS compartments.

## Keywords

blood–brain barrier, blood–cerebrospinal fluid barrier, cerebrospinal fluid, concentration-dependent antibiotics, time-dependent antibiotics

## INTRODUCTION

Pharmacokinetics relates to what the body does to the drug [1], whereas pharmacodynamics to what the drug does to the body – and in infectious diseases, what the drug does to the microorganisms in the infected compartment(s). Pharmacologically, the central nervous system (CNS) is divided into several compartments. These compartments are protected by a system of barriers. The barriers protect the CNS from the invasion of pathogens [2], making infections of the CNS comparatively rare events and thereby enabling the CNS to maintain conditions relatively independent of the composition of the blood. Conversely, once infectious organisms have entered the CNS, these barriers impede the entry of many drugs into the CNS, i.e. the treatment of CNS infections often poses great challenge. This is particularly the case in infections caused by penicillin-resistant pneumococci, methicillin-resistant staphylococci, *Nocardia* spp., *Acinetobacter* spp. and other multiresistant gram-negative aerobic bacilli and several fungi (e.g. *Aspergillus* spp., *Scedosporium apiospermum*) which primarily

affect the CNS in immunocompromised patients or after surgery [3]. This review aims to increase awareness of the uniqueness of the pharmacokinetics and pharmacodynamics of anti-infectives in the CNS compartments.

## METHODS

We screened all publications in PubMed from January 2015 to August 2017 identified by the following search terms:

- (1) Pharmacokinetics – cerebrospinal or meningitis or brain abscess or cerebritis

<sup>a</sup>Department of Geriatrics, Evangelisches Krankenhaus Göttingen-Weende, <sup>b</sup>Department of Neuropathology and <sup>c</sup>Department of Medical Microbiology, University of Göttingen, Göttingen, Germany

Correspondence to Roland Nau, MD, MSc, Department of Geriatrics, Evangelisches Krankenhaus Göttingen-Weende, An der Lutter 24, D-37075 Göttingen, Germany. Tel: +49 551 5034 1560; fax: +49 551 5034 1562; e-mail: rnau@gwdg.de

**Curr Opin Infect Dis** 2017, 30:000–000

DOI:10.1097/QCO.0000000000000418

## KEY POINTS

- Moderate lipophilicity, low molecular mass and low binding to plasma proteins continue to be the determinants of drug entry into the central nervous compartments.
- Due to the increasing incidence of CNS infections by highly resistant pathogens, in particular *Acinetobacter* spp., intrathecal in addition to intravenous therapy has regained attention in recent years.
- Daptomycin and tigecyclin have emerged as new compounds for intrathecal therapy with few side effects.

- (2) Pharmacodynamics – meningitis or encephalitis or brain abscess or cerebritis.

Studies published before 2010 are summarized by [3<sup>11</sup>,4<sup>11</sup>]. Details on individual compounds can be found in the Supplemental tables to [3<sup>11</sup>]. The entry of antiretroviral agents into the CNS and their complex pharmacodynamics have recently been reviewed [5<sup>11</sup>]. If not otherwise indicated, data are given as means ± SDs.

## ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS IN ANTIBIOTIC TREATMENT OF CENTRAL NERVOUS SYSTEM INFECTIONS

The main intracranial compartments are the cerebrospinal fluid (CSF) space and the extracellular and intracellular space of the brain and spinal cord (Fig. 1). Healthy adults produce approximately 500-ml CSF daily, with CSF production showing a circadian variation with a minimum at approximately 6 p.m. and nightly peak production. About two-thirds of CSF is produced by the choroid plexus in the ventricles, the other third stems from the interstitial space of the nervous tissue. The concept of 'sink action' of the CSF suggests a function similar to the lymphatic system in other tissues: the extracellular fluid (ECF) of the nervous tissue drains via the CSF space into the venous blood by means of the arachnoid granulations and along cranial and spinal nerve roots. The arachnoid granulations are protrusions of the arachnoidea through the dura mater into the venous sinuses and act as one-way valves for the entry of CSF into the venous blood without filtration; large molecules, bacteria, erythrocytes or leukocytes can pass them [7<sup>11</sup>]. The ECF of the brain does not only drain into the CSF, but also via capillary basement membranes by the pericapillary and periarterial route into the lymphatic system of

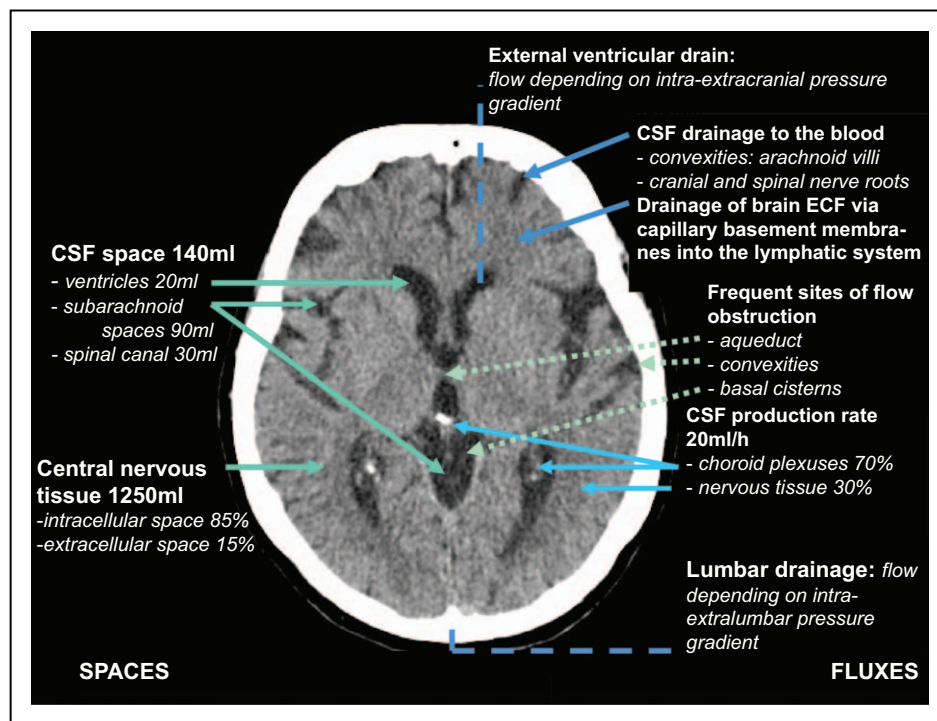
the neck, and therefore is partly separated from the CSF [8<sup>11</sup>].

The morphological correlate of the blood–brain barrier are the cells of the cerebrovascular endothelium linked by tight junctions. Between dura mater and arachnoidea, several flat cell layers are linked by tight junctions and tight gap junctions and covered by an incomplete basement membrane. In some brain regions [median eminence of the hypothalamus, area postrema at the floor of the fourth ventricle and subfornical organ at the roof of the third ventricle (approximately 1/5000 of the capillary surface) [7<sup>11</sup>]], the capillary endothelia do not possess tight junctions. Via these regions, large hydrophilic molecules, which cannot penetrate tight junctions and cell membranes, enter the interstitial space of the brain and the CSF. The morphological correlate of the blood–CSF barrier is the cylindrical epithelium of the choroid plexus linked by tight junctions [7<sup>11</sup>,9]. No tight barrier exists between the CSF and the interstitial fluid of the brain, i.e. molecules with a molecular mass of several kDa can enter the brain from the CSF space by diffusion, albeit against the direction of the flow of interstitial fluid [7<sup>11</sup>,9].

