Mortality rate in patients with nosocomial *Acinetobacter* meningitis from a Brazilian hospital

ABSTRACT

Background: The mortality rate due to *Acinetobacter baumannii* nosocomial meningitis (ANM) is high. **Objective:** The aim of this study was to evaluate the factors that have influence over the outcomes in ANM patients. **Methods:** A retrospective analysis of 22 cases of ANM was conducted in a hospital with high incidence of multidrug resistance. **Results:** The mean age of patients was 43 years (21 to 91) and 54.5% were male. All ANM cases occurred within 60 days of admission and the mean duration of illness was of 18.2 days. All cases were associated with previous neurosurgical procedures: elective surgery (27.2%), external shunt (54.4%) and emergency surgery due to trauma (18.1%). Imipenem resistance was observed in 40.9% of cases, but ampicillin/sulbactam resistance was lower (27.2%). The mortality rate of ANM patients was of 72.7%. The only risk factor associated with mortality was inappropriate therapy within five days after CSF collection. All patients who survived the meningitis episode had received appropriate therapy, in contrast to only 69.2% of those who did not survive (OR = 5.15; IC = 0.45-54.01). **Conclusions:** The high mortality rate observed in our study suggests the need for aggressive empirical treatment with addition of drugs, including intrathecal therapy, where multi-resistant *A. baumannii* is endemic.

Keywords: *Acinetobacter*; meningitis; *Acinetobacter baumannii*; neurosurgery; imipenem; ampicillin/sulbactam.

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INTRODUCTION

Acinetobacter meningitis is a rare complication following neurosurgical procedures. Currently, *Acinetobacter* is the second most common agent of nosocomial meningitis in some hospitals.[1] The mortality rate is high and those who outlive the infectious episode usually have severe neurological deficits.[2] The estimated 15% mortality rate of nosocomial meningitis[3] increases to 40% if caused by *Acinetobacter*.[4] In developing countries, it can reach up to 70%.[5]

There have been no randomized controlled studies conducted to evaluate different treatments for *Acinetobacter* meningitis. The current treatment regimen is based on case reports and pharmacological data.

Intrathecal therapy remains controversial due to divergent outcomes. The aim of this study was to evaluate the risk factors associated with treatment failure of nosocomial *Acinetobacter* meningitis in a cohort from a Brazilian hospital.

METHODS

The hospital records of 22 patients diagnosed with nosocomial *Acinetobacter* meningitis admitted from January 2006 to January 2009 were retrospectively reviewed. Inclusion criteria were: (i) clinical evidence of central nervous system infection, (ii) isolation of *A. baumannii* from cerebrospinal fluid, and (iii) acquisition of the infection more than 72 hours after hospital admission. Central nervous system infection was defined as increased white cell count (> 50% polymorphonuclear leucocytes), increased protein and/or decreased glucose (< 15 g/dL) in cerebrospinal fluid. *A. baumannii* identification without cerebrospinal fluid alterations was considered contamination/colonization.[1]

Variables abstracted from the patient record, summarized in Table 1 and 2, were: gender, age, cerebrospinal fluid (number of leukocytes/mm³, glucose, and protein levels), history of trauma, presence of external shunt at the time of meningitis diagnosis, days of

Table 1. Clinical findings and cerebrospinal characteristics of 22 patients with **Acinetobacter meningitis**

Case	Age	Gender	Leukocytes (cells/mm³)	Neutrophils (%)	Lymphocytes (%)	Glucose (mg/dL)	Protein (mg/dL)	Trauma	External shunt	Outcome
#1	38	F	1536	89	11	2	1258	N	N	Death
#2	45	F	20	3	12	44	191	N	Y	Death
#3	30	M	5	0	0	40	45	Y	N	Death
#4	59	M	410	100	0	17	352	N	Y	Death
#5	38	M	18	10	0	1	92	N	Y	Death
#6	21	M	69	10	84	45	41	N	Y	Death
#7	57	F	876	70	22	73	32	N	N	Survival
#8	53	F	540	100	0	1	134	N	Y	Death
#9	23	F	350	100	0	1	43	N	Y	Death
#10	39	M	35	85	13	55	33	Y	Y	Survival
#11	40	F	53	44	56	101	94	N	Y	Death
#12	78	M	15	3	97	1	119	N	Y	Death
#13	38	M	960	60	40	38	128	N	Y	Survival
#14	25	M	12800	96	4	1	590	Y	N	Survival
#15	46	M	150	42	54	43	37	Y	Y	Death
#16	56	M	683	79	19	2	161	N	Y	Death
#17	49	M	890	89	11	55	315	N	Y	Death
#18	27	F	19	68	27	54	32	N	N	Survival
#19	91	F	9300	98	2	13	722	N	Y	Death
#20	56	M	1700	100	0	5	176	N	N	Death
#21	64	F	1250	100	0	1	428	N	Y	Death
#22	2	F	2218	95	2	56	1844	N	Y	Survival

