SVOA Neurology

ISSN: 2753-9180

ScienceVolks Open Access

Research Article

Emerging Antibiotics Resistance Patterns in Postcranial Surgery CNS Infections, A Tertiary Center Experience

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***Received:** September 03, 2021* ***Published:** November 30, 2021*

Abstract

Background: Postoperative central nervous system infections (PCNSI) in patients undergoing neurosurgical procedures represent a serious problem that requires immediate attention. They commonly require prolonged antibiotic treatment and additional surgical interventions for successful eradication and frequently result in significant morbidity, prolonged hospitalization, and increased health care expenses. There is variability on the rate of PCNSI in literature (1 – 11 %) probably due to differences in operational definitions and methodologies used. There is limitation in reports concerning this issue from underdeveloped nations and resource constrained setups like ours.

Objective: The objective of the study is to assess the incidence, associated factors, clinical and microbiologic profile of postoperative CNS infections at Tikur Anbessa Specialized Hospital.

Methodology: This is a hospital based prospective cohort study of patients who underwent elective trans-cranial surgery from November 1, 2018 – September 30, 2019, at Tikur Anbessa Specialized Hospital. Patients were followed for the development of deep CNS infections according to the CDC/NHSN criteria (2008) till discharge. Clinical data was collected using well designed questionnaire and encoded to IBM/SPSS 25. Bivariate and multivariate correlational analysis was done to pick strongly associated variables with p value <.05 considered significant.

Results: A total of 256 surgeries were included in the study out of which 29(11.3%) fulfilled the criteria for diagnosis of PCNSIs. Meningitis/ventriculitis were the commonly diagnosed infection types (82.8%). 41.4% of the cases are instrument related infections (EVD/VP-shunt). Infections are common in the infratentorial surgery group contributing to 55.2% of cases. The median period of diagnosis was 9th postop day. Fever (100%) and meningismus (75.9%) are the common clinical signs. Deterioration in mentation or confusion was seen in 55.2% of the patients. Seventeen (58.9%) patients had growth of etiologic organisms at least from a single sample. The strongest independent risk factor is postoperative CSF leak (OR=22). Superficial incisional infections (OR=5), EVD stay >3days (OR=7) and ICU stay >3days (OR=5) are also independent risk factors. Acinetobacter spp. and Klebsiella pneumoniae are the frequently isolated organisms (37.9% and 27.6% respectively). Acinetobacter spp. show 100% resistance for Ceftazidime, 80% resistance for Meropenem, and 50% resistance for Amikacin. Five patients had documented death from sepsis or neurologic complication of infection. This is ~20% of the overall surgical mortality.

Conclusion: There is higher incidence of postoperative CNS infections (11.3%) in comparison to other studies. The moderately high rates of postsurgical CSF leak and superficial incisional infections are strong risk factors in our setup. Prolonged EVD stay and prolonged ICU stay are also risk factors especially for Gram negative bacterial infections. The emerging multidrug resistance patterns of *Acinetobacter spp.* are also a challenge in our setup. Mortality from PCNSIs has a significant contribution to the overall surgical mortality (~20%).

***Keywords:** postcranial Surgery, CNS infections, neurosurgery, Postoperative central nervous system infection (PCNSI)*

Acronyms) **AAU:** Addis Ababa University, **CDC:** Centers for Disease Control and Prevention, **CNS:** Central nervous system, **CONS:** Coagulase negative staphylococcus, **CSF:** Cerebrospinal fluid, **EVD:** External ventricular drain, **ETV:** Endoscopic third ventriculostomy, **HCP:** Hydrocephalus, **ICU:** Intensive care unit, **KPS:** Karnofsky performance scale, **LP:** Lumbar puncture, **NHSN:** National Healthcare Safely Network, **PCNSI:** Postoperative central nervous system infection , **SSI:** Surgical site infections, **TASH:** Tikur Anbessa Specialized Hospital, **VP-Shunt:** Ventriculo-peritoneal shunt

1. Introduction

1.1 Background

Since the origin of neurosurgery, postoperative central nervous system infections (PCNSI) has posed a formidable challenge to the field. PCNSI in patients undergoing neurosurgical procedures represents a serious problem that requires immediate attention. PCNSI most commonly manifests as meningitis, subdural empyema, and/or brain abscess. They are also significant burden to the medical system as they are associated with prolonged hospital stays, unacceptably high medical cost and poor post-surgical outcomes.[1, 2, 3]

The overall incidence of PCNSI is variable in different literatures (ranging from 1-10 %) probably because of differences in definitions and methodology. As to the authors knowledge there is paucity of publications regarding PCNSI in resource limited setups in developing countries like us. Probably the only unpublished paper that can be mentioned in this regard is by Mulualem et al., on which he tried to assess ventriculostomy associated infections retrospectively on 2018 and reported overall incidence of 25.8% which is comparably in the higher ranges.[4] The main goal of this study will be to become a baseline for future large scale works.