## DRUG CONCENTRATIONS IN THE CENTRAL NERVOUS SYSTEM COMPARTMENTS AFTER SYSTEMIC ADMINISTRATION

Generally, in the presence of meningeal inflammation, the CSF concentrations of drugs administered systemically are higher than with uninflamed meninges. This phenomenon is most pronounced with large hydrophilic molecules and is caused by two joint mechanisms: first, increased permeability of the blood–CSF and blood–brain barrier and, second, decreased CSF flow as a consequence of an increased CSF outflow resistance due to obstruction of the arachnoid granulations and cranial and spinal nerve sheaths. In young adults, the CSF is renewed four to five times every 24 h. With increasing age, as a consequence of brain atrophy the CSF space increases and the CSF production rate moderately declines, reducing the CSF turnover to three times a day at the age of 77 years [10]. In conjunction with the age-related decline of renal function, the reduced CSF turnover rate tends to increase CSF drug concentrations in old age.

Due to the complexity of the mechanisms involved, CSF concentrations in individual patients with CNS infections are barely predictable. For this reason, drug concentrations and areas under the concentration–time curves (AUC) in serum (AUC<sub>Serum</sub>) and CSF (AUC<sub>CSF</sub>) as well as AUC ratios



**FIGURE 1.** The intracranial fluid compartments illustrated on a normal cranial computer tomogram. The different spaces and their average volumes are listed on the left side. The volumes of these spaces vary greatly. They depend on age, skull volume, genetic factors and underlying diseases. Tight diffusional barriers with active inward and outward transport systems separate blood and brain tissue (blood–brain barrier) and blood and cerebrospinal fluid (blood–cerebrospinal fluid barrier). The cerebrospinal fluid and the extracellular fluid of the brain are not separated by a tight barrier. The arachnoid granulations allow the passage of bacteria and red and white blood cells from cerebrospinal fluid to blood. The cerebrospinal fluid space and the interstitial space of the nervous tissue are no homogeneous compartments: the concentrations of a drug in ventricular and lumbar cerebrospinal fluid can strongly differ. The sites of cerebrospinal fluid production and drainage are listed on the right side. Cerebrospinal fluid flow has a circadian rhythm and depends on underlying diseases, blood and intracranial pressure and drugs influencing the activity of the choroid plexus or the permeability of the blood–brain barrier. In addition to physiological drainage sites, external ventricular and lumbar catheters are also symbolized: in many pharmacokinetic studies, cerebrospinal fluid was drawn from in-dwelling catheters. Regions where the cerebrospinal fluid flow is often interrupted in diseases are also depicted. Blockade of the cerebrospinal fluid flow can separate the cerebrospinal fluid space in different compartments. The average volumes and fluxes were taken from Davon *et al.* (1987). The host-dependent determinants of cerebrospinal fluid kinetics of an anti-infective make it very difficult to predict the course of the concentration–time curves in the cerebrospinal fluid of individual patients. The cranial computer tomogram was kindly provided by Dr Johannes Gossner, Department of Radiology, Evangelisches Krankenhaus Göttingen-Weende, Germany. Modified from [6].

( $AUC_{CSF}/AUC_{Serum}$ ) measured in patients in the absence of meningeal inflammation, are of great importance (Table 1). They represent the minimum concentrations which can be encountered in CNS infections, particularly at the beginning or during resolution of inflammation.

### Beta-lactam antibiotics

Based on the measurement of plasma and CSF levels in an adult, intravenous (i.v.) administration of 2 g of flucloxacillin every 4 h (daily dose 12 g) resulted in a maximum CSF concentration of 0.3 mg/l [11], which is close to the minimal

inhibitory concentration ( $MIC_{50}$ ) of methicillin-susceptible *Staphylococcus aureus*.

In five patients with external ventriculostomy, after i.v. administration of 600-mg ceftaroline every 12 h (one patient received 300 mg twice daily because of impaired renal function), maximum CSF concentrations of  $0.07 \pm 0.05$  mg/l were observed. The trough concentrations of  $0.04 \pm 0.06$  mg/l were unable to inhibit the growth of methicillin-susceptible and methicillin-resistant staphylococci, but killed a *Streptococcus pneumoniae* strain *in vitro*. The mean ceftaroline CSF penetration in the absence of CNS infections, assessed as  $AUC_{CSF}/AUC_{Serum}$  after at least two doses, was  $0.011 \pm 0.010$  [12], which is

**Table 1.** Approximate cerebrospinal fluid penetration and clinical use of different classes of antibiotics

Antibiotic class and mode of action T – time-dependent killing C – concentration-dependent killing B – bacteriostatic	Uninflamed or mildly inflamed meninges AUC <sub>CSF</sub> /AUC <sub>Serum</sub>	Strong meningeal inflammation AUC <sub>CSF</sub> /AUC <sub>Serum</sub>	Relation of CSF concentrations to the MICs with usual doses	Compounds with broad clinical experience for CNS infections	Comment
Penicillins T	0.02	0.2	CSF concentrations with uninflamed meninges and usual doses close to the MICs of moderately susceptible bacteria	Penicillin G, ampicillin, amoxicillin	Low toxicity, daily dose can be increased up to 1.5–20 g (ampicillin)
$\beta$ -lactamase inhibitors T	0.07	0.1	CSF concentrations with inflamed and uninflamed meninges below the concentration used <i>in vitro</i> for susceptibility testing (1– 4 mg/l)	(Subbactam)	Little experience with <i>in-vivo</i> activity in meningitis in humans. High-dose subbactam (up to 8g/day) was used successfully to treat <i>Acinetobacter meningitis</i>
Cephalosporins T	0.007–0.1	0.15	CSF concentrations with uninflamed meninges close to the MICs of moderately susceptible bacteria. Because of binding to plasma proteins, AUC <sub>CSF</sub> /AUC <sub>Serum</sub> of ceftriaxone is approx one order of magnitude lower than that of cefotaxime	Cefazolin, cefotaxime, ceftriaxone, ceftazidime cefepime, ceftiprome	Low toxicity, daily dose can be increased up to 12–24 g (cefotaxime)
Carbapenems T	0.2	0.3	CSF concentrations with uninflamed meninges close to the MICs of moderately susceptible bacteria	Meropenem	Meropenem meningitis dose 6g/ day; high proconvulsive activity of imipenem precludes its use in CNS infections
Aminoglycosides C	0.2	Not available	CSF concentrations with uninflamed meninges close to the MICs of moderately susceptible bacteria	Gentamicin, netilmicin, amikacin	High toxicity precludes strong increase of the daily dose; consider intrathecal application
Fluoroquinolones C	0.3–0.7	0.7–0.9	CSF concentrations above the MIC of susceptible bacteria with uninflamed and inflamed meninges	Ciprofloxacin, (lev)ofloxacin, moxifloxacin	Effective compounds with favorable CNS pharmacokinetics, suitable therapy for susceptible bacteria (gram-negative aerobic bacilli, <i>Listeria monocytogenes</i> )
Chloramphenicol B	0.6–0.7	0.6–0.7	CSF concentrations above the MIC of susceptible bacteria with uninflamed and inflamed meninges	Chloramphenicol	Bacteriostatic, risk of aplastic anemia, reserve antibiotic
Macrolides T	Not available	0.18	Despite adequate CSF concentrations bacteriostatic against <i>Streptococcus</i> <i>pneumoniae</i>	Erythromycin, clarithromycin	Case reports suggest effectiveness in CNS infections caused by <i>Mycoplasma</i> , <i>Chlamydia</i> and <i>Legionella</i> spp.
Tetracyclines T	0.2	0.2	CSF concentrations close to the MIC of susceptible bacteria	Doxycycline	Documented effectiveness for neuroborreliosis, neurobrucellosis and neurosyphilis
Fosfomycin T	0.2	Not available	CSF concentrations above the MIC of susceptible pathogens both with inflamed and uninflamed meninges	Fosfomycin	Reserve antibiotic for <i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i> CNS infections

