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Differential bacteriology of extradural, subdural, and intra-parenchymal suppuration at Chris Hani Baragwanath Academic Hospital (CHBAH): a 5-year review of records

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Title: Differential bacteriology of extradural, subdural, and intra-parenchymal suppuration at Chris Hani Baragwanath Academic Hospital (CHBAH): a 5-year review of records

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirement for the degree of Master of Medicine in Neurosurgery.

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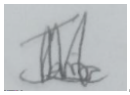
Declaration

I, Olalekan Maroof Jaiyeola, hereby declare that this thesis is my own work. It is being submitted for the Degree of Master of Medicine in the specialty of Neurosurgery at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other University.

Signature: ……..

……25th…day of October……..2020……

Dedication

Dedicated to the glory of God Almighty.

Dedicated to my loving family whose support has been invaluable through the course of this study.

Acknowledgement

My profound gratitude to my supervisors, Prof John Richard Ouma and Dr Prenika Jaglal for their advice and guidance towards the completion of this study. I am also grateful to the staff of National Health Laboratory Service (NHLS), Chris Hani Baragwanath Academic Hospital Neurosurgery and Radiology Departments; for their assistance in obtaining the required data for this study. My gratitude is also extended to a friend and colleague, Dr Jimi Fadahun for his assistance with the data analysis.

Abstract

This study reports on 365 patients who presented to Chris Hani Baragwanath Academic Hospital between July 2013 and June 2018, with intracranial suppuration of which 240 patients had surgical drainage. The study aimed at determining differences in the types of bacterial isolates and their respective antimicrobial susceptibility profiles from Extradural Empyema (EDE), Subdural Empyema (SDE), and Brain Abscess (BA). EDE accounted for 37 (15.4%) of the intracranial collections; SDE group were 85 (35.4%); while BA accounted for 118 (49.2%).

One hundred and thirty (54.2%) of the patients who had surgical drainage had positive bacterial cultures from an intracranial collection while the remaining 110 (45.8%) had negative cultures.

Males contributed to the majority of the patients with intracranial suppuration; 172 males (71.7%) and 68 females (28.3%), respectively. This was attributed to a larger number of male patients with intracranial infections as a result of trauma.

A total of 167 bacterial isolates were cultured in 140 patients as some specimens grew multiple organisms. Twenty nine organisms were cultured from EDE, 62 from SDE and 76 from BA. Gram positive bacteria were the most common organisms cultured, comprising 53% of total bacterial isolates. Fifty nine percent of EDE (17 out of 29) and 68% SDE (42 out of 62) isolates were Gram positive organisms. BA cultured mostly Gram negative organisms (43%) followed by Gram positive isolates which made up 38% (29 out of 76). Some patients with Human Immunodeficiency Virus (HIV)-related BA were found to have opportunistic infections such as Tuberculosis and Nocardia.

Overall, *Staphylococcal* and *Streptococcal species* were the most common organisms cultured. EDE, SDE, and BA had a frequency of *Staphylococcal* culture of 76% (13/17), 33% (14/42), and 52% (15/29), respectively. EDE, SDE, and BA had a frequency of *Streptococcal* culture of 12% (2/17), 52% (22/42), and 38% (11/29) respectively.

The antimicrobial sensitivities of the specific organisms isolated were similar irrespective of the cavity (EDE, SDH, or BA) from which they were obtained. The default empiric treatment

of ICS was a broad spectrum Cephalosporin (covering GPB and GNB) and anti-anaerobic agent (Metronidazole). Based on the findings of this study, it is recommended that empiric antimicrobial choice should be based on source of primary infection. BA resulting from different sources of infection have higher incidence of GNB and may require the use of Carbapenems if resistant to commonly used antibiotics. Post neuro-surgical nosocomial infections have higher incidence of Staphylococcal and Extended Spectrum Beta Lactamase (ESBL) Gram negative infections, hence, may require Vancomycin and a Carbapenem empirically.

Patients with associated immunodeficiency may be suspected of having opportunistic infections, e.g. Tuberculosis or Nocardia if other sources of infections were ruled out and radiologic imaging are in support of such infections.

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List of Abbreviations

AIDS - Acquired Immune Deficiency Syndrome

BA - Brain Abscess

Bactrim – Trimethoprim + Sulfamethoxazole (TMP+SMZ)

CCHD - Congenital Cyanotic Heart Disease

CDW - Corporate Data Warehouse

CEO - Chief Executive Officer

CHBAH – Chris Hani Baragwanath Academic Hospital

CNS - Coagulase Negative *Staphylococcus*

CRE - Carbapenem Resistant *Enterobacteriaceae*

CRP - C-Reactive Protein

CSF - Cerebrospinal Fluid

CT - Computerised Tomography

DCT - Double Carbapenem Therapy

E.Coli - *Escherichia coli*

EDE - Extradural Empyema

ESBL - Extended Spectrum Beta-Lactamase

GIT - Gastrointestinal Tract

GNB - Gram Negative Bacteria

GPB - Gram Positive Bacteria

GSW - Gunshot Wound

HCT - Haematocrit

HIV - Human Immunodeficiency Virus

ICP - Intracranial Pressure

ICS - Intracranial Suppuration

MC&S - Microscopy, Culture, and Sensitivity

MDR - Multidrug Resistant

MIC - Minimum Inhibitory Concentration

MRI - Magnetic Resonance Imaging

MRSA - Methicillin Resistant *Staphylococcus aureus*

MSSA - Methicillin Sensitive *Staphylococcus aureus*

MTB - *Mycobacterium tuberculosis*

NHLS - National Health Laboratory Service

PDR - Pan Drug Resistant

PO_2 - Partial Pressure of Oxygen

SDE - Subdural Empyema

SMZ - Sulfamethoxazole

Spp - *Species*

TB - Tuberculosis

TMP - Trimethoprim

UK - United Kingdom

US - United States

VRE - Vancomycin Resistant *Enterococcus*

XDR - Extensively Drug Resistant

1. INTRODUCTION

Intracranial suppuration includes Extradural Empyema (EDE), Subdural Empyema (SDE), and Brain (cerebral and cerebellar) Abscesses (BA). These conditions form a subset of intracranial infections for which surgical drainage of pus collection may be required. These infective conditions although relatively uncommon, could be serious and life-threatening. They are a source of significant morbidity and mortality, and a huge burden to the health care system. These conditions constitute a sizeable proportion of patients seen at Chris Hani Baragwanath Academic Hospital (CHBAH) neurosurgical unit on a daily basis. To minimise the impending morbidity and mortality, early commencement of an appropriate empirical antimicrobial regimen is essential for both surgically-treated and conservatively managed patients.

An EDE is a suppurative collection within the extradural space. The extradural space is a potential space bounded externally by the cranial bone and internally by the endosteal layer of the dura mater.

A SDE is a suppurative collection within the subdural space. The subdural space is bounded externally by the dural sheath and internally by the thin arachnoid mater.

A BA is the collection of pus in the substance of the cerebrum or cerebellum.

There seems to be a paucity of studies comparing the bacteriology of different suppurative collections of extradural, subdural and brain abscesses. The literature search did not reveal any comparative studies regarding the bacteriology of different suppurative collections, however, bacteriology of collections from different primary sources of infections have been well documented.

The aim of the study was to analyse the microbial profile of these intracranial collections and to determine whether there is a significant difference in their bacteriology. The findings of the study will help to guide our empiric antimicrobial choice for both surgically-treated and non-surgically managed cases.

1.1 LITERATURE REVIEW

Intracranial suppurations are classified according to their anatomical locations as extradural, subdural, and brain (cerebral/cerebellar) abscesses. They may also be classified according to their aetiologic microbial agents.

Suppurative intracranial collections may originate from infections of contiguous structures e.g. otitis media, dental infection, mastoiditis, and sinusitis. They may also be secondary to haematogenous spread from a remote site, especially in patients with cyanotic congenital heart disease; after skull fracture or neurosurgical procedures, and rarely following meningitis. No source of infection can be identified in 15%-20% of cases. BA and SDE constitute the 2 most common forms of intracranial suppuration.[1]

The bacteriology of EDE, SDE, and BA are identical to that of the primary sites of infection. High numbers of intracranial abscesses are polymicrobial.[2, 3] In a study in Vancouver, Canada, a study of a paediatric population showed EDE secondary to trauma or surgery to be due to Gram negative bacilli or *Staphylococcus aureus*. In cases due to otitis media, mastoiditis and sinusitis; *Streptococcus pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*, coagulase negative staphylococcus and anaerobes were the organisms cultured. In the same study, the most common isolate for SDE was *Streptococcus viridans*, which accounted for a third of the cases. Bacterial isolates from cerebral abscesses were identical to those recovered from the source of infection with *Streptococcus species* being the most frequently cultured organism.[3]

In a single site study in Istanbul, Turkey, analysis of 23 patients seen over a period of 15 years showed *Proteus mirabilis*, *Pseudomonas species*, *Peptostreptococcus species*, *Enterococcus avium, Mycobacterium tuberculosis* complex, and *Toxoplasma gondii* in 6 (37.5%) patients out of the 16 patients that had surgical pus drainage.[4]

In a United Kingdom (UK) paediatric series, out of 42 children, 17 had BA, 23 had SDE, while 2 had both BA and SDE. *Streptococcus anginosus* group organisms were the most common, accounting for 57% (13), while 10% (3) had resistant Gram negative pathogens. These pathogens were identified as *Enterobacter cloacae* resistant to amoxicillin and ceftazidime;

mixed growth *of Morganella morganii, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, all resistant to amoxicillin and ceftazidime.[5]

1.1.1 Epidemiology

A study in Transkei region of Eastern Cape, South Africa, showed an incidence of intracranial suppuration of about 1:100,000/year.[6] In the United States (US), before the Acquired Immune Deficiency Syndrome (AIDS) pandemic, BA were estimated to account for 1 in 10,000 hospital admissions or 1500-2500 cases annually, with a male to female ratio of 1.5-3:1.[1,9] Studies in South Africa and other non-African countries also showed an increased male to female ratio of 2:1 or higher. This may be due to increased rates of intracranial abscesses secondary to trauma in males.[6]

SDE is less common compared to BA in ratio of 1:5, and found in 32 of 10,000 autopsies. SDE is located in brain convexity in 70-80% of cases and parafalcine in 10-20% of cases.[9]

In another study, 145 patients were seen over a period of 8 years, 93 (64%) were males while 52 (36%) were females. There ages ranged from 1month to 61 years; of which 75% of the patients were in the age group 0-20 years.

