Thesis for doctoral degree 2011

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INFECTIONS IN NEUROSURGICAL PATIENTS
INCIDENCE, MICROBIOLOGY AND RISK FACTORS FOR POSTCRANIOTOMY MENINGITIS

FROM THE

DEPARTMENT OF INTERNAL MEDICINE
DEPARTMENT OF NEUROSURGERY
UNIVERSITY OF CRETE SCHOOL OF MEDICINE

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IRENE S. KOURBETI, MD

Στη μνήμη της μητέρας μου

Acknowledgments

I wish to thank my mentors, Professors Georgios Samonis and Dimitrios T. Boumpas for their guidance for this dissertation. They have been models of clinicians and academic physicians, continuous sources of motivation and I owe them this achievement. I am grateful to the third member of the Board, Assistant Professor Antonis Vakis who was a constant help by giving me the necessary guidance in Neurosurgery and the neurosurgical techniques and for providing me with unlimited access to the medical records of the Department of Neurosurgery. Special thanks to the members of the Dissertation Board Professors Eleni Papadaki, Nikolaos Siafakas and Dimitrios Georgopoulos and Lecturer Diamantis Kofteridis for their assistance with the writing of the dissertation and their constructive advice.

I would like to express my gratefulness to Dimitris Karabetsos, M.D. for his great help with the patients' databases and the collection of the samples for the Section 2.6 of the Dissertation. Dr. George Bertsias, has been a continuous source of inspiration and the most valuable help with the statistics and the editing of the papers and the several abstracts published during the preparation of the Thesis. I wish to express my special appreciation to Drs. Sofia Maraki, Director of the Microbiology Laboratory for performing the microbiological studies of the Section 2.6 and Miranda Anastasaki, Director of the Intensive Care Unit, for her invaluable help with data collection. Special thanks to my mentor in New York City, NYU Professor Robert S. Holzman who is the one who inspired me to study infections in neurosurgical patients during my training in Infectious Diseases and to my friend Mary Koutourousiou M.D. for helping me with the literature.

I am eternally obliged to my students Christodoulos Neophytou, Maria Filippou and Antonis Ioannou for offering precious help with data collection and spending endless nights in correcting the databases. This work would have never been completed without the statistical analyses of my wonderful collaborators, Dr. Ioannis Papadakis of the Department of Internal Medicine, UOC, and Assistant Professor Sotirios Tsiodras and Dr. Panos Ziakas of the University of Athens.

Finally, I am grateful to my family for their support, patience and understanding. I am especially thankful to my father Stergios-Stylianos Kourbetis for being a constant motivation.

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A. SHORT CURRICULUM VITAE OF THE CANDIDATE

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Senior Attending Physician
General Hospital of Chalkida

Diplomas and Credentials

2005: Greek Board of Infectious Diseases
2001: Greek Board of Internal Medicine
2000: American Board of Internal Medicine-Infectious Disease
1998: American Board of Internal Medicine
1998- 2000: Teaching Assistant in Infectious Disease/ Clinical Instructor in Physical Diagnosis- NYU School of Medicine
1998: Limited Permit for the state of NY
1996: USMLE Step 3
1995: ECFMG Certification
1993: USMLE Step 1
1992: USMLE Step 2
1992: License to Practice Medicine in Greece
1991: Diploma in Medicine (M.D.)

Postgraduate Training and Scientific Evolution

2008- To date: Attending Physician – General Hospital of Chalkida
2003- 2008: Attending Physician- University Hospital of Crete
2002: Infectious Disease Consultant- Onassis Heart Surgery Center
2002: Associate Consultant in Nosocomial Infectious Control Division- Hellenic Center for Infectious Disease Control
2001- 2002: Attending Physician- "Athens Medical", Athens
2000- 2001: Resident in Internal Medicine- "Laiko Hospital", Athens
1998- 2000: Fellow in Infectious Disease- NYU Medical Center
1995- 1998: Resident in Internal Medicine- SHUSGME
1993- 1995: Resident in Internal Medicine, General Hospital of Chalkida
1992- 1993: General Practitioner

Scholarships

EACS- Exchange Program for Young HIV Physicians: 2002

Publications

1. PD Ziakas, **IS Kourbeti**, M. Voulgarelis, E. Mylonakis. Effectiveness of systemic antifungal prophylaxis in patients with neutropenia after chemotherapy: a meta-analysis of randomized controlled trials. Clin Ther. 2010; 32: 2316-36

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Posters and Oral Presentations

In International Conferences: 24

In Greek Conferences: 23

Citations: 140

Reviewer in 11 Journals

B. ABBREVIATIONS

Abbreviation	
ASA	American Society of Anesthesiologists
ASCVD	Atherosclerotic Cardiovascular Disease
BSI/CAB	Blood Stream Infections/Cather Associated Bacteremia
CDAD	Clostridium difficile-associated disease
CEA	Cranial Epidural Abscess
CI	Confidence Interval
CNS	Central Nervous System
CoNS	Coagulase-Negative Staphylococci
COPD	Chronic Obstructive Pulmonary Disease
CRF	Chronic Renal Failure
CSE	Cranial Subdural Empyema
CSF	Cerebrospinal Fluid
EVD	External Ventricular Device
ESR	Erythrocyte Sedimentation Rate
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
ICP	Intracranial Pressure
ICU	Intensive Care Unit
LOS	Length of Stay
LP	Lumbar Puncture
MDR	Multidrug Resistant
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
NICU	Neurosurgical Intensive Care Unit
NNIS	National Nosocomial Surveillance System
NYU	New York University

OR	Odds Ratio
PCM	Post-craniotomy meningitis
RCT	Randomized Controlled Trials
SEA	Spinal Epidural Abscess
Spp.	Species
SSI(s)	Surgical Site Infection(s)
TBI	Traumatic Brain Injury
UOC	University of Crete
UTI	Urine Tract Infections
VP shunt	Ventriculoperitoneal shunt
WBC	White blood Count

C. Extended Summary in english

Nosocomial infections of the Central Nervous System (CNS) are a relatively small but important category of hospital-acquired infections. These infections span a spectrum from superficial wound infections, to ventricular shunt infections, meningitis and deep-seated abscesses of the brain parenchyma. These infections are usually serious, if not life threatening and can be associated with a poor outcome. Infections in neurosurgical patients have not been extensively described in Greece. In this extensive study in the University of Crete Medical Center, we attempted to define the risk factors associated with post-craniotomy meningitis (PCM) in Crete and compare them with the risk factors that were associated with post-craniotomy meningitis in a cohort in New York University Medical Center. Since traumatic brain injury was the main reason for admission in the UOC Medical Center-Department of Neurosurgery, we specifically analyzed the infections in this population. The author tried to confirm the results from the retrospective studies with a prospective study on risk factors associated with PCM. The studies performed are summarized as follows:

Study 1: Overview of the neurosurgical infections in the University Hospital of Crete based on a 3-year retrospective study

The medical records of the patients >18 years old that were admitted to the Department of Neurosurgery between 2004 and 2006 were reviewed. A total of 1,112 events were analyzed. Trauma was the most common cause for admission (56.3%). Craniotomy was the most common procedure performed (21.8%) but one-third of the patients admitted during that time period did not undergo any major procedures.

The prevalence of Surgical Site Infections (SSIs) during the aforementioned time period was 12.5% with superficial wound infections being the most common. VAP (Ventilator-Associated Pneumonia) was the most common non-SSI infection encountered in this cohort. The rate of SSIs was higher in patients who also developed VAP, urinary tract infections (UTI) and blood stream infections/catheter associated bacteremia (BSI/CAB).

In multivariate analysis, malignancy, surgery for a vascular reason, shunt replacement surgery, placement of any drain, and surgery through a sinus were all independent predictors for SSIs development. The development of any infection was independently associated with a history of malignancy, performance of surgical

procedures for trauma or cerebrovascular events, shunt replacement surgery and the placement of any drains or an ICP monitor device.

Infections, including SSIs, were associated with a prolonged hospitalization, both in the ICU and the wards, but not with an increased mortality. The most common pathogens isolated in SSIs were the gram-positive. *Acinetobacter* spp. were the most common isolates in VAP (58.3%), a fact with a particular significance, due to the increased resistance of the pathogens.

Therefore with this retrospective study, we demonstrated that the rate of SSIs was considerably high. Malignancy was for the first time demonstrated as a risk factor for infection development and SSIs in particular. Development of both SSIs and other infections were associated with a prolonged length of stay and consequently increased hospital costs but not an increased mortality.

Study 2: Retrospective study regarding the risk factors associated with post-craniotomy meningitis in New York University Medical Center- Department of Neurosurgery

This retrospective study was performed in New York University (NYU) Medical Center. The purpose was to determine the rate, bacteriology and risk factors for post-craniotomy meningitis (PCM). The study included patients >18 years old that underwent non-stereotactic craniotomies between January 1996 and March 2000. Operations for burr holes, ICP and shunt placements were excluded. Host factors, craniotomy type and pre- and postoperative variables were evaluated as risk factors for meningitis.

Four hundred and fifty three patients were included. Among them, there were 25 cases of meningitis. Most cases analyzed were operated for an oncological reason (45%), therefore they were elective cases. Ninety-two percent of the patients received antibiotic prophylaxis, mainly a first generation cephalosporin (78%). There was a doubling in the risk in the patients who did not receive prophylactic antibiotics but this was not statistically significant (p= 0.148)

The rate of meningitis was 5.5%, higher than noted in some studies, but not all. Eight out of 12 culture-positive cases revealed gram-positive cocci [mainly coagulase-negative staphylococci (CoNS)]. These results probably reflect the emergence of gram-positive as nosocomial pathogens during that time-period.

In multivariate analysis the risk for meningitis was increased by surgery that entered a sinus (OR 4.49), an increased ASA score (OR 1.72) and increase in the

number of days of external ventricular drainage (EVD) (OR 1.21) and intracranial pressure monitoring (ICP) (OR 1.24).

On conclusion, access of upper airway bacteria to the surgical wound, host factors as expressed by the ASA score and duration of device-related postoperative communication of the cerebrospinal fluid (CSF) and the environment are major risk factors for PCM development.

Study 3: Retrospective study regarding the risk factors associated with post-craniotomy meningitis in University of Crete Medical Center

This retrospective study was performed in the University of Crete Medical Center between January 1999 and December 2005. The purpose was to determine the rate, bacteriology and risk factors for post-craniotomy meningitis (PCM) for the first time in a cohort in Greece. The study included patients >18 years old that underwent non-stereotactic craniotomy. Host factors and pre- and postoperative variables were evaluated as risk factors for meningitis.

Six hundred nineteen craniotomies performed in 479 patients were analyzed. Traumatic brain injury (TBI) was the most common cause for craniotomy. 26% of the patients developed at least one infection. VAP was the most common infection recorded (13.1%). Meningitis/ventriculitis was encountered in 37 procedures (6.1%). Seventy-seven percent of the LP samples were positive. Gram-negative pathogens represented 48% of the culture-documented cases and gram-positive represented 43%.

In the multivariate analysis the risk for meningitis was independently associated with the development of another SSI (odds ratio [OR] 4.5), VAP/pneumonia (OR 4.4), UTI (OR 6.2), malignancy (OR 3.6), presence of a ventricular drainage (OR 12.7), presence of a lumbar drainage (OR 91.8) and an emergent procedure (OR 2.9).

Device-related postoperative communication of the CSF and the environment, SSI other than meningitis and infections outside the surgical field were defined as major risk factors for PCM.

On comparison, this retrospective cohort differed from the NYU cohort, in the percentage of emergent procedures which represented 51.4% in the UOC cohort whereas they represented only 34.2% in the NYU population. This mainly reflects the difference in the TBI population included in each cohort. The difference in the meningitis cases between the two cohorts (6.1% vs 5.5%) was not statistically significant. There was a slight preponderance of gram-negative pathogens in the UOC cohort, probably representing the fact that UOC cohort included patients until the year

2005. The trend in the preponderance of gram-negative pathogens (especially *Acinetobacter* spp.) as PCM pathogens seem to be universal. A major drawback of the UOC cohort was the lack of ASA evaluation as a risk factor. For the first time malignancy was an independent risk factor for PCM in the UOC cohort. The presence of a lumbar drain carried an independent association with PCM in the UOC cohort but in the NYU cohort there was no association. In the UOC cohort the presence of other infections in the association with PCM development was underscored.

Study 4: Prospective study regarding the risk factors associated with post-craniotomy meningitis in University of Crete Medical Center

In this prospective study we attempted to determine the rate, bacteriology and risk factors for PCM. The need for a prospective cohort was imperative for the confirmation of the risk factors for PCM defined in the retrospective studies of the Thesis. Patients >18 years old that underwent non-stereotactic craniotomies between January 2006 and December 2008 were included. Host factors and pre- and postoperative variables were evaluated as risk factors for meningitis.

Three hundred thirty four craniotomies were analyzed. Men represented 65.6% of them and TBI was the most common cause for craniotomy. 39.8% of the patients developed at least one infection. VAP was the most common infection recorded (22.5%). Meningitis/ventriculitis was encountered in 16 procedures (4.8%). One hundred percent of the LP samples cultured in suspected meningitis cases were positive. Gram-negative pathogens (*Acinetobacter* spp, *Klebsiella* spp, *Pseudomonas aeruginosa*, *E.cloacae* and *Proteus mirabilis*) represented 88% of them. In the multivariate analysis the risk for meningitis was independently associated with the perioperative steroid use (OR 11.55), CSF leak (OR 48.03), and postoperative ventricular drainage (OR 70.52).

Device-related postoperative communication of the CSF and the environment, CSF leak and perioperative steroid use were defined as major risk factors for PCM in this prospective study. The great preponderance of gram-negative pathogens (especially *Acinetobacter* spp), reconfirmed their predominance as nosocomial pathogens after the year 2000. Postoperative ventricular drainage was reconfirmed as a risk factor for PCM as in the two retrospective cohorts. CSF leak was a major risk factor as reported in previous studies. Perioperative steroid use was described for the first time as an independent risk factor for PCM. A major advantage of this study is the description of the microbiology and the sensitivities of the pathogens involved in

the PCM and the other infections encountered in patients undergoing craniotomy (especially VAP). This will provide great help in the empirical choice of antibiotics upon the presentation of the infections.

Study 5: Retrospective study regarding the infections in traumatic brain injury (TBI) in the University of Crete Medical Center- Risk factors associated with the development of surgical site infections (SSIs) and meningitis in TBI population

Admission and surgery for TBI was the most common in UOC Medical Center-Department of Neurosurgery. The purpose of this study was to delineate the frequency, types and risk factors for infection in TBI patients. This was a retrospective surveillance for all TBI patients, aged ≥18 years, cared at the Department of Neurosurgery of the University Hospital of Heraklion between 1999 and 2005.

Seven hundred and sixty patients (75% men- median age 41) were included. Two hundred fourteen infections were observed. The majority were infections of the lower respiratory tract (47%), mainly ventilator associated pneumonia (VAP) (33%), followed by surgical site infections (SSI) (17%). Multivariate analysis has shown that SSI development was independently associated with performance of ≥2 surgical procedures, presence of concomitant infections, namely VAP and urinary tract infections, insertion of lumbar and ventricular drains and cerebrospinal fluid (CSF) leak. Meningitis was associated with prolonged hospitalization, and insertion of lumbar and ventricular drains. There was a predominance of *Acinetobacter* spp as a VAP pathogen, gram positive organisms remained the most prevalent in SSI.

Respiratory tract infections were the most common among TBI patients. Device-related communication of the CSF with the environment and prolonged hospitalization were independently associated with the development of SSIs and meningitis in this particular cohort. The prevalence of the pathogens must be determined upon institutional basis for the establishment of proper treatment of these serious infections

Study 6: Association between operative site microbial counts and procedure classification in neurosurgery: A prospective study-Interim Report

No association between bacterial skin counts at the operative site and SSI has been reported. In this study we investigated the bacterial skin counts at the operative site, the association with procedure classification in neurosurgery and the impact on the development of SSI.

This was a prospective study performed in UOC Medical Center. Over a period of 18 months (February 2007- July 2008), three samples from neurosurgical patients were obtained while the patient was in the operating room and cultured. All samples were obtained at about 1 cm from the surgical incision, one pre-preparation sample, one post-preparation and one pre-closure sample. Patients having any type of procedure were included.

Ninety-three sample sets from 83 procedures were analyzed in this interim report. CoNS were the most frequently isolated organisms irrespectively of the time of the sampling and independently of the procedure classification. *P. acnes* was the second most frequently isolated organism. There was no statistical difference in the sampling positivity according to the sampling site or in the sampling positivity according to the procedure classification. Bacterial colony forming units (CFU) irrespectively of sampling time were not associated with procedure classification or revision surgery. CFU counts in the pre-preparation samples did not correlate with post-preparation or pre-closure samples. Pre-closure sample counts had a trend to increase with increased duration of surgery, especially if this exceeded the 3-hour duration. There was a trend to increased numbers of *P. acnes* and diphtheroids in the pre-closure samples.SSI development did not carry a significant association with the skin microbial CFU counts at any sampling and for any procedure classification. The positivity of the pre-preparation and the pre-preparation samples did not differ from a previous report.

In this pilot prospective study which is on-going we were unable to detect an association between procedure classification in neurosurgery, CFU counts in three different sampling times and SSI development

D.Εκτενής Περίληψη (ελληνικά)

Οι νοσοκομειακές λοιμώξεις το Κεντρικού Νευρικού Συστήματος (ΚΝΣ) αποτελούν μια σχετικά μικρή αλλά ιδιαίτερα σημαντική κατηγορία νοσοκομειακών λοιμώξεων. Αυτές οι λοιμώξεις περιλαμβάνουν ένα φάσμα από επιφανειακές λοιμώξεις της χειρουργικής τομής, λοιμώξεις των κοιλιοπεριτοναϊκών παροχετεύσεων, μηνιγγίτιδα/κοιλιίτιδα έως και εν τω βάθει αποστήματα του εγκεφαλικού παρεγχύματος. Αυτές οι λοιμώξεις είναι συνήθως σοβαρές, αν όχι και επικίνδυνες για τη ζωή και μπορούν να συνδέονται με κακή εξέλιξη. Οι λοιμώξεις στους νευροχειρουργικούς ασθενείς, δεν έχουν περιγραφεί διεξοδικά στην Ελλάδα. Σε αυτές τις εκτενείς μελέτες στο Ιατρικό Κέντρο του Πανεπιστημίου της Κρήτης προσπαθήσαμε να καθορίσουμε τους παράγοντες κινδύνου που σχετίζονται με τη μηνιγγίτιδα μετά κρανιοτομή (PCM) στην Κρήτη και να συγκρίνουμε τα αποτελέσματα με τους παράγοντες κινδύνου για PCM όπως καθορίσθηκαν σε πληθυσμό στο Ιατρικό Κέντρο του Πανεπιστημίου της Νέας Υόρκης (NYU). Ο τραυματισμός κεφαλής ήταν η κύρια αιτία εισαγωγής στην Νευροχειρουργική Υπηρεσία του Πανεπιστημίου της Κρήτης, αναλύσαμε και τις λοιμώξεις στον ειδικό αυτό πληθυσμό. Η συγγραφέας προσπάθησε να επιβεβαιώσει τα αποτελέσματα από τις αναδρομικές μελέτες με μία προοπτική μελέτη πάνω στους παράγοντες κινδύνου που σχετίζονται με PCM. Οι μελέτες συνοψίζονται ως εξής:

Μελέτη 1: Επισκόπηση των νευροχειρουργικών λοιμώξεων στο Πανεπιστημιακό Νοσοκομείο της Κρήτης βασισμένη σε μια αναδρομική μελέτη 3 ετών

Ανασκοπήθηκαν οι ιατρικοί φάκελοι των ασθενών >18 ετών που εισήχθησαν στο Νευροχειρουργικό Τμήμα του Πανεπιστημίου της Κρήτης μεταξύ Ιανουαρίου 2004 και Δεκεμβρίου 2006. Αναλύθηκαν ένα σύνολο 1112 εισαγωγών. Ο τραυματισμός κεφαλής ήταν η πιο κοινή αιτία για εισαγωγή (56.3%). Η κρανιοτομία ήταν η πιο συχνή επέμβαση (21.8%) αλλά το ένα τρίτο των ασθενών που εισήχθησαν σε αυτό το διάστημα δεν υπεβλήθησαν σε καμία μεγάλη επέμβαση.

Η συχνότητα των λοιμώξεων χειρουργικής τομής (SSIs) κατά την περίοδο αυτή ήταν 12.5% με πιο συχνή την επιφανειακή λοίμωξη της χειρουργικής τομής. Η πνευμονία του αναπνευστήρα (VAP), ήταν η πιο συχνή λοίμωξη εκτός χειρουργικού πεδίου. Η συχνότητα των SSIs ήταν υψηλότερη σε ασθενείς που επίσης ανέπτυξαν VAP, λοιμώξεις του ουροποιητικού (UTI) και βακτηριαιμίες/λοιμώξεις που συνδέονται με ενδαγγειακούς καθετήρες (BSI/CAB).

Στην πολυπαραγοντική ανάλυση, η κακοήθεια, η επέμβαση για αγγειακά συμβάματα, η επέμβαση για αντικατάσταση κοιλιοπεριτοναϊκής παροχέτευσης, η τοποθέτηση οποιασδήποτε περιεγχειρητικής παροχέτευσης και η επέμβαση με παραβίαση ενός παραρρινίου κόλπου ήταν ανεξάρτητοι προγνωστικοί παράγοντες για την ανάπτυξη SSIs. Η ανάπτυξη οποιασδήποτε λοίμωξης συνδεόταν ανεξάρτητα με το ιστορικό κακοήθειας, την επέμβαση για τραυματισμούς ή αγγειακά συμβάματα, η επενεπέμβαση για κοιλιοπεριτοναϊκή παροχέτευση και η τοποθέτηση οποιασδήποτε παροχέτευσης ή μετρητή ενδοκρανίου πίεσης (ICP).

Η ανάπτυξη λοιμώξεων, συμπεριλαμβανομένων των SSIs, συνδέονταν με παρατεταμένη νοσηλεία, τόσο στην ΜΕΘ όσο και στην κλινική αλλά όχι με αυξημένη θνητότητα. Τα πιο συχνά παθογόνα των λοιμώξεων χειρουργικού πεδίου ήταν τα θετικά κατά Gram. Τα στελέχη *Acinetobacter* ήταν τα πιο κοινά παθογόνα στη VAP (58.3%), ένα στοιχείο με ιδιαίτερη σημασία λόγω της αυξημένης ανθεκτικότητας στα αντιβιοτικά.

Με αυτήν την αναδρομική μελέτη, αποδείξαμε ότι η συχνότητα των SSIs ήταν σημαντικά υψηλή. Η κακοήθεια για πρώτη φορά αναδείχθηκε σαν παράγων κινδύνου για ανάπτυξη λοιμώξεων και ιδιαίτερα SSIs στους νευροχειρουργικούς ασθενείς. Η ανάπτυξη τόσο των SSIs όσο και άλλων λοιμώξεων συνδεόταν με παρατεταμένη νοσηλεία και κατά συνέπεια υψηλότερο συνολικό κόστος νοσηλείας αλλά όχι αυξημένη θνητότητα.

Μελέτη 2: Αναδρομική μελέτη για τους παράγοντες κινδύνου που σχετίζονται με τη μηνιγγίτιδα μετά από κρανιοτομή στο Ιατρικό Κέντρο του Πανεπιστημίου της Νέας Υόρκης

Αυτή είναι μια αναδρομική μελέτη από το Ιατρικό Κέντρο του Πανεπιστημίου της Ν. Υόρκης (NYU). Σκοπός της ήταν ο καθορισμός της συχνότητας, της μικροβιολογίας και των παραγόντων κινδύνου για μηνιγγίτιδα μετά από κρανιοτομή (PCM). Η μελέτη περιελάμβανε ασθενείς >18 ετών που υπεβλήθησαν σε μη στερεοτακτική κρανιοτομία μεταξύ Ιανουαρίου 1996 και Μαρτίου 2000. Οι κρανιοανατρήσεις, και η απλή τοποθέτηση μετρητών ICP ή οι απλές τοποθετήσεις παροχετεύσεων δεν περιελήφθησαν στη μελέτη. Παράγοντες των ασθενών, ο τύπος της κρανιοτομίας και προ- και μετεγχειρητικές μεταβλητές μελετήθηκαν ως παράγοντες κινδύνου για PCM.

Μελετήθηκαν τετρακόσιοι πενήντα τρεις ασθενείς. Ανάμεσά τους υπήρχαν 25 περιπτώσεις PCM. Οι περισσότερες περιπτώσεις κρανιοτομίας σε αυτή τη μελέτη έγιναν για ενδοκράνιους όγκους (45%). Ενενήντα δύο τοις εκατό των ασθενών

έλαβαν προεγχειρητική προφύλαξη, που ήταν στις περισσότερες φορές μια κεφαλοσπορίνη 1ης γενιάς (78%). Ο κίνδυνος PCM διπλασιαζόταν σε όσους δεν έλαβαν αντιβιοτική χημειοπροφύλαξη αλλά αυτό δεν ήταν στατιστικά σημαντικό (*p*= 0.148).

Το ποσοστό που ανέπτυξε PCM ανήλθε στο 5.5%, ποσοστό μεγαλύτερο από τις περισσότερες μελέτες. Οκτώ από τις δώδεκα θετικές καλλιέργειες ανέπτυξαν θετικούς κατά gram κόκκους [κυρίως κατά κοαγκουλάση αρνητικούς σταφυλοκόκκους (CoNS)]. Αυτό το αποτέλεσμα αντανακλά πιθανώς την επικράτηση των κατά gram θετικών οργανισμών σα νοσοκομειακά παθογόνα τη δεδομένη χρονική περίοδο.

Στην πολυπαραγοντική ανάλυση ο κίνδυνος μηνιγγίτιδας αυξανόταν με τις χειρουργικές επεμβάσεις που παραβίαζαν έναν παραρρίνιο κόλπο (OR 4.49), ένα υψηλό ASA score (OR 1.72) και η παρατεταμένη παραμονή κοιλιακής παροχέτευσης (OR 1.21) και μετρητή ενδοκρανίου πίεσης (OR 1.24).

Συμπερασματικά, η πρόσβαση των βακτηρίων των ανώτερων αεραγωγών στη χειρουργική τομή, παράγοντες του ασθενούς όπως εκφράζονται με το ASA score και η διάρκεια της μετεγχειρητικής επικοινωνίας του εγκεφαλονωτιαίου υγρού και του περιβάλλοντος, ήταν μείζονες παράγοντες για την ανάπτυξη PCM.

Μελέτη 3: Αναδρομική μελέτη σχετικά με τους παράγοντες κινδύνου που σχετίζονται με τη μηνιγγίτιδα μετά από κρανιοτομή στο Ιατρικό Κέντρο του Πανεπιστημίου της Κρήτης

Αυτή η αναδρομική μελέτη πραγματοποιήθηκε στο Ιατρικό Κέντρο του Πανεπιστημίου της Κρήτης μεταξύ Ιανουαρίου 1999 και Δεκεμβρίου 2005. Σκοπός της ήταν να καθορίσει τη συχνότητα, τη μικροβιολογία και τους παράγοντες κινδύνου για την ανάπτυξη μηνιγγίτιδας μετά από κρανιοτομία (PCM) για πρώτη φορά σε ελληνικό πληθυσμό. Η μελέτη συμπεριέλαβε ασθενείς άνω των 18 ετών που υπεβλήθησαν σε μη στερεοτακτική κρανιοτομία.

Αναλύθηκαν εξακόσιες δεκαεννέα κρανιοτομίες σε 479 ασθενείς. Ο τραυματισμός της κεφαλής (TBI) ήταν η πιο συχνή αιτία για κρανιοτομία. Εικοσιέξι τοις εκατό των ασθενών ανέπτυξαν τουλάχιστον μία λοίμωξη. Η πνευμονία του αναπνευστήρα (VAP) ήταν η πιο συχνή καταγεγραμμένη λοίμωξη (13.1%). Μηνιγγίτιδα/κοιλιίτιδα αναπτύχθηκε μετά από 37 επεμβάσεις (ποσοστό 6.1%). Εβδομήντα επτά τοις εκατό των δειγμάτων εγκεφαλονωτιαίου υγρού (ENY) ήταν θετικά για μικροοργανισμούς. Τα κατά Gram αρνητικά παθογόνα αποτελούσαν το

48% των θετικών καλλιεργειών ενώ τα κατά Gram θετικά παθογόνα αντιπροσώπευαν το 43%.

Στην πολυπαραγοντική ανάλυση ο κίνδυνος PCM σχετιζόταν ανεξάρτητα με την ανάπτυξη μιας άλλης λοίμωξης του χειρουργικού πεδίου (SSI) (OR 4.5), με λοίμωξη του κατώτερου αναπνευστικού (OR 4.4), με λοίμωξης του ουροποιητικού (OR 6.2), παρουσία κακοήθειας (OR 3.6), με την παρουσία κοιλιακής παροχέτευσης (OR 12.7), την παρουσία οσφυϊκής παροχέτευσης (OR 91.8) και την πραγματοποίηση επείγουσας επέμβασης (OR 2.9).

Η μετεγχειρητική επικοινωνία ΕΝΥ και περιβάλλοντος, οι SSIs εκτός μηνιγγίτιδας και οι λοιμώξεις εκτός χειρουργικού πεδίου καθορίσθηκαν ως μείζονες παράγοντες κινδύνου για την ανάπτυξη PCM.

Σε σύγκριση με τον πληθυσμό του NYU, υπήρχαν πολύ περισσότερες επείγουσες επεμβάσεις στον πληθυσμό της Κρήτης (51.4% vs 34.2%). Αυτό κυρίως αντιπροσωπεύει τη διαφορά στο ποσοστό των ασθενών που είχαν TBI. Η διαφορά μεταξύ των περιπτώσεων μηνιγγίτιδας μεταξύ των δύο πληθυσμών δεν ήταν στατιστικά σημαντική (6.1% vs. 5.5%). Στον πληθυσμό της Κρήτης υπήρχε μία μικρή υπεροχή των κατά Gram αρνητικών παθογόνων, γεγονός που πιθανώς αντιπροσωπεύει ότι οι ασθενείς της Κρήτης αναλύθηκαν μέχρι το 2005 ενώ ο πληθυσμός της Ν. Υόρκης αναλύθηκε μέχρι το έτος 2000. Η τάση για την επικράτηση των κατά Gram αρνητικών παθογόνων (ιδίως των *Acinetobacter* spp.) σαν αιτίες PCM φαίνεται να είναι παγκόσμια παρατήρηση. Ένα μεγάλο μειονέκτημα της μελέτης αυτής είναι η έλλειψη της εκτίμησης των ασθενών με το ASA score. Η παρουσία κακοήθειας αναδείχθηκε για πρώτη φορά ως ανεξάρτητος παράγων για την ανάπτυξη PCM. Η παρουσία οσφυϊκής παροχέτευσης συσχετιζόταν ανεξάρτητα με την ανάπτυξη PCM στον πληθυσμό της Κρήτης ενώ στον πληθυσμό της Ν. Υόρκης δεν υπήρχε καμιά συσχέτιση. Επίσης στον πληθυσμό της Κρήτης υπογραμμίστηκε η ανάπτυξη λοιμώξεων εκτός του χειρουργικού πεδίου και η συσχέτιση τους με την ανάπτυξη PCM.

Μελέτη 4: Προοπτική μελέτη για τους παράγοντες κινδύνου για την ανάπτυξη κινδύνου μετά από κρανιοτομία στο Ιατρικό Κέντρο του Πανεπιστημίου της Κρήτης

Σκοπός της προοπτικής μελέτης ήταν ο καθορισμός της συχνότητας, της μικροβιολογίας και των παραγόντων κινδύνου για την ανάπτυξη μηνιγγίτιδας μετά από κρανιοτομία (PCM). Η ανάγκη για προοπτική μελέτη ήταν επιτακτική για την

επιβεβαίωση των παραγόντων κινδύνου όπως καθορίσθηκαν από τις αναδρομικές μελέτες που προηγήθηκαν. Η μελέτη συμπεριέλαβε ασθενείς άνω των 18 ετών που υπεβλήθησαν σε κρανιοτομία μεταξύ Ιανουαρίου 2006 και Δεκεμβρίου 2008.

Αναλύθηκαν 334 κρανιοτομίες. Οι άντρες αντιπροσώπευαν το 65.6% του πληθυσμού και ο τραυματισμός της κεφαλής ήταν η πιο συχνή αιτία για κρανιοτομία. Το 39.8% των ασθενών ανέπτυξαν τουλάχιστον μία λοίμωξη. Η πιο συχνή λοίμωξη που καταγράφηκε ήταν η πνευμονία του αναπνευστήρα (VAP) (22.5%). Μηνιγγίτιδα/κοιλιίτιδα παρατηρήθηκε σε 16 περιπτώσεις (4.8%). Το 100% των δειγμάτων ΕΝΥ που καλλιεργήθηκαν ήταν θετικά για την ανάπτυξη μικροοργανισμών. Τα αρνητικά κατά Gram παθογόνα (*Acinetobacter* spp, *Klebsiella* spp, *Pseudomonas aeruginosa, E.cloacae* και *Proteus mirabilis*) αντιπροσώπευαν το 88% των καλλιεργειών. Στην πολυπαραγοντική ανάλυση, ο κίνδυνος μηνιγγίτιδας σχετιζόταν ανεξάρτητα με την περιεγχειρητική χρήση στεροειδών (OR 11.55), την διαφυγή ΕΝΥ (OR 48.03), και την μετεγχειρητική κοιλιακή παροχέτευση (OR 70.52).

Η μετεγχειρητική επικοινωνία μεταξύ ΕΝΥ και περιβάλλοντος, η διαφυγή ΕΝΥ και η περιεγχειρητική χρήση στεροειδών ήταν οι κυριότεροι παράγοντες κινδύνου για την ανάπτυξη PCM σε αυτή την προοπτική μελέτη. Η μεγάλη επικράτηση των αρνητικών κατά Gram παθογόνων (ειδικά των *Acinetobacter* spp), επαναεπιβεβαίωσαν την κυριαρχία τους σα νοσοκομειακά παθογόνα μετά το έτος 2000. Η μετεγχειρητική κοιλιακή παροχέτευση επανακαθορίσθηκε σαν παράγων κινδύνου για PCM όπως και στις αναδρομικές μελέτες. Η διαφυγή ΕΝΥ ήταν σημαντικός παράγων κινδύνου όπως έχει αναδειχθεί και στη βιβλιογραφία. Η περιεγχειρητική χρήση στεροειδών περιγράφηκε για πρώτη φορά σαν ανεξάρτητος παράγων συνδεόμενος με PCM. Ένα μεγάλο πλεονέκτημα της συγκεκριμένης μελέτης ήταν η περιγραφή της μικροβιολογίας και των ευαισθησιών των παθογόνων που καλλιεργήθηκαν στις περιπτώσεις μηνιγγίτιδας καθώς και άλλων λοιμώξεων (ειδικά στη VAP). Πιστεύουμε ότι αυτό θα φανεί πολύ χρήσιμο στην εμπειρική επιλογή των αντιβιοτικών με την εμφάνιση της λοίμωξης.

Μελέτη 5: Αναδρομική μελέτη σχετικά με τις λοιμώξεις στους ασθενείς που είχαν τραυματισμό κεφαλής (TBI) στο Ιατρικό Κέντρο του Πανεπιστημίου της Κρήτης. Καθορισμός των παραγόντων κινδύνου για την ανάπτυξη μηνιγγίτιδας και λοιπών λοιμώξεων χειρουργικού πεδίου (SSIs)

Οι εισαγωγές και οι επεμβάσεις για TBI ήταν οι πιο συχνές αιτίες εισαγωγής στη Νευροχειρουργική υπηρεσία του Ιατρικού Κέντρου του Πανεπιστημίου της Κρήτης.

Σκοπός της μελέτης ήταν ο καθορισμός της συχνότητας και των παραγόντων κινδύνου για την ανάπτυξη λοιμώξεων σε ασθενείς με TBI. Η μελέτη ήταν αναδρομική και περιελάμβανε όλους τους ασθενείς με TBI, ηλικίας άνω των 18 ετών που εισήχθησαν μεταξύ Ιανουαρίου 1999 και Δεκεμβρίου 2005.

