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Does antimicrobial usage before meningitis lead to a higher risk of adult postsurgical *Acinetobacter baumannii* meningitis than that of Enterobacteriaceae meningitis?

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SUMMARY

Acinetobacter baumannii and Enterobacteriaceae are two pathogens responsible for postneurosurgical meningitis. The aim of this retrospective study was to evaluate the factors that influenced the outcomes in patients with postneurosurgical meningitis caused by *A. baumannii* and Enterobacteriaceae. Patients with post-surgical meningitis were identified from infection control committee charts between 2007 and 2015. Subjects over 16 years old who had positive cerebral spinal fluid cultures for *A. baumannii* or Enterobacteriaceae were enrolled in the study. Clinical and laboratory data for 30 patients with *A. baumannii* meningitis were compared with those of 12 patients with Enterobacteriaceae meningitis. The mean age of patients was 51.9 years and 57.1% were male. Eleven patients had comorbidities, the most common being diabetes mellitus. Most patients were due to intracranial haemorrhage (78.6%). The rate of the patients who received an appropriate antimicrobial therapy was 35.7%, and the crude mortality rate was 64.3%. In univariate analysis, previous antibiotic use, an infection before meningitis and mechanical ventilation had an increased risk of *A. baumannii* meningitis. Moreover, intrathecal antimicrobial use, inappropriate empirical antimicrobial use, antimicrobial resistance and alanine aminotransferase elevation were significantly higher in patients with *A. baumannii* meningitis than in those with Enterobacteriaceae meningitis. Antimicrobial use before meningitis (8.84 times) and mechanical ventilation (7.28 times) resulted in an increased risk of *A. baumannii* meningitis. None of the results affected 30-day mortality. Avoidance of unnecessarily prolonged antimicrobial usage may help to prevent a selection of *A. baumannii*.

Keywords: Multidrug resistant Gram negative, intracranial haemorrhage, post-surgical meningitis, *Acinetobacter baumannii*, Enterobacteriaceae.

INTRODUCTION

Trauma and neurosurgery lead to increase the number of inflammatory cells in the cerebrospinal fluid (CSF), and it is difficult to discriminate between bacterial meningitis and sterile inflammation [1]. Diagnosis of postoperative meningitis is troublesome; moreover, early and appropriate antimicrobial treatment is crucial for the patients. Incidence of postoperative meningitis is variable (0.5-8%). The most common causative pathogens in the intensive care unit (ICU) are Gram negative bacteria (GNB) [2]. In recent years, the frequency of Acinetobacter infections has increased in ICU due to intensive antibiotic

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use and the selection of resistant microorganism [1]. Surgical procedures and accordingly carbapenem use for post-surgical meningitis have risen. For many years, the most common causative GNB agent has been *A. baumannii*; however, all *Acinetobacter baumannii* strains have a chromosomal resistance gene such as OXA-51, and it can develop carbapenem resistance easily [3, 4]. An appropriate initial antimicrobial therapy for post-neurosurgical meningitis caused by GNB is important in terms of mortality [5]. The other common agents are Enterobacteriaceae whose detection is increased after extra ventricular drainage [6]. To date, there are limited data on post-surgical Enterobacteriaceae meningitis and there are no data on the comparison of the risk factors and outcomes of post-surgical *A.baumannii* and Enterobacteriaceae meningitis.

PATIENTS AND METHODS

Definitions *A. baumannii* meningitis was defined as described previously [3]. Enterobacteriaceae meningitis was defined as having clinical and laboratory features of acute meningitis accompanying isolation of Enterobacteriaceae in one or more CSF cultures. Contamination was defined as growth of a Gram negative bacillus from a CSF sample in a patient without clinical features of meningitis, who did not deteriorate in the absence of three days or more of appropriate antibiotic treatment and repeated CSF sampling did not result in isolation of a Gram negative bacillus [3]. Thirty-day mortality was categorized as meningitis attributable, if mortality was caused by meningitis or its complications [7]. Cure was defined as complete resolution of the signs and symptoms of meningitis. Treatment failure was defined as death by meningitis or a relapse of GNB meningitis. Appropriate antimicrobial therapy was defined as use of one or more active agents against the strains, given adequate dose and route of administration.

Patients and study design

Adult patients (age ≥16 years) with a diagnosis of bacterial meningitis after a neurosurgical procedure and with the CSF cultures positive for *A. baumannii* or Enterobacteriaceae between January 2007 and May 2015 were retrospectively evaluated through the patient charts of the Infection Control Committee of Erciyes University, a 1,300-bed university hospital and tertiary referral center in Kayseri, Central Anatolia, which has 35 clinical neurosurgical beds and 14 ICU beds. Each patient was enrolled once in this study. This study was approved by the local ethics committee (2013/490).

