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Multidrug-resistant *Acinetobacter* meningitis in neurosurgical patients with intraventricular catheters: assessment of different treatments

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***Background*: The treatment of multidrug-resistant *Acinetobacter baumannii* meningitis is a serious therapeutic problem due to the limited penetration of antibiotics into the CSF. We describe the clinical features and the outcome of a group of patients with nosocomial neurosurgical meningitis treated with different therapeutic options.**

***Methods*: All patients with nosocomial post-surgical meningitis due to *A. baumannii* diagnosed between 1990 and 2004 were retrospectively reviewed.**

***Results*: During the period of study, 51 cases of this nosocomial infection were identified. Twenty-seven patients were treated with intravenous (iv) monotherapy: carbapenems (21 cases), ampicillin/sulbactam (4 cases) and other antibiotics (2 cases). Four patients were treated with iv combination therapy. Nineteen patients were treated with iv and intrathecal regimens: colistin by both routes (8 cases), carbapenems plus iv and intrathecal (4 cases) or only intrathecal (5 cases) aminoglycosides, and others (2 cases). Seventeen patients died due to the infection. One patient died without treatment. The mean (SD) duration of therapy was 17.4 (8.3) days (range 3–44). Although no patients treated with colistin died, we did not observe statistically significant differences in the mortality among the groups with different treatments.**

***Conclusions*: Nosocomial *Acinetobacter* meningitis has a high mortality. Combined therapy with iv and intrathecal colistin is a useful and safe option in the treatment of nosocomial *Acinetobacter* meningitis.**

Keywords: nosocomial meningitis, *Acinetobacter baumannii*, colistin treatment, intrathecal colistin, neurosurgery

Introduction

Acinetobacter baumannii is an important cause of nosocomial infections including meningitis related to neurosurgical procedures or intraventricular catheters.[1,2] Recently, an increased rate of infections caused by *A. baumannii* strains resistant to the antibiotics traditionally used in this therapy has been reported.[3–7] This is an especially severe event in the case of post-surgical meningitis because the election of the antibiotic depends not only on the susceptibility of *A. baumannii*, but also on the penetration of the chosen antibiotic through the blood–brain barrier. Therefore, the aim of this study is to describe the characteristics of neurosurgical meningitis caused by *A. baumannii* emphasizing the factors influencing the outcome and to compare the efficacy of different therapeutic regimens.

Materials and methods

The study was performed at the Hospital Central de Asturias (HUCA), Oviedo and Hospital Ramon y Cajal (HRC), Madrid. Both are tertiary university hospitals with neurosurgery units and have 1200 and 1100 beds, respectively. All adult patients (age >18 years) with nosocomial post-surgical meningitis due to

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A. baumannii related to intraventricular catheters diagnosed in both hospitals between 1990 and 2004 were retrospectively reviewed. The patients were identified by reviewing the CSF cultures registered in the Microbiology laboratory.

Epidemiological data

Information about underlying diseases and isolation of other microorganisms, as well as mean time of stay before surgery, history of colonization and antibiotic treatment previous to the appearance of *A. baumannii* meningitis were obtained by reviewing the medical charts of each patient. Previous antibiotic treatment was defined as treatment for at least 48 h during the 10 days before the diagnosis of meningitis.

All patients received antibiotic prophylaxis with intravenous (iv) cefazolin (1 g every 8 h for three doses). Nosocomial meningitis was defined according to the CDC definitions.[8,9] CSF infection must have met at least one of the following two criteria: presence of an organism isolated from CSF culture and fever $>38^{\circ}C$ in the absence of another recognized cause and any of the following: increased white cells (>10 cells/mm^3 with $>50\%$ polymorphonuclear leucocytes), increased protein (>45 mg/dL) and/or decreased glucose levels (<40 mg/dL) in CSF. A positive CSF culture or Gram stain with normal levels of glucose, proteins and cell count in the absence of symptoms was considered as a contamination and discarded.[9] Patients were considered to have mixed bacterial infections when two or more microorganisms were isolated from CSF cultures. Most patients received dexamethasone (up to a maximum of 4 mg/8 h) for at least 5 days after surgery.

