Published in final edited form as:
Lancet Infect Dis. 2009 April ; 9(4): 245–255. doi:10.1016/S1473-3099(09)70055-6.

Management of meningitis due to antibiotic-resistant *Acinetobacter* species

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Abstract

Acinetobacter meningitis is becoming an increasingly common clinical entity, especially in the postneurosurgical setting, with mortality from this infection exceeding 15%. Infectious Diseases Society of America guidelines for therapy of postneurosurgical meningitis recommend either ceftazidime or cefepime as empirical coverage against Gram-negative pathogens. However, assessment of the pharmacodynamics of these cephalosporins in cerebrospinal fluid suggests that recommended doses will achieve pharmacodynamic targets against fewer than 10% of contemporary acinetobacter isolates. Thus, these antibiotics are poor options for suspected acinetobacter meningitis. From in vitro and pharmacodynamic perspectives, intravenous meropenem plus intraventricular administration of an aminoglycoside may represent a superior, albeit imperfect, regimen for suspected acinetobacter meningitis. For cases of meningitis due to carbapenem-resistant acinetobacter, use of tigecycline is not recommended on pharmacodynamic grounds. The greatest clinical experience rests with use of polymyxins, although an intravenous polymyxin alone is inadvisable. Combination with an intraventricularly administered antibiotic plus removal of infected neurosurgical hardware appears the therapeutic strategy most likely to succeed in this situation. Unfortunately, limited development of new antibiotics plus the growing threat of multidrug-resistant acinetobacter is likely to increase the problems posed by acinetobacter meningitis in the future.

Introduction

Acinetobacter baumannii is a nosocomial pathogen of increasing importance.[1] Outbreaks of infection with the organism have been noted in every inhabited continent in the past decade, with nosocomial pneumonia being the most common clinical manifestation.[2] Of substantial concern has been the increasing prevalence of multidrug resistance in hospital isolates of *A*

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baumannii during the past decade. The organism can possess an impressive armamentarium of resistance mechanisms—the end result being resistance to all, or almost all, commercially available antibiotics.[2]

The purpose of this Review is to concentrate on the entity of acinetobacter meningitis. Speciation of organisms in the genus *Acinetobacter* is sometimes difficult,[3,4] so this Review describes infection with all *Acinetobacter* spp. The epidemiology of this infection is reviewed, and management of this infection is discussed in detail. In particular, the management of infection is discussed from the standpoint of pharmacodynamics of antibiotics for infections of cerebrospinal fluid (CSF).

Clinical characteristics

Frequency of meningitis due to *A baumannii*

A baumannii seems to be an exceedingly rare cause of community-acquired meningitis, but is an increasingly important pathogen associated with postneurosurgical meningitis. In a review of six studies comprising 1737 adults with community-acquired bacterial meningitis, just 0.2% (three patients) had meningitis due to *Acinetobacter* spp.[5–10] The organism was also a rare cause of community-acquired bacterial meningitis in children.[11] By contrast, in a review of four studies comprising 281 adult patients with hospital-acquired bacterial meningitis, 3.6% (ten patients) had meningitis due to *Acinetobacter* spp.[5,7,8,12] The authors of one evaluation of children with nosocomial meningitis reported that acinetobacter accounted for 11.2% (20/178) of cases.[13] In large series in the USA and Taiwan, acinetobacter ranked the fifth most common genus to be associated with nosocomial meningitis.[5,8] However, two recent studies from Turkey have documented acinetobacter as the leading cause of Gram-negative postneurosurgical meningitis.[14,15]

Risk factors

Acinetobacter meningitis typically occurs following neurosurgery (table 1). Patients at risk for post-neurosurgical bacterial meningitis include those with cerebrospinal leakage,[63] concomitant incision infection,[63] prolonged duration of surgery,[63] surgery that enters a sinus,[64] increased severity of illness,[64,65] prolonged external ventricular drainage,[64,65] and need for repeat surgery.[66] The median time to develop acinetobacter meningitis after a neurosurgical procedure is 12 days (range 1–40 days).[58] Prior use of extended-spectrum cephalosporins was identified as a common feature of patients with acinetobacter meningitis in one study,[44] although case-control studies assessing the issue of specific antibiotic risk factors for the infection have not been done.

