Infections in patients undergoing craniotomy: risk factors associated with post-craniotomy meningitis

*Irene S. Kourbeti, MD, PhD,¹ Antonis F. Vakis, MD, PhD,² Panayiotis Ziakas, MD, PhD,³ Dimitris Karabetsos, MD,² Evangelos Potosidis, MD,⁴ Silvana Christou, MD,⁵ and George Samonis, MD, PhD⁶

¹Department of Internal Medicine, General Hospital of Chalkida; Departments of ²Neurosurgery and ⁶Department of Internal Medicine/Infectious Disease, University Hospital of Heraklion; ⁴Department of Internal Medicine, General Hospital of Volos, Greece; ³Department of Internal Medicine, Division of Infectious Disease, Warren Alpert Medical School, Brown University, Providence, Rhode Island; and ⁵Department of Internal Medicine, General Hospital of Nicosia, Cyprus

OBJECT The authors performed a prospective study to define the prevalence and microbiological characteristics of infections in patients undergoing craniotomy and to clarify the risk factors for post-craniotomy meningitis.

METHODS Patients older than 18 years who underwent nonstereotactic craniotomies between January 2006 and December 2008 were included. Demographic, clinical, laboratory, and microbiological data were systemically recorded. Patient characteristics, craniotomy type, and pre- and postoperative variables were evaluated as risk factors for meningitis

RESULTS Three hundred thirty-four procedures were analyzed (65.6% involving male patients). Traumatic brain injury was the most common reason for craniotomy. Almost 40% of the patients developed at least 1 infection. Ventilator-associated pneumonia (VAP) was the most common infection recorded (22.5%) and *Acinetobacter* spp. were isolated in 44% of the cases. Meningitis was encountered in 16 procedures (4.8%), and CSF cultures were positive for microbial growth in 100% of these cases. Gram-negative pathogens (*Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Proteus mirabilis*) represented 88% of the pathogens. *Acinetobacter* and *Klebsiella* spp. demonstrated a high percentage of resistance in several antibiotic classes. In multivariate analysis, the risk for meningitis was independently associated with perioperative steroid use (OR 11.55, $p = 0.005$), CSF leak (OR 48.03, $p < 0.001$), and ventricular drainage (OR 70.52, $p < 0.001$).

CONCLUSIONS Device-related postoperative communication between the CSF and the environment, CSF leak, and perioperative steroid use were defined as risk factors for meningitis in this study. Ventilator-associated pneumonia was the most common infection overall. The offending pathogens presented a high level of resistance to several antibiotics.

<http://thejns.org/doi/abs/10.3171/2014.8.JNS132557>

KEY WORDS craniotomy; meningitis; infection; ventilator-associated pneumonia; surgical site infections

Neurological meningitis is mainly seen in neurosurgical patients. This complication may result in severe morbidity, with a prolonged length of stay, multiple surgeries, and higher hospital costs.^{12,27} Patients who undergo neurosurgery are also prone to the development of a variety of infections that may pose significant problems for them.¹⁴

Comprehensive studies have been published on the risk factors for post-craniotomy meningitis (PCM).^{12,14,24,28} In this study we publish the prospective 3-year experience from the University of Crete on the risk factors associated

with PCM. We also analyzed the infections in patients undergoing craniotomies in terms of the prevalence, microbiology, and sensitivities of the offending pathogens.

Methods

Identification of Patients

This study took place at the University of Crete. Patients were eligible if they were at least 18 years of age, underwent elective or emergency craniotomy between 2006 and 2008, and survived at least 7 days after surgery.

ABBREVIATIONS CAB/BSI = catheter-associated bacteremia/blood stream infection; EVD = external ventricular drain; ICP = intracranial pressure; ICU = intensive care unit; LOS = length of stay; PCM = post-craniotomy meningitis; SSI = surgical site infection; UTI = urinary tract infection; VAP = ventilator-associated pneumonia.

SUBMITTED November 19, 2013. **ACCEPTED** August 26, 2014.

INCLUDE WHEN CITING Published online October 24, 2014; DOI: 10.3171/2014.8.JNS132557.

DISCLOSURE Dr. Samonis reports receiving non-study related clinical or research support from Pfizer, Novartis, Gilead, and MSD.

* Drs. Kourbeti and Vakis contributed equally to this work.

Major craniotomies were included. Patients having only CSF shunt or external ventricular drain (EVD) implantations, bur hole trepanation, or stereotactic surgery were excluded. The patients were prospectively followed for the development of meningitis during the first 30 postoperative days and during the 1st postoperative year if a foreign body was implanted. It was assumed that the occurrence of meningitis would result in readmission; although it is possible that admission to another institution may have resulted in some missed cases, it is highly unlikely.

