External ventricular drain infections: a retrospective analysis at a central hospital in KwaZulu-Natal, South Africa

By

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PREFACE

This study represents original work by the author and has not been submitted in any other form to another University. Where use was made of work of others, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Microbiology, School of Laboratory Medicine and Health Sciences, University of KwaZulu-Natal, South Africa, under the supervision of Dr Y. Mahabeer and co-supervision of Dr K. Swe Swe-Han.

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DECLARATION

I, Dr Jenine Naomi de Meyer (student number: 993215908), declare as follows:

1. The research presented in this dissertation, unless otherwise stated, represents original work.

2. The work described in this dissertation has not been submitted to UKZN or any other institution for the purposes of an academic qualification, whether by me or any other party.

3. This dissertation does not contain other persons' data, pictures, graphs, or other information, unless specifically acknowledged as being sourced from other persons.

4. My contribution to the project was the role of the primary researcher. The role encompassed conceptualisation of the project, development of the methodology and protocol and liaison/applications for ethical clearance and relevant consents. Data curation and formal data analysis and completion of the final written dissertation was also the responsibility of the primary author.

5. The contributions of others to the project include those of Dr Yesholata Mahabeer and Dr Khine Swe Swe-Han (National Health Laboratory Service and Department of Medical Microbiology at the University of KwaZulu-Natal) and Dr Basil Enicker (Department of Neurosurgery at the University of KwaZulu-Natal). Dr Y. Mahabeer's contribution encompassed the role of project supervisor, which included synthesis of the protocol and editing and review of the dissertation. Dr K. Swe Swe-Han encompassed the role of project co-supervisor which included review of dissertation and assessment of my MMED progress as Head of Department. Dr B. Enicker contributed to the clinical aspects of the project.

DEDICATION

To my two moms.

Thank you for your encouragement, love and support.

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List of Abbreviations

A. baumannii	*Acinetobacter baumannii*
BREC	Biomedical Research Ethics Committee
C. acnes	*Cutibacterium acnes*
CDC	Centre for Disease Control
C. difficile	*Clostridioides difficile*
CLSI	Clinical and Laboratory Standards Institute
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CSF	Cerebrospinal fluid
E. cloacae	*Enterobacter cloacae*
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
ER	Emergency room
ESBL	Extended spectrum β-lactamase
EVD	External ventricular drain
EVDRI	External ventricular drain-related infections
GCS	Glasgow coma scale
IALCH	Inkosi Albert Luthuli Central Hospital
ICH	Intracranial haemorrhage
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
ITH	Intrathecal

IV	Intravenous
IVH	Intraventricular haemorrhage
K. aerogenes	*Klebsiella aerogenes*
K. oxytoca	*Klebsiella oxytoca*
K. pneumoniae	*Klebsiella pneumoniae*
LOC	Level of consciousness
MDR	Multidrug resistant
M. hominis	*Mycoplasma hominis*
M. morganii	*Morganella morganii*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NHLS	National Health Laboratory Service
P. aeruginosa	*Pseudomonas aeruginosa*
P. mirabilis	*Proteus mirabilis*
R. mucilaginosa	*Rhodotorula mucilaginosa*
SAH	Subarachnoid haemorrhage
S. aureus	*Staphylococcus aureus*
S. epidermidis	*Staphylococcus epidermidis*
WCC	White cell count
XDR	Extensively drug-resistant

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CHAPTER ONE:

INTRODUCTION

1.0. INTRODUCTION AND BACKGROUND

External ventricular drains (EVDs) are used to monitor and manage intracranial pressure for certain neurosurgical conditions. Due to the invasive nature of EVDs, patients are at risk for acquiring infections and other complications. Infections lead to prolonged hospital stay, increased morbidity and mortality and microorganisms may become more resistant with exposure to the environment and antimicrobial agents. There is minimal data published on the diagnostics of external ventricular drain-related infections (EVDRIs) and currently no consensus on the best way to distinguish infections from colonisation and contamination. There is also no single cerebrospinal fluid (CSF) laboratory or microbiological parameter and no single blood test that can be used to differentiate infection from aseptic meningitis. There is also minimal data on antimicrobial susceptibility patterns of microorganisms causing EVDIs.

1.1. Indications for EVD insertion

EVDs are used for the short-term management and monitoring of intracranial pressure (ICP) in all age groups. ICP is considered to be elevated at a pressure of > 15 – 25 mm H_2O.[1] There are many conditions that may require the insertion of EVDs which include hydrocephalus, intracranial haemorrhage (ICH) including subarachnoid haemorrhage (SAH), tumours causing CSF outflow obstruction, meningitis, traumatic brain injury and ventriculoperitoneal shunt failure. Insertion may also be required for the administration of intrathecal antibiotics in patients with active meningitis.

1.2. External ventricular drain sepsis

1.2.1. Mode/route of infection

An EVD connects CSF in the ventricles via the intracranial cavity to the external environment. This provides a route for retrograde colonisation or infection. Mounier et al. postulated that there are four mechanisms that may lead to EVDRIs.[2] Infections may occur during insertion of the catheter thereby introducing skin flora into the ventricles, during disconnection or manipulation of the EVD system, colonisation of the drain occurring at the insertion site of the drain or less commonly via haematogenous spread.[2]

1.2.2. Incidence

The incidence of EVDRIs varies widely in studies. This may be due to challenges when diagnosing infections as definitions vary and abnormalities in CSF chemistry, white cell count (WCC) and clinical manifestations may be caused by conditions other than EVDRIs. According to the Centre for Disease Control (CDC), the reported incidence varies from less than 1% to 45 %.[3] The Infectious Diseases Society of America (IDSA) found that the incidence of EVDRIs was slightly lower and ranged from 0 – 22%.[4] According to a meta-analysis of 35 studies, a pooled incidence of 11.4 per 1000 catheter days was found.[5] In the majority of studies, EVDRI rates were predominantly reported in patients with traumatic brain injuries who required EVD insertion. In a large retrospective study done on patients with aneurysmal SAHs, 32% of these patients required EVD insertion with a mean annual infection rate of 7.3%.[6] A study conducted in South Africa, found that the incidence of ventriculitis in a paediatric population was 28.3%.[7] Walek et al. observed a significant reduction in EVDRIs from 6.68 per 1000 catheter days (from 2007 to 2009) to 1.98 per 1000 catheter days (from 2017 to 2019) after eliminating routine EVD surveillance cultures, use of chlorhexidine antisepsis and use of a modified tunnelling insertion techniques of catheters.[8]

Various authors have conducted studies on the risk of acquiring infection with placement of EVDs in various hospital settings such as the operating room, intensive care unit (ICU) and emergency room (ER). Some authors found that there was a lower infection rate when EVDs were inserted in the operating room than when inserted in the ICU or ER.[9,10] Other authors found that there was no difference in the infection rate when inserting EVDs in the operating room, ICU or the ER.[11,12]

1.2.3. Definitions

1.2.3.1. Infection

EVDRIs include catheter exit site infections, subcutaneous tunnel infections or ventriculitis. There is no standard definition for EVDRIs and therefore it is difficult to diagnose. This limits the study, surveillance and comparison of practices for EVDRIs. Lewis et al. found sixteen different definitions for EVDRIs of which nine were subjective. After applying these definitions to a test cohort, the frequency of infection ranged from 22% to 94%, thereby showing a large variability when defining EVDRIs.[13]

Most studies consider a high CSF WCC, low glucose level and high protein level as important parameters used concurrently with microbiology results when diagnosing EVDRIs.[3,14,15] In Table 1, Reyes et al. summarised definitions that were utilised by various authors to identify EVDRIs.[3]

Table 1: Comparison of External Ventricular Drain-Related Ventriculitis Surveillance Definitions

Reference	Definition criteria	Culture criteria	Gram stain	Clinical criteria	CSF analysis criteria	Other criteria
CDC/NHSN[3]	• Culture criteria alone OR • 2 of 3 clinical criteria and: ○ All CSF analysis criteria OR ○ Abnormal Gram stain OR ○ Positive blood culture	Any growth	Organism present	• Fever > 38ºC • Meningeal signs • Cranial nerve signs	• ↑ nucleated cells And • ↓ CSF glucose And • ↑ CSF protein	
Honda[16]	• Culture alone OR If skin flora*, then at least one CSF analysis criteria must be met	Any growth	Should match culture growth		• CSF WCC $\geq$ 10 cells/µL Or • CSF glucose < 1.4mmol/l Or • CSF protein > 0.5g/L	Only to consider if at least 48 hours after EVD insertion
Gozal[14]	Culture AND Clinical criteria AND CSF analysis criteria	Any growth		Fever > 38.6ºC	• CSF glucose < 2.8 mmol/l Or • CSF glucose/serum glucose ratio $\leq$ 50%	Included even those in which criteria met within 72h of EVD removal
Citerio[15]	Culture criteria AND Clinical criteria AND CSF analysis criteria	Any growth		Fever > 38ºC	• CSF WCC > 5 cells/μl And • CSF glucose/serum glucose ratio $\leq$ 50%	
Schade[17]	Culture criteria AND Clinical criteria	Any growth		Fever Headache Nuchal rigidity Altered mental status		

*Common skin flora: Coagulase negative staphylococci, *Corynebacterium* spp, *Bacillus* spp, *Micrococcus* spp, *Cutibacterium* spp.