Despite the lack of objective data concerning PCNSI at Tikur Anbessa Specialized Hospital (TASH), the Neurosurgical staff believe that the incidence is high. To address this issue improving preventive, diagnostic and therapeutic measures will be of ultimate importance especially for resource limited setups.

1.2 Statement of the problem

PCNSI in patients undergoing neurosurgical procedures represent a serious problem that requires immediate attention. They commonly require prolonged antibiotic treatment and additional surgical interventions for successful eradication and frequently result in significant morbidity, prolonged hospitalization, and increased health care expenses.[5] In resource limited setups like us PCNSI pose extra challenge in providing efficient neurosurgical service and unacceptably compromise good short- and long-term outcomes. At TASH we face challenges daily in diagnosing, treating and following patients who develop PCNSIs. There are diagnostic limitations in confirming these infections and treatment is usually tailored by clinical judgment and is empirical. We have limited options of antibiotics, poor preventive and therapeutic practices that further complicate the management of PCNSIs.

1. 3 Significance of the study

This study will be significant in giving clear outlook of the burden of PCNSIs and suggesting recommendations to improve in preventive, diagnostic and therapeutic practices of the setup. It also assesses the emerging antibiotic resistance patterns of causative organisms which might implicate the need to revise choice of antibiotics. The study might also point out any gaps in patient care that might predispose for development of PCNIs or lead to delay in diagnosis and management. It will also be a baseline paper for future investigations.

2. Literature review

Postoperative central nervous system infection (PCNSI) in patients undergoing neurosurgical procedures represents a serious problem that requires immediate attention. Although mortality rates have decreased markedly, they commonly require prolonged antibiotic treatment and additional surgical interventions for successful eradication and frequently result in significant morbidity, prolonged hospitalization, and increased health care expenses.[5]

The diagnosis of infection after craniotomy is often challenging. Many of the typical correlates of infection are nonspecific in the postoperative setting, and recognition of infection may frequently be delayed. An accurate understanding of the clinical, laboratory, and radiographic manifestations of postcraniotomy infection is critical to enable timely medical and surgical intervention and to limit the neurological sequelae of infection.

Postoperative infections are typically categorized according to anatomic site as superficial incisional, subgaleal space and bone flap, autogenous/synthetic cranioplasty, subdural empyema, brain abscess and meningitis. The Centers for Disease Control and Prevention (CDC) defines *superficial incisional infections* as those limited to the skin and subcutaneous tissue, whereas *deep incisional infections* may involve the subgaleal space and bone flap. *Deep organ space* infections include subdural empyema, brain abscess, and meningitis/ventriculitis.[6, 7]

The incidence of infection after craniotomy is difficult to estimate from the neurosurgical literature because of differences in definitions and methodology. Two factors potentially contribute to the broad range of SSI incidences reported in the literature. First, some studies grouped superficial incisional SSI, deep incisional SSI, and organ space SSI together. However, great variation is noted in the incidence of and risk factors for different sites of infection. [7] Several large prospective studies have reported postcraniotomy infection rates ranging from 1% to 10%. [2, 8, 9] There is paucity of publications from African neurosurgical centers to mention the true incidence. Adeleye reported an incidence of 4.3 %(9 cases from 211 craniotomies) in his study of post-craniotomy surgical site infections in a developing country (Ibadan, Nigeria). [10] In our Hospital, Mulualem et al. specifically assessed ventriculostomy associated infections retrospectively and reported prevalence of 25.8%.[4]

Meningitis is the most common deep organ space infection, representing 22% of postcraniotomy infections, whereas other intracranial infections, including subdural empyema and brain abscess, account for 14 %.[8]

Infections after craniotomy are most commonly associated with gram-positive bacteria, *S. aureus* (~50 %), and coagulase -negative staphylococci. Other bacteria isolated from postcraniotomy infections include *enterococci*, *Streptococcus* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Klebsiella pneumoniae*, *Escherichia coli*, miscellaneous other gram-negative bacilli, and yeast.[3, 9, 11]

Several factors specific to craniotomy have been identified as raising the risk for postoperative infection. In a prospective multicenter trial, Korinek identified postoperative CSF leakage and early subsequent reoperation as independent risk factors for SSI, suggesting that careful attention to closure techniques and meticulous hemostasis may potentially result in lower rates of postoperative infection.[2] Multiple other studies have also established CSF leakage as a major risk factor for infection.[11, 15, 20]

Other identified independent predictors of postoperative infection after craniotomy are surgery lasting longer than 4 hours, emergency surgery, clean-contaminated and contaminated surgery, and neurosurgical intervention in the preceding month.[14] Furthermore, patients with meningitis had significantly longer hospital stays and were more likely to be admitted to intensive care units and to have prolonged intubation periods.[15]

The association of a variety of other risk factors with infection after craniotomy has been less reliably demonstrated; placement of drains or intracranial pressure monitors, poor neurological status, paranasal sinus entry, diabetes mellitus, and foreign body implantation (other than shunts) have been identified as risk factors in some retrospective studies.[2, 11, 16]