Increased incidence of sinusitis-related Intracranial Suppuration (ICS) between June and August is associated with increased incidence of sinusitis during winter period.[6]

Intracranial suppuration, although uncommon, has a relatively higher incidence in the lower socioeconomic class where lack of modern culture techniques makes isolation of organisms difficult.[3, 7] The prevalence of ICS is higher in HIV infected people, usually caused by opportunistic Tuberculosis (TB), fungal, and protozoan infections.

In a Taiwanese study, pathogens and routes of infection in children and adults were found to be different.[8] Cyanotic congenital heart disease is a common predisposing factor in children.[3]

1.1.2 Morbidity and Mortality

Due to increasing availability of imaging techniques such as Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI), the mortality rate of brain abscesses has reduced

to less than 15-25%. Associated co-morbidities such as stroke, older age, septicaemia, pneumonia, and meningitis were associated with increased risk of in-hospital mortality. The rupture of a brain abscess is associated with higher mortality of about 80%. Frequency of neurological sequelae in survivors of brain abscesses vary widely between 20-79% and this is predicated on how quick a diagnosis is made and how soon appropriate treatment is commenced.[1]

1.1.3 Brain Abscess (BA)

Brain Abscess Pathogens

Pathogens vary with the primary source of infection. *Streptococcus species* is the most common organism seen in patients. Twenty to forty percent are anaerobic and microaerophilic organisms. Multiple organisms may be involved in 14-28% of cases and usually include anaerobes, commonly *Bacteroides species*. *Streptococcus anginosus* may be seen secondary to a fronto-ethmoidal sinusitis. Multiple organisms including anaerobic *Streptococci, Bacteroides species* and *Enterobacteriacae (Proteus species)* are found in cases secondary to an otitis media, mastoiditis or lung abscess. *Staphylococcus aureus* and *Enterobacteriacae* are seen in post-traumatic cases while *Staphylococcus aureus* and *Staphylococcus epidermidis* are seen in post neurosurgical procedures. In some series, cultures were negative in 0-43% of cases of BAs.[9]

Classification of BA causative organisms includes:

1. **Bacteria**- They are the commonest cause of intracranial abscesses and will be the focus of this study. Common organisms include *Streptococcus species*, *Staphylococcus aureus*, *Bacteroides* and *Listeria species*. Less commonly are Gram negative bacteria such as *Proteus species, Klebsiella species,* and *Escherichia coli*. ICS frequently originate from the infections of adjacent structures e.g. otitis media, dental infection, mastoiditis and sinusitis.[3]
2. **Fungi**- Organisms encountered in practice include *Aspergillus, Candida, Cryptococcus, Coccidiodes, Histoplasma* and *Blastomyces species*. The frequency of

fungal brain abscesses has increased because of the repeated use of broad-spectrum antibiotics, immunosuppressive drugs, corticosteroids or immunosuppressive diseases such as AIDS and TB.[9]

3. **Parasites:**

(a) Protozoa- These includes: *Toxoplasma gondii, Entamoeba histolytica, Trypanosoma cruzi* and *Schistosoma species*.

(b) Helminths- *Taenia solium* is a rare cause of intracranial infestation.

Predisposing Factors

BA may arise from haematogenous spread, contiguous spread from infected adjacent structures or by direct inoculation from trauma. Risk factors include pulmonary abscesses, arteriovenous fistulas, congenital cyanotic heart disease, immune compromised status, dental caries and procedures, chronic sinusitis and otitis media.[9]

Symptoms of a brain abscess are similar to other mass lesions in the brain, but they tend to progress rapidly as opposed to neoplastic lesions of the brain. Peripheral white blood cells may be normal or mildly elevated while C-Reactive Protein (CRP) is usually elevated.[9]

Streptococci are the most common organisms involved and it may be found in a polymicrobial infection in approximately 70% of cases.[9]

In another South African study, the predisposing factors were as follows in order of frequency:

- Oto-rhino infections (38%)
- Trauma (37%)
- Pulmonary infections (7%)
- Unknown causes (4%)
- Post-surgical (3.2%)
- Meningitis (3%)
- Cardiac (3%)[7]

In a case series at a children's hospital in Houston, Texas, 108 paediatric patients having mastoiditis with or without intracranial extension were reviewed. *Streptococcus pneumoniae* was found to be the most common organism cultured. Anaerobes were found in 29.4% of the patients with intracranial complications and in 5.7% of patients without an intracranial complication.[10] There was an increased incidence of anaerobic organisms in patients with an intracranial complication compared to those without intracranial complication, indicating the importance of anaerobic cover in empiric treatment.

In a Cambridge, UK study of 27 children aged 12.9 $^{+}$/$_{-}$3.4 years with sinogenic intracranial abscesses, *Streptococcus anginosus* were isolated in 67% (18) of cases.[11] Hence empiric treatment at this centre covers *Streptococcus anginosus.*

Fungi, *Mycobacterium* (MTB), and *Listeria monocytogenes* are common in immunocompromised hosts such as transplant and AIDS patients.

Worldwide, variations in microbiological profile of ICS have been observed hence this has necessitated a local study to determine the bacterial pathogen profile to guide empiric antimicrobial treatment.

Haematogenous spread

Abscesses that arise by haematogenous route are multiple in 10-50% of cases, with the chest being the most common source in adults. In children, Congenial Cyanotic Heart Disease (CCHD) has an estimated risk of BA in 4-7% of cases, especially in Tetralogy of Fallot. The increased Haematocrit (HCT) and low Partial Pressure of Oxygen (PO_2) provides a hypoxic environment suitable for abscess proliferation. Those with right to left (veno-atrial) shunts, additionally loose the filtering function of the lungs and the brain is a preferential site for this infection compared to other organs of the body.[9]

No source of infection can be identified in about 25% of cases.[9] A BA may follow a dental abscess and/or dental procedures as *Streptococcal* oral flora is frequently isolated.

Gastrointestinal Tract (GIT) or pelvic infections may be transmitted to the brain via the Batson's plexus of veins. In patients with septic embolisation; risk of BA is higher in tissues with previous infarction and ischaemia.[9]

Contiguous Spread

1. Contiguous spread from a purulent sinusitis is by local osteomyelitis or phlebitis of emissary veins, resulting usually in a singular lesion.[6] It is rare in infants because they lack aerated paranasal and mastoid air cells.[9] In the western world, this route has become less common due to improved treatment of sinus disease.

(a) Middle ear and mastoid air sinus infections: result in temporal lobe and cerebellar abscess formation. Risk of BA in an adult with chronic otitis media is approximately 1/10,000 per year, but the life time risk is 1 in 200.[9]

(b) Ethmoidal and frontal sinusitis result in frontal lobe abscesses.

(c) Sphenoid sinusitis is the least common sinusitis but with high incidence of intracranial complications due to venous extension to the adjacent cavernous sinus, resulting in a temporal lobe abscess.[9]

2. Odontogenic infection leads to frontal lobe abscesses and may be seen about 4 weeks post dental procedure.[9] This may also spread haematogeneously.

Penetrating Cranial Trauma or Post Neurosurgical Procedures

BA may arise post-operatively particularly when air sinuses are traversed. Abscesses following Intracranial Pressure (ICP) monitoring devices and application of skull traction devices have been reported. Risk of a BA following a Gunshot Wound (GSW) to the head is low with the use of prophylactic antibiotics except in cases of Cerebrospinal Fluid (CSF) leak not surgically repaired following traversal of an air sinus.[9] Abscess following GSW may be treated by aspiration like other cases. Open surgery and debridement of foreign material and devitalised tissue may also be required.

Treatment of Brain Abscesses (BA)

There is no single best treatment for a BA. Treatment may involve surgical drainage or excision of a primary site of infection of the BA as well as long term antibiotic use. In patients with a BA, tissue diagnosis by Microscopy, Culture, and Sensitivity (MC&S) is essential; preferably before commencement of antibiotics.[9] Of note, in our practice at CHBAH, many patients are already commenced on broad spectrum antibiotics for the primary infection before the diagnosis of an intracranial infection is made. This may impact on the ability to get a viable culture from the pus specimen derived during surgery. Purely medical treatment of an early abscess (cerebritis stage) is controversial. Medical treatment alone may be considered in abscesses smaller than 2.5 cm in diameter, multiple small abscesses, and those in deep or dominant locations or for patients who are extremely poor surgical candidates.[3, 9]. However, in one series, no abscess larger than 2.5 cm resolved without surgical therapy.[9]

Blood culture is rarely helpful as most are negative for bacterial growth. Lumbar punctures should be avoided to prevent coning. Anticonvulsant for seizure treatment or prophylaxis is advocated. The use of steroid is also controversial; although it does help to reduce oedema but may also impede therapy.[9] Corticosteroids, mannitol and hyperventilation may be beneficial where there is increased intracranial pressure. Routine use of corticosteroids in the absence of increased intracranial pressure is not recommended.[2] Steroids can retard the encapsulation process, increase necrosis, reduce antibiotic penetration into the abscess, and alter CT scans findings. It can also produce a rebound effect when discontinued. If used to reduce cerebral oedema, it should be for a short period of time.[1]

Antibiotics- the choice of antibiotics when the causative organism is unknown depends on the epidemiology of the suspected organisms in the unit as well as the primary source of infection. If no history of trauma and risk of Methicillin Resistant *Staphylococcus aureus* (MRSA) is low, treatment advocated is a third generation Cephalosporin and Metronidazole or Chloramphenicol.[9]

Antifungal- fungal isolates are treated with broad spectrum antifungals; Amphotericin B 0.5-1mg/kg/day is used.