Adapted from Reyes et al.[3]

Schade et al. defined EVDRIs using only clinical criteria and microbiological findings. The definition included the presence of one positive CSF culture plus clinical manifestations of meningitis such as headache, fever, nuchal rigidity and a reduced level of consciousness (LOC).[17]

IDSA does not provide a definition but rather guidelines to identify EVDRIs. The following recommendations are given; an elevated CSF WCC and/or low CSF: serum glucose ratio with ≥ 1 positive cultures, or an increasing CSF WCC with clinical manifestations of meningitis suggest infection. A low CSF: serum glucose ratio and a high CSF protein concentration are also suggestive of EVDIs. CSF cultures that grow *S. aureus,* aerobic Gram-negative bacilli or fungal pathogens are also indicative of infection.[4]

According to the CDC, healthcare-associated ventriculitis or meningitis includes the following criteria; microorganisms cultured from CSF, or 2 or more symptoms with no other cause found in each of the 2 groups of patients. These include patients >1 year-old with headache, focal neurological signs and fever >38°C, or patients ≤1 year-old with apnoea, hypothermia or fever >38°C, irritability or bradycardia. In the criteria there must also be at least 1 of the following findings; elevated CSF WCC and protein and a low CSF: serum glucose ratio, organisms visualised on the Gram stain of CSF or organisms cultured from blood culture.[3]

As summarised in Table 2, Lozier et al. categorised infections according to suspected EVDRIs, EVDRIs and ventriculitis. A suspected EVDRI was defined as a progressively decreasing CSF glucose level, increasing CSF protein level, increasing CSF WCC and the absence of a positive CSF culture or Gram stain. An EVDRI was defined as a progressively decreasing CSF glucose level, increasing CSF protein level, increasing CSF WCC, ≥ 1 positive CSF cultures or Gram stains and negligible clinical symptoms other than fever. Ventriculitis was defined as a low CSF glucose level, high CSF protein level, high CSF WCC, fever and clinical signs of meningitis.[18]

Other authors found that CSF chemistry and WCC analysis provided no additional value in diagnosing EVDRIs in patients who had concurrent intraventricular haemorrhage (IVH).[5]

Clinical manifestations of meningitis and ventriculitis include headache, fever, nausea and vomiting, new or worsening altered LOC, nuchal rigidity and focal neurological deficit.[3]

1.2.3.2. Colonisation

Schade et al. defined colonisation as ≥ 2 positive CSF cultures with the same pathogen in the absence of clinical manifestations.[17] According to IDSA guidelines, colonisation should be considered in the presence of multiple positive CSF cultures or Gram stain, with normal CSF parameters in the absence of clinical manifestations.[4] As summarised in Table 2, Lozier et al. defined colonisation as multiple positive CSF cultures and/or Gram stains, an expected CSF glucose and protein level, an expected CSF WCC and lack of clinical manifestations other than fever.[18]

1.2.3.3. Contamination

Schade et al. defined contamination as a single positive CSF culture with a common skin pathogen with no further positive cultures and no clinical manifestations of ventriculitis/meningitis.[17] According to the IDSA guidelines, contamination should be considered if a microorganism is known to be a common contaminant cultured from an enrichment broth only or from only 1 of multiple cultures with normal CSF parameters and no clinical manifestations or when there is an isolated CSF culture or Gram stain with normal CSF parameters and no clinical manifestations.[4] A polymicrobial CSF culture from a single specimen may also be considered a contaminant in patients with no symptoms of infection or in the absence of an elevated CSF WCC.[4] As summarised in Table 2, Lozier et al. defined contamination as an isolated positive CSF culture and/or Gram stain with an expected CSF glucose and protein level and an expected CSF cell count.[18]

Table 2: Definitions of EVD-related infections, colonisation and contamination

Episode	**Definition**
Contamination	Isolated positive CSF culture and/or Gram stain Expected CSF glucose and protein profile Expected CSF cell count
Colonisation	Multiple positive CSF cultures and/or Gram stain Expected CSF glucose and protein profile Expected CSF cell count Lack of clinical manifestations other than fever
Suspected EVD-related infection	Progressively decreasing CSF glucose level Increasing CSF protein levels Increasing CSF pleocytosis Absence of CSF culture/Gram stain
EVD-related infection	Progressively decreasing CSF glucose level Increasing CSF protein level Increasing CSF pleocytosis One or more positive CSF cultures/Gram stains Paucity of clinical symptoms other than fever
Ventriculitis	Low CSF glucose level High protein level CSF pleocytosis Fever Clinical signs of meningitis (nuchal rigidity, photophobia, decreased LOC, seizures, moribund)

Adapted from Lozier et al.[18]

1.2.4. Risk factors

Factors associated with increased risk of infection include the presence of blood in CSF such as IVH or SAH, cranial fractures with CSF leaks, neurosurgical operations, co-infection, frequent catheter irrigation, intrathecal administration of drugs, frequent CSF sampling, leaking of CSF around the drain insertion site and prolonged duration of catheterisation. In children less than one-year old, risk factors for developing an EVDRI also includes diminished skin integrity and hydrocephalus secondary to IVH.[19]

1.2.5. Complications

Complications associated with EVD insertion include misplacement, dislodging or blockage of the drain, excessive CSF drainage leading to subdural haemorrhage, fluid and electrolyte imbalances, CSF leaks and infection.[20] These infections include ventriculitis, meningitis, subdural empyema and brain abscesses.

1.3. Diagnosis - laboratory parameters, microbiology, clinical manifestations

1.3.1. Laboratory parameters

1.3.1.1. CSF Glucose

There are no established cut-off values for hypoglycorrhachia but rather a ratio of CSF to serum glucose is used. Hypoglycorrhachia is only 80% sensitive and specific for meningitis/ ventriculitis in neurosurgical patients.[21] Up to 50% of patients may have normal CSF glucose levels in the presence of bacterial meningitis.[22] Abnormalities in CSF glucose may not reliably exclude meningitis or ventriculitis as there are causes other than infection that may contribute to hypoglycorrhachia. These conditions include chemical meningitis, ICH or stroke, malignancy, inflammatory conditions, neuro-sarcoidosis and hypoglycaemia. In a pooled analysis from 5 studies, the mean glucose concentration was lower in the 109 patients with EVDRIs when compared to the 671 patients who did not acquire infection from an indwelling EVD. A CSF to blood glucose ratio < 0.6 was found to be a strong indication for an EVDRI, although the sensitivity was low.[19] Guardado et al. found that the median CSF glucose in EVDRIs was low (1.6mmol/L) however the range was very wide (0.55 – 4.1 mmol/L).[23]

1.3.1.2. CSF Protein

Normal CSF protein may not reliably exclude infection in patients with meningitis or ventriculitis. Dorresteijn et al. found that an elevated protein concentration is a non-specific marker for EVDRIs. A significant difference in CSF protein concentration was observed in pooled studies including 199 episodes of EVDRI and 869 non-infected patients.[19]

Conversely, in another pooled study which included 90 patients with EVDRI and 253 non-infected patients, there was no difference found in the CSF protein concentrations.[19] Guardado et al. also found no significant increase in CSF protein levels in patients with EVDRIs with a median CSF protein level of 0.4 g/L and a range of 0.09 – 0.89 g/L.[23] Elevated CSF protein levels may however also be caused by conditions other than infection. These include ICH, malignancy, certain inflammatory conditions, Guillain Barré syndrome, multiple sclerosis, some endocrine abnormalities and certain medications.[22]

1.3.1.3. Other CSF parameters

sTREM-1

In a study conducted by Gordon et al, a CSF marker called soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) was useful in the diagnosis of EVDRIs and they suggested that it could be used to distinguish between episodes of colonisation and infection.[24]

CSF Lactate

Martin et al. found CSF lactate to be a useful biomarker in the diagnosis of bacterial EVDRIs as it had a better sensitivity and specificity than standard laboratory parameters.[21] This was also observed in a pooled meta-analysis conducted by Sakushima et al, where they observed a sensitivity of 93% and specificity of 96%.[25] CSF lactate my however be increased in non-infectious conditions such as seizures, stroke, hypoxia or traumatic brain injuries.[21]

CSF Presepsin

Abudeev et al. conducted a study on a CSF biomarker produced by microglial cells called presepsin. This marker is not affected by the presence of red blood cells in CSF. They found that the biomarker had a moderate diagnostic accuracy.[26] However, when combined with CSF lactate, Zheng et al. found that the accuracy was boosted (sensitivity of 82.8% and specificity of 73.5%).[27]

1.3.2. Microbiology

1.3.2.1. CSF WCC

A CSF leukocyte count of > 5 cells/μL (100% lymphocytes) in adults is considered abnormal, however a raised CSF WCC is often present in neurosurgery patients without infection.[21] A raised CSF WCC may be absent in 20% of patient with ventriculitis-associated infections.[21] An elevated CSF WCC is not limited to infection but may be caused by other conditions such as seizures, ICH, malignancy and inflammatory conditions. A confounding factor is that cells may not be distributed homogenously within the CSF leading to inconsistent cell counts when specimens are collected. This may be caused by patient movement and gravity sedimentation of blood as observed in a study conducted by Bådholm et al.[28] Another confounding factor is that blood causes aseptic inflammation which results in migration of leukocytes into CSF.[28] The greater the volume of intraventricular blood, the greater the aseptic response will be. Therefore, the presence of erythrocytes contributes to the number of white cells within the CSF.[28] Martin et al. found that post-operative neurosurgical patients with chemical or aseptic meningitis account for 60 – 75% of cases and therefore it is difficult to distinguish from true bacterial meningitis.[21]