Data Abstraction

Data were abstracted from the medical charts to a standard database. We recorded comorbidities such as diabetes, malignancy, atherosclerotic cardiovascular disease, chronic renal failure, chronic obstructive pulmonary disease, and perioperative steroid use; prophylactic antibiotic use; characteristics of the procedure performed, such as procedure urgency (elective or emergent), surgery duration, multiple procedures performed at the same time (simultaneous orthopedic or abdominal surgery or facial reconstruction); and the presence of any postoperative CSF drainage, reoperations, or CSF leaks. An operation was considered a revision surgery whenever it was performed through the same incision as a previous operation, regardless of the interval between the 2 procedures. Postoperative CSF leak was recorded when CSF drainage was diagnosed after surgery on the basis of otorrhea, rhinorrhea, or leakage from the surgical wound.

Meningitis was diagnosed according to the definitions of the Centers for Disease Control.⁸ The definition of the disease was as follows: 1) organisms cultured from CSF, 2) at least 1 of the following signs or symptoms with no other recognized cause: fever ($> 38^{\circ}\text{C}$), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability *and* if diagnosis was made antemortem, attending physician instituted appropriate antimicrobial therapy, *and* at least *one* of the following: a) increased WBC count, elevated protein level, and/or decreased glucose level in CSF; b) organisms seen on gram stain of CSF; c) organisms cultured from blood; d) positive antigen test of CSF, blood, or urine; e) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen. We recorded the postoperative day on which the diagnostic lumbar puncture was performed, the organisms identified by CSF culture, and all the infections (ventilator-associated pneumonia [VAP], urinary tract infection [UTI], pneumonia, bacteremia) that developed in this cohort. The data were transferred to a database and were analyzed using SPSS software (Version 16.0, SPSS Inc.). Continuous variables were compared using the Student t-test or the Mann-Whitney U-test, whereas categorical variables were compared using the Fisher exact test. In univariate analysis, odds ratios and 95% confidence intervals were calculated using the Mantel-Haenszel test. Stepwise multivariate logistic regression was used to model the interactions of those variables significantly associated with surgical site infections (SSIs) or meningitis in univariate analyses. A backward elimination model was used with $P_{\text{enter}} = 0.20$ and $P_{\text{leave}} = 0.05$ to identify independent predictors for meningitis. When a continuous variable such as the number of days of ventricular drainage, was

shown to be a statistically significant risk factor, the relationship was modeled further using suitably coded dummy variables. Power calculations were performed using the PASS software (PASS 2008, <https://www.ncss.com>).

Results

Study Population and Procedure Characteristics

The study included 334 procedures in 239 patients who met the inclusion criteria; 65.6% of the procedures were performed in men. Meningitis developed after 16 (4.8%) of the procedures. The median age was 48 years for the patients who developed meningitis (interquartile range [IQR] 22–58 years) and 51 (IQR 27–67 years) for those who did not. Traumatic brain injury was the most common reason for craniotomy (accounting for 49.7% of the procedures). The rest of the craniotomy indications included space-occupying lesions (in 34% of cases), vascular conditions (10%), abscess (1%), and a variety of other reasons (3%); 18.6% of the procedures were revision surgeries, and 49.7% were emergent procedures. Only 3.3% of the patients had concurrent procedures. Almost 40% of the patients who underwent craniotomy developed at least 1 infection. SSIs developed after 9% of the procedures. The overall mortality rate was 15%. There was no statistically significant difference in mortality rate between patients who did and did not develop meningitis.

The median time from admission to surgery was 3 days. The median duration of surgery was 2 hours (IQR 2.0–4.0 hours) for the procedures after which meningitis did not develop and 4 hours (IQR 3.0–6.0 hours) for those after which it did. The median length of stay (LOS) was 27 days (IQR 12–79). Patients who developed meningitis had a much longer LOS (median 191 vs 24.5 days, $p < 0.001$). Patients who developed meningitis had a greater propensity to be admitted to the intensive care unit (ICU) ($p < 0.001$) and a prolonged intubation beyond the time of surgery ($p < 0.001$).