Antiparasitic agents- In AIDS patients, *Toxoplasma gondii* is a common pathogen, and empiric Sulfadiazine plus Pyrimethamine is used.[9]

Duration of treatment for bacterial isolates – 6 to 8 weeks of intravenous antibiotics is recommended. Duration of treatment may be reduced if surgical excision with the abscess capsule was undertaken. Oral antibiotic is continued after intravenous treatment. Five to twenty percent of brain abscesses may recur within 6 weeks of discontinuing antibiotics.[9]

Outcome- In the pre-CT era, mortality rate ranged between 40-60%. Improvement in modern imaging with CT and MRI, antibiotic therapy and surgery, has reduced mortality to 10%; however, morbidity remains high with permanent neurological deficit or seizure in about 50% of cases. A worse prognosis is associated with poor neurological function, intraventricular rupture of abscess, and almost 100% mortality with fungal intracranial abscesses in transplant recipients.[9]

Unusual Organisms Producing an Abscess

Nocardia- Nocardiosis is primarily caused by *Nocardia asteroides (*previously called *Nocardia asteroides complex)*, a soil-borne aerobic actinomycete (a bacterium, not a fungus), that is usually inoculated through trauma or inhaled via the respiratory tract and produces a localised or disseminated infection. Other *Nocardia* species such as *Nocardia brasiliensis* are less common. Nocardia is responsible for 2% of BAs, the majority of which is *Nocardia asteroides*.[9] It is seen in patients with chronic debilitating illnesses which includes:

a. Neoplasm e.g. leukaemia, lymphoma
b. Conditions which require prolonged corticosteroid use
c. Cushing's disease
d. Paget's disease of bone

e. AIDS

f. Renal or cardiac organ transplant recipients

The diagnosis is suspected in high risk patients such as above.

Diagnosis: brain biopsy might not be necessary in a patient with confirmed Nocardia from extracranial sites except in AIDS patients as the risk of a polymicrobial infection or infection plus tumour particularly lymphoma is considerable.[9]

Surgical Treatment: as for other BAs by means of burrhole drainage or craniotomy excision of the brain lesion(s).

Medical Treatment: primary choice is Bactrim/Cotrimoxazole (Trimethoprim, TMP + Sulfamethoxazole, SMZ), start with 15mg/kg/day of TMP and 75mg/kg/day of SMZ ivi or par oral in 2-4 divided doses. After 3-4weeks, decrease to 10mg/kg/day of TMP in 2-4 divided doses. Serum levels of the medication should be monitored. Addition of Imipenem and Amikacin empirically to Bactrim provides enhanced antimicrobial activity.

Duration of treatment: because of a risk of relapse, treatment is recommended for at least 12 months in patients with BA.

1.1.4 Subdural Empyema (SDE)

This refers to pus collection in the subdural space which has no anatomic barrier to spread. Antibiotic penetration of the subdural space is poor. SDE may be complicated with brain abscesses in a number of cases. Cortical venous thromboses with risk of venous infarction or localised cerebritis may occur.[9]

Aetiology: SDE usually result from direct extension of local infection and rarely from septicaemia. Spread of infection may be via the valveless deploic veins often resulting in thrombophlebitis. In the pre-antibiotic era, chronic otitis media was a leading cause of SDE but has now been replaced by paranasal sinus disease, especially with frontal sinus involvement.[9] It may also result from mastoid sinusitis. Rarely it may result from cranial traction or rarely seen as a result of secondary infection of chronic subdural haematoma, traumatic skull fractures or penetrating injuries.

Organisms: as in brain abscess, varies depending on the source of infection.

Treatment: as for brain abscess, may include surgical and medical treatment.

Outcome: neurological deficit in 50% of cases on discharge. Age above 60 years, obtundation or coma at presentation, SDE resulting from trauma or surgery has a worse prognosis. Fatal cases may have venous infarction of the brain. Some patients may have persistent seizures, residual hemiparesis and mortality may be considerable depending on the extent of the disease.

1.1.5 Extradural Empyema (EDE)

This refers to extradural space suppurative collection. Cranial EDE occurs less frequently compared to SDE and BA but also has a potentially devastating disease process if not properly managed. In a study in Durban, South Africa, out of 4623 cases of intracranial sepsis over a period of 15 years (1983-1997), only 82 (1.8%) were EDE. One (1.2%) patient with EDE died in this series. The global outcome of EDE in terms of morbidity and mortality is good compared to SDE.[12]

The bacteriology of EDE is similar to both SDE and BA depending on the site of primary infection and patient population. Sterile cultures (no organism growth) were found in 12 (14.6%) patients and 2 organisms were isolated in 5 (6.1%) patients. *Streptococcus anginosus* was the commonest organism isolated in 8 (9.8%) patients with chronic otogenic sepsis. *Staphylococcus aureus* was cultured in 5 (6.1%) patients, all of which were traumatic EDE.[12]

1.2 AIM

This study aimed to determine the bacterial pathogens responsible for extradural, subdural, and brain intra-parenchymal abscess at CHBAH from July 2013 to June 2018 in order to guide empiric treatment.

1.3 OBJECTIVES

(i) To describe the demographics of intracranial suppuration at CHBAH

(ii) To determine the bacterial profile of EDE, SDE, and BA of the sample population.

(iii) To determine if there is a significant difference in the microbial pattern of EDE, SDE, and BA.

(iv) To determine the antimicrobial susceptibility profile/antibiogram of bacterial isolates involving the different intracranial suppurations.

2. METHODS

2.1 STUDY DESIGN

A retrospective review of patients' records was performed.

2.2 SITE OF STUDY

The study was conducted at the Neurosurgery Department, Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa. The neurosurgical unit of the hospital serves a large part of Johannesburg city, with an annual total patient admission rate of about 1,850. Patients with intracranial suppuration from different departments within the hospital as well as from other referring hospitals are accepted for admission into the unit if the intracranial collection is considered appropriate for surgical drainage.

2.3 STUDY POPULATION

The study population included patients of all ages presenting with surgically treated intracranial suppuration at CHBAH neurosurgery department over the period of study (July 2013-June 2018). This centre had approximately 70 to 75 cases of intracranial suppuration per year (total of 365 for the period of study), of which 48 had surgical intervention.

2.3.1 Sample size including statistical rationale

Over a study period of 5 years, 240 patients with intracranial suppuration were treated surgically. One hundred and thirty of these patients had a total of 167 organisms isolated from their pus specimens, while the remaining 110 patients had culture negative pus specimens. This was due to the fact that some specimens had polymicrobial growth.

2.3.2 Inclusion Criteria

- All patients of all ages with surgically drained intracranial suppuration at CHBAH during period of study.
- All patients with positive bacterial cultures of pus from an intracranial suppuration.
-

2.3.3 Exclusion Criteria

- All participants with incomplete microbiological data e.g. lost pus specimens as well as lost or incomplete hospital records.

2.4 MEASURING TOOL OR INSTRUMENT

- A data collection sheet containing patient's clinical data, radiological images as well as bacterial identification and anti-microbial sensitivity profile of intracranial pus specimens were used (see appendix 1).

2.5 DATA COLLECTION

- This study was conducted retrospectively over a period of 5 years (July 2013-June 2018); as approved by the ethics committee and neurosciences assessor group.
- Patients with surgically treated intracranial suppuration were identified from the ward's admission and discharge records.
- Relevant demographic data were obtained from patient records.

- Intracranial pus specimen Microscopy, Culture and Sensitivity (MC&S) results were supplied by the NHLS Corporate Data Warehouse (CDW); and radiologic image reports were obtained from radiology database respectively.

2.5.1 Variables

The following variables were retrieved from the patients' records

- Age
- Gender
- Types of intracranial abscess (EDE, SDE, or BA)
- Types of bacterial organisms in EDE, SDE and BA
- Sources of infection and/or predisposing conditions
- Antimicrobial sensitivity profile of cultured bacterial organisms from intracranial pus specimens

2.6 DATA ANALYSIS

Data was collected and entered into an MS excel sheet and then transferred to Stata 15 for statistical analysis.

1. STATA 15.0 was used for data cleaning and analysis.
2. Descriptive statistics was used to describe participant's biodata: age, gender, microbial pattern and antimicrobial sensitivity. Frequency, mean, standard deviation, and ranges were reported as appropriate.

Table 2.1: Below is a table illustrating the data analysis

Objective	**Data test/tool**	**Outcome measures**
1. To describe the	Descriptive statistics Gender	Frequencies and percentages.

demographics of intracranial suppuration at CHBAH.	Age	Mean and Standard deviation.
2. To determine the microbial profile of EDE, SDE and BA	Descriptive statistics Identification of bacterial organisms cultured from data provided by the NHLS CDW.	Frequencies and percentages of bacterial isolates.
3. To determine the anti-microbial sensitivity profile of bacteria isolated from an intracranial suppuration.	Descriptive statistics Describe the antibiogram of the bacterial isolates from data provided by the NHLS CDW	Percentage susceptibility of bacterial isolates to their corresponding antibacterial agents.

2.7 ETHICS

A written consent was obtained from the Chief Executive Officer (CEO) of CHBAH prior to commencement of the study for the use of patients' hospital records. The approval of University of the Witwatersrand Human Research Ethics Committee for this study was also obtained with clearance certificate M180735 issued. Permissions were obtained from CHBAH radiology department and NHLS CDW for access to the brain CT and pus MC&S databases, respectively.

All patient-identifying information such as names and hospital numbers were omitted from the data sheets and only a patient allocation tracking number and laboratory result tracking reference were used.

2.8 LIMITATIONS

Some of the patients with the pathology under study were already commenced on antibiotics before referral to this study centre. This may have impacted on the microbial culture yield, hence the amount of negative culture specimens (110/240) recorded.