In a study conducted by Smith et al, they noted a very wide CSF WCC range from 0 to 8050 in uninfected patients and noted that the WCC increased with an increased duration of the indwelling EVD.[29]

Martin et al. suggested that these limitations may be overcome by monitoring sequential CSF parameters over time or observing an increase in the CSF cell index (CSF WCC/red cell count ratio divided by the peripheral blood WCC/red blood cell ratio). A CSF cell index of > 5 is suggestive of an EVDRI, however this calculation method requires validation.[21]

1.3.2.2. Gram stain

A Gram stain is a useful tool when microorganisms are observed however it has a lower sensitivity for device-associated meningitis or ventriculitis. A negative CSF Gram-stain does not exclude the presence of infection, especially in patients who have received previous antimicrobial therapy.[4] Schade et al. evaluated the Gram stain in 1735 CSF specimens. Results showed that 2.2% of the specimens had a positive Gram stain, therefore the sensitivity of the Gram stain was 39.8% and the specificity 99.9%.[17] The positive predictive value was 97.4%, and the negative predictive value 96.5%.[17]

Culture

Culture is considered to be the gold standard for diagnosing EVDRIs, however it may not be specific because microorganisms may cause colonisation and contamination. Disadvantages of culture are that fastidious microorganisms may not grow, cultures may be negative with patients on antimicrobial therapy, it can be time consuming and it may take up to 10 days for some microorganisms such as *C. acnes* to grow.[19] Dorresteijn et al. conducted a study on 449 patients with EVDs in situ. Of these patients, only 98 CSF specimens were identified with positive CSF cultures and only 32 of these patient episodes required treatment for EVDRIs. Therefore 68 patient episodes had good outcomes without antimicrobial therapy.[19]

1.3.3. Clinical manifestations

Clinical manifestations of EVDRIs are not specific and may overlap with signs and symptoms caused by the underlying neurosurgical condition. These include headache, fever, nausea and vomiting, new or worsening LOC, nuchal rigidity and focal neurological deficit.[30] The classic triad of meningitis which includes fever, nuchal rigidity and altered LOC, has a low sensitivity of approximately 40 – 50% for healthcare-associated ventriculitis or meningitis and is observed in a minority of neurosurgical patients.[21]

Sam et al. found that the median Glasgow Coma Scale (GCS) of patients prior to surgery or endotracheal intubation was 8 with a range of 3 – 15.[31] In a meta-analysis reviewed by Dorresteijn et al, fever was present in 72% of patients with EVDRIs and 29% of patients had fever in the absence of infection. Headache was infrequently reported but was present in 62% of patients with EVDRIs. There was no difference in alteration of LOC between patients with infection (38%) and those without infection (41%) and nuchal rigidity was only observed in 27% of patients with EVDRIs.[32]

A large retrospective study analysed by Martin et al, found that clinical manifestations had a poor sensitivity. For patients with EVDRIs, 48.5% experienced a headache, 40.5% had a fever, 40.6% had altered LOC and 39.5% of patients experienced nausea and vomiting. The low sensitivity was thought to be due to use of treatment to reduce fever, administration of analgesia, anti-emetics and sedation and infections caused by low virulence organisms that elicit less meningeal inflammation and symptoms.[21]

Stocchetti et al. found that although fever is an important sign of infection, it is observed in up to 87% of patients with severe brain injuries. They also observed that approximately 50% of patients with brain injuries who presented with fever were non-infectious in nature.[33]

1.4. Aetiological profile of EVD-related infections

The microbial profile of healthcare-associated ventriculitis and meningitis is determined by the underlying neurosurgical condition of the patient and the type of surgery performed.

The aetiology of EVDRIs is broad ranging from skin pathogens to drug-resistant hospital-acquired pathogens. Most cases of ventriculitis associated with EVD use are caused by staphylococci but the proportion of Gram-negative bacteria are increasing. A multicentre study done in the United Kingdom and Ireland found that coagulase-negative staphylococci (CoNS) caused the majority of infections (34.5%) followed by *S. aureus* (20.7%), *Enterococcus* spp. (10.3%), Enterobacterales *(Enterobacter* spp, *K. pneumoniae, M. morganii, E. coli)* and infrequently *P. aeruginosa, Corynebacterium* spp. and *Streptococcus* spp.[20] Martin et al. found that there has been an increase in Gram-negative infections caused by Enterobacterales (*E. coli, Enterobacter* spp, *Klebsiella* spp.) and non-fermenters (*P. aeruginosa, A. baumannii*).[21] In a study conducted by Sam et al, 75.6% of episodes of EVDRIs were caused by Gram-negative organisms with *A. baumannii* being the most common organism identified (29.2%) with a mortality rate of 64.3%. This was followed by 14.6% of episodes caused by CoNS and 6.2% of episodes caused by *S. aureus*.[31] The reason for this is thought to be due to the administration of antimicrobial prophylaxis targeting Gram-positive bacteria, prolonged hospitalisation and the increasing complexity of neurosurgical care.[34]

In a study conducted by Mehreen et al, 76.9% of EVDRIs were caused by Gram-negative bacteria, 23% caused by Gram-positive bacteria, 30% caused by multi-drug resistant (MDR) organisms (2 isolates of *K. pneumoniae* and 1 isolate of *A. baumannii*) and 48% of episodes were culture negative.[35] A predominance of Gram-negative EVDRIs was also noted by Camacho et al. and Lyke et al. with 77% and 82% of infections respectively.[36,37] Chatzi et al. reported that 81% of EVDRIs were due to MDR Gram-negative bacteria, mainly *A. baumannii*.[38]

In a study done by Walti et al. the aetiology was predominantly monomicrobial (57%) with the most predominant microorganism being CoNS, followed by *C. acnes* and *S. aureus*. Other microorganisms identified contributed to 3% of EVDRIs. These organisms included *Acinetobacter* spp, *Corynebacterium* spp, *Micrococcus* spp, *M. hominis* and *Bacillus* spp. Polymicrobial infections contributed to 10% of EVDRIs and culture-negative infections were 11%.[30] Martin et al. found that most EVDRIs were bacterial and monomicrobial with Gram-positive organisms contributing to 50 to 60% of infections, predominantly *S. epidermidis* and *S. aureus*. *C. acnes* was also commonly found to cause infection and rarely *Corynebacterium jeikeium.*[21]

EVD-related fungal infections are rare and are mostly observed in immunocompromised patients or in outbreak settings. The most common fungal pathogen causing EVDRIs is *Candida* spp.[34] A study conducted by Tsioutis et al, found a fungal infection rate of 5.2% with *Candida albicans* and *Candida parapsilosis* isolated.[39]

Table 3 summarises the aetiology of EVD-related infections globally.

Table 3: **Aetiology of EVD-related infections**

Country	Author	Year published	Percentage (%)	Predominant pathogens
India	Mehreen et al.[35]	2022	23 (67% MDR) 15 (50% MDR) 15	*K. pneumoniae* *A. baumannii* *P. aeruginosa*
Malaysia	Sam et al.[31]	2018	29.2 20.8 14.6	MDR *A. baumannii* *P. aeruginosa* CoNS
UK & Ireland	Jamjoom et al.[20]	2017	34.5 20.7 10.3	CoNS *S. aureus* *Enterococcus* spp
France	Mounier et al.[34]	2015	22 16 13	*S. epidermidis* *P. aeruginosa* *K. pneumoniae*
Greece	Chatzi et al.[38]	2014	44.8 6.8 6.8	*A. baumannii* *CRE K. pneumoniae* Gram-negative polymicrobial
Switzerland	Walti et al.[30]	2012	63 15 11	CoNS *C. acnes* *S. aureus*
Brazil	Camacho et al.[36]	2010	27.3 (50% MDR) 18.2 13.6 13.6	*A. baumannii* *K. pneumoniae* *Enterobacter* spp *P. aeruginosa*
USA	Lyke et al.[37]	2001	36 18 18	*K. pneumoniae* *E. cloacae* CoNS