Table 1 (Continued)

Antibiotic class and mode of action T – time-dependent killing C – concentration-dependent killing B – bacteriostatic	Uninflamed or mildly inflamed meninges AUC <sub>CSF</sub> /AUC <sub>Serum</sub>	Strong meningial inflammation AUC <sub>CSF</sub> /AUC <sub>Serum</sub>	Relation of CSF concentrations to the MICs with usual doses	Compounds with broad clinical experience for CNS infections	Comment
Linezolid T	0.9	Not available	CSF concentrations above the MIC of susceptible pathogens both with inflamed and uninflamed meninges	Linezolid	Reserve antibiotic for <i>S. aureus</i> and <i>Enterococcus</i> spp. CNS infections
Metronidazole C	Not available	0.9	CSF concentrations above the MIC of susceptible pathogens both with inflamed and uninflamed meninges	Metronidazole	Standard therapy for CNS infections by anaerobic bacteria
Rifamycins Rifampicin C	0.2	Not available	At high doses CSF concentrations above the MIC of susceptible pathogens both with inflamed and uninflamed meninges	Rifampicin	Standard therapy of tuberculous meningitis, favorable clinical experience with <i>S. aureus</i> and <i>S. pneumoniae</i> CNS infections
Trimethoprim Sulfamethoxazole B	0.2 0.1	0.4–0.5 0.25–0.3	With high doses CSF concentrations above the MIC of susceptible pathogens both with inflamed and uninflamed meninges	Co-trimoxazole	Reserve antibiotic for <i>L. monocytogenes</i> and <i>Toxoplasma gondii</i> CNS infections
Glycopeptides Vancomycin T	0.15	0.30	With uninflamed meninges below or close to the MICs of susceptible bacteria	Vancomycin	Standard therapy for CNS infections by methicillin-resistant <i>S. aureus</i> and multiresistant <i>S. pneumoniae</i> High CSF-to-serum ratios were determined during continuous infusion of a high vancomycin dose (60 mg/kg/h). Other reports suggest lower CSF penetration
Lipopeptides Daptomycin C	Not available	0.01	With high doses CSF concentrations close to MICs of susceptible pathogens	Daptomycin	Minimal penetration into the CSF in patients with suspected or documented meningitis or ventriculitis
Antituberculosis drugs Isoniazide Pyrazinamide Ethambutol Streptomycin Ethionamide	0.3 0.2 0.8 <sup>a</sup>	0.85	Although AUC ratios are not available for most compounds, isoniazide, pyrazinamide and ethionamide readily enter the CSF. Streptomycin behaves like other aminoglycosides	Isoniazide, pyrazinamide, ethambutol, streptomycin	Limited data suggest moderate CSF penetration of ethambutol
Antitherpesvirus nucleoside analogues Aciclovir Valaciclovir Ganciclovir Foscarnet	0.3 0.2 0.8 <sup>a</sup> 0.3	Not available 0.5	CSF concentrations above the IC of susceptible viruses both with inflamed and uninflamed meninges	Aciclovir Ganciclovir Foscarnet	High-dose intravenous aciclovir and ganciclovir are the treatment of choice for CNS infections by herpesviruses Reserve compound for cytomegalovirus CNS infections

Table 1 (Continued)

Antibiotic class and mode of action T – time-dependent killing C – concentration-dependent killing B – bacteriostatic	Uninflamed or mildly inflamed meninges AUC <sub>CSF</sub> /AUC <sub>Serum</sub>	Strong meningial inflammation AUC <sub>CSF</sub> /AUC <sub>Serum</sub>	Relation of CSF concentrations to the MICs with usual doses	Compounds with broad clinical experience for CNS infections	Comment
Antifungal drugs Flucytosine Azoles Amphotericin B	Not available	0.75 0.8 low	Fluconazole, flucytosine and voriconazole readily enter the CSF in the absence and presence of meningial inflammation and reach therapeutic levels With both conventional and liposomal amphotericin B, CSF levels are low	Fluconazole, flucytosine, voriconazole, amphotericin B	Standard therapy for CNS mycoses amphotericin B, flucytosine, fluconazole, (Cryptococcus neoformans, Candida albicans; voriconazole (Aspergillus spp.). Consider concomitant intrathecal therapy with amphotericin B

AUC<sub>CSF</sub>/AUC<sub>Serum</sub>: Estimates of CSF penetration of the antibiotic class or individual compound based on available data (either AUC<sub>CSF</sub>/AUC<sub>Serum</sub> or CSF/Serum concentration ratios in steady state; single CSF/Serum concentration ratios were not considered). AUC, area under curve; CNS, central nervous system; CSF, cerebrospinal fluid; IC<sub>50</sub>, inhibitory concentration; MIC, minimal inhibitory concentration. Modified from Supplemental Tables 1, 1–4, and 2 of Ref. [3<sup>■</sup>] and Tables of Ref. [4<sup>■</sup>] and few recent data cited in the text.  
<sup>a</sup>Extracellular fluid of the brain: microdialysis data from a patient with glioblastoma.

close to the AUC<sub>CSF</sub>/AUC<sub>Serum</sub> observed with other beta-lactam antibiotics [3<sup>■</sup>].