A number of patients were considered not surgical candidates for drainage of their intracranial collection based on clinical grounds and radiological location/size of the lesion. This had limited the study sample size.

3. RESULTS

3.1 RECORDS REVIEWED

Over a period of 5 years, 1st July 2013 to 30th June 2018, 365 cases of intracranial suppuration were seen at CHBAH, of which 240 (66%) of them were surgically drained. The surgically drained patients had pus specimens submitted to the National Health Laboratory Services (NHLS) microbiology laboratory for microscopy, culture and sensitivity testing. A hundred and thirty of these specimens had positive bacterial growth of at least one organism. A total of 167 bacteria were isolated from these specimens.

Table 3.1: Total Yearly Distribution of Intraoperative Pus Specimens 2013 -2018

Year	**No of Specimen**
2013 (July-Dec)	6
2014	36
2015	55
2016	73
2017	44
2018 (Jan-June)	26
Total	**240**

3.2 AGE

There was a wide age distribution of patients with intracranial suppurative conditions seen during the period of study, ranging from infants to the elderly in their seventies. Of note, these cases were notably low in the extremes of ages as shown in table 3.2 below.

Table 3.2: Age Distribution of Intracranial Suppuration

Age Range (Years)	Frequency	Percentage
Infants	2	0.8%
1-5	6	2.5%
6-10	21	9%
11-20	85	35.4%
21-30	40	17%
31-40	29	12%
41-50	21	9%
51-60	21	9%
61-70	14	6%
71-80	1	0.4%
Total	**240**	**100%**

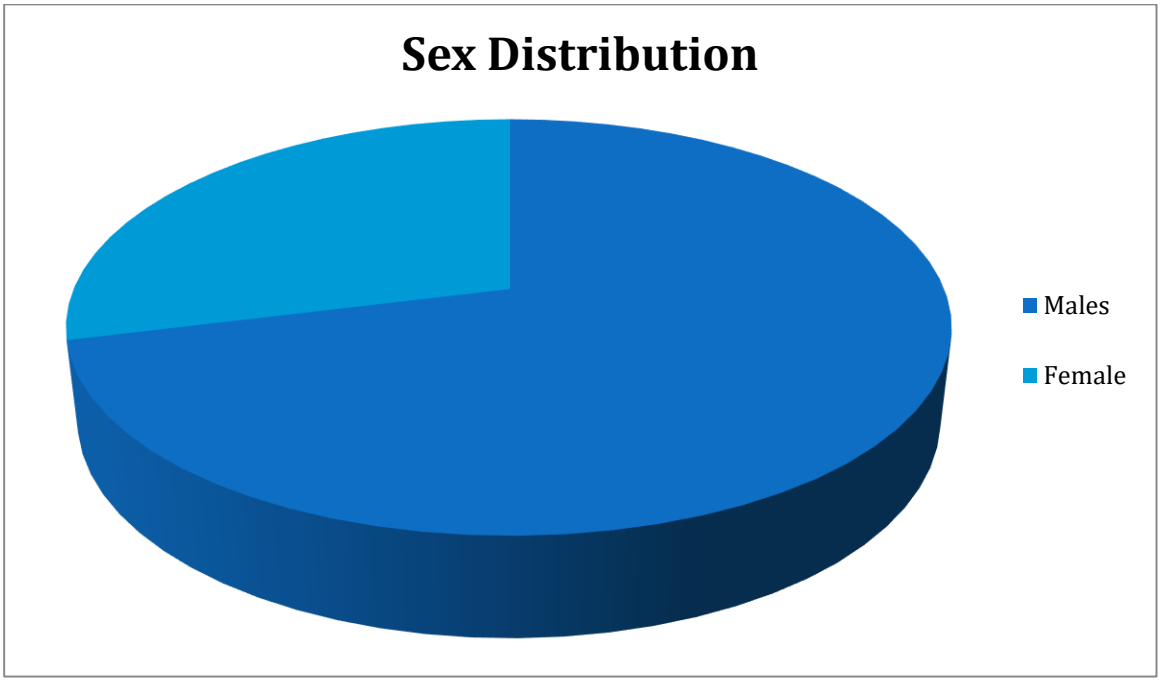
3.3 GENDER

Gender distribution showed a male preponderance of 71.7% (n=172) and female 28.3% (n=68). Below is the yearly gender distribution of the patients, table 3.3.

Table 3.3: Yearly gender distribution

2013 July-Dec		2014		2015		2016		2017		2018 Jan-June	
M	F	M	F	M	F	M	F	M	F	M	F
4	2	25	11	40	15	55	18	27	17	21	5

Figure 3.1: Gender Distribution



Year 2013 and 2018 were not full year data, but 2nd (July 2013 to December 2013) and 1st (January 2018 to December 2018) halves of the years, respectively.

3.4 TYPES OF INTRACRANIAL ABSCESSES

Patients with intracranial suppuration presented with either an extradural, subdural or brain abscess. Below is the distribution of the surgically-treated intracranial suppuration during the period of study, table 3.4.

Table 3.4: Frequencies of EDE, SDE, and BA

2013 July-Dec			2014			2015			2016			2017			2018 Jan-June			
EDE	**SDE**	**BA**	**EDE**	**SDE**	**BA**	**EDE**	**SDE**	**BA**	**EDE**	**SDE**	**BA**	**EDE**	**SDE**	**BA**	**EDE**	**SDE**	**BA**	**TOTAL**
3	1	2	9	14	13	3	20	32	8	26	39	8	15	21	6	9	11	240

Table 3.5: Total EDE, SDE, and BA 2013-2018

Intracranial Suppuration	Frequency	Percentage
EDE	37	15.4%
SDE	85	35.4%
BA	118	49.2%
TOTAL	**240**	**100%**

Table 3.6: Yearly Mean Distribution of EDE, SDE, and BA

Intracranial Suppuration	Frequency	Mean/Year
EDE	37	7.4
SDE	85	17
BA	118	23.6
TOTAL	**240**	**48**

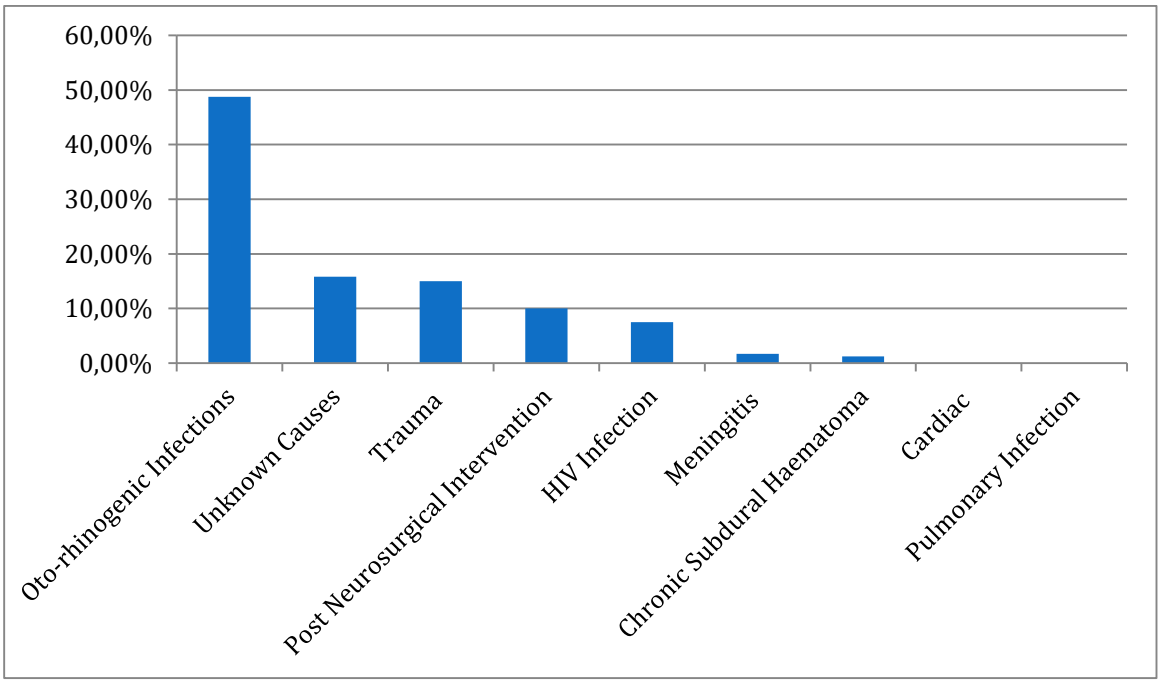
3.5 SOURCES OF INTRACRANIAL SUPPURATION

The oto-rhinogenic sources of infection were by far the commonest sources of infection, with a total of 117 (49%), followed by those with unidentified sources of infection and traumatic inoculation which accounted for thirty eight (15.8%) and thirty six (15%) cases respectively. Less commonly were those with post-neurosurgical infections; HIV infection as a predisposing factor; recent meningitis and secondary infection of chronic subdural haematoma.

Table 3.7: Sources of Infection

Sources of Infection	EDE	SDE	BA	TOTAL	Percentage
Oto-rhinogenic Infections	15	61	41	117	48.8%
Unknown Causes	3	6	29	38	15.8%
Trauma	9	6	21	36	15%
Post Neurosurgical Intervention	10	8	6	24	10%
HIV Infection	0	1	17	18	7.5%
Meningitis	0	0	4	4	1.7%
Chronic Subdural Haematoma	0	3	0	3	1.3%
Cardiac	0	0	0	0	0%
Pulmonary Infection	0	0	0	0	0%
Total	37	85	118	240	100%

Figure 3.2: Sources of Infection



3.6 TYPES OF ORGANISMS CULTURED IN EXTRADURAL, SUBDURAL AND BRAIN ABSCESS

There were various groups of bacteria isolated from EDE, SDH and BA during the period of study. A large amount of the ICSs were caused by Gram positive bacteria such as *Staphylococcus species* (25%) and *Streptococcus species* (21%). Ten patients with BA had *Mycobacterium tuberculosis* cultured, while another 2 patients had Nocardial infection. A total of 110 (45.8%) of the 240 pus specimen had negative bacterial cultures.