Clinical and laboratory features

Fever and change in conscious state are typical signs of acinetobacter meningitis.[60] Meningeal signs, focal neurological signs, and seizure are found in a minority of patients.[60] Increased CSF white blood cell counts (ranging from 100 to several thousand cells per μL) are typical,[19,21,23,27–32,35,37,44,53,58,60] with higher counts presumably found in those with delays in clinical suspicion of infection. However, cases of true infection that have no CSF white blood cells have been reported.[60] Typically, 75–100% of the white blood cells are polymorphonuclear cells.[58,60] CSF protein is almost always raised, most typically being between 150 mg/L and 200 mg/L.[58,60] CSF glucose may be normal or depressed.[58]

Pseudomeningitis

Acinetobacter spp are increasingly prevalent in the hospital environment. Although CSF is considered sterile, there is the possibility that acinetobacter may contaminate CSF during its

collection. Cases of pseudomeningitis with acinetobacter (ie, CSF is culture positive for acinetobacter in the absence of clinical and laboratory features of meningitis) have been well described.[67,68] The finding of multiple CSF specimens growing acinetobacter is highly suggestive of active CNS infection.[60]

Outcome

All-cause mortality from acinetobacter meningitis ranges from 15% to 71%.[56–61] Highest mortality rates have been observed in neonates (40% [ten of 25] with acinetobacter meningitis died)[56] and in units where large numbers of carbapenem-resistant acinetobacter were observed (71% [20 of 28] with acinetobacter meningitis died).[57] In a study, in which just one of 13 patients had a carbapenem-resistant isolate, mortality from acinetobacter meningitis was 30% (four of 13 patients died) compared with 29.4% (20 of 68 patients) from other causes of Gram-negative meningitis.[59] By contrast, all nine patients with meningitis due to carbapenem-resistant *A baumannii* died in an evaluation from a hospital where carbapenem-resistant *A baumannii* was endemic.[57] None of these nine patients received appropriate empirical therapy, defined as receipt of one or more agents active against *A baumannii* not later than 2 h after the CSF culture is obtained.[57]

Treatment

Cefepime and ceftazidime

Current recommendations from the Infectious Diseases Society of America (IDSA) regarding empirical antimicrobial therapy for postneurosurgical meningitis, are for intravenous vancomycin plus either cefepime, ceftazidime, or meropenem.[69] Published experience for ceftazidime as a treatment of acinetobacter meningitis extends to 11 patients, of whom six had a successful outcome.[33,34,37,44,59,70] The published clinical experience with cefepime for acinetobacter meningitis extends to three patients, of whom one died.[59]

Acinetobacter spp are frequently resistant to cefepime or ceftazidime. In a recent evaluation of more than 2000 acinetobacter isolates collected worldwide, 44.6% of isolates were susceptible to ceftazidime and 47.7% to cefepime.[71] When isolates were carbapenem-resistant, just 5% of the isolates were susceptible to ceftazidime or cefepime.[71] Thus, these cephalosporins are less useful as empirical agents in patients from neurosurgical units where acinetobacter meningitis is common.

Ceftazidime achieves CSF concentrations in patients with meningitis of roughly 10 μg/mL for at least 2–3 h after 30 min infusions of 2 g.[72] By contrast, in patients with non-inflammatory occlusive hydrocephalus who had undergone external ventriculostomy, maximal CSF concentrations were only 0.73–2.80 μg/mL after a 30 min infusion of 3 g ceftazidime.[73]

Given the importance of having sufficient drug exposure at the site of infection, Lodise and colleagues[74] modelled serum and CSF ceftazidime concentration-time data from a pharmacokinetic study[73] to characterise the ability of ceftazidime to penetrate into the CSF and to achieve pharmacodynamic targets (50% and 100% time above the minimum inhibitory concentration [$T_{>MIC}$]) associated with a maximal bactericidal effect for beta-lactams in plasma and CSF, respectively.[74–84] Ceftazidime was not found to penetrate into the CSF particularly well, and the median (interquartile range) penetration into the CSF, as measured by the area under the concentration-time curve $(AUC)_{CSF}/AUC_{serum}$ ratio, was 4% (2–8%). The probability of 2 g of intravenous ceftazidime every 8 h (0.5 h infusion) achieving 50% and 100% $T_{>MIC}$ in CSF only exceeded 80% for MICs of 0.5 μg/mL or less and 0.25 μg/mL or less, respectively.[74] The 6 g maximal ceftazidime daily dose, given as a continuous infusion (2 g load, then 250 mg/h as a continuous intravenous infusion) or as a prolonged infusion (2 g intravenously every 8 h, infused over 3–4 h), only modestly improved the probability of target

attainment. The probabilities of achieving 50% and 100% $T_{>MIC}$ was greater than 80% at an MIC value of 0.5 μg/mL, but was less than 70% for MIC values 1.0 μg/mL or more.

These results should be viewed as a conservative estimate, since these patients only had minimal inflammation of the meninges. Increased inflammation would facilitate greater penetration into the CSF. However, it is important to note that most nosocomial CSF infections are associated with minimal to mild disturbances in the blood–CSF barrier.[75,80,85–87] Thus, the probabilities of target attainment calculated in this study should be readily applicable to clinical practice.