Meningitis Risk

The median time from surgery to lumbar puncture was 6.5 days in those cases in which meningitis was diagnosed. Table 1 lists all variables that were examined for their contribution to the risk of meningitis. Individual variables that were statistically significant at a p value less than 0.05 included female sex, perioperative steroid use, increased duration of surgery, presence of CSF leak, ICU admission, use of a central line, and use of ventricular drains. The presence of drains overall was not associated with the development of meningitis. The presence of another SSI was associated with meningitis risk ($p < 0.001$). Among the patients who had an SSI other than meningitis, 41% also developed meningitis. Emergency status of the procedure (i.e., emergent or not) was not associated with the development of meningitis. “Time to surgery” and the presence of skull fractures also were not associated with the development of meningitis. Overall, 14 patients (4%) had open wound trauma. Patients with open wound trauma were more likely to develop an SSI than those without (36% vs 11%, $p = 0.02$). Also, open-wound trauma patients had a higher risk for meningitis

TABLE 1. Comparison of the 2 groups regarding the development of meningitis

Variable	Meningitis	No Meningitis	p Value
No. of procedures	16	318	
Female sex	10 (59%)	105 (33%)	0.04
Age (yrs)			0.14
Median	48	51	
IQR	22–58	27–67	
LOS (days)			<0.001
Median	191	24.5	
IQR	120–259	12–70	
Diabetes	1 (6%)	23 (7%)	1.0
Malignancy	2 (12%)	55 (17%)	0.74
ASCVD	4 (24%)	94 (30%)	0.79
CRF	0 (0%)	9 (3%)	1.0
COPD	0 (0%)	5 (2%)	1.0
Steroid use	9 (53%)	75 (24%)	0.02
Emergency	8 (48%)	158 (50%)	1.00
Duration in hrs			0.003
Median	4	2	
IQR	3–6	2–4	
CSF leak	6 (35%)	21 (7%)	0.001
Multiple procedures	0 (0%)	11 (3%)	1.00
Revision	2 (12%)	60 (19%)	0.75
Entered sinus	0 (0%)	23 (8%)	0.23
Open wound	2 (12%)	12 (4%)	0.16
Dural substitute	10 (59%)	156 (49%)	0.44
ICU admission	16 (100%)	170 (54%)	<0.001
Intubation	15 (88%)	127 (40%)	<0.001
TPN	2 (12%)	26 (8%)	0.64
Central line	15 (88%)	154 (49%)	<0.002
Drain	16 (94%)	273 (86%)	0.49
Ventricular drains	11 (65%)	16 (5%)	<0.001
ICP placement	5 (29%)	88 (28%)	0.88
Prophylactic antibiotics	16 (94%)	324 (97%)	0.41

ASCVD = atherosclerotic cardiovascular disease; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; TPN = total parenteral nutrition.

(14% vs 5%), but this association failed to reach statistical significance ($p = 0.16$). Crossing a sinus during a procedure was not associated with the development of meningitis ($p = 0.23$).

Variables that were statistically significant at $p \leq 0.20$ in the univariate analysis were included in a multivariate regression (Table 2). Presence of ventricular drainage (OR 70.52), CSF leak (OR 48.03), and perioperative steroid use (OR 11.55) remained in the model as independent predictors with $p < 0.05$.

CSF Features in Patients With Meningitis

Postoperative meningitis developed in 16 cases. The characteristics of the CSF in these cases are shown in Table 3.

TABLE 2. Multivariate analysis for the risk for meningitis

Covariate	OR (95% CI)	p Value
Sex (F vs M)	2.70 (0.68–10.79)	0.16
Steroids (yes vs no)	11.55 (2.08–64.13)	0.005
Duration of surgery	1.03 (0.68–1.55)	0.89
CSF leak (yes vs no)	48.03 (6.75–341.8)	<0.001
Intubation (yes vs no)	9.35 (0.78–111.7)	0.08
Central line	0.36 (0.02–4.44)	0.42
EVD (yes vs no)	70.52 (10.83–459.1)	<0.001

Microbiology of Meningitis

Meningitis was documented by positive CSF culture in all 16 cases. Gram-negative organisms predominated. *Acinetobacter* spp. were the main isolates (present in 45% of cases). The other pathogens included: *Klebsiella* spp. (4 cases), *Pseudomonas aeruginosa* (2 cases), *Enterobacter cloacae* (1 case), *Proteus mirabilis* (1 case), coagulase-negative staphylococci (1 case), *Staphylococcus aureus* (1 case), and *Candida albicans* (1 case). *Acinetobacter* spp. were fully resistant to β -lactams, aztreonam, aminoglycosides, and quinolones but they were fully sensitive to colistin. *Klebsiella* spp. were 100% resistant to β -lactams, cephalosporins, aztreonam, and quinolones. *Pseudomonas aeruginosa* isolates were fully resistant to the carbapenems, but they retained full susceptibility to ticarcillin/clavulanate, piperacillin/tazobactam, cefepime, aztreonam, amikacin, gentamicin, colistin, and ciprofloxacin (Table 4).