All the ten patients with TB brain abscesses and the two patients with Nocardia infection were HIV-infected individuals. Likewise, most patients with Staphylococcal infection were either acquired by direct traumatic inoculation or post neurosurgical procedures. The majority of intracranial collections resulting from oto-rhinogenic infections were caused by *Streptococcus species.*

Table 3.8 below illustrates the cultured bacterial isolates and their frequencies.

Figure 3.3

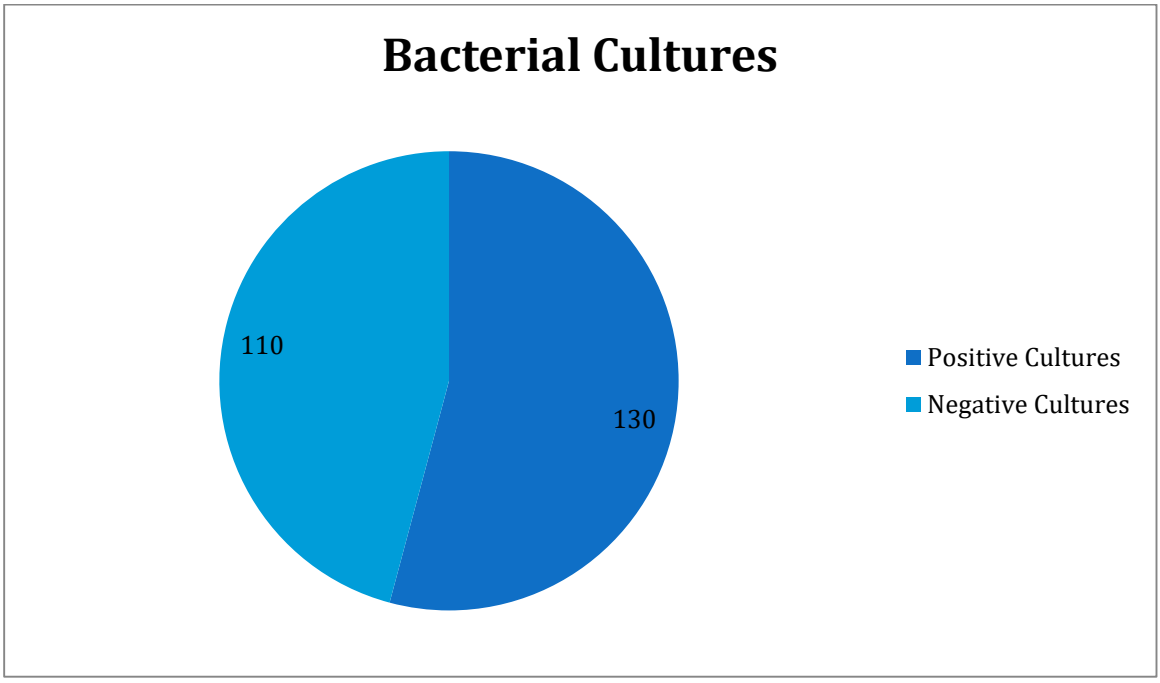
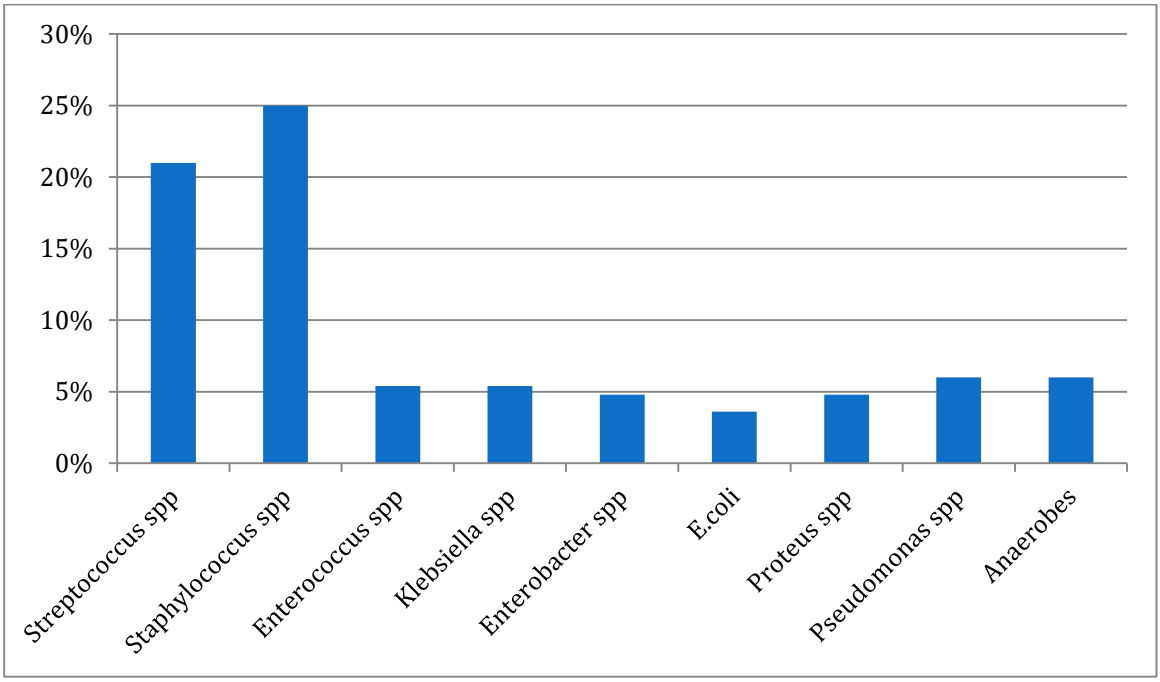


Table 3.8: List of Cultured Organisms and the Frequency for EDE, SDE, and BA

Organisms (Gram Positive Bacteria/GPB)	**EDE**	**SDE**	**BA**	**TOTAL**
1. Streptococcus anginosus	1	10	4	15
2. Streptococcus pyogenes	1	3	1	5
3. Streptococcus pneumoniae	0	0	1	1
4. Streptococcus viridans (mitis/oralis/mutans)	0	9	5	14
*5. Staphylococcus aureus (*MSSA)	11	9	10	30
*6. Methicillin-Resistant Staphylococcus aureus (*MRSA*)*	1	2	3	6
*7. Coagulase Negative Staphylococcus (*CNS)	1	3	2	6
8. Enterococcus faecalis	1	4	1	6
9. Enterococcus faecium	1	0	0	1
10.Enterococcus gallinarum	0	1	0	1
11.Enterococcus durans	0	1	0	1
12.Nocardia species	0	0	2	2
Total	**17**	**42**	**29**	**88**
Organisms (Gram Negative Bacteria/GNB)	**EDE**	**SDE**	**BA**	**TOTAL**
Enterobacteriacae:				
13. Klebsiella pneumoniae	2	2	1	5
14. Klebsiella species	2	1	1	4
15. Escherichia coli	1	1	4	6
16. Citrobacter koseri	2	0	0	2
17. Enterobacter cloacae	2	1	5	8
18. Serratia marcescens	1	1	0	2
19. Salmonella species	0	2	0	2
20. Proteus mirabilis/vulgaris	0	1	7	8
21. Hafnia alvei	0	1	0	1

22. Morganella morganii	0	0	1	1
Total	**10**	**10**	**19**	**39**
Non-fermenters:				
23. Acinetobacter baumannii	0	1	4	5
24. Pseudomonas aeruginosa	2	2	6	10
25. Alcaligenes faecalis	0	0	1	1
26. Stenotrophomonas maltophilia	0	0	1	1
27. Brevibacterium species	0	0	2	2
Total	**2**	**3**	**14**	**19**
Fastidious GNB:				
28. Eikenella corrodens	0	1	0	1
Total	**0**	**1**	**0**	**1**
Anaerobic organisms:				
29. Anaerobes isolated	0	2	0	2
30. Prevotella buccae/disiens/oralis/intermedia	0	3	3	6
31. Anaerobic Gram Negative Bacillus	0	0	1	1
32. Anaerococcus prevotii	0	1	0	1
Total	**0**	**6**	**4**	**10**
Mycobacteria/Acid fast bacilli:				
33. Mycobacterium tuberculosis	0	0	10	10
Total	**0**	**0**	**10**	**10**
Grand Total Bacterial Isolates	**29**	**62**	**76**	**167**

Figure 3.4: Common Organisms Cultured



The bacterial isolates are further classified as follows:

Table 3.9: Groups of Bacteria Cultured

Bacterial Groups	EDE	SDE	BA	Total	Percentage (%)
GPB	17	42	29	88	52.7
Enterobacteriacae GNB	10	10	19	39	23.4
Non Fermenters GNB	2	3	14	19	11.4
Fastidious GNB	0	1	0	1	0.6
Anaerobes	0	6	4	10	6.0
Mycobacteria	0	0	10	10	6.0
Total	29	62	76	167	100%

EDE had 58.6% (17/29) of its isolates as GPB, with (76%, 13/17) majority being *Staphylococcus species*. Sixty eight percent (42/62) of isolates from SDE were GPB with majority (35.5%, 22/62) being *Streptococcus species.* The proportion of GPB was relatively lower (38%, 29/76) in BA, in which case GNB predominated with 43% (33/76) of its total

isolates. BA had 38% (29/76) GPB isolates and 13% (10/76) being *Mycobacterium tuberculosis.*