1.5. Management of EVD sepsis

1.5.1. Prevention

1.5.1.1. EVD indwelling time

There is no consensus on time to change EVDs periodically and several authors have suggested that infection is independent of EVD indwelling time, thereby recommending that the EVD may remain in situ until it becomes infected, blocked or is no longer required.[40] Conversely some reports found that infection rates increase with prolonged EVD indwelling time with a recommendation that catheters should be replaced after 5 days.[40] Most studies found that EVDRIs occur if the catheter has been in situ for more than 5 days. In a study conducted by Walti et al, EVDRIs occurred 6 days after insertion with a range of 1 – 17 days and in 47% of patients meningitis occurred 1 – 10 days after EVD removal.[30] Jamjoom et al. found that the risk of EVDRIs occurred after a catheter indwelling time of ≥ 8 days.[20] In a study conducted by Khalaveh et al, infections occurred at a mean duration of 25.6 days with a wide range of 7 to 163 days, thereby indicating that prolonged use of EVDs increases the risk of acquiring infection.[41] In an analysis conducted by Fried et al, there was evidence of increasing risk of infection in the first week after catheter insertion. However, evidence is contradictory after 1 week of EVD indwelling time with various studies suggesting that the risk of infection increases, decreases or plateaus.[42] This may be as a result of the varying definitions of EVDRIs and different study methodologies. Sam et al. found that time from EVD insertion to EVDRI ranged from 2 to 21 days with a median of 9 days and those with EVDs in situ for a prolonged period of time had poor outcomes.[31] Korinek et al, assessed EVD indwelling time of more than 5 days and more than 10 days and found that there was no difference in infection rates between these 2 groups.[43] A study conducted by Arabi et al, found that the risk of developing an EVDRI increases steadily until catheter indwelling time at day 7 and thereafter plateaus. They found that there was a significant risk of infection for each day that the EVD remained in situ in the first 7 days, followed by an insignificant increased risk thereafter as depicted in a Figure 1.[9] Motloba et al found that there was a correlation between the number of EVDs inserted and the incidence of ventriculitis.[7]

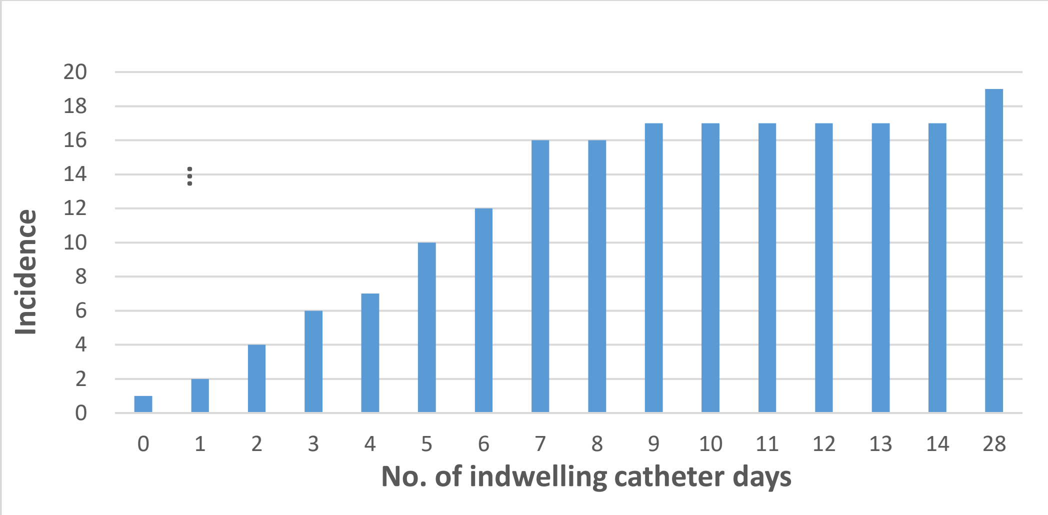

Figure 1: Cumulative risk of acquiring EVD-related infections

Adapted from Arabi et al.[9]

1.5.1.2. EVD Catheter type

There are 3 types of external ventricular drains; standard, antibiotic-impregnated and silver-impregnated drains. Winkler et al. compared antibiotic-impregnated with silver-ionised catheters. They found that there was no difference in the infection rate when using either catheter and they recommended that silver-impregnated catheters may be a safe and cost-effective alternative to antibiotic-impregnated catheters.[44] A randomised controlled trial conducted by Zabramski et al, found that positive cultures were less frequently observed in patients with antibiotic-impregnated catheters (1.3%) than in the group with standard silicone catheters (9.4%).[45] Pople et al. conducted a randomised controlled trial on 2 groups of patients, those with antibiotic-impregnated catheters and those with standard catheters. They found that there was no difference in the infection rate in the control group assigned with standard catheters (2.8%) and the test group assigned with antibiotic-impregnated catheters (2.3%). This may however have been due to a high number of patients in both groups receiving concomitant intravenous antimicrobial therapy.[46] Motloba et al. found that there was no difference in the infection rate between children who were treated with antibiotic-impregnated catheters versus those treated with standard catheters. They also found that administration of prophylactic antibiotics did not reduce the risk of infection.[7]

Antimicrobial prophylaxis

Use of antimicrobial prophylaxis is controversial and no consensus has been reached. Antimicrobial prophylaxis can either be administered perioperatively or may continue for the duration that the EVD remains in situ. Most trials compared these two methods of prophylaxis and found that results were inconclusive to prove that one was more superior than the other. In a study conducted by Fu et al, the infection rate was 2.7% in the group receiving vancomycin prophylaxis versus 11.9% in the group that was not receiving prophylaxis.[47] The risk of using systemic antimicrobial prophylaxis for the duration of indwelling catheter time is that it may lead to growth of MDR organisms and increased rates of *C.difficile* infections.[42]

1.5.1.3. Clinical methods

Recommendations to further reduce EVDRIs include removal of the EVD when it is no longer used, avoidance of routine CSF sampling, strict maintenance of a closed EVD system, implementation of EVD care bundles and staff education. To prevent spread of MDR organisms such as *A.baumannii*, it is recommended to implement infection control protocols, isolate or cohort colonised or infected patients, hand hygiene and environmental disinfection.[31]

1.5.2. Treatment

When treating EVDRIs, selection of empiric antimicrobials depends on the institution's local antibiogram patterns for the causative organisms. Most institutions commence an antipseudomonal β-lactam (ceftazidime, cefepime, meropenem) for broad spectrum Gram-negative cover and vancomycin for broad Gram-positive cover (including CoNS and MRSA). Thereafter, antibiotics are altered based on culture results and susceptibility patterns.[34]

Colistin may be the only available treatment option for organisms such as XDR *A. baumannii*, however it has poor central nervous system (CNS) penetration. Ziaka et al. found that combined administration of intravenous and intrathecal colistin resulted in higher CSF concentrations and therefore recommended the use of both administration methods when treating EVDRIs caused by MDR organisms.[48]

1.6. Antimicrobial resistance in EVD sepsis

Few studies have investigated antimicrobial susceptibility patterns for microorganisms causing EVDRIs.

In a study conducted by Wang et al, antimicrobial resistance patterns were assessed for Gram-negative organisms causing post-neurosurgical meningitis and ventriculitis. *A. baumannii* complex was isolated from seven CSF specimens; all were resistant to third and fourth generation cephalosporins, six isolates were resistant to carbapenems and four isolates were resistant to the aminoglycosides. Two CSF specimens where *E. coli* was isolated, were extended spectrum β-lactamase (ESBL) positive.[49] Sam et al. evaluated the antimicrobial susceptibility patterns of a number of antimicrobial agents against *A. baumannii*. Only 14.3% of *A. baumannii* isolates were susceptible to carbapenems, 14.3% were susceptible to ceftazidime, 50% were susceptible to amikacin, 42.9% were susceptible to gentamicin and 28.6% of isolates were susceptible to trimethoprim-sulfamethoxazole.[31] In a study conducted by Chatzi et al, 81.2% of organisms isolated in EVDRIs were MDR Gram-negative bacteria. *A. baumannii* was present in 75% of these isolates, followed by carbapenemase-producing *K. pneumoniae.*[38]

Tsioutis et al. observed that 63.6% of Gram-negative isolates were resistant to third generation cephalosporins, 54.5% were resistant to carbapenems and 40.9% were MDR.[39]

In a study conducted by Walti et al, 41% of CoNS were resistant to methicillin and 14% resistant to rifampicin.[30] Tsioutis et al. found that 72.7% of their CoNS isolates were methicillin-resistant.[39]

In a study conducted by Wang et al, 38 patients were identified with EVDRIs caused by vancomycin-resistant enterococci over a 25-year period.[50] In a case report written by Cearns et al, a patient was successfully treated with a 2-week course of intravenous linezolid for an EVDRI secondary to vancomycin-resistant *E. faecium.*[51] However according to the literature, Gram-positive antimicrobial resistance remains rare.

1.7. Significance of study

There is no standard definition for EVDRIs and no consensus in the literature on which parameters are best to use when defining these infections making diagnosis difficult. This study will identify if certain parameters used in combination or alone (microbiology, laboratory parameters and clinical signs and symptoms) are useful in the diagnosis of EVDRIs. The study is also important as we identify pathogens causing infection, colonisation and contamination and to identify their antimicrobial susceptibility patterns. This will guide clinicians on the best empiric therapy to commence when treating suspected EVDRIs and which infection prevention and control strategies to employ.

1.8.Aims and Objectives:

1.8.1. Aim

To retrospectively analyse the clinical and laboratory characteristics of EVDRIs at a central referral hospital in KwaZulu-Natal from 2019 – 2021.

1.8.2. Objectives

1. To describe the demographic profile of patients with suspected EVD-related sepsis.
2. To assess the length of external ventricular drain indwelling time and its correlation with infection, colonisation and contamination.
3. To correlate clinical criteria and CSF cell count and chemistry with positive CSF cultures in patients suspected of having EVDRIs, colonisation or contamination.
4. To analyse the microbial aetiology of EVDRIs, colonisation and contamination.
5. To determine the antimicrobial susceptibility patterns of the major causative microorganisms of EVDRIs, colonisation and contamination.