### Fluoroquinolones

After intravenous moxifloxacin in a patient with CSF shunt infection, the ratio of the AUC<sub>CSF</sub> to the AUC<sub>Serum</sub> was 0.7, indicating excellent CSF penetration [13<sup>■</sup>]. This is in accordance with older studies on ciprofloxacin, (lev)ofloxacin and moxifloxacin in the absence or presence of meningeal inflammation [3<sup>■</sup>]. **Fluoroquinolones remain the group of antibacterials with the highest percentage of CSF penetration; however, their antibacterial activity is not ideal for the treatment of community-acquired CNS infections, and their neurotoxicity limits dosage increases for moderately susceptible pathogens.**

### Vancomycin

In postoperative neurosurgical patients after i.v. vancomycin administration, the CSF **albumin level as an indicator of an impairment of the blood–CSF barrier strongly determined CSF vancomycin concentrations** [14]. Patients with external ventriculostomy had significantly lower trough concentrations of vancomycin (5.8 ± 3.3 mg/l) than patients in the nondrainage group (9.9 ± 5.4 mg/l, P = 0.017). High doses of vancomycin were required to achieve optimum serum and CSF vancomycin concentrations in patients with **ventricular drainage** [15<sup>■</sup>].

### Daptomycin

In six neurosurgical patients with in-dwelling external CSF shunts who had suspected or documented meningitis or ventriculitis, the entry of daptomycin into the CSF was studied after a single intravenous dose of 10 mg/kg. The maximum concentrations were 93.7 ± 17.3 mg/l in serum at 0.5 h after infusion and 0.46 ± 0.51 mg/l in CSF at 6 h after infusion. AUC<sub>CSF</sub>/AUC<sub>Serum</sub> was approximately 0.008 ± 0.007 [16]. In experimental rabbits with *S. pneumoniae* meningitis, the CSF/serum concentration ratio of daptomycin was higher (approximately 0.10 [17<sup>■</sup>]).

### Antituberculosis drugs

The entry of once-daily oral dosages of isoniazid (5 mg/kg), pyrazinamide (25 mg/kg) and rifampicin (10 mg/kg) into the CSF was studied in 100 Vietnamese patients below 15 years of age suffering from tuberculous meningitis. Whereas concentrations of isoniazid and pyrazinamide in CSF were comparable

with those in plasma, rifampicin concentrations in CSF were lower than the minimum inhibitory concentration of susceptible bacteria in all except two children. Children displayed lower plasma levels of rifampicin than adults at a dosage of 10 mg/kg. Therefore, dosages of 15–20 mg/kg were recommended for children to achieve a CSF concentration above the MIC for rifampicin-susceptible *Mycobacterium tuberculosis* strains [18<sup>\*</sup>]. CSF rifampicin concentrations correlated with plasma levels [19]. Based on a population pharmacokinetic/pharmacodynamic model, a daily rifampicin dosage of 30 mg/kg orally or 15 mg/kg intravenously was suggested for children [20]. In a study on 60 Indonesian patients with tuberculous meningitis, surviving patients had higher rifampicin plasma  $AUC_{0-6h}$ , plasma and CSF  $C_{max}$ . A rifampicin plasma  $AUC_{0-6h}$  of  $\sim 70$  mg h/l ( $AUC_{0-24h}$  of  $\sim 116$  mg h/l) and a  $C_{max}$  of  $\sim 22$  mg/l were suggested as minimum target values, thus advocating higher rifampicin doses than 450 mg, the oral standard dose of this study [21].

Rifampicin and moxifloxacin are substrates of P-glycoprotein; other relevant antituberculosis drug-exporter interactions have not been reported (available data summarized by [22<sup>\*\*</sup>]). As it remains difficult (with the exceptions isoniazid and pyrazinamide) to attain effective concentrations of antituberculosis drugs in the central nervous compartments, efflux pump inhibitors (e.g. verapamil) have been used in animal experiments to increase drug concentrations in the CNS. Another approach is the addition of an inhibitor of the efflux pump of bacteria to partially restore drug susceptibility of resistant bacterial strains *in vitro* and *in vivo*. This appears to be an option in the management of infections by multiresistant mycobacteria [23]. At present, none of these approaches are ready for use in clinical practice [22<sup>\*\*</sup>,23].

The CSF concentrations of bedaquiline, a selective inhibitor of the mycobacterial ATP synthase complex used for the treatment of multidrug-resistant tuberculosis, were undetectable despite therapeutic levels in serum during oral therapy at standard doses. This indicates that bedaquiline is among the second-line antituberculosis drugs with poor CSF penetration [24].

### Antiviral agents

Azidothymidine is actively transported out of the CNS. The conjugation of azidothymidine to ursodeoxycholic acid produced a prodrug able to elude these efflux transport systems. After nasal administration, chitosan chloride-based microparticles increased the uptake of azidothymidine-

ursodeoxycholic acid into the CSF of rats [25]. In HIV-infected patients treated with darunavir at a dosage of 600 or 800 mg/day, the median (range) of darunavir CSF concentrations was 17.08 (5.79–30.19) and 13.23 (3.47–32.98)  $\mu\text{g/l}$ , respectively. The median (range) of the darunavir CSF:plasma ratios was 0.010 (0.005–0.022) in patients receiving darunavir 600 mg/day and 0.008 (0.004–0.017) in those receiving 800 mg/day [26]. With efavirenz at dosages of 400 or 600 mg daily, CSF concentrations were 16.5 (13–21) and 19.5 (15–25)  $\mu\text{g/l}$ , respectively (geometric mean with 90% confidence intervals), levels considered adequate to inhibit HIV replication [27]. In 174 highly active antiretroviral therapy-treated HIV-infected adults, CSF concentrations of antiretroviral drugs were measured by mass spectrometry, and inhibitory quotients (CSF concentrations divided by *in-vitro* 50 and 95% inhibitory concentrations) were compared among different drugs and related to CSF HIV RNA levels. Twice-daily darunavir, once-daily darunavir and efavirenz had the highest CSF 95% inhibitory quotients (18.5, 8.2 and 6.4). Optimum treatment (CSF 95% inhibitory quotient  $>1$ ) protected from retroviral replication in the CNS as assessed by CSF viral load [28<sup>\*</sup>]. Whether high CNS penetration of antiretrovirals protects against or promotes cognitive decline (possibly as side effects of antiretroviral drugs), is unclear. In a large study in antiretroviral therapy-naive individuals, initiation of a combined antiretroviral therapy regimen with a high CNS penetration effectiveness score increased the risk of dementia, but not of opportunistic infections of the nervous system [29].

A patient suffering from a glioblastoma with an intracerebral microdialysis catheter received valganciclovir, the L-valinyl ester of ganciclovir, orally. Ganciclovir concentrations in serum and the brain ECF reached  $C_{max}$  values of 5.0 and 2.6 mg/l at 3 h,  $t_{1/2}$  values were 3.2 and 4.5 h, and plasma and brain ECF  $AUC_{0-\infty}$  values achieved 23.1 and 19.4 mg h/l, corresponding to an  $AUC_{ECF}/AUC_{Serum}$  of 0.84 [30]. In a BT4C rat glioma model, concentrations of ganciclovir were analyzed by *in-vivo* microdialysis after a single intraperitoneal dose of 25 mg/kg ganciclovir. The  $AUC_{0-5h}$  of unbound ganciclovir in blood, brain ECF and tumor ECF reached values of 26.2, 7.0 and 20.6 mg h/l, meaning that ganciclovir reached much higher concentrations in the ECF around the tumor than in the ECF of normal brain tissue. Ganciclovir is known to be poorly taken up by cells [31].