Unfortunately, just 2% of acinetobacter isolates have ceftazidime MICs equal or below 0.5 μg/mL.[88–95] Therefore, these data would suggest that ceftazidime dosed at 2 g every 8 h (the dose recommended by IDSA guidelines for meningitis), even as a continuous or extended infusion, would be insufficient for the vast majority of cases of acinetobacter meningitis (table 2).

The potential efficacy of the antibiotic may be improved if an alternative dosing strategy is used (eg, use of higher daily doses administered as a continuous infusion). Nau and colleagues[73] have suggested that the daily dose of ceftazidime should be increased to 12 g/day for Gram-negative meningitis when the blood–CSF barrier is minimally impaired. It is important to note that doubling the daily dose will only increase $T_{>MIC}$ by one halflife, which is typically 1–2 h. Whereas an additional halflife will extend the $T_{>MIC}$ by roughly 12–25% for an 8 h dosing interval (intermittent dosing), its effect on the pharmacodynamic probability of target attainment profile is minimal. Even with administration of 12 g of ceftazidime as a continuous infusion, the probability of achieving 50% and 100% $T_{>MIC}$ was greater than 80% for MIC equal or below 1.0 μg/mL but was less then 70% for MIC values of 2.0 μg/mL or more. We are not aware of any clinical reports in which such dosing has been given.

Similar to ceftazidime, Lodise and colleagues[96] characterised the pharmacodynamic profile of the IDSA recommended cefepime dose for bacterial meningitis (2 g cefepime every 8 h). Using cefepime concentration-time data from a pharmacokinetic study of hospitalised patients with external ventriculostomies that received cefepime to treat an extracerebral infection,[97] the median (interquartile range) penetration of cefepime into the CSF, as measured by AUC_{CSF}/AUC_{serum} ratio was 8% (3–22%). The measured CSF cefepime concentrations ranged from 0.34 μg/mL to 11.8 μg/mL.[97] Additionally, they observed that the probability of achieving 50% and 100% $T_{>MIC}$ in the CSF only exceeded 80% for MICs equal or below 0.5 μg/mL and 0.25 μg/mL, respectively, when administering 2 g cefepime every 8 h as a 30 min infusion.[96] A higher probability of target attainment was observed with the administration of the 6 g maximal daily cefepime dose as a continuous infusion (2 g loading, then 250 mg/h as a continuous intravenous infusion) or a prolonged infusion (each dose infused over 3–4 h). However, continuous and prolonged infusions were only slightly better than intermittent dosing; the probability of achieving 50% and 100% $T_{>MIC}$ was greater than 80% at MIC value of 0.5 μg/mL but was less than 80% for MIC values equal or greater than 1.0 μg/mL.

These aforementioned probabilities of target attainment estimates are worrying in view of the acinetobacter MIC distributions from recent surveillance programmes, in which just 6–8% of acinetobacter isolates had a cefepime MIC of 0.5 μg/mL or below.[88–95] As mentioned previously, the dose of cefepime recommended in the IDSA guidelines for Gram-negative meningitis is 2 g every 8 h.[69] Clearly, this dose is likely to be inadequate for acinetobacter meningitis. Even administering cefepime as a 2 g load followed by a 6 g/day continuous or prolonged infusion, or doubling the cefepime daily dose to 12 g/day, would not substantially improve the likelihood of target attainment versus *Acinetobacter* spp.[96] Moreover, cefepime use may be limited by neurotoxicity.[98–104]

In summary, pharmacodynamic considerations would suggest that ceftazidime or cefepime would be poor choices for therapy of acinetobacter meningitis even against susceptible strains.

Carbapenems

Both imipenem and meropenem have been used in the treatment of acinetobacter meningitis. Doripenem has not yet been evaluated in meningitis, although it has in-vitro activity against many *A baumannii* strains.[105] Imipenem use appears to be problematic for meningitis due to the possibility of seizures with the high doses needed to adequately treat the infection. Indeed, clinically significant seizure activity was noted in three of 15 patients with acinetobacter meningitis treated with imipenem.[24,26,27,29,34,38,42,44] It is acknowledged that the seizures may have been a clinical manifestation of acinetobacter meningitis or an underlying neurosurgical condition, rather than being due to imipenem. Meropenem seems to be associated with a very low risk of seizure, even in the presence of meningitis.[106] In animals, doripenem also has minimal epileptogenic activity.[107]