Microbiology

The antimicrobial susceptibility test was performed by using the VITEK 2 automated system for hospital acquired Gram negative microorganism, and the Etest method was used for colistin and tigecycline according to the Clinical and Laboratory Standards Institute criteria [8].

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The chi-square or Fisher's exact test was performed for categorical variables and the Student's t-test for continuous variables, as appropriate in univariate analysis. Multivariate binary logistic regression analysis was used for selected variables. All tests were two-tailed, and a p value of <0.05 was considered significant.

RESULTS

The mean age of all patients was 51.9 years and 24 (57.1%) of them were male. The study included 42 cases of nosocomial meningitis caused by *A. baumannii* or Enterobacteriaceae. Thirty patients had *A. baumannii* meningitis, and 12 patients had Enterobacteriaceae meningitis, including *Klebsiella pneumoniae* (n=8), *Enterobacter aerogenes* (n=3) and *Serratia marcescens* (n=1). The demographic characteristics and clinical findings of the patients are shown in Table 1.

The reasons for neurosurgical procedures in all patients were subarachnoid hemorrhage in 28 patients (66.7%), subdural hematoma in five patients (11.9%), brain tumors in four patients (9.5%), cervical injury in three, and ventriculoperitoneal shunting in two.

Eleven patients had comorbidities, including diabetes mellitus (DM) in eight patients (19.0%), congestive heart failure in two, and warfarin use after mitral valve replacement surgery in one patient. There was no difference between patients with *A. baumannii* and Enterobacteriaceae in terms of co-

Table 1 - Overall characteristics of patients with nosocomial *Acinetobacter baumannii* and Enterobacteriaceae meningitis.

Characteristics	*Total, n=42, (%)*	*A. baumannii, n=30, (%)*	Enterobacteriaceae, *n=12, (%)*	*Multiple analysis*		
				p	RR (95%CI)	p
Age (years), mean (±SD)	51.9±16.1	51.4±16.2	53.3±16.4	0.736		
Gender (male)	24 (57.1)	17 (56.7)	7 (58.3)	0.921		
Comorbidity	11 (26.2)	8 (26.7)	3 (25.0)	0.825		
Diagnosis for hospitalisation						
Intracranial hemorrhagy	33 (78.6)	24 (80.0)	9 (75.0)			
Intracranial malignity	4 (9.5)	2 (6.7)	2 (16.7)			
Cervical injury	3 (7.1)	3 (10.0)	0 (0.0)	0.461		
Hydrocephalus	2 (4.8)	1 (3.3)	1 (8.3)			
Postoperative period (days)	10.9±5.7	11.8±5.9	8.7±4.8	0.109		
Presence of EVD	34 (81.0)	24 (80.0)	10 (83.3)	0.804		
Presence of mechanical ventilation	36 (85.7)	28 (93.3)	8 (66.7)	0.026	7.28 (0.85-62.18)	0.070
Presence of infection before meningitis	16 (38.1)	16 (53.3)	0 (0.0)	0.001		
Antimicrobial use before meningitis	21 (50.0)	19 (63.3)	2 (16.7)	0.007	8.84 (1.46-53.35)	0.018
Appropriate empirical antimicrobial treatment	15 (35.7)	7 (23.3)	8 (66.7)	0.008		
Intratechal antibiotic administration	14 (33.3)	13 (43.3)	1 (8.3)	0.030		
CSF sterilization (n=39)	20 (51.3)	16 (57.1)	4 (36.4)	0.209		
Sterilization time of CSF (days) n=18	5.9±2.9	6.1±3.2	5.3±1.7	0.602		
Resolving fever after treatment (n=33)	19 (57.6)	13 (54.2)	6 (66.7)	0.405		
Duration of therapy (days)	12.2±8.9	12.6±8.1	11.3±11.1	0.697		
Imipenem resistance	27 (64.3)	27 (90.0)	0 (0.0)	0.001		
Amikacin resistance	28 (66.7)	28 (93.3)	0 (0.0)	0.001		
Tigecycline resistance	5 (11.9)	4 (13.3)	1 (8.3)	0.554		
ESBL producing strains	35 (83.3)	30 (100)	5 (41.7)	0.001		
Quinolone resistance	31 (73.8)	27 (90.0)	4 (33.3)	0.001		
Mean day of mortality	19.5	22.0±17.2	13.3±11.2	0.111		
30-day mortality	27 (64.3)	18 (60.0)	9 (75.0)	0.359		

EVD: extraventricular drainage, MV: mechanical ventilation, CSF: cerebrospinal fluid, ESBL: extended spectrum beta-lactamase, CI: Confidence interval, RR: risk ratio.

morbid conditions (p=0.825). Sixteen patients had a previous infection before meningitis (nosocomial pneumonia in 13 and urinary tract infection in 2). *A. baumannii* meningitis developed in all patients with a previous infection. Although the frequency of previous infection in patients with *A. baumannii* meningitis was higher than in those with Enterobacteriaceae meningitis, the postoperative period before meningitis observed in patients with *A. baumannii* meningitis was not significantly longer than that in Enterobacteriaceae meningitis patients (11.8 vs. 8.7 days) (Table 1).