Some other papers couldn't find any risk factor may be due to lower rates of PCNSIs. [2, 17]

PCNSIs tend to be particularly difficult to resolve because of the complex anatomic changes resulting from craniotomy and the frequent involvement of virulent organisms. Early and decisive intervention is critical to limit morbidity, and the keystone of successful treatment is effective source control (i.e., drainage of abscesses and infected fluid collections and debridement of necrotic tissue). Once source control has been achieved, initiation of appropriate antibiotic therapy is necessary to eliminate any residual infection.[5]

As postoperative infections may have severe neurological sequelae or cause death, empirical treatment of postoperative infections should include coverage for the full spectrum of potential pathogens, including resistant gram-positive organisms (e.g., MRSA) and nosocomial gram-negative bacilli (e.g., *Pseudomonas* and *Acinetobacter* spp.). Infections that may have an anaerobic component (brain abscess, paranasal sinus approach) should also be treated empirically with metronidazole. Suitable empirical regimens for postcraniotomy infections typically include a combination of vancomycin and a drug such as a third- or fourth generation cephalosporin that has antipseudomonal activity (e.g., ceftazidime, cefepime), with the addition of metronidazole when anaerobic infection is possible. Owing to activity against gram negative and anaerobic bacteria, a carbapenem (e.g., meropenem) may be substituted for the combination of a third-generation cephalosporin and metronidazole. [18, 19] Antibiotic selection should be tailored once species identification and results of susceptibility testing by a microbiologic specimen are available. The duration of treatment may depend on the offending organism and its antibiotic susceptibility pattern as well as on other complicating factors, such as the presence of parameningeal foci or the patient's underlying immune status.

The approach to treatment of postoperative brain abscesses is similar to that for spontaneous abscesses, although the increased frequency of bacterial pathogens resistant to multiple antibiotics and the extension of infection into adjacent anatomic compartments in the postoperative setting may complicate treatment. In most cases, a combination of surgical drainage and a prolonged course of intravenous antibiotics is required.[5]

Postoperative infections after neurosurgical procedures carry a high morbidity rate and not uncommonly have a life-threatening potential.

3. Objective

3.1 General objective

To assess overall burden of postoperative CNS infections in our Neurosurgical practice

3.2 Specific objectives

- To describe the incidence of deep incisional and organ space CNS infections after elective cranial surgeries
- To identify strong perioperative factors associated with these infections
- To describe the clinical and microbiological profile of these infections
- Describe the surgical mortality attributable to PCNSIs
- To point out any identified gaps in practice that increase incidence of these infections

4. Methodology

4.1 Study setting and design

The study was conducted at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. It is the teaching Hospital of Addis Ababa University and the main referral center for most neurosurgical cases from all over the country. According to the recent(2017/18/19) monthly audit reports of the Neurosurgical unit, average of 20 – 30 elective cranial surgeries are done monthly.

This is a hospital based prospective cohort study, where patients are followed from admission till discharge.

4.2 Study population

The study population are all patients who underwent cranial surgery as elective basis in the mentioned institute from November 1, 2018 – September 30, 2019.

4.2.1 Inclusion criteria

All patients fulfilling the listed criteria were included in the study population;

- All patients undergoing cranial surgery as elective basis
- All patients undergoing reoperation and surgeries > 30 days apart
- All patients fulfilling the diagnostic criteria for deep incisional or organ space postoperative infection within 30 days post-surgery will be included in the infection cohort.

4.2.2 Exclusion criteria

Patients with the following criteria were excluded from the study population;

- Trauma or emergency surgeries
- Patients operated for infectious pathology from the outset (e.g. Abscess, Tuberculous meningitis…) and confirmed by intra op or pathologic findings
- Patient who died intraop or within three days of surgery
- Patients diagnosed with sole superficial incisional surgical site infection are not included in the infection cohort

4.2.3 Sampling method

Convenient sampling method including all available patients was used.

4.3 Study variables

4.3.1 Independent variables

The variables analyzed are age, sex, type and duration of surgery, presence and duration of stay of EVD or other CSF diversion, presence of CSF leak, presence of superficial incisional infections preoperative KPS, preoperative steroid use, systemic medical illness, reoperation, total days of ICU stay.

4.3.2 Dependent variables

The dependent variable diagnosis of PCNSI (fulfilling the CDC criteria).

4.4 Operational definitions

The operational definitions used here are adopted from CDC/NHSN surveillance definitions of health care–associated infection and criteria for specific types of infections in the acute care setting with slight modifications to fit our center practice. (Horan, et al., June, 2008)[6]

1. **Superficial incisional infections -** infections limited to the skin and subcutaneous tissue
2. **Deep incisional infections -** involve the subgaleal space and bone flap.
3. **Deep organ space infections -** include subdural empyema, brain abscess, and meningitis/ventriculitis.
4. **Diagnostic criteria for Intracranial infection** (brain abscess, subdural or epidural infection, encephalitis)

- Intracranial infection must meet at least 1 of the following criteria:

   1. Patient has organisms cultured from brain tissue or dura.
   2. Patient has an abscess or evidence of intracranial infection seen during a surgical operation or histopathologic examination.