In patients with non-inflammatory occlusive hydrocephalus who had undergone external ventriculostomy, maximal CSF concentrations of meropenem after receiving an initial 2 g meropenem dose, administered over 30 min, were 0.13–1.60 μg/mL (mean concentration 0.63 μg/mL).[108] Employing these data in a population pharmacokinetic modelling and Monte Carlo simulation analysis, Lodise and colleagues[74] reported that the median (interquartile range) penetration of meropenem into the CSF, as measured by the AUC_{CSF}/AUC_{serun} ratio was 4% (2–8%). Additionally, they showed that meropenem 2 g every 8 h as a 30 min infusion (IDSA recommended dose for bacterial meningitis) had a greater than 80% probability of achieving 50% and 100% $T_{>MIC}$ for MICs of less than or equal to 0.25 μg/mL and 0.125 μg/mL, respectively. Use of the maximal daily dose of meropenem (6 g daily) administered as a continuous infusion (2 g loading dose, then 250 mg/h as a continuous intravenous infusion) or a prolonged infusion (2 g intravenously every 8 h, each dose infused over 3–4 h) did not result in any appreciable improvement in probability of attainment; the probability of achieving 100% $T_{>MIC}$ exceeded 80% for a MIC value of 0.25 μg/mL but was less than 70% for MICs 0.5 μg/mL and higher. In recent assessments, only 27–28% of acinetobacter isolates had meropenem MICs of 0.25 μg/mL or less.[88–95]

Of concern are three reports of emergence of carbapenem resistance during carbapenem therapy.[24,29,40] It is important to note that in one of these reports the pretherapy MIC represents the susceptibility breakpoint for imipenem. This may actually increase the risk of treatment failure and the development of resistance. The mechanisms of development of carbapenem resistance are not described in these reports. Loss of outer membrane proteins has been described in *A baumannii*,[2] and it could be speculated that this may occur during carbapenem therapy of this organism. Two reports of carbapenem use for *Pseudomonas aeruginosa* have described low rates of development of carbapenem resistance during therapy with extended infusions of the antibiotic.[109,110] Given the theoretical advantages of this treatment strategy, we recommend use of extended infusion (that is, each dose administered over 3–4 h) when carbapenems are used for therapy of acinetobacter meningitis. At the present time there are insufficient data to conclude that combination therapy with an aminoglycoside reduces the risk of emergence of resistance to carbapenems.

Sulbactam

Sulbactam is of potential use in serious *A baumannii* infections given its in-vitro activity against the organism, including some carbapenem-resistant strains.[71,111] Sulbactam is available in some countries as a single agent, while in others it is available in combination with ampicillin or cefoperazone.

CSF penetration of sulbactam is variable and depends on the presence of meningeal inflammation.[112] The percentages of serum concentrations that appear in the CSF range from less than 1% in patients without meningitis to 33% in patients with meningitis.[113,114] In patients with meningitis, 1 g of sulbactam administered intravenously achieved highly variable CSF concentrations, depending on the degree of meningeal inflammation.[115] CSF concentrations in those with meningitis but less severe inflammation of the meninges (defined as CSF protein less than 1 mg/mL) were 0.65–3.50 μg/mL 90 min after a 1 g sulbactam dose.

Clinical experience with sulbactam in the treatment of acinetobacter meningitis has been mixed.[28,29,31,40,41,55,116] Jimenez-Mejias and colleagues[41] evaluated eight patients with *A baumannii* meningitis—seven treated with 2 g of ampicillin and 1 g of sulbactam every 6 h and one with the same dose administered every 8 h. Six of the seven patients on the 6-hourly schedule were cured, while the patient on the 8-hourly schedule died. All patients in this evaluation had meningeal signs and high CSF protein. Cawley and colleagues[31] reported success using an aggressive dosing strategy aimed at maximising CSF concentrations: they used 4 g of ampicillin and 2 g of sulbactam administered every 6 h for 12 doses, and then 2 g of ampicillin and 1 g of sulbactam every 3 h for 21 days. Unfortunately, CSF concentrations of sulbactam were not measured in this evaluation. There were no apparent adverse effects of this dosing strategy.

In summary, conventional sulbactam dosing (2 g of ampicillin and 1 g of sulbactam every 6 h) may only be sufficient for therapy of acinetobacter meningitis when: marked meningeal inflammation is present, and the organism is reported as susceptible using Clinical and Laboratory Standards Institute (CSLI) breakpoints (susceptible regarded as 4 μg/mL or less).[117]

Fluoroquinolones

Fluoroquinolones may sometimes be active against *Acinetobacter* spp,[118] with levofloxacin tending to have lower MICs than ciprofloxacin.[88,119] Experience with fluoroquinolones for *A baumannii* meningitis is limited to just four patients, all of whom were cured.[36,120,121] Ciprofloxacin concentrations in the CSF reach 6–37% of serum concentrations.[122]