Microbiological studies

Samples of CSF were obtained through an intraventricular catheter if present and by lumbar puncture in the rest. Incubation, microbiological evaluation and subcultures were performed, as previously recommended.[10] The identification of *A. baumannii* was based on its growth at 37°C, 41°C and 44°C, negative oxidase and catalase reactions, motility testing and production of acid from glucose, and it was confirmed using a commercial identification system. Antimicrobial susceptibilities were tested using a microdilution commercial system. An *A. baumannii* strain was considered resistant or susceptible to the different antimicrobials according to CLSI guidelines.[11] *A. baumannii* isolates were considered susceptible to sodium colistin if their MIC was ≤ 2 mg/L and resistant if it was ≥ 4 mg/L.[11,12] An *A. baumannii* strain was considered as multiresistant if it showed resistance to four different families of antibiotics.

Evolution and treatment

An empirical antimicrobial therapy was considered as adequate if it included at least an effective antibiotic. After receiving the antibiogram results, the treatments included the following parenterally administered antibiotics: imipenem 1 g/8 h, meropenem 2 g/8 h, ceftazidime 3 g/8 h, amikacin 500 mg/8 h, ampicillin/sulbactam 3 g/8 h and colistin sulfomethate sodium 5 mg/kg/day administered in three doses. Intrathecal treatments were colistin (10 mg/12 h), gentamicin or tobramycin (both at 10 mg/24 h) or amikacin (20 mg/24 h).

Cure was achieved when two successive cultures were negative and clinical signs of infection (fever and meningismus) were absent. To assess survival, patients were followed-up until they died in the hospital or were discharged.

Statistical analyses

Continuous values were expressed as means and compared using Student's *t*-test or the Mann–Whitney *U*-test. Categorical values were expressed as absolute and relative frequencies and were compared using Fisher's exact test or χ^2 test. A P value less than 0.05 was considered as statistically significant. A binary logistic regression analysis using a stepwise (Wald) approach to determine the factors influencing the mortality of the infection and the efficacy of the different therapies was used.

Results

Epidemiological data and predisposing factors

Between the years 1990 and 2004, 51 positive CSF cultures for *A. baumannii* were found in 51 different patients (8 admitted to the HRC and the rest to the HUCA). During the period of the study, 150 cases of post-surgical meningitis were diagnosed in the HRC and 315 in the HUCA. *A. baumannii* was the responsible agent for 10.9% of the meningitis cases (5.3% for HRC and 13.6% for HUCA, respectively). Of these episodes of meningeal infection, 75% occurred in men, with a mean age of 44 ± 16 years (range 15–78). A total of 70.6% of the infections were detected in the intensive care unit (ICU) and the rest in the neurosurgical ward.

The most frequent underlying diseases were brain haemorrhage (51%), head trauma (25.5%) and brain neoplasms (23.5%). All the patients had undergone surgical procedures. The mean time that elapsed between the surgery and the onset of the infection was 25 ± 15 days (range 7–89). In 29 cases, the intraventricular catheters were connected to an Ommaya reservoir. The mean permanence of intraventricular catheter before the diagnosis of the meningeal infection was 22.7 ± 14 days (range 5–72).

Thirty-five patients had received previous antibiotic therapy for other infections. In 48 patients, seriated colonization screenings were done, and *A. baumannii* colonization was detected in 18 patients in the previous 7 days before the onset of the infection.

Clinical data

From a clinical point of view, fever was the most frequent symptom (100%), followed by a low level of consciousness (49%), headache (26%) and seizures (7.8%). Meningismus was detected in only two patients. The mean delay from the onset of the symptoms to the diagnosis of meningitis was 35 ± 16 h (range 2–72). The characteristics of CSF were white cell count 2632 ± 5551/mm^3 (range 310–36 000), protein 349 ± 167 mg/dL (range 93–891), and glucose 28 ± 15 mg/dL (range 10–74).