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CHAPTER TWO

External ventricular drain infections: a retrospective analysis at a central hospital in KwaZulu-Natal, South Africa

Prepared according to the Instructions for Authors of **World Neurosurgery**

External ventricular drain infections: a retrospective analysis at a central hospital in KwaZulu-Natal, South Africa

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Keywords: External ventricular drain, infection, ventriculitis, cerebrospinal fluid

ABSTRACT

Objectives

We describe clinical, laboratory and microbiological characteristics of patients with suspected EVD-related infections (EVDRIs), colonisation and contamination.

Methods

An observational analytical retrospective descriptive cohort study was conducted on all positive cerebrospinal fluid (CSF) cultures from external ventricular drains (EVDs) at a referral hospital from 2019 - 2021. Episodes were categorised as infection, colonisation or contamination based on pre-defined clinical and laboratory characteristics. Demographic data, clinical information and identification and susceptibility results of microbes isolated from CSF were analysed for each of these episodes.

Results

One hundred and sixty-three patients were included with 337 positive CSF cultures. Positive cultures were grouped into 213 episodes; 76 (36%) infection, 13 (6%) colonisation and 124 (58%) contamination. The median duration of EVD insertion to infection was 17 days. In the infection group 58 episodes (76%) had low CSF glucose, persistently low or decreasing CSF glucose. Sixty-seven patient episodes (88%) had high CSF protein or increasing protein. The CSF white cell count (WCC) was higher in the infection group versus colonisation and contamination groups with a wide range. The causative organisms of EVDRIs were predominantly Enterobacterales (33%), extensively drug-resistant (XDR) *A. baumannii* (27.6%) and coagulase-negative staphylococci (CoNS) (13%). The causative organisms of EVD-related colonisation and contamination were predominantly CoNS.

Conclusion

Laboratory parameters (CSF glucose, protein and WCC) were useful to distinguish EVDRIs from colonisation and contamination. However clinical manifestations require correlation with laboratory abnormalities to diagnose EVDRIs. Multidrug resistant (MDR) Enterobacterales and extensively drug-resistant (XDR) *A. baumannii* were the commonest cause of EVDRIs.

Abbreviations and Acronyms: CDC, Centre for Disease Control; CoNS, coagulase-negative staphylococci; CSF, cerebrospinal fluid; ESBL, extended β-lactamase; EVD, External ventricular drain**;** EVDRI, External ventricular drain-related infection; IALCH, Inkosi Albert Luthuli Central Hospital; IDSA, Infectious Diseases Society of America; ITH, intrathecal; IV, intravenous; LOC, level of consciousness; MDR, multidrug resistant; MRSA, methicillin-resistant *S. aureus*; NHLS, National Health Laboratory Service; WCC, White cell count; XDR, extensively drug-resistant.

INTRODUCTION

External ventricular drains (EVDs) are used for the short-term management and monitoring of intracranial pressure in all age groups. Infections, which are a complication associated with EVDs, include ventriculitis, meningitis, subdural empyema and brain abscesses.[1]

The incidence of external ventricular drain-related infections (EVDRIs) varies widely in studies. This may be due to challenges when diagnosing infections as definitions vary and abnormalities in cerebrospinal fluid (CSF) chemistry, white cell count (WCC) and clinical manifestations may be caused by conditions other than EVDRIs. According to the Centre for Disease Control (CDC), the reported incidence varies from less than 1% to 45 %[2], however; the Infectious Diseases Society of America (IDSA) found that the incidence of EVDRIs was slightly lower and ranged from 0 – 22%.[3]

There is no standard definition for EVDRIs and therefore it is difficult to diagnose. This limits the study, surveillance and comparison of practices for EVDRIs. EVDRI diagnostic criteria may include parameters such as microbiology results, clinical manifestations of meningitis or ventriculitis and abnormal CSF results. Some authors do not consider laboratory parameters to be of use in the diagnosis of EVDRIs while other authors include microbiology results and/or clinical manifestations and/or laboratory parameters as important aspects when diagnosing EVDRIs.[2–4] Definitions for colonisation include the following criteria: ≥ 2 positive CSF cultures with the same pathogen in the absences of clinical manifestations with some authors also including the absence of abnormal laboratory parameters.[2–4] The definitions of contamination are variable. Some authors describe contamination as the isolation of a common contaminant cultured from an enrichment broth only, from just one of multiple CSF cultures or multiple organisms isolated from a single CSF sample with no clinical manifestations. Other authors include the absence of abnormal laboratory parameters.[2–4] Further, clinical manifestations of EVDRIs are not specific and may overlap with signs and symptoms caused by the underlying neurosurgical condition.[5]

Most studies consider high CSF WCC, low glucose levels and high protein levels as important parameters used concurrently with microbiology results when diagnosing EVDRIs, however; abnormalities in CSF cell count, glucose, and/or protein may not be reliable to diagnose healthcare-associated ventriculitis and meningitis. Moreover, normal CSF cell count, glucose, and protein may not reliably exclude infection in patients with healthcare-associated ventriculitis and meningitis. In addition, a negative CSF Gram stain does not exclude the absence of infection, particularly in those who have received antimicrobial therapy.[3]

The aetiology of EVDRIs is broad, ranging from skin pathogens to drug-resistant hospital-acquired pathogens. Coagulase-negative staphylococci (CoNS) cause the majority of infections followed by *S. aureus*, *Enterococcus* spp and Enterobacterales.[6] Although staphylococci cause the majority of EVDRIs, the incidence of Gram-negative bacterial infections are increasing with the emergence of XDR *A. baumannii*.[7]

Few studies have investigated antimicrobial susceptibility patterns for microorganisms causing EVDRIs, however some studies have found high rates of MDR organisms causing EVDRIs.[8–10]

We describe the clinical, laboratory and microbiological characteristics of patients with suspected EVDRIs with the aim of classifying these as true EVDRIs, colonisation or contamination.

METHODS

Study design, location and period

This was a retrospective, observational, descriptive cohort study of EVDRIs at the Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital (IALCH) for the period of 2019 - 2021. The Neurosurgery Department services the entire KwaZulu-Natal province, with referrals from the Eastern Cape Province with approximately 740 admissions per year.

Data collection

Data was accessed from the National Health Laboratory Service laboratory information system for CSF laboratory parameters (glucose, protein, WCC), CSF Gram stain, culture and antimicrobial susceptibility. The hospital information system (Meditech) was used to retrieve patient ages, gender, clinical manifestations (fever, headache, nuchal rigidity, nausea and vomiting, level of consciousness (LOC), date of EVD insertion and removal and number of EVD changes.

Inclusion Criteria

The study population included patients of all ages admitted to IALCH neurosurgery wards with EVDs (silver-impregnated polyurethane) in situ who had positive CSF cultures from 1 January 2019 to 31 December 2021.

Exclusion criteria

The following patients were excluded from the study:

Patients who presented with blocked or infected ventriculoperitoneal shunts who had subsequent insertion of an EVD.

Patients with a pre-existing meningitis for whom an EVD was inserted to administer intrathecal antibiotics.

Patients with leaking myelomeningoceles or encephaloceles who required insertion of an EVD.

Patients with culture negative EVDRIs.

Definitions[2,11–13]

Patients' episodes were categorised according to the following criteria:

Infection:

- ≥ 1 positive CSF cultures AND
- Low CSF glucose + high CSF protein + CSF pleocytosis in a single sample OR
- Decreasing CSF glucose + increasing CSF protein + increasing WCC in serial samples AND/OR
- Clinical manifestations compatible with ventriculitis/meningitis.

Colonisation:

- > 1 positive CSF culture with the same microorganism AND
- Clinical manifestations NOT compatible with ventriculitis/meningitis AND
- Expected CSF parameters that are not worsening (abnormal CSF parameters secondary to causes other than infection).

Contamination:

- A single positive CSF culture or culture only from the enrichment broth AND
- Clinical manifestations NOT compatible with ventriculitis/meningitis AND
- Expected CSF parameters that are not worsening (abnormal CSF parameters secondary to causes other than infection).

Laboratory criteria

CSF parameters were defined as:

- Hypoglycorrhachia: CSF ≤ 2.8 mmol/L. This value was utilised as plasma glucose levels were infrequently tested concomitantly with CSF glucose.[12]
- CSF protein of > 0.45 g/L was used as high protein level as per NHLS reference range.
- WCC: Neutrophilic CSF pleocytosis > 5 cells/µL.[13]

Clinical manifestations

Clinical parameters were recorded on the day that the positive CSF specimen was taken. Fever was defined as a temperature of $\geq$ 38.0°C. Patients with fever secondary to meningitis or ventriculitis were included in the infection group. Headache, nuchal rigidity, nausea and vomiting and LOC were also documented.