Ciprofloxacin 400 mg every 8 h resulted in a peak plasma concentration of 10.29 μg/mL; at that time the CSF concentration was 0.91 μg/mL.[123] The estimated CSF AUC in this patient was 22 μg·h/mL.[123] It is widely regarded that the optimal plasma AUC/MIC ratio for effective killing of Gram-negative bacilli is greater than 125, for lower respiratory tract infections, wound or soft tissue infections, bacteraemia, and complicated urinary tract infections.[124] It is unknown whether the optimal CSF AUC/MIC ratio is the same for effective treatment of meningitis due to Gram-negative bacilli. Acinetobacter is considered susceptible based on CLSI breakpoints for ciprofloxacin if the MIC is 1 μg/mL or less.[117] Thus, CSF AUC/MIC ratios of greater than 125 would only occur with some susceptible isolates (that is, those with MICs of less than 0.25 μg/mL). Even higher doses of ciprofloxacin (800 mg every 8 h) have been used in treatment of meningitis due to Gram-negative bacilli. This high dose resulted in a peak CSF concentration of 2.6 μg/mL, with no seizures reported in the patient.[125]

IDSA guidelines for management of bacterial meningitis reserve ciprofloxacin for patients who have not responded to, or cannot receive, alternate antimicrobial therapy.[69] Such a concern is reinforced by the limited clinical data available for treatment of acinetobacter meningitis with ciprofloxacin. Given the pharmacodynamic issues mentioned above, we would recommend a dosing regimen of 400 mg ciprofloxacin, or higher, every 8 h if the drug was to be used for acinetobacter meningitis. 750 mg levofloxacin every 24 h offers pharmacodynamic advantages over 500 mg every 24 h.[126,127] However, this dosing schedule of levofloxacin has not been

evaluated thus far in the management of meningitis. 500 mg levofloxacin every 12 h has been successfully used in meningitis due to other organisms.[128–130]

Aminoglycosides

The poor penetration of aminoglycosides through the blood–CSF and blood–brain barrier means that intravenous administration can only result in low CSF concentrations,[131] with less than 1% of the plasma concentration appearing in the CSF.[132,133] Therefore, the contribution of aminoglycosides to a meningitis regimen largely rests upon its administration by an intraventricular route. A retrospective review of cases of Gram-negative meningitis showed that mortality was lower after intraventricular rather than after systemic therapy in both children[134] and adults.[135] There are several reports in which intraventricular aminoglycosides have been used in the therapy of acinetobacter meningitis.[21,24,25,39–41,44,47,52,53] Most of these reports involve use of intraventricular aminoglycosides in combination with systemically administered antibiotics (such as carbapenems and polymyxins). In reviewed studies, 15 of 19 (79%) patients treated with intraventricular aminoglycosides had a clinical cure of their acinetobacter meningitis.[21,24,25,39–41,44,47,52,53]

An evaluation by Rahal and colleagues[131] showed that intrathecal administration of 4 mg gentamicin typically resulted in CSF concentrations of 19–46 μg/mL. The pharmacokinetic parameter that best correlates with a positive outcome for serious infections when gentamicin is administered intravenously, is the ratio of peak serum concentration (C_{max}) to MIC (optimally the ratio should be greater than ten).[136] It is not known whether this ratio of CSF concentrations to MIC also predicts outcome in Gram-negative meningitis. However, MICs for gentamicin in susceptible strains of *Acinetobacter* spp are typically 0.5–8.0 μg/mL.[88] Thus, a peak CSF concentration to MIC ratio will likely exceed ten when MICs are 2 μg/mL or less and, quite possibly, even when MICs are 4 μg/mL or less. IDSA guidelines for therapy of bacterial meningitis recommend a daily intraventricular gentamicin dose of 4–8 mg.[69] From a pharmacodynamic perspective, higher doses would seem prudent in patients infected with organisms with MICs of 4–8 μg/mL. Using 10 mg intraventricular gentamicin, Lorber and colleagues produced peak CSF levels of 80 μg/mL.[137] Although an absence of toxicity was demonstrated in a patient with CSF peak gentamicin concentrations of 450 μg/mL,[138] others have demonstrated seizures and transient hearing loss after 10 mg intraventricular gentamicin.[139] Intrathecal gentamicin (10 mg) has been reported to produce radicular pain and myelographic arachnoiditis.[140]

Amikacin seems to have greater in-vitro activity against acinetobacter than gentamicin.[88] IDSA guidelines recommend daily intraventricular doses of amikacin of 5–50 mg, with 30 mg being the most commonly used daily dose.[69] There are few studies assessing CSF concentrations when amikacin is administered intraventricularly. In neonates, ventricular levels 2–4 h after administration of a 5 mg intraventricular amikacin dose consistently resulted in concentrations greater than 100 μg/mL.[134] In a 3-year-old child with acinetobacter meningitis, an 8 mg intraventricular amikacin dose resulted in peak amikacin levels of about 150 μg/mL.[141] Given that the MIC of amikacin against acinetobacter is usually 16 μg/mL or less,[117] a C_{max}/MIC of ten or more is likely to be achieved against most susceptible strains if these concentrations are reached. The caveat to this statement is that while a small number of studies have assessed CSF amikacin concentrations in adults,[142,143] these do not give enough information to determine true peak concentrations, and therefore the likelihood of meeting pharmacodynamic targets.