Figure 3.5: Groups of Bacteria Cultured in EDE, SDE, and BA

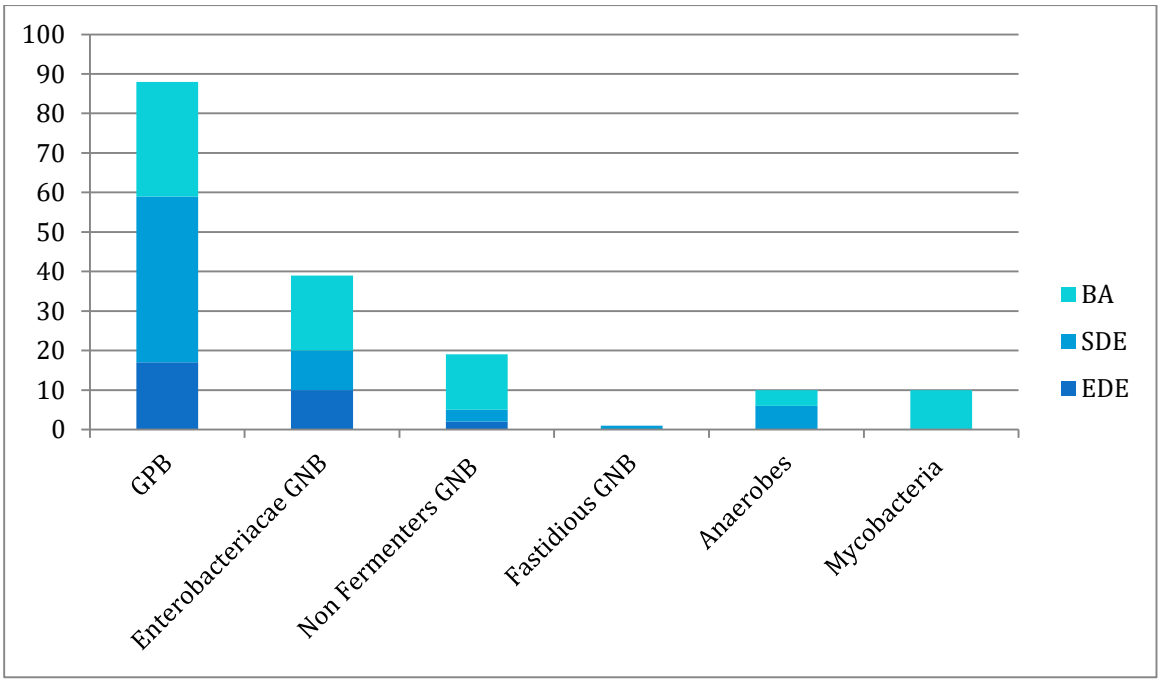


Table 3.10: Gram Positive Bacteria (GPB), n=88

Groups	EDE	SDE	BA	Total	% of GPB
Streptococci species	2	22	11	35	39.8%
Staphylococci	13	14	15	42	47.7%
Others	2	6	3	11	12.5%
Total	17	42	29	88	100%

3.7- ANTIMICROBIAL SUSCEPTIBILITY PROFILE OF CULTURED BACTERIAL ORGANISMS FROM INTRACRANIAL PUS SPECIMENS.

Table 3.11 shows the bacterial isolates and their corresponding antimicrobial sensitivity profile/antibiogram.

Table 3.11: List of Cultured Organisms in All Intracranial Cavities and Their Respective Antimicrobial Sensitivity Profiles.

Organisms (Gram Positive Bacteria/GPB)	**Antimicrobial Sensitivity**
1. Streptococcus anginosus	Penicillin, Ampicillin, Ceftriaxone, Cefotaxime
2. Streptococcus pyogenes	Penicillin, Ampicillin, Ceftriaxone, Cefotaxime
3. Streptococcus pneumoniae	Penicillin, Ampicillin, Ceftriaxone, Cefotaxime
4. Streptococcus viridans (mitis/oralis/mutans)	Penicillin, Ampicillin, Ceftriaxone, Cefotaxime
*5. Staphylococcus aureus (*MSSA)	Cloxacillin, Vancomycin
*6. Methicillin-Resistant Staphylococcus aureus (*MRSA*)*	Vancomycin
*7. Coagulase Negative Staphylococcus (*CNS)	Cloxacillin, Vancomycin
8. Enterococcus faecalis	Ampicillin, Vancomycin
9. Enterococcus faecium	Vancomycin
10.Enterococcus gallinarum	Ampicillin
11.Enterococcus durans	Vancomycin
12.Nocardia species	Sulfamethoxazole + Trimethoprim, Linezolid, Ceftriaxone, Amikacin
Organisms (Gram Negative Bacteria/GNB)	
Enterobacteriacae:	
13. Klebsiella pneumoniae	Ertapenem, Meropenem, Imipenem, Amikacin, Piperacillin + Tazobactam
14. Klebsiella species	Ertapenem, Meropenem, Amoxicillin+Clavulanate,
15. Escherichia coli	Amoxicillin+Clavulanate, Ceftriaxone, Cefotaxime,

	Meropenem
16. Citrobacter koseri	Amoxicillin+Clavulanate, Meropenem
17. Enterobacter cloacae	Ertapenem, Meropenem, Imipenem, Ciprofloxacin, Gentamycin
18. Serratia marcescens	Ertapenem, Imipenem, Cefepime
19. Salmonella species	Ciprofloxacin, Ceftriaxone/Cefotaxime, Meropenem
20. Proteus mirabilis/vulgaris	Amoxicillin+Clavulanate, Ciprofloxacin, Ceftazidime, Ceftriaxone, Cefotaxime, Meropenem, Imipenem
21. Hafnia alvei	No antibiotic sensitivity reported
22. Morganella morganii	No antibiotic sensitivity reported
Non-fermenters:	
23. Acinetobacter baumannii	Colistin, Piperacillin + Tazobactam, Ceftazidime
24. Pseudomonas aeruginosa	Ertapenem, Meropenem, Imipenem, Amikacin, Piperacillin + Tazobactam, Gentamycin, Ciprofloxacin, Ceftazidime
25. Alcaligenes faecalis	Meropenem, Imipenem, Amikacin, Piperacillin + Tazobactam, Gentamycin, Ciprofloxacin, Ceftazidime, Cefepime,
26. Stenotrophomonas maltophilia	Sulfamethoxazole + Trimethoprim
27. Brevibacterium species	Amoxicillin + Clavulanate
Fastidious GNB:	
28. Eikenella corrodens	
Anaerobic organisms:	
29. Anaerobes isolated	
30.Prevotella buccae/disiens/oralis/intermedia	
31.Anaerobic Gram Negative Bacillus	

32. Anaerococcus prevotii	
Mycobacteria/Acid fast bacilli:	
33*. Mycobacterium tuberculosis*	Rifampicin, Isoniazid

3.7.1 Common Bacterial Isolates and their Susceptibility Profile against Common Antibiotics

All *Streptococcus species* were sensitive to Ceftriaxone and Vancomycin. All *Streptococcus anginosus* isolates were penicillin susceptible. Twelve (86%) of the fourteen *Streptococcal viridans* cultured were also sensitive to Penicillin.

Table 3.12: *Streptococcus viridans* Sensitivity (n=14)

Antibiotics	Frequency	Percentage (%)
Penicillin	12/14	86
Ceftriaxone	14/14	100
Vancomycin	14/14	100

A total of 36 *Staphylococcus aureus* and 6 Coagulase negative Staphylococci (CNS) were cultured from all sites. Thirty (83.3%) were Methicillin Sensitive *Staphylococcus aureus* (MSSA), sensitive to Cloxacillin, while 16.6% (6/36) were Methicillin Resistant *Staphylococcus aureus* (MRSA) Cloxacillin resistant and Vancomycin sensitive.

Table 3.13: *Staphylococcus aureus* Susceptibility Results (n=36)

Antibiotics	Frequency	Percentage (%)
Cloxacillin	30/36	83.3
Vancomycin	36/36	100

Most (66%) of the *Enterococcus species* were *Enterococcus faecalis* (6/9) sensitive to Ampicillin. The remaining 33% (3/9) were *Enterococcus faecium* & *Enterococcus durans* which were resistant to Ampicillin and sensitive to Vancomycin while *Enterococcus gallinarum* was reported resistant to Vancomycin but sensitive to Ampicillin.

Table 3.14: *Enterococci species* Susceptibility Results (n=9)

Antibiotics	**Frequency**	**Percentage**
Ampicillin	7/9	77.7
Vancomycin	8/9	88.8

Thirty one common *Enterobacteriacae* were isolated namely *Klebsiella species* (n=9), *Proteus species* (n=8), *Enterobacter cloacae* (n=8) and *Escherichia coli* (n=6). Five (5/9, 56%) of the cultured *Klebsiella* species were Extended Spectrum Beta Lactamase (ESBL) producing bacteria (resistant to Ceftriaxone); while the remaining 4 (44%) were sensitive to Ceftriaxone and none were sensitive to Ampicillin. Of the total *Proteus species* isolated, none were reported ESBL producers; all were sensitive to Ceftriaxone while only one (12.5%) was sensitive to Ampicillin. All of the *Enterobacter cloacae* cultured were ESBL producers. None of the *Escherichia* coli were ESBL; only one (17%) was sensitive to Ampicillin, while all were sensitive to Ceftriaxone.

Table 3.15: Common *Enterobacteriacae species* Susceptibility Results (n=31)

Enterobacteriacae	**Meropenem**	**Ceftriaxone**	**Ampicillin**
Klebsiella species	9/9, 100%	4/9, 44%	0/9, 0%
Enterobacter cloacae	8/8, 100%	0/8, 0%	0/8, 0%
Proteus species	8/8, 100%	8/8, 100%	1/8, 12.5%
Escherichia coli	6/6, 100%	6/6, 100%	1/6, 17%

Pseudomonas aeruginosa isolates were 70% sensitive to Ceftazidime, 80% to Meropenem, and 60% sensitive to Cefepime. There were 3 MDR *Pseudomonas aeruginosa* isolates cultured but no XDR strains.