Αναλύθηκαν 760 ασθενείς (75% άνδρες) με διάμεση ηλικία 41 έτη. Παρατηρήθηκαν 214 λοιμώξεις. Η πλειονότητα αποτελείτο από λοιμώξεις του κατώτερου αναπνευστικού, κυρίως πνευμονία του αναπνευστήρα (VAP) ενώ ακολουθούσαν οι λοιμώξεις του χειρουργικού πεδίου. Η πολυπαραγοντική ανάλυση έδειξε ότι ότι η ανάπτυξη SSI συσχετιζόταν ανεξάρτητα με την τέλεση ≥2 χειρουργικών επεμβάσεων, την παρουσία λοιμώξεων εκτός χειρουργικού πεδίου κυρίως VAP και λοιμώξεων του ουροποιητικού, την παρουσία κοιλιακών και οσφυϊκών παροχετεύσεων και τη διαφυγή ΕΝΥ. Η μηνιγγίτιδα συσχετιζόταν ανεξάρτητα με παρατεταμένη νοσηλεία και παρουσία κοιλιακών και οσφυϊκών παροχετεύσεων. Υπήρχε επικράτηση των στελεχών *Acinetobacter* σαν παθογόνο VAP, όμως τα κατά gram θετικά παθογόνα επικρατούσαν σαν αίτια SSI.

Οι λοιμώξεις του αναπνευστικού ήταν οι πιο συχνές σε ασθενείς μετά TBI. Η επικοινωνία μεταξύ ΕΝΥ και περιβάλλοντος και η παρατεταμένη νοσηλεία συσχετίζονταν ανεξάρτητα με την ανάπτυξη SSIs και μηνιγγίτιδας στον πληθυσμό με TBI. Οι υπεύθυνοι μικροοργανισμοί πρέπει να καθορίζονται σε κάθε διαφορετικό νοσηλευτικό ίδρυμα για την καταλληλότερη εμπειρική θεραπεία των σοβαρών αυτών λοιμώξεων.

Μελέτη 6: Συσχέτιση μεταξύ των αριθμών των μικροβίων της εγχειρητικής τομής και της κατηγοριοποίησης των νευροχειρουργικών επεμβάσεων: Μία προοπτική μελέτη

Δεν έχει αποδειχθεί η συσχέτιση μεταξύ των αριθμών μικροβίων στη χειρουργική τομή και στην ανάπτυξη λοιμώξεων του χειρουργικού πεδίου μετά από νευροχειρουργικές επεμβάσεις. Σκοπός της μελέτης είναι η διερεύνηση της συσχέτισης μεταξύ του αριθμού των μικροβίων της χειρουργικής τομής και της κατάταξης της νευροχειρουργικής επέμβασης και την επίδραση στην ανάπτυξη SSIs.

Πρόκειται για προοπτική μελέτη που διεξήχθη στο Ιατρικό Κέντρο του Πανεπιστημίου της Κρήτης μεταξύ Φεβρουαρίου 2007 και Ιουλίου 2008. Σε αυτό το διάστημα τρία δείγματα λαμβάνονταν από κάθε ασθενή όσο ήταν στο χειρουργικό τραπέζι. Τα δείγματα λαμβάνονταν σε απόσταση περίπου ενός εκατοστού από τη χειρουργική τομή, ένα πριν την αποστείρωση, ένα αμέσως μετά την αποστείρωση, κι

ένα αμέσως πριν το κλείσιμο της τομής. Συμπεριελήφθησαν ασθενείς που υπεβλήθησαν σε οποιαδήποτε νευροχειρουργική επέμβαση.

Αναλύθηκαν 93 δείγματα από 83 επεμβάσεις. Οι κοαγκουλάση-αρνητικοί σταφυλόκοκκοι (CoNS) ήταν οι επικρατούντες μικροοργανισμοί ανεξάρτητα από την χρονική στιγμή λήψεως του δείγματος και ανεξάρτητα από την κατηγοριοποίηση της επέμβασης. Το *P. acnes* ήταν ο δεύτερος πιο συχνός μικροοργανισμός. Δεν υπήρχε στατιστικά σημαντική διαφορά στη θετικότητα του δείγματος ανάλογα με το σημείο λήψης ή ανάλογα με την κατηγοριοποίηση της επέμβασης. Οι βακτηριακές «μονάδες σχηματισμού αποικιών» (CFUs) ανεξάρτητα από τη χρονική στιγμή λήψης του δείγματος δε συσχετίζονταν με την κατηγορία της επέμβασης ή το αν η επέμβαση ήταν επαναληπτική. Οι αριθμοί των CFUs στο προ-αποστείρωσης δείγμα δε συσχετίζονταν σημαντικά με τους αριθμούς είτε μετα-αποστείρωση είτε προ-συρραφή. Οι αριθμοί των μικροβίων προ-αποστείρωσης δε συσχετίζονταν σημαντικά με τους αριθμούς στα δείγματα μετα-αποστείρωσης ή προ-συρραφής. Τα προ-συρραφής δείγματα είχαν μια αυξητική τάση όσο αύξανε η διάρκεια της επέμβασης, ιδιαίτερα αν αυτή ξεπερνούσε τις τρεις ώρες. Υπήρχε μια τάση για αυξημένους αριθμούς *P. acnes* και διφθεροειδών στα προ-συρραφής δείγματα. Η ανάπτυξη SSIs δε συσχετιζόταν σημαντικά με τον αριθμό των CFUs σε οποιαδήποτε στιγμή δειγματοληψίας και για οποιαδήποτε κατηγορία επέμβασης. Το ποσοστό θετικότητας των δειγμάτων προ και μετά αποστείρωσης δε διέφεραν από προηγούμενη μελέτη.

Σε αυτή την πιλοτική προοπτική μελέτη που συνεχίζεται δεν διαπιστώσαμε συσχέτιση μεταξύ κατηγορίας της νευροχειρουργικής επέμβασης, αριθμού CFUs σε τρεις διαφορετικές χρονικές στιγμές και ανάπτυξης SSIs.

1. Introduction
Infections in patients undergoing neurosurgery

1.1 Surgical Site Infections and Central Nervous System Infections in Patients undergoing neurosurgery

Nosocomial infections related to the central nervous system (CNS) are a relatively small but important category of hospital-acquired infections. These infections span a spectrum from superficial wound infections, to ventricular shunt infections, meningitis and deep-seated abscesses of the brain parenchyma. The patient populations affected are equally diverse, involving neonates, children, and adults.

Nosocomial infections of the CNS are usually serious, if not life threatening, and are frequently associated with a poor outcome [1-8]. These nosocomial infections present many challenges in diagnosis. A heightened awareness has fostered declining rates of infection. In spite of improving techniques and new preventive strategies, however, the threat is constant, and the stakes remain painfully high.

1.1.1 Risk Factors

The patients at greatest risk for acquiring nosocomial CNS infections are the neurosurgical patients. These patients are subjected to procedures that traverse the skin and scalp, violate meningeal coverings, impinge upon the paranasal sinuses, implant foreign bodies, and expose tissues to hematogenous sources of infections. Infection in this setting is often facilitated by the presence of a cerebrospinal fluid (CSF) leak that occurs when the dura is disrupted and the subarachnoid space communicates with the skin, nasal cavity, paranasal sinuses, or middle ear [9-11]. The group at risk includes adult and pediatric patients undergoing common neurosurgical and neuroinvasive procedures such as craniotomy, spinal fusion, laminectomy, insertion of halo pins, burr hole placement, and implantation of ventricular shunts and reservoirs. Less common procedures include stereotactic brain biopsy, hypophysectomy, paranasal sinus surgery, acoustic neuroma resection, temporary ventricular drainage, placement of intracranial monitoring devices, nerve stimulator placement, lumbar puncture, spinal anesthesia, and skull/spinal fixation.

Patients who have suffered head trauma are another population at increased risk to develop meningitis. These individuals have sustained trauma or fractures to the basilar skull and facial bones, facilitating the formation of a CSF fistula. This posttraumatic condition substantially increases the likelihood of CSF infection,

particularly bacterial meningitis [12, 13]. A post-traumatic CSF leak was a predisposing factor in approximately 9% of cases of nosocomial bacterial meningitis [4].

Risk factors for SSIs can be classified into host factors and surgical factors. Examples of host factors include age, sex, American Society of Anesthesiologists (ASA) physical status classification (Appendix, Table I), underlying diseases such as diabetes mellitus, nutritional status, presence of other remote infections, and duration of preoperative stay. Age and diabetes mellitus have been associated with increased risk of SSIs in some studies but not all [14-16]. In a well-designed retrospective study regarding meningioma patients age as a risk factor for infections did not achieve statistical significance (p= 0.059)[17]. Obesity has not been shown to increase the incidence of SSIs [18]. ASA score>2 has been confirmed as an independent risk factor for the development of meningitis [19] but it has been associated with the development of meningitis in other studies too [1, 20].

Surgical factors include whether the procedure was an emergency or elected [20], hair removal technique, surgeon, use of perioperative antibiotics, and duration of surgery, especially if this exceeds >2-4 hours [15, 20-23]. In a very important study including patients undergoing neurosurgical procedures, the presence of a postoperative CSF leak was associated with a more than 13-fold increase in the infection risk [16]. That has been confirmed in most recent studies [23-25]. Also, a remote concurrent infection increased the infection risk by six times [16]. Generally, a concurrent remote or incision infection and previous shunt infections have been associated with postoperative infections [25, 26]. In the Mollmann study three other risk factors (paranasal sinus entry, placement of a foreign body, and use of postoperative drains) were associated with an increased risk of infection, although this association was not statistically significant [16]. Other authors have confirmed the importance of prolonged ICP monitoring use for >5 days [19, 25], prolonged ventricular drain use [19, 26], placement of a foreign body [26], and repeat or additional neurosurgical procedures [19, 20, 22, 24]. Factors not associated with an increased risk of infection included use of the operative microscope, steroid administration, and acute therapy for seizures.

A prospective study of postoperative neurosurgical infections demonstrated a validated five-category classification system for neurosurgical infections based on specific definitions. It was found that infection rates were highest for contaminated

cases (contamination known to occur, 9.7%), followed by dirty cases (established sepsis at the time of surgery, 9.1%), clean contaminated (risk of contamination of operative site during surgery, 6.8%), clean with temporary or permanent foreign body (6.0%), and clean (no identifiable risk factors present, 2.6%). In this study, surgery lasting longer than 4 hours was associated with an infection rate of 13.4% [27] (Table 1.1.1).

In addition to patients undergoing neurosurgery, patients undergoing invasive diagnostic or therapeutic procedures that penetrate the CNS are at risk for developing a nosocomial CNS infection. A subgroup of neurosurgery patients at high risk for nosocomial CNS infections is those with ventricular shunts. Since most shunt infections (70%) have an onset within 2 months of surgery, it is likely that the infecting microorganism is introduced during surgery or in the postoperative period. There appears to be no association between the shunt infection rates and type of shunt and underlying disease. In older studies the rate of infection is also reported to vary with the neurosurgeon [28].

Table 1.1.1. Classification of Neurosurgical operations (according to Narotam et al, Neurosurgery 1994; 34: 409-16)

Category	Definition	Examples	Infection Rate
Dirty	Established sepsis at the time of surgery	Brain abscess, subdural or parafalcine empyema, osteitis, ventriculitis, meningitis, purulent skin infections	9.1%
Contaminated	Contamination is known to have occurred	Compound skull fracture, open scalp lacerations, CSF fistulae, subsequent operations (early)	9.7%
Clean contaminated	Risk of contamination of operative site during surgery	Entry into paranasal air sinuses, transsphenoidal procedures, prolonged surgery, breaches in surgical technique	6.8%
Clean with foreign body	Either a temporary or permanent foreign body left in situ	Shunt surgery, ICP monitors, clamps, ventricular drains, acrylic cranioplasties, metal rods	6%
Clean	No identifiable risk factors present	Ideal operating conditions, drainage not exceeding 24 hours	2.6%

1.1.2 Device-Related Risk Factors

Infection is a well-recognized complication of ventriculostomy catheters used for monitoring and drainage [29]. Aucoin et al. [30] noted that the rate of infection was associated with the type of monitor used. The lowest infection rate was associated with the subarachnoid screw (7.5%), followed by a rate of 14.9% for the subdural cup catheter and a 21.9% rate for the ventriculostomy catheter. An intracranial monitoring technique, the Camino intraparenchymal fiberoptic catheter system, is associated with an infection rate of 2.5% [31] (Figure 1.1.1). In the very important prospective study by Munch et al, the infectious complications comprised only 0.7% when the complications regarding technical aspects were 23.5% [32]. Generally, the infection rate reported ranges from 0-40% with an average of 10% [25, 26]. In a very good recent study the ICP bolt positivity was reported at 8.5% with absence of a cutaneous infection at the site of bolt insertion. In this study they mention again that placement of the ICP monitor in the operating room or in the ICU does not affect the infection rate [33]. Other factors reported to predispose patients to infection included open trauma or hemorrhage, use of an irrigating solution such as bacitracin, presence of a CSF leak, concurrent infection outside the CNS and duration of intracranial pressure (ICP) monitor greater than 4 days [25, 30]. To reduce the risk of ICP monitor related infections, it is recommended that the device be inserted using aseptic technique, that the device be removed as soon as possible and preferably before 5 days, and that a closed system be maintained. Use of prophylactic antibiotics did not significantly reduce the risk of infection [25, 34].

In a study by Mayhall et al. [7] of ventriculostomy-related infections, risk factors significantly associated with infection included an intracerebral hemorrhage with intraventricular hemorrhage, performance of a neurosurgical operation, ICP of 20 mm Hg or higher, ventricular catheterization for longer than 5 days, and irrigation of the system. The incidence of infection was not related to where the catheter was inserted when the intensive care unit was compared with the operating room. Two additional studies confirm the relationship of ventriculitis to monitoring duration and supports removal of catheters as soon as possible [35, 36]. It seems though that there is a rising risk over the first 10 days but infection then becomes very unlikely despite a population that continues to be at risk [36]. Risk factors associated with ventriculitis were sepsis, pneumonia, depressed skull fracture requiring surgery, craniotomy, and

intraventricular hemorrhage. The use of prophylactic catheter exchange although proposed by some authors, is not currently justified by the available data [29].

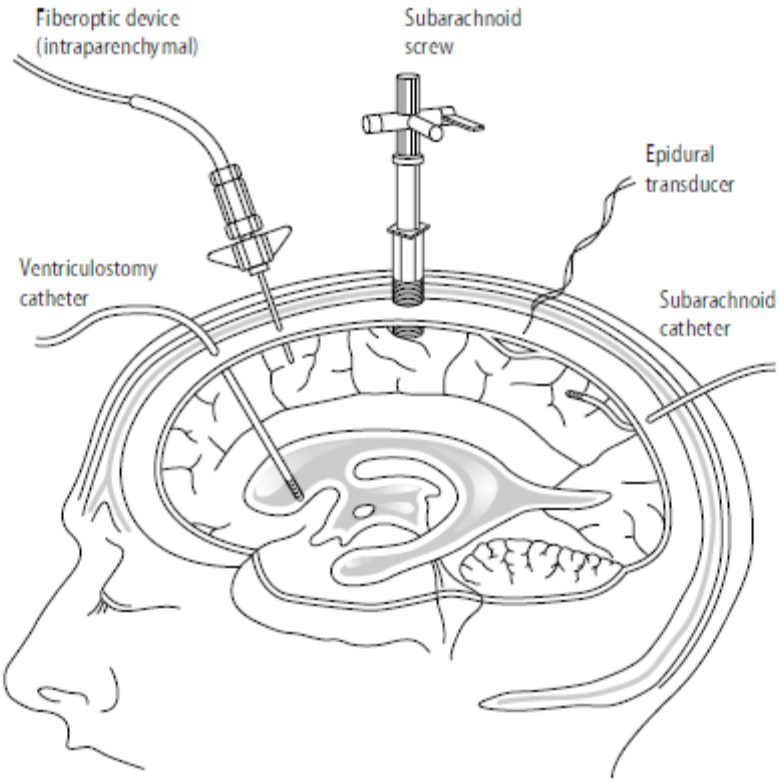


Figure 1.1.1. Methods of monitoring intracranial pressure

1.1.3 Sources of Infecting Microorganisms in Neurosurgical Infections

Although many sources of contamination of a neurosurgical operation have been described, it is usually impossible to document with certainty the source for a given SSI. Probably most infections occur at the time of surgery from either direct inoculation of residual flora of the patient's skin or from contiguous spread from infected host tissue. Direct inoculation of microorganisms can also occur occasionally from the hands of surgical team members via a tear in a glove. Rarely, the source of infection is traced to contaminated surgical material such as a solution, device, or instrument. In two neurosurgical patients with postoperative Bacillus cereus meningitis, the source of the microorganisms was found to be heavily contaminated linen [37]. Occasionally, during the postoperative period, an SSI results from direct inoculation of microorganisms. Airborne contamination at the time of surgery, either from the patient or from operating room personnel, accounts for some neurosurgical

infections [1]. Lastly, a postoperative infection rarely results from hematogenous seeding of a wound from an infected intravenous line or other remote infection.

1.1.4 Incidence and distribution

Nosocomial infections of the CNS (excluding wound or SSIs) are relatively uncommon, accounting for approximately 0.4% of all nosocomial infections. Meningitis accounts for 91% of these infections, followed by intracranial suppurations (8%) and isolated spinal abscess (1%). When infection rates are examined using data reported from 163 hospitals participating in the NNIS system, 0.56 CNS infections per 10,000 hospital discharges occurred from 1986 through early 1993. While these numbers are relatively small, it must be noted that CNS infections directly related to neurosurgical procedures (SSIs) are not reflected in these numbers. The majority of nosocomial CNS infections occurring in this setting are designated under the larger category of SSIs (16% of all nosocomial infections) by CDC/NNIS system surveillance criteria. These infections accounted for 8% of hospital-acquired infections following craniotomy and 34% of infections after spinal surgery in NNIS system hospitals from 1986 to 1992 [38].

In addition, certain nosocomial CNS infections may represent a greater proportion of specific types of infection. For example, a retrospective study of acute bacterial meningitis in adults over a 27-year period at the Massachusetts General Hospital found 40% of 493 total episodes to be nosocomial in origin [4]. Among NNIS system hospitals in the period 1986 through 1992, CNS infections and SSIs were responsible for 3.3% and 12% of all nosocomial neurosurgical infections, respectively [38]. Recently, the overall SSI rate in the neurosurgical population has been determined to 6.2% [4].

Table 1.1.2 shows the distribution of SSIs complicating neurosurgical procedures and illustrates the significant proportion of deep infections that occur in relation to the surgical site according to the CDC/NNIS data. Taking into account some of the problems mentioned above, most hospital series report infection rates of less than 5%. When individual neurosurgical procedures are compared, differences in infection rate become more apparent. The incidence of all CNS infection following typically clean craniotomy may vary from less than 1% to nearly 9%, whereas the rates following laminectomy range from 0.6% to 5%. Postoperative meningitis after clean craniotomy has a reported incidence of 0.5% to 2% when perioperative antibiotics are given [39-

42]. Without antibiotic prophylaxis, other studies have found rates ranging from 2% to 7% [42-44].

Analysis of infection rates following ventricular shunt surgery is particularly complex. Depending on the use of a case rate (occurrence per patient) or operative rate (occurrence per procedure) of infection and the duration of follow-up, an extremely wide variation in incidence may be seen. Perhaps, when in 1916 Cushing stated, “There has never been any infection, even of a stitch in the scalp, in something over 300 cranial operations in the writer's series”, he underestimated the situation.

Examination of SSIs reported from NNIS system hospitals shows infection rates in uncomplicated procedures with minimum risk factors to be 0.56/100 operations for craniotomies, 0.70/100 operations for spinal fusion, and 3.85/100 operations for ventricular shunts [45]. The last rate is the fifth highest among all operative procedures [45]. Importantly, these surveillance rates by definition include both superficial and deep infections related to operative site [46].

1.1.5 Types of Nosocomial Central Nervous System Infections

Nosocomial infections related to the CNS may be broadly divided into two major categories (Table 1.1.3): postsurgical infections and nonsurgical infections, including those related to neuroinvasive or neurodiagnostic procedures. The first category consists of SSIs [38]. Infections of this type may occur following craniotomy, ventriculostomy, and spinal column surgery. Rarely, SSIs complicate other neurosurgical operations, such as peripheral nerve surgery and carotid endarterectomy. SSIs are further classified as superficial or deep incisional SSIs, using the fascial plane as divider. Previously termed deep surgical infections unrelated to soft tissues are now classified as organ/space SSIs by the aforementioned CDC criteria [38]. These infections may present as a local and/or diffuse infectious process. Local suppurative infections complicating neurosurgical procedures include the following: parenchymal brain abscess, subdural empyema, epidural abscess, discitis, subgaleal collection, and osteomyelitis of the cranium or spine (Figure 1.1.2). Diffuse infection of the subarachnoid space defines meningitis or ventriculitis. This latter distinction is somewhat arbitrary.

Table 1.1.2. Surgical Site Infections following neurosurgical procedures (according to CDC/NNIS data)

Procedure	Men	SA	SSI	IC	IAB	Bone	Disc	Other
Craniotomy	22%	-	62%	12%	-	-	-	4%
Laminectomy	1%	3%	86%	-	-	4%	6%	-
VP shunt	76%	-	18%	-	4%	-	-	2%
Head and neck	3%	-	90%	-	-	2%	-	5%
Miscellaneous	8%	2%	82%	-	8%	-	-	-

Men: Meningitis, SA: Spinal abscess, SSI: Surgical Site Infection, IC: Intracranial Infection, IAB: Intra-abdominal abscess

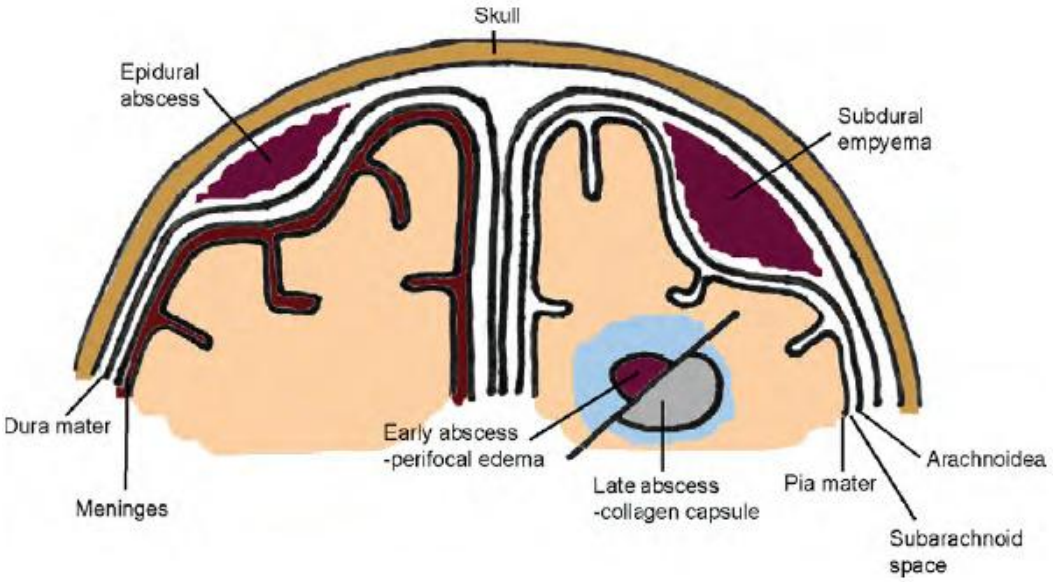


Figure 1.1.2. Schematic coronal view of the sites of common bacterial CNS infections

Table 1.1.3. Nosocomial Central Nervous System Infections

Postsurgical	Nonsurgical
Surgical Site Infections	Continuous focus or hematogenous
Superficial	Epidural abscess
Deep	Subdural empyema
Local suppurative infections	Brain abscess
Osteomyelitis	Meningitis
Discitis	
Subgaleal collection	
Epidural abscess	
Subdural empyema	
Diffuse infections	
Meningitis	
Ventriculitis	

1.1.6 Definitions, Diagnostic Criteria and Clinical Presentation

Doubt over hospital versus community acquisition of an infection is a constant problem compounded by the ubiquity of the major pathogens. For SSIs related to implantable devices, nosocomial infection may be diagnosed up to 1 year after surgery. Some experts consider 60 days a more reasonable length of time for nosocomial ventricular shunt infections, as the majority of infections occur within this period [47]. In addition, the diagnosis of infection ultimately may be left to the discretion of the attending physician and is inherently subjective. A prospective study by Taylor et al. [48] demonstrated that 40% of neurosurgical wound infections were diagnosed using nonstandardized criteria by the surgeon. The potential effect on infection rates is obvious. Ventricular shunt infections illustrate several of these problems. CSF profiles may be nondiagnostic, the microorganism involved may be from the normal flora, and the infection may become evident weeks after hospital discharge.

1.1.6.1 Surgical Site and Related Surgical Infections

Commonly SSIs are classified in the surgical literature as either superficial or deep. Superficial neurosurgical infections are considered to be limited by the cranial or lumbodorsal fascia. Deep wound infections encompass soft tissue infections below the fascia, discitis, osteomyelitis, and bone flap infections. However, infections below the dura (ventriculitis, meningitis, brain abscess) have been included under deep wound infections too (Figure 1.1.2). To improve surveillance and clarify potential overlap in reporting, the CDC definitions include the category of organ/space SSI to cover additional sites adjacent to the operative site. Specific organ/space SSIs related to neurosurgery include the following: meningitis, ventriculitis, disc space infection, osteomyelitis, intracranial abscess, and spinal abscess [38]. With the exception of infections related to implantable devices, other SSIs occur within 30 days of the operative procedure.

1.1.6.2 Incisional Surgical Site Infections

The diagnosis of SSIs is usually made clinically. Neurosurgical site infections must be promptly identified because of the propensity to spread to deeper spaces [49]. Superficial incisional SSIs tend to be diagnosed at an early stage, usually within the first postoperative week [50]. Generally, the area is swollen and erythematous with

local tenderness. Purulent discharge and/or microorganisms isolated from drainage or a wound aspirate complete the picture. Temperature and the white blood count (WBC) are not uniformly elevated; the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be increased, there may be fever and chills or hyperglycemia in diabetic patients. Patients often complain of increased pain at the surgical site [2, 26]. Deep incisional SSIs present later postoperatively with a course that may be insidious or progressive. The average time between surgery and the diagnosis of a deep infection in spinal surgery may vary from 10 to 15 days, with the range extending several weeks [26]. A relatively normal appearance of the overlying surgical site contributes to this delay in many cases.

Infections of bone flaps following craniotomy are well described [1, 40, 51]. By definition, infection involves either the free (devitalized) or osteoplastic bone flap following a supratentorial craniotomy. These infections may be obviously symptomatic with high fever, scalp tenderness, and suppuration [52] or more indolent with a persistent fistula [2]. The use of computed tomography (CT) or magnetic resonance imaging (MRI) is invaluable in establishing a diagnosis. In general, a cranial bone flap infection is diagnosed clinically with either radiographic or microbiologic confirmation. A subgaleal abscess occasionally occurs adjacent to a scalp surgical site. In this case, a localized collection forms in the space between the galea of the scalp and the pericranium. Scalp tenderness, erythema, fever, and regional adenopathy may be seen. Osteomyelitis or intracranial spread of infection can occur secondarily if the underlying skull integrity has been compromised. Diagnosis of most deep incisional SSIs may be established clinically, via culture of a deep aspirate, or, rarely, with the assistance of radiologic studies. Evaluation of a soft tissue fluid collection with sonography or CT scan can be helpful [26].

1.1.6.3 Organ/Space Surgical Site Infections

Discitis (infection of the intervertebral disc space) is a relatively uncommon but potentially serious postoperative complication of spinal surgery [53]. Patients typically present with recurrent back pain after surgery and initial improvement of preoperative symptoms. In a series of 111 cases of discitis described by Iversen et al. [54], back pain appeared at an average of 16 days postoperatively. Neurologic deficits are unusual. Fever is variably present, and the superficial surgical site frequently appears normal. Most notable is the severe and persistent low back pain out of

proportion to the findings on physical examination. Routine laboratory studies such as the WBC are generally unremarkable, with the exception of the ESR [54]. A significantly elevated ESR more than 2 weeks postoperatively correlates positively with disc space infection.

Currently, MRI with gadolinium enhancement has become the procedure of choice and it may distinguish disc space and vertebral body infection from the normal postoperative spine with a high degree of accuracy [55, 56]. Diagnosis of infectious discitis should be confirmed by biopsy despite a consistent clinical and radiographic picture. Peripheral blood cultures are rarely positive for the offending microorganism [56]. Percutaneous needle aspiration of the affected disc space under fluoroscopic or CT guidance is the method of choice. Ideally, antibiotics should be withheld until after the procedure is complete. The results of the Gram stain and/or culture are diagnostic in up to 70% of cases, and histological examination may indicate a septic picture in cases lacking positive microbiology [56]. Isolated vertebral osteomyelitis is very uncommon following laminectomy and related procedures. When present, it is usually associated with progressive infection of the contiguous disc space. Clinical presentation and diagnoses are virtually the same as outlined above for discitis [56].

1.1.6.4 Meningitis

Nosocomial meningitis is a rare complication following neurosurgical procedures and it is associated with high morbidity and mortality. Its diagnosis requires a high index of clinical suspicion and support from CSF analysis. Its incidence has varied in different studies from 0.34-2.7% [57, 58], but it was in 8.3% of patients who underwent a translabyrinthine approach for the resection of acoustic neuromas [59]. Independent risk factors for the development of post-neurosurgical meningitis include the duration of ventricular drainage, a CSF leak, an increased APACHE III score and repeat surgery [58]. The risk factors associated with higher mortality were a GCS<10 on presentation, low CSF glucose level, presence of a concurrent nosocomial infection, Gram-negative pathogens as etiology and an increased APACHE III score [57].

Excluding ventricular shunt infections, most cases of meningitis following neurosurgery are diagnosed in the early postoperative period. Several series have shown that the majority of cases develop within 10 days of surgery, and virtually all are diagnosed within 28 days [3, 5, 6, 19, 51]. Posttraumatic bacterial meningitis

associated with a CSF leak may occur days to years after the initial injury. In the review of 197 nosocomial meningitis episodes by Durand et al. [4], 97% of patients were diagnosed more than 48 hours after admission or within 1 week of discharge. Interestingly, 41 episodes (10 patients) in this study were recurrent during the same hospitalization. Other studies indicate a similar pattern of presentation [6].

The standard clinical signs and symptoms suggestive of meningitis are often of little help in diagnosing nosocomial infection. Fever appears to be the most ubiquitous finding in all nosocomial cases [3, 5, 6, 19, 60]. Neurosurgical patients commonly demonstrate an altered level of consciousness, neck stiffness, and headache reflecting some combination of their underlying disease and the surgical procedure itself in the absence of infection. These relatively nonspecific findings may become more useful if a change over time is noted or a new fever develops. Findings indicative of meningeal irritation are more useful in nonsurgical patients, especially when combined with fever and a change in mental status. Aseptic meningeal inflammation is a common postoperative condition that may further confound the diagnosis. Clinical parameters have been consistently unable to distinguish aseptic from bacterial meningitis [61]. It seems that an altered level of consciousness is the most specific sign to distinguish bacterial from aseptic meningitis [51] but again this could be difficult to evaluate in the neurosurgical patient. The use of corticosteroids may blunt the signs and symptoms of inflammation in surgical patients. Finally, the administration of perioperative antibiotics may alter the natural course of clinical responses and laboratory findings.

The signs and symptoms of posttraumatic bacterial meningitis are often similar to those seen in acute bacterial meningitis [62]. However, as with the neurosurgical patient, clinical findings may be more difficult to interpret in the patient with considerable head trauma. In these patients at increased risk, it is important to establish evidence of CSF leakage when meningitis is a concern. Radiographic studies are the procedures of choice to document and localize CSF leakage. CT scanning and MRI are superior to plain films in diagnosing basilar skull fractures and identifying fistulae [26]. Examination of the CSF assumes a critical role.

Analysis of CSF obtained from hospitalized patients at risk for developing meningitis is often difficult. Neurosurgical patients commonly have abnormal CSF profiles secondary to underlying disease (tumor), procedures, intracranial bleeding, and seizure activity. Perioperative antibiotics will influence the results of cultures of

CSF. Despite these limitations, the results are revealing, and examination of the CSF should be performed routinely in all suspected cases. The CDC definition for nosocomial meningitis does not specify abnormal values for routine CSF parameters. As with community-acquired bacterial meningitis, most cases of nosocomial meningitis are associated with an increased CSF white cell count, neutrophilic pleocytosis, elevated protein, and depressed glucose [2, 3, 4, 6, 49, 60, 62]. Neurosurgical patients with culture-proven meningitis usually have more than 100 WBCs/mm^3 with over 50% neutrophilia [6, 49, 60]. In the series by Berk and McCabe [60], all patients were noted to have over 100 WBCs/mm^3, with the majority having more than 1,000 cells/mm^3 (median 2,500). In 72 episodes of culture-negative nosocomial meningitis described by Durand et al. [4], 97% of patients had more than 300 WBCs/mm^3, and 96% had more than 50% neutrophils. Since an intracerebral bleed or subarachnoid hemorrhage allows both WBCs and RBCs to enter the CSF, a correction formula may be used to better approximate the number of abnormal white blood cells. A CSF protein level greater than 100 mg/dL and a glucose level less than 40 mg/dL are present in the majority of nosocomial cases [4, 6, 49, 60]. Unfortunately, several studies have found no significant difference in cell counts and other CSF parameters in (early) postoperative patients with septic versus aseptic meningitis [61]. In these patients, a significantly lowered glucose level (less that 20 mg/dL) might be the best indicator of an infectious etiology in the absence of culture data [61].

Routinely, the CSF should be Gram-stained and set up for bacterial culture. In immunocompromised patients, fungal cultures, mycobacterial studies, and viral cultures may be indicated as well. The yield on Gram-stained CSF is lower than in community-acquired cases and approximates 50% overall [4]. Although a positive culture remains the gold standard, it is impossible to make this requirement for nosocomial cases if the clinical data and CSF profile are otherwise supportive. In the series of Durand et al., a positive culture was obtained in 83% of nosocomial cases and a comparable percentage of community-acquired cases [4]. Clearly, the diagnostic value of CSF sampling, under any circumstance, can be greatly influenced by the administration of intravenous antibiotics. The effect of antibiotics prior to lumbar puncture is most marked on the Gram stain and culture with little alteration of the other standard parameters. A negative Gram stain and culture will commonly occur after 24 hours of appropriate therapy. The CSF glucose and white cell count usually

remain abnormal for at least several days. When combined with the baseline abnormal CSF of the craniotomy patient the effect of prior antibiotics on diagnosis is substantial, and second-line tests assume greater importance. Final mention should be made concerning the role of neuroimaging in the diagnosis of bacterial meningitis. Although contrast enhancement of meninges may be seen on CT or MRI early in the course of illness, these findings are nonspecific and contribute little to establishing the diagnosis [26]. A better use of these modalities is to exclude other CNS pathology or to diagnose intracranial complications of meningitis.

The suspected pathogens in cases with a basilar skull fracture are *S. pneumoniae*, *H. influenzae* and group A β-hemolytic streptococci. The recommended empirical treatment in such a case is Vancomycin plus a third generation cephalosporin (cefotaxime or ceftriaxone). The pathogens to be considered in head trauma and postneurosurgery are *S. aureus*, CoNS (especially *S. epidermidis)* and aerobic gram-negative bacilli (including *P. aeruginosa*). In cases of suspected post-neurosurgical meningitis, a reasonable regimen includes Vancomycin plus either ceftazidime, cefepime, or meropenem [63].