admission before infection and total length of hospital stay, elective surgery, previous use of antibiotics, susceptibility tests for *Acinetobacter*, antibiotic therapy (intravenous and intrathecal) used, and patient outcome. *Acinetobacter baumannii* was identified using biochemical methods. Antibiotic susceptibility was assayed by diffusion disc according to CLSI.[6]

Appropriate therapy was defined as administration of one or more active agents against *A. baumannii* in adequate doses and routes of administration.

Patient outcome was deemed successful if the patient had been discharged from hospital without re-admission within the following three months. All other outcomes were considered failure.

Statistical analyses were performed using the SPSS software (version 11; Chicago, IL, USA). Distribution of variables in the surviving and non-surviving groups was assessed by χ^2 test or Fishers exact test for categorical variables, and by the Mann–Whitney test for continuous variables. Variables significantly associated with mortality in univariate analysis will be included in a binary multivariate logistic regression model.

RESULTS

In this case study, we report 22 cases of meningitis caused by *A. baumannii*. The mean age of patients was 43.6 year (21 to 91) and 54.5% were male. Cerebrospinal fluid culture grew *A. baumannii* within 60 days of admission, and the mean length of hospital stay was 18.2 days. Patients and cerebrospinal characteristics are described in Table 1. Two patients were excluded due to contamination/colonization.

All cases had previous neurosurgery procedures, including elective surgery (27.3%), external shunt (54.5%), and emergency surgery due to trauma (18.1%).

Antibiotic susceptibility pattern of isolated *A. baumannii* is described in Table 2. Susceptibility to imipenem and ampicillin/sulbactam was ascertained in 13 (59%) and 16 (73%) of the isolates, respectively. The fatality rate among ANM patients was of 72.7%. None of the evaluated risk factors was significantly associated to patient mortality. Out of 22 patients, only 17 (77.2%) received treatment, including two patients who received intrathecal therapy in addition to systemic antibiotics. The reason for abstaining from antimicrobial treatment in four cases was death

Table 2. Comparison of risk factors, antibiotic susceptibilities and outcomes of 22 patients with Acinetobacter meningitis according to their survival status

Variable	Survived (6 cases)	Died (16 cases)	All (22 cases)
Gender (male)	2 (50.0%)	10 (62.5%)	12 (54.5%)
Age (Mean with Range)	39 [27-57]	45.5 [21-91]	43 [21-91]
Days of admission before infection (Mean with Range)	12 [3-32]	17 [3-60]	16 [3-60]
Total hospitalization (Mean with Range)	50 [9-115]	30.5 [10-96]	40 [9-115]
Trauma	1 (16.6%)	3 (18.7%)	4 (18.1%)
Elective surgery	2 (33.3%)	4 (25.0%)	6 (27.2%)
After shunt	3 (50.0%)	9 (56.3%)	12 (54.5%)
Previous antibiotic use	3 (50.0%)	14 (87.5%)	17 (77.2%)
Antibiotic sensibility			
Amikacin	3 (50%)	4 (25%)	7 (31.8%)
Gentamycin	3 (50%)	4 (25%)	7 (31.8%)
Tobramycin	3 (50%)	6 (37.5%)	9 (40.9%)
Ampicillin/Sulbactam	5 (83.3%)	11 (68.8%)	16 (72.7%)
Aztreonam	2 (33.3%)	0 (0%)	2 (9.1%)
Cefepime	3 (50%)	2 (12.5%)	5 (22.7%)
Ciprofloxacin	3 (50%)	3 (18.8%)	6 (27.3%)
Imipenem	5 (83.3%)	8 (50.0%)	13 (59.1%)
Meropenem	5 (83.3%)	7 (43.8%)	12 (54.5%)
Piperacillin/Tazobactam	3 (50%)	5 (31.3%)	8 (36.4%)
Treatment			
Intrathecal therapy	0 (0.0%)	2 (12.5%)	2 (9.9%)
Systemic antibiotic	4 (66.6%)	13 (81.2%)	17 (77.2%)
Appropriate therapy according to antimicrobial resistance*	4 (100.0%)	9 (69.2%)	13 (59.0%)