Individualisation of dosing can be achieved when using intraventricular aminoglycosides by measuring peak CSF aminoglycoside concentrations and determining the MIC of the antibiotic for the infecting strain.

Polymyxins (colistin and polymyxin B)

Polymyxins (colistin and polymyxin B) may be needed to treat meningitis due to multidrug-resistant *A baumannii*. The penetration of the polymyxins in the CSF has not been well studied. In part, this relates to difficulties in measuring concentrations of the antibiotic, since intravenous administration of colistin is actually in the form of colistin methanesulphonate (as sodium salt), a microbiologically inactive pro-drug of colistin. Very few analytical methods have been described that can differentiate these two components (colistin methanesulphonate versus colistin).[144] A bioassay has been used to measure the combined concentration of both colistin methanesulphonate and colistin;[30,32] using this assay the maximum CSF concentration of 1.25 μg/mL occurred 1 h after the administration of 1 million International Units (equal to 80 mg) of colistin methanesulphonate.[30,32] Future studies should be done with a specific high performance liquid chromatography assay.[145]

There is some published experience with intravenous colistin methanesulphonate in the treatment of acinetobacter meningitis. Eight patients have been described who were treated with intravenous colistin methanesulphonate as the sole therapeutic agent,[18,30,32,146] where all except one of the patients were cured. The doses reported were 225 mg every 8 h[18] or 1.25 mg/kg every 6 h.[30,32] Two other reports exist in which intravenous colistin methanesulphonate was given, but the therapy failed; sterilisation of the CSF was achieved only when the drug was administered by the intraventricular route.[19,26] The intravenous doses in these two cases were 2.5 million International Units (ie, 200 mg colistin methanesulfonate) every 12 h[19] and 2 million International Units (ie, 160 mg colistin methanesulfonate) every 6 h.[26]

Given these reports, and uncertainty surrounding the penetration of colistin methanesulphonate and the formed colistin into the CSF, it appears that use of intravenous colistin methanesulphonate alone for management of acinetobacter meningitis may be inadvisable. There is accumulating experience with intraventricular or intrathecal use of polymyxins. Experience before 2007 was summarised by Falagas and colleagues.[147] They reviewed 64 cases of Gram-negative meningitis in which intraventricular or intrathecal polymyxins were used. Cure was achieved in ten of 11 episodes of meningitis due to *Acinetobacter* spp. Toxicity potentially related to local administration of polymyxins was noted in 17 of 60 patients—in 12 of these meningeal irritation was reported. No irreversible toxicity was reported.[147] In a recent retrospective study of 51 cases of postsurgical meningitis due to *A baumannii*, none of eight patients treated with both intravenous and intrathecal colistin died and none developed neurotoxicity.[55]

The recommended dosage in IDSA guidelines for polymyxin B administered by the intraventricular route is 5 mg daily in adults and 2 mg daily in children.[69] The recommended dose of colistin or colistin methane-sulphonate by the intraventricular route is 10 mg daily.[69] Unfortunately, it is not clear from the guideline whether this represents colistin base activity or colistin methanesulphonate—it seems likely it is colistin methanesulphonate.

Rifampicin

Rifampicin may be useful in the therapy of multidrug-resistant *A baumannii* infections in combination with other drugs such as polymyxins,[148,149] sulbactam,[150] and carbapenems.[23,151] In vitro synergy is frequently observed between polymyxins and rifampicin.[152–154] One case has been published in which intravenous rifampicin (10 mg/kg every 12 h) was combined with intrathecal colistin (5 mg for the first day and 10 mg/day for subsequent days) for treatment of meningitis due to carbapenem-resistant *A baumannii*—sterilisation of the CSF was achieved within 72 h.[149] Given the positive experience observed with use of rifampicin-containing regimens in conditions such as tuberculous meningitis, this drug deserves consideration as part

of combination therapy in the management of meningitis due to carbapenem-resistant *A baumannii*.

Tigecycline

The pharmacokinetics of tigecycline do not support this antibiotic as a treatment for meningitis due to *A baumannii*. Penetration of tigecycline into the CSF of patients with uninflamed meninges is minimal, with mean CSF concentrations of about 0.015 μg/mL (concomitant serum concentration 0.306 [SD 0.15] μg/mL) at 90 min after a single 100 mg intravenous dose.[155] 24 h after the dose the CSF concentration was 0.025 μg/mL (0.062 μg/mL in the serum).[155] This is far below the typical MIC of tigecycline versus *A baumannii*. There is only one clinical case report of use of tigecycline in the treatment of acinetobacter meningitis,[17] and no cases in patients with meningitis in which tigecycline CSF concentrations have been measured. In the case described, multidrug-resistant acinetobacter meningitis developed after insertion of a lumbar drain in a patient with head injury and was successfully treated with tigecycline 50 mg intravenously twice daily.[17]