### Antifungals

Flucytosine and azoles penetrate well into the CNS, whereas amphotericin B penetration into the CNS is

poor [3<sup>22</sup>,32]. In children and adolescents with acute myeloid leukemia who received prophylactic voriconazole, the median CSF/plasma concentration ratio was 0.57 (range: 0.35–1.04), suggesting good CSF penetration [33]. In cryptococcal meningitis, amphotericin B and 5-flucytosine (and fluconazole) therapy led to the most rapid fungal clearance and lowest mortality. 5-flucytosine is not available in many countries. Amphotericin B and fluconazole appears to reduce mortality compared with amphotericin B monotherapy [34].

After i.v. infusion of the echinocandin caspofungin (molecular mass 1093.3 g/mol) in 10 pediatric hematological/oncological patients without and three with signs of CNS infection, 11 of 13 CSF levels were below the limit of detection at 0.084 mg/l. Two of three measurable concentrations (0.3 and 0.09 mg/l) were observed in patients with bacterial meningitis. This poor CNS penetration argues against the use of caspofungin for fungal CNS infections [35].

### Miscellaneous

In a patient suffering from granulomatous amebic encephalitis, the CSF miltefosine concentration upon hospital admission on day 12 was 0.4 mg/l, and the serum concentration on day 37 was 15.3 mg/l suggesting some blood–brain barrier penetration of miltefosine [36].

## DRUG CONCENTRATIONS IN THE CENTRAL NERVOUS COMPARTMENTS AFTER INTRATHECAL OR COMBINED INTRATHECAL/INTRAVENOUS ADMINISTRATION

The effectiveness of intraventricular administration of antibiotics has been documented by case reports but not by randomized studies. As only case reports of successful intrathecal treatment are likely to be reported, there probably is substantial publications bias. A randomized study comparing systemic and intraventricular therapy of gentamicin (2.5 mg once daily in infants) with systemic therapy alone in gram-negative neonatal meningitis resulted in a higher mortality in infants after intraventricular gentamicin (42.9 versus 12.5%) [37]. Therefore, intrathecal treatment should only be used as a last resort when i.v. treatment fails or is very likely to fail based on in-vitro susceptibility testing [3<sup>22</sup>]. Suggested doses and frequent side effects of intrathecal anti-infectives are listed in Table 2.

### Vancomycin

After intraventricular vancomycin administration, CSF concentrations in 13 patients depended on CSF

output and the interval between dosing and sample withdrawal, not on CSF protein, CSF leukocyte count or glucose concentration [39<sup>22</sup>]. Combined vancomycin treatment (1 g intravenously over 2 h twice daily, simultaneous intraventricular injection of 10 mg) resulted in a 1 h serum vancomycin concentration of  $46.38 \pm 33.39$  mg/l and trough serum concentration at 48 h of  $8.10 \pm 7.11$  mg/l; the CSF vancomycin peak concentrations at 0.25 h were  $382.17 \pm 421.00$  mg/l, and the 48-h trough concentrations were  $30.82 \pm 29.53$  mg/l. These concentrations highly exceeding the MICs of susceptible bacteria were achieved without apparent side effects [48].

### Daptomycin

Case reports have shown the potential of intraventricular daptomycin (5–10 mg every 24–48 h) to strongly increase CSF concentrations [42,43], thereby reliably achieving bactericidal concentrations in patients.

### Tigecycline

Tigecycline, a lipophilic compound with a molecular mass of 585.65 g/mol, is an important reserve antibiotic active against gram-positive and gram-negative bacteria including multiresistant organisms. Varying dosages (49-mg intravenously and 1-mg intraventricularly every 12 h, 45-mg intravenously and 5-mg intraventricularly every 12 h and 40-mg intravenously and 10-mg intraventricularly every 12 h) were well tolerated and effective [45<sup>22</sup>]. After a dose of 1-mg intraventricularly every 12 h, CSF peak/trough concentrations were approximately 30/0.3 mg/l, and after 10-mg intraventricularly every 12 h, approximately 250/1.6 mg [45<sup>22</sup>]. The elimination half-life of tigecyclin in CSF estimated from these data was 0.54 h (0.31–0.84 h) [median (range)]. Conversely, the elimination half-life of vancomycin after intraventricular injection ranged from 3.0–20.5 h (median = 5.2 h) [3<sup>22</sup>]. The relative short half-life of tigecyclin compared with vancomycin after intraventricular injection is probably due to the ability of tigecycline to cross the lipid layers of the blood–brain and blood–CSF barrier, whereas the large hydrophilic vancomycin primarily is eliminated by CSF bulk flow.

In a patient with meningitis caused by a pan-drug-resistant *Acinetobacter baumannii* strain, tigecycline (100 mg twice daily), meropenem (2 g thrice daily) and vancomycin (1 g twice daily) were given intravenously. As CSF cultures stayed positive for *Acinetobacter*, intraventricular therapy with

**Table 2.** Intraventricular application of antibiotics to reach effective concentrations within the central nervous system

Antibiotic	Dose in adults	Severe reported side effects	References
Gentamicin	5 (4–10) mg every 24 h	(Temporary) hearing loss, epileptic seizures, aseptic meningitis, eosinophilic CSF pleocytosis	[38 <sup>■</sup> ]
Tobramycin	5 (–10) mg every 24 h	Similar as gentamicin	[38 <sup>■</sup> ]
Amikacin	30 (5–50) mg every 24 h	(Temporary) hearing loss	[38 <sup>■</sup> ]
Streptomycin	Up to 1 mg/kg every (24–)48 h	(Temporary) hearing loss, epileptic seizures, radiculitis, transverse myelitis, arachnoiditis, paraplegia	[3 <sup>■</sup> ]
Vancomycin	10–20 mg every 24 h	(Temporary) hearing loss	[3 <sup>■</sup> ,39 <sup>■</sup> ]
Colistin (polymyxin E) base (30 000 IU = 1 mg)	250 000 IU every 12–24 h 125 000 IU (20 000–250 000 IU) every 24 h	Meningeal inflammation, with high doses epileptic seizures, loss of appetite, agitation, eosinophilia, edeme, pain, albuminuria	[3 <sup>■</sup> ,40,41 <sup>■</sup> ]
Daptomycin	5–10 mg every 24–72 h	Fever	[42,43]
Meropenem	10 mg every 12 h	None reported; beta-lactam antibiotics at high concentrations can cause epileptic seizures	[44]
Tigecycline	1 mg every 12 h and 49 mg i.v., 5 mg every 12 h and 45 mg i.v. 10 mg every 12 h and 40 mg i.v.	No severe side effects reported	[45 <sup>■</sup> ]
	2 mg every 24 h, 2 mg every 12 h, 4 mg every 24 h		[46 <sup>■</sup> ]
	3 mg every 24 h, 4 mg every 12 h		[47 <sup>■</sup> ]
Amphotericin B	0.1–0.5 mg every 24 h	Tinnitus, fever, shivering + fever, Parkinson syndrome	[3 <sup>■</sup> ]