3. Patient has at least 2 of the following signs or symptoms with no other recognized cause: headache, dizziness, fever (>38^{0}C), localizing neurologic signs, changing level of consciousness, or confusion

And at least 1 of the following:

- organisms seen on microscopic examination of brain or abscess tissue obtained by needle aspiration or by biopsy during a surgical operation or autopsy
- radiographic evidence of infection, (e.g., abnormal findings CT scan or MRI)

And if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

5. Diagnostic criteria for meningitis or ventriculitis.

Meningitis or ventriculitis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from cerebrospinal fluid (CSF).

2. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (>38^{0}C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability

And at least 1 of the following:

a. increased white cells, elevated protein, and/ or decreased glucose in CSF

b. organisms seen on Gram's stain of CSF

c. organisms cultured from blood

And if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

6. Operative mortality - any death, regardless of the cause occurring within 30 days after surgery in or out of the hospital and after 30 days during the same hospitalization subsequent to the operation.

4.5 Data collection and analysis

Data was collected by recruited associates (residents) and by the principal investigator using questionnaire method which was filled starting from the day of admission and subsequent hospital stays until discharge or death.

The collected data was cleaned, coded and entered into IBM/SPSS 25.0 statistics software for analysis. Participants' socio -demographic characteristics and other variables are presented using the relevant descriptive statistics. Bivariate correlational analysis assuming normal distribution of variables (Pearson correlation) was done at 10% level of significance to filter potentially significant independent variables. Multivariate binary logistic regression analysis was performed to variables with statistically significant correlation with the dependent variable. Adequacy of the final model was checked using the Hosmer and Lemeshow goodness of fit test and the final model was fitted for the data well (*p-value = 0.769*). The final result is reported by significance level (*p<0.05*), 95% confidence interval and adjusted odds ratio.

4.6 Ethical considerations

This study is conducted in accordance with the ethical principles stated in applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

Patient's medical record numbers and codes given by data collector are used as identification and medical records are only handled by the principal investigator. Data will be used only for this research purpose and will not be passed to any other third party.

Patients or responsible caregiver was informed and consent was taken before enrollment into the cohort. The research also has no intervention in any parts of patient management.

The research proposal was passed through IRB of TASH and got clearance before commencement of the research.

5. Results

5.1 Socio-demographic characteristics of participants

A total of 261 elective cranial surgeries were done between November 1, 2018 and September 30, 2019 at TASH. This study includes 256 cases who fulfilled the inclusion criteria. Among these, six cases (2.3%) were reoperations done for residual/ recurrent pathologies. Five cases were excluded as three of them died within 3 days of postop period and the rest two had infectious pathology from the outset.

Among 256 cases constituting the series 52.7% were males and 47.3% were females. The mean age is 33.3 years (SD ±15.9) and ranges from 10 months to 72 years. More than 60% of the population were in their 3rd to 5th decades of life. The majority of the patients (32.4%) came from the capital city, Addis Ababa. (Table - 1)

Variables	Frequency	Percent (%)
Sex		
Female	121	47.3
Male	135	52.7
Age in years		
≤10	23	9.0
11-20	30	11.7
21-30	72	28.1
31-40	51	19.9
41-50	44	17.2
51-60	30	11.7
61-70	4	1.6
>70	2	.8
Address		
Addis Ababa	83	32.4
Oromia	71	27.7
Tigray	1	.4
Amhara	68	26.6
Afar	1	.4
SNNPR	27	10.5
Somalia	4	1.6
Gambella	1	.4

Table 1: Socio-demographic characteristics of study population.

5.2 Operative results

About half of the procedures, 49.2 % (126 cases) were supratentorial craniotomies, of which 85 procedures for extra-axial mass lesion excision and 41 procedures for intra-axial mass lesions. Transsphenoidal surgeries involve 46 cases (18%). Infratentorial craniotomies constituted 45 cases (17.6%), where 24 of them are done for intra-axial and 21 craniotomies for extra-axial infratentorial mass lesions.

Other operative interventions were ETV in 17 cases (6.6%), Occipitocervical decompression in 11 cases (4.3%), VP-shunt insertion in 4 cases (1.6%) and miscellaneous (endoscopic fenestrations, cranioplasties…) 7 cases (2.7%). (Table - 2)

Most of the surgeries were completed under 4 hrs. (n=140, 54.7%) and the rest 41.4% (n=109) of the surgeries were completed within 4-8hrs.

Fifty seven patients (22.3 %) had hydrocephalus diagnosed preoperatively by imaging and clinical presentation, out of which 20 patients didn't need intervention before the definitive surgery, 20 patients were intervened with ETV, 14 patients with VP-shunting, and 3 patients with EVD.