1.1.6.5 Cerebrospinal fluid shunt infections and infections associated with Intracranial Pressure monitoring devices

A variety of temporary and permanent prosthetic devices are used to access, drain, divert, and monitor the CSF. These devices may be internalized for chronic use or externalized for use in the acute setting. Internalized devices consist of shunts (ventriculoperitoneal, ventriculoatrial, lumboperitoneal) and reservoirs (lumbar, ventricular). Externalized devices facilitate drainage (ventriculostomy, lumbar drain, external shunt) or measure ICP when the device (intraventricular, epidural, subdural) is connected to a transducer. Insertion of a ventriculoperitoneal shunt is the most common surgical procedure performed for the long-term control of hydrocephalus. Infections complicating these devices may occur at any site or compartment traversed by the prosthesis. Proximal infections include meningitis, ventriculitis, empyema, abscess, and infection involving the surgical site (wound infection, cellulitis, osteomyelitis). Distal infections include tunnel infections along the catheter tract, bacteremia, pleuritis, peritonitis, and related intraabdominal infections. Infections of temporary devices are almost always nosocomial, because their insertion and use requires hospitalization. The current CDC guidelines define infection secondary to an

implantable device as nosocomial if it occurs within 1 year of the operative procedure and the two appear to be related [26, 38]. Because of the clustering of shunt infections within 60 days of implantation [64, 65], shorter periods have been suggested to designate a shunt infection as nosocomial [47].

The incidence of CSF shunt infection is usually in the range of 4-15%. The operative incidence (i.e. the occurrence of infection per procedure has ranged from 2.8% to 14% although more recent series have generally reported operative infection rates of less than 4%. Several factors have been reported to be associated with an increased risk of CSF shunt infection (Table 1.1.4). Children are considered to be more susceptible to shunt infections perhaps as a result of longer hospital stays, higher concentrations of bacteria on the skin, an immature immune system or the presence of more adherent strains of bacteria [66]. The infection rate may be especially high in those undergoing three or more revisions although that has not been observed in all studies [66]. In patients undergoing revision after treatment for an infected CSF shunt, the operative incidence of infection is considerably higher (12-26%) [64]. The same organism has been cultured at least one half to two thirds of the time, suggesting that the initial infection has not been adequately treated [66].

Table 1.1.4. Factors associated with an Increased Risk of CSF Shunt Infection

Premature Birth
Younger age
Previous shunt infection
Experience of the neurosurgeon
Number of people traversing the operating theater
Exposure to perforated surgical gloves (Double gloving when handling implantable devices may reduce infection risk)
Intraoperative use of the neuroendoscope
Length of the operative procedure
Insertion of catheter below T7 in ventriculoatrial shunting
Patient skin preparation
Shaving of the skin
Cause of hydrocephalus (e.g. purulent meningitis, hemorrhage, myelomeningocele)
Exposure of large areas of patient's skin during the procedure
Shunt revision (the risk may be especially high in patients undergoing ≥ revisions)

(Modified from Mandell, G, Douglas R, Bennett J, eds. Principles and practices of infectious disease, 7th ed. New York: Churchill Livingstone 2010, Chapter 89)

Table 1.1.5. Bacterial Etiologic agents in CSF Shunt Infections

Etiologic Agent	Incidence (%)
Staphylococci †	55-95
Gram-negative bacteria	6-20
Streptococci	8-10
Diphtheroids‡	1-14
Anaerobes	6
Mixed cultures	10-15

†Mainly CoNS ‡ Including P. acnes

(Modified from Mandell, G, Douglas R, Bennett J, eds. Principles and practices of infectious disease, 7th ed. New York: Churchill Livingstone 2010, Chapter 89)

Table 1.1.6. Antimicrobial agents administered by the intraventricular route

Antimicrobial Agent	Daily Intraventricular Dose
Vancomycin	5-20 mg (most studies have used a 10-20 mg dose)
Gentamicin	4-8 mg
Tobramycin	5-20 mg
Amikacin	5-50 mg
Polymyxin B	5 mg
Colistin	10 mg
Teicoplanin	5-40 mg
Quinipristin/dalfopristin	2-5 mg
Amphotericin B	0.1-0.5 mg

In patients with external devices, infectious complications most commonly range from 5-10% [29, 67]. Factors associated with an increased risk of infection are intraventricular hemorrhage, subarachnoid hemorrhage, cranial fracture with CSF leak, catheter irrigation, craniotomy, and duration of catheterization. Although controversy exists regarding the relationship between the duration of catheterization and risk of infection, most studies consider extended catheter duration (usually exceeding 5 days) to be an important risk factor for subsequent infection [29].

The etiologic agents identified in CSF shunt infections are shown in Table 1.1.5. As seen in the Table, staphylococcal species account for the majority of isolates in these patients, with *Staphylococcus epidermidis* being the most frequently isolated followed by *Staphylococcus aureus*. In recent years an increasing prevalence of diphtheroids (including *P. acnes*) has been found in CSF shunt infections. That could be the result of better culture techniques [68]. Fungal shunt infections are rare, although the frequency of *Candida* shunt infections has increased in recent years (ranging from 6-17%). A previous ventricular shunt may also increase the risk of subsequent *Candida* meningitis [69]. Shunts terminating in the peritoneal cavity may have a greater risk of infection with gram-negative organisms [66, 70]; mixed infections may be seen when the catheter has perforated a hollow viscus [70]. Gram-positive cocci account for the majority of meningitis cases associated with external drains [29].

The most frequent mechanism is colonization of the shunt at the time of surgery [67]. A recent study though has proven that in 13 shunt infections in 108 placements, only one CSF shunt infection had an isolate that was similar to perioperative surgical site culture. This result leads to the conclusion that the vulnerable period for bacterial colonization of shunts may extend throughout the postoperative period of wound healing [71].

The clinical manifestations of infections related to CSF shunts, reservoirs, and monitoring devices are quite variable and often nonspecific. Infections of the surgical site or subcutaneous tunnel in the early postoperative period are the most easily recognized, as purulent drainage, erythema, warmth, and tenderness are usually present [26]. It has been suggested that CSF shunts be viewed as composed of a proximal and a distal segment with specific signs and symptoms of infection referable to each section [67]. Since infection of one shunt section may spread contiguously to

involve the entire length of the prosthesis, a patient may present with any combination of signs and symptoms related to the proximal, distal, and intervening sections of the shunt [26, 72].

In general, fever appears to be the most constant feature of shunt infection [73]. Several studies have shown that virtually all patients have a temperature greater than 100 °F with the majority febrile to 102 °F or higher [72, 74]. Unfortunately, the absence of fever cannot be used to rule out infection, as others have demonstrated a small but significant percentage of asymptomatic patients. In the several studies, fever has been reported in as few as 14% to as many as 92% of cases [66]. Proximal infection of shunts with a ventricular origin is usually associated with symptoms secondary to shunt obstruction or malfunction. Typical clinical manifestations include nausea, vomiting, seizure, malaise, lethargy, irritability, headache, and other indications of increased ICP [8, 73, 74]. Classic signs of meningeal irritation (meningismus, photophobia) are present in only one third of patients [62]. This is due to the inability of CSF to pass into the subarachnoid space of patients with obstructive hydrocephalus or to eventual closure of the aqueduct of Sylvius in shunted patients with communicating hydrocephalus. Meningeal signs are more frequently seen in patients with infected lumboperitoneal shunts [72]. Manifestations of distal shunt infection depend on the site of the terminal portion. Nearly one third of patients with infected ventriculoperitoneal shunts present primarily with abdominal symptoms in the absence of ventriculitis [74, 75]. Pain, often related to infection at the peritoneal or pleural endings of the shunt, may be absent in as many as 60% of the infections [66]. In patients with infected VP shunts, symptoms of peritonitis appear as the peritoneal inflammation becomes more severe, and fever, anorexia, and other signs and symptoms of an acute abdomen develop [66]. Some shunt infections are so insidious that may only present with intermittent low-grade fever or general malaise. The patient may present with an unexplained conclusion of an open-ended peritoneal catheter or failure of peritoneal CSF absorption. Early inflammation about the shunt catheter may result in impaired CSF absorption and loculation of fluid with formation of a peritoneal cyst. This CSF-oma may present as a palpable mass in younger patients and may represent either a sterile process or an overt infection [76]. The clinician must consider the possibility of CSF shunt infection in patients with generalized malaise and signs of possible occlusion [66].

Progressive inflammation results in full-blown peritonitis with fever and abdominal tenderness [73]. An acute abdomen similar to appendicitis may be seen, and intestinal obstruction, bowel perforation, and intraabdominal abscess have all been described in small numbers [26, 77]. Infection complicating a ventriculopleural shunt can lead to formation of an empyema [78]. In contrast, patients with vascular shunt (ventriculoatrial) infections tend to present subacutely with lethargy and fever.

Lumbar or ventricular drains become infected from organisms introduced through the drainage system or through the skin site [7, 67, 79]. Infections are generally more frequent with external devices than CSF shunts and may be caused by hospital flora. The change in mental status that occurs in patients with possible meningitis or ventriculitis may be a manifestation of the underlying disease [66].

The diagnosis of CSF shunt infections is established by direct culture of the shunt CSF or of fluid within or around the shunt or the ventricular reservoir. The reservoir is punctured after sterile preparation. In patients who undergo frequent aspirations, infection may ensue in about 12% of the patients [66, 80]. CSF cultures may be negative, particularly if the patient has received prior antibiotic therapy [81, 82]. The peripheral WBC is generally elevated but may be below 10,000/mm^3 in 25% of patients [73, 82]. In patients with ventriculoatrial shunts and chronic bacteremia, positive blood cultures may be obtained in 90% of patients who have not recently received antibiotics [72, 74]. Conversely, ventriculoperitoneal shunts have a rate of blood culture positivity that approximates only 25% [72, 74]. In the early postoperative period, cultures of an infected surgical site or of aspirate obtained from an erythematous subcutaneous tract are always indicated, but the correlation with more definitive CSF cultures is less than perfect. Aspiration of any fluid collection adjacent to the shunt apparatus is also helpful, as a communication with the CSF pathway often exists. Lumbar punctures in patients with ventriculoperitoneal shunts may not reveal evidence of more proximal infection [67]. These limitations make direct sampling of the CSF from the shunt apparatus the most reliable diagnostic test [67, 74, 81]. Performing a shunt aspiration enables assessment of shunt function as well as a detailed fluid analysis. Lumbar puncture is of little use; as cultures are usually negative [82]. Routine chemical tests are of little value, as an elevated protein or depressed glucose level is a nonspecific and inconsistent finding [81].

The CSF WBC averages 75 to 150 cell/mm^3; greater than 100 cell/mm^3 correlates with a subsequent positive culture in 90% of confirmed cases [83]. When the cell

count is under 20 cells/mm^3, a positive culture is obtained in less than 50% of cases. CSF white blood cell counts and lactate concentrations were normal in approximately 20% of episodes in one recent study of adults with shunt-associated infection [80]. The predictive value of a negative CSF culture may also be substantially decreased in patients whose distal catheters are blocked. CSF cultures may require several days to weeks of incubation before they can be called negative [66]. Neuroradiologic studies such as CT or MRI may give indirect evidence of infection by suggesting obstruction of CSF circulation.

In patients with lumbar drains or ventriculostomies, definite infection is defined as a positive CSF culture (obtained from the catheter) associated with CSF pleocytosis. There may be a paucity of clinical symptoms other than fever and headache [29]. Progressively decreasing CSF glucose and increasing CSF protein accompanied by advancing CSF pleocytosis, in the absence of positive CSF cultures or Gram stains characterizes a suspected infection [66]

Polymerase chain reaction (PCR) has been evaluated to detect the presence of bacterial DNA in CSF from patients with EVDs and VP shunts. The detected pathogens in cases where PCR was used were *P. acnes* and *S. aureus*. In the culture-negative/PCR- positive group, there was a history of prolonged intravenous antibiotic use. Most studies are needed before the routine use of the method can be recommended [84].

Infection that is essentially restricted to the distal portion of a ventriculoperitoneal shunt is more difficult to diagnose. Peritoneal signs may be present with a normal functional assessment of the shunt and laboratory assessment of the CSF, especially if obtained proximally. Diagnosis may necessitate a trial of externalization of the distal end with appropriate cultures and close observation for prompt clinical improvement [77].

Generally, in patients bearing ICP monitors, the risk of infection is between 2.9-10.3%. Infections of ICP monitoring devices present as proximal shunt infections do. Fever is the most frequent indication of infection, as signs of meningeal irritation are usually absent, and these patients often have an altered sensorium [85].

In summary, an infection should be strongly suspected in any febrile patient with an indwelling CNS prosthesis. It is important to always consider occult infection as a potential cause of shunt dysfunction. All available clinical and laboratory parameters must be utilized in an effort to make an accurate diagnosis. Blood cultures are usually

positive in patients with ventriculoatrial shunts, and CSF cultures are positive in the majority of patients with ventriculoperitoneal shunts. It should be emphasized that the CSF may be sterile in a significant number of documented infections.

As far as it concerns the treatment of EVD and the VP shunts except for the selection and duration of antimicrobial treatment, one should consider the timing of hardware removal and the timing of shunt replacement. Lack of standardization of these practices in published studies is a major issue. The choice of antibiotics depends on the coverage of the offending pathogens. Direct instillation of antimicrobial agents into the ventricles is occasionally necessary in patients with shunt infections that are difficult to eradicate or when the patient is unable to undergo the surgical components of therapy although the indications for intraventricular treatment are not well defined [67, 86]. The use of the intraventricular antibiotics has not been approved by FDA and the doses of antimicrobial agents for intraventricular use have been determined empirically (Table 1.1.6).

The success of treatment of CSF shunt infections without removal of the devices was low and the approach carried a high mortality rate [87]. The ability of the organisms to adhere to the prostheses and survive antimicrobial therapy probably precludes optimal treatment in situ. In one observational study of treatment with systemic and intraventricular antimicrobial agents (instilled via a separate ventricular access device) resulted to a success rate of 92% for infections caused by bacteria other than *S. aureus* [88], suggesting that conservative management may be appropriate for selected infections caused by less virulent microorganisms such as CoNS. The combination of shunt removal and intravenous antimicrobial therapy cures approximately 65%-75% of patients with shunt infections [87]. The other option includes delayed shunt replacement in order to treat the infection in the absence of any foreign devices. The combination of antimicrobial use and removal of all components of the infected shunt with EVD placement appears to be the most effective treatment [67, 89]. The shunt removal in combination with shunt externalization and intravenous antibiotic administration was the most popular method used by the members of the American Society of Pediatric Neurosurgeons (ASPN) [89]. In the same survey they conclude that determining the most effective duration of antibiotic therapy in an effort to shorten hospitalization and minimize complications without sacrificing efficacy will require further study [89].

The ventriculitis of shunt infections appears to clear more quickly with external drainage. The EVD placement ensues the continuous treatment of hydrocephalus. With this approach, success is greater than 85% [67, 87, 90]. A longer duration of the ventriculostomy presence appears to increase the risk but prophylactic catheter exchange every 5 days does not significantly decrease the likelihood of CSF infection [36, 91]. Probably, a single EVD can be used as long as clinically indicated unless a change is necessary because of CSF infection or catheter malfunction [66]. There was no statistical difference in the incidence of infections between the group that had regular EVD exchanges and the one who did not [66]. In the treatment of infection caused by an EVD the removal of the device is an important adjunctive measure [66]. The optimal duration of antimicrobial therapy for CSF shunt infections is not fully defined. In patients with infections caused by CoNS and with normal CSF findings, the negative CSF cultures for 48 hours after externalization generally confirms that removal of the hardware effected a cure and the patient can be reshunted on the third day after removal. If repeat cultures are positive antimicrobial treatment is continued until CSF cultures remain negative for 10 consecutive days before a new CSF shunt is placed. The same approach can be recommended for P. acnes infections [67, 68]. For shunt infections caused by *S. aureus* or gram-negative bacilli, 10 days of antimicrobial with negative cultures are recommended before reshunting [67], although some would consider a 21-day course when gram-negative bacilli are isolated. These recommendations have not been extensively studied. Careful follow up after reimplantation is critical to ensure that the patient has been cured [67]

1.1.6.6 Cranial Epidural Abscess/ Spinal Epidural Abscess

An epidural abscess or empyema represents a relatively uncommon infection that occurs between the dura mater and overlying bone of the cranium (a “potential space”) or spine (a “true space”). Conditions predisposing to the development of a cranial epidural abscess (CEA) include head trauma, craniotomy, osteomyelitis, paranasal sinusitis, mastoiditis, otitis, fetal scalp monitoring, halo pin penetration, craniotomy and the application of skull tongs [1, 50, 63, 92]. Risk factors for a spinal epidural abscess (SEA) include hematogenous spread from multiple sources, adjacent osteomyelitis, spinal wound, decubitus ulcers, lumbar puncture, nonpenetrating back trauma, epidural catheters, spinal anesthesia/injection, and spinal surgery. The reported risk of these infections related to the most common neurosurgical and

neuroinvasive procedures appears to be relatively small. Hematogenous spread occurs in 25- 50% of cases, secondary to infections of the skin, urinary tract infections, periodontal abscesses, pharyngitis, pneumonia or mastoiditis [63].

Nosocomial CEA generally occurs as a complication of craniotomy or head trauma. Symptoms include fever, headache, altered mental status, local swelling, erythema, focal neurologic signs, and occasionally seizures [92]. Fever and headache are the most common complaints but the patient may otherwise feel well leading to a delay in diagnosis unless the clinical course is complicated [63]. Progression of the abscess is often accompanied by subdural extension and can lead to deterioration of neurologic status, increased ICP, and cerebral herniation. The CSF profile (lumbar puncture may be contra indicated) reflects parameningeal infection [93].

The clinical findings in patients with spinal epidural abscess may develop within hours to days or the course may be more chronic, over weeks to months. The presentation in most patients with SEA progresses from backache and focal vertebral pain to nerve root pain, spinal cord dysfunction and paraplegia. Fever is reported in 60-70% of the patients [63]. MRI with gadolinium enhancement is the diagnostic procedure of choice for CEA and SEA.

The management of CEA requires a combined medical and surgical approach. Treatment is usually continued for 3-6 weeks after surgical drainage or longer (6 to 8 weeks) if osteomyelitis is present. Surgical drainage is also required and the preferred modalities include craniotomy or craniectomy. The principles of therapy for SEA are prompt surgical decompression, drainage of the abscess and long term antimicrobial therapy. Duration of antimicrobial therapy is usually 4-6 weeks; 6-8 weeks are recommended in patients with contiguous osteomyelitis because relapse is less likely with prolonged treatment [63]. Surgical decompression is a medical emergency in order to minimize the likelihood of permanent neurologic sequelae [63]. Surgery is not likely to be a viable option in patients who have experienced a complete paralysis for longer than 24-36 hours, although some authors would perform surgical therapy in patients if complete paralysis has lasted less than 72 hours. Nonsurgical management may also be appropriate for patients with panspinal infection or in those with a high surgical risk. Irreversible paralysis continues to affect 4-22% of the patients and the mortality of SEA ranges from 5-32% [63].

1.1.6.7 Subdural Empyema

Subdural empyema refers to a collection of pus in the space between the dura and arachnoid. Infection can progress rapidly, as there is little anatomic barrier to spread in this space. As with CEAs, most cranial subdural empyemas (CSEs) are related to paranasal sinusitis, otitis media, trauma, and neurosurgical procedures and infection of a preexisting subdural hematoma [63]. Rare predisposing factors include cranial traction devices, nasal surgery, ethmoidectomy and nasal polypectomy. CSEs may be found in conjunction with an osteomyelitis or epidural abscess in 50% of cases. Mortality, near 100% before effective antibiotic therapy, has declined to 9% in one series but it usually ranges from 10-20% [63, 94].

A number of bacterial species have been isolated in patients with cranial subdural hematoma including aerobic streptococci (25-45%), staphylococci (10-15%), aerobic gram-negative bacilli (3-10%) and anaerobic streptococci and other anaerobes (33-100%). Polymicrobial infections are common [63]. Postoperative and post-traumatic infections are more commonly caused by staphylococci and aerobic gram-negative bacilli. *Propionibacterium acnes* can be a pathogen isolated from subdural empyemas as a result of trauma, neurosurgical procedures or use of dural allografts [63].

Clinically, patients present with rapid onset of altered sensorium, meningismus, seizures, focal neurologic findings, and signs of increased ICP following a period characterized by headache and fever [92, 94]. The most common focal neurologic signs are hemiparesis, hemiplegia, ocular palsies, dysphasia, homonymous hemianopsia, dilated pupils and cerebellar signs [63]. Seizures are seen in 25-80% of the cases. A more subacute presentation of CSE has been described in postoperative infections or in patients who have received prior antimicrobial therapy and those with infected subdural hematomas [63, 95]. In case of traumatic subdural empyema, the mean time from initial trauma to presentation is usually 19 days (range 4-60 days). Neutrophilic pleocytosis in the CSF is usually present, although in most of the cases in most cases the findings are not specific and there may be a mononuclear pleocytosis [63].

CT scanning or MRI is currently the procedure of choice for diagnosis of CSE, although false negatives may occur [26]. A contrast study will show a crescent-shaped hypodense area with intense enhancement at the brain periphery. MRI provides better clarity and it particularly helpful in detecting CSEs located at the base of the brain,

along the falx cerebri or in the posterior fossa [63]. Spinal subdural empyema is extremely rare; the few cases reported in the literature have been associated with distant sources of infection. MRI is the diagnostic procedure of choice [63, 96].

Subdural empyema is a medical emergency and its treatment requires a combined medical and surgical approach. Surgical decompression by burr hole trepanation or craniotomy is useful for controlling increased intracranial pressure and completely evacuate the empyema. Generally, limited procedures (through burr hole or craniectomy) are recommended in patients with septic shock and patients with localized parafalcine collections [63]. The choice of antibiotics depends on the most probable offending pathogens. Parenteral antibiotic therapy should be continued for 3-4 weeks after drainage; longer periods of intravenous and perhaps additional oral therapy may be required if the patient has accompanying osteomyelitis. Survival rates are greater than 90% for those who are awake and alert at presentation but <50% for those who present unresponsive to pain. CSEs may also be complicated by septic venous thrombosis, localized cerebritis and cerebral abscesses [63, 94].

1.1.6.8 Brain Abscess

A brain abscess is a focal suppurative process, confined to the brain parenchyma. Hospital-acquired brain abscess is an unusual complication of routine neurosurgical procedures, paranasal sinus infection, sinus surgery, and transient bacteremia, but may occur following penetrating craniocerebral trauma and in immunocompromised patients [51, 97, 98]. In the civilian population the mechanisms of brain abscess after trauma (incidence 2.5- 10.9%), include compound depressed skull fractures, dog bites, rooster pecking, tongue piercing and especially in children injury from lawn darts and pencil tip [99]. Gunshot injuries to the head associated with retained bone fragments or contamination with bacteria from skin, clothes and the environment constitute a particularly high-risk condition [99, 100]. The incidence of brain abscess after head trauma ranges from ranges from 3 to 17% in military populations [99]. Retained foreign bodies did not seem to increase the infection rate except in cases associated with CSF leak. Brain abscesses have also rarely complicated the application of cranial tongs and halo fixation devices. Brain abscesses have been reported in patients with malignant gliomas who were treated with craniotomy and Gliadel wafers which may serve as a nidus for subsequent infection [101, 102].

Finally, a brain abscess may follow cranial wound infections, meningitis, shunt infections, or any of the previously discussed CNS-related nosocomial infections [26].

The clinical presentation of a nosocomially acquired brain abscess may vary from a relatively acute postcraniotomy suppuration to a more subacute or chronic infection developing secondary to a gunshot wound or indwelling ventricular shunt. Most of these infections appear to present within several weeks of a neuroinvasive procedure. As expected, the nosocomial etiology of these infections is often difficult to determine, and supportive evidence is derived from the clinical setting and available microbiology. The presenting features of a brain abscess depend on the size, location, virulence of the microorganism, and condition of the host. Abscesses that evolve secondarily by direct intracranial extension are usually solitary and typically found in the frontal and temporal lobes [26]. Infections related to cranial surgery or trauma generally occur in close proximity to the wound (or foreign body), whereas hematogenously spread infection may cause multiple lesions predominantly in a middle cerebral artery distribution [100]. Fever, headache, and focal neurologic findings (the classic triad) are the most common clinical manifestations, seen in approximately 50% of all cases [103]. Nausea, vomiting, papilledema, seizures, and meningismus are seen in 25% to 50% of patients [104]. Unfortunately, most of these signs and symptoms are difficult to interpret in the neurosurgical patient. The differential diagnosis includes a variety of underlying conditions (e.g., tumor, hydrocephalus, hemorrhage, infarction, thrombosis, and other CNS infections). Any unexpected alteration in mental status or change in the neurologic examination, especially if combined with fever, should prompt a more detailed evaluation. The most common symptoms and signs in brain abscess are shown in 1.1.7.

Peripheral blood studies are rarely useful in the diagnosis of a brain abscess. The WBC may vary from normal to moderately increased, the ESR is nonspecifically elevated in most cases, and blood cultures are nearly always negative [26]. Lumbar puncture is generally contraindicated in any patient suspected of having a CNS mass lesion because of the high risk and low yield. When obtained, CSF fluid analysis reveals a mild pleocytosis, elevated protein, and normal glucose consistent with a parameningeal focus of infection [105]. Cultures are rarely positive unless there is concurrent meningitis or ventricular rupture has occurred [106]. Rapid clinical deterioration and death (presumably from tentorial or brainstem herniation) may occur when CSF is sampled in the presence of a brain abscess, further substantiating the

poor risk/benefit ratio of this procedure [103, 104]. The responsible pathogens depend on the underlying risk factor (Table 1.1.8). In postneurosurgical cases and in penetrating traumas, the offending pathogens include *S. aureus*, streptococci, Enterobacteriacae and *Clostridium* spp. [99].

The best approach for the early diagnosis and subsequent management of a brain abscess is provided by radiographic imaging. The advent of CT scanning has provided a rapid, sensitive, and relatively specific method for diagnosing this intracranial infection. The early phases of cerebritis are characterized by a low-density region on noncontrast scans representing the necrotic center of the abscess. Ring enhancement with contrast occurs variably but may become apparent if delayed images are obtained. With formation of a collagen capsule, ring enhancement with contrast is seen in early images surrounding a hypodense center [98]. Both edema and contrast enhancement may be attenuated by corticosteroids with minimal effect on a mature lesion. Although the sensitivity of CT scans exceeds 95%, the typical findings mentioned above are not pathognomonic and may be seen with neoplasm, infarction, resolving hematoma, and radiation necrosis [26]. Features favoring the diagnosis of abscess include intraparenchymal gas, ependymal or leptomeningeal enhancement, corticomedullary location, multiloculation, ring thickness, and homogeneous capsular enhancement [26, 98].

MRI may be the most accurate imaging technique for the diagnosis of brain abscess. Subtle edema and cerebritis may be detected at an earlier stage on gadolinium-enhanced T2-weighted MRI images than on a corresponding CT scan [26]. Other potential advantages of MRI over CT include the use of nonionizing radiation, minimal artifact from bone, better delineation of the posterior fossa, and increased ability to differentiate edema from liquefaction necrosis. Although the sensitivity of MRI is impressive, the clinical superiority of MRI over CT has not been established [26].

Despite the proper clinical setting and suggestive radiology, an interventional procedure is frequently required to establish the diagnosis, define the etiology, and assist therapeutically. The initial procedure of choice is currently a CT-guided stereotactic aspiration. This highly efficacious technique has an overall diagnostic accuracy exceeding 90% with a reported complication rate (e.g., hematoma, infection, seizure) of approximately 1% [107, 108]. Specific indications for this procedure include (a) the presence of multiple lesions, (b) deep-seated lesions, (c) evaluation for

noninfectious etiologies, and (d) the need for external drainage [108]. Laboratory evaluation of aspirated material should include histologic examination, Gram stain, cultures for aerobic and anaerobic bacteria, wet mount and fungal cultures. In patients with a likely bacterial brain abscess, 16S rRNA sequencing and amplification may serve as an adjunctive tool in patients with negative culture results but with histopathologic and Gram stain findings suggestive of a bacterial abscess [99]. The application of stereotactic biopsy has largely circumvented the use of completely empiric antibiotics as well as the need for a craniotomy.

In postneurosurgical cases or in cases of penetrating skull trauma, the initial empirical combination of vancomycin plus a third or fourth generation cephalosporin (cefortaxime, ceftriaxone, ceftazidime or cefepime), seems appropriate. Therapy with corticosteroids should be initiated in patients with significant edema and an associated mass effect. Phenytoin should be considered to prevent seizures during the early stages of therapy [99]. Some patients with bacterial brain abscess require surgical management for optimal therapy either with a burr hole trepanation or a complete excision after craniotomy. The latter is now infrequently performed but it may be required in patients with multiloculated abscesses, abscesses containing gas or abscesses that fail to resolve. Post-traumatic abscesses containing foreign bodies or retained bone fragments usually require excision [99].

Table 1.1.7. Common signs and symptoms in brain abscess

Symptom or Sign	Frequency (%)
Headache	49-97
Mental status changes	28-91
Focal neurologic deficits	23-66
Fever	32-79
Triad of headache, fever, and focal deficit	<50
Seizures	13-35
Nausea and vomiting	27-85
Nuchal rigidity	5-41
Papilledema	9-51

Table 1.1.8. Predisposing Conditions and Microbiology of Brain Abscess

Predisposing Condition	Usual Microbial Isolates
Otitis media or mastoiditis	Streptococci (anaerobic or aerobic), *Bacteroides* and *Prevotella* spp., Enterobacteriacae
Sinusitis	Streptococci, *Bacteroides* spp, Enterobacteriacae, *Staphylococcus aureus*, *Haemophilus* spp.
Dental infection	Mixed *Fusobacterium*, *Prevotella*, *Actinomyces* and *Bacteroides* spp., streptococci
Penetrating trauma or postneurosurgical	*S. aureus*, streptococci, Enterobacteriacae, *Clostridiu*m spp.
Lung abscess, empyema, bronchiectasis	*Fusobacterium*, *Actinomyces*, *Bacteroides* and *Prevotella* spp., streptococci, *Nocardia* spp.
Bacterial endocarditis	*S. aureus*, streptococci
Congenital heart disease	Streptococci, *Haemophilus*
Neutropenia	Aerobic gram-negaive bacilli, *Aspergillus* spp., Mucorales, *Candida* spp., *Scedosporium* spp.
Transplantation	*Aspergillus* spp., *Candida* spp., Mucorales, *Scedosporium* spp., Enterobacteriacae, *Nocardia* spp., *Toxoplasma gondii*

(Modified from Mandell, G, Douglas R, Bennett J, eds. Principles and practices of infectious disease, 7th ed. New York: Churchill Livingstone 2010, Chapter 89)

1.1.7 Pathogens involved in the neurosurgical infections

Coagulase-negative staphylococci, *S. aureus*, and gram-negative aerobic bacilli account for nearly 70% of neurosurgical infections collected through the NNIS system from 1986 to 1992. Figures 1.1.3, 1.1.4 and 1.1.5 show the pathogens involved in neurosurgical site infections. As expected, gram-positive cocci are responsible for the majority of skin and soft tissue infections associated with neurosurgical procedures, mainly *S. aureus* and coagulase-negative staphylococci [15, 19, 20, 22, 23, 24, 25, 27, 36, 109-114]. Recently, *Staphylococcus aureus* and *Acinetobacter* spp. were the most frequently isolated pathogens [57]. *Propionibacterium acnes*, a gram-positive anaerobic rod, continues to be an increasingly recognized pathogen in craniotomy infections.

Organ/space SSIs may include meningitis, discitis, and intracranial or spinal abscess. Gram-negative aerobic bacilli are major pathogens in this group, often with significant resistance to antibiotic regimens. Yeast (mostly *Candida albicans*) and filamentous fungi (mostly *Aspergillus* species) are involved in an increasing number of CSF shunt infections as the number of susceptible hosts becomes larger. The pathogens in certain infections can be observed to change with the host population (e.g., oncology patients), a particular device, or the duration of follow-up (e.g., CSF shunts).

To a great extent, the pathogens responsible for skin and soft tissue infections following neurosurgery are similar to those found in other surgical infections. The close proximity to and often open communication with the CNS underscores the importance of these infections. There is a strong association between microorganisms cultured from neurosurgical wounds and isolates obtained from the CSF. *S. aureus* is generally the most common isolate from superficial and deep wound infections following both craniotomy and laminectomy procedures [1, 16, 40, 51, 115]. The frequency of invasive *S. aureus* infections after neurosurgical procedures has been estimated to be 0.62 per 100 procedures [116]. Several studies have identified gram-negative bacilli among the top three isolates. Other important microorganisms in decreasing frequency of occurrence include *S. epidermidis*, streptococci, diphtheroids (including *P. acnes*), and *Clostridium* species [1, 16, 40, 51].

Infections with MRSA are a growing problem in the neurosurgical population. Most cases are hospital-acquired, associated with placement of intracranial devices

and usually with longer hospital stays [117, 118]. Several cohort studies reported concern of high rates (in some cases up to 75 or 80% of isolates) of methicillin-resistant *Staphylococcus aureus* [20, 22, 23, 24, 109, 110, 112, 113, 119] and coagulase-negative staphylococci among patients undergoing a variety of neurosurgical procedures at their institutions [22, 23, 25. 112].

Initial antibiotic coverage for patients presenting with community acquired neurosurgical infections, particularly epidural space abscesses should be active against MRSA. Postoperative MRSA wound infections were a bigger concern than community-acquired MRSA infections at a tertiary neurosurgical center in a recent report [120] (70 vs. 30% of total MRSA neurosurgical infections, respectively). The evidence suggests that since MRSA shows a significant increase in recent years so vancomycin should be included in the empirical treatment of meningitis in post-neurosurgical patients [121]. Patients with prior MRSA colonization or infection were found to be at high risk for MRSA postoperative complications [120]. Linezolid, a bacteriostatic drug against gram-positive bacteria offers new options for the treatment of MRSA infections, even in the presence of foreign bodies. The CSF levels of the drug reach up to 70% of the serum levels when the vancomycin CSF levels reach only approximately 20% [122].

Enterococcal meningitis is a rare complication of neurosurgical procedures. The most frequent underlying diseases for postoperative enterococcal meningitis are intracerebral hemorrhage (55%), brain neoplasms (25%), head trauma (15%) and hydrocephalus (5%). Predisposing risk factors include CSF devices and a CSF leak [123, 124]. Data from the literature show that enterococcal meningitis mortality is high and the lack of removal of the devices is an important adverse prognostic factor [124]. *E. faecalis* accounts for about 90% of the isolates, the rest being *E. faecium* and *E. durans* [123]. Previous third generation cephalosporin use plays an important role in the appearance of enterococcal meningitis [123]. In patients with intraventricular devices or CSF leakage, enterococcal meningitis may be part of a polymicrobial infection [124]. Linezolid has been promising in the treatment of cases caused by VRE [123].

Initially thought as a contaminant, *P. acnes* has been increasingly recognized as a cause of postoperative infections since the 1970s [125-127]. It has most commonly complicated neurosurgical shunt procedures, but it has rarely been reported as a primary cause of intracranial infection in the absence of a foreign body [126, 128].

Trauma has often been reported as a predisposing factor for intracranial *P. acnes* infections [128]. Infections due to this pathogen can complicate neurosurgical procedure as late as 10 years after surgery even in the absence of shunts or other foreign bodies [129]. The indolence of CNS infection with *P acnes* has been well described. In a large series, the median time from neurosurgical procedures to infection was 54 days with a range from 12 days to more than 4 years [129].

Spores of *Bacillus* are highly resistant to commonly used skin disinfectants. Post-neurosurgical infections caused by *Bacillus* spp. are usually associated with the shunt placements [130]. The most common species associated with neurosurgical infections are *B. subtilis* and *B. cereus*.

Gram-negative bacilli are generally a rare cause of central nervous system in adults but they have become increasingly common in patients with a history of head trauma and neurosurgical procedures [59, 131-133]. In the previous decades Gram-negative pathogens comprised 60- 70% of the meningitis cases post neurosurgery [134], whereas Gram-negative rods were also the predominant pathogens isolated from patients with recurrent meningitis (46%) [58]. The percentage of previously colonized patients before the development of meningitis approaches 65-75% [132, 134]. The mortality rates in patients with post-neurosurgical Gram-negative bacterial meningitis approach 33% -80% in several series [131, 134]. Antibiotic resistance has emerged since the late ’90s [133].

P. aeruginosa meningitis is commonly associated with neurosurgical procedures, and carries a high mortality rate. The median time between the neurosurgical procedure and the diagnosis of meningitis has been reported to be 20 days (range 3-720 days) [135]. *K. oxytoca* has been reported as the most common cause of post-neurosurgical meningitis among *Klebsiella* spp. [136]. *Klebsiella pneumoniae* remains an important pathogen though [137, 138].