Table 3.16: Pseudomonas aeruginosa Susceptibility Results (n=10)

Antibiotics	**Frequency**	**Percentage**
Ceftazidime	7/10	70%
Meropenem	8/10	80%
Cefepime	6/10	60%

Acinetobacter baumannii were culture from four intraparenchymal and one subdural pus specimens. Four specimens were sensitive to Colistin only *(*XDR *A. baumannii*), one was sensitive to both Colistin and Ceftazidime (MDR *A. baumannii*), but none were sensitive to Meropenem.

Table 3.17: *Acinetobacter baumannii* Susceptibility Result (n=5)

Antibiotics	**Frequency**	**Percentage**
Colistin	5/5	100
Ceftazidime	1/5	20
Meropenem	0/5	0

Susceptibility testing for anaerobes is not routinely performed by the local Microbiology laboratory at CHBAH.

All 10 intraparenchymal pus specimens that were positive for *Mycobacterium tuberculosis* were all sensitive to Rifampicin and Isoniazid.

Two patients' pus specimens yielded *Nocardia species* that were sensitive to Sulfamethoxazole + Trimethoprim (Bactrim), Linezolid, Ceftriaxone, and Amikacin. It is worth

mentioning that these two patients were HIV positive patients and represented 1.7% of the total brain abscesses.

4. DISCUSSION

4.1 STUDY SAMPLE

The study was conducted retrospectively over a period of 5 years: July 2013 to June 2018.

Over the 5 year period, 365 cases of intracranial suppuration were seen at CHBAH, of which 240 (66%) were surgically drained. A total of 167 organisms were cultured from 130 pus specimens as some of the specimens had a polymicrobial growth of bacterial organisms.

The large number of specimens with no growth may be attributed to use of antibiotics by the patients before being referred to CHBAH for surgical care. Other factors to note are delays in specimen transport to the lab that might compromise organism viability, especially anaerobes. Also observed as per patients' records were, some patients who were not prescribed antibiotics prior to referral, and had negative microbial culture findings. High negative culture rate was in keeping with reviewed literature stating varying lower rates of negative cultures.[9, 12] The Durban study had 14.6% negative cultures in EDE[12] while other studies had as much as 25% negative cultures.[9]

4.2 YEARLY DISTRIBUTION

The yearly distribution of patients with ICS showed significant variation. It is worth noting that the years 2013 (July to December) and 2018 (January to June) were half years of the study. There were only six patients recorded for the year 2013 and 26 patients for the year 2018. Low patient turn out for the first half of the year 2013 may be attributed to pre-winter season. Increased incidence of complicated sinusitis during winter resulting in ICS is well documented in literature.[6]

The full years of 2014 to 2017 had 36, 55, 73, and 44 patients recorded respectively. The mean yearly patient distribution over the 5-year period of study were 48 patients per annum.

4.3 AGE DISTRIBUTION

The age distribution of the patients with ICS at CHBAH varied widely from infants (2 in number) to one patient in his 70s. Majority (64.2%) of the patients were teenagers and young adults between the ages of 11 to 40 years. The mean age of presentation was 27.5 years and standard deviation of 17.6years.

Teenagers and young adult males contributed to the majority of patients as a result of higher incidence of traumatic and post-operative ICS in this group.

Age of presentation of patients with ICS is of importance as morbidity and mortality is worse in the extremes of ages.

4.4 GENDER

Gender distribution showed a male preponderance of 71.7% (n=172) and female 28.3% (n=68) due to increased incidence of trauma in young males compared to females. This finding is comparable to that of the reviewed studies.[6]

4.5 CLASSIFICATION OF INTRACRANIAL SUPPURATION (ICS)

For the purpose of this study, ICS is classified based on the intracranial cavity occupied by the suppurative collection. Patients with ICS presented with EDE, SDE or BA. Over the 5-year period of study, BA had the largest frequency of 118 patients (49.2%), followed by SDE with 85 patients (35.4%), and lastly EDE in 37 patients (15.4%).

The yearly mean distribution of EDE, SDE and BA were 7.4, 17 and 23.6 respectively. This amounts to a yearly mean of 48 cases of intracranial suppuration that were surgically drained during the period of study.

4.6 SOURCES OF INTRACRANIAL SUPPURATION

The bacteriology of extradural, subdural, and intra-parenchymal suppuration are identical to that of the primary sites of infection in majority of the patients. In the Vancouver study, a study of a paediatric population showed EDE secondary to trauma or surgery to be due to

Gram negative bacilli or *Staphylococcus aureus*. In the same study, cases due to otitis media, mastoiditis and sinusitis; *Streptococcal pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*, Coagulase negative Staphylococci and anaerobes were the cultured organisms. The findings of this study were similar with respect to the types of organisms we have isolated. The most common isolate for Subdural Empyema (SDE) was *Streptococcus viridans*, which accounted for a third of the cases. Cerebral abscesses also showed similar bacterial isolates to the source of infection with *Streptococcus species* being the most cultured organism.[3]

This study found Staphylococcal infections to be more frequent than Streptococcal infections as a result of post traumatic and post-surgical incidence in the younger male population. Streptococcal infection from oto-rhinogenic sources accounted for 39.8% of the Gram positive infections, majority causing SDE.

Other sources of infections accounted for the remaining 10% of sources of intracranial suppuration. A South African study had documented patients with haematogenous spread from cardiac and pulmonary sources of about 3% and 7% respectively[7]. In contrast to other reviewed studies, this study did not find any patient with underlying cardiac or pulmonary pathology as the cause of the intracranial infection during the period of study.

Out of the 10 patients with tuberculous brain abscess, 8 (80%) of them had either been treated for tuberculosis in the past or were having active pulmonary TB at the time of diagnosis of the brain abscess. None of these 10 intraparenchymal pus specimens were Multidrug Resistant (MDR) or Extensively Drug Resistant (XDR) *Mycobacterium tuberculosis*. Tuberculous ICS may be seen in immunosuppressive states as an opportunistic infection.

4.7 TYPES OF ORGANISMS CULTURED IN EXTRADURAL, SUBDURAL AND BRAIN ABSCESSES

Various groups of bacteria were isolated from EDE, SDE and BA during the period of the study. The isolated microbes were grouped into: Gram Positive Bacteria (GPB),

Enterobacteriacae, Gram Negative Non-fermenter, Gram Negative Fastidious organisms, Anaerobes and Mycobacteria/Acid fast bacilli.

Gram positive bacteria were cultured from majority of the pus specimens (n=88, 52.7%), with *Staphylococcus and Streptococcus species* being the predominant isolates. There was a wide range of Gram negative bacteria, of which the *Enterobacteriacae* (*Klebsiella species, Escherichia coli, Citrobacter koseri, Enterobacter cloacae, Proteus species,* etc.) constituted 23.4% (n=39) of the total positive cultures. Anaerobic bacteria (*Prevotella species, Anaerococcus prevotii,* etc.) and Acid fast bacilli (*Mycobacterium tuberculosis*) were each cultured from 10 (6%) specimens.

The *Streptococcus* (n=35) and *Staphylococcus* (n=42) groups of bacteria were the most common isolates cultured from EDE, SDE, and BA (Tables 3.7 and 3.9).

GPB cultured were 88 in total with a frequency of 17 (19.3%), 42 (47.7%), and 29 (33%) for EDE, SDE, and BA respectively.

Enterobacteriacae cultured were 39 in total with a frequency of 10 (25.6%), 10 (25.6%), and 19 (48.7%) for EDE, SDE, and BA respectively. Non fermenter Gram negative bacteria were also recovered at a higher rate from brain abscesses with a frequency of 2/9 (10.5%), 3/9 (15.8%), and 14/19 (73.7%) for EDE, SDE, and BA respectively.

Thirty one (31/130, 24%) of the pus specimens had polymicrobial growth of bacteria. Twenty eight pus samples had 2 bacterial isolates each, while 3 pus specimens grew 3 bacterial isolates each. This finding is comparable to one of the cited literature which reported polymicrobial bacterial cultures in 10-30% of cases, which usually include anaerobes.[9]

The primary source of the intracranial infection and the predisposing factors, such as an immunosuppressive state, seemed to be the main determinants of the type of causative organism rather than the intracranial space being occupied by the suppurative collection.

4.8 ANTIMICROBIAL SENSITIVITY PROFILE OF BACTERIA ISOLATED FROM INTRACRANIAL PUS SPECIMENS.

The antimicrobial sensitivity profile of intracranial suppuration at CHBAH during the 5-year period of study for each of the different groups of organisms were similar in the 3 cavities (extradural, subdural and intraparenchymal) sampled.

Among the Gram positive organisms, *Streptococcus species* were sensitive to penicillin and the third generation Cephalosporins, namely Ceftriaxone/Cefotaxime and comprised of 21% (35/167) of the total isolates cultured from intracranial pus specimens. *Staphylococcus aureus* (MSSA and MRSA) and CNS were recovered from 25% (42/167) of isolates and were sensitive to Cloxacillin (MSSA [30/42]) and Vancomycin (MRSA [6/42]) respectively. MRSA is the most common community acquired Multidrug Resistant (MDR) bacteria, with greatest impact on morbidity and mortality. The main threats on the horizon are the multidrug resistant *Enterobacteriacae*.[13] *Enterococcus species* were isolated in 5.4% (9/167) of samples with 77.7% (7/9) of them sensitive to Ampicillin and 88.8% (8/9) sensitive to Vancomycin. Notably, *Enterococcus gallinarum* (1/9) was the only Vancomycin resistant isolate that was cultured. *Enterococcus gallinarum* exhibits low level intrinsic resistance to Vancomycin but still retains Ampicillin susceptibility.[14] These Gram-positive organisms' antimicrobial sensitivities were similar in EDE, SDE, and BA.