Duration of therapy

The IDSA guidelines for management of bacterial meningitis recommend antibiotic therapy for Gram-negative meningitis for 21 days.[69] No randomised trials have ever been done of different durations of therapy for Gram-negative meningitis. Clearly, administration of antibiotics should continue until CSF cultures are negative. Given that most patients with acinetobacter meningitis have undergone neurosurgical procedures and have readily accessible CSF via external ventricular drains, follow-up CSF cultures can be readily done. The optimal number of negative cultures to indicate successful eradication of CSF infection is not known, but it seems prudent to continue intraventricular therapy until at least three consecutive CSF cultures from separate days produce negative results.[156] Intravenous antibiotics should be used in conjunction with intraventricular therapy and should be continued after intraventricular therapy has ended.[156] In patients in whom external ventricular drains or other ready CSF access is not present, repeat lumbar puncture to sample CSF should be done after 4 days of intravenous therapy, since the median duration of therapy needed to sterilise the CSF is roughly 3 days.[18,20,24,32,35,39] If the CSF still grows acinetobacter, it would be prudent to consider changing therapy and repeating CSF culture in a further 4 days.

Adjunctive treatment with corticosteroids

At present, dexamethasone is neither recommended as a specific adjunct to antibiotic treatment of meningitis due to Gram-negative bacilli (with the exception of *Haemophilus influenzae* type B) nor for neonatal meningitis.[69,157]

Removal of shunts and other CNS devices

In a recent study by Rodriguez-Bano,[158] *A baumannii* shunt-related meningitis and other catheter-related infections were caused by biofilm-forming strains. Therefore, an important adjunct to treatment of postneurosurgical acinetobacter meningitis in patients with ventricular shunts may be shunt removal. In a review of treatment of shunt infections (of all types, not just those due to *Acinetobacter* spp), retention of the shunt resulted in poor cure rates regardless of whether there was use of intravenous antibiotics (cure rate of 24%) or use of intravenous plus intrathecal antibiotics (cure rate 40%). Combining the removal of colonised shunt hardware with immediate shunt replacement (plus use of intravenous antibiotics) cured 75% of patients. The greatest success was achieved with use of antibiotics combined with external drainage of the CSF; this cured more than 90% of patients.[159] The ventriculitis of shunt infections appears to clear more quickly with external drainage.[159] Drainage may be accomplished by externalisation of the distal end of the shunt, or, preferably, by removal of the entire shunt with

placement of a new external ventriculostomy.[159] Externalisation allows continued treatment of the underlying hydrocephalus. Placement of a reservoir in the shunting system allows CSF sampling to test for cure of the infection plus allows easy access for intraventricular antibiotic administration.[159]

Secondary infection of an external ventriculostomy or infection of other external devices also mandates complete removal of the hardware and the initiation of antibiotic therapy. If continued use of the device is required, such as the need for intracranial pressure measurement, another device should be placed at a new location.[159]

Conclusions

Unfortunately, acinetobacter meningitis is becoming an increasingly common clinical entity. More likely than not, the organism is multidrug resistant when it is encountered in intensive care units or neurosurgical wards. Unlike other body compartments, the lack of opsonins and effective phagocytosis in the CSF dictates that bactericidal levels of antibiotics are essential to ensure eradication of an infection.[156] Intraventricular antibiotics appear to have an important role in therapy of acinetobacter meningitis since MICs of antibiotics commonly used intravenously for meningitis are typically high. Thus, adequate CSF concentrations may not be attained when these antibiotics are administered intravenously. It is vital that any agent given intraventricularly be made up in a preservative-free medium to prevent toxicity.[156] Summary recommendations for treatment of acinetobacter meningitis are given in table 3. Additionally, we would recommend that antimicrobial therapy be combined with removal of all neurosurgical hardware to maximise the chances of cure of this infection. Prevention of meningitis due to multidrug-resistant *A baumannii* largely rests on prevention of cross-infection from the environment and other patients, and use of perfect technique when caring for and accessing neurosurgical devices.

Search strategy and selection criteria

The relevant studies were retrieved through searches of PubMed (January, 1980 to July, 2008) and references cited in relevant articles. The search term used in PubMed was: acinetobacter and (meningitis or ventriculitis). Studies that did not present data regarding the clinical course and therapy of acinetobacter meningitis were not included in this review. Only English language papers were reviewed in detail.

Acknowledgments

Conflicts of interest

DLP is supported by research grants from the National Institutes of Health (R01A1070896-01A1), the Centers for Disease Control and Prevention (U01 CI000283-02), AstraZeneca, Astellas, and Elan. He is a consultant to Acureon, AstraZeneca, Merck, Sanofi-Aventis, Three Rivers Pharmaceuticals, Advanced Life Sciences, and Johnson and Johnson. RN and JL are supported by research grants from the National Institutes of Health (R01A1070896-01A1). B-NK was supported by the Inje Research and Scholarship Foundation in 2007.