EVD-related data

Catheter days were calculated as the total number of indwelling EVD-days per patient, all patient EVD-days were then added together for the total period of the study.[14] The device-associated infection rate was calculated by dividing the total number of EVDRIs by catheter days and multiplying by 1000 to give an EVDRI rate per catheter days.[14]

Bacterial identification and susceptibility testing

Standard laboratory techniques were used to process CSF specimens for cell count and culture.[15] After centrifugation, the sediment was inoculated into Thioglycolate broth and onto Chocolate and Blood agar (Diagnostic Media Products), followed by incubation at 35 – 37 °C for 24 hours. A Gram stain was also performed on the sediment of the CSF.[15]

Microorganisms were identified and their antimicrobial susceptibility patterns established with the Vitek 2 Advanced Expert System™ (bioMerieux) or manual methods such as Kirby-Bauer disk diffusion and antimicrobial susceptibility interpreted according to CLSI guidelines.[16] Susceptibility testing for systemic and intrathecal antimicrobial drugs used for central nervous system infections were analysed. Antimicrobial agents tested for Gram-positive organisms included ampicillin, penicillin, cloxacillin, third-generation cephalosporins, vancomycin, linezolid and rifampicin. Agents tested for Gram-negative organisms included third-generation cephalosporins, carbapenems, aminoglycosides, trimethoprim-sulfamethoxazole and tigecycline. Colistin susceptibility was not reported in this study. Extensively drug-resistant Gram-negative organisms were sent to a reference laboratory to perform broth microdilution[16] as this test is not offered in our laboratory.

<u>Resistance phenotypes were classified as follows</u>:

Extended spectrum β-lacatamase (ESBL) producing Gram-negative bacilli - resistant to third-generation cephalosporins.

Amp-C producing Gram-negative bacilli - resistant to penicillin, second- and third-generation cephalosporins and cephamycins.

MDR – resistant to ≥ 1 agent in ≥ 3 antimicrobial categories.[17]

XDR Gram-negative bacilli - resistant to ≥ 1 agent in all but ≤ 2 categories.[17]

Methicillin resistant *Staphylococcus aureus* (MRSA) - resistant to cloxacillin.

Statistical analysis

Descriptive statistics were used to describe the data. Frequencies and percentages were used for categorical data. Anova was used to determine if there was a difference in means between the 3 groups (infection, colonisation and contamination groups). Further to this, t-test analysis was used comparing two groups at a time to determine which of the means were significantly different by evaluating the p-values. Susceptibility of each drug was reported as the percentage susceptible.

Ethical considerations

The study received approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00004111/2022), IALCH, NHLS and the KwaZulu-Natal Department of Health.

RESULTS

During the study period, there were 163 patients with 337 positive CSF cultures. The median patient age was 31 years (range: 2 months – 68 years) with a predominance of males (72%). Patient characteristics are summarised in Table 1.

Categorisation of infection, colonisation and contamination

After analysis of the 337 positive CSF cultures, the specimens were grouped into 213 patient episodes and categorised into 76 episodes of infection (36%), 13 episodes of colonisation (6%) and 124 episodes of contamination (58%) as per definitions. Some patients with prolonged hospital stay, were identified with multiple episodes of infection, colonisation, contamination or a combination thereof. Of the 163 patients, twenty-two patients (14%) had a combination of infection, colonisation and/or contamination (see Table 2). Forty-seven patients (29%) exclusively developed EVDRIs with six of these patients having two episodes of infection during their admission. Five patients (3%) had exclusive episodes of colonisation with one patient having two episodes of colonisation. Eighty-nine patients (55%) had exclusive episodes of contamination with ten of these patients having two episodes of contamination and three patients having three episodes of contamination.

EVD-related data

Fifty-one percent of patients (n = 83) required more than one EVD, inserted concomitantly or sequentially. Of the 15 patients who required the insertion of more than five EVDs, the median number of EVDs utilised was 12 (range: 6 – 17). The median EVD-indwelling time was 24 days (range 2 – 148 days) and the median time from EVD insertion to infection was 17 days (range: 1 – 120 days). The median time from EVD insertion to colonisation was 19 days (range: 4 – 65 days) and to contamination was 13 days (range: 1 – 63 days). The device-associated infection rate was 19.3 per 1000 EVD days considering the total time of EVDs in place (3928 days). Table 3 displays EVD-related data.

Clinical manifestations

The predominant clinical manifestations in the infection group were fever, alteration in the LOC and nuchal rigidity. Fever was present in 27 episodes (36%), alteration in LOC in 14 episodes (18%) and nuchal rigidity in 8 episodes (11%) in the infection group. Fever was documented in one episode in the colonisation group (8%) and in 15 episodes in the contamination group (12%) which was caused by infections other than EVD sepsis.

Laboratory criteria

CSF Glucose

The median CSF glucose was significantly lower in the infection group than the colonisation ($p < 0.001$) and contamination groups ($p < 0.001$) but not between the colonisation and contamination group ($p = 0.42$). Only 13 % of patients with EVDRIs had a normal CSF glucose. In the infection group, 58 episodes (76%) had an initial low CSF glucose (median: 1.9 mmol/L), persistently low glucose or decreasing CSF glucose in subsequent specimens.

This was not observed in the colonisation (median: 3.9 mmol/L) or contamination (median: 4.9 mmol/L) groups.

CSF Protein

The median CSF protein was higher in the infection group in comparison with the colonisation ($p = 0.028$) and contamination groups ($p < 0.001$) but not between the colonisation and contamination group ($p = 0.30$). Only 5 patients (7%) with EVDRIs had a normal CSF protein. In the infection group, 67 episodes (88%) had high initial CSF protein (median: 1.8 g/L) or rising protein levels in subsequent CSF specimens. This was not observed in the colonisation (median: 0.80 g/L) or contamination (median: 0.67 g/L) groups.

CSF WCC

The median polymorphonuclear neutrophil (PMN) count was much higher in the infection group (326/μL) versus the colonisation (9.7/μL) and contamination (31/μL) groups.

There was a statistically significant difference between the infection and colonisation group ($p = 0.016$) and the infection and contamination group ($p < 0.001$) but not the colonisation and contamination group ($p = 0.19$). However, the range (0 - > 1000) was very wide in the infection and contamination groups.

Clinical manifestations and laboratory parameters are summarised in Table 4.

Aetiology

The aetiology of EVDRIs, colonisation and contamination is summarised in Table 5. Monomicrobial cultures were predominant in all categories (> 90%). Microorganisms cultured from broth cultures only were seen in 22 episodes of the contamination group (10%) and 2 episodes were categorised into the infection group (3%) due to deranged laboratory parameters, the presence of clinical manifestations and commencement of antimicrobial therapy.

The causative organisms of EVDRIs were predominantly *A. baumannii* isolated in 26 episodes (34.2%), Enterobacterales isolated in 25 episodes (33%) and followed by CoNS isolated in 10 episodes (13%). *K. pneumoniae* was the most common Enterobacterales causing infection, contributing to 11 episodes (14%). Four of these episodes (36%) were secondary to ESBL-producing *K. pneumoniae* and one episode (9%) due to XDR *K. pneumoniae*. Amp-C producing Enterobacterales caused nine episodes (12%) of infection and XDR *A. baumannii* contributed to 21 episodes (27.6%) of infection. The causative organisms of EVD-related colonisation and contamination were predominantly CoNS (92% and 64% respectively) of which *S. epidermidis* was the most common microorganism. Both Enterobacterales and *A. baumannii* each contributed to 11 episodes (9%) of contamination. Fungal isolates were infrequent and responsible for two contamination episodes (2%).

Antimicrobial susceptibility

The overall antimicrobial susceptibility results for the study period are summarised in Table 6. Of the Enterobacterales isolated, 16 (48%) were susceptible to the third-generation cephalosporins, 34 (97%) to meropenem, 22 (76%) to imipenem, 28 (90%) to amikacin and 22 (71%) to gentamicin. Twenty-seven isolates (73%) of *A. baumannii* isolates were XDR. Twenty-six isolates (27%) of CoNS isolated were susceptible to cloxacillin and 4/6 (67%) *S. aureus* isolates were susceptible to cloxacillin. Of the streptococci (including enterococci), 6 isolates (50%) were susceptible to ampicillin. All Gram-positive organisms were susceptible to vancomycin.

DISCUSSION

We analysed clinical and laboratory characteristics of EVDRIs and compared them with those in the colonisation and contamination groups. CSF glucose was significantly lower and CSF protein and WCC were significantly higher in patients with EVDRIs compared to those from the colonisation and contamination groups. We observed a high rate of infection which was predominantly caused by Gram-negative bacteria (Enterobacterales and *A. baumannii*) while the majority of the contaminants were CoNS. A high rate of resistance to third-generation cephalosporins, carbapenems and cloxacillin were detected among Enterobacterales, *A. baumannii* and CoNS isolates respectively.

The incidence of EVDRIs varies widely in studies. The device-associated infection rate in our study was 19.3 per 1000 EVD-days which was higher than that seen in studies done by Hagel et al. where the infection rate was 10.4 per 1000 catheter days and in a meta-analysis done by Champey et al, where the overall pooled incidence of 35 studies of EVDRI was 11.4 per 1000 catheter days.[1,18] The risk of EVDRIs increases with every day that an EVD is in situ.[6,19] Arabi et al. found that the risk of EVDRIs increased steadily in the first 7 days and thereafter plateaus. In their study the infection rate was higher than ours at 32 per 1000 catheter days.[20] We did not find that the length of catheter indwelling time contributed to infections as there was no significant difference in time to infection versus colonisation and contamination.