Infections Other Than Meningitis

Ventilator-associated pneumonia was the most common infection in this population (22.5%) with 9% of patients developing an SSI other than meningitis, 9% a UTI, and 15% pneumonia not associated with mechanical ventilation. Among SSIs, wound infections predominated (75%). Postsurgical subdural and epidural abscesses represented only 11% of the SSIs. Ventriculostomy site, bone cement and bone infections, and subdural empyemas were rare, representing a total of 12% of the SSIs.

When the meningitis pathogens were compared with the catheter-associated bacteremia/blood stream infection (CAB/BSI) isolates, in 3 cases the same pathogens grew from the CSF and the blood (namely *E. cloacae*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*).

Microbiology of Other Infections

In VAPs, *Acinetobacter* spp. were the main pathogens, isolated in 44% of the cases. *Pseudomonas aeruginosa*

TABLE 3. CSF characteristics of the 16 patients who had meningitis

Variable	Median	IQR
Protein (mg/dl)	120	91–634
Glucose (mg/dl)	47	40–59
Glucose CSF/serum ratio	0.40	0.40–0.47
WBC (cells/ml)	300	220–560

TABLE 4. Antibiotic resistance in pathogens isolated from meningitis and VAP*

Antibiotic	Meningitis			VAP		
	<i>Acinetobacter</i> spp.	<i>Klebsiella</i> spp.	<i>Pseudomonas</i> spp.	<i>Acinetobacter</i> spp.	<i>Klebsiella</i> spp.	<i>Pseudomonas</i> spp.
Cephalothin	100%			100%	67%	
Cefuroxime	100%	100%		100%	67%	
Ceftriaxone	100%	100%	100%	100%	67%	
Cefepime	100%	100%	0%	100%	67%	37%
Tetracycline	100%	0%		76%	22%	
Colistin	0%	20%	0%	0%	33%	0%
Ticarcillin/clavunate	100%	100%	0%	100%	67%	42%
Piperacillin/tazobactam	100%	100%	0%	85%	67%	37%
Imipenem	33%	60%	100%	67%	33%	21%
Meropenem	17%	40%	100%	18%	33%	26%
Aztreonam	100%	100%	0%	100%	67%	37%
Amikacin	100%	80%	0%	79%	33%	16%
Gentamicin	100%	80%	0%	61%	33%	5%
TMP-SMZ	100%	100%	100%	82%	67%	100%
Ciprofloxacin	100%	100%	0%	100%	78%	21%
Moxifloxacin	100%	100%		79%	67%	

* The percentage values given indicate the percentage of resistance to the antibiotic listed.

was the second most prevalent isolate (25%). The resistance patterns are shown in Table 4. Of note, the *Acinetobacter* spp. retained full susceptibility to colistin. The resistance to imipenem approached 67%. *Pseudomonas aeruginosa* isolates were also fully susceptible to colistin. In UTIs, *Klebsiella* spp. were the most prevalent pathogens (31%). The isolates were 100% resistant to β -lactams, aztreonam, and quinolones and 75% resistant to imipenem and colistin.

In SSIs, *Acinetobacter* spp. predominated, with *Klebsiella* spp. being the second in prevalence. Gram-positive pathogens were the third most common category. In CAB/BSI, coagulase-negative staphylococci were the most prevalent pathogens. Gram-positive organisms generally predominated in these infections. Among the gram-negative organisms, *A. baumannii* was the most common.

Survival Analysis

After a cumulative follow up of 18,795 days (median 27 days, range 1–318 days), 50 patients had died (15%)—among them, 5 (29%) of the 16 patients who had meningitis, 1 (4%) of the 23 who had an SSI other than meningitis, 24 (24%) of the 98 who had other nosocomial infections, and 20 (10%) of the 194 who had no infection. Estimated survival rates at Day 30 were 0.94 (95% CI 0.65–0.99) for patients with meningitis, 1.0 for patients with other SSIs, 0.84 (95% CI 0.74–0.90) for patients with other nosocomial infections, and 0.90 (95% CI 0.84–0.94) for those without infections. The corresponding age- and sex-adjusted hazard ratios for patients with infection compared with those without infection were 0.80 (95% CI 0.22–2.84) for meningitis, 0.38 (95% CI 0.05–2.89) for other SSIs, and 1.43 (95% CI 0.77–2.63) for other nosocomial infections. The results of all between-group comparisons were also insignificant. Only age predicted an adverse

outcome (HR for death 1.03 [95% CI 1.02–1.05] per year increase in age). In conclusion, there was no statistically significance difference between the study groups with respect to mortality rates (Fig. 1, Table 5).