Gram-negative *Enterobacteriacae* and Non-Fermenters were cultured from 39 (23.4%) and 19 (11.4%) pus specimens respectively, with different antimicrobial sensitivity profiles. *Klebsiella species* were largely sensitive to the Carbapenems (Ertapenem, Meropenem and Imipenem), with none being a CRE. Fifty six percent (5/9) of the *Klebsiella species* isolated were ESBL producers. All (6/6) of *Escherichia coli (E.coli)* isolates were sensitive to Ceftriaxone/Cefotaxime, and only 17% (1/6) sensitive to Ampicillin. None of the *E. coli* were ESBL producers. *Enterobacter cloacae* isolates had 100% sensitivity to the Carbapenems; none were CRE strains. The two subdural pus specimens with *Salmonella species* were both sensitive to Ciprofloxacin and Ceftriaxone/Cefotaxime; none were ESBL or carbapenemase producing strains. *Proteus mirabilis/vulgaris* were prevalent in intraparenchymal pus

specimens with 12.5% (1/8) sensitive to Ampicillin; 100% (8/8) sensitive to Ceftriaxone/Cefotaxime and Carbapenems. None of the *Proteus* isolates were ESBL producers.

ESBL bacteria are those that produce the enzyme, beta-lactamase which has the ability to break down commonly used antimicrobial agents such as Penicillins and Cephalosporins thereby render them inactive but remain sensitive to the Carbapenems and are considered as Multidrug Resistant (MDR) bacteria. MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively Drug Resistant (XDR) *Enterobacteriacae* is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two antimicrobial categories). Pan Drug Resistant (PDR) is defined as nonsusceptibility to all agents in all antimicrobial categories.[15]

None of the above Gram negative bacteria were Carbapenem-resistant *Enterobacteriacae* (CRE). Carbapenem-resistant *Enterobacteriacae* have reduced susceptibility to any Carbapenem or are documented to produce Carbapenemase enzymes.[16] Treatment options for CRE infections are limited. The Polymyxins (Colistin or Polymyxin B) and Tigecycline were historically considered as drugs of choice for treatment.[17]

The multidrug resistant organisms Gram negative Non-Fermenters identified were *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The *Acinetobacter baumannii* cultured were largely (80%) XDR strains that were sensitive to Colistin while 20% (1/5) were MDR sensitive to both Colistin and Ceftazidime. All *Acinetobacter baumannii* isolates were Carbapenem resistant.

Pseudomonas aeruginosa isolates reported susceptibilities were 70% sensitive to Ceftazidime, 80% sensitive to Meropenem, and 60% sensitive to Cefepime. There were 3 MDR *Pseudomonas aeruginosa* isolates cultured, but no XDR strains.

Two patients' pus specimens were positive for *Nocardia species* that were sensitive to Sulfamethoxazole + Trimethoprim (Bactrim), Linezolid, Ceftriaxone, and Amikacin. These were HIV-positive patients and represented 1.7% of the total brain abscesses.

This rate is comparable to that reported in literature. *Nocardia* is reported to be responsible for about 2% of brain abscesses, the majority of which is *Nocardia asteroides*.[9] It is seen in patients with chronic debilitating immunosuppressive illnesses which includes: neoplasia e.g. leukaemia, lymphoma; conditions which require prolonged corticosteroid use; Cushing's disease; Paget's disease of bone; AIDS; and renal or cardiac organ transplant recipients.

Susceptibility testing for anaerobes was not routinely performed by the local Microbiology laboratory at CHBAH.

All 10 intraparenchymal pus specimens that were positive for *Mycobacterium tuberculosis* were all sensitive to Rifampicin and Isoniazid.

Conclusion

Management of intracranial suppuration is an important part of neurosurgical practice in South Africa. The burden of disease stem from its attendant stress of morbidity and mortality to the patients and their families and also the cost of care to the health system.

The vast majority of the cases were found in young male population because of higher incidence of trauma among other causes in this group of people. Immunosuppression from HIV infection was noted as a risk factor, particularly in BA.

The primary source of infection played a major role in the type of bacterial isolates cultured from each of the intracranial cavities. Oto-rhinogenic sources of infection predominated in all 3 intracranial cavities; followed by those from an unknown aetiology and as a result of trauma. Patients with penetrating cranial injuries or following neurosurgical procedures were more prone to a Staphylococcal infection, while patients with oto-rhinogenic infections were more prone to SDE with Streptococcal infections. BAs were found to be commonly caused by GNB, followed by GPB (*Streptococcal* and *Staphylococcal species*) and *Mycobacterium tuberculosis.* Anaerobic bacteria were not routinely cultured because of their fastidious nature and possible loss of viability during transit to the laboratory. Anaerobic susceptibility testing were not reported as it is a specialised technique not routinely performed at CHBAH laboratory.

The antimicrobial susceptibility profile of the same organism strain from each of the 3 intracranial cavities was noted to be similar.

Recommendation

In view of the findings of this study, it is recommended that empiric antimicrobial therapy for intracranial suppuration should be guided by the primary source of the infection; the intracranial cavity (extradural, subdural or intraparenchymal); and associated medical condition. For example, intracerebral abscesses in HIV-infected patients may be caused by opportunistic infections such as Tuberculosis or Nocardia.

The importance of prompt and appropriate empiric antimicrobial therapy cannot be overemphasised to prevent or minimise morbidity and mortality arising from ICS. An informed choice of antimicrobial agent may then be made when MC&S results are obtained.

It is safe to empirically start a patient with ICS without an open cranial trauma with a broad spectrum Cephalosporin (Ceftriaxone) to cover for GPB and GNB. Coverage for anaerobic organisms (Metronidazole) is also recommended in these patients. The decision to include an anti-anaerobe to the broad spectrum therapy is supported by studies that stated as much as 35-50% of cases of ICS involved anaerobic organisms.[9, 10] It is also supported by the fact that the yield for isolating anaerobes from the pus samples in the microbiology lab is poor as they require low oxygen tensions to survive.

In the case of ICS resulting from open contaminated intracranial injury, coverage for *Staphylococcus aureus* is recommended due to higher incidence of this organism in these group of patients. BAs resulting from different sources of infection have higher incidence of resistant GNB and may require the use of Carbapenems or Colistin if resistant to commonly used antibiotics. Post neuro-surgical nosocomial infections have higher incidence of Staphylococcal and Gram negative ESBL producing infections, hence, may require Vancomycin and a Carbapenem empirically.

Some patients with BA with history, clinical features, HIV infection, and radiological imaging suggestive of TB suppuration may require empiric anti-TB therapy. Patients with deep-

seated, small, relatively inaccessible lesions with good clinical and radiologic response to TB treatment might not have to be surgically treated.

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APPENDIX A

DATA COLLECTION SHEET
CODE NUMBER

Biodata

(1) Age:

(2) Gender

Male ( )
Female ( )

(3) Radiologic Findings:

Extradural Collection ( )
Subdural Collection ( )
Cerebral/Cerebellar Collection ( )

(4) Source of Infection/Predisposing Factors:

Contiguous Spread: Sinusitis, Otitis Media, Mastoiditis, Dental Infection ( )
Trauma ( )
Post-Surgery ( )
Meningitis ( )
Chronic Subdural Haematoma ( )
HIV Infection ( )
Haematogenous Spread: Cardiac or Pulmonary Lesions ( )
Unknown sources ( )

(5) Types of Organisms:

Bacteria ( )
Fungi ( )
Parasites ( )

(6) Number of Cultured Organisms:

One ( )
Two ( )
Three ( )
Four ( )
>Four ( )

(7) List of Bacterial Organisms and their Antibiogram:

Sensitive(S) or Resistant(R)

Organisms	Antibiotic S/R 1	Antibiotic S/R 2	Antibiotic S/R 3	Antibiotic S/R 4	Antibiotic S/R 5	Antibiotic S/R 6

APPENDIX B – Ethics Approval Certificate

R14/49 Dr Olalekan Jaiyeola

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180735

NAME: Dr Olalekan Jaiyeola
(Principal Investigator)
DEPARTMENT: Neurological Surgery
National Health Laboratory Service
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: Differential bacteriology of extradural, subdural, and intra-parenchymal suppuration at Chis Hani Baragwanath Academic Hospital: A 5 year review of records

DATE CONSIDERED: 27/07/2018

DECISION: Approved Unconditionally

CONDITIONS:

SUPERVISOR: Dr J Ouma and Dr P Jaglal

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

APPROVED BY:

Doctor CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/111 18

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which **I** am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C- NHLS Approval Letter

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6290
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

19 November 2018

Applicant: Dr Olalekan Jaiyeola
Institution: Chris Hani Baragwanath
Department: Neurosurgery
Email: lakeenson@yahoo.com
Cell: 079 571 9411

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "**Differential Bacteriology of Extradural, Subdural and Intra-parenchymal Suppuration at Chris Hani Baragwanath Academic Hospital: A 5 Year Review of Records**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***without patient names*** to conduct the proposed study as outlined in the submitted application.

Please note that final approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.

Please note that this letter constitutes provisional approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed as follows: NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

APPENDIX D- Radiology Approval Letter

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL – UNIVERSITY OF THE WITWATERSRAND
DEPARTMENT OF RADIOLOGY

To whom it may concern,

RE: RESEARCH PROJECT IN CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Project title - Differential bacteriology of extradural, subdural, and intra-parenchymal suppuration at Chris Hani Baragwanath Academic Hospital: a 5 year review of records

Period of study: July 2013 to June 2018

Study type: Retrospective

We hereby support Dr O.M Jaiyeola's application, a Masters student from the University of the Witwatersrand, to conduct research in our hospital for purposes of a Masters of Medicine qualification (FC Neurosurg SA, MMED). This will include permission to access the radiologic images and reports of all patients with intracranial suppuration (extradural, subdural and intraparenchymal abscesses) during the study period using the radiology database PACS system. A comparison of the bacterial agents in these intracranial cavities will be made from this study.

All data will be anonymous by assigning a pseudo number to each patient.

Permission is granted to Dr O.M Jaiyeola, subject to him obtaining ethical clearance to conduct research from the Ethics Committee of the University of the Witwatersrand, Johannesburg and by abiding to its terms.

I have been informed about Dr O.M Jaiyeola's research.

Yours sincerely,

_____ _____

Dr A.Rauf **Date**
Acting HOD – Radiology
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011-933-8393