Although specific clinical manifestations are observed in EVDRIs, these signs and symptoms may also be caused by other factors like the underlying neurosurgical condition. The classic triad of meningitis which includes fever, nuchal rigidity and altered LOC, has a low sensitivity of approximately 40 – 50% for health-care associated ventriculitis or meningitis and is observed in a minority of neurosurgical patients.[21] About a third of our patients in the infection group had fever. Stocchetti et al. found that although fever is an important sign of infection, it is observed in up to 87% of patients with severe brain injuries and approximately 50% of patients with brain injuries who presented with fever did not have infections.[22] In our study, decreased LOC was found in 18% of patients with EVDRIs which was lower than expected. This may have been due to the low GCS on admission secondary to the primary neurosurgical condition. In a large retrospective study analysed by Martin et al, they found that clinical manifestations had a poor sensitivity. For patients with EVDRIs, 48.5%

experienced a headache, 40.5% had a fever, 40.6% had altered LOC and 39.5% of patients experienced nausea and vomiting.[21]

Hypoglycorrhachia is commonly used to aid in the diagnosis of EVDRIs however it is only 80% sensitive and specific for meningitis/ventriculitis in neurosurgical patients.[21] A CSF to blood glucose ratio <0.6 was found to be a strong indication for an EVDRIs, although the sensitivity was low.[23] In our study, the median CSF glucose was significantly lower in the infection group than the colonisation and contamination groups. In a pooled analysis from 5 studies, the mean glucose concentration was lower in the 109 patients with EVDRIs when compared to the 671 patients who did not acquire infection following insertion of an indwelling EVD. Guardado et al. found that the median CSF glucose in EVDRIs was low

(1.6mmol/L) however the range was very wide (0.55 – 4.1 mmol/L).[24] Our study correlated with Guardado et al. where our median CSF glucose (1.9mmol/L) was low with a wide range (0 – 6.2mmol/L).

Normal CSF protein may not reliably exclude infections in patients with meningitis or ventriculitis, however in our study the median CSF protein was higher in the infection group in comparison with the colonisation and contamination groups. Dorresteijn et al. found that an elevated protein concentration is a non-specific marker for EVDRIs.[23] A significant difference in CSF protein concentration was observed in pooled studies including 199 episodes of EVDRI and 869 non-infected patients. Conversely, in another pooled study which included 90 patients with EVDRI and 253 non-infected patients, there was no difference found in the CSF protein concentrations.[23] Guardado et al. also found no significant increase in CSF protein levels in patients with EVDRIs with a median CSF protein level of 0.4 g/L and a range of 0.09 – 0.89 g/L.[24] Our CSF protein levels were much higher (median: 1.8g/L) and our range much wider than that found in the study conducted by Guardado et al.

The median PMN count was much higher in our infection group versus the colonisation and contamination groups although; the range was very wide in both the infection and contamination groups. Therefore, the CSF WCC may be useful to aid in the diagnosis of infection. A confounding factor is that cells may not be distributed homogenously within the CSF caused by patient movement and gravity sedimentation of blood as observed in a study conducted by Bådholm et al.[25] Another confounding factor is that blood causes aseptic inflammation which results in migration of leukocytes into CSF.[25]

The aetiology of EVDRIs is broad ranging from skin pathogens to drug-resistant hospital-acquired pathogens.

In multiple studies done, the skin colonisers, CoNS, most commonly caused EVDRIs[5,21,26], however in our setting, the predominant causative organisms of EVDRIs were predominantly Enterobacterales (32%) and XDR *A. baumannii* (27%), followed by CoNS (13%). The majority of the patients in our study were admitted to an ICU or high care setting where the risk of becoming colonised or infected with drug-resistant organisms increases, therefore our results were to be expected. This correlates with another study conducted in South Africa, where Gram-negative organisms were the predominant cause of ventriculitis in children.[27] Martin et al. also found an increase in Gram-negative infections caused by Enterobacterales and non-fermenters (*P. aeruginosa*, *A. baumannii*).[21] In a study conducted by Sam et al. 75.6% episodes of EVDRIs were caused by Gram-negative organisms with *A. baumannii* being the most common organism identified. This was followed by 14.6% of episodes caused by CoNS and 6.2% of episodes caused by *S. aureus*.[28] The reason for this is thought to be due to the administration of antimicrobial prophylaxis targeting Gram-positive bacteria, prolonged hospitalisation and the increasing complexity of neurosurgical care.[28] The majority of infections in our study were monomicrobial which correlates with other studies.[5,21]

The causative organisms of EVD-related colonisation and contamination were predominantly caused by the skin colonisers, CoNS; however, we noted that Gram-negative organisms also contributed to colonisation and contamination. This correlates with a study conducted by Khalaveh et al, in which 42% of episodes were classified as colonisation with *S. epidermidis* being the predominant coloniser.[26] Other reports did not include organisms other than CoNS as cause of colonisation and contamination and did not compare rates of infection versus colonisation and contamination.[2,29] Eleven isolates (9%) of *A. baumannii* contributed to contamination. *A. baumannii* is known to be an environmental organism which could likely have contributed to this high rate of contamination however it can also lead to infection in vulnerable patients.

Few studies have investigated antimicrobial susceptibility patterns for organisms causing EVDRIs. In our study only 27% of CoNS isolated were susceptible to cloxacillin. Walti et al. found that 41% of CoNS isolates were resistant to methicillin.[5] Only 2 cases of MRSA EVDRIs were detected in our study, which is in keeping with other reports.[1,5]

We found that the majority of our Enterobacterales isolates were resistant to third-generation cephalosporins which was similarly observed by Zheng et al. and Tsioutis et al. with 92% and 63.6% resistance.[10,30] However, in contrast to these authors who observed high rates of resistance of Enterobacterales to carbapenems, the majority of our isolates were susceptible to carbapenems.[10,30]

We reported a high rate of EVDRIs caused by XDR *A. baumannii* which was also found by Wang et al.[8] Furthermore, Sam et al. found only 14.3% of *A. baumannii* isolates were susceptible to carbapenems, with low susceptibility rates to other antimicrobials tested.[28]

There are limited treatment options available for XDR Gram-negative organisms. According to Velkov et al, a small portion of intravenous (IV) polymyxin permeates the CNS, therefore it should be used in combination with intrathecal (ITH) colistin.[31] Although combination of treatment with colistin has a significant effect against XDR organisms such as *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*, it can cause nephrotoxicity and neurotoxicity.[32] Tigecycline is a salvage drug which may also be used to treat XDR Gram-negative organisms in combination with colistin. Intravenous tigecycline has a poor CSF penetration rate of only 11%, therefore; it is also recommended to be used in combination with ITH administration.[32]

Limitations: The results of this study cannot be generalised to other settings, hospitals or patient profiles as a single centre was utilised for the analysis. Patients with culture-negative EVDRIs were not included in the study. Most patients did not have a paired CSF and serum glucose done, therefore a CSF glucose $\leq$ 2.8 mmol/L was utilised to define hypoglycorrhachia. The CSF white cell count could not be performed when blood clots were present in specimens. In some patients, CSF chemistry was not performed concomitantly with microbiology. Clinical information related to treatment and outcomes were not included in this study.

In conclusion, isolated derangements in laboratory parameters (CSF WCC, glucose and protein) were observed in the colonisation and contamination groups; however, there was a significant difference in these parameters when compared with the infection group. Therefore, we found that laboratory parameters were useful to distinguish EVDRIs from colonisation and contamination. Clinical manifestations alone were not useful to identify EVDRIs and should be used concomitantly with laboratory parameters and microbiology. Enterobacterales followed by XDR *A. baumannii* was a common cause of EVDRIs while CoNS were found as colonisers and contaminants in a majority of cases. In our setting we recommend the use of meropenem and vancomycin as empiric therapy, encourage strict infection prevention and control measures and the implementation of EVD care bundles.

DISCLOSURES

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TABLES

Table 1: Demographic data for all patients

Characteristics	**Patients (n = 163)**
Age, median (range) – months to years	31 (2months – 68 years)
Gender	
▪ Males	118 (72%)
▪ Females	45 (28%)

Table 2: Episodes of infection, colonisation, contamination or combination thereof

Episodes	**Patients (n = 163)**
Infection	47 (28.8%)
Colonisation	5 (3.1%)
Contamination	89 (54.6%)
Infection and colonisation	3 (1.8%)
Infection and contamination	15 (9.2%)
Infection, colonisation and contamination	3 (1.8%)
Colonisation and contamination	1 (0.6%)

Table 3: EVD-related data

	Patients (n = 163)	Catheter days
EVD indwelling time, median (range) - days		
	24 (2 – 148 days)	
Number of EVDs per patient (sequential)		
▪ 1	80 (49%)	1541
▪ 2	23 (14%)	786
▪ 3	20 (12%)	604
▪ 4	14 (9%)	377
▪ 5	11 (7%)	200
▪ > 5	15 (9%)	420
Time to – days median (range): n = Episodes		
Infection (n = 76)	**Colonisation (n = 13)**	**Contamination (n = 124)**
17 (1 – 120)	19 (4 – 65)	13 (1 – 63)