CSF, cerebrospinal fluid; i.v., intravenous.

tigecycline was started (2 mg/day). i.v. treatment with tigecycline was continued, but meropenem and vancomycin were stopped. After 10 days with the new treatment concept, bacterial titers in CSF increased again. Then, intraventricular administration of tigecycline was increased to 2 mg twice daily and colistin (60 000 IU twice daily for 2 days, then escalated to 120 000 IU twice daily intraventricularly), also adding meropenem (2 g thrice daily, intravenously). Meningitis was finally cleared by intraventricular administration of tigecycline (4 mg/day) and concomitant therapy with i.v. tigecycline, i.v. meropenem and dexamethasone [46<sup>■</sup>]. In another patient with an intracranial infection caused by *A. baumannii*, tigecycline was given intraventricularly (3 mg/day) together with tigecycline i.v. (100 mg twice daily) and cefoperazone–sulbactam (3 g twice daily). When CSF cultures remained positive for *A. baumannii* after 6 days of treatment, the dose of intraventricular tigecycline was increased to 4 mg twice daily, resulting in negative CSF cultures within 3 days [47<sup>■</sup>]. Therefore, high-dose intraventricular tigecycline may be an option for treating bacterial meningitis caused by drug-resistant bacteria [45<sup>■</sup>–47<sup>■</sup>,49].

## Aminoglycosides

A systematic review covering the years 1946–2015 reported intrathecal doses ranging from 4 to 10-mg gentamicin daily, 5–10-mg tobramycin daily and 5–50-mg amikacin daily to be effective and well tolerated [38<sup>■</sup>]. However, the optimum dosages still remain unclear.

## PHARMACODYNAMICS OF ANTI-INFECTIVES IN THE CENTRAL NERVOUS SYSTEM

As repeated CSF punctures in most cases of human CNS infections are not indicated, pharmacodynamics studies in general are performed in experimental animals. This review includes data on pharmacodynamics of anti-infective drugs in the CNS when CSF or tissue concentrations were reported. The pharmacodynamic principles of antibacterials in CSF were elucidated in the last century [50]. The activity of many anti-infectives depends on the speed of replication of the infecting agent. In CSF or brain tissue, replication of the pathogen is often slower than in blood. The pH of the CSF in meningitis is often lower than in other body sites. Generally,

$\beta$ -lactam agents, fosfomycin, linezolid and vancomycin are time-dependent, whereas the quinolones and aminoglycosides are concentration-dependent antibiotics [50,51]. The pharmacokinetic properties of hydrophilic drugs in the CSF space (delayed drug entry and elimination), however, blur the differences between time-dependent and concentration-dependent compounds [3<sup>11</sup>,50]. Once-daily doses of aminoglycosides were as effective as multiple-daily dosage regimens in experimental meningitis models, probably because of drug-induced prolonged effects. Fluoroquinolones produced less prolonged effects in meningitis than in other infections, and in meningitis, they were slightly less effective when administered once daily. In contrast to infections at other sites, quinolone concentrations needed to continuously exceed the minimum bactericidal concentration for maximal effectiveness, i.e. in CNS infections, fluoroquinolones showed some features of time-dependent antibiotics [50,52]. Animal studies suggest that to reduce meningeal inflammation and neuronal injury caused by bacterial products it may be advantageous to administer bactericidal, nonbacteriolytic antibiotics instead of  $\beta$ -lactam antibiotics (data summarized in [53]).

In a lapine model of penicillin-resistant and cephalosporin-resistant pneumococcal meningitis, the concomitant administration of dexamethasone reduced daptomycin CSF concentrations. Low-dose (15 mg/kg/day) daptomycin was less bactericidal when dexamethasone was given concomitantly. At a high daptomycin dose (25 mg/kg/day), the coadministration of dexamethasone did not reduce the bactericidal efficacy [17<sup>1</sup>].

A single i.v. dose of 20 mg/kg liposomal amphotericin B in mice infected with *Cryptococcus neoformans* led to a profound antifungal effect and prevented fungal regrowth for at least 6 days. The terminal elimination half-life of liposomal amphotericin B in plasma and cerebrum was approximately 133 h [54]; due to the long  $t_{1/2}$ , it is difficult to assess whether amphotericin B acted as a dose-dependent or concentration-dependent antiinfective. In an observational study, intrathecal amphotericin B lipid emulsion (2.5 mg) administered once daily for 7 days in addition to systemic amphotericin B and fluconazole resulted in a reduction of mortality from 66 to 44% compared with treatment with systemic amphotericin B and fluconazole alone. Drug concentrations were not reported in this study [55<sup>1</sup>].

The maximum kill rate of cryptococci in the murine brain with liposomal amphotericin B alone was  $0.15 \pm 0.05 \Delta \log \text{CFU/g brain tissue/h}$  and with fluocytosine alone  $0.08 \pm 0.03 \Delta \log \text{CFU/g/h}$ , i.e. killing of cryptococci was approximately one order of magnitude slower than maximum killing of

bacteria by antibiotics. Cotreatment with liposomal amphotericin B and flucytosine had an additive fungicidal effect [56].

## CONCLUSION

Entry of antiinfectives into the CNS compartments is determined by the physicochemical properties of the drug or the host, or both. The most important drug properties are lipophilicity at a neutral pH, molecular mass and drug binding to serum proteins [6,52]. For many drugs, in clinical practice active transport is of minor importance. In recent years, intrathecal injection of antiinfectives in addition to systemic therapy has regained attention as a means to achieve high CSF concentrations for drugs that only poorly cross the blood–CSF barrier. The classification of antibacterials and antifungals into time-dependent and concentration-dependent compounds is also valid for the CNS compartments [50,52]. As concentration-versus-time curves in the CNS compartments lag compared with blood, for many drugs, the differences between peak and trough concentrations in the CNS are smaller than in the blood [3<sup>11</sup>]. Animal studies suggest that bactericidal nonbacteriolytic antibiotics should be administered to reduce neuronal injury [53].

## Acknowledgements

*We thank Cynthia Bunker for careful language-editing of the article.*

## Financial support and sponsorship

*R.N. received honoraria for lectures from Bayer Vital, Pfizer, Bristol-Myers Squibb, for consulting from Desitin, and research support from Novartis. J.S., H.E. and R.N. are supported by Innovationsausschuss, Gemeinsamer Bundesausschuss, Germany.*

## Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Benet LZ. Pharmacokinetic parameters: which are necessary to define a drug substance? *Eur J Respir Dis Suppl* 1984; 134:45–61.
  2. Coureuil M, Lécuyer H, Bourdoulous S, Nassif X. A journey into the brain: insight into how bacterial pathogens cross blood–brain barriers. *Nat Rev Microbiol* 2017; 15:149–159.
  3. Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood–cerebrospinal fluid/blood–brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 2010; 23:858–883.
- The review including the supplemental tables available online summarizes pharmacokinetic data of antiinfectives published before 2010 in detail.