Acinetobacter spp. are non-fermentative, aerobic, gram-negative coccobacilli widely distributed in soil and water. They are also common colonizers of the respiratory tract and skin, particularly in the ICU [139]. Skin carriage of *Acinetobacter* spp, may persist for weeks or even months. Cross contamination of patients colonized with *Acinetobacter* spp is common in the ICUs and this could be due to colonized hands or contaminated fomites [139]. *Acinetobacter* meningitis is becoming an increasingly common clinical entity especially in the postneurosurgical setting. The mortality from the infection exceeds 15% [140]. Whereas the incidence

of *Acinetobacter*-related community-acquired meningitis has been determined to just 0.2%, the incidence in nosocomial meningitis has been 3.6% [140]. In some countries it has been documented as the leading cause of Gram-negative postneurosurgical meningitis [140]. The most important risk factors associated with post-neurosurgical meningitis are the presence of a ventriculostomy and its duration and heavy use of antimicrobial agents in the neurosurgical ICU setting [141]. *Acinetobacter* meningitis is usually associated with additional septic foci such as pneumonia, septicemia, brain abscess, surgical wounds and urine tract infections [141]. The physicians should be aware of the entity of pseudomeningitis that has been described. This could be due to the lack of an aseptic CSF collection technique or due to contaminated specimen transport media or extrinsic contamination of skin antiseptics associated with the lumbar puncture [139]. The above mentioned factors can account for *Acinetobacter* meningitis "pseudooutbreaks" that are encountered in the ICUs.

The main problem with the *Acinetobacter* infections is the increasing resistance to the antibiotics [142]. The emergence of carbapenem-resistant *Acinetobacter* meningitis is an important factor, it complicates therapy and it has been associated with a high rate of mortality [142, 143]. In some institutions *Acinetobacter* spp. are reported as resistant to almost all antibiotics [144, 145]. Colistin has retained a good activity against *Acinetobacter* spp., covering up to 98% of the isolates [145]. CNS penetration of colistin is poor, but the drug has been increasingly being used in intraventricular or intrathecal administration [58, 145]. Colistin heteroresistance in *Acinetobacter* spp. has been reported. The incidence of this phenomenon remains unknown because of its difficult detection. Ampicillin/sulbactam has been used successfully for the treatment of MDR *A. baumannii* meningitis. Intrathecal aminoglycosides are recommended in such situations, but this option can also be obviated by the emergence of resistance to amikacin and other antibiotics in this category [142].

Infections due to *Enterobacter* spp. is an infrequent post-neurosurgical complication. Treatment is often complicated by its resistance to third generation cephalosporins [146]. Co-infection with other bacterial pathogens, especially *K. pneumoniae*, is rather common [147]. *Serratia* spp are rare causes of adult CNS infection even after neurosurgical procedures [148]. *Stenotrophomonas maltophilia* is a rare cause of post-neurosurgical infections, especially in association with shunts, drains, Ommaya reservoir placement Predisposing factors include intracranial

hemorrhage and malignancy, a long hospital stay, ICU exposure and previous broad-spectrum antimicrobial treatment (especially carbapenems) [149- 151]. The physicians should be aware of this pathogen, especially in the case that the meningitis does not respond to empirical treatment and also of the possibility of generalized infection [149, 151].

Candida meningitis is a significant complication in adults following neurosurgery. Prolonged antibiotic exposure, multiple neurosurgical procedures, prior or concurrent bacterial meningitis and persistent CSF leak are significant risk factors for this infection [152]. It has been recently reported following Gliadel wafer placement in patients with brain tumor resection [153]. Fungi are a rare cause of neurosurgical shunt infection. Most of them are due to *C. albicans,* but other species including *C. tropicalis*, *C. parapsilosis* and *C. glabrata* have been identified. Most of the cases have been reported in neonates [154].

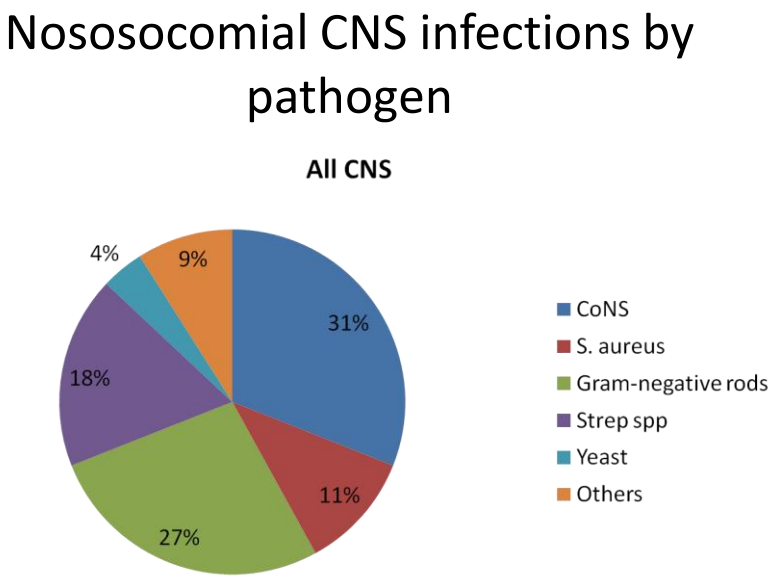


Figure 1.1.3. Nosocomial CNS infections by pathogen (NNIS data, from Gantz NM in Mayhall CG, Hospital Epidemiology and Infection Control, 3rd edition, Lippincott, Williams and Wilkins, 2004)

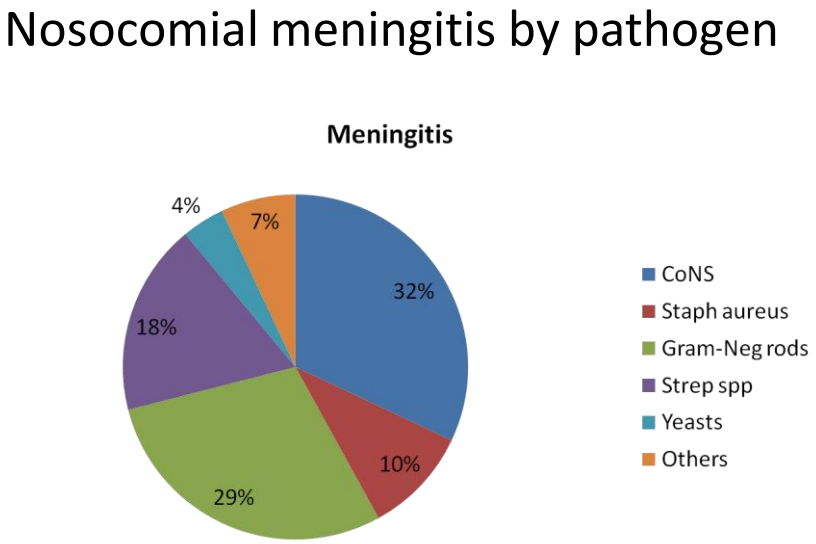


Figure 1.1.4. Nosocomial meningitis by pathogen (NNIS data, from Gantz NM in Mayhall CG, Hospital Epidemiology and Infection Control, 3rd edition, Lippincott, Williams and Wilkins, 2004)

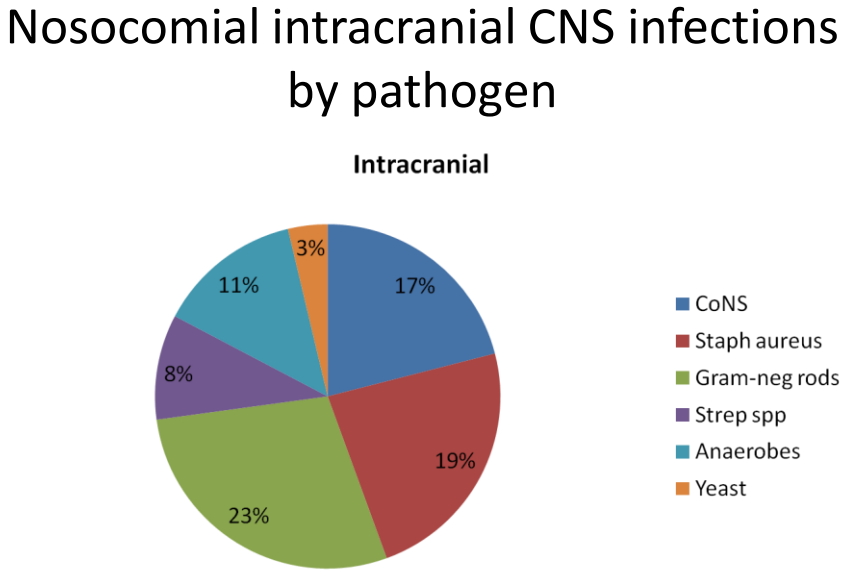


Figure 1.1.5. Nosocomial intracranial infections by pathogen (NNIS data, from Gantz NM in Mayhall CG, Hospital Epidemiology and Infection Control, 3rd edition, Lippincott, Williams and Wilkins, 2004)

1.1.8 Prevention of infections in neurosurgery

1.1.8.1 Antibiotic prophylaxis

Prior to the 1980s, use of prophylactic antibiotics in neurosurgery was based mainly on data from uncontrolled trials. In the 1980s and 1990s, data from prospective randomized placebo-controlled trials demonstrated the efficacy of antibiotic prophylaxis in patients having clean neurosurgery.

Nosocomial central nervous system infections are low in incidence but have potentially serious consequences and poor outcomes including death. Neurosurgical procedures are the principal risk for their development. The majority of neurosurgical site infections and other postoperative infections typically occur within two weeks to one month [15, 23, 119]. A classification system for neurosurgery, validated by Narotam and colleagues, divides procedures into five categories: clean, clean with foreign body, clean-contaminated, contaminated, and dirty [27] (Table 1.1.1).

Clean procedures in neurosurgery include elective craniotomy, spinal procedures, and laminectomy. Those with foreign body procedures are those with either a temporary or permanent foreign bodies left *in situ (e.g.* shunt, intracranial pressure monitors, clamps, ventricular drains, acrylic cranioplasties and metal rods). The reported incidence of postoperative infection, including meningitis, in clean procedures (primarily craniotomy) ranges from 0.15% to 6.1% with antimicrobial prophylaxis [19, 22, 23, 27, 36, 109, 155] and 2% to 9.7% with placebo or no antimicrobial prophylaxis [20, 22, 23, 26, 155]. Postoperative central nervous system shunt infections are associated with serious morbidity and mortality with incidence reported up to 20% [25, 27, 65, 110, 111, 112, 119, 156, 157]. Clean-contaminated procedures are those with a risk of contamination during the procedures with entry into paranasal air sinuses, and transsphenoidal or transoral procedures [27]. Contaminated procedures have known preoperative contamination (e.g. compound skull fractures, open scalp lacerations, cerebrospinal fluid (CSF) fistulae) or established sepsis at the time of procedure [27] (Table 1.1.1).

Administration of antimicrobial agents for surgical prophylaxis represents one of the most frequent uses and misuses of antibiotic therapy in hospitals. Clean neurosurgical procedures with no implantation of prosthetic devices carry a low risk of postoperative infection [158]. However, since the 1732 study [159] reporting the absence of infection in 1732 major clean operative cases by using antibiotic

prophylaxis, many neurosurgeons routinely use prophylaxis in clean surgical procedures such as craniotomy. Malis used an intraoperative regimen consisting of intramuscular gentamicin or tobramycin, intravenous vancomycin, and streptomycin irrigating solution, with no preoperative or postoperative antibiotics [159]. Malis's results were very impressive because of the lack of any single SSI after 1732 clean neurosurgical procedures. Ever since, the prophylaxis issue has been investigated extensively. Several randomized studies [42-44, 160-163] and meta-analyses [155, 164] have concluded in favor of antibiotic prophylaxis for craniotomy.

In 1982, Haines et al tried the Malis regimen with a slight modification. The regimen did not eliminate postoperative infection [165]. In 1984, Geraghty et al proved that the regimen of vancomycin and gentamicin significantly reduced the infection rate in clean neurosurgical cases [44]. In a review of the guidelines regarding the antimicrobial prophylaxis in the neurosurgical population, prophylaxis in craniotomy was given the highest grading and hence it was supported by the strongest evidence [166].

In spinal surgery, although individual randomized controlled trials have failed to prove a benefit from antibiotic prophylaxis in spinal surgery, the difference between the raw pooled infection rates (2.2% in the antibiotic group and 5.9% in the nonantibiotic group) in a metaanalysis was statistically significant [167, 168]. Antibiotics were beneficial even when expected infection rates without treatment are low [168].

Recently, in a tertiary care center the authors presented data that prophylactic antibiotics active against MRSA such as vancomycin compared with standard regimens such as cephalosporins [169] can lower postoperative wound infection rates in MRSA-colonized patients [120]. In the same study the authors proved that revised wound care practice by maintaining a surgical dressing while in the ICU for 3–7 days with chlorhexidine cleansing during dressing changes has reduced the intrafacility transmission rate of MRSA [120]. In the past oxacillin has been successfully used in prolonged clean neurosurgery [162].

Several studies had demonstrated at least a three- to fourfold reduction in the incidence of infection after craniotomy using an antistaphylococcal antibiotic such as cefazolin or vancomycin. Some studies have also added gentamicin to the antistaphylococcal antibiotic. There are no data comparing the various antibiotics for prophylaxis. Antibiotic prophylaxis is usually administered for 24 hours. Some of the

studies used, in addition to the parenteral antibiotics, a bacitracin irrigation solution. In a study of 356 patients given oxacillin or placebo for prolonged clean neurosurgery, there was an eightfold reduction in the incidence of infection in those given parenteral oxacillin compared with the placebo group (170). Use of an antibiotic irrigating solution in that study was not mentioned.

In an uncontrolled study to assess the efficacy of intravenous cloxacillin prophylaxis in patients undergoing craniotomy, the infection rate was 4% [171]. Patients with a penicillin allergy received erythromycin. Antibiotics were given for 24 hours. In operations when prophylactic antibiotics were inadvertently omitted, the infection rate was 27%. The authors concluded that an antistaphylococcal penicillin such as cloxacillin was effective in reducing the incidence of craniotomy infections to less that 5% compared with the usual rates of 5% to 15% without additional prophylaxis.

Efficacy for Clean Neurosurgical Procedures. Antimicrobial prophylaxis is recommended for adult and pediatric patients undergoing craniotomy and spinal procedures. One meta-analysis of six studies found decreased odds of meningitis in patients undergoing craniotomy who received antimicrobial prophylaxis (1.1%) compared with no prophylaxis (2.7%) ($p=0.03$) [155] (Table 1.1.9). Two cohort studies [22, 23] in patients undergoing craniotomy at the same institution found that antibiotic prophylaxis with cloxacillin or amoxicillin/clavulanate, clindamycin for penicillin allergic patients, and other antibiotics (not listed) had a significantly lower infection rate (5.8%) than no prophylaxis (9.7%) ($p < 0.0001$) [22]. A significantly lower infection rate of 4.6% was seen in low-risk patients (clean craniotomy, no implant) with antimicrobial prophylaxis versus those without (4.6% vs. 10%, $p < 0.0001$). A significantly lower incidence of scalp infections, bone flap osteitis and abscess or empyema was seen with antimicrobial prophylaxis compared with no prophylaxis. Antimicrobial prophylaxis demonstrated no difference in postoperative meningitis [22, 23] and infection rate in high-risk patients (emergency, clean-contaminated and dirty procedures, operative time longer than 4 hours, and reoperation) [22].

Prospective studies involving large numbers of patients have also demonstrated lower neurosurgical postoperative infection rates when antimicrobial prophylaxis is used [30, 165, 172]. One such study in craniotomy, spinal, and shunting procedures

was stopped early because of an excessive number of surgical site infections in the placebo group [173].

Choice of antibiotics. Studies of clean neurosurgical procedures reported antibiotic regimens including clindamycin [22, 23, 155], vancomycin [20, 155], cefotiam [163], piperacillin [155, 160], cloxacillin [22, 23, 155], oxacillin [22], cefuroxime [174], cefotaxime [109], sulfamethoxazole/trimethoprim, cefazolin [15, 20], penicillin G [20] and amoxicillin/clavulanate [20, 22, 23]. No significant difference was noted between various antimicrobial regimens (single-dose regimens of clindamycin, vancomycin or cefotiam; three doses of piperacillin; four doses of cloxacillin; and six doses of oxacillin) in incidence of post-craniotomy meningitis in a meta- analysis [155].

A randomized, open-label, multicenter study of 613 adult patients undergoing elective craniotomy, shunt or stereotactic procedures found no difference in single-doses of cefotaxime and trimethoprim/sulfamethoxazole in postoperative abscess formation and surgical site and shunt infections [109]. The routine use of vancomycin as antimicrobial prophylaxis is not recommended, but may be reserved for patients with a beta-lactam allergy, with a previous history of MRSA infection, at institutions with a high rate of methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE) surgical site infections or patients colonized or infected with MRSA [114, 118].

Duration. The majority of studies included single-doses of antibiotics; therefore the use of single-dose antibiotic prophylaxis given within minutes prior to incision in patients undergoing neurosurgery is generally recommended [22, 23, 109, 155, 174, 175]. Additional intraoperative doses of antimicrobial agents are recommended if the procedure is more than three or four hours in duration or if the duration of the procedure exceeds two half-lives of the antibiotics administered preoperatively, or if major blood loss occurs.

1.1.8.2 Prevention of Cerebrospinal Fluid Shunt Infections

Antimicrobial prophylaxis is recommended for adults undergoing placement of a cerebrospinal fluid shunt. Prophylaxis in patients undergoing ventriculostomy or intraventricural prophylaxis at the time of ventriculoperitoneal shunt insertion has shown some benefit in reducing infection, but remains controversial due to limited evidence. A recent meta-analysis of the prophylactic use of antibiotics for

intraventricular shunt placement found a decreased rate of shunt infection in patients receiving antibiotics for 24 hours; no additional benefit accompanied longer duration of antibiotic administration [176]. The benefit of prophylactic antibiotics administered pre- and postoperatively for EVD catheters is unclear [176- 178]. A randomized study of perioperative injection of 10 mg of vancomycin into the EVD did not enroll enough patients to determine whether this approach reduced the incidence of CNS infection [179]. Regardless of shunt type, if prophylactic antibiotics are administered they should cover CoNS and *S. aureus*.

Because CNS infections after shunting procedures are responsible for substantial mortality and morbidity, especially in children, the possible role of prophylactic antimicrobials in such procedures has been studied in numerous small, well-conducted, randomized, controlled trials [170, 177, 180, 181, 182, 183]. Meticulous surgical and aseptic technique and short procedure time were determined to be important factors in lowering infection rates after shunt placement. Although the number of patients studied in each trial was small, two meta-analyses of these data demonstrated that antimicrobial prophylaxis use in CSF-shunting procedures reduces the risk of infection by approximately 50% [184, 185]. In one of the meta-analyses, including 12 controlled randomized trials (1,359 patients), antibiotic prophylaxis at the time of CSF shunt placement decreased the rate of infection by 50% [185].

Most of the studies have generally been performed in a pediatric population. In the one study including adult patients, oxacillin reduced the infection rate from 20% in the control group to 3.3% in the treated group [170]. Various antimicrobial agents were used in the rest of the trials, including cloxacillin, trimethoprim-sulfamethoxazole, cephalosporins such as cephalothin, vancomycin, and gentamicin. The duration of prophylaxis ranged from less than 24 hours to up to 48 hours after surgery. The ideal agent to prevent CSF shunt infections is unknown, since comparative studies are unavailable. Based on the results of susceptibility testing, vancomycin might be the preferred drug. Despite the suggested benefit from antibiotic prophylaxis in the meta-analysis of the 12 studies, infection rates in the treated group still averaged 6.8%, with a range of 1.9% to 17%. Infection rates in the control groups for these studies averaged 13%, with a range of 5.5% to 24% [185]. Such high rates in the groups that received prophylaxis for clean surgery suggest the need for other approaches to prevent infection such as the use of shunts with antimicrobial or antiadherence properties.

There is no consensus on the use of antimicrobial prophylaxis in patients with extraventricular drains (EVD) or intracranial pressure (ICP) monitors [186]. Catheters impregnated with two antibiotics have been widely used for shunts and have led to a significant reduction in infection rates in clinical trials [187]. Recently, external ventricular drainage using antibiotic-impregnated catheters in cerebrovascular critical care patients proved beneficial [188]. Two randomized controlled studies comparing antibiotic-impregnated shunts to standard, non-antibiotic-impregnated shunts along with antimicrobial prophylaxis (an intravenous cephalosporin), found a decrease in rates of shunt and a significant decrease in CSF infections [112, 189]. In a randomized clinical trial (RCT) antibiotic impregnated catheters were proven as effective as systemic antibiotics [190, 191]. Unfortunately, the Codman Bactiseal ventricular catheter [Codman, a Johnson and Johnson Company, Raynham, Massachusetts], impregnated with 0.15% clindamycin and 0.54% rifampin that was used in this protocol was discontinued because of unacceptably high occlusion rate [188]. In this study that comprised of two periods the VentriClear catheter (Cook Medical, Bloomington, Indiana) was used in the second part of the study. This device was coated with minocycline and rifampin and it had a much lower occlusion rate than the Codman device; this is presumed to be a consequence of larger diameter fenestrations at the tip [188]. The use of this minocycline/rifampin impregnated catheter resulted in a significant reduction of ventriculostomy infections and is recommended in adult neurosurgical population [188]. In a limited sample of patients that were included in an underpowered retrospective analysis, EVD catheters impregnated with silver nanoparticles and an insoluble silver salt were shown to reduce the risk of catheter-related infections [192]. The Cochrane collaboration meta-analysis suggested antibiotic-impregnated catheters reduced the incidence of shunt infection, but requested additional clinical trials to confirm the potential benefit [176].

Choice. In CSF-shunting procedures, no single antimicrobial has been demonstrated to have greater efficacy over others [109, 110, 111, 119, 157, 193]. There is a lack of data on CNS penetration of antimicrobials as it relates to prevention of infection in CNS shunting procedures.

Duration. The majority of studies support use of single-dose prophylaxis regimens or regimens with a duration of 24 to 48 hours postoperatively [25, 110, 112, 113, 114, 119, 157]. There is a lack of data evaluating the continuation of extraventricular drains with and without antimicrobial prophylaxis. One retrospective single-center

cohort of patients with EVDs placed for three or more days received antimicrobial prophylaxis for the duration of EVD use (n = 209) compared with patients receiving cefuroxime 1.5 grams intravenously every 8 hours for three doses or less periprocedurally [178]. The overall infection rate of bacterial ventriculitis was 3.9% with eight (3.8%) in the extended use group and four (4%) in the short-term prophylaxis group, which was not statistically significant. The majority of neurosurgical shunt infections occur within 2 months of surgery. Most infections result from the direct inoculation of bacteria during surgery and in the perioperative period. Antibiotic prophylaxis is usually directed against coagulase-negative staphylococci, the most frequent cause of shunt infections.

Table 1.1.9 Randomized controlled trials included in the Barker FG II meta-analysis: Prophylactic antibiotics against meningitis after craniotomy [155]

Series (ref no)	Craniotomy patients enrolled	Antibiotic regimen	Blinding	Trial odds ratio (95% CI)
Savitz and Malis [39]	55	Clindamycin, 1 dose	Double	0.31 (0.049- 1.5)
Blomstedt and Kytta [42]	353	Vancomycin, 1 dose	Single	0.49 (0.0083- 9.6)
Bullock et al. [168]	196	Piperacillin, 3 doses	Double	0.38 (0.0064- 7.5)
Van Ek et al. [161]	248 (operations)	Cloxacillin, 4 doses	Double	0.74 (0.05- 10.8)
Djindjian et al. [162]	216	Oxacillin, 6 doses	Double	0 (0-4.3)
Gaillard and Gilsbach [163]	661 (operations)	Cefotiam, 1 dose	Single	0.31 (0.052- 1.3)

2. Studies consisting the Dissertation

2.1 An Overview of the Neurosurgical Infections in the University Hospital of Crete based on a 3-year Retrospective Study

2.1.1 Introduction

Infections in neurosurgical patients are associated with high morbidity, prolonged hospitalization and increased hosts. The recognition of risk factors for the development of infections in neurosurgical patients is of great importance as it would allow the early identification of "high-risk" patients who should receive special and intensified care. In this retrospective study we aimed to determine the incidence, bacteriology and risk factors for infections in patients who underwent neurosurgical procedures in the University of Crete Medical Center

2.1.2 Patients and Methods

The medical records of the patients admitted to neurosurgery between 2004 and 2006 were retrospectively reviewed. All patients >18 years were included in the analysis. Epidemiological, clinical, laboratory, microbiological and outcome data were recorded in standard forms. Data were analyzed using the Statistical Package for Social Sciences (SPSS, v13.0). Statistical analysis included independent samples t-test or the χ^2 test for categorical data. Logistic regression analysis was performed and the ORs were calculated for each of the independent variables entered in a multivariate model.

2.1.3 Results

A total of 1,112 events were analyzed. Males comprised 68.5% of the sample and the median age was 48 (range 18-96). The median length of hospitalization was 13 days (range 1-388). Trauma was the most common cause of admission to the neurosurgical department (Figure 2.1.1). Craniotomy was the most common procedure performed (21.9%), but one-third of the patients underwent no surgical operations (Figure 2.1.2).

Surgical Site and other Infections: The SSIs were defined according to NNIS criteria. The prevalence of SSIs during the 3-year period was 12.5%. Superficial wound infections were the most common (48.9% of the total SSIs). Meningitis/ventrivulitis comprised 33.8% and shunt infections 10.6%. On the contrary, osteomyelitis/bone flap infections (3.0%), epidural empyema (3.0%) and abscesses (0.8%) were rare (Figure 2.1.3). Ventilator-associated pneumonia was the

most common non-SSI infection encountered in this cohort (36.1%) with UTI being second (20%). BSI/CAB developed in 8.5% (Figure 2.1.4). The prevalence of SSIs was higher in patients who developed VAP (p=0.002), UTI (p<0.001) and BSI/CAB (p=0.016)

Univariate analysis revealed that age, history of malignancy, surgery vs. no surgery, surgery for a vascular event, placement of any drain and ICP placement were associated with increased risk for infections (Table 2.1.1). In multivariate analysis, malignancy, surgery for a vascular reason, shunt replacement, placement of any drain and surgery through a sinus were all independent predictors for SSI development (Table 2.1.2). The development of any infection was independently associated with a history of malignancy, performance of a surgical procedure for trauma or for cerebrovascular events, performance of craniectomy, shunt replacement and the placement of an ICP monitor device and of any drains (Table 2.1.2)

Infections, including SSIs were associated with a prolonged hospitalization but not with increased mortality (Figures 2.1.5, 2.1.6 and 2.1.9). The differences in duration of hospitalization were statistically significant for both the ICU and ward stay (Figures 2.1.5 and 2.1.6). The most common pathogens isolated with SSIs were the Gram-positives. Among them, S. *aureus* was the most prevalent (42% of the isolated Gram-positive). CoNS comprised 37% and *Corynobacterium* spp. comprised only 2% of the gram-positive isolates. Among the Gram-negatives, *P. aeruginosa* was the most prevalent isolate in SSIs (24%). Other isolates included *P. mirabilis*, *E.coli*, *Acinetobacter* and *Klebsiella* spp. (Figure 2.1.7). Gram-positive pathogens predominated among meningitis/ventriculitis cases. The most commonly isolated pathogens were CoNS (43.6% of the total isolates) with S. aureus coming second (7.3%). Among the Gram-negative, *Acinetobacter* spp. were the most prevalent (23.6%), with *P. aeruginosa* and *Enterobacter* spp. coming second (5.5% each) (Figure 2.1.7).

Acinetobacter spp. were the most common isolates in VAP (58.3%) with *S. aureus* coming second (29.2%) (Figure 2.1.8). Other pathogens isolated from VAP include *P. aeruginosa* (20.8%), *Serratia* spp. (12.5%) and *H. influenzae* (8.3%). The most common urine isolates included *P. aeruginosa* (58.3%), *Candida* spp. (41.7%), *E.coli* and *E.faecalis* (8.3% each) and *S. aureus, Klebsiella* spp., and *Enterobacter* spp. (4.2% each).

2.1.4 Discussion and Conclusions

In this retrospective study, the rate of SSIs was 12.5%, a rate that is considerably higher than reported in the literature. In one of the older reports in the literature [194], the rate of SSIs was 3.05%. In the study by Blomstedt et al there was a 7% infection rate [51] whereas Mollmann et al have reported an impressive low of 1.1% [16]. In the prospective study by Lietard et al, the rate for neurosurgical site infections was 4.1% [24]. More than half of our infections comprised of superficial wound infections, which affected 6% of the cohort. In Blomstedt et al study [51] the superficial SSIs reached only 1.5% of the population, and in the Balch study it was only 1% [194]. On the contrary bone flap infections and epidural empyemas were much less in our cohort, and affected 0.36% of the population whereas in the Blomstedt study the rate was 5%. The rate of shunt infections was 9% in the Blomstedt study [51] but only 1.35% in our cohort.

In one of the largest neurosurgical studies [195] that investigated postoperative central nervous system infections in 2111 procedures, the infection rate was <1% (0.8%), more than six times lower than that reported in series of comparable numerical size. This study went under extensive critique since all the procedures included were elective, although not all of them were "clean" [196, 197]. The authors' conclusion that the infection rate is neurosurgery may be overestimated was characterized as rather excessive [196]. Probably the true incidence of postoperative central nervous system infection is in the middle between the McClelland's results and the ones reported in the past [197]. The same authors have reported that the postoperative wound infection after intracranial neurosurgery was nearly three times more likely in European versus North American studies [198].

The prevalence of meningitis in this general neurosurgical population was 4.2%, very similar to rates reported before [51], although Federico et al. have reported a low 1.4% [199]. It has been reported that CSF culture is not always positive although the clinical picture suggests bacterial meningitis. Previously used antibiotics may account for the culture negativity. The reduction in the level of consciousness is a significant factor to distinguish aseptic from bacterial meningitis [51, 61].

Regarding the rate of CAB/BSIs there was a significant percentage of our population with positive blood cultures reaching 8.5%. This is a very significant number when compared with older reports (0.4%) [51] and most recent studies from

Greece (3.0%) [200]. Surprisingly, in the Blomstedt study there is no report of *S. epidermidis* or other CoNS isolation. In the study from Greece CoNS were isolated in 4.3% of the total BSIs.

In this retrospective study a history of malignancy remained an independent risk factor for the development of any infections and SSIs in particular. History of malignancy in our cohort was defined either as a CNS malignancy that led to a neurosurgical procedure or an active malignancy in another system. This is a risk factor that has not been associated with infections development in other neurosurgical cohorts. Patients who were admitted for a vascular event had an increased probability for developing both infections in general and SSIs. The placement of any drain was associated with an increased risk for infections. Surgery through a sinus was marginally associated with the development of SSIs. In the Mollmann et al. study [16] the entry in the paranasal sinuses or the drain placements did not achieve a statistical significance. On the contrary, CSF leak was a substantial risk for postoperative wound infection [16]. CSF leakage was confirmed as independent risk factor by Lietard et al. which also confirmed external shunts as risk factors [24]. In the Mollmann study the authors emphasize the role of controlling any concurrent infections prior to performing any neurosurgical procedure [16]. In our cohort, the prevalence of SSIs was significantly higher in patients who also developed VAP, UTI and BSI/CAB.

In our cohort of general neurosurgical population we did not prove any increase in mortality in patients who developed any kind of infection and SSIs in particular (Figure 2.1.9). On the contrary there was an increased duration of ICU hospitalization and an increased LOS for the patients who developed any infection and SSIs in particular (Figures 2.1.5 and 2.1.6).

In this cohort, gram-positive pathogens (mainly *S. aureus*) predominated among SSIs, including meningitis/ventriculitis. This finding agrees with the pathogens reported by Federico et al [199]. What is impressive is the significant predominance of *Acinetobacter* spp. as VAP pathogens, an organism that has been well described to cause infections and difficult to control outbreaks in the Neurosurgical Intensive Care population [201].

Infections are common in neurosurgical patients and they may have a great impact on the length and consequently the costs of hospitalization. Some risk factors, such as the history of malignancy are not modifiable. The infection rate may be minimized with careful management of the drains, careful surgical techniques and

early discharge from the ICU. The knowledge of the offending pathogens institution by institution is important for appropriate empirical treatment.