The commonly performed concurrent procedure intraop was EVD either for drainage or prophylaxis (n=31, 12.1%), followed by frontal sinus obliteration/cranialization for breech of sinus (n=16, 6.3%).

The infratentorial procedures were associated with higher rate of EVD insertion whether open or closed (n=37) and transfer to ICU (n=36).

Type of Surgery	Frequency	Percent (%)
Supratentorial craniotomy for extra axial tumor/mass lesion	85	33.2
TSS	46	18.0
Supratentorial craniotomy for intra axial tumor or mass lesion	41	16.0
Infratentorial craniotomy for intra axial tumor or mass lesion	24	9.4
Infratentorial craniotomy for extra axial tumor or mass lesion	21	8.2
ETV only	17	6.6
Occipitocervical decompression	11	4.3
Miscellaneous	7	2.7
VP shunt only	4	1.6
Total	**256**	**100.0**

Table 2: Type of elective cranial surgeries performed from November 1, 2018 - September 30, 2019.

5.3 Diagnosis of PCNSI

The diagnosis of PCNIs was entertained in 41 cases (16%), but only 29 cases (11.3%) fulfilled the CDC criteria and were subjected to further analysis.

Among the 29 cases, 62.1% were males. The mean age was 27.6years(SD±17.1), ranging from 2 to 61 years.

More than half of the infections, 16 cases (55.2%) were in those patients operated for infratentorial mass lesions (accounting for 35.6% of the infratentorial craniotomies). Seven cases (24.1%) were in the supratentorial group (accounting for 5.6% of the supratentorial craniotomies).

There is significant correlation between infratentorial surgeries and diagnosis of PCNSIs ($p<0.001$).

Variables	Frequency	Percent (%)
Sex		
Female	11	37.9
Male	18	62.1
Age in years		
≤10	5	17.2
11-20	5	17.2
21-30	9	28.1
31-40	5	17.2
41-50	1	3.4
51-60	3	10.3
61-70	1	3.4

Type of Surgery		
Supratentorial craniotomy for extraaxial tumor/mass lesion	6	20.7
Occipitocervical decompression	1	3.4
Supratentorial craniotomy for intraaxial tumor or mass lesion	1	3.4
Infratentorial craniotomy for extraaxial tumor or mass lesion	7	24.1
Infratentorial craniotomy for intraaxial tumor or mass lesion	9	31.0
TSS		
ETV only	3	10.3

Table 3: Summary of socio-demography and type of surgery in patients diagnosed with PCNSI

5.4 Perioperative factors analysis

Twelve clinical, pre-, intra- and post- surgical parameters (i.e. age, sex, systemic medical illness, preoperative steroids, preoperative KPS, type of surgery, duration of surgery, days of stay in the ICU, days of stay with EVD open, CSF leak, superficial incisional infections and reoperations excluding CSF diversions and wound revisions) were subjected for analysis.

Bivariate correlational analysis assuming normal distribution of variables (Pearson correlation) picked type of surgery, days of stay in the ICU, days of stay with EVD open, CSF leak, superficial incisional infections, reoperation and duration of surgery as having strong correlation with diagnosis of infection. This was also crosschecked with partial correlational analysis of variables but shows significant intervariable correlation with infratentorial surgeries versus total days of EVD stay, superficial incisional infections and total days of ICU stay. So, this variable was controlled while doing Multivariate binary logistic regression analysis. (Table 4)

	Fulfils criteria for the CDC infection diagnosis	
Presence of CSF leak or not	Pearson Correlation	.525**
	Sig.	<.001
	N	256
Total days of stay in the ICU	Pearson Correlation	.409**
	Sig.	<.001
	N	256
Superficial incisional infections	Pearson Correlation	.493**
	Sig.	<.001
	N	256
Reoperations other than CSF diversions and wound revisions	Pearson Correlation	.199**
	Sig.	.001
	N	256
Total days with EVD open	Pearson Correlation	.401**
	Sig.	<.001
	N	256
Duration of surgery	Pearson Correlation	.180**
	Sig.	.004
	N	256

Table 4: Variables with strong correlation with diagnosis of infection in bivariate correlational analysis

Comparison of means of the groups with and without PCNSIs was done for the continuous variables total days of with EVD open and total days of ICU stay, with independent sample T-test. The mean days of stay with open EVD for patients without PCNSIs was 0.3 days (SD 1.9) versus 5.2 days (SD 9.4) in the group with PCNSIs. The mean days of stay in the ICU in patients without PCNSIs is 1.4 days (SD 3.6) versus 7.8(SD 9.1) Significant correlation (*p<0.001*) for both continuous variables was detected at cut point of >3days.

A total of 33(12.9%) patients had CSF leak out of which 18(54.5%) patients developed PCNIs. Twenty patients (7.8%) had superficial incisional infections out of which 13(65.0%) patients developed PCNIs.