Antibacterial use before meningitis was detected in 21 patients (50%), consisting of beta-lactam beta-lactamase inhibitor combination (n=10), carbapenem (n=9) and glycopeptide (n=1) and tigecycline (n=1). The patients who received an antimicrobial treatment before meningitis and those needing mechanical ventilation (MV) had a 8.84 times and 7.28 times higher risk of *A. baumannii* meningitis (Table 1). Presence of extraventricular drainage (EVD) was not a risk factor for *A. baumannii* meningitis.

Because protein and glucose results in the CSF

could not be obtained in four cases, only microbiological analyses of CSFs were made. Control CSF samples after antimicrobial therapy were not sent in three patients (Table 2).

Gram staining of CSF samples revealed Gram negative bacilli in 25 samples and Gram positive diplococci in 2 samples. No microorganism was observed in 15 CSF samples. There was no significant difference between groups with *A. baumannii* and Enterobacteriaceae meningitis in terms of what was observed on Gram staining of the samples (p=0.615).

The common empirical antimicrobial therapies were vancomycin plus meropenem in 17 patients, meropenem alone in 7, colistin alone in 2, colistin-meropenem in 2, and meropenem plus sulbactam in 2. There was no difference between groups of patients with *A. baumannii* and those with Enterobacteriaceae meningitis in terms of empirical antimicrobial use (p=0.069). However, the rate of an appropriate antimicrobial treatment in Enterobacteriaceae group was higher than those in *A. baumannii* group (66.7% vs. 23.3%).

Three patients could not be given an appropriate antimicrobial therapy due to the fact that they died before their susceptibility tests were obtained. Moreover, 14 patients were administered intrathecal (IT) colistin (n=11) and netilmicin (n=3). The rate of IT administration was significantly higher in patients with *A. baumannii* meningitis than in those with meningitis sustained by Enterobacteriaceae (Table 1).

All Enterobacteriaceae isolates and three *A. baumannii* isolates were susceptible to imipenem. All isolates except one Enterobacteriaceae were susceptible to colistin. The rates of extended spectrum beta-lactamase (ESBL) producing strains were 100% and 41.7% in *A. baumannii* and Enterobacteriaceae, respectively (p=0.001).

The rates of inappropriate empirical antimicrobial treatment (76.7% vs. 23.3%), and resistance to imipenem (90% vs. 0%) and quinolones (90% vs. 33.3%) were higher in *A. baumannii* than Enterobacteriaceae (p=0.008, p<0.001, and p<0.001 respectively). The mean alanine aminotransferase (ALT) level was higher (95.9 vs. 25.8) in patients with *A. baumannii* meningitis than in those with Enterobacteriaceae (p=0.007). The laboratory results are listed in Table 2.

Mortality at day thirty in Enterobacteriaceae group was higher than in *A. baumannii* group and, mean day of death in Enterobacteriaceae group was shorter than in *A. baumannii* group, even if not statistically significant (Table 1).

DISCUSSION

A. baumannii is a common and wide-ranging infectious agent, due to its high rate of resistance to the most common antibacterial agents used in ICU. *A. baumannii* may lead to nosocomial meningitis especially after neurosurgical procedure [9, 10]. Some studies from Turkey showed that *Acinetobacter spp*. was the second causative agent of nosocomial meningitis related to ventriculo-peritoneal shunt and 37 cases with *A. baumannii* meningitis were reported from a tertiary care hospital [5, 11]. Regarding postneurosurgical Enterobacteriaceae meningitis, a number of studies have been published including 15 cases, 9 cases, 19 cases and 9 postsurgical meningitis, most related to *K. pneumoniae* alone [6, 12-14]. In our study, 30 patients with *A. baumannii* and 12 patients with Enterobacteriaceae meningitis were compared with each other to identify their risk factors. Many studies have been published about *A. baumannii* or Enterobacteriaceae meningitis

Table 2 - Laboratory findings of patients with postsurgical meningitis.