4. Donald PR. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. *Tuberculosis (Edinb)* 2010; 90:279–292. The review summarizes pharmacokinetic data of antituberculosis agents published before 2010 in detail.
5. Decloedt EH, Rosenkranz B, Maartens G, Joska J. Central nervous system penetration of antiretroviral drugs: pharmacokinetic, pharmacodynamic and pharmacogenomic considerations. *Clin Pharmacokinet* 2015; 54:581–598. The review gives a comprehensive update on the entry of antiretroviral drugs into the central nervous system (CNS) and the consequences concerning the prevention of cognitive decline in HIV infections.
6. Djukic M, Munz M, Sörgel F, *et al.* Overton's rule helps to estimate the penetration of anti-infectives into patients' cerebrospinal fluid. *Antimicrob Agents Chemother* 2012; 56:979–988.
7. Davson H, Welch K, Segal MB. Physiology and pathophysiology of the cerebrospinal fluid. Edinburgh – London: Churchill Livingstone; 1987. A comprehensive review on the anatomy and physiology of the cerebrospinal fluid (CSF) and the exchange between blood and intracranial compartments.
8. Morris AW, Sharp MM, Albargothy NJ, *et al.* Vascular basement membranes as pathways for the passage of fluid into and out of the brain. *Acta Neuropathol* 2016; 131:725–736. The study presents new insight into the drainage of the extracellular fluid of the brain.
9. Saunders NR, Dreifuss JJ, Dziegielewska KM, *et al.* The rights and wrongs of blood–brain barrier permeability studies: a walk through 100 years of history. *Front Neurosci* 2014; 8:404.
10. Sakka L, Coll G, Chazal J. Anatomy and physiology of cerebrospinal fluid. *Eur Ann Otorhinolaryngol Head Neck Dis* 2011; 128:309–316.
11. Chew R, Woods ML. Flucloxacillin does not achieve therapeutic cerebrospinal fluid levels against methicillin-sensitive *Staphylococcus aureus* in adults: a case report and review of the literature. *Int J Antimicrob Agents* 2016; 47:229–231.
12. Stein GE, Yasin F, Smith C, *et al.* A pharmacokinetic/pharmacodynamic analysis of ceftazolin prophylaxis in patients with external ventricular drains. *Surg Infect (Larchmt)* 2015; 16:169–173.
13. Zhang B, Huang X, Fan H, *et al.* Pharmacokinetics of intravenous moxifloxacin in the cerebrospinal fluid of a patient with central nervous system shunt infection. *Diagn Microbiol Infect Dis* 2016; 84:249–251. The report gives a recent overview on the CSF penetration of moxifloxacin, the quinolone most frequently used for the treatment of neurotuberculosis.
14. Li X, Wu Y, Sun S, *et al.* Population pharmacokinetics of vancomycin in postoperative neurosurgical patients. *J Pharm Sci* 2015; 104:3960–3967.
15. Ichie T, Urano K, Suzuki D, *et al.* Influence of cerebral fluid drainage on the pharmacokinetics of vancomycin in neurosurgical patients. *Pharmazie* 2015; 70:404–409. The study demonstrates the dependence of vancomycin CSF concentrations on CSF flow.
16. Kullar R, Chin JN, Edwards DJ, *et al.* Pharmacokinetics of single-dose daptomycin in patients with suspected or confirmed neurological infections. *Antimicrob Agents Chemother* 2011; 55:3505–3509.
17. Vivas M, Force E, Tubau F, *et al.* Effect of dexamethasone on the efficacy of daptomycin in the therapy of experimental pneumococcal meningitis. *Int J Antimicrob Agents* 2015; 46:28–32. The work in experimental rabbits demonstrates that the entry of daptomycin into the CSF is reduced by concomitant dexamethasone treatment.
18. Pouplin T, Bang ND, Toi PV, *et al.* Naïve-pooled pharmacokinetic analysis of pyrazinamide, isoniazid and rifampicin in plasma and cerebrospinal fluid of Vietnamese children with tuberculous meningitis. *BMC Infect Dis* 2016; 16:144. Pharmacokinetic data advocating the application of increased doses of rifampicin in children to achieve CSF concentrations above the minimal inhibitory concentration of *Mycobacterium tuberculosis*.
19. Yunivita V, Dian S, Ganiem AR, *et al.* Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients. *Int J Antimicrob Agents* 2016; 48:415–421.
20. Savic RM, Ruslami R, Hibma JE, *et al.* Pediatric tuberculous meningitis: model-based approach to determining optimal doses of the antituberculosis drugs rifampin and levofloxacin for children. *Clin Pharmacol Ther* 2015; 98:622–629.
21. Te Brake L, Dian S, Ganiem AR, *et al.* Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis. *Int J Antimicrob Agents* 2015; 45:496–503.
22. Te Brake LHM, de Knecht GJ, de Steenwinkel JE, *et al.* The role of efflux pumps in tuberculosis treatment and their promise as a target in drug development: unravelling the black box. *Annu Rev Pharmacol Toxicol* 2017; doi: 10.1146/annurev-pharmtox-010617-052438. [Epub ahead of print] The review summarizes the present knowledge concerning the influence of efflux pumps on the concentrations of antituberculosis drugs in the CNS.
23. Pule CM, Sampson SL, Warren RM, *et al.* Efflux pump inhibitors: targeting mycobacterial efflux systems to enhance TB therapy. *J Antimicrob Chemother* 2016; 71:17–26.
24. Akkerman OW, Odish OF, Bolhuis MS, *et al.* Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. *Clin Infect Dis* 2016; 62:523–524.
25. Dalpiaz A, Fogagnolo M, Ferraro L, *et al.* Nasal chitosan microparticles target a zidovudine prodrug to brain HIV sanctuaries. *Antiviral Res* 2015; 123:146–157.
26. Di Yacovo MS, Moltó J, Ferrer E, *et al.* Antiviral activity and CSF concentrations of 600/100 mg of darunavir/ritonavir once daily in HIV-1 patients with plasma viral suppression. *J Antimicrob Chemother* 2015; 70:1513–1516.
27. Winston A, Amin J, Clarke A, *et al.* ENCORE Cerebrospinal Fluid (CSF) Substudy Team; ENCORE Cerebrospinal Fluid CSF Substudy Team. Cerebrospinal fluid exposure of efavirenz and its major metabolites when dosed at 400 mg and 600 mg once daily: a randomized controlled trial. *Clin Infect Dis* 2015; 60:1026–1032.
28. Calcagno A, Simiele M, Alberione MC, *et al.* Cerebrospinal fluid inhibitory quotients of antiretroviral drugs in HIV-infected patients are associated with compartmental viral control. *Clin Infect Dis* 2015; 60:311–317. Comprehensive review on the pharmacokinetics and pharmacodynamics of antiretroviral drugs in the CNS.
29. Caniglia EC, Cain LE, Justice A, *et al.* HIV-CAUSAL Collaboration. Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. *Neurology* 2014; 83:134–141.
30. Peredo I, Helldén A, Wolmer-Solberg N, *et al.* Ganciclovir concentrations in the cerebral extracellular space after valganciclovir treatment; a case study. *BMJ Case Rep* 2015. doi: 10.1136/bcr-2014-207694.
31. Gynther M, Kääriäinen TM, Hakkarainen JJ, *et al.* Brain pharmacokinetics of ganciclovir in rats with orthotopic BT4C glioma. *Drug Metab Dispos* 2015; 43:140–146.
32. Bellmann R, Smuszkievicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. *Infection* 2017; doi: 10.1007/s15010-017-1042-z. [Epub ahead of print]
33. Kobayashi R, Sano H, Kishimoto K, *et al.* Voriconazole concentrations in cerebrospinal fluid during prophylactic use in children with acute myelogenous leukemia. *Pediatr Infect Dis J* 2016; 35:297–298.
34. Concha-Velasco F, González-Lagos E, Seas C, Bustamante B. Factors associated with early mycological clearance in HIV-associated cryptococcal meningitis. *PLoS One* 2017; 12:e0174459.
35. Strenger V, Farowski F, Müller C, *et al.* Low penetration of caspofungin into cerebrospinal fluid following intravenous administration of standard doses. *Int J Antimicrob Agents* 2017; 50:272–275.
36. Roy SL, Atkins JT, Gennuso R, *et al.* Assessment of blood–brain barrier penetration of miltefosine used to treat a fatal case of granulomatous amebic encephalitis possibly caused by an unusual *Balamuthia mandrillaris* strain. *Parasitol Res* 2015; 114:4431–4439.
37. McCracken GH Jr, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. *Lancet* 1980; 1:787–791.
38. LeBras M, Chow I, Mabasa VH, Ensom MH. Systematic review of efficacy, pharmacokinetics, and administration of intraventricular aminoglycosides in adults. *Neurocrit Care* 2016; 25:492–550. State-of-the-art summary of the evidence for the intraventricular administration of aminoglycosides.
39. Popa D, Loewenstein L, Lam SW, *et al.* Therapeutic drug monitoring of cerebrospinal fluid vancomycin concentration during intraventricular administration. *J Hosp Infect* 2016; 92:199–202. Detailed description of the pharmacokinetics of vancomycin after intraventricular and intravenous administration.
40. Cascio A, Conti A, Sinaridi L, *et al.* Postneurosurgical multidrug-resistant *Acinetobacter baumannii* meningitis successfully treated with intrathecal colistin. A new case and a systematic review of the literature. *Int J Infect Dis* 2010; 14:e572–e579.
41. Tafelski S, Wagner L, Angermair S, Deja M; ABx Study Group. Therapeutic drug monitoring for colistin therapy in severe multiresistant *Acinetobacter* intracerebral abscess: a single case study with high-dose colistin and review of literature. *SAGE Open Med Case Rep* 2017; 5:2050313X17711630. Detailed description of an intracranial infection with multiresistant *Acinetobacter* requiring combined systemic and intrathecal colistin administration.
42. Erritouni M, Ktaich N, Rahal JJ, *et al.* Use of daptomycin for the treatment of methicillin-resistant coagulase-negative staphylococcal ventriculitis. *Case Rep Med* 2012; 2012:593578.
43. Mueller SW, Kiser TH, Anderson TA, Neumann RT. Intraventricular daptomycin and intravenous linezolid for the treatment of external ventricular-drain-associated ventriculitis due to vancomycin-resistant *Enterococcus faecium*. *Ann Pharmacother* 2012; 46:e35.
44. Li X, Sun S, Wang Q, Zhao Z. Population pharmacokinetics of combined intravenous and local intrathecal administration of meropenem in aneurysm patients with suspected intracranial infections after craniotomy. *Eur J Drug Metab Pharmacokinet* 2017; doi: 10.1007/s13318-017-0422-1. [Epub ahead of print]
45. Wu Y, Chen K, Zhao J, *et al.* Intraventricular administration of tigecycline for the treatment of multidrug-resistant bacterial meningitis after craniotomy: a case report. *J Chemother* 2017; 1–4; doi: 10.1080/1120009X.2017.1338846. [Epub ahead of print] Recently published experience with the intrathecal administration of tigecycline for highly drug-resistant bacteria.