After performing multivariate binary logistic regression analysis of the variables (ICU stay >3 days, EVD stay >3 days, presence of CSF leak, reoperations and duration of surgery), two of the variables i.e. reoperations and duration of surgery had no significant association with the development of PCNSIs.

Summary of the significant variables, their significance level, 95% CI and Odds ratio is depicted below. (Table 5).

		Fulfills criteria for the diagnosis of infection		Sig.	Exp(B)	95% C.I. for EXP (B)	
		No	Yes			Lower	Upper
ICU stay above 3 days	No	206	14	.010*	5.594	1.503	20.830
	Yes	21	15				
EVD stay above 3 days	N0	221	21	.019*	7.020	1.383	35.643
	Yes	6	8				
Presence of CSF leak	No	212	11	<.001*	22.957	6.464	81.540
	Yes	15	18				
Superficial incisional infections	No	220	16	.021*	5.153	1.276	20.806
	Yes	7	13				
Reoperations other than CSF diversions and wound revisions	N0	222	25	.070	5.490	.872	34.574
	Yes	5	4				
Duration of surgery	<4hrs	132	8	.819	1.126	.407	3.113
	≥4hrs	95	21				

Table 5: Crosstabulation and multivariate binary logistic regression results for strongly associated factors with PCNSIs.

5.5 Clinical and Microbiologic profile of patients diagnosed with PCNSIs

The median postoperative day for the diagnosis of PCNSIs is 9th day (there are cases diagnosed as early as 4th day and as late as 24th postop day). All patients diagnosed with PCNIS had fever record of ≥38^{0}C and 75.9% had meningismus (meningeal signs). Radiologic diagnosis was made in 17.2% of the cases.

Seventeen (58.9%) patients had growth of etiologic organisms from samples and five patients (17.2%) from blood cultures.

The commonest pattern of infection is meningitis/ventriculitis (n=24, 82.8%) followed by subgaleal abscess/ bone flap infections (n=4, 13.8%) and brain abscess (n=1, 3.4%). PCNSIs were related to instrumentation (EVD/ VP-shunt) in 12 (41.4%) patients.

		Frequency	Percent (%)
Fever ≥38⁰C	No	0	0
	Yes	29	100
Meningismus	No	7	24.1
	Yes	22	75.9
Headache	No	13	44.8
	Yes	16	55.2
Deterioration in mentation or confusion	No	13	44.8
	Yes	16	55.2
Radiologic evidence of infection	No	24	82.8
	Yes	5	17.2
Growth of organisms on CSF/Surgical tissue/ abscess at least 1x	No	12	41.4
	Yes	17	58.6
Growth of organisms on blood culture at least 1x	No	9	31.0
	Yes	5	17.2
	NA	15	51.7
Infection diagnosed	Meningitis/Ventriculitis	24	82.8
	Subgaleal abscess/bone flap infections	4	13.8
	Brain abscess	1	3.4
Instrument related(EVD/ VP shunt) infections	No	17	58.6
	Yes	12	41.4

Table 6: Summary of clinical profile of patients with PCNSIs.

Among the 29 patients with PCNIS a total of 77 culture and sensitivity tests were done, 62 samples from CSF /surgical tissue/abscess and 15 of them were from blood. Thirty- five (45.5%) of the samples grew organisms, 29 of them were from CSF/abscess/surgical tissue and 6 from blood samples. Organisms isolated from CSF/abscess/surgical tissue includes *Acinetobacter spp.* (n=11, 37.9%), *Klebsiella pneumoniae* (n=8, 27.6%) and *Pseudomonas spp.* (n=2, 3.2%). CoNS is isolated only in one CSF sample (1.6%), but it was the commonest organism cultured from three blood samples (20%).

More than one etiologic organism was identified in seven patients (2 from a single sample), Klebsiella pneumoniae and Acinetobacter spp. are the joint organisms commonly identified in this scenario (4 patients).(Table - 7)

Organisms identified	Frequency
CSF culture	
No Growth	**33(53.2%)**
Acinetobacter spp.	11(17.7%)
Klebsiella pneumoniae	8(12.9%)
Pseudomonas spp.	2(3.2%)
Staphylococcus aureus	1(1.6%)
CONS	1(1.6%)
Bacillus spp.	1(1.6%)
Enterococcus spp.	1(1.6%)
Klebsiella ozenae	1(1.6%)
Klebsiella oxytoca	1(1.6%)
Proteus mirabilis	1(1.6%)
E. Coli	1(1.6%)
Total	62

Blood Culture	
Not done	15
No Growth	9
CONS	3
Klebsiella pneumonia	2
Colynebacter spp.	1

Table 7: Etiologic organisms identified from CSF samples, surgical tissues/abscess and blood cultures

Sensitivity tests done for *Acinetobacter spp.* show 100% resistance for Ceftazidime (5 cases), 80% resistance for Meropenem (8 cases) and 50% resistance for Amikacin (4 cases). Concerning *Klebsiella pneumoniae* 83.3% show resistance for Ceftazidime (5 cases), 37.5% show resistance for Meropenem (3 cases) and 0% resistance for Amikacin. All the sensitivity tests done for Ceftriaxone show resistance (100%). (Table 8)