Discussion

Prevalence and Microbiology of Post-Craniotomy Meningitis

The incidence of meningitis in this study was 4.8%, higher than incidences noted in some series^{2,12,13} but not in all. Reichert et al.²⁸ in their prospective study reported a rate of 8.9%. In a recent retrospective study from the US, the incidence of post-craniotomy meningitis (PCM) was 5.5%.¹⁴ Gram-negative organisms predominated as meningitis pathogens in this prospective cohort. In studies published after 1993, Enterobacteriaceae and other gram-negative rods played a major role.^{1,6,9,18,28} Our results seem to reflect this trend. In this cohort there were no culture-

FIG. 1. Kaplan-Meier survival estimates for the patients undergoing craniotomy.

TABLE 5. Cox regression analysis for mortality according to the type of infections (age-sex adjusted)

Variable	HR	95% CI	p Value
Age (per yr increase)	1.03	1.02–1.05	<0.001
Sex	0.78	0.42–1.45	0.43
Type of infection			
Meningitis	0.80	0.22–2.84	0.72
SSI	0.38	0.05–2.89	0.35
Other	1.42	0.77–2.63	0.26

negative cases, which can make treatment decisions very difficult, and the cases were 100% culture proven.

Acinetobacter spp. were isolated in 45% of cases, with *Klebsiella* spp. and *P. aeruginosa* the next most common isolates. The increase in the rate of *Acinetobacter* PCM has been extensively described in the years following 2000, although in the previous years it was reported as a rare occurrence.^{4,5,18,22,28,32,36} The main issue with the *Acinetobacter* spp. is their increasing resistance to almost all antibiotic classes (including carbapenems), which has been a significant problem in the recent years.^{1,4,10,16,22,25,30,36} *Klebsiella* spp. were the second most commonly isolated pathogens in this cohort, with the isolates carrying a high degree of resistance to third-generation cephalosporins and carbapenems (Table 4). One hundred percent of the isolates were sensitive to tetracycline, but during the study period the sensitivity to tigecycline was not routinely recorded.

The median CSF glucose/serum glucose ratio was 0.40 (IQR 0.40–0.47). Since all the cases were culture-positive, it is safe to assume that this rate is very suggestive of microbial meningitis as it has been reported previously.¹⁶ The 100% culture positivity rate is a rare occurrence in the literature. A positivity rate of 32% was reported in another prospective study.²⁸ Retrospective studies by Kourbeti et al. have demonstrated a positivity rate ranging from 50%¹⁴ to 74% (unpublished data). In those studies there were not any differences in the CSF characteristics between culture-positive and culture-negative cases.¹⁴ The mean duration from operation to the onset of symptoms was 6.5 days, an interval similar to that reported before.^{14,15,28}

Risk Factors

The independent risk factors identified by the multivariate analysis were use of perioperative steroids, CSF leak, and the use of EVDs.

Craniotomies with an EVD carry a higher risk for meningitis.^{15,19,20,24,28} Ventriculitis in association with ventricular drain placement was a frequent problem and was observed in 11% of general neurosurgical patients in the series by Mayhall et al.²⁰ There is little agreement among various series regarding the relation between duration of drainage and infection incidence; in one report, no relation was observed.¹⁹ Lozier et al.¹⁷ have commented on the controversy regarding the significance of the duration of EVD use with respect to the development of infections. At the University of Crete there were no routine changes of EVDs. Leaving

an uninfected drain in place may be the best policy.¹⁵ In our institution, dressings were changed daily, the catheters were replaced at the first sign of infection or malfunction. Antibiotic-coated catheters were not routinely placed; we used them after the first catheter change for any reason or in patients who already had signs of infection and needed an EVD placed because of intraventricular hemorrhage or obstructive hydrocephalus.

Previous studies demonstrated postoperative CSF leak to be a significant risk factor for the development of meningitis.^{2,11,12,23,26} In our series, the presence of CSF leak was associated with a 48-fold increase in the risk of meningitis, and this was statistically significant. This is much higher than the risk we had identified in a previous retrospective study,¹⁵ in which the CSF leak increased the risk of meningitis by a factor of 1.7 but was not a statistically significant risk factor. Surgeons should be very vigilant in correcting a CSF leak. When a patient with a post-craniotomy CSF leak develops a fever, the possibility of meningitis should be strongly considered.