Characteristics	*Total No= 38*	*A. baumannii No = 27*	Enterobacteriaceae *No=11*	*p*
Leukocyte x1000/mm^3, mean±SD	14.1±6.1	14.7±6.8	12.7±3.6	0.346
CSF leukocyte x1000/mm^3, median (range)	7.55 (7-74.00)	9.26	3.37	0.340
CSF protein (mg/dl) ±SD	268±193	254±204	301±167	0.511
CSF/serum glucose (range)	0.16 (0.01-0.56)	0.18±0.21	0.11 ± 0.11	0.360
CSF/serum glucose <0.4, No (%)	31 (81.6)	20 (74.1)	11 (100.0)	0.062
ALT (U/L), mean (range)	75.8 (6-532)	95.9	25.8	0.007

CSF: cerebrospinal fluid, ALT: alanine aminotransferase, SD: standard deviation.

alone; however, to our knowledge, no comparative study after neurosurgical procedure has been performed [12, 15, 16].

The risk factors for postneurosurgical *A. baumannii* meningitis are cerebrospinal fluid leakage, prolonged surgery duration and EVD, severe illness and requirement for repeated surgery [9, 17, 18]. EVD devices, inappropriate antimicrobial use before meningitis ineffective against Enterobacteriaceae have been published as independent risk factors of Enterobacteriaceae meningitis [6]. In this study, no difference between patients with *A. baumannii* and Enterobacteriaceae meningitis was detected in terms of frequency of EVD devices; however, the rates of antimicrobial use and infection before meningitis were higher in patients with *A. baumannii* meningitis than in those with Enterobacteriaceae meningitis. Although EVD devices were a risk factor for both meningitis in the literature, it was not in our study.

MV was 7.28 times more frequent in patients with *A. baumannii* meningitis. MV is a risk factor for *A. baumannii* infection and related to mortality whereas, to our best knowledge, no cause-effect relationship between MV and *A. baumannii* meningitis has been verified [19].

Appropriately administered perioperative antimicrobial prophylaxis prevents development of surgical site infection (SSI) including meningitis, but prolonged or inappropriate antimicrobial prophylaxis may lead to higher cost, selection of resistant bacteria and does not prevent development of SSI [20, 21]. In our study, although infection before meningitis occurred in 16 patients, antimicrobial usage was found in 21 patients. At least five patients who were receiving ampicillin-sulbactam had prolonged prophylaxis. Using an antibacterial for a long time might have lead to the selection of multidrug resistant *A. baumannii*, and the risk of *A. baumannii* meningitis increased 8.84 times.

Because *A. baumannii* has intrinsic chromosomal carbapenemase like OXA-51, it can easily become resistant to carbapenems [22]. Recently, carbapenem resistant *A. baumannii* (CRAb) infections has increased in ICUs, and treatment of CRAb infections is a concern due to the remaining limited drug options, such as colistin, and tygecycline [9, 23, 24]. In our study, none of Enterobacteriaceae and 90% of *A. baumannii* isolates were resistant to carbapenems. *A. baumannii* meningitis was 8.84 times more frequent in patients treated with an antimicrobial drug before meningitis. The rate of the intratechal (IT) route of antimicrobials' administration was higher in patients with *A. baumannii* meningitis. This high rate may have arisen from the necessity to administer colistin which cannot penetrate the CSF sufficiently [25]. Due to the fact that the resistance rate of the *A. baumannii* strains to imipenem was very high (90%), IT colistin administration was unavoidable [5]. In our hospital, *Acinetobacter* strains isolated from bloodstream infections have a high rate of antimicrobial resistance, especially in ICU [26].

As expected, the rate of appropriate empirical antimicrobial treatment was lower in patients with *A. baumannii* meningitis. The empirical therapy of nosocomial meningitis is based on local epidemiology [7]. The empirical antimicrobial preference for nosocomial meningitis in our center was a vancomycin and meropenem combination (17/42), and a regimen containing colistin was preferred in four patients.

The mortality rate for Acinetobacter meningitis ranges from 15% to 71% and this rate was 14% for Enterobacteriaceae meningitis [6, 9]. The predictors of mortality in post-neurosurgical meningitis are Gram negative etiology and severity of illness [17]. Inappropriate empirical therapy has also been associated with mortality [5]. In this study the overall mortality was quite high (64.3%) which may have arisen from the Gram negative etiology. Another risk factor for the development of postsurgical meningitis is severe illness, but in our study, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score could not be calculated because it was not possible to obtain all patients' data for APACHE II [18]. Higher levels of ALT and receipt of MV were more frequently observed in patients with *A. baumannii* meningitis. These findings may be associated with more severe disease in these patients.

Need of MV (7.28 times) and antibiotic use before meningitis (8.84 times) were associated with an increased risk of *A. baumannii* meningitis. Avoidance of unnecessarily prolonged antimicrobial usage may help to prevent a selection of *A. baumannii.*

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