Strain	Ceftazidime			Meropenem			Amikacin		
	S	R	NA	S	R	NA	S	R	NA
Acinetobacter spp.	0 (0%)	5 (100%)	6	2 (20%)	8 (80%)	1	4 (50%)	4 (50%)	3
Klebsiella pneumoniae	1(I) (16.7%)	5 (83.3%)	2	5 (62.5%)	3 (37.5%)	0	5 (100%)	0 (0%)	3

Table 8: Sensitivity pattern of commonly isolated Gram negative bacteria

S= sensitive, **R=** resistance, **I=** intermediate sensitivity, **NA=** Not done

5.6 Treatment outcome, Morbidity and Mortality

All patients diagnosed with PCNIs were treated with antibiotics. First line of antibiotic regimen (Ceftazidime + Vancomycin) were given for 26 patients (89.7%) but in 50% of these patients the regimen changed to a second line (Meropenem ± Vancomycin). Four patients were treated with Amikacin/ Ciprofloxacin/Linezolid as third line regimen. Additional Intrathecal treatment were given in three patients, (i.e. Gentamycin in 2 and Colistin in one).

Seventeen patients (58.6%) had documented response for antimicrobial therapy with improved clinical parameters. Four patients deteriorated despite treatment and were taken by family members against medical advice.

The overall surgical mortality is 9.8% (n=25). Mortality in patients with PCNSIs is 27.6 % (n=8). Deaths in five of the patients was documented as attributable to sepsis or neurologic complications of infection. So PCNIs may contribute to 20% of the overall surgical mortality. (Table 9)

		Frequency	Percent (%)
Overall morbidity & mortality			
Overall surgical mortality	Alive	231	90.2
	Death	25	9.8
Patient status at 30 days postop	In Hospital	20	7.8
	Discharged	214	82.8
	Death	22	9.4
Morbidity and mortality in patients diagnosed with infection			
Surgical mortality	Alive	21	72.4
	Death	8	27.6
Patient status at 30 days postop	In Hospital	16	55.2
	Discharged	7	24.1
	Death	6	20.7

Table 9: Mortality of patients diagnosed with PCNSIs

6. Discussion

There is no difference of proportions in socio-demographic data of patients with postsurgical CNS infections and study population in this series. Age has been a controversy in some of the studies, with relatively younger patients thought to have higher risk to develop PCNSIs.[11,28]

The incidence of deep incisional and organ space postoperative CNS infections is 11.3% (fulfilling the criteria by CDC/ NHSN implicating high likelihood of infection). This is higher than the range for typical rates of postop infections which is 1 – 10 %. This wide range of incidence is probably due to inconsistent diagnostic approaches that detect definite infection, non-uniform categorization of infection patterns and differences in methodology. Commonly reported incidence rates in the literature are summarized on Table 10.

	Incidence rates
McClelland et al. (2007)[3]	0.8%
Kourbeti et al. (2014)[15]	4.8%
Zhong-Hua et al. (2016)[28]	6.8%
Yi Fang et al. (2018)[17]	2.0%
Dwarakanath et al. (2011)[22]	2.2%
Sami et al. (2013)[27]	4.8%
Bryan et al. (2015)[23]	1.9%
Adeleye et. al. (2017)[10]	4.3%
Erman et. al. (2005)[16]	6.2%
Valentini et. al. (2008)[14]	0.72%
Zhan et. al. (2013)[11]	7.4%

Table10: Incidence of postoperative CNS infections in the literature

The common pattern of infection is meningitis/ventriculitis which consists of 82.8%. The rest are subgaleal abscess/ bone flap infections (13.8%) and brain abscess (3.4%). This is in accordance with most other studies.[2,3,10,17]

Infections are common in the infratentorial surgery group contributing to 55.2% of cases. This is also the case with Zhong hua et.al. showing tumors located in the infratentorial or intraventricular regions were more vulnerable to PCNSIs compared to supratentorial tumors.[28]

The possible explanation for this from our series is higher rates of CSF diversion procedures (EVD & VP-shunt) and prolonged ICU stay characteristic for these kinds of surgeries.

Significant portion of the infections (41.4%) are instrument related (EVD/VP-shunt).

Concerning the possible risk factors in our series there were no statistically significant associations of postoperative CNS infections with age, sex, presence of systemic medical illness, prolonged preoperative steroid use, poor preoperative performance status(unfit or KPS<70%), longer durations of surgery and early reoperations(other than wound revisions and CSF diversions). These factors are inconsistently mentioned in other studies. Our sample size might be a limitation on this regard.[2,3,11,14,28]

The strongest risk factor identified in this series is presence of CSF leak, increasing chance of developing infection ~22 times. This is the commonly identified risk factor with strong association in multiple other series.[3,11,25,28] The other risk factors identified are prolonged EVD stay (>3 days) (*OR= 7*), prolonged ICU stay (>3 days) (*OR= 5*) and superficial incisional infections (*OR=5*).