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Table 1

Summary of 76 patients previously reported with acinetobacter meningitis (1980–July 2008)*

	Number of patients (%)
Primary neurosurgical diagnosis	
Spontaneous intracranial haemorrhage	25 (32.9)
Traumatic head injury	18 (23.7)
Brain tumour	16 (21.1)
Others	6 (7.9)
No neurosurgical disease	11 (14.5)
Prior procedure(s)	
Craniotomy	37 (48.7)
Insertion or exchange of external ventricular drain (EVD)	33 (43.4)
Ventriculoperitoneal shunt	11 (14.5)
Insertion of lumbar drain	3 (3.9)
Others	3 (3.9)
No neurosurgical procedure	15 (19.7)
Carbapenem non-susceptibility in *Acinetobacter* spp†	37/51 (72.5)
Final antimicrobial therapy with survival rate	
Polymyxin containing regimens	20/20 (100)
Carbapenem containing regimens	12/15 (80.0)
Sulbactam containing regimens	8/12 (66.7)
Others not containing any of the above	21/29 (72.4)
Surgical therapies	
Removal of internal shunt, lumbar drain, and EVD	13 (17.1)
EVD insertion	10 (13.2)
EVD replacement	3 (3.9)
Removal of meningeal prosthesis (dura patch)	3 (3.9)
Externalisation of internal shunt	1 (1.3)
Omaya reservoir insertion	1 (1.3)
Adverse effect from antibiotic therapy	5 (6.6)
Mortality	
Overall	15/76 (19.7)
Intrathecal/intraventricular therapy including a polymyxin or aminoglycoside	3/32 (9.4)
No intrathecal/intraventricular therapy	12/44 (27.3)

Data are ranged by clinical characteristics.

*Data for this table were extracted from studies (n=76) reported from 1980 to July 2008.[16–54] A number of reviewed studies (involving 195 patients) [55–62] were not included in this table since patient specific details were not included. Duplicate patient descriptions[34,38] or cases of recurrent infection[44] are omitted from our analysis.

†In three cases for which carbapenem susceptibility changed during the course, the final results of susceptibility to carbapenem antibiotics were chosen for this table. Results of carbapenem susceptibility were not reported in 25 patients.

Table 2

Pharmacokinetic (PK) or pharmacodynamic (PD) considerations in treatment of acinetobacter meningitis*

	PK or PD parameter most predictive of efficacy	Dosing regimen	MICs (μg/mL) of antibiotic versus *Acinetobacter* spp where antibiotic is likely to be effective at this dosing regimen	Percentage of acinetobacter isolates with the breakpoint MIC based on PK or PD for CSF for each antibiotic[88]
Ceftazidime, intravenous	$T_{>MIC}$	2 g every 8 h, intravenously	≤0.5	2%
Cefepime, intravenous	$T_{>MIC}$	2 g every 8 h	≤0.5	8%
Meropenem, intravenous	$T_{>MIC}$	2 g every 8 h	≤0.25	27%
Gentamicin, intrathecal or intraventricular	C_{max}/MIC	4 mg daily	≤2	44%
Amikacin, intrathecal or intraventricular	C_{max}/MIC	30 mg daily	≤16	60%

Data are ranged by antibiotics. C_{max}=maximum concentration.

* There is insufficient information on the pharmacokinetic or pharmacodynamic parameter that best predicts efficacy of sulbactam or polymyxins versus *Acinetobacter* spp.

Table 3

Recommendations for antimicrobial therapy of patients with acinetobacter meningitis, by clinical setting

	Regimen
Empirical if risk factors for acinetobacter*	Meropenem 2 g every 8 h IV±aminoglycoside IT or IVR (4 mg gentamicin daily or 30 mg amikacin daily)
Resistant to carbapenems and other beta-lactam antibiotics	Colistin methanesulphonate IV (2.5–5 mg/kg colistin base activity[144] per day [equal to 6.67–13.3 mg/kg colistin methanesulphonate] in two to four divided doses for patients with normal renal function, depending on the severity of the infection†) or Polymyxin B IV (1.5–2.5 mg polymyxin B base per kg per day in two divided doses for adults and children with normal renal function) plus aminoglycoside IT or IVR (doses as above) with or without rifampicin IV or PO (600 mg/day)

IV=intravenous. IT=intrathecal. IVR= intraventricular. PO=oral.

*CNS abnormality; prior neurosurgery or neurosurgical procedures such as craniotomy, ventriculoperitoneal shunt insertion, ventriculostomy, and lumbar puncture; and prior use of third-generation cephalosporins.

†Recommended dosage regimens are from the product information[160,161] and not specific for acinetobacter meningitis.