In the next studies we will investigate the rates, microbiology and associated risk factors with post-craniotomy meningitis in retrospective and prospective cohorts in Crete, GR and New York, NY. Since the greatest percentage of the patients admitted to the Neurosurgical Department of the University of Crete included patients with traumatic brain injury, we present a retrospective study of the infections encountered in this population with an attempt for definition of the risk factors associated with the development of SSIs and meningitis

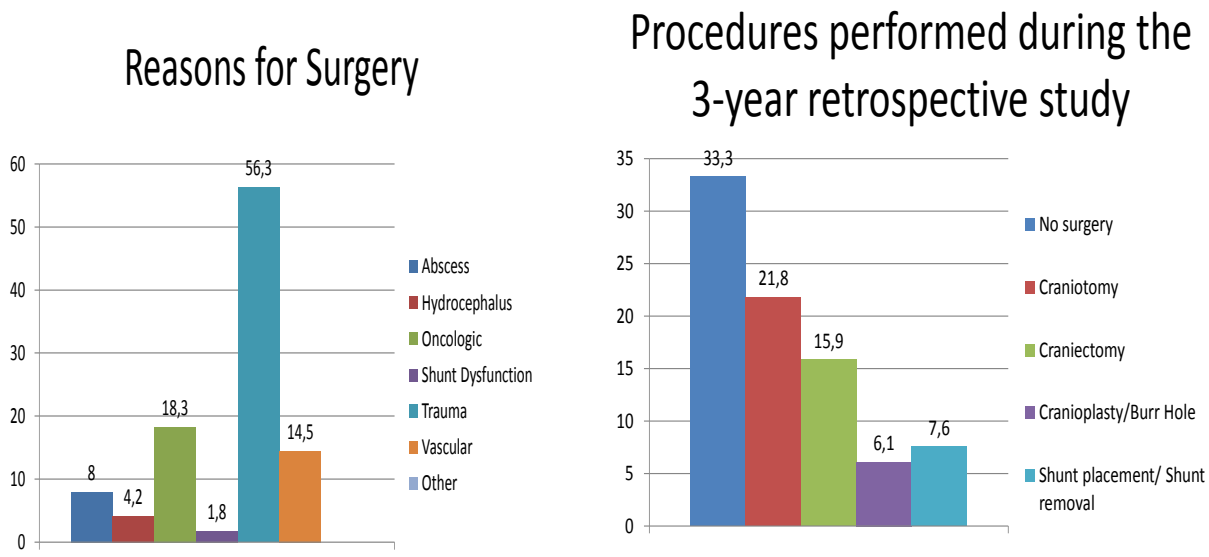


Figure 2.1.1 & 2.1.2: Reasons for surgery in patients admitted in the Department of Neurosurgery, UOC, during the 2004-2006 period. One third of the patients admitted did not undergo any procedures. Craniotomy was the most common procedure performed

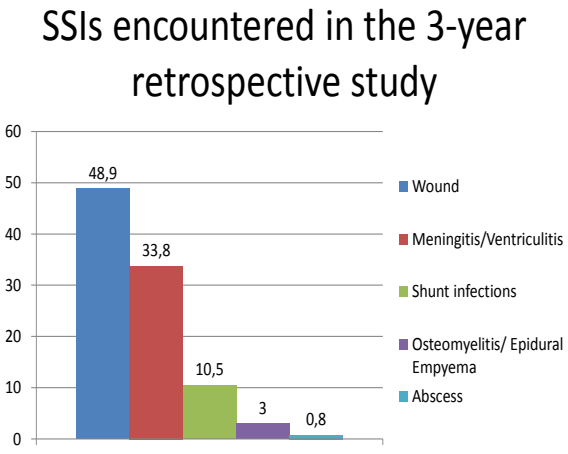


Figure 2.1.3: Wound infection was the most common among the SSIs

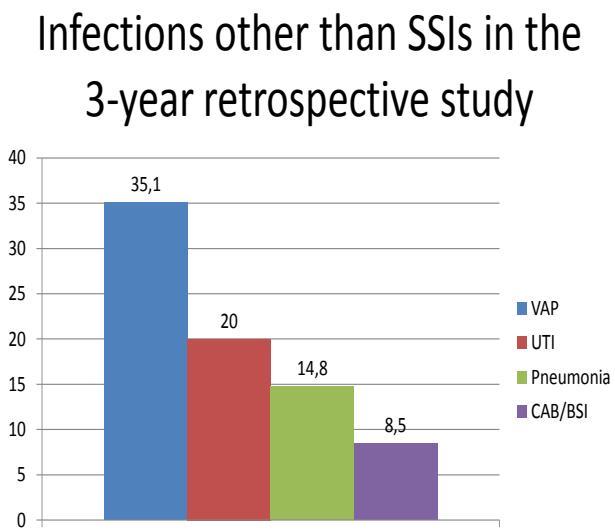


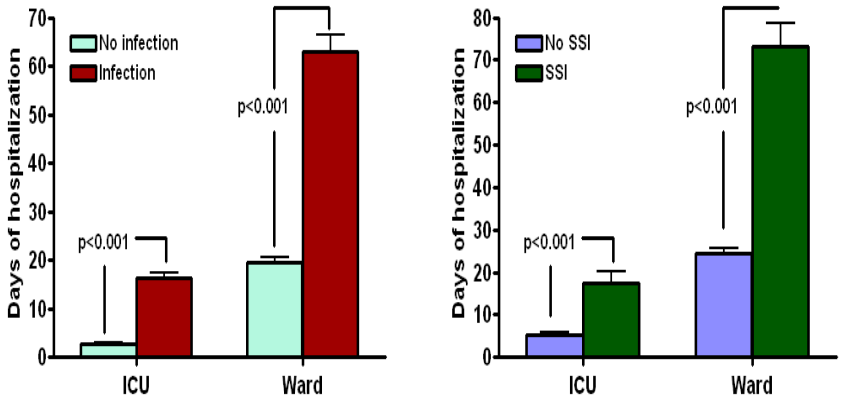
Figure 2.1.4: VAP was the most common infection among the non-SSIs

	Infection (any type)		
	NO	YES	P-value
Age (years)	49.7 ± 23.4	45.7 ± 21.8	0.042
≤ 25	24.6%	27.0%	
> 70	26.7%	14.6%	
History of malignancy	3.3%	8.1%	0.001
Surgery	60.6%	84.8%	<0.001
Craniectomy	8.7%	24.3%	<0.001
Vascular surgery	8.6%	23.2%	<0.001
Drainage	11.4%	34.2%	<0.001
ICP	9.3%	29.2%	<0.001

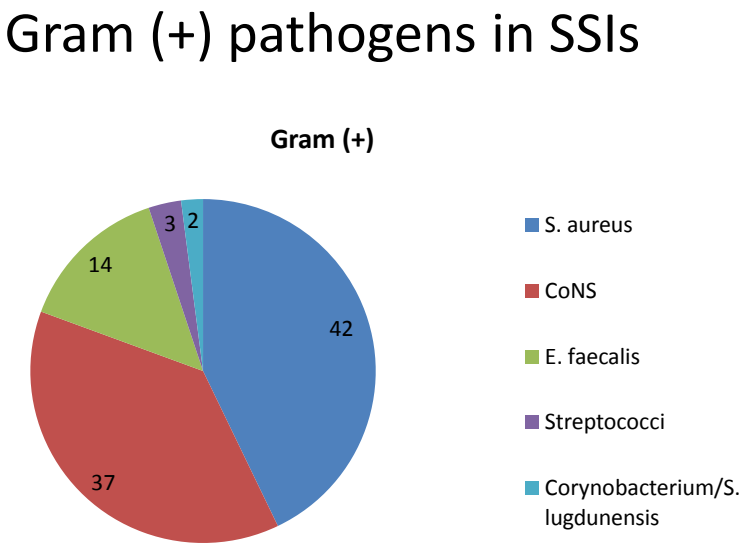
Table 2.1.1. Univariate analysis of the risk factors for development of neurosurgical infections in patients admitted to the Department of Neurosurgery, UOC

	Infection (any)		SSI	
	OR (95% CI) [#]	p-value	OR (95% CI)	p-value
Malignancy	4.63 (2.11–10.18)	<0.001	3.56 (1.55–8.16)	0.003
Reason for surgery				
Trauma	2.54 (1.52–4.25)	<0.001	–	–
Vascular events	5.73 (2.93–11.2)	<0.001	2.63 (1.30–5.31)	0.007
Type of surgery				
Craniectomy	1.84 (1.11–3.05)	0.018	1.80 (0.98–3.32)	0.059
Shunt replacement	4.87 (1.95–12.2)	<0.001	5.58 (2.15–14.5)	0.001
Drain	2.55 (1.63–3.99)	<0.001	4.17 (2.43–7.14)	<0.001
ICP	3.10 (1.89–5.10)	<0.001	–	–
Surgery through sinus	2.82 (0.95–8.42)	0.063	3.32 (1.01–11.0)	0.049

Table 2.1.2. Multivariate analysis of the risk factors associated with the development of any infection and of SSIs



Figures 2.1.5 and 2.1.6. The development of any infection, and the development of SSIs, was associated with increased ICU stay and LOS in general



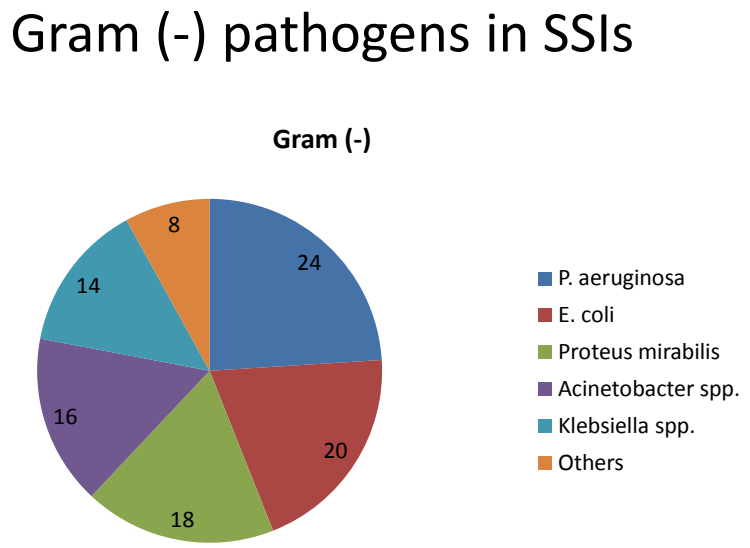
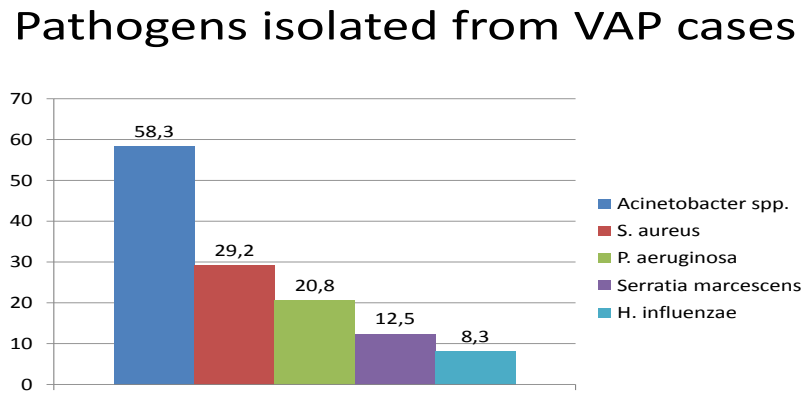
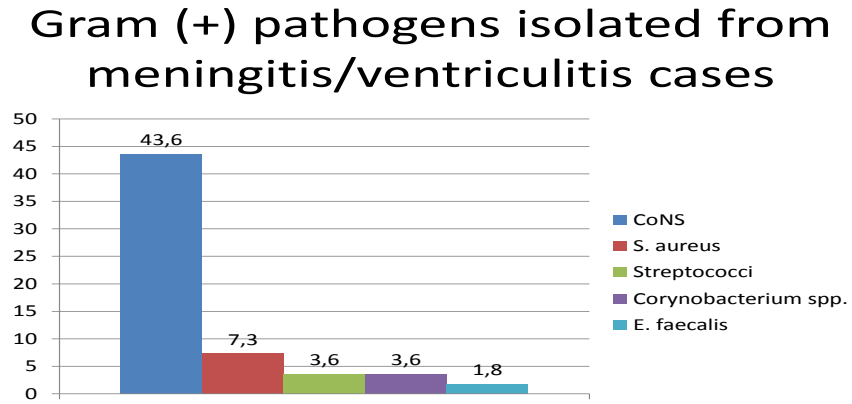


Figure 2.1.7. Gram (+) and Gram (-) pathogens isolated from neurosurgical infections in Department of Neurosurgery, UOC during the 3-year retrospective period





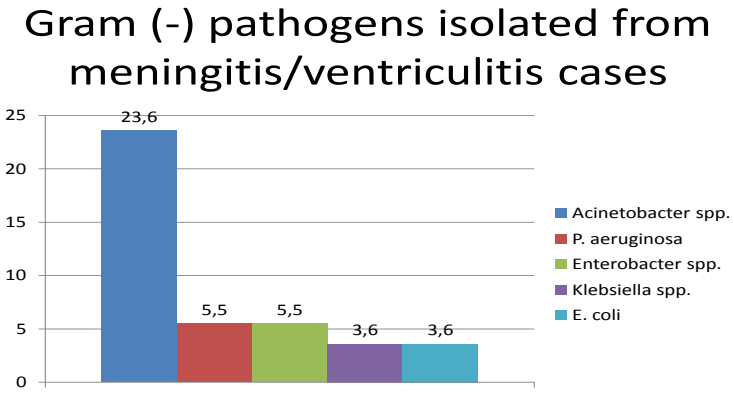


Figure 2.1.8. Acinetobacter spp. were the most common isolates in VAP. Acinetobacter spp. predominated among Gram (-) in meningitis whereas CoNS were the most common Gram (+)

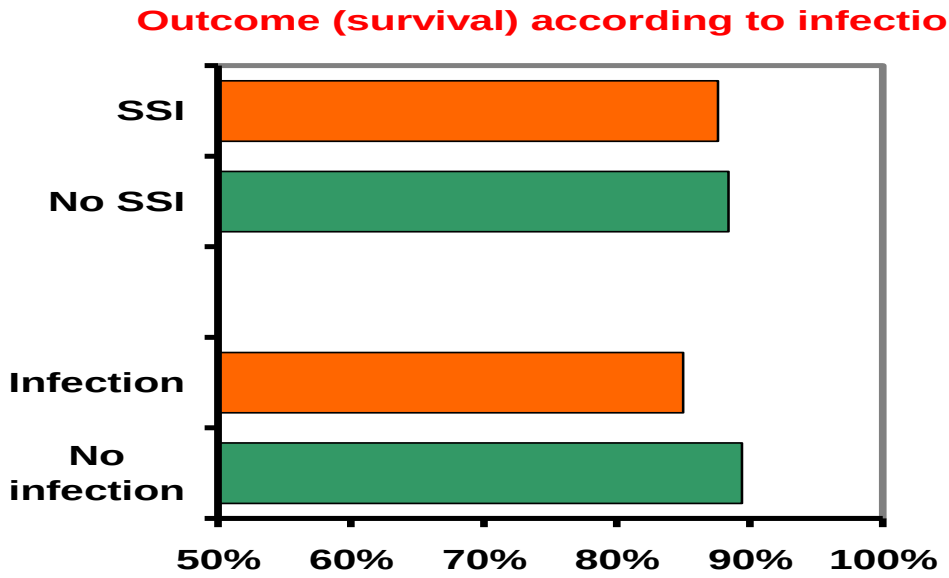


Figure 2.1.9. The development of any infection and of SSIs in particular, were not associated with increased mortality in this neurosurgical cohort

2.2 Retrospective study regarding the risk factors associated with postcraniotomy meningitis in the New York University (NYU) Medical Center

2.2.1 Abstract

Objective: Retrospective study for the determination of rate, bacteriology and risk factors for postcraniotomy meningitis (PCM)

Methods: Patients older than 18 years who underwent nonstereotactic craniotomies. Operations for burr holes and shunt placements were excluded. Host factors, craniotomy type and pre- and postoperative variables were evaluated as risk factors for meningitis

Results: Among 453 patients there were 25 cases of meningitis. Eight out of 12 culture-positive cases revealed gram-positive cocci. Ninety-two percent of the patients received antibiotic prophylaxis. In multivariate analysis the risk for meningitis was increased by surgery that entered a sinus (odds ratio [OR], 4.49; p=0.018), an increased American Society of Anesthesiologists (ASA) score (OR 1.72, p=0.023) and increase in the number of days of external ventricular drainage (OR 1.21, p=0.049) and intracranial pressure monitoring (OR 1.24, p=0.002)

Conclusion: Access of upper airway bacteria to the surgical wound, host factors as expressed by the ASA score and duration of device-related postoperative communication of the cerebrospinal fluid (CSF) and the environment are major risk factors for postoperative meningitis after craniotomy

2.2.2 Patients and Methods

Computer-based medical record indexes were reviewed at Bellevue and Tisch Hospitals at New York University (NYU) Medical Center. Patients were eligible if they were at least 18 years of age, underwent elective or emergency craniotomy between January 1996 and March 2000 and survived at least 7 days after surgery. Major craniotomies were included in the review. Patients having only cerebrospinal (CSF) shunt or external ventricular device implantations, burr hole trepanation or stereotactic surgery were excluded. The medical records of the eligible subjects were surveyed for the presence of meningitis during the first thirty postoperative days and during the first year if a foreign body was implanted. Data were abstracted from the medical chart to a standard database. Characteristics of the patients such as presence of diabetes, malignancy, atherosclerotic vascular disease (ASCVD), chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), and preoperative American Society of Anesthesiologists (ASA) score were recorded. Indications for surgery (tumor, vascular, trauma, brain abscess or other), presence and type of any foreign device, site of surgery (supra- or infratentorial), procedure urgency (elective or emergent), length of surgery, concomitant procedures (simultaneous orthopedic or abdominal surgery, facial reconstruction), implantation of a foreign body and the of any postoperative CSF drainage were also recorded. Other parameters recorded included details of hair removal, prophylactic antibiotics regimens, reoperations and CSF leak (leakage from the surgical wound, otorrhea, rhinorrhea)

Meningitis was diagnosed according to the definitions of the National Nosocomial Surveillance System. The criteria for the diagnosis of meningitis or ventriculitis were the following: 1. Organisms cultured from CSF 2. At least one of the following signs or symptoms with no other recognized cause: fever (>38° C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability *and* if diagnosis is made antemortem, attending physician institutes appropriate antimicrobial therapy *and* at least *one* of the following: a. increased white cells, elevated protein and/or decreased glucose 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 fourfold increase in paired sera (IgG) for pathogen [202, 203] . We recorded the postoperative day on which the diagnostic lumbar puncture (LP) was performed, the antibiotic or steroid regimen or both

initiated before and at the time of the lumbar puncture, all organisms identified by CSF culture and any recorded concurrent infections outside the nervous system including superficial wound and bone flap infections.

Data were transferred to a database (Epi Info, Version 6.04, Centers for Disease Control, Atlanta, GA) and were analyzed using either Epi Info or SPSS software. Rate ratios and their 95% confidence intervals (CIs) were computed using the StatCalc module of Epi Info version 6.04. Odds ratios (OR) and their CIs were computed by logistic regression in SPSS. Stepwise logistic regression was used to model the interactions of those variables significantly associated with postoperative meningitis in univariate analyses. A backward elimination model was used with P_{enter}=0.20 and P_{leave}=0.05. When a continuous variable such as the number of ventricular drainage days was shown to be a statistically significant risk factor, the relationship was modeled further using suitably coded dummy variables. Power calculations were performed using PEPI for Windows version 1.31 (www.brixtonhealth.com)

2.2.3 Results

The study included 453 patients who met the inclusion criteria. Twenty five (5.5%) patients experienced postcraniotomy meningitis (PCM). Fourteen out of 275 men (5.1%) and 11 out of 178 women (6.2%) experienced PCM. The average age (± standard deviation) of meningitis patients was 49.3 ± 17.1 years; the average age for those without meningitis was 51.8 ± 13.0 years. The median ages of those with and without meningitis were 54 years (quartiles 43, 60) and 48 years (quartiles 32, 62) respectively. Two patients (8.0%) in whom meningitis developed died before discharge as did 31 (7.3%) of those without meningitis. Neither of the two patients with meningitis died as a result of this specific infection.

Four hundred twenty (92.7%) out of 453 patients received perioperative antibiotic prophylaxis. Seventy-eight percent received a first-generation cephalosporin, 2.6% received another cephalosporin, 14.7% received vancomycin. 0.4% received a penicillinase-resistant penicillin and one patient received penicillin G. Four percent of the patients received an antibiotic combination. The median duration of surgery was 4 hours (quartiles 3.0, 6.0) for those in whom meningitis did not develop and 6 hours (quartiles 3.75, 7.25) for those in whom it did. Sixty-one percent of the patients had some kind of drain inserted after surgery.

Meningitis Risk: Table 2.2.1 lists all variables that were examined for their contribution to the risk of meningitis. Individual variables that were statistically significant at a *p* value of less than 0.05 included the presence of infection at another site before the diagnosis of meningitis, performance of multiple procedures at the time of craniotomy, emergency scheduling, increased ASA score, increased duration of surgery, surgery for a vascular indication, use of vascular clips, use and duration of intracranial pressure (ICP) monitoring, use and duration of ventricular drainage and use and duration of a galeal drain.

Among 178 patients with no postoperative CSF drainage, four patients (2.3%) experienced meningitis. The insertion of any kind of drain was associated with a 3.3-fold increase in the rate of meningitis (95% CI, 1.2-9.5). For ventricular drainage the increase was 9.2-fold (95% CI, 2.8- 29.6), for ICP monitoring the increase was 5.6 (95% CI, 1.8- 17.4); for subgaleal drainage the increase was 3.1 (95% CI, 1.2- 8.0) and for lumbar drainage the increase was 2.1 (95% CI, 0.7- 6.5). The risk of meningitis increased with increasing duration of drainage. The relation of the rate ratio for meningitis with duration of device use is depicted in Figure 3.2.1 for ventricular drainage, Figure 3.2.2 for subgaleal drainage and Figure 3.2.3 for ICP monitoring.

Thirty-three patients received no prophylactic antibiotics, 10.5% of whom experienced meningitis, in contrast to the 5.1% who did receive prophylactic antibiotics. The observed doubling of risk was not statistically significant (p=0.148, Fisher's exact test)**.**

None of the following were associated with the development of meningitis: age, sex, duration of the hospitalization before the craniotomy, timing of administration of prophylactic antibiotics, type of antibiotic administered, presence of cranial fracture in patients with trauma, use of steroids before surgery, type of depilation, craniotomy approach (supra- or infratentorial), previous craniotomy during the same admission, presence of a foreign body other than a vascular clip, postoperative CSF leak and placement of the ICP drain in the intensive care unit (ICU) rather than in the operating room.

Statistically significant variables in the univariate analysis were included in a multivariate logistic regression. Table 2.2.2 compares the results of univariate analysis for each variable with a *p* value of 0.20 or less and the results of the

multivariate modeling. The multivariate odds ratio is shown for variables remaining in the model. For the variables removed from the model, the table lists the p value for removal of the variable from the final model

Surgery through a sinus (OR 4.49), increasing ASA score (OR 1.73), duration of ICP monitoring (OR 1.24) and duration of ventricular drainage (OR 1.21) remained in the model as independent predictors with *p* values of less than 0.05. Use of vascular clips, duration of surgery, duration of galeal drainage, and presence of a concomitant or previous infection were variables that were removed from the model but had *p* values between 0.05 and 0.10. By comparing various logistic models, it was determined that the association with use of vascular clips was actually because patients having operations with vascular clipping also had a significantly prolonged course of drainage and ICP monitoring.

The relation between the use of galeal drains and a traumatic indication for craniotomy was also investigated. Galeal drains were used in 95 (81.9%) out of 116 patients in whom trauma was an indication and in 92 (45.1%) out of 204 oncological patients. The interaction of indication and galeal drainage was examined in this subset of the 320 patients. The data suggested a role for galeal drainage in explaining any increased risk in operations for trauma, but no role for trauma in explaining the association with galeal drainage.

Clinical Manifestations and CSF Features: Fever was the main presenting sign in 96% of the meningitis patients. The mean interval between the date of surgery and the development of symptoms was 6.7 days, with a minimum of 1 day and a maximum of 65 days. Fourteen of the infected received postoperative antibiotics for reasons other than prophylaxis before meningitis developed. The mean duration for such antibiotic was 2.6 days. The characteristics of the CSF in patients with postoperative meningitis are shown in Table 2.2.3. There were no important or significant differences between culture-positive and culture-negative patients.

Microbiology: Meningitis was documented by positive CSF culture in 12 (50%) out of 24 patients whose fluid was cultured. Gram-positive organisms predominated. Coagulase-negative staphylococci were isolated from five patients, *Staphylococcus aureus* from two patients and *Enterococcus* species from one patient. Other isolates included *Bacillus* spp., *Serratia* spp, *Haemophilus influenzae* and *Candida* spp. In three patients two different species were isolated. Concomitant infections were

documented in 17 of the meningitis patients (48%), most commonly nosocomial pneumonia.

Table 2.2.1. Univariate factors analyzed

Factor	No. at risk	Rate in at-risk group (%)	Odds ratio (95% confidence interval)	*P* value
Meningitis in total study population	453	5.5		
Age (no. of yr)	453	5.5	1.00 (0.98–1.03)	0.463
Age greater than median age (48 yr)	209	6.3	1.33 (0.59–3.00)	0.487
Male sex	275	5.1	0.81 (0.36–1.83)	0.62
Presence of another infection before meningitis	77	16.9	6.16 (2.69–14.11)	<0.001
Surgery through a sinus	29	13.8	3.06 (0.98–9.60)	0.055
Multiple procedures at time of craniotomy	40	15.0	3.85 (1.43–10.35)	0.007
Emergency procedure	155	9.7	2.48 (0.61–3.80)	<0.001
ASA score (numeric)			2.02 (1.32–3.09)	0.001
1	26	0	1	
2	206	2.4	0.33 (0.14–0.78)	0.012
3	144	8.3	0.90 (0.38–2.14)	0.819
4	57	12.3	5.42 (1.99–14.77)	0.001
5	11	9.1	16.00 (177–144.72)	0.014
Surgery duration (h)				
Total	447	5.3	1.12 (1.01–1.24)	0.031
<2	49	2.0	1[b]	
>2 and ≤4	177	4.0	1.97 (0.237–16.46)	0.529
>4 and ≤6	125	5.6	2.85 (0.341–23.77)	0.334
>6 and ≤8	61	8.2	4.29 (0.150–42.48)	0.191
>8 and ≤10	20	5.0	2.53 (0.15–42.48)	0.520
>10	15	20.0	12.00 (1.15–125.82)	0.038
Reason for surgery				
Oncological	204	4.4	1[b]	
Trauma	116	6.0	1.39 (0.50–3.84)	0.524
Vascular	71	11.3	2.75 (1.02–7.43)	0.046
Brain abscess	12	0	0	
Other	50	2.0	0.44 (0.55–3.57)	0.444
Chronic obstructive lung disease	8	12.5	2.45 (0.29–20.75)	0.410
Diabetes	38	10.5	2.16 (0.70–6.66)	0.179
Atherosclerotic cardiovascular disease	27	3.7	0.63 (0.08–4.84)	0.630
Cancer	50	2.0	0.32 (0.04–2.38)	0.262
Intracranial pressure monitor	79	12.7	3.47 (1.50–8.04)	0.004
Duration of pressure monitoring (d)			1.29 (1.50–1.56)	<0.001
No drain	178	2.3		
Any drain (versus no drain)	278	7.6	3.49 (1.18–10.35)	0.024
Use of ventricular drain	34	20.6	5.78 (2.22–15.03)	<0.001
Duration ventricular drainage (d)			1.30 (1.10–1.53)	0.002
Use of lumbar drain	28	10.7	2.20 (0.616–7.84)	0.225
Duration of lumbar drainage (d)			1.17 (0.882–1.562)	0.272
Use of Galeal drain	257	7.8	3.22 (1.19–8.75)	0.022
Duration of Galeal drainage (d)			1.37 (1.14–1.64)	0.001
Foreign body placement during surgery				
None	189	5.6		
Clips	22	22.7	5.99 (2.00–17.87)	0.001
Cranium	50	6.0	1.11 (0.32–3.83)	0.875
Dural	51	3.9	0.66 (0.15–2.90)	0.586
Craniotomy type				
Infratentorial	67	6.0	1[b]	
Supratentorial	377	5.3	0.88 (0.29–2.67)	0.825
Both	9	11.1	1.97 (0.19–19.86)	0.566
Other (Leibegger or Synthes)	169	5.3	0.94 (0.41–2.18)	0.889
Duration from admission to surgery (d)			1.02 (0.96–1.07)	0.581
Cranial fracture among patients with trauma	45/116	4.4	0.61 (0.11–3.31)	0.570
No use of prophylactic antibiotics	20	10.0	1.98 (0.433–9.06)	0.378
CSF leak	11	9.1	1.70 (0.21–13.87)	0.618
Previous craniotomy during the same admission	47	4.3	0.74 (0.17–3.23)	0.685
Use of steroids	133	6.0	1.19 (0.492–2.88)	0.699
Placement of ICP drain in ICU rather than operating room	18/122[c]	11.1	1.32 (0.26–6.68)	0.738

Figure 2.2.1. Relation between the number of ICP monitoring days and PCM

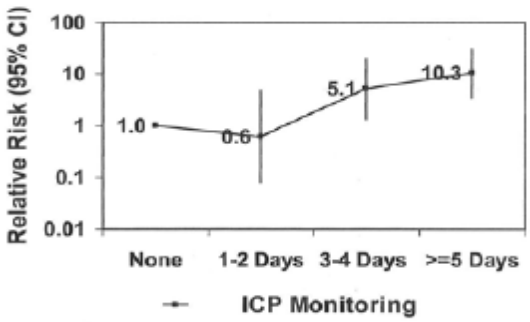


Table 2.2.2. Odds ratios for the variables studied by multivariate logistic regression

	Univariate analysis		Multivariate analysis	
Factor	Odds ratio[b]	*P* value	Odds ratio (95% confidence interval)	*P* value[c]
Surgery through sinus	3.06	0.055	4.49 (1.30–15.58)	0.018
ASA score	2.02	0.001	1.73 (1.08–2.765)	0.023
Days of ICP monitoring	1.27	<0.001	1.24 (1.08–1.42)	0.002
Days of ventricular drain	1.30	0.002	1.21 (1.00–1.47)	0.049
Presence of another infection	6.16	<0.001		0.083
Vascular clipping	5.99	0.001		0.077
Ventricular drain	5.78	<0.001		0.621
Multiple procedures	3.85	0.007		0.191
Intracranial pressure monitor	3.47	0.004		0.772
Galeal drain	3.22	0.022		0.253
Vascular procedure	2.75	0.048		0.539
Emergency scheduling	2.48	<0.001		0.874
Lumbar drain	2.20	0.225		0.733
Diabetes	2.16	0.179		0.804
Days of galeal drainage	1.37	0.001		0.096
Days of lumbar drain	1.17	0.225		0.944
Hours of surgery	1.12	0.031		0.059
Cancer	0.32	0.262		0.482

[a] ASA, American Society of Anesthesiologists; ICP, intracranial pressure.
[b] Confidence intervals may be found in *Table 1*.
[c] *P* values are for the odds ratios of included variables or for the removal of the variables that were not in the final model (italicized). The criterion for removal was a *P* value less than 0.05.

Figure 2.2.2.Relation between the subgaleal drain days and PCM

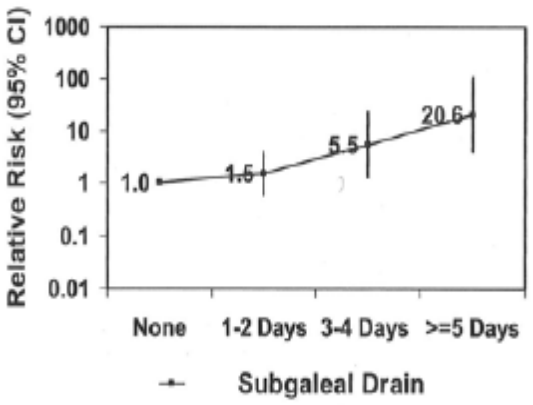


Figure 2.2.3. Relation between the number of ventricular drainage days and PCM

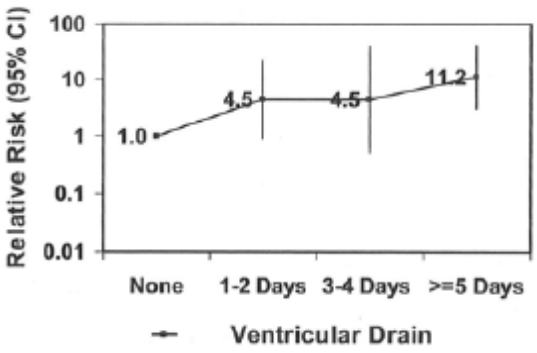


Table 2.2.3. Distribution of CSF values in cases of PCM

Laboratory values	Patients	Mean	Minimum	Percentile 25	Percentile 50	Percentile 75	Maximum
WBC (/ml)	All	2,129	0	235	364	1190	19,250
	Culture +			53	340	2400	
	Culture–			270	388	910	
Glucose (mg/dl)	All	57	9	31	58	80	158
	Culture +			32	60	82	
	Culture–			26	55	70	
Protein (mg/dl)	All	268	15	67	167.5	211	1304
	Culture +			46	99	213	
	Culture–			93	182	228	
CSF/blood glucose ratio	All	0.41	0.07	0.21	0.36	0.55	1.21
	Culture +			0.21	0.41	0.57	
	Culture–			0.24	0.35	0.53	

[a] WBC, whole blood count; +, positive; –, negative; CSF, cerebrospinal fluid.

2.2.4 Discussion

Meningitis Rate and Microbiology: The rate of meningitis in this study was 5.5%, higher than those noted in some series [2, 20, 199, 204]. Reichert et al. [1] in their prospective study reported a rate of 8.9%. The overall fatality rate of 8% is comparable with that reported by others [199] by neither death in our cohort could be attributed to the meningitis. Gram-positive organisms predominated as meningitis pathogens in this cohort. In studies published after 1993, Enterobacteriacae and other gram-negative rods played a greater role [1, 205-210], representing 70- 80% of the pathogens in some series [211]. Our results seem to reflect a reemergence of gram-positive organisms as nosocomial pathogens and they are in agreement with both older and some of the most recent series [20, 27, 50, 51, 204, 212]

Clinical Manifestations: The mean duration from operation to the onset of symptoms was 6.7 days, an interval similar to that reported in other studies [1]. Differentiation between bacterial and aseptic meningitis is still a problem after craniotomy, especially

in the early stages when treatment should be started [61, 213, 214, 215]. The culture-negative patients in our cohort were treated as meningitis because of the high clinical suspicion for infection. Although aseptic meningitis has been reported to complicate neurosurgery, especially procedures of the posterior fossa [61, 216], modern methods some of which use polymerase chain reaction techniques, suggest that at least some of these apparently aseptic cases may be bacterial [217, 218]. The use of BacT/ Alert system (bioMérieux, Inc, Durham NC) has also been reported as a more sensitive culture method for the detection of microorganisms in patients with PCM than the conventional method [219].

Risk Factors: The independent risk factors identified by the multivariate analysis were entry into the paranasal sinuses, increased ASA score and the prolonged use of ICP monitoring and ventricular drainage. After the final analysis, surgery that included the entering of a sinus was the most significant risk factor for the development of meningitis ($p < 0.018$). This finding is in accordance with the experience of some studies [16, 204] but not all [220]. The association observed in this study was not as significant in previous reports [16, 204] and it was independent from the presence of CSF leakage that could predispose to meningitis. A surgical approach through the paranasal sinuses qualifies for the characterization of the procedure as clean-contaminated, a category that has traditionally been associated with a higher infection rate [27]. The delay in the expansion of the brain to seal the communication into the anterior fossa seems to be responsible for the bacterial contamination; therefore, immediate mucosal repair is recommended to prevent infection [221- 223]**.**

An increasing ASA score was an independent risk factor for PCM. As can be seen in Table 2.2.1, the risk was elevated with scores 4 and 5, the two highest categories; 68 (15%) of our patients fell into these categories. The ASA score is included in the Risk Index Score for the Surgical Site Infections (SSIs) proposed by the NNIS system, although it seems that this index cannot effectively predict the risk of SSIs in craniotomy [202, 203]. Although it has been associated with the development of infections occurring after neurosurgery in the past [1, 20], it was not previously reported as an independent risk factor.

Craniotomies with an external ventricular drainage carry a higher risk for meningitis [7, 27, 50, 224, 225]. Ventriculitis in association with ventricular drain

placement was a frequent problem and was observed in 11% of general neurosurgical patients in the series of Mayhall et al. [7]. In the Mayhall study the risk of infection was 9% at Day 5, but it was 21, 37 and 42% by days 8, 10 and 11, respectively. There is little agreement among various series regarding the relation between duration of drainage and infection incidence; in one report, no relation was observed [225].

In our study, the duration of ventricular drainage was significantly associated with the risk of meningitis. It remained an independent risk factor when adjusted for the presence of other drains, especially when drainage continued for 5 days or more (Figure 2.2.3). These findings are in accordance with other recent literature demonstrating a significant association between the duration of use of a ventricular device and the meningitis [226], although this relationship has not been observed in all studies [81]. Schade et al [227] considered the duration of drainage to be the most significant risk factor after both 5 and 15 days of drainage. In the study of Park et al [228], the infection rate rose daily until the fourth day after insertion and plateaued thereafter. Lozier et al [29] documented that controversy exists in the literature regarding the relationship between the duration of catheterization and the risk of infection, but also observed that risk increased during the first 10 days. They make the point that evaluating the risk of infection when drainage exceeds duration of 10 days is problematic because such prolonged external ventricular drainage is rare.

In the study institutions no standard practice was followed for routine changes of drainage tubing. Based on our data and that of Mayhall et al [7], it is logical to recommend that a ventricular catheter should be removed or changed after 5 days to minimize the risk of infection. Arguing against this suggestion is the data of Holloway et al [36], who noted that the relationship of ventriculitis to monitoring duration is neither simple nor linear. In their experience, risk of infection became unlikely after the first 10 days, and they concluded that there was no benefit from catheter exchange after the fifth day. It can be seen in Figure 2.2.3 that the risk of infection on Days 1 and 2 was similar to the risk on Days 3 and 4 in our series. If the per-day risk of infection does not increase over time, leaving an uninfected drain in place may be the best policy. In one randomized controlled trial a policy of routine change was found not to be of clinical benefit [91]. Additional studies are needed to resolve the issue.

Whether the ventricular catheter was inserted in the neurosurgery intensive care unit (NICU) or in the operating room did not significantly alter the incidence of ventriculostomy-related infection in accordance with previously reported experiences

[7, 228]. Prophylactic antibiotics in ventriculostomy have proven to be of no benefit [34, 226, 229].

Meningitis or positive CSF culture has been described as the most frequent complication of ICP monitoring [25, 230]. During the study period, ICP monitoring devices were placed either in the parenchyma (Camino; NeuroCare, San Diego, CA) or in the ventricles and were attached to an external transducer. In our experience and that of others, infection is rare if the patient is monitored for less than 4 days but rises thereafter (Figure 2.2.1) [25, 85]. However, Winfield et al [230] examined the daily risk of infection and concluded that routine replacement of ICP devices is unwarranted; this has been confirmed in most recent studies [32]. The role of prophylactic antibiotics while pressure is monitored has not been clearly resolved [25, 34].