Table 4: Clinical manifestations and laboratory parameters

Episodes:	Infection			Colonisation			Contamination		
	76 (36%)			**13 (6%)**			**124 (58%)**		
CLINICAL MANIFESTATIONS									
Headache	4			0			1		
Nausea and vomiting	1			1			2		
Fever	27			1			15		
Alteration in LOC	14			0			5		
Nuchal rigidity	8			1			1		
LABORATORY FINDINGS	**Median**	**Range**	**IQR**	**Median**	**Range**	**IQR**	**Median**	**Range**	**IQR**
CSF Glucose (mmol/L)	1.9	0 – 6.2	2.3	3.9	1.8 – 8.3	1.8	4.0	0.2 – 6.5	1.2
CSF Protein (g/L)	1.8	0.17 – 9.76	1.39	0.80	0.14 – 2.47	0.7	0.68	0.06 – 4.89	0.61
CSF PMN (µL)	326	0 - > 1000	367	9.7	0 – 30	10	31	0 – 726	20.7

Table 5: Microbial aetiology of EVDIs, colonisation and contamination

Organism	Infection	Colonisation	Contamination
Polymicrobial	3 (4%)	1 (8%)	10 (8%)
Monomicrobial	73 (96%)	12 (92%)	114 (92%)
Broth Cultures only	2	0	22
GRAM POSITIVES (n = isolates)			
CoNS	10 (13%)	12 (92%)	79 (64%)
S. aureus (MSSA)	1		3
MRSA	1		1
E. faecium	4		1
Enterococcus spp.	3		1
Viridans Group streptococci	2		7
Bacillus spp.			4
Corynebacterium spp.	2		3
GRAM NEGATIVES			
XDR *A. baumannii*	21 (27.6%)		6 (5%)
A. baumannii	5 (6.6%)		5 (4%)
P. aeruginosa	2		1
XDR *P. aeruginosa*	2		
Aeromonas hydrophila	1		
Enterobacterales	25 (33%)	1 (8%)	11 (9%)
E. cloacae	5		4
K. aerogenes	1		2
E. coli	1		1
P. mirabilis	2		1
K. pneumoniae	6		1
ESBL *K. pneumoniae*	4		1
XDR K. pneumoniae	1		
K. oxytoca	1		1
S. marcescens	4		
*Other			5
FUNGI			
Candida spp.			1
R. mucilaginosa			1

*** Other:** *Acinetobacter lwoffii*, *Pseudomonas* spp, *Ochrobactrum anthropi*

Table 6: Overall antimicrobial susceptibility results for the study period

	No. of isolates susceptible	Total isolates tested	% susceptible
CoNS (n = 101)			
Cloxacillin	26	98	27
Vancomycin	101	101	100
Linezolid	89	89	100
Rifampicin	46	89	52
***S. aureus* (n = 6)**			
Cloxacillin	4	6	67
Vancomycin	6	6	100
Linezolid	6	6	100
Rifampicin	4	5	80
***Enterococcus* spp (n = 4)**			
Ampicillin	3	4	75
Vancomycin	4	4	100
Linezolid	3	3	100
***Streptococcus* spp (n = 8)**			
Ampicillin	3	6	50
Vancomycin	5	5	100
Linezolid			
Enterobacterales (n = 36)			
Cefotaxime	16	33	48
Meropenem	34	35	97
Imipenem	22	29	76
Amikacin	28	31	90
Gentamicin	22	31	71
Trimethoprim-sulfamethoxazole	19	31	61
Tigecycline	28	28	100
Non-fermenters (n = 43)			
Ceftazidime	13	41	32
Meropenem	12	43	28
Imipenem	10	41	24
Amikacin	4	5	80
Gentamicin	15	42	36
Trimethoprim-sulfamethoxazole	9	37	24
Tigecycline	33	37	89

*Some data not available

List of Abbreviations

A. baumannii	*Acinetobacter baumannii*
BREC	Biomedical Research Ethics Committee
CDC	Centre for Disease Control
CLSI	Clinical and Laboratory Standards Institute
CoNS	Coagulase-negative staphylococci
CSF	Cerebrospinal fluid
E. cloacae	*Enterobacter cloacae*
E. coli	*Escherichia coli*
E. faecium	*Enterococcus faecium*
ESBL	Extended β-lactamase
EVD	External ventricular drain
EVDI	External ventricular drain infection
GCS	Glasgow coma scale
IALCH	Inkosi Albert Luthuli Central Hospital
IDSA	Infectious diseases Society of America
ITH	Intrathecal
IV	Intravenous
LOC	Level of consciousness
K. aerogenes	*Klebiella aerogenes*
K. oxytoca	*Klebsiella oxytoca*
K. pneumoniae	*Klebsiella pneumoniae*
MDR	Multi-drug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
P. aeruginosa	*Pseudomonas aeruginosa*
P. mirabilis	*Proteus mirabilis*
R. mucilaginosa	*Rhodotorula mucilaginosa*
S. aureus	*Staphylococcus aureus*

S. epidermidis	*Staphylococcus epidermidis*
S. marcescens	*Serratia marcescens*
WCC	White cell count
XDR	Extensively drug-resistant

APPENDICES

APPENDIX A

Study protocol

The study protocol was approved by UKZN Bioethics Research Committee, the Department of Health, Inkosi Albert Luthuli Central Hospital and the National Health Laboratory Service

University of KwaZulu-Natal

College of Health Sciences

School of Laboratory Medicine and Medical Sciences

(Microbiology)

External ventricular drain infections: a retrospective analysis at a central referral hospital in KwaZulu-Natal, South Africa

Masters in Medicine (Pathology – Microbiology)

Principal investigator: Dr Jenine Naomi de Meyer

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1. BACKGROUND:

External ventricular drains are used for certain neurosurgical conditions to monitor and manage intracranial pressure. Due to the invasive nature of external ventricular drains, patients are at risk for acquiring infections and other complications. Infections lead to prolonged hospital stay and microorganisms may become more resistant with exposure to the environment and antimicrobial agents. There is minimal data published on the diagnostics of external ventricular drain infections and currently no consensus on the best way to distinguish infections from colonisation and contamination. There is also minimal data on antimicrobial susceptibility patterns of microorganisms causing external ventricular drain infections.

2. LITERATURE REVIEW:

External ventricular drains (EVDs) are used for the short-term management and monitoring of intracranial pressure in all age groups. Conditions that may require insertion of EVDs include hydrocephalus, intracranial or subarachnoid haemorrhage, tumours causing cerebrospinal fluid outflow obstruction, meningitis and traumatic brain injury.

Complications associated with EVD insertion include misplacement, dislodging or blockage of the drain, excessive cerebrospinal fluid (CSF) drainage leading to subdural haemorrhage, fluid and electrolyte imbalances, CSF leaks and infection.[1] These infections include ventriculitis, meningitis, subdural empyema and brain abscesses. EVD infections are defined as catheter exit site infections, subcutaneous tunnel infections or ventriculitis.[2] According to Infectious Diseases Society of America (IDSA), the incidence of EVD infections ranges from 0 – 22%.[3] Factors associated with increased risk of infection include intraventricular or subarachnoid haemorrhage, cranial fracture with CSF leak, surgery, co-infection, frequent catheter irrigation or intrathecal administration of drugs and duration of catheterisation.

The aetiology of EVD infections is broad ranging from skin pathogens to drug-resistant hospital-acquired pathogens. A multicentre study done in the United Kingdom and Ireland found that coagulase-negative staphylococci caused the majority of infections (34.5%) followed by *Staphylococcus aureus* (20.7%), *Enterococcus* spp. (10.3%), Enterobacterales *(Enterobacter* spp, *Klebsiella pneumoniae, Morganella morganii, Escherichia coli)* and infrequently *Pseudomonas aeruginosa, Corynebacterium* species and *Streptococcus* species.[4]

In a study done by Walti *et al*, the aetiology was predominantly monomicrobial (57%) with the most predominant microorganism being coagulase negative staphylococci, followed by *Propionibacterium acnes* and *Staphylococcus aureus*. Other microorganisms identified contributed to 3% of EVD-related infections. These organisms included *Acinetobacter* species, *Coynebacterium* species, *Micrococcus* species, *Mycoplasma hominis* and *Bacillus* species. Polymicrobial infections contributed to 10% of EVD infections and culture-negative infections were 11%.[5]

Most cases of ventriculitis associated with EVD use are caused by staphylococci but the proportion of Gram-negative bacteria are increasing. Chatzi *et al.* reported that 81% of EVD infections were due to multi-drug resistant Gram-negative bacteria, mainly *Acinetobacter baumannii*.[6]

CSF cultures that grow *Staphylococcus aureus*, aerobic gram-negative bacilli or fungal pathogens are likely to represent true infection, whereas minimal growth of coagulase-negative *Staphylococcus* in the setting of normal CSF and lack of a fever are most likely indicative of a contaminant.[7]

Very few studies have investigated antimicrobial susceptibility patterns for microorganisms causing external ventricular drain infections. In a study conducted by Wang *et al*, antimicrobial resistance patterns were assessed for Gram-negative organisms causing post-neurosurgical meningitis and ventriculitis. In seven CSF specimens cultured, *Acinetobacter baumannii* complex was isolated. All seven isolates were resistant to third and fourth generation cephalosporins, six isolates were resistant to carbapenems and four isolates were resistant to the aminoglycosides. Of the two CSF specimens where *E. coli* was isolated, both were extended spectrum β-lactamase (ESBL) positive.[8]