46. Lauretti L, D'Alessandris QG, Fantoni M, *et al.* First reported case of intraventricular tigecycline for meningitis from extremely drug-resistant *Acinetobacter baumannii*. *J Neurosurg* 2017; 127:370–373.  
Recently published experience with the intrathecal administration of tigecycline for highly drug-resistant bacteria.
47. Fang YQ, Zhan RC, Jia W, *et al.* A case report of intraventricular tigecycline therapy for intracranial infection with extremely drug resistant *Acinetobacter baumannii*. *Medicine (Baltimore)* 2017; 96:e7703.  
Recently published experience with the intrathecal administration of tigecycline for highly drug-resistant bacteria.
48. Chen K, Wu Y, Wang Q, *et al.* The methodology and pharmacokinetics study of intraventricular administration of vancomycin in patients with intracranial infections after craniotomy. *J Crit Care* 2015; 30: 218.e1–218.e5.
49. Mei S, Luo X, Li X, *et al.* Development and validation of an LC-MS/MS method for the determination of tigecycline in human plasma and cerebrospinal fluid and its application to a pharmacokinetic study. *Biomed Chromatogr* 2016; 30:1992–2002.
50. Lutsar I, McCracken GH, Friedland IR. Antibiotic pharmacodynamics in cerebrospinal fluid. *Clin Infect Dis* 1998; 27:1117–1127; quiz 1128–1129.
51. Scheerans C, Wicha SG, Michael J, *et al.* Concentration-response studies and modelling of the pharmacodynamics of linezolid: *Staphylococcus aureus* versus *Enterococcus faecium*. *Int J Antimicrob Agents* 2015; 45:54–60.
52. Andes DR, Craig WA. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. *Infect Dis Clin North Am* 1999; 13:595–618.
53. Nau R, Djukic M, Spreer A, *et al.* Bacterial meningitis: an update of new treatment options. *Expert Rev Anti Infect Ther* 2015; 13:1401–1423.
54. Lestner J, McEntee L, Johnson A, *et al.* Experimental models of short courses of liposomal amphotericin B for induction therapy for cryptococcal meningitis. *Antimicrob Agents Chemother* 2017; 61: pii: e00090-17. doi: 10.1128/AAC.00090-17.
55. Alvarez-Uria G, Midde M, Pakam R, *et al.* Short-course induction treatment with intrathecal amphotericin B lipid emulsion for HIV infected patients with cryptococcal meningitis. *J Trop Med* 2015; 2015:864271.  
Intrathecal amphotericin B lipid emulsion once daily for 7 days in addition to systemic amphotericin B and fluconazole resulted in a reduction of mortality from 66 to 44% compared with treatment with systemic amphotericin B and fluconazole alone.
56. O'Connor L, Livermore J, Sharp AD, *et al.* Pharmacodynamics of liposomal amphotericin B and flucytosine for cryptococcal meningoencephalitis: safe and effective regimens for immunocompromised patients. *J Infect Dis* 2013; 208:351–361.