* The percentage was calculated for all patients using systemic antibiotics.

before final culture results. Appropriate antibiotic therapy was initially administered to 100% of the surviving patients, whereas only 69% (9/16) of patients who did not survive received it. There was no significant difference between survivors or therapies (OR = 5.15; IC = 0.45-54.01). Ventricular shunts were removed from all patients with confirmed meningitis.

DISCUSSION

The mortality rate observed in this study was high (73%). Mortality rates ranging from 30%-70% have been previously reported and are generally higher in developing countries.[4,5,7,8] Studies assessing the mortality rate associated with meningitis have confirmed higher mortality rates associated with *Acinetobacter* as compared to other Gram-negative bacilli.[4,9]

Treatment of *A. baumannii* is an issue of concern, specifically because of the increasing prevalence of carbapenem resistance and colistin and polymyxin use. In our study, treatment with carbapenem would have failed in more than 40% of cases. The reason for the failure attributed to carbapenems is not clear. *A. baumannii* showed increased susceptibility to sulbactam. In our hospital, all strains were routinely tested using the diffusion disc assay for polymyxin susceptibility, but this method is not reliable. Sulbactam is an effective drug against *Acinetobacter*, as confirmed by in vitro and in vivo studies, as well as by several clinical trials.[10] However, physicians continue to avoid this drug, preferring colistin/polymyxin. Resistance to polymyxins is rare, even in a hospital with high incidence of carbapenem-resistant *P. aeruginosa*, although some cases have been published.[11]

Polymyxins penetrate the cerebrospinal fluid and produce sustained bactericidal concentrations. Intrathecal therapy further improves patient outcomes.[12] Association of antibiotics have been suggested to improve patient outcome, but the literature regarding this issue is scarce.[7,13-15] Rifampicin and aminoglycosides are drugs that can be used in association with polymyxins or carbapenems.

Tigecycline is a therapeutic option; however, its effectiveness for meningitis has not been studied yet. Wadi and Rub published an ANM case successfully treated with tigecycline.[16] Pharmacokinetic and pharmacodynamic data indicate that tigecycline blood concentrations seem to be suboptimal for exerting maximal antibacterial activity at this compartment. Aggressive treatment of *A. baumannii* meningitis using a multidrug regimen, including intrathecal therapy, appears to be indicated. In our study, only two patients were treated with intrathecal therapy. This could be one explanation for the high mortality rate. In a recent review, intrathecal plus systemic therapy was recommended for treatment of ANM patients.[17]

Risk factors are important in predicting the outcomes of ANM patients. A case-control study showed a higher incidence of hydrocephaly in patients with *Acinetobacter*.[8] Although not technically defined as a risk factor, previous colonization with *Acinetobacter* is thought to increase risk of developing ANM.[18-20] In our institution, *A. baumannii* is the most common cause of ventilator-associated pneumonia and is commonly isolated from several sites in the patient.

In conclusion, *Acinetobacter* meningitis is a hazardous infection in neurosurgery units. Actions aiming at reducing post-surgery or shunt infection must be evaluated routinely. The high mortality rate observed in our study suggests the need for treatment with active agents against *Acinetobacter*, especially in settings where this microorganism is endemic. It is also recommended the addition of intrathecal therapy after identification of the bacterium. Prospective trials with intrathecal and intravenous colistin could help defining an appropriate therapy for *A. baumannii* meningitis.

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