The presence and the duration of use of a subgaleal drain have not been associated with an increased risk for meningitis in previous studies. In this cohort, it was found to be a significant risk factor in the univariate analysis; however, its statistical significance declined to less than 0.05 in the multivariate analysis (Table 2.2.2). In trying to assess if subgaleal drainage covaried with other risk factors, we determined that its association with meningitis was not because it was used in 81.9% of trauma cases, but rather 45.2% of oncological patients and 63.4% of vascular patients. Subgaleal drains were less likely to be used in higher risk patients in whom the ASA score was more than 3 or in whom the duration of surgery was more than the seventy-fifth percentile for the group. The latter two risk factors are components of the National Nosocomial Infection Surveillance System risk stratification system. The presence and the duration of a lumbar drain carried a low risk of meningitis, in accordance with previous reports [231], although in the Coplin et al study the patients comprised of individuals with subarachnoid hemorrhage and CSF leaks after traumatic dural rents [231].

The presence of an infection outside the operative site at the time of surgery has been reported to increase the risk of developing meningitis after surgery [1, 16, 204, 232]. In our experience, it was associated with a sixfold increase in the infection incidence, a magnitude of association reported before [16]. The presence of a concomitant infection did not remain a significant independent risk factor in the multivariate analysis, although a trend toward significance was observed ($p<0.083$;

Table 2.2.2). On that basis, we recommend that, whenever possible, such infections be treated and controlled before surgery.

In contrast to previous reports, duration of surgery did not remain an independent risk factor in the multivariate analysis [50, 232]. Age, sex, diabetes, and corticosteroid administration before surgery were not significant risk factors for the development of meningitis, a finding consistent with previous data [204]. Repeat surgery, which has been a major risk factor in recent [1] and older reports [50, 232], was not a risk factor in our cohort. Previous studies demonstrated postoperative CSF leak to be a significant risk factor for the development of meningitis [16, 20, 51, 204]. In our series, the presence of CSF leak was associated with a 1.7-fold increase in the risk of meningitis, but this was not statistically significant. The limitations of this study include the fact that it was retrospective and depends on the accuracy of the data in the clinical chart. In addition, the power to assess a risk factor depends on the frequency of its presence. For example, the presence or absence of diabetes could be assessed for 445 persons in the study. Thirty-eight were diabetic and four of them had meningitis, a twofold increase in risk, which was not statistically significant. Given these data, it may be determined that the study has a power of 80% to detect a 3.75-fold increase in risk, but only a 22% power to detect a twofold increase. Thus, this study had adequate power to detect risk factors of moderate strength. Recent attempts to reduce the frequency of drainage associated infection have included impregnation of ventricular shunt catheters with antimicrobial agents. Such catheters retain their activity for at least 6 weeks [112, 187, 233]. A controlled trial of ventricular shunting has shown such treatment to be associated with a reduced frequency of infection and in animal models of closed internal drainage. The approach may prove effective but requires evaluation in the postoperative setting of external drainage in humans because it already looks promising in a rabbit model [234]. A recent, in vitro antimicrobial study on sliver-processed catheters for external ventricular drainage proved no eradication of MRSA or *E. coli* but only some activity against *S. epidermidis* [235].

2.3 Retrospective study in the University of Crete (UOC) Medical Center: Infections in Patients undergoing craniotomy-First attempt to identify risk factors associated with post-craniotomy meningitis in Greece

2.3.1 Abstract

Objective: Retrospective study for the determination of incidence, bacteriology of infections in patients undergoing craniotomy clarification of risk factors for postcraniotomy meningitis for the first time in a cohort in Greece

Methods: Patients older than 18 years who underwent nonstereotactic craniotomies were included. Operations for burr holes, ICP and shunt placements were excluded. Demographic, clinical, laboratory and microbiological data were systemically recorded in specially designed forms. Host factors and pre- and postoperative variables were evaluated as risk factors for meningitis

Results: Six-hundred and nineteen craniotomies in 479 patients were analyzed. TBI was the most common cause for craniotomy. 26% of the patients developed at least one infection. VAP was the most common infection recorded (13.1%). Meningitis/ventriculitis was encountered in 37 procedures (6.1%). Seventy-four percent of the LP samples were positive. Gram-negative pathogens represented 48% of them, whereas gram-positive pathogens represented 43%. In the multivariate analysis the risk for meningitis was independently associated with the development of another SSI (odds ratio [OR], 4.5), VAP/pneumonia (OR 4.4), UTI (OR 6.2), malignancy (OR 3.6), presence of a ventricular drainage (OR 12.7) and a lumbar drainage (OR 91.8) and an emergent procedure (OR 2.9).

Conclusion: Device-related postoperative communication of the CSF and the environment, SSI other than meningitis and infections outside the surgical field were defined as major risk factors for PCM

2.3.2 Patients and Methods

Charts and available records were reviewed at UOC Medical Center. Patients were eligible if they were at least 18 years of age, underwent elective or emergency craniotomy between 1999 and 2005 and survived at least 7 days after surgery. Major craniotomies were included in the review. Patients having only CSF shunt or external ventricular device implantations, burr hole trepanation or stereotactic surgery were excluded.

Data were abstracted from the medical chart to a standard database. Characteristics of the patients such as presence of diabetes, malignancy, ASCVD, CRF, COPD were recorded. The ASA score was not recorded as a routine in the anesthesia evaluation, so this parameter was not analyzed as a risk factor due to missing data. Indications for surgery (tumor, vascular, trauma, brain abscess or other), presence and type of any foreign device, procedure urgency (elective or emergent), length of surgery, concomitant procedures (simultaneous orthopedic or abdominal surgery, facial reconstruction), implantation of a foreign body and the of any postoperative CSF drainage were also recorded. Other parameters recorded included prophylactic antibiotics regimens, reoperations and CSF leak (leakage from the surgical wound, otorrhea, rhinorrhea)

Meningitis was diagnosed according to the definitions of the National Nosocomial Surveillance System [202, 203]. We recorded the postoperative day on which the diagnostic LP was performed, the antibiotic or steroid regimen initiated before and at the time of the lumbar puncture, all organisms identified by CSF culture and any recorded concurrent infections outside the nervous system including SSIs.

Data were transferred to a database and were analyzed using SPSS software (Version 16.0; SPSS Inc., Chicago, IL). Continuous variables were compared using Student's *t* test or the Mann-Whitney *U* test, whereas categorical variables were compared using Fisher's exact test. In univariate analysis, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenzel statistic. Stepwise multivariate logistic regression was used to model the interactions of those variables significantly associated with SSIs or meningitis in univariate analyses. A backward elimination model was used with $P_{enter}=0.20$ and $P_{leave}=0.05$ to identify independent predictors for SSI and meningitis. Power calculations were performed using the PASS software (PASS 2008, https://www.ncss.com)

2.3.3 Results

The study included 479 patients (64.6% men) who met the inclusion criteria. The median age was 48 (range 18- 89). They underwent 619 procedures. Traumatic Brain Injury (TBI) was the most common reason for craniotomy (41% of the craniotomy cases). 11.6% of the procedures were revision surgeries and 51.4% were emergent procedures. Twenty six percent of the people who underwent craniotomy developed at least one infection. SSIs developed in 12.3% of the patients. Thirty one out of the 479 patients (6.5%) patients experienced postcraniotomy meningitis (PCM) (6.1% for the total of procedures). Six patients developed ≥2 episodes of meningitis (1.3% of the total cohort). Recurrent meningitis was associated with a prolonged intubation (p=0.043). The development of SSI and/or other infections were associated with longer ICU stay and a longer intrahospital LOS in general (p<0.001). Overall mortality was 13.4%. The mortality among the patients who developed meningitis was 31.6% whereas among the patients who did not develop meningitis it was 12.3%. The difference was statistically significant (OR 3.3, p<0.001)**.** Mortality was significantly associated with the development of pneumonia (p=0.002) and marginally with the development of SSIs other than meningitis (p=0.055).

The median delay from admission to surgery was 2 days. The median duration of surgery was 2 hours (quartiles 2.0, 3.0, range 1-8 hours) for those in whom meningitis did not develop and 2 hours (quartiles 2.0, 3.5, range 1-7 hours) for those in whom it did.

The median length of stay (LOS) was 19 days. The LOS was significantly associated with an adverse final outcome (p=0.020). People who developed meningitis had a much longer LOS (mean 97.5 vs. 31.4 days, p<0.001). LOS was also prolonged in patients who developed SSIs other than meningitis (p<0.001), VAP (p<0.001), BSI/CAB (p=0.005), pneumonia (p<0.001) and UTI (p<0.001). Patients who developed meningitis had a longer duration of intubation (p<0.001)

Meningitis Risk: Table 2.3.1 lists all variables that were examined for their contribution to the risk of meningitis. Individual variables that were statistically significant at a p value of less than 0.05 included the presence of concomitant infections, including the presence of other SSIs, surgery through a sinus, emergency scheduling, increased duration of surgery, presence of any drain, presence particularly of ventricular and lumbar drains, use of a dural substitute, presence of CSF leak,

revision surgery, malignancy, admission and hospitalization to Intensive Care Unit (ICU) and duration of ICU hospitalization.

The insertion of any kind of drain was associated with a 3.3-fold increase in the rate of meningitis (95% CI 1.7- 6.4). For ventricular drainage the increase was 4.6-fold (95% CI 2.1- 10.4) and for lumbar drainage the increase was 75.5 fold (95% CI 16- 356.4).

Among the prophylactic antibiotics used, the use of a second generation cephalosporin was associated with a decrease (p=0.009) but on the contrary the use of vancomycin was associated with an increase in the prevalence of SSIs (p=0.002). The prevalence of meningitis was increased when a third generation cephalosporin was used as prophylaxis (p=0.029). These conclusions cannot be generalized since they are based on retrospective data.

None of the following were associated with the development of meningitis: age above median, sex, duration of hospitalization before the craniotomy, presence of cranial fracture in patients with trauma (although it approached the statistical significance with p=0.086), co morbidities other than malignancy, multiple procedures at the same time with the craniotomy, presence of a foreign body other than a dural substitute and placement of an ICP drain.

Statistically significant variables in the univariate analysis were included in a multivariate logistic regression. Table 2.3.2 compares the results of univariate analysis for each variable with a p value of 0.20 or less and the results of the multivariate modeling. Another SSI (OR 4.5), presence of VAP/pneumonia (OR 4.4), presence of UTI (OR 6.2), presence of malignancy (OR 3.6), presence of ventricular drainage (OR 12.7), presence of a lumbar drainage (OR 91.8) and an emergent procedure (OR 2.9) remained in the model as independent predictors with p values of less than 0.05.

CSF Features in Patients with Meningitis: The median interval between the surgical procedure and the diagnostic LP was 13 days (range 0-63). The median number of WBC in diagnostic LPs in cases of meningitis was 215 (range 7- 16000).

Infections other than meningitis: VAP was the most common infection in this population (13.1%). 6.9% developed a wound infection, 6.5% developed UTI and 6% developed pneumonia. Patients who had craniotomy for a vascular reason had an increased propensity to develop infections outside the surgical field (p<0.001).

Revision surgery was associated with an increase in the risk for SSIs other than meningitis.

Microbiology: In lower respiratory tract infections the main pathogens were the following: *Acinetobacter* spp (42%), *S. aureus* (25%) and *P. aeruginosa* (21%). The three main pathogens in UTI were: *P. aeruginosa* (50%), *E. coli* (13%) and *E. faecalis* (10%). The main pathogens in Blood stream infections/Catheter associated bacteremias (BSI/CAB) were: *Acinetobacter* spp (61.5%), *E. faecalis* (46.2%) and *P. aeruginosa* (38.5%). In wound infections, the main pathogens were: *S. aureus* (43%), Coagulase-negative staphylococci (CoNS) (31%), *P. aeruginosa* (14%) and *E. coli* (11%) (Table 2.3.4).

Meningitis was documented by positive CSF culture in 77% of the meningitis cases. Gram-negative organisms predominated (37% of the total number of LPs cultured). The isolated pathogens were: CoNS (23%), *Acinetobacter* spp (16%), *P. aeruginosa*, *C. albicans* (7%), *E. coli*, *K. pneumoniae* and *S. aureus* (4.7%), and *Corynobacterium* spp, *E. cloacae*, *E. faecalis* and *E. aerogenes* (2.3%) (Table 2.3.3)

Table 2.3.1. Risk factors for post-craniotomy meningitis (Univariate analysis)

	No meningitis	Meningitis	
	% or mean - SD		P-value * (OR; 95% CI)
Age above median	49	50	0.706
Male Sex	66	63	0.729
Concomitant infections (any)	21.3	70.7	<0.001 (9.0; 4.4–18.3)
VAP/pneumonia	17.4	46.3	<0.001 (4.1; 2.1- 8.0)
UTI	5.8	39	<0.001 (10.4; 4.9–22.0)
BSI/CAB	1.2	9.8	0.005 (8.8; 2.3- 34.4)
Presence of another SSI	6.3	36.6	<0.001 (8.6; 4.1- 18.2)
Surgery through sinus	5.3	17.1	0.010 (3.7; 1.5- 9.2)
Multiple procedures	1.2	2.4	0.434
Emergency procedure	51.0	70.7	0.021 (2.3; 1.2- 4.7)
Co morbidity (any)	33.8	46.3	0.123
ICP presence	21.1	26.8	0.426
Drain (any)	34.5	63.4	<0.001 (3.3; 1.7- 6.4)
Ventricular Drain	6.5	24.4	0.001 (4.6; 2.1–10.4)
Lumbar Drain	0.5	26.8	<0.001 (75.5;16.0–356.4)
Dural substitute	12.6	34.1	0.001 (3.6; 1.8–7.3)
Time to surgery	9.4 - 36.3	15.3 - 46.4	0.434
Skull fracture	58.2	88.9	0.086
CSF leak	3.9	12.2	0.032 (3.5; 1.2–10.0)
Revision surgery	6.5	22.0	0.002 (1.8; 1.8–9.3)
ICU admission	69.8	85.4	0.045 (2.5; 1.0–6.2)
ICU stay (days)	7.1 - 7.2	23.5 - 19.1	<0.001
Duration of surgery (hours)	2.7 - 1.5	4.2 - 3.0	0.031

Table 2.3.2. Risk Factors for PCM (Multivariate analysis)

	Meningitis Risk		
Independent Variables	**Odds ratio**	**95% CI**	***P*-value**
Other SSI	4.5	1.7- 12.0	0.002
VAP/pneumonia	4.4	2.0- 9.6	<0.001
UTI	6.2	2.3- 17.0	<0.001
Malignancy	3.6	1.3- 10.1	0.011
Ventricular Drain	12.7	5.1- 32.6	<0.001
Lumbar Drain	91.8	18.9- 446.3	<0.001
Emergency procedure	2.9	1.0- 8.0	0.046

2.3.4 Discussion- Comparison between the retrospective studies in NYU and UOC on PCM

Comparison of the populations: In the NYU cohort, only 34.2% of the procedures were emergent whereas in the UOC cohort, 51.4% of the craniotomies were emergent (p<0.001). This is also reflected in the difference of the study population. In the NYU cohort the Trauma patients represented only 25.6% of the patients but in the UOC cohort the percentage was 41% (p<0.001). The median age was 48 for both cohorts. The percentage of male patients was 61% for the NYU cohort and 64.6% for the UOC cohort (NS). The overall fatality rate was 8% in the NYU cohort and 13.4% in the UOC cohort (p=0.005)

Incidence and Microbiology of PCM: The incidence of PCM in the UOC study was 6.1%, higher than the 5.5% noted in the NYU cohort but the difference was not statistically significant. In the NYU cohort we had investigated if the supratentorial or the infratentorial surgical approaches had any impact on the development of meningitis. There was no difference between the two approaches. We had no subanalysis for translabyrinthine approach. The difference between the approaches was not investigated in the UOC cohort.

Culture-documented cases of meningitis were more in the UOC cohort (50 vs. 77%, NS). Gram-positive organisms predominated as meningitis pathogens among the culture-documented cases in the NYU cohort but in the UOC cohort there was a Gram-negative preponderance. In studies published after 1993, Enterobacteriacae and other gram-negative rods played a greater role [1, 133, 205- 209]. *Acinetobacter* spp., which has been the emergent pathogen in postneurosurgical meningitis [140], was cultured in 16% of the cases in the UOC cohort, when in the NYU cohort it represented 4%. NYU cohort included patients from 1996-2000, whereas the UOC cohort included patients undergoing craniotomy from 1999-2005. This reflects the recent emergence of *Acinetobacter* spp. as pathogens. The results in the NYU seem to reflect a reemergence of gram-positive organisms as nosocomial pathogens in that time period and they are in agreement with both older and some of the most recent series [20, 27, 50, 51, 204, 212]. The data from UOC cohort are consistent with the most recent reports. In both cohorts, the susceptibilities of the pathogens were not investigated.

Clinical Manifestations of PCM: The mean duration from operation to the onset of symptoms was 6.7 days in the NYU cohort, an interval similar to that reported in other studies [1]. The median time from surgery to the diagnostic LP was 13 days in UOC cohort. The culture-negative patients in the both cohorts were treated as meningitis because of the high clinical suspicion for infection.

Risk factors for PCM: In the UOC cohort, the independent risk factors identified by the multivariate analysis were the presence of another SSI, presence of lower respiratory tract infections (VAP and pneumonia), presence of UTI, presence of malignancy, presence of ventricular and lumbar drains and marginally the emergency of the procedure. The ASA score was not documented in the majority of the cases in this retrospective study so its impact was not analyzed in the UOC cohort. This is a great limitation for the analysis since the ASA score is included in the Risk Index Score for the Surgical Site Infections (SSIs) proposed by the NNIS system [202]. From the non-modifiable patients' characteristics, malignancy was an independent risk factor for PCM. Malignancy was defined as a malignant tumor for which the patient underwent craniotomy or the presence of a malignant tumor in another body system or the presence of a hematologic malignancy. After the final analysis, surgery that included the entering of a sinus was not an independent risk factor for PCM in the

UOC cohort while it was the most significant risk factor for the development of meningitis in the NYU cohort.

As mentioned in the Discussion section of the NYU cohort, craniotomies with an external ventricular drainage carry a higher risk for meningitis [7, 27, 50, 224, 225]. There is little agreement among various series regarding the relation between duration of drainage and infection incidence; in one report, no relation was observed [225]. In the UOC cohort the duration of drainage was not independently associated with the development of meningitis. As mentioned in the previous section though, there is recent literature demonstrating a significant association between the duration of use of a ventricular device and the meningitis [226], although this relationship has not been observed in all studies [81]. Lozier et al [29] documented that controversy exists in the literature regarding the relationship between the duration of catheterization and the risk of infection, but also observed that risk increased during the first 10 days.

Based on the above mentioned literature and the results from NYU cohort [19], it is logical to recommend that a ventricular catheter should be removed or changed after 5 days to minimize the risk of infection. Arguing against this suggestion we should also mention the data published by Holloway et al [36], who noted that the relationship of ventriculitis to monitoring duration is neither simple nor linear. We should also mention the randomized controlled trial [91] where the policy of routine change was found not to be of clinical benefit.

The incidence of meningitis following lumbar drain placement has been reported in various series ranging from 0-25.6% [236] and it is highest when placed after subarachnoid or intraventricular hemorrhage [231]. In a well-designed prospective study where the drain associated infection occurrence was related to the number of drainage days (DD), infections associated with lumbar drains seemed to occur more frequently compared with EVD [237]. After exclusion of 15 contaminations, a total of 26 cases of meningitis were reported, accounting for an overall associated meningitis rate of 8.6 infections/1000 DD. The infections associated with lumbar drains were 19.9/1000 DD whereas the ones associated with EVD were 6.3/1000 DD [237]. In this study the drains were inserted for various reasons, but there is no mention if the individuals had any other neurosurgical procedures that could further contribute to the development of meningitis. Independent risk factors were the history of TBI and subarachnoid hemorrhage. The presence of a LD versus the presence of an EVD was not an independent risk factor for the development of meningitis [237]. In the editorial

they comment that the EVD infection rates were excellent but the reasons why lumbar drains should have worse rates remain unclear [238].

These data are in discordance with previous reports that suggested lumbar drains as safe alternatives to ventriculostomies or serious lumbar punctures [231]. In the Abadal-Centellas et al. study on TBI individuals, there was no CSF infection during the lumbar drain use [239]. In the studies that investigated the risk factors for postoperative infections after craniotomies, the risk of meningitis has not been associated with lumbar drainage in most of the studies [1, 14, 16, 19, 20, 22, 51, 57, 161, 199, 204, 212, 232] but not in all [3]. In our study we noted this significant association between the development of PCM and the postoperative lumbar drainage.

The association of PCM with the development of other infections was underscored in this cohort (Table 2.3.2). As mentioned before in the analysis of the NYU cohort, the concomitant infections have been reported to increase the risk of PCM [1, 16, 57, 204, 232]. In the NYU cohort the risk of PCM increased by six-fold but concomitant infections did not remain an independent risk factor in the multivariate analysis. The increase in the risk is of magnitude that has been reported before [16]. Emergency scheduling achieved statistical significance in the multivariate analysis in the UOC cohort but not in the NYU cohort. The association of PCM with emergency scheduling has been associated with the development of meningitis in very good studies in the past [20, 22].

Age and sex failed to achieve statistical significance as risk factors for PCM in both cohorts analyzed. Age>65 was examined as a risk factor for infections in patients undergoing craniotomy for meningioma and it did not achieve statistical significance [17]. Malignancy that achieved statistical significance in our cohort has not been associated with the development of PCM in the past.

Microbiology of infections other than meningitis: In the NYU cohort there was no documentation of the pathogens of the infections other than PCM in the patients that underwent craniotomy. In the UOC cohort we attempted to do a complete description of the infections affecting patients who undergo craniotomy. 26% of the patients who underwent craniotomy developed at least one infection, a fact that underscores the significance of very good nosocomial care of these individuals.

Respiratory tract infections were the most common in this cohort. There was a significant predominance of *Acinetobacter* spp. in respiratory tract infections which seem as emerging pathogens. The most important issue in *Acinetobacter* spp.

infections is their increased resistance to the antibiotics. In the prospective cohort, presented in the next section we investigated the sensitivity patterns of all the pathogens isolated from patients who undergo craniotomy. *S. aureus* was the second most commonly isolated pathogen in pneumonias (Table 2.3.4). *S. aureus*, has been associated with VAP more in the neurosurgical population than other ventilated patients [240]. In the Espersen et al. study these patients who may be treated with hyperventilation, sedation, cooling and steroids had a significantly higher frequency of *S. aureus* pneumonia (25.9%) and *S. aureus* colonization (27.8%) compared with other ventilated patients (1.2% and 4.6% respectively) [240]. In a recent study, the significance of periodontal disease in pneumonia after elective craniotomy has been demonstrated [241]. In order to avoid postoperative pneumonia, the authors suggest dental examination in elective surgery for the identification of patients at high risk to develop postoperative respiratory infections [241].

The rate of BSI/CAB was 2.1%. This is comparable to other reports from Greece, although in the Tsitsopoulos et al. study the patients comprised of general neurosurgical population and not only of patients undergoing craniotomy [200]. *Acinetobacter* spp. were the main pathogens of BSI/CAB in our cohort (61.5%), whereas in the other study the main isolates included *K. pneumoniae* and *P. aeruginosa* [200].

Table 2.3.3. Pathogens associated with PCM in NYU and UOC retrospective cohorts

NYU Cohort		UOC Cohort	
No pathogen	50%	**No Pathogen**	23%
CoNS	21%	**CoNS**	23%
S. aureus	8%	**Acinetobacter spp**	16%
Enterococcus spp.	4%	**P. aeruginosa, C. albicans**	7%
Bacillus spp	4%	**E. coli, K. pneumoniae, S. aureus**	4.7%
Serratia spp.	8%	**Corynobacterium spp, E. cloacae, E. faecalis, E. aerogenes**	2.3%
Acinetobacter spp	4%		
P. aeruginosa	4%		
H. influenzae	4%		
Candida spp.	4%		

Table 2.3.4. Sites of infection and pathogenic bacteria most commonly isolated in patients undergoing craniotomy

Infection site	Percentage of patients	Organisms isolated
Respiratory tract infections	19%	Acinetobacter spp (42%) S.aureus (25%), P. aeruginosa (21%)
Wound infection	6.9%	S. aureus (43%), CoNS (31%), P. aeruginosa (14%), E. coli (11%)
Urine Tract Infection	6.5%	P. aeruginosa (50%), E. coli (13%), E. faecalis (10%)
BSI/CAB	2.1%	Acinetobacter spp. (61.5%), E. faecalis (46.2%), P. aeruginosa (38.5%)

2.4 Prospective study in the University of Crete (UOC) Medical Center: Infections in Patients undergoing craniotomy-Risk factors associated with post-craniotomy meningitis

2.4.1 Abstract

Objective: Prospective study to define the incidence, bacteriology of infections in patients undergoing craniotomy and clarification of risk factors for postcraniotomy meningitis

Methods: Patients older than 18 years who underwent nonstereotactic craniotomies were included. Demographic, clinical, laboratory and microbiological data were systemically recorded in specially designed forms. Host factors, craniotomy type and pre- and postoperative variables were evaluated as risk factors for meningitis

Results: Three hundred thirty four craniotomies were analyzed. Men represented 65.6% of them TBI was the most common cause for craniotomy. 39.8% of the patients developed at least one infection. VAP was the most common infection recorded (22.5%). Meningitis/ventriculitis was encountered in 16 procedures (4.8%). One hundred percent of the LP samples were positive. Gram-negative pathogens (*Acinetobacter* spp, *Klebsiella* spp, *Pseudomonas aeruginosa*, *E.cloacae*, *Proteus mirabilis*) represented 88% of them. In the multivariate analysis the risk for meningitis was independently associated with the perioperative steroid use (OR 11.55, $p=0.005$), CSF leak (OR 48.03, $p<0.001$), and ventricular drainage (OR 70.52, $p<0.001$).

Conclusion: Device-related postoperative communication of the CSF and the environment, CSF leak and perioperative steroid use were defined as major risk factors for PCM in this prospective study

2.4.2 Patients and Methods

Charts and available records were reviewed at UOC Medical Center. 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. Major craniotomies were included in the review. Patients having only CSF shunt or external ventricular device implantations, burr hole trepanation or stereotactic surgery were excluded.

Data were abstracted from the medical chart to a standard database as described in the methods of the other cohorts. The ASA score was not recorded as a routine in the anesthesia evaluation, so this parameter was not analyzed as a risk factor due to missing data.

Meningitis was diagnosed according to the definitions of the National Nosocomial Surveillance System [202, 203]. Data were transferred to a database and were analyzed using SPSS software (Version 16.0; SPSS Inc., Chicago, IL). Continuous variables were compared using Student's *t* test or the Mann-Whitney *U* test, whereas categorical variables were compared using Fisher's exact test. In univariate analysis, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenzel statistic. Stepwise multivariate logistic regression was used to model the interactions of those variables significantly associated with SSIs or meningitis in univariate analyses. A backward elimination model was used with $P_{enter}=0.20$ and $P_{leave}=0.05$ to identify independent predictors for SSI and meningitis. Power calculations were performed using the PASS software (PASS 2008, https://www.ncss.com)

2.4.3 Results

The study included 334 procedures (65.6% males) who met the inclusion criteria. The median age was 51 (IQR 27, 66). Traumatic Brain Injury (TBI) was the most common reason for craniotomy (49.7% of the craniotomy cases). 18.7% of the procedures were revision surgeries and 49.7% were emergent procedures. Almost forty percent of the people who underwent craniotomy developed at least one infection. SSIs developed in 9% of the patients. Sixteen patients (4.8%) experienced postcraniotomy meningitis (PCM). Overall mortality was 15%.

The median delay from admission to surgery was 3 days. The median duration of surgery was 2 hours (quartiles 2.0, 4.0) for those in whom meningitis did not develop and 4 hours (quartiles 3.0, 6.0) for those in whom it did (p=0.003).

The median length of stay 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 ICU ($p<0.001$) and have a prolonged intubation beyond the surgical time ($p<0.001$)

Meningitis Risk: Table 2.4.1 lists all variables that were examined for their contribution to the risk of meningitis. Individual variables that were statistically significant at a *p* value of less than 0.05 included female sex, perioperative steroid use, increased duration of surgery, presence of CSF leak, admission and hospitalization to Intensive Care Unit (ICU) and use of ventricular drains.

Statistically significant variables in the univariate analysis were included in a multivariate logistic regression. Table 2.4.2 compares the results of univariate analysis for each variable with a *p* value of 0.20 or less and the results of the multivariate model. Presence of ventricular drainage (OR 70), CSF leak (OR 48) and perioperative steroid use (OR 11.55) remained in the model as independent predictors with *p* values of less than 0.05.

CSF Features in Patients with Meningitis. The characteristics of the CSF in patients with postoperative meningitis are shown in Table 2.4.3.

Microbiology of meningitis: Meningitis was documented by positive CSF culture in 16/16 (100%) patients whose fluid was cultured. Gram-negative organisms predominated. *Acinetobacter* spp. were the main isolates (45%). The other pathogens included: *Klebsiella* spp. (4), *Pseudomonas aeruginosa* (2), *Enterobacter cloacae* (1), *Proteus mirabilis* (1), CoNS (1), *Staphylococcus aureus* (1) and *Candida albicans* (1). *Acinetobacter* spp. were fully resistant to β-lactams, aztreonam, aminoglycosides and quinolones. 33% were resistant to imipenem and 17% to meropenem. The isolates were fully sensitive to colistin. *Klebsiella* spp. were 100% resistant to β-lactams, cephalosporins, aztreonam and quinolones. The resistance to aminoglycosides was 80% (both to gentamicin and amikacin). The resistance to colistin was 20%, to imipenem 60% and 40% to meropenem. *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 2.4.4).

Infections other than meningitis: VAP was the most common infection in this population (22.5%). 9% developed an SSI other than meningitis, 9% developed UTI and 15% developed pneumonia. Among SSIs, wound infections predominated (75%). Post-surgical subdural and epidural abscesses represented 11% of the SSIs. Ventriculostomy site, Palacos and bone infections and subdural empyema were rare, representing a total 12% of the SSIs.

When the meningitis pathogens were compared to the CAB/BSI isolates, in three cases the same isolate grew from the CSF and the blood (namely *E. cloacae*, *A. baumannii* and *K. pneumoniae*).

Microbiology of other infections: In VAP, *Acinetobacter* spp. were the main pathogens isolated in 44% of the cases. *Pseudomonas aeruginosa* was the second most prevalent isolate (25%). The *Acinetobacter* spp. were 100% resistant to cephalosporins, ticarcillin/clavulanate, aztreonam, and ciprofloxacin. They retained full susceptibility to colistin. The resistance to imipenem approached 67% whereas the resistance to meropenem was 18%. *Pseudomonas aeruginosa* isolates were fully susceptible to colistin but the resistance to piperacillin/tazobactam, cefepime and aztreonam was 37%. They maintained a very good susceptibility to carbapenems (79% to imipenem, 74% to meropenem). In UTI, *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 (Table 2.4.5). The *Acinetobacter* spp. isolates were only sensitive to colistin.

In SSIs, *Acinetobacter* spp. predominated with *Klebsiella* spp. being the second in prevalence. Gram-positive pathogens were in the third place. In CAB/BSI, CoNS were the most prevalent pathogens. Gram-positive generally predominated. Among the gram-negative organisms, *Acinetobacter baumanii* were the most common. The isolates were 100% sensitive to colistin but only 29% to imipenem and 14% to meropenem.

***Survival Analysis*:** After cumulative follow up of 18795 days (median 27, range 1-318), 50 patients died (15%). Among them, 5/16 patients who had meningitis died (29%), 1/23 (4%) of the patients who had an SSI other than meningitis, 24/98 (24%) of the patients who had other nosocomial infections and 20/194 (10%) without infection. Estimated survival rates at day 30 were 0.94 (95% CI 0.65 to 0.99) for meningitis, 1.0 for other SSI, 0.84 (95% CI 0.74 to 0.90) for other nosocomial infections and 0.90 (95% CI 0.84 to 0.94) for those without infections. The

corresponding age-sex adjusted HRs compared to those without infection were 0.80 (0.22 to 0.84) for meningitis, 0.38 (0.05 to 2.89) for other SSI, and 1.43 (0.77 to 2.63) for other nosocomial infections. All between-group comparisons were also insignificant. Only age predicted an adverse outcome 1.03 (1.02 to 1.05) per year increase. In conclusion there was no difference in mortality between the study groups (Figure 2.4.1)

2.4.4 Discussion

Incidence and Microbiology: The incidence of meningitis in this study was 4.8%, higher than those noted in some series [2, 20, 22, 199, 204] but not in all. Reichert et al. [1] in their prospective study reported a rate of 8.9%. Gram-negative organisms predominated as meningitis pathogens in this prospective cohort. In studies published after 1993, Enterobacteriacae and other gram-negative rods played a major role [1, 205- 210]. Our results seem to reflect this trend.

Clinical Manifestations: The mean duration from operation to the onset of symptoms was 6.5 days, an interval similar to that reported in other studies [1, 19].

Risk Factors: The independent risk factors identified by the multivariate analysis were use of perioperative steroids, CSF leak and the use of ventricular drains.

Craniotomies with an external ventricular drainage carry a higher risk for meningitis [7, 27, 50, 224, 225]. 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. [7]. There is little agreement among various series regarding the relation between duration of drainage and infection incidence; in one report, no relation was observed [225].

Previous studies demonstrated postoperative CSF leak to be a significant risk factor for the development of meningitis [16, 20, 51, 204]. 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.

Meningitis or positive CSF culture has been described as the most frequent complication of ICP monitoring [25, 230]. During the study period, ICP monitoring devices were placed either in the parenchyma (Camino; NeuroCare, San Diego, CA) or in the ventricles and were attached to an external transducer. The presence of an ICP monitoring device did not affect the development of meningitis.

In contrast to previous reports, duration of surgery did not remain an independent risk factor in the multivariate analysis [50, 232]. Age, sex and diabetes were not significant risk factors for the development of meningitis, a finding consistent with previous data [204]. Repeat surgery, which has been a major risk factor in recent [1] and older reports [50, 232], was not a risk factor in our cohort.

The use of perioperative steroids achieved a statistical significance in this prospective cohort. This has not been described before in studies regarding the PCM and wound infections post-craniotomy in general and it was not a finding in our retrospective cohorts [1, 19, 20, 22, 23, 57, 199, 204]. This has not been described either in studies regarding postoperative wound infections in general neurosurgical populations [14, 16, 40, 232]. Prolonged intubation after the surgical procedure was not independently associated with the development of PCM.

In this cohort, the meningitis cases were culture-proven in 100%. According to the most recent trend, gram-negative organisms predominated. *Acinetobacter* spp. were isolated in 45%, with *Klebsiella* spp. and *P. aeruginosa* following. The increase in the rate of Acinetobacter PCM has extensively been described in the years following 2000, although in the previous years it was reported as a rare occurrence [1, 14, 57, 132, 134, 139, 141, 143, 144, 199, 204, 210, 242]. 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 [57, 58, 132, 133, 134, 139, 140-145, 205, 242, 243]. *Klebsiellae* spp. were the second most commonly isolated pathogens in this cohort with the isolates carrying a high degree of resistance even to carbapenems (Table 2.4.4). This is in accordance with older and most recent reports. In some of the older reports, Klebsiella spp. were the most common gram-negative isolates in PCM [131, 132, 133, 134, 136, 137, 138, 205, 210, 245]. In our cohort the PCM *Klebsiella* isolates were completely resistant to third generation cephalosporins, retaining a 80% sensitivity to colistin , 40% to imipenem and 60% to meropenem. 20% of the isolates were sensitive to amikacin and gentamicin. 100% of the isolates were sensitive to tetracycline, but during the study period the sensitivity to tigecycline was not routinely recorded.

Acinetobacter spp. were the predominant pathogens in VAP in this cohort (44%), in accordance with the literature in critically ill patients [246-249]. These pathogens are of extreme importance since is some series the death rates in such infections may reach 78% [248]. The VAP isolates were 100% to colistin as the PCM isolates, and

they had a better sensitivity profile to carbapenems (33% sensitive to imipenem and 82% to meropenem) and aminoglycoside (21% sensitive to amikacin and 39% sensitive to gentamicin).

In conclusion in this prospective study we were able to confirm the importance of perioperative ventricular drains and CSF leak in the development of PCM. We demonstrated the significance of perioperative steroids in the development of meningitis. The duration of surgery was not a significant risk factor for PCM as we demonstrated in the retrospective cohorts. The first prospective surveillance of infections in patients undergoing craniotomy in Greece was very 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 choice of empirical antibiotics in this population.