Microbiological data

Polymicrobial meningitis was found in 17 patients (33.3%). The other microorganisms involved were *Pseudomonas aeruginosa* (five cases), *Staphylococcus epidermidis* (five cases), *Staphylococcus aureus* (three cases), *Enterococcus faecalis* (two cases) and *Enterobacter cloacae* (two cases). The microorganism was found in the intraventricular catheter in 18 cases (35.3%). The study of susceptibilities showed different

antimicrobial resistances (Table 1). In 8 cases, the microorganism isolated was only susceptible to colistin; in 4 cases, the microorganism was susceptible to ampicillin/sulbactam and colistin; and in 13 cases, the microorganism was susceptible to carbapenems, colistin and ampicillin/sulbactam.

Treatment

All the patients had received empirical antibiotic treatments that were adequate in 42% of the cases. After receiving the antibiogram, the antibiotic therapy was reassessed and was considered inadequate in five patients. One patient died before the instauration of a definitive treatment. Twenty-seven patients received iv monotherapy with carbapenems (21 cases), ampicillin/sulbactam (4 cases), ciprofloxacin (1 case) and amikacin (1 case). In four cases, a combined parenteral therapy was used with imipenem (three cases) or ceftazidime (one patient) and aminoglycosides. Nineteen patients received a combined iv and intrathecal therapy with colistin (eight cases), iv carbapenems and iv and intrathecal (four cases) or only intrathecal (five cases) aminoglycosides, iv ceftazidime and intrathecal tobramycin (one case) and iv ampicillin/sulbactam and iv and intrathecal amikacin (one case). The mean duration of treatment was 17.4 $\pm$ 8.3 days (range 3–44). In 36 cases, treatment was associated with the removal of the intraventricular catheter. The characteristics of the treatments are shown in Table 2. The patients treated with colistin did not develop nephrotoxicity during the treatment.

Table 1. Resistances found during the study

Antibiotics	Susceptible (%)	Resistant (%)	Number of isolates studied
Ampicillin/sulbactam	10 (30%)	23 (70%)	33
Piperacillin/tazobactam	12 (30%)	29 (70%)	41
Ticarcillin	1 (7%)	13 (93%)	14
Cefotaxime	1 (5%)	17 (95%)	18
Ceftazidime	10 (15%)	54 (85%)	64
Cefepime	0 (0%)	18 (100%)	18
Imipenem	53 (83%)	11 (17%)	64
Meropenem	7 (25%)	21 (75%)	28
Gentamicin	8 (12%)	56 (88%)	64
Tobramycin	20 (31%)	44 (69%)	64
Amikacin	29 (45%)	35 (55%)	64
Ciprofloxacin	0 (0%)	53 (100%)	53
Trimethoprim/ sulfamethoxazole	11 (23%)	36 (77%)	47
Aztreonam	0 (0%)	30 (100%)	30
Tetracycline	0 (0%)	8 (100%)	8

Evolution and mortality

Brain abscesses were diagnosed by computerized tomography in 6 of 39 patients in whom head image studies were performed. A lower frequency of brain abscesses in those patients treated with carbapenems when compared with those on other therapies was observed [0 versus 6 patients, $P = 0.027$, odds ratio (OR): 1.43 (1.07–1.9)]. This finding was confirmed by the multivariate analysis [$P = 0.041$, OR: 0.076 (0.006–0.902)].

Cure of the meningeal infection was reported in 34 cases, and the remaining 17 patients died as a direct consequence of the infection (33.3%). The differential characteristics between patients who died and those who survived are shown in Table 3. Mortality was significantly associated with the lack of removal of the intraventricular catheters [$P = 0.027$, OR: 4.88 (1.27–19.48)], a high number of leucocytes in CSF (4988.35 versus 1341, $P = 0.001$), age (50 versus 40, $P = 0.037$), a longer time lapse between the onset of clinical symptoms and the diagnosis (37 versus 34 h, $P = 0.004$) and with a worse level of consciousness during meningitis (14 versus 3, $P = 0.001$, OR: 10.5 (2.462–44.781)]. The mortality was lower in patients treated with colistin iv and intrathecal [0 versus 8, $P = 0.04$, OR: 1.69 (1.32–2.16)] than in those treated with carbapenem only and in the patients on intrathecal and iv therapies than in those on exclusive parenteral treatment (3 versus 14 patients, $P = 0.073$). In contrast, the outcome of the infection was not affected by the baseline neurological disorder or the presence of polymicrobial cultures (Table 3). In the multivariate analysis, mortality was only influenced by age, leucocytes and foreign body removal (Table 3).