Meningitis or positive CSF culture has been described as the most frequent complication of intracranial pressure (ICP) monitoring.²⁷ In this study, however, the presence of an ICP monitoring device did not affect the development of meningitis.

In contrast to findings of a previous prospective study,²⁶ in our study duration of surgery did not remain an independent risk factor in the multivariate analysis.²⁶ Age, sex, and diabetes were not significant risk factors for the development of meningitis, a finding consistent with previously reported data.¹² Repeat surgery, which has been a major risk factor in recent²⁸ and older²⁶ reports, was not a risk factor in our cohort. Scheduling the procedure as an emergency or not an emergency was not a risk factor for PCM, a finding that we had described before.¹⁵ Entering a sinus was not a risk factor in this prospective study, in contrast to our retrospective report,¹⁵ and the reports of others.^{11,23}

The use of perioperative steroids achieved a statistical significance in this prospective study. This has not been described before in studies regarding PCM and in most studies regarding postoperative wound infections in general neurosurgical patients.^{4,5,12–15,23,26,28,33} The effect of steroids on patients undergoing neurosurgical procedures has been variably reported.²¹ In certain studies, the steroid effect has not been specifically investigated.^{4,12,13} Walcott et al.³⁵ mention that for rare events such as infections in neurosurgery, it may be difficult to accomplish proof for the association of certain variables. In the study by Erman et al.,⁵ perioperative steroid use did not remain an independent risk factor for the development of SSIs in the multivariate analysis. In the prospective study by Reichert et al.²⁸ and the retrospective study by Kourbeti et al.¹⁵ on the risk factors associated with PCM, steroid administration did not reach a statistical significance. In studies in which steroids were administered to patients undergoing implantation of subdural electrodes, steroids had no effect on the incidence of infection.^{7,34} McPhee et al.²¹ demonstrated a significant increase in postoperative wound infection and breakdown with steroid use in the setting of spinal operations for metastases, but they did not mention the effect on the development of meningitis.²¹ Shinoura et al.³¹ did not

find that steroid use was a significant factor in a population of patients undergoing craniotomy for brain tumors. In summary, this is a matter that is highly controversial in the literature. Well-designed prospective studies will be needed in order to define the safe period for steroid use in neurosurgical patients.

Microbiology of Other Infections

Acinetobacter spp. were the predominant pathogens in VAP in this cohort (identified in 44% of cases), in accordance with the literature in critically ill patients.^{3,29} These pathogens are of extreme importance because they may be associated with a high rate of mortality (78% in one series²⁹). The VAP isolates were 100% sensitive to colistin, like the PCM isolates, but their sensitivity to carbapenems and aminoglycosides was better than that of the PCM isolates.

Our study contains a tremendous amount of data on this prospective cohort of patients undergoing craniotomy. We believe that the prospective nature of the study and the sound statistical methods increase the power of our findings. Nevertheless, our population consisted mainly of patients with traumatic brain injury (50%), so the overall severity of illness was high. Our results are sound, but still they do not allow us to make recommendations on the mitigation of the risk factors that predispose to meningitis. What we do suggest, however, is that in a patient who has received perioperative steroids, is being treated with a ventricular drain, has a CSF leak, or has a combination of these risk factors and has new-onset fever, meningitis should be considered. The fact that we detected culture-positive meningitis in 100% of the cases is probably due to the fact that several of the risk factors had been described before and we had an increased awareness for diagnosis of the infection in our cohort. This is very important especially since PCM often presents with subtle symptoms.¹⁴

Our results are largely confirmatory, and no new findings were demonstrated, except for the risk factor of the perioperative steroids, which has not been extensively discussed in the literature before. The description of the pathogens and their resistance profiles might be applicable to our academic center only. Despite this limitation, we believe that this extensive description of infections and pathogens may assist physicians to choose antibiotics that cover the most prevalent pathogens in patients presenting with fever after a craniotomy. *Acinetobacter* spp. remain very important pathogens with an increasing resistance to several antibiotic classes, a disturbing occurrence that affects patients' care all over the world.¹⁰ The finding that almost 40% of patients who underwent craniotomy in our prospective study developed at least one infection is disturbing, and it should alert physicians and investigators to search for the factors that will help in the mitigation of such complications in neurosurgical patients.

Conclusions

In this prospective study we were able to confirm the importance of perioperative ventricular drains and CSF leak in the development of PCM. We also demonstrated

the significance of perioperative steroids in the development of meningitis. The duration of surgery was not a significant risk factor for PCM. As the first prospective surveillance of infections in patients undergoing craniotomy in Greece, this study is important because the offending pathogens and sensitivities for the most prevalent infections were described. We believe that this will greatly help physicians with the proper empiric choice of antibiotics in this population.

References

1. Briggs S, Ellis-Pegler R, Raymond N, Thomas M, Wilkinson L: Gram-negative bacillary meningitis after cranial surgery or trauma in adults. *Scand J Infect Dis* **36**:165–173, 2004
2. Blomstedt GC: Craniotomy infections. *Neurosurg Clin N Am* **3**:375–385, 1992
3. Chastre J, Fagon JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* **165**:867–903, 2002
4. Erdem I, Hakan T, Ceran N, Metin F, Akcay SS, Kucukercan M, et al: Clinical features, laboratory data, management and the risk factors that affect the mortality in patients with postoperative meningitis. *Neurol India* **56**:433–437, 2008
5. Erman T, Demirhindi H, Göçer AI, Tuna M, Ildan F, Boyar B: Risk factors for surgical site infections in neurosurgery patients with antibiotic prophylaxis. *Surg Neurol* **63**:107–113, 2005
6. Gulati S, Kapil A, Das B, Dwivedi SN, Mahapatra AK: Nosocomial infections due to *Acinetobacter baumannii* in a neurosurgery ICU. *Neurol India* **49**:134–137, 2001
7. Hersh EH, Virk MS, Shao H, Tsiouris AJ, Bonci GA, Schwartz TH: Bone flap explantation, steroid use, and rates of infection in patients with epilepsy undergoing craniotomy for implantation of subdural electrodes. Clinical article. *J Neurosurg* **119**:48–53, 2013
8. Horan TC, Andrus M, Dudeck MA: CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* **36**:309–332, 2008
9. Hsu GJ, Young TG, Chou JW, Peng MY, Chang FY, Chou MY: Gram-negative bacillary meningitis in adults. *J Formos Med Assoc* **92**:317–323, 1993
10. Kim BN, Peleg AY, Lodise TP, Lipman J, Li J, Nation R, et al: Management of meningitis due to antibiotic-resistant *Acinetobacter* species. *Lancet Infect Dis* **9**:245–255, 2009
11. Korinek AM: [Prevention of meningitis after craniotomy in scheduled surgery.] *Ann Fr Anesth Reanim* **11**:711–715, 1992 (Fr)
12. Korinek AM, French Study Group of Neurosurgical Infections, SEHP, C-CLIN Paris-Nord: Risk factors for neurosurgical site infections after craniotomy: a prospective multicenter study of 2944 patients. *Neurosurgery* **41**:1073–1081, 1997
13. Korinek AM, Golmard JL, Elcheick A, Bismuth R, van Effenterre R, Coriat P, et al: Risk factors for neurosurgical site infections after craniotomy: a critical reappraisal of antibiotic prophylaxis on 4,578 patients. *Br J Neurosurg* **19**:155–162, 2005
14. Kourbeti IS, Jacobs AV, Koslow M, Karabetsos D, Holzman RS: Risk factors associated with postcraniotomy meningitis. *Neurosurgery* **60**:317–326, 2007
15. Kim BN, Peleg AY, Lodise TP, Lipman J, Li J, Nation R, et al: Management of meningitis due to antibiotic-resistant *Acinetobacter* species. *Lancet Infect Dis* **9**:245–255, 2009
16. Leib SL, Boscacci R, Gratzl O, Zimmerli W: Predictive value of cerebrospinal fluid (CSF) lactate level versus CSF/blood glucose ratio for the diagnosis of bacterial meningitis following neurosurgery. *Clin Infect Dis* **29**:69–74, 1999

17. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES Jr: Ventriculostomy-related infections: a critical review of the literature. **Neurosurgery** **51**:170–182, 2002
18. Lu CH, Chang WN, Chuang YC, Chang HW: Gram-negative bacillary meningitis in adult post-neurosurgical patients. **Surg Neurol** **52**:438–444, 1999
19. Mahé V, Kermarrec N, Ecoffey C: [Infections related to external ventricular drainage.] **Ann Fr Anesth Reanim** **14**:8–12, 1995 (Fr)
20. Mayhall CG, Archer NH, Lamb VA, Spadora AC, Baggett JW, Ward JD, et al: Ventriculostomy-related infections. A prospective epidemiologic study. **N Engl J Med** **310**:553–559, 1984
21. McPhee IB, Williams RP, Swanson CE: Factors influencing wound healing after surgery for metastatic disease of the spine. **Spine (Phila Pa 1976)** **23**:726–733, 1998
22. Metan G, Alp E, Aygen B, Sumerkan B: Carbapenem-resistant *Acinetobacter baumannii*: an emerging threat for patients with post-neurosurgical meningitis. **Int J Antimicrob Agents** **29**:112–113, 2007
23. Mollman HD, Haines SJ: Risk factors for postoperative neurosurgical wound infection. A case-control study. **J Neurosurg** **64**:902–906, 1986
24. Narotam PK, van Dellen JR, du Trevou MD, Gouws E: Operative sepsis in neurosurgery: a method of classifying surgical cases. **Neurosurgery** **34**:409–416, 1994
25. Nguyen MH, Harris SP, Muder RR, Pasculle AW: Antibiotic-resistant *Acinetobacter* meningitis in neurosurgical patients. **Neurosurgery** **35**:851–855, 1994
26. Patir R, Mahapatra AK, Banerji AK: Risk factors in postoperative neurosurgical infection. A prospective study. **Acta Neurochir (Wien)** **119**:80–84, 1992
27. Rebuck JA, Murry KR, Rhoney DH, Michael DB, Coplin WM: Infection related to intracranial pressure monitors in adults: analysis of risk factors and antibiotic prophylaxis. **J Neurol Neurosurg Psychiatry** **69**:381–384, 2000
28. Reichert MCF, Medeiros EAS, Ferraz FAP: Hospital-acquired meningitis in patients undergoing craniotomy: incidence, evolution, and risk factors. **Am J Infect Control** **30**:158–164, 2002
29. Rello J: *Acinetobacter baumannii* infections in the ICU: customization is the key. **Chest** **115**:1226–1229, 1999
30. Rodriguez CH, Bombicino K, Granados G, Nastro M, Vay C, Famiglietti A: Selection of colistin-resistant *Acinetobacter baumannii* isolates in postneurosurgical meningitis in an intensive care unit with high presence of heteroresistance to colistin. **Diagn Microbiol Infect Dis** **65**:188–191, 2009 (Erratum in **Diagn Microbiol Infect Dis** **66**:341, 2009)
31. Shinoura N, Yamada R, Okamoto K, Nakamura O: Early prediction of infection after craniotomy for brain tumours. **Br J Neurosurg** **18**:598–603, 2004
32. Siegman-Igra Y, Bar-Yosef S, Gorea A, Avram J: Nosocomial *acinetobacter* meningitis secondary to invasive procedures: report of 25 cases and review. **Clin Infect Dis** **17**:843–849, 1993
33. Srinivas D, Veena Kumari HB, Somanna S, Bhagavatula I, Anandappa CB: The incidence of postoperative meningitis in neurosurgery: an institutional experience. **Neurol India** **59**:195–198, 2011
34. Van Gompel JJ, Worrell GA, Bell ML, Patrick TA, Cascino GD, Raffel C, et al: Intracranial electroencephalography with subdural grid electrodes: techniques, complications, and outcomes. **Neurosurgery** **63**:498–506, 2008
35. Walcott BP, Redjal N, Coumans JVCE: Infection following operations on the central nervous system: deconstructing the myth of the sterile field. **Neurosurg Focus** **33**(5):E8, 2012
36. Wroblewska MM, Dijkshoorn L, Marchel H, van den Barselaar M, Swoboda-Kopec E, van den Broek PJ, et al: Outbreak of nosocomial meningitis caused by *Acinetobacter baumannii* in neurosurgical patients. **J Hosp Infect** **57**:300–307, 2004

Author Contributions

Conception and design: Kourbeti, Vakis, Ziakas, Samonis. Acquisition of data: Kourbeti, Vakis, Karabetsos, Potolidis, Christou. Analysis and interpretation of data: Ziakas. Drafting the article: Kourbeti, Vakis, Ziakas, Karabetsos, Potolidis, Samonis. Critically revising the article: Kourbeti, Vakis, Samonis. Reviewed submitted version of manuscript: Kourbeti, Vakis, Karabetsos, Potolidis, Christou, Samonis. Approved the final version of the manuscript on behalf of all authors: Kourbeti. Statistical analysis: Ziakas. Administrative/technical/material support: Vakis, Samonis. Study supervision: Kourbeti, Vakis, Ziakas, Karabetsos, Samonis.

Supplemental Information

Previous Presentation

Portions of this work were presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), London, March 31–April 3, 2012.

Correspondence

Irene S. Kourbeti, Department of Acute and Emergency Medicine, Furness General Hospital, Dalton Ln., Barrow in Furness, Cumbria LA14 4LF, United Kingdom. email: irenekourbeti@hotmail.com.