Table 2.4.1. Univariate analysis for the risk factors for the development of PCM

Variables	Meningitis	No meningitis	P
N	17	317	
Female sex	10 (59%)	105 (33%)	0.04
Median age (IQR)	48 (22, 58)	51 (27, 67)	0.14
Median LOS (IQR), days	191 (120, 259)	24.5 (12, 70)	<0.001
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 procedure	8 (48%)	158 (50%)	1.0
Median duration (IQR), hours	4 (3, 6)	2 (2, 4)	0.003
CSF leak	6 (35%)	21 (7%)	0.001
Multiple procedures	0 (0%)	23 (8%)	0.23
Revision surgery	2 (12%)	60 (19%)	0.75
Surgery through sinus	0 (0%)	23 (8%)	0.23
ICU admission	17 (100%)	170 (54%)	<0.001
Intubation	15 (88%)	127 (40%)	<0.001
Drains	16 (94%)	273 (86%)	0.49
Ventricular Drain	11 (65%)	16 (5%)	<0.001
ICP placement	5 (29%)	88 (28%)	0.88

Table 2.4.2. Multivariate analysis for the development of PCM

Variables	OR (95% CI)	*P*
Sex (female vs. male)	2.7 (0.68-10.79)	0.16
Steroids	11.55 (2.08-64.13)	0.005
Duration of surgery	1.03 (0.68- 1.55)	0.89
CSF leak	48.03 (6.75-341.8)	<0.001
Intubation	9.35 (0.78-111.7)	0.08
Ventricular Drain	70.52 (10.83- 459.1)	<0.001

Table 2.4.3. CSF Characteristics in Prospective Meningitis Cohort

	Median	IQR 25, 75
Protein	120	91, 634
Glucose	47	40, 59
Glucose CSF/Serum Ratio	0.40	0.40, 0.47
White Blood Count	300	220, 560

Table 2.4.4. Pathogens isolated from meningitis cases and their resistances (% Resistant Isolates, R/T Resistant/Total, S/T Sensitive/Total)

	Klebsiella spp		***Pseudomonas aeruginosa***		***Acinetobacter spp***		***Enterobacter cloacae***		***S. aureus***		***Coagulase negative staph***	
	R/T	**%**	**R/T**	**%**	**R/T**	**%**	**R/T**	**S/T**	**R/T**	**S/T**	**R/T**	**S/T**
Amoxicillin/Clavunate					6/6	100	1/1		1/1		1/1	
Cephalothin	5/5	100			6/6	100	1/1		1/1		1/1	
Cefuroxime	5/5	100			6/6	100		1/1	1/1		1/1	
Tetracycline	0/5	0			6/6	100		1/1	1/1		1/1	
Colistin	1/5	20	0/3	0	0/6	0		1/1				
Rifampicin										1/1		1/1
Ticarcillin/Clavunate	5/5	100	0/3	0	6/6	100		1/1				
Ceftriaxone	5/5	100	3/3	100	6/6	100		1/1				
Cefepime	5/5	100	0/3	0	6/6	100		1/1				
Imipenem	3/5	60	3/3	100	2/6	33		1/1	1/1		1/1	
Meropenem	2/5	40	3/3	100	1/6	17		1/1				

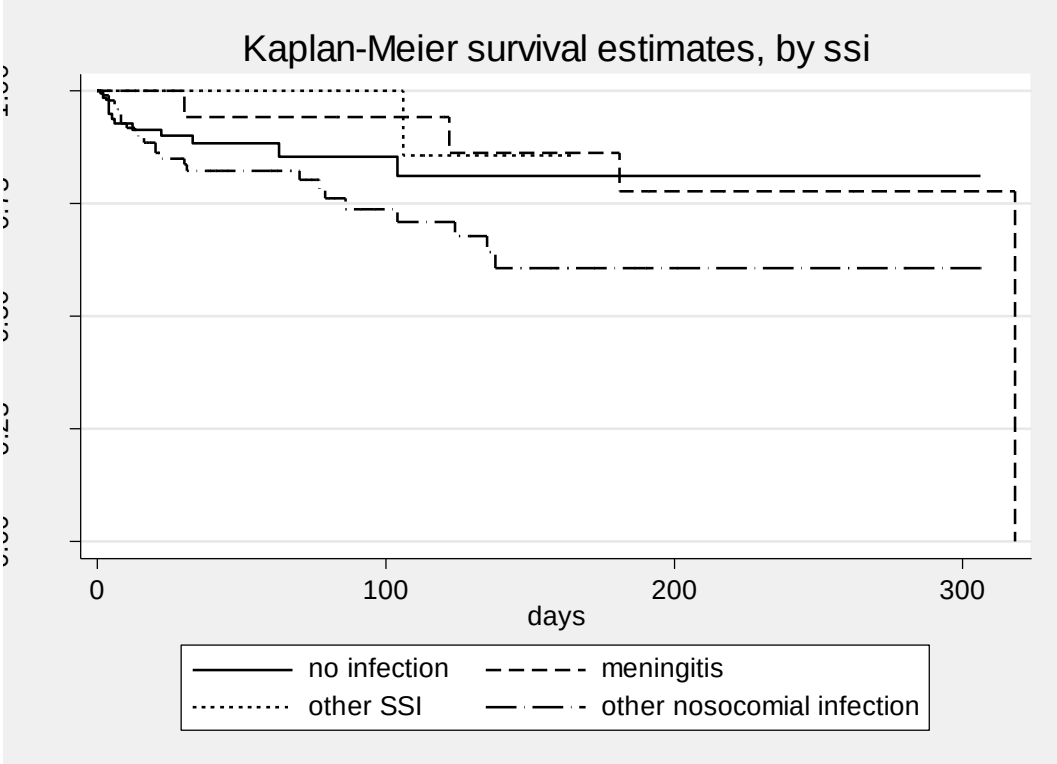
Aztreonam	5/5	100	0/3	0	6/6	100	1/1		
Amikacin	4/5	80	0/3	0	6/6	100	1/1		
Gentamicin	4/5	80	0/3	0	6/6	100	1/1	1/1	1/1
TMP/SMX	5/5	100	3/3	100	6/6	100	1/1	1/1	1/1
Ciprofloxacin	5/5	100	0/3	0	6/6	100	1/1	1/1	1/1
Moxifloxacin	5/5	100			6/6	100		1/1	1/1
Levofloxacin									
Piperacillin/Tazobactam	5/5	100	0/3	0	6/6	100	1/1		
Ampicillin									
Vancomycin								1/1	1/1
Erythromycin								1/1	1/1
Clindamycin								1/1	1/1
Penicillin G								1/1	1/1
Oxacillin								1/1	1/1
Linezolid								1/1	1/1

Table 2.4.5. Pathogens isolated from VAP and their resistances (% Resistant isolates)

	Pseudomonas		*Proteus mirabilis*		*Stenotrophomonas maltophilia*		*Haemophilus influenzae*		*Serratia marcescens*		*Klebsiella spp*		*Acinetobacter spp*		*S. aureus*	
	R/T	%	R/T	%	R/T	%	R/T	%	R/T	%	R/T	%	R/T	%	R/T	%
Amoxicillin/Clavunate			2/2	100	2/3	67	0/7	0	4/4	100	6/9	67	33/33	100	3/16	19
Cephalothin			2/2	100	2/3	67			4/4	100	6/9	67	33/33	100	3/16	19
Cefuroxime			2/2	100	2/3	67			2/4	50	6/9	67	33/33	100	3/16	19
Tetracycline			2/2	100	0/3	0	2/7	28	2/4	50	2/9	22	25/33	76	5/16	31.25
Colistin	0/19	0			0/3	0	0/7	0	4/4	100	3/9	33	0/33	0		
Rifampicin							0/7	0							1/16	6.25
Ticarcillin/Clavunate	8/19	42	0/2	0	2/3	67			0/4	0	6/9	67	33/33	100		
Ceftriaxone			0/2	0	2/3	67			0/4	0	6/9	67	33/33	100		
Cefepime	7/19	37	0/2	0	2/3	67			0/4	0	6/9	67	33/33	100		
Imipenem	4/19	21	0/2	0	3/3	100			0/4	0	3/9	33	22/33	67	3/16	19
Meropenem	5/19	26	0/2	0	3/3	100			0/4	0	3/9	33	6/33	18		
Aztreonam	7/19	37	0/2	0	3/3	100			0/4	0	6/9	67	33/33	100		

Amikacin	3/19	16	0/2	0	0/3	0	2/7	28	0/4	0	3/9	33	26/33	79		
Gentamicin	1/19	5	0/2	0	1/3	33	0/7	0	0/4	0	3/9	33	20/33	61	2/16	12.5
TMP/SMX	19/19	100	1/2	50	0/3	0	1/7	14			6/9	67	27/33	82	2/16	12.5
Ciprofloxacin	4/19	21	1/2	50	1/3	33	0/7	0	0/4	0	7/9	78	33/33	100	2/16	12.5
Moxifloxacin			2/2	100	1/3	33			0/4	0	6/9	67	26/33	79	2/16	12.5
Levofloxacin															2/16	12.5
Piperacillin/Tazobactam	7/19	37	0/2	0	2/3	67			0/4	0	6/9	67	28/33	85		
Ampicillin							0/7	0								
Chloramphenicol							0/7	0								
Erythromycin							0/7	0							4/16	25
Clindamycin															4/16	25
Penicillin G							4/7	57							11/16	69
Oxacillin															3/16	19
Linezolid/ Vancomycin															0/16	0

Figure 2.4.1 Kaplan-Meier survival estimates



2.5 Retrospective study regarding the infections in traumatic brain injury (TBI) patients in the University of Crete (UOC) Medical Center- Risk Factors associated with the development of SSIs and meningitis in TBI population

2.5.1 Abstract

Objective: Admission and surgery for TBI was the most common in UOC Medical Center- Department of Neurosurgery. The purpose of this study was to delineate the frequency, types and risk factors for infection in TBI patients

Methods: Retrospective surveillance for all TBI patients, aged ≥18 years, cared at the Department of Neurosurgery of the University Hospital of Heraklion, Greece between 1999 and 2005.

Results: 760 patients (75% men- median age 41) were included. Two hundred fourteen infections were observed. The majority were infections of the lower respiratory tract (47%), mainly ventilator associated pneumonia (VAP) (33%), followed by surgical site infections (SSI) (17%). Multivariate analysis has shown that SSI development was independently associated with performance of ≥2 surgical procedures, presence of concomitant infections, namely VAP and urinary tract infections, insertion of lumbar and ventricular drains and cerebrospinal fluid (CSF) leak. Meningitis was associated with prolonged hospitalization, and insertion of lumbar and ventricular drains. There was a predominance of *Acinetobacter* spp as a VAP pathogen, gram positive organisms remained the most prevalent in SSI.

Conclusions: Respiratory tract infections were the most common among TBI patients. Device-related communication of the CSF with the environment and prolonged hospitalization were independent risk factors for SSIs and meningitis. The prevalence of the pathogens must be determined upon institutional basis for the establishment of proper treatment of these serious infections

2.5.2 Patients and Methods

Patients admitted for TBI to the Department of Neurosurgery of University Hospital of Heraklion, Greece during the years 1999-2005 were evaluated. They were considered eligible if they were at least 18 years of age. Medical records were surveyed retrospectively for the development of surgical site infections (SSIs) - including meningitis- and infections outside the surgical field. Data were collected to a standard form. The presence of any co-morbid conditions, the type of procedure performed (craniotomy, craniectomy, cranioplasty, burr-hole or other), implantation and type of foreign bodies (acrylic implants, dural substitutes), procedure urgency, duration of surgery, concomitant procedures, intensive care unit (ICU) stay and the presence of any drain were recorded. Re-operations and reports of CSF leak were noted. Infections were determined according to the definitions of the CDC/NHSN (Centers for Disease Control/ National Healthcare Safety Network) [250]. The organisms isolated from each site were also recorded.

Data were analyzed using SPSS software (Version 16.0; SPSS Inc., Chicago, IL). Continuous variables were compared using Student's *t* test or the Mann-Whitney *U* test, whereas categorical variables were compared using Fisher's exact test. In univariate analysis, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel statistic. Stepwise multivariate logistic regression was then used to model the interactions of those variables significantly associated with SSIs or meningitis in univariate analyses. A backward elimination model was used with Penter =0.20 and Pleave =0.05 to identify independent predictors for SSI and meningitis. Power calculations were performed using the PASS software (PASS 2008, https://www.ncss.com).

2.5.3 Results

***Study Population*:** Seven hundred and sixty patients (75.4% men) were studied. Causes of TBIs included motor vehicle accidents (58.9%), fall (36.5%) and assault (2.8%). Gunshot injuries were not encountered during the study period. The median age was 41 (range 18- 96) years. Two hundred fifty eight patients (33.3% of TBI admissions) underwent a total of 342 surgical procedures. Fifty three patients (20.5% of those who underwent surgery) had at least two procedures performed (range 2- 8). The median age for patients undergoing 1 procedure was 66 years (range 18- 93) and for the ones undergoing ≥2 procedures was 30 (range 18- 89). Younger patients had a

greater chance to undergo ≥2 procedures ($p<0.001$). The most common procedure performed was burr-hole (29.2%) with craniotomy a close second (28.9%). The median length of hospitalization was 7 days (range 0-249) and the median length of stay before the procedures were performed was 1 day (range 0- 136). Fifty three of the TBI admissions (6.3%) were complicated with at least one SSI, superficial or deep seated. The most common SSI was the wound infection (2.2%), followed by meningitis/ventriculitis (2.0 %). However shunt infections (0.8%), bone flap/osteomyelitis or Palacos infections (0.4%), abscesses (0.1%), and epidural empyemas (0.2%) were extremely rare. There was a total of 6 SSIs (1.2%) in patients who did not undergo neurosurgery. These included two trauma wound infections, two intracranial pressure (ICP) insertion site infections (0.4% of the non-operated patients each), one meningitis and one ventriculostomy site infection (0.2% each). The total fatality rate in the present cohort was 8.3%, (5% for the patients that did not undergo neurosurgery and 12.8% for patients who did). The difference was statistically significant (OR 2.8, CI 1.65- 4.8). Among the total number of infections encountered, ventilator associated pneumonia (VAP) was the most common (33.2%) with surgical site infections (SSIs) (17%), urine tract infections (UTIs) (15.4%), pneumonia (14.0%), catheter associated bacteremias/blood stream infections (CAB/BSI) (10.7%) and meningitis following (7.9%).

The median duration of surgery was 2 hours (range 0.5- 4.5). In 23% of the patients there was insertion of some kind of drain and in 14.8% they had intraparenchymal Camino® ICP (Camino Laboratories, San Diego, CA) or Codman MicroSensor® (Johnson and Johnson Medical Ltd, Raynham, MA) catheter inserted.

Infection Risk, Incidence and Microbiology: Several variables were examined for their contribution to the risk of SSI development, both superficial and deep- seated including meningitis. These included: performance of a surgical procedure other than the simple drain or ICP placement, ≥2 procedures performed, presence of concomitant infection(s), surgical procedure(s) through a sinus, CSF leak, history of malignancy, use of a dural substitute, revision surgeries, intubation beyond the surgical time, brain protection protocol, presence of any drain, in particular ventricular and lumbar drains, presence of an ICP catheter and presence duration , hospitalization in the ICU, especially if prolonged and marginally the low GCS score on admission. Results are shown in 2.5.1. Variables for the development of meningitis included a low admission GCS, performance of a procedure other than the lone drain or ICP placement, ≥2

procedures performed, revision surgery, presence of concomitant infections, surgery through a sinus, history of malignancy, use of dural substitutes, presence and duration of ICP monitoring catheter, development of another SSI, presence of ventricular and lumbar drains, CSF leak, hospitalization in the ICU especially if prolonged, and prolonged intubation beyond the surgery, performance of tracheostomy and in general a longer length of stay. TBI patients who underwent neurosurgery had an OR 25.0 (95% CI 3.3- 189.6) for developing meningitis compared to patients who did not. The median time between the surgery and the meningitis diagnosis was 7 days (range 2-41) (Table 2.5.2).

Among the 194 cases with a drain, 13.4% developed an SSI and 6.7% developed meningitis. There was an association between the duration of the drainage of any kind and development of SSI and meningitis (Figures 2.5.1 and 2.5.2, respectively). Insertion of a ventricular drain was associated with a 9.3-fold (95% CI, 3.6- 24.0) increase in the rate of SSI and a 12.6-fold (95% CI, 3.8- 41.9) increase in the rate of meningitis. Insertion of a lumbar drain was associated with a 45- fold (95% CI, 10.8-186.7) increase in the rate of SSI and an 87-fold (95% CI, 20.7- 363.2) increase in the rate of meningitis. The presence of a ventricular drain for >7 days carried an increased risk for the development of meningitis (OR 47.1, $p<0.001$).

Low admission Glasgow Coma Scale (GCS) score significantly correlated with a longer length of stay ($p<0.001$), an adverse final outcome ($p<0.001$), low Glasgow Outcome Scale (GOS) score ($p<0.001$) and a greater propensity for development of infections namely VAP ($p<0.001$), pneumonia ($p<0.001$), CAB/BSI ($p<0.001$), UTI ($p<0.001$) and meningitis ($p=0.015$) and marginally with the development of SSIs ($p=0.052$). The TBI patients who underwent neurosurgery had a significantly lower admission GCS, they were more prone to be intubated, to be admitted to the Intensive Care Unit, and bear ICP catheters and drains. They were also more prone to develop meningitis, SSI, other concomitant infections and had increased mortality (Table 2.5.3).

Table 2.5.1 Univariate analysis for the factors associated with the development of SSIs in TBI patients

Factor	No at Risk	Rate in at Risk Group (%)	Odds Ratio (95% CI)	*P* value
SSI in Total Study Population	848	6.9		
Age greater than median (41)	415	4.1	0.71 (0.38- 1.35)	0.34
Female sex	211	5.2	1.09 (0.53- 2.19)	0.85
Surgical procedure	342	10.5	9.9 (4.12- 23.77)	<0.001
≥ 2 surgical procedures	53	30.2	21.73 (6.87-68.65)	<0.001
Concomitant infections	123	18.7	8.6 (4.52- 16.36)	<0.001
VAP	71	19.7	6.61 (3.3- 13.26)	<0.001
Pneumonia	30	16.7	4.25 (1.54- 11.7)	0.013
CAB/BSI	23	14.3	7.78 (2.89- 20.92)	0.001
UTI	33	28.6	15.05 (6.78- 33.40)	<0.001
Surgery through a sinus	31	35.5	6.29 (2.71- 14.59)	<0.001
Emergency procedure	298	11.4	2.71 (0.63- 11.68)	0.29
Duration of surgery				0.507
CSF leak	37	27	9.07 (4.05- 20.34)	<0.001
Co-morbid conditions				
Malignancy	14	42.9	16.73 (5.51- 50.76)	<0.001
ASCVD	57	0		0.105
Diabetes	48	0		0.163
CRD	6	0		1.0
Admission GCS				0.052
Intubation	165	11.5		<0.001
Tracheostomy	85	11.8	3.76 (1.99- 7.09)	0.006
Dural substitute	39	28.2	3.07 (1.45- 6.48)	0.001
Revision surgery	36	30.6	4.37 (1.95- 9.81)	<0.001
Intracranial Pressure Monitoring (ICP)	126	12.7	4.95 (2.18- 11.21)	<0.001
ICP Days			3.92 (2.04- 7.55)	0.025
Skull Fracture	290	4.5		0.74
Any drain	194	13.4	0.86 (0.44-1.69)	<0.001
Ventricular Drain	24	29.2	6.22 (3.26- 11.86)	<0.001
Lumbar drain	9	66.7	9.34 (3.64- 23.99)	<0.001
Drain days			44.89 (10.8-186.7)	<0.001
Ventricular Drain Days				0.972
Lumbar Drain Days				0.272
ICU admission	246	9.8		<0.001
ICU Days			3.54 (1.88- 6.64)	0.002
Brain Protection Protocol	37	21.6	6.34 (2.7-14.91)	<0.001
Length of Stay				<0.001
Adverse final outcome	41	12.3	2.9 (1.28- 6.57)	0.016

Table 2.5.2. Univariate analysis for the factors associated with the development of meningitis

Factor	No at Risk	Rate in at Risk Group (%)	Odds ratio (95% CI)	*P* value
Meningitis in Total Study Population	848	2		
Age greater than median (41)	415	1.4	0.55 (0.20- 1.51)	0.328
Female Sex	211	2.4	1.27 (0.44- 3.66)	0.58
Surgical procedure	342	4.7	25.03 (3.3- 189.6)	<0.001
≥ 2 procedures	53	10.2	11.55 (2.58- 51.7)	<0.001
Concomitant infections	123	9.76	15.67 (5.42- 45.35)	<0.001
VAP	71	12.7	14 (5.23- 37.68)	<0.001
Pneumonia	30	3.33	1.74 (0.22- 13.58)	0.46
CAB/BSI	23	23.5	13.23 (3.95- 44.34)	0.001
UTI	33	35.3	16.34 (5.63- 47.46)	<0.001
Other SSI	29	13.8	9.98 (3.04- 32.78)	0.002
Surgery through a sinus	31	19.4	7.22 (2.43- 21.51)	0.001
Emergency Procedure	298	5.4	1.05 (1.03- 1.09)	0.24
CSF leak	37	10.8	7.49 (2.32- 24.2)	0.005
Co- morbid conditions				
Malignancy	14	21.4	16.07 (4.04- 63.98)	0.002
ASCVD	57	0		0.62
Diabetes	48	0		0.62
CRD	6	0		1.0
Admission GCS				0.015
Intubation	165	6.7	8.12 (2.96- 22.29)	<0.001
Tracheostomy	85	5.9	3.9 (1.35- 11.46)	0.02
Revision surgery	36	11.1	3.06 (0.93- 10.06)	0.07
Intracranial Pressure Monitoring (ICP)	126	7.1	6.9 (2.6- 18.28)	<0.001
ICP Days				0.022
Skull Fracture	290	3.1	2.22 (0.85- 5.82)	0.12
Dural substitute	39	12.8	3.9 (1.28- 11.9)	0.02
Any Drain	194	6.7	11.76 (3.79- 36.5)	<0.001
Ventricular Drain	24	16.7	12.55 (3.76- 41.9)	0.001
Lumbar Drain	9	55.6	86.67 (20.7- 363.2)	<0.001
Drain Days				<0.001
Ventricular Drain Days				0.907
Lumbar Drain Days				0.751
ICU Admission	246	5.7	12.15 (3.46- 42.66)	<0.001
ICU Days				0.002
Brain Protection Protocol	37	8.1	5.05 (1.39- 18.42)	0.034
Length of Stay				<0.001
Adverse final outcome	17	4.6	2.42 (0.68- 8.66)	0.16

Figure 2.5.1. Association between drain (any type), days and risk for SSI in TBI patients

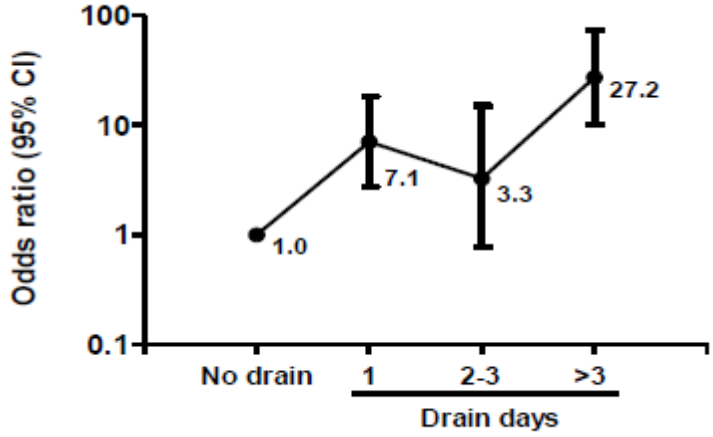


Figure 2.5.2. Association between drains and risk for meningitis in TBI patients

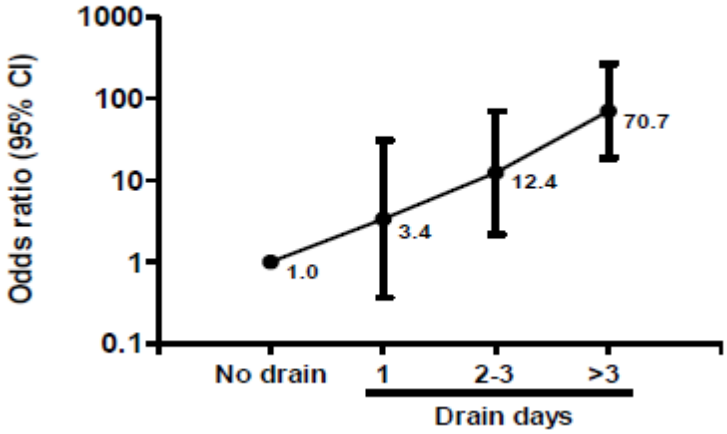


Table 2.5.3. Comparison of TBI patients that did and did not undergo neurosurgery

Feature	Surgery (Rate at Risk Group or mean ± SD)	Non-surgery (Rate at Risk Group or mean ± SD)	Odds Ratio (95% CI)	*P* value
Meningitis development	4.7	0.2	25 (3.3-189.6)	<0.001
Surgical site infections development	10.5	1.18	9.9 (4.12- 23.77)	<0.001
Concomitant infections	22.2	9.2	2.82 (1.9- 4.2)	<0.001
VAP	12.9	5.3	2.65 (1.6- 4.36)	<0.001
Pneumonia	5.6	2.2	2.67 (1.25- 5.69)	0.012
CAB/BSI	5	1.2	4.4 (1.72- 11.28)	0.001
UTI	6.7	2.0	3.61 (1.7- 7.69)	0.001
Admission GCS	11.3 ± 3.9	12.9 ± 2.9		<0.001
Intubation	29.8	12.3	3.02 (2.12- 4.29)	<0.001
Tracheostomy	15.2	6.5	2.60 (1.64- 4.11)	<0.001
Intracranial Pressure Monitoring	24.9	8	3.79 (2.53- 5.67)	<0.001
(ICP)	6.0 ± 3.9	5.9 ± 3.3		0.97
ICP Days	6.4	4	17.5 (4.09-	<0.001
Ventricular Drain	2.3	2	74.91)	0.004
Lumbar drain	3.5 ± 4.8	4.0 ± 2.8	12.22 (1.52-	0.883
Drain days	44.4	18.4	98.1)	<0.001
ICU admission	11.6 ± 13.4	8.1 ± 7.6		0.055
ICU Days	7	2.5	3.55 (2.60- 4.83)	0.003
Brain Protection Protocol	31.2 ± 44.4	8.7 ± 11.5		<0.001
Length of Stay (days)	12.8	5	2.89 (1.45- 5.76)	<0.001
Adverse final outcome			2.8 (1.65- 4.8)	

Multivariate analysis showed that independent risk factors for SSI included the performance of ≥2 surgical procedures (OR 16.7, p<0.001), the insertion of lumbar (OR 34.5, p=0.002) and marginally of ventricular drains (OR 4.0, p=0.05), the presence of concomitant infections, namely UTI (OR 8.8, p=0.001) and VAP (OR 5.7, p=0.004) and marginally the CSF leak (OR 3.8, p=0.05). Independent risk factors for meningitis included the prolonged length of stay (p<0.001), the ICU stay when prolonged for >7 days (OR 25.5, p=0.009) and only marginally for ≤7 days (OR 10.5, p=0.054) and the insertion of lumbar (OR 296.9, p<0.001) and ventricular drains (OR 9.1, p=0.017) (Table 2.5.4). Regarding the isolated pathogens, *Acinetobacter* spp were the predominant pathogens in respiratory tract infections with *S. aureus* being second. In SSI and meningitis/ventriculitis gram positive pathogens predominated. The pathogens isolated from the various infections are demonstrated in Table 2.5.5.

2.5.4 Discussion

The most common sites of infection in our center were similar to those previously reported in TBI patients [251, 252] and in trauma patients in general [247, 253]. We noticed a predominance of *Acinetobacter* spp. in respiratory tract infections which seem to be the emerging pathogens in discordance with earlier reports [246- 248, 251-256]. Coagulase-negative staphylococci (*CoNS*) and *S. aureus* remain the most frequently isolated pathogens in wound infections [251, 253]. The SSI incidence is similar to that of previous reports in TBI individuals [251], but it is significantly higher than in the general neurosurgical population [16].

VAP was the most common infection in the present cohort (8.4%), in accordance with previous studies [246, 249, 251, 252, 257, 258]. In the severely head-injured patient requiring long-term mechanical ventilation, the incidence of pneumonia has been reported to be 35-70% with up to 50% mortality. Head injured patients having ICP monitoring or receiving barbiturates or steroid therapy are at additional risk [259, 260]. GOS score was affected by VAP, but not mortality, an observation also reported before [261]. The main pathogens included *Acinetobacter* spp. (38.0%), *S. aureus* (22.5%), *P. aeruginosa* (16.9%) and *Haemophilus influenzae* (12.7%). Among them *Acinetobacter* is an emergent pathogen in TBI population. Of note, patients who underwent neurosurgical procedures had an increased risk for developing VAP (OR 2.65). Early enteral feeding seems to be a protective factor for early-onset VAP in TBI patients, whereas barbiturate use is an important risk factor for the infection [262]. Interestingly, pneumonia not associated with mechanical ventilation led to adverse final outcome, a finding previously unreported, in contrast with the increased mortality with VAP [260].

The percentage of CAB/BSI was 2.7%, lower than the 8% reported in the literature [251]. Urine tract infections (UTIs) were encountered in a percentage of 3.9%, in the range reported in the literature [251]. Superficial wound infections were the most common SSIs in our population (2.24%) [251]. The percentages of osteomyelitis, abscesses or empyemas are comparable or even lower to those reported before [245, 251]. The percentage of meningitis/ventriculitis- which has always been considered a serious complication of TBI [62, 263, 264] - reached 2%. Baltas et al reported a 1.4% meningitis rate in TBI population, but in their cohort only 20% of the patients underwent a surgical procedure; therefore their results are not comparable to

the present ones [265]. In several studies the incidence of acute bacterial meningitis after head trauma ranges from 0.2-17.8% [101, 266].

Gram-positive pathogens represented 66.6% of the positive CSF cultures in our patients. These results reflect their reemergence as nosocomial pathogens [19, 20, 51] in the time period that this retrospective study was performed although classically it is estimated that 60- 70% of the episodes of post-neurosurgical bacterial meningitis are caused by Gram negative bacilli [1, 58, 205, 267]. If meningitis occurs within 3 days in a patient after a closed head injury or nondepressed skull fracture, *S. pneumoniae* is almost always the causative pathogen [101].

The development of SSI marginally carried an independent association with CSF leak, in agreement with the results of previous studies [16, 51]. However, CSF leak was not associated with the development of meningitis in our cohort [20, 62]. Classically, CSF leak after head trauma has been associated with meningitis development. In one study that examined the incidence of bacterial meningitis in 1587 head injury patients, the incidence was only 0.38%, but it increased to 18% and 9% when the injury was complicated by otorrhea and rhinorrhea respectively [268]. Others have noted the development of bacterial meningitis after a CSF leak with an incidence ranging from 3-50% [101].

The insertion of any drain was associated with the development of both SSI and meningitis in particular in the univariate analysis. The duration of the drainage seemed to increase the risk for SSIs including meningitis, especially if the drainage exceeded 3 days. Although no definite conclusions can be drawn from this observation, it would be prudent to suggest the earlier removal of the drains when they are not needed.

The presence of lumbar and ventricular drains was independent risk factor for the development of both SSI in general and meningitis in particular. Deep seated infections have not been extensively associated with the use of lumbar drains [231, 239]; their association with SSI other than meningitis has not been previously reported. Ventricular drain placement has repeatedly been associated with the development of meningitis in prospective and retrospective studies [1, 7, 9, 19, 36, 224, 232, 269, 270]. TBI has been associated with increased risk for ventriculostomy-related infections (VRI) in some [29] but not all studies [29, 268, 270].

ICP placement did not remain an independent risk factor for SSIs in multivariate analysis. ICP monitoring duration had no effect on the SSI or meningitis

development. Concomitant infections (namely VAP and UTI) remained an independent risk factor for the development of SSI. Infections outside the surgical field have repeatedly been associated as risk factors for SSI development in the general neurosurgical population but there is a paucity of data regarding TBI patients [1, 16, 19, 232]. The performance of ≥2 surgeries has been reported as independent risk factor for SSI and especially meningitis in the past [1, 20]. In this cohort it remained an independent risk factor only for SSI in general. ICU hospitalization was strongly associated with the development of meningitis. The OR was 13.4 (p=0.03) but when the ICU days were taken into concern in the logistic regression model, then ICU hospitalization for ≤ 7 days approached statistical significance (OR 10.5) but admission for > 7 days was clearly independently associated with meningitis development (OR 25.5). ICU hospitalization has recently been associated with SSI development in the University of Crete Medical Center [244] but this is the first time that such an association is being described in a TBI patients' cohort. The total length of stay (LOS) was independently associated with meningitis risk with a 2% increased risk for every day of hospitalization.

The importance of the level of consciousness upon admission as measured by the GCS score to predict morbidity and mortality has been described before, mainly but not exclusively, in gunshot and landmine injuries [271- 275]. Indeed the present study has shown that admission GCS is significantly associated with the LOS, the final outcome, the GOS score, and the development of infections outside the surgical operational field. These associations underline the significance of the initial clinical evaluation.

The use of prophylactic antimicrobial therapy in patients with basilar skull fracture and CSF leak is controversial. In some studies, the use of prophylactic antibiotics seems to even increase the incidence of meningitis [276]. The data could be characterized presently insufficient to make a recommendation regarding prophylactic antimicrobial therapy in the cases of basilar skull fracture with CSF leak. In our cohort, there was initiation of antibiotics in patients with depressed skull fractures or in cases of a "closed" head trauma associated with basal skull fracture and CSF leaks whether they underwent neurosurgery or not. Also, all the patients that underwent neurosurgery they all received prophylactic antibiotics, therefore the impact of them on the development of SSIs or meningitis could not be evaluated. The

presence of a skull fracture was not associated with the development of SSIs or meningitis.

In this study there were no gunshot wound cases. This subpopulation of TBI patients needs special attention for a variety of reasons [277]. CSF leaks are common after such a trauma. The risk of brain abscess is three times greater than in other TBI patients, especially in the presence of retained bone fragments [101]. In the military experience, the post-gunshot wound infection rate is about 4-6% in most series [278, 279]. One study in the civilian population identified an incidence of CNS infections of 8.5% [280].

A limitation of the study is that it is retrospective and depended on the accuracy of the data in the clinical chart. However regarding its statistical power the interesting point is that considering the total number of cases and a 20% prevalence of an independent predictor, the study had a power of 80% to detect of 2.5-fold increase in risk, and 23% power to detect a 1.5-fold increase. Thus, the study was adequately powered to detect risk factors of moderate-to-high strength. Nonetheless, the final regression models with the independent risk factors were able to predict the risk for SSIs by 44% and the risk for meningitis by 51% (Nagelkerke R^2 = 0.44 and 0.51 respectively).

Table 2.5.4 Multivariate logistic regression for the factors associated with the development of SSI and meningitis

SSI (dependent)		
Independent variables	OR (95% CI) [1]	P value
Lumbar drain	34.5 (3.8-309.3)	0.002
Multiple procedures (≥2)	16.7 (5.4-51.8)	<0.001
UTI	8.8 (2.3-33.7)	0.001
VAP	5.7 (1.7-18.0)	0.004
Ventricular drain	4.0 (1.0-16.3)	0.050
CSF leak	3.8 (1.0-14.2)	0.050
Meningitis (dependent)		
Independent variables	OR (95% CI)	P value
Lumbar drain	296.9 (22.8-3864)	<0.001
ICU admission		
Admission ≤7 days (vs. no ICU)	10.5 (1.0-114.2)	0.054
Admission >7 days (vs. no ICU)	25.5 (2.3-286.7)	0.009
Ventricular drain	9.1 (1.5-55.5)	0.017
LOS	1.02 (1.01-1.03)	0.001

Table 2.5.5. Pathogenic bacteria most commonly isolated in infections in TBI patients

Infection site	**Number of Infections (%)**	**Organisms isolated (%)**
Ventilator Associated Pneumonia (VAP)	71 (8.37)	*Acinetobacter* spp (38.0) *S. aureus* (22.5) *P. aeruginosa* (16.9), *H. influenzae* (12.7)
Pneumonia	30 (3.54)	*Acinetobacter* spp (36.6) *S. aureus* (26.7) *K. pneumoniae* (20)
Urinary Tract Infections (UTI)	33 (3.9)	*P. aeruginosa* (27.2) *Candida* spp (24.2) *Enterococcus* spp (15)
Surgical Site Infections (SSI) [Other than meningitis]	36 (4.25)	Coagulase (-) *staphylococci* (CoNS) (28) *S. aureus* (25) *P. aeruginosa* (5.5)
Meningitis/ventriculitis	17 (2)	CoNS (41.1) *Acinetobacter* spp (23.5) *Enterobacter* spp., *E. faecalis* (5.9)
Catheter Associated Bacteremia/ Blood Stream Infections (CAB/BSI)	23 (2.7)	CoNS (43.4) *Enterococcus* spp (26.1) *S. aureus* (21.7) *Acinetobacter* spp. (13)

2.6 Association between operative site microbial counts and procedure classification in neurosurgery: A prospective study- Interim Report

2.6.1 Abstract

Objective: Surgical site infections (SSIs) continue to be a significant problem in neurosurgery. No association between bacterial skin counts at the operative site and SSI has been reported. In this prospective study we investigate the bacterial skin counts at the operative site, the association with procedure classification in neurosurgery and the impact on the development of SSI.

Methods: Prospective study performed in UOC Medical Center. Over a period of 18 months (February 2007- July 2008), three samples from neurosurgical patients were obtained and cultured while the patient was in the operating room. Patients having any type of procedure were included.

Results: Eighty-three procedures were analyzed. CoNS were the most frequently isolated organisms irrespectively of the time of the sampling and independently of the procedure classification. *P. acnes* was the second most frequently isolated organism. There was no statistical difference in the sampling positivity according to the sampling site or in the sampling positivity according to the procedure classification. Bacterial colony forming units (CFU) irrespectively of sampling time were not associated with procedure classification or revision surgery. CFU counts in the pre-preparation samples did not correlate with post-preparation or pre-closure samples. Pre-closure sample counts had a trend to increase with increased duration of surgery, especially if this exceeded the 3-hour duration. There was a trend to increased numbers of *P. acnes* and diphtheroids in the pre-closure samples.SSI development did not carry a significant association with the skin microbial CFU counts at any sampling and for any procedure classification

Conclusions: In this pilot prospective study which is on-going we were unable to detect an association between procedure classification in neurosurgery, CFU counts in three different sampling times and SSI development

Surgical site infection (SSI) continues to be a significant problem, particularly after neurosurgery, where infection can result in rehospitalization, multiple operative procedures, and aggressive antibiotic therapy. Most of these infections are caused by organisms that are part of normal skin flora, such as *Staphylococcus* species, *Propionibacterium acnes*, and gram-negative bacilli [114, 212]. Further, an increasing number of infections are caused by organisms that are resistant to multiple classes of antibiotics. A few studies have examined the role of the density of the patient's endogenous flora in SSI and have suggested that there may be a correlation between bacterial counts on the skin at the operative site and SSI [281].

2.6.2 Patients and Methods

Setting and sample. The study took place in academic health center in the University of Crete Medical Center in the neurosurgical service. Patients of any age who underwent any type of neurosurgical procedure and of any category (clean, clean/contaminated, clean with a foreign body, contaminated and dirty) [27] (Table 1.1.1) were included.

Procedure, Sampling and microbiologic techniques. Three skin cultures were obtained in the operating room ~1 cm from the surgical site by the operating team. No instructions for any special skin-cleaning regimen before surgery were given to the patients. Hair removal was performed by shaving after the induction of anesthesia. Scrubbing was performed three times by povidone iodine scrub 10% followed by painting by povidone iodine 10% (three times). Isolation of the surgical site was achieved by gauze compresses held by metallic clips followed by draping by sterile sheets. The skin preparation was performed by the neurosurgical resident or the attending physician. Perioperative prophylactic antibiotics were administered to all patients. Samples were obtained from head, back and abdomen, according to the procedure performed, e.g. the abdominal samples were obtained in people who underwent ventriculoperitoneal shunt (VP shunt) placements.

The first sample (the pre-preparation culture) was taken after hair removal and before the application of any antiseptic agent. The second sample (post-preparation culture) was collected after the application of antiseptic agents and immediately before the surgeon draped the area for the incision. A third sample was collected immediately before the closure (pre-closure sample). The sampling was done using sterile cotton swabs, which were placed in Amies transport medium (BioMérieux,

Marcy L'Etoile, France). The samples were identified as I, II, III according to the order of sample collection. They were transferred to the microbiology laboratory immediately after the surgery and were processed within 2h. The samples were diluted 10-fold in Schaedler broth with vitamin K3, up to 10^{-4}, and were spread plated on Columbia blood agar, colistin-nalidixic acid agar, MacConkey agar and incubated at 37^0 C for 48 hours aerobically. Additionally, Schaedler blood agar plates were inoculated and incubated at 37^0 C for 48 hours under anaerobic conditions. Bacteria were identified according to standard laboratory identification methods. For each sample, total bacterial counts were enumerated and the 3 more prevalent organisms were recorded in order of density.

Information on other variables was obtained via chart review. These included sex, age, duration of preoperative hospital stay, surgical procedure, duration of surgery, perioperative antibiotic use, length of hospital stay, use of steroids, and use of perioperative drains. Surveillance for SSI was performed by the attending physicians and the infectious disease physician by use of the CSC/NNIS definitions for SSIs. Infections were classified as superficial incisional, deep incisional (soft tissue), or organ/ space infections (intracranial, osteomyelitis, disc space, spinal abscess, meningitis, or ventriculitis). All patients were followed for at least 60 days postoperatively. Both inpatient and post-discharge surveillance methods were used.

2.6.3 Results

Ninety three sample sets obtained during 83 procedures from 70 patients were analyzed. Seventy-four percent of the patients were men. Their median age was 57 (IQR 32-67). Median duration of stay before surgery was 4 days (IQR 1-16). 63.2 % of the procedures were performed ≥2 days after the admission. The median preoperative GCS score was 15 (IQR 13- 15). Most of the procedures performed in our cohort were clean (42.1%) (Figure 2.6.1). The main reason for surgery was trauma (41%) (Figure 2.6.2). The most common procedure performed in the cohort was craniotomy (31.7%) (Figure 2.6.3). The median duration of surgery was 2.5 hours (IQR 2-4). 22.5% of the surgeries lasted >4 hours. The median doses of prophylactic antibiotics were 3 (IQR 3-9). In 20.2% of the procedures, perioperative steroids were used. 38.9% of the patients were hospitalized in the ICU. 66.3% of the patients had a perioperative drain. 25.5% of the patients had a dural substitute placed. The median LOS was 18.5 days (IQR 11- 49)

Microbiology and Associations with Procedure Classification: The positivity of pre-preparation, post-preparation and pre-closure samples was respectively 90.3, 29 and 44%. The growth of organisms according to sampling time is shown in Figure 2.6.4. There was no statistical difference in the positivity of sampling according to the sampling site (head, back or abdomen) (Table 2.6.1). There was no statistical difference in the positivity of sampling according to the procedure classification (clean, clean/contaminated, clean with a foreign body, contaminated and dirty) (Table 2.6.2).

CoNS were the most frequently isolated organisms irrespectively of the time of the sampling (61.2%, 18.3% and 29% for samples 1,2 & 3) and independently of the procedure classification (Figure 2.6.5). There was a trend for statistically significant increased counts in pre-closure sampling when skull fracture was present. *P. acnes* was the second most frequently isolated organism irrespectively of the time of the sampling and independently of the procedure classification (Figure 2.6.6). *P. acnes* was significantly more associated from head vs. other specimen sites (p=0.019). The CFU logs for CoNS and *P. acnes* cultured from each sample are shown in Table 2.6.3. CFU counts irrespectively of the sampling time were neither associated with the procedure classification (Table 2.6.4) nor with revision surgeries. *P. acnes* post-preparation CFU counts were significantly associated with skull fracture (p=0.013).

The CFU counts of the pre-preparation samples did not correlate with post-preparation or pre-closure CFU counts. The pre-closure sample counts had a trend to increase with increased surgery duration (p=0.077) and especially with surgery duration for >3 hours (p=0.09). There was a specific trend to increased numbers of *P. acnes* (p=0.056) and diphtheroids (p=0.08) in the pre-closure sample counts, especially for the diphtheroids for surgical duration for >3 hours (p=0.077).

Surgical Site Infections: 7.6% of the patients in this cohort developed an SSI. Superficial SSI developed in 1.9% and deep in 5.7%. Meningitis/ventriculitis developed in 2.5% of the total cohort. The mortality in this cohort was 10.2%. Most of the patients were discharged with a GOS score of 5 (68.8%).

In the multivariate analysis, the days of ICU stay remained the most important predictor for SSI development. There was a trend for association with a surgery duration for >3 hours (p=0.069). For SSI development there was a trend for association with malignancy (p=0.12), steroid use (p=0.055), revision surgery (p=0.12), CSF leak (p=0.067), drain days (p=0.09) and also a trend for association

with pre-preparation sample *P. acnes* CFU counts. There was no association with the duration of surgery as a constant variable. The development of SSI was associated: with prolonged LOS (p=0.01), length of ICU stay (p=0.002), lower discharge GOS scores (p=0.029) and adverse final outcomes (p=0.045).

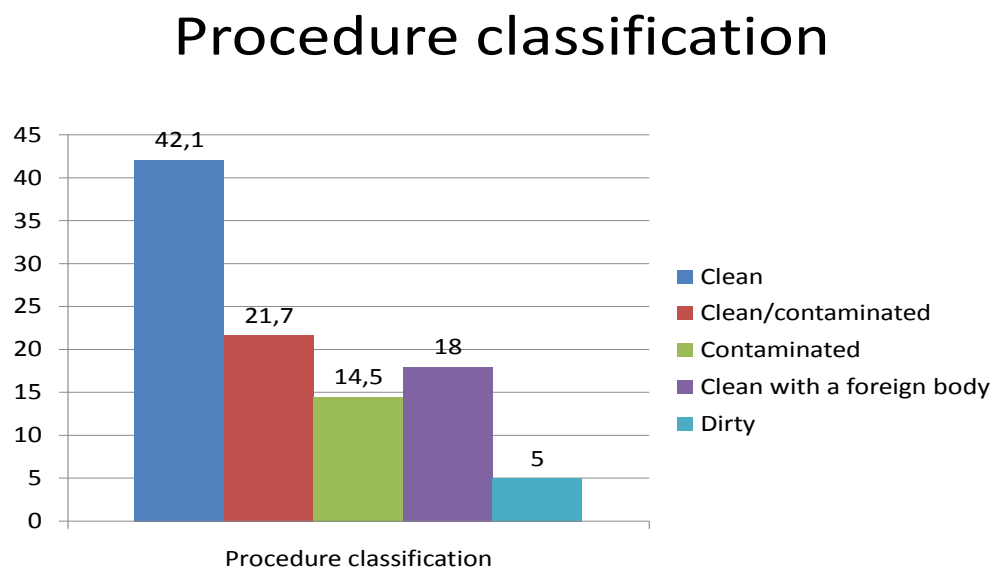


Figure 2.6.1. Most of the procedures performed in our cohort were clean

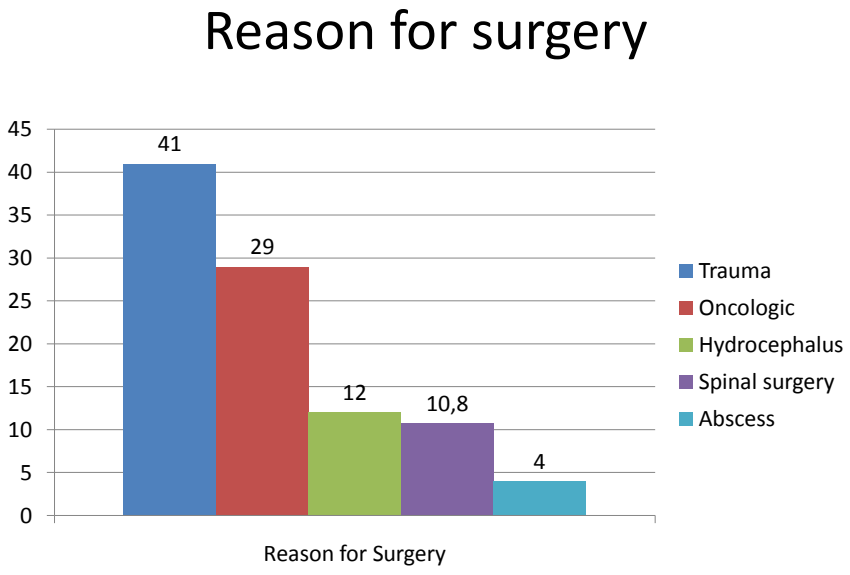


Figure 2.6.2. Trauma was the most common reason for surgery in this cohort

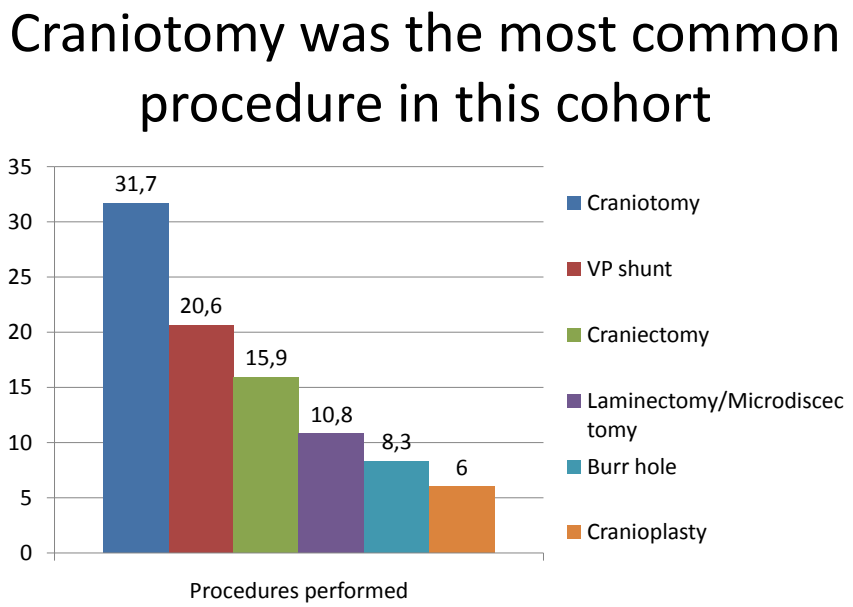


Figure 2.6.3 Craniotomy was the most common procedure in this cohort

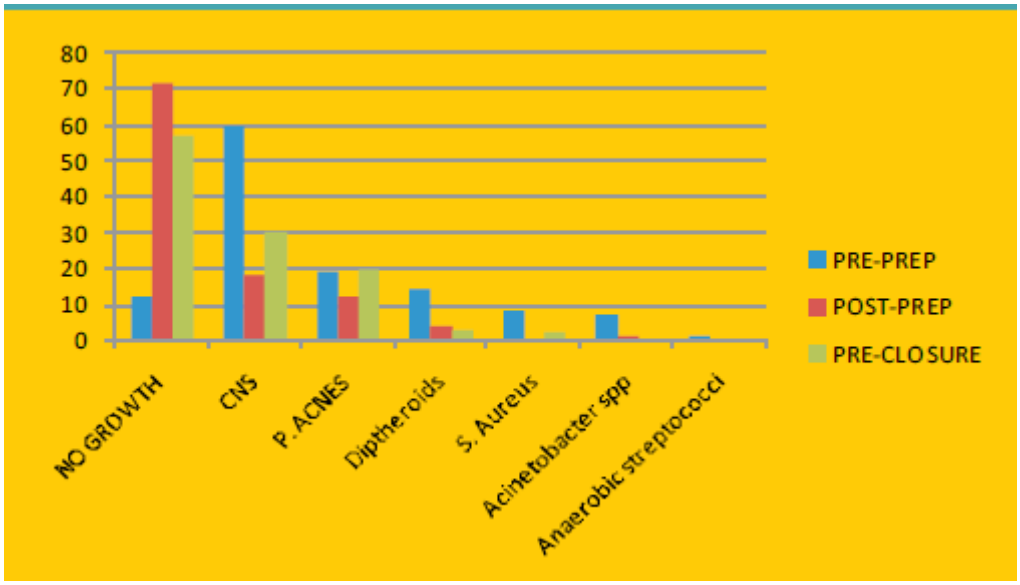


Figure 2.6.4. Growth of organisms according to the sampling time

Samples	Head %	Back %	Abdomen %	Total %
Pre-preparation	87	80	77.7	**90.3**
Post-preparation	25.6	30	22.2	**29**
Pre-closure	48	40	22.2	**44**

Table 2.6.1. There was no statistical difference in the positivity of sampling according to the sampling time

	Clean (%)	Clean/cont (%)	Clean/ Foreign Body (%)	Contaminated (%)	Dirty (%)
Pre-preparation	**88.6**	**88.8**	**82.6**	**91.6**	**100**
Post-preparation	**37**	**22.3**	**21.7**	**33.3**	**0**
Pre-closure	**48.6**	**55.5**	**23**	**50**	**25**

Table 2.6.2. There was no statistical difference in the positivity of sampling according to the procedure classification

	Median	Min	Percentiles 25th	Percentiles 75th	Max
CoNS					
pre-prep	2.7	2	2.3	3.3	6
post-prep	2.47	2	2	3.1	3.69
pre-closure	2.3	2	2.2	2.7	4
P. acnes					
pre-prep	3.8	2.3	2.3	4.3	5.53
post-prep	2.9	2	2	3.5	3.77
pre-closure	4	2	3	4.6	5.39

Table 2.6.3 CFU logs for P. acnes and CoNS for each sampling time

	Clean (%)	Clean/cont (%)	Clean/For (%)	Contam (%)	Dirty (%)
Pre-prep (1)					
CoNS	62.8	72.2	61	66.6	25
P. acnes	25.7	27.7	4.3	16.6	25
Post-prep (2)					
CoNS	20	16.6	21.7	16.6	0
P. acnes	14.3	5.6	4.3	25	0
Pre-closure (3)					
CoNS	31.4	27.7	21.7	41.6	25
P. acnes	25.7	27.7	4.3	25	0

Table 2.6.4 Positivity of samples 1, 2 & 3 of the two most prevalent organisms according to the procedure classification

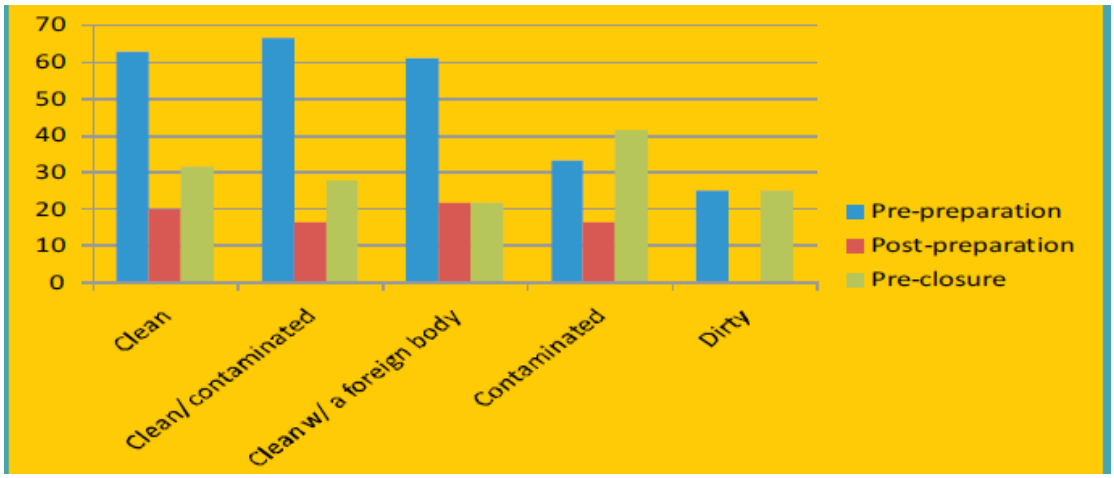


Figure 2.6.5. Positivity of samples 1, 2 & 3 (%) to CoNS according to procedure classification

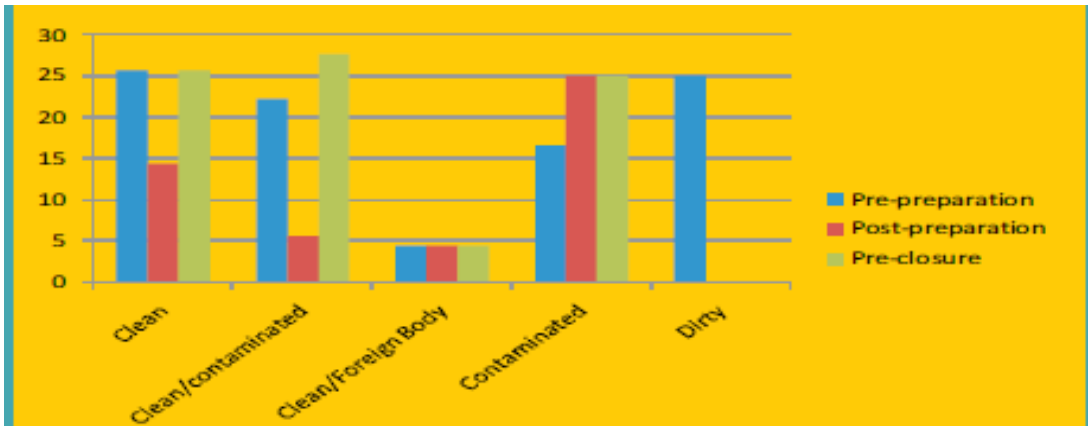


Figure 2.6.6. Positivity of samples 1, 2 & 3 (%) to *P. acnes* according to procedure classification

2.6.4 Discussion

Microbiology. These microbiologic findings are generally consistent with those of other investigators [281]. The composition of skin flora on the body varies from site to site depending on many factors, including the amount of sebum, the location of sweat glands, and moisture content. Pre-preparation samples from the back and abdomen had considerably lower CFU counts than those taken from the head. *P. acnes* was more prevalent on the head, an area with relatively high sebum production. CoNS were by far the most prevalent and abundant group of organisms in most samples. The predominance of CoNS and *P. acnes* irrespectively of sampling site and timing is in concordance with previous reports [281]. The pathogens' CFU counts did not differ significantly among the three samples which is different than reported before [281]. Previous researchers have described that long-stay patients have higher CFU counts [282]. In this analysis we have not analyzed the impact of the pre-surgical LOS on the CFU counts. It is very important to emphasize on the positivity of samples even after preparation. This has been well known to the surgeons and has described in general surgical patients for five decades [283]. After the preoperative skin preparation, there was no difference between samples taken from the head, abdomen or the back in terms of CFU counts and the type of flora isolated.

The CFU counts of the pre-preparation samples did not correlate significantly with post-preparation or pre-closure CFU counts, as reported before [281]. As expected, the pre-closure samples had a trend to increase with increased duration of surgery, especially if this lasted for more than three hours. Since they have not examined pre-closure CFU counts in the neurosurgery before, we cannot compare these findings to previous reports. Nevertheless the difference was not statistically significant. There was a specific trend to increased numbers of *P. acnes* in the pre-closure counts which raises the question of the source of the organism during the procedure.

Pre-, post-preparation and pre-closure CFU counts were not associated with the class of the procedure performed. To our knowledge, this is the first attempt for an association between the procedure classification and the intraoperative skin microbial CFU counts.

SSI. In this study of neurosurgical patients, we found no association between high bacterial counts on the skin of operative sites, either before or after the skin preparation, and subsequent SSI. Although skin flora varies greatly between people, for an individual, its composition and quantity are stable over time . Preoperative skin preparation can remove surface bacteria, but not flora at deeper layers of the skin. Brown et al. [284] have found that people with higher counts on the skin surface also have higher counts in the stratum corneum. They postulated that these bacteria can serve as a reservoir for infection, so higher surface counts would pose a higher risk for infection. Investigators have reported a significant association between bacterial counts on the skin near intravenous catheters and catheter tip colonization, but a link with sepsis has not been conclusively demonstrated [285]. Among pediatric neurosurgical patients, Leclair et al. [286] compared the efficacy of several preoperative shampoos on operative site bacterial counts and demonstrated a correlation between pre-surgical CFU counts and levels of intra- and postoperative wound contamination, but the study did not have sufficient statistical power to examine an association with SSI. It is interesting to note, however, that 48% of scalp cultures were positive immediately before wound closure and 30% were positive immediately after closure, and no patients developed SSI.

The present study directly examined the relationship between SSI and three intra-operative bacterial CFU counts. Our data on pre-preparation, post-preparation and pre-closure counts and SSI show no association, although there was a trend for pre-preparation *P. acnes* counts. If pre-preparation bacterial counts are associated with risk for SSI, it is reasonable to expect that predictors of bacterial counts might also be risk factors for SSI and this is something that requires further investigation.

Surprisingly, in this study there was no association between the procedure classification and the development of SSI. The procedure classification can predict the SSIs rate [27] (Table 1.1.1). We believe that the significant predominance of clean procedures in the cohort did not allow for significant differences.

Many studies have shown that prolonged duration of surgery increases risk of postoperative infection [20, 114]. The longer duration can be a marker for the complexity of the procedure, the surgeon’s skill, or the amount of trauma to the tissues. In our cohort and in the multivariate analysis, there was a trend for significant association with surgery duration >3 hours. This needs to be further investigated but it seems that the 4-h cutoff for surgical duration may not be as helpful in predicting SSI.

In conclusion, this is the first study where the association between procedure classification and intraoperative microbial skin counts is attempted. In this pilot study, which is on-going, we were unable to detect an association between procedure classification in neurosurgery and CFU counts. To our knowledge, this is the first study where three samples are taken, including a pre-closure sample in order to clarify the nature of the skin flora during the neurosurgical procedure. We failed to demonstrate an association between procedure classification and SSI development. We also failed to clarify the role of skin flora in three different sampling times and subsequent SSI development.

3. General Conclusions

Nosocomial infections related to the central nervous system are a relatively small but important category of hospital- acquired infections. These infections span a spectrum from superficial wound infections to ventricular shunt infections, meningitis and deep-seated abscesses of the brain parenchyma. They are serious infections, if not life threatening and can be associated with a poor functional outcome. These infections may present many challenges in diagnosis. Nevertheless, a heightened awareness may result to declining rates of infections. The association of neurosurgical infections with certain risk factors may further help in the prevention or the early diagnosis of the neurosurgical infections. The determination of the most commonly isolated offending pathogens and their sensitivities may lead to the most effective treatment.

Neurosurgical infections have not been extensively investigated in Greece. With this research we attempted to further determine the bacteriology, the rates and the factors associated with neurosurgical infections. Since there are not detailed reports on post-craniotomy meningitis (PCM) in the international literature, we performed three studies on this subject (two retrospective and one prospective). One of these retrospective studies was performed in NYU Medical Center where the candidate was an Infectious Disease fellow. The retrospective studies were performed in different time periods in NYU Medical Center and in the Medical Center of the University of Crete and we had the opportunity to compare the trends in the offending pathogens and the associated risk factors.

In the University of Crete there was a report on the infections after craniotomy in a Thesis for doctoral degree presented in 2008 by M. Roumbelaki, RN. In this Thesis, the rate of SSIs after craniotomy was reported to be 11.1% [287], which was higher when compared with countries such as USA and Spain. Nevertheless, there was no specific mention on the rates of meningitis/ventriculitis after craniotomy, and no mention on the SSIs in the general neurosurgical population. In the retrospective study we performed in a 3-year period and in 1112 general neurosurgical patients, the rate of SSIs was 12.5%. This is a rate that is considerable higher than the ones reported in the literature [16, 24, 51, 194, 195]. In one of the largest studies on postoperative infections in neurosurgery, the infection rates was <1% (0.8%) [195]. This study underwent extensive critique since all the procedures were elective, although not all of them were “clean”. The same group of authors has reported that

the postoperative wound infection after intracranial neurosurgery is nearly three times more likely in European vs. North American studies [198]. Our population mainly consisted of Trauma patients (56.3%) and this could account for the high rate of infections. Meningitis rate was higher than reported in the literature (4.2%). Malignancy was for the first time reported as an independent risk factor in patients undergoing neurosurgery. The placement of drains achieved a statistical significance in the development of infections and the prevalence of SSIs was significantly higher in patients who also developed VAP, UTI and BSI/CAB. The most important result of this study was the absence in mortality increase among patients who developed SSIs and any infection in general but there was an increased duration of ICU hospitalization and an increased length of stay (LOS) in general, therefore increasing the hospital costs. This is a topic that should be further investigated in the future.

The first retrospective study on post-craniotomy meningitis (PCM) was performed in NYU Medical Center and it included patients that underwent elective or emergency craniotomy between January 1996 and March 2000. The second retrospective study on PCM was performed in the UOC Medical Center between January 1999 and December 2005. The cohorts in comparison consisted of similar rates of male patients but the UOC population included more trauma patients and consequently more emergent procedures. The PCM rate was higher in the UOC cohort but the difference was not statistically significant. The offending pathogens in the NYU cohort were mainly gram-positives, a fact that reflected the general re-emergence of gram-positive as nosocomial pathogens in the mid-1990s. In the UOC cohort there was a slight predominance of the gram-negatives with *Acinetobacter* spp. being the most prevalent with a percentage of 16%. These data are consistent with most recent reports. A great limitation of the UOC study is the lack of ASA score inclusion in the risk factor analysis. ASA score is included in the Risk Index Score (RIS) for the SSIs as proposed by the NNIS system [202]. Nevertheless the RIS does not effectively stratify the risk development after craniotomy and CSF shunt placement [202, 203]. Malignancy was determined as an independent risk factor for PCM in the UOC cohort, which has not been reported before. Entering a sinus was a major risk factor for PCM in the NYU cohort but not in the UOC cohort. This probably reflects the trend for avoiding generally this technique in the most recent years. The presence of ventricular drainage was confirmed as independent risk factor in both cohorts but the duration of EVD was an independent risk factor in the NYU

cohort. The role of lumbar drains in the development of meningitis was extensively underscored in the UOC retrospective study although it had not been as well recognized in the past. Based on our results and those of recent reports [237], we should emphasize on the role of lumbar drains and the need for removal by the clinicians when they are no longer needed. ICP monitoring and its duration were confirmed as independent risk factors in the NYU cohort but not in the UOC cohort. In the UOC cohort the significance of other infections was underscored for the development of PCM, a fact that should alert the clinicians for prophylaxis against the development of any infection in order to avoid PCM. The percentage of craniotomy patients that developed any kind of infection reached 26%, a percentage that underscores the significance of the very good nosocomial care of these individuals.

A prospective study on PCM was performed in the UOC Medical Center for the time period between 2006 and 2008. In this time period traumatic brain injury (TBI) was the most common reason for craniotomy. The percentage of 4.8% for PCM was consistent with the literature. The results of the cultures seem to reflect the increasing role of gram-negative pathogens (especially *Acinetobacter* spp. which represented 45% of the isolates) in the neurosurgical infections. In this analysis, the use of ventricular drains was once more confirmed as an independent risk factor for the development of PCM, but the duration of EVD drainage was not. CSF leak was demonstrated as an independent risk factor for PCM as repeatedly in previous reports [16, 20, 51, 204]. The use of perioperative steroids achieved statistical significance, an association that has not been described before. The main advantage of this study is the fact that the sensitivities of the offending pathogens were described. *Acinetobacter* spp. were fully resistant to beta-lactams, aztreonam, aminoglycosides and quinolones, 33% resistant to imipenem and 17% resistant to meropenem. *Klebsiella* spp., the second most common isolate were fully resistant to beta-lactams, cephalosporins, aztreonam and quinolones, 80% resistant to aminoglycosides, 20% to colistin, 60% to imipenem and 40% to meropenem. VAP was the most common infection in this craniotomy cohort with *Acinetobacter* spp. and *P. aeruginosa* being the most common isolates. We believe that these findings are of extreme importance since it may help the clinician to decide on the empirical treatment of the infections in craniotomy patients. The resistance in the pathogens is consistent with the literature. In this first prospective study of the infections in patients undergoing craniotomy in

Greece, the development of PCM and infections other than SSIs did not affect the mortality of patients.

Since the TBI was the most common reason for admission in the UOC, we performed a retrospective study on 760 patients admitted with this diagnosis. Traumatic brain injury patients are considered especially prone to the development of infections. Since 33% of all the TBI patients underwent neurosurgery we compared the two subgroups of TBI patients. The ones who underwent neurosurgery had a significantly lower Glasgow Coma Scale (GCS) score, they were more prone to be intubated beyond the surgical time, to be admitted to the ICU and bear ICP catheters and various drains. They were also more prone to develop meningitis, SSIs or other infections and had a significantly increased mortality. In this study we underscored the significance of the initial clinical evaluation of the TBI patients, since a low admission GCS significantly correlated with a longer LOS, an adverse final outcome, a low Glasgow Outcome Scale (GOS) score and a greater propensity for the development of infections. The perioperatrive communication of CSF and the environment was an important risk factor for the development of meningitis and SSIs in general. The most common infection in this TBI population was VAP. The patients with TBI were proven to be of increased propensity to infections and therefore they merit special care for the avoidance of complications.

In the final study derived from this research, we attempted to identify any associations between the surgical site microbial counts and procedure classification in neurosurgery. The surgical site microbial counts have not been extensively investigated in neurosurgery. There was only one report in the literature with samples taken before and after preparation of the surgical site and only in clean neurosurgery [281]. In our study we attempted to define how the surgical site microbial counts vary between the pre-, post-preparation and pre-closure samples and how the duration of surgery affects them. To our knowledge this was the first study where three samples were obtained in order to clarify the nature of the skin flora during the neurosurgical procedures. In this pilot study which is ongoing, we were unable to detect an association between procedure classification in neurosurgery and microbial skin counts. We also failed to clarify the role of skin flora in three different sampling times and subsequent SSI development. We expect the analysis of the final data in order to further investigate these associations.

In conclusion, neurosurgical infections merit further investigation in Greece. They are important infections that they may lead to increased length of stay and increased hospital costs. Our studies were limited in a single center in Greece and we do not know if the results represent the rest of the country. More muticentered studies, with a prospective design if possible, will be necessary for the full clarification of the rates of the SSIs in neurosurgery and their risk factors.

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5. Appendix

I. ASA physical status classification systems

ASA class	Physical Status	Mortality
1	Healthy, no disease outside surgical process	<0.03%
2	Mild to moderate systemic disease, medically well controlled, with no functional limitation	0.2%
3	Severe systemic disease that results in functional limitation	1.2%
4	Severe incapacitating disease process that is a constant threat to life	8%
5	Moribund patient not expected to survive 24 hours without an operation	34%
6	A declared brain-dead patient being maintained for harvesting of organs	
E	Suffix to indicate emergency surgery for any class	Increased risk

II. Head Injury Classification

Category	Acute GCS	Clinical Features
Mild	13-15	Loss of consciousness for <20 minutes, no deterioration of GCS, no focal neurological deficit or complication, no intracranial mass lesion or intracranial surgery
Moderate	9-12	Includes GCS>12, with complication or focal brain lesion seen on computed tomography scan, and may include patients rapidly recovered from coma
Severe	3-8	No eye opening, no motor response to command, no verbal response or speech. Coma duration must be >6 hours

III. Glasgow Outcome Scale

GOS score	
1	**Death**
2	**Vegetative State:** Apparent absence of cognitive function, may have eye-opening and sleep/wake cycles, demonstration of a variety of spontaneous or reflexive motor actions
3	**Severe disability:** Patients conscious but dependent, they must rely on a caregiver. In some patients physical functioning may remain relatively intact but they may be disinhibited or apathetic
4	**Moderate disability:** Independent but disabled patients are included. Although they may live alone, these patients have a degree of cognitive or physical handicap that limits them. Many patients continue to work although they are unable to assume their previous level of occupational responsibility
5	**Good recovery:** Independent patients who are capable of returning to their work and activities without major limitations. They may have persisting neurological or cognitive deficits which do not interfere with their general functioning. They are socially competent and without a suggestion of marked personality change