Discussion

A. baumannii meningitis is an infrequent infection mostly associated with intraventricular catheters, CSF fistula or head trauma.[2,13,14] Previous studies showed that *A. baumannii* was

Table 2. Characteristics of the main antibiotics used

Antibiotic therapy	No. of cases	Adequate	Duration, days (SD)	Mortality
Parenteral monotherapy				
with carbapenems	21	20	15 (6)	9 (42%)
with ampicillin/sulbactam	4	4	22.2 (5.2)	1 (25%)
Combined parenteral	4	3	14.2 (7.4)	1 (25%)
Combined (parenteral and intrathecal)				
colistin	8	8	21 (4.45)	0 (0%)
aminoglycosides+carbapenems	9	9	20.6 (11.82)	2 (22%)
No antibiotics	1	0	—	1 (100%)

Table 3. Differential characteristics between the dead and surviving patients: clinical aspects

Characteristics	Dead ($n = 17$)	Cure ($n = 34$)	Univariate analysis		Multivariate analysis *P* value
			P value	odds ratio	
Demographic characteristics					
age (years)	50 (11)	40 (17)	0.037	0.735 (0.221–2.444)	0.022
sex (male/female)	13/4	25/9	NS	NS	NS
ICU/neurosurgery	9/8	27/7	0.053	3.429 (0.969–12.137)	NS
Stay before the surgery (days)	28 (21)	23 (11)	NS	NS	NS
Underlying diseases					
haemorrhagia	13	13	0.022	5.25 (1.21–24.51)	NS
brain neoplasm	3	9	NS	NS	NS
head trauma	1	12	0.021	8.73 (0.98–198)	NS
Pure culture/mixed flora	11/6	23/11	NS	NS	NS
CSF characteristics					
leucocytes (cells/mm^3)	4988.35 (8837)	1341 (1327)	0.001	1.648 (1.417–5.171)	0.036
glucose (mg/dL)	23.24 (13.36)	31.48 (15.71)	NS	NS	NS
proteins (mg/dL)	371.7 (155)	338 (175.4)	NS	NS	NS
Treatment (yes/no)					
carbapenems	9/8	12/22	NS	NS	NS
carbapenem+intrathecal therapy	2/15	7/27	NS	NS	NS
iv colistin+intrathecal colistin	0/17	8/26	0.04	1.69 (1.32–2.16)	NS
ampicillin/sulbactam	1/16	3/31	NS	NS	NS
combined parenteral therapy	1/16	3/31	NS	NS	NS
Foreign body removal (yes/no)	8/9	27/7	0.027	4.88 (1.27–19.48)	0.007
Intrathecal treatment (yes/no)	3/14	15/19	0.073	0.271 (0.066–1.122)	NS

NS, not significant.

responsible for 4.5% of meningitis in post-surgical patients[7] and 11% in those with intraventricular catheters,[15,16] as in the present study (10.9%).

The clinical manifestations of *A. baumannii* post-surgical meningitis are unremarkable, mostly fever and progressive loss of consciousness. Therefore, these manifestations are attributed to the underlying disease, thus delaying the final diagnosis of meningeal infection and representing a prognostic factor of mortality.[16] These findings make routine CSF Gram staining and culturing imperative in all patients with intraventricular catheters or those who undergo neurosurgical procedures with low degree fever of unknown origin.