The CSF leak rate in our study is 12.9 % (vs. 62.1% in patients with PCNSIs). The incidence of superficial incisional infections is 7.8 % (vs. 44.8% in patients with PCNSIs).

Common clinical signs in patients fulfilling criteria for PCNSIs are fever >38^{0}C (100%), meningeal irritation signs (75.9%). Deterioration in mentation or confusion are also frequent (55.2%). The median post op day for the diagnosis of infection was 9th day, similar to Zhong with more than 80% of patients diagnosed within 2 weeks of surgery. [28]

The frequently isolated organisms are Gram negatives, mainly *Acinetobacter spp.* (37.9%) and *Klebsiella pneumoniae* (27.6%). This is in contrast to many reports that the common etiologic agents of postoperative CNS infections are CONS and *Staphylococcus aureus.*[9,11,16,17,28] But other studies also show similar microbiologic profile to us with *Acinetobacter baumanii* and *Klebsiella pneumoniae* being the commonly isolated etiologic agents.[10,12,13,22,24] The possible explanations for this are; indolent natures of gram positive infections contributing to decreased rates of diagnosis, higher rates of instrument related infections which are commonly associated with Hospital environment gram negative drug resistant bacteria or might be part of the shift of etiologic organisms noticed elsewhere.

There is high rate of resistance for commonly used antibiotics by Acinetobacter spp. which is the commonest etiologic agent in our series (100% for Ceftazidime, 80% for Meropenem and 50% for Amikacin).

All bacteria isolated are resistant for Ceftriaxone. This rise in multidrug resistant gram negatives is also an emerging problem in many centers in Africa and worldwide.[21,22,26,29] But we can see the rapid increase of resistant strains in our setup considering the relatively shorter period since we started using these antibiotics (Meropenem and Amikacin).

The surgical mortality in patients with PCNSIs is 27.6 % (vs. 9.8% overall surgical mortality). Though this study lacks systematic evaluation methods for causes of death, at least five patients had documented death attributable to sepsis or neurologic complications of infection. SO PCNSIs probably are responsible for ~20% of overall mortalities. This is comparable with Zhong Hua's report of 14 %.[28]

7. Study Limitation

This is a single institution study so results might not be applicable to other centers. The study duration and sample size might be a limitation not to pick potential risk factors other than mentioned here. This research was not designed to assess sterility techniques and surgical factors (sutures, incidents, central lines…) both intraop and in the postop period, and the administration of prophylaxis antibiotics which are important stages in avoiding postoperative CNS infections.

8. Conclusion

There is higher incidence of postoperative CNS infections (11.3%) in comparison to other studies. The moderately high rates of postsurgical CSF leak and superficial incisional infections are strong risk factors in our setup. Prolonged EVD stay and prolonged ICU stay are also risk factors especially for Gram negative bacterial infections. The emerging multidrug resistance patterns of *Acinetobacter spp.* are also a challenge in our setup. Mortality from PCNSIs has a significant contribution to the overall surgical mortality (~20%).

9. Recommendations

Based on our analysis of postoperative CNS infections at TASH, Neurosurgery unit we recommend on the following measures to decrease the incidence and improve treatment outcomes.

Concerning CSF leaks, attention to meticulous dural closure, early identification and aggressive treatment of hydrocephalus might improve the infection rates. This also applies to wound cares both intraop and postop. There should be a lower threshold for initiating diagnostic workups and treatment in patients with the risk factors mentioned.

There is a high rate of resistance (~100%) for the routine prophylaxis antibiotics (Ceftriaxone) we use in our setups. There is also an alarming increase in multidrug resistant gram negatives *(Acinetobacter spp. and klebsiella pneumonia).* The authors strongly recommend systematic reevaluation of the Hospital microflora and resistance patterns and change or modification of both prophylactic and firstline therapeutic antibiotics. Reevaluation of decontamination practices and other sterility techniques of ICU tools (ventilations, suctioning, beds…) might help in decreasing rate of colonization of incision sites and drainage tubes by organisms particularly Gram negative bacteria.

Due to the complexities and challenges in managing cases with multidrug resistant organisms, we believe multidisciplinary care by actively involving infectious disease specialists helps a lot.

10. Acknowledgement

I would like to forward my gratitude to my advisors and mentors Dr. Abat Sahlu and Dr. Thomas Bogale. I would also like to thank my fellow residents Dr. Bethlehem Yishak, Dr. Merhawi Leake and Dr. Samuel Masresha for their help in collecting data.

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Citation: Gizaw A, Sahlu A, Bogale T "Emerging Antibiotics Resistance Patterns in Postcranial Surgery CNS Infections, A Tertiary Center Experience". SVOA Neurology 2:5 (2021) Pages 162-175.