Acinetobacter is a genus with a tendance to quickly develop resistance to multiple antimicrobials. This complicates the treatment of *Acinetobacter* infections requiring the search for new agents and the return of old drugs.[3] Until the appearance of resistances, carbapenems alone or combined with amikacin was the gold standard in the treatment of these infections. However, resistance to new antibiotics in the last few years has led to the use of alternative agents such as ampicillin/sulbactam or colistin.[17] Sulbactam was introduced in the eighties as a β-lactamase inhibitor in combination with β-lactam antibiotics[6] with '*in vitro*' activity against *Acinetobacter* spp., enhanced by its affinity for penicillin-binding proteins. Only 1% of iv sulbactam penetrates the blood–brain barrier, but increases up to 32% with meningeal inflammation.[6,18] The combination of ampicillin/sulbactam has been used by some authors at doses of 2 g/6 or 8 h with mortalities of 25%, near to that reported in the present work (33.3%).[6,18]

The presence of multiresistance and the poor penetration of many drugs through the blood–brain barrier have forced the use of intrathecal therapies, initially with aminoglycosides and most recently with colistin. The use of intrathecal and iv amikacin has been reported in the treatment of meningitis refractory to standard therapy in a small number of cases with cure rates of 50% to 60%.[19,20] The exact dose of intrathecal amikacin has not been established. In our study, a 20 mg/day dose was used with a cure rate of 80% and without side effects. Our results show significant differences between the patients on iv monotherapy with carbapenem and those who also received intrathecal therapy. These findings suggest therapy by both routes, especially in cases of multiresistance.

Colistin has been reintroduced in clinical practice as a last resort for the treatment of nosocomial infections caused by multiresistant *A. baumannii*.[21–23] Its role in the treatment of meningitis was initially limited due to its poor CSF penetration (25% of serum levels), without modification in the presence of meningeal inflammation.[22,23] However, it has been used in isolated clinical cases by intrathecal and iv routes with good results.[5,21,22] The dose of intrathecal colistin is variable; most of the authors use 5 mg/12 h. In our study, doses of 10 mg/12 h were used without increasing side effects. In our series, all the patients treated with iv and intrathecal colistin survived. Although the small number of cases limits the statistical meaning of our findings, our data show that colistin can be an effective and safe alternative for this infection.

Multiresistance has led to different antimicrobial combinations being tested. Saballs *et al.*[24] studied, recently, the

combination of imipenem and rifampicin in the treatment of *Acinetobacter* infections. However, the results showed *in vitro* development of high resistance to rifampicin (70%) during the treatment, so although rifampicin has a synergistic effect with sulbactam and carbapenems,[25,26] the use of these combinations in the treatment of carbapenem-resistant *A. baumannii* requires further study. Rifampicin has shown a bactericidal effect higher than colistin in *in vitro* and in animal models. The combination of 2 million units of colistin three times a day with 600 mg of iv rifampicin/day for at least 12 days obtained cure in 64% of the patients. A higher number of clinical studies would be necessary to evaluate the efficacy and safety of the combination of colistin with carbapenems or rifampicin, which has proved useful in *in vitro* assays.[27] New antibiotics have recently appeared, such as tigecycline, a member of a new class of antibiotics, the glycylcyclines. In animal studies of meningitis, tigecycline at a dose of 20 mg/kg/day has shown CSF concentrations higher than 1 mg/L 3 h after the infusion. However, enough data regarding its ability to pass the blood–brain barrier and its future use in the treatment of meningitis are lacking.[28]

Regarding mortality, most of the series reported mortalities of 15% to 34%, similar to that found in the present series (33.3%).[2,5] The lack of removal of intraventricular catheters is associated with higher mortality. Therefore, the early removal of intraventricular devices is imperative to cure the infection. The other factor resulting in a higher mortality was the delay in starting therapy, emphasizing the value of adequate empirical treatment.

The present study has some limitations. It is a retrospective study and it shows a high variability in the prescribed antimicrobial regimens. In spite of that some interesting findings have to be underlined. First, the demonstration that the combination of iv and intrathecal colistin is as safe and effective as iv imipenem, so far the gold standard for the treatment of this infection. Secondly, the finding that the combined iv and intrathecal therapy gives better results than the iv therapy alone.

In conclusion, nosocomial meningitis caused by *A. baumannii* associated with intraventricular devices or neurosurgical procedures is an infection with high mortality. Although the appearance of resistance has complicated its treatment, the combination of intrathecal and iv colistin is an option as safe and effective as that of carbapenems.

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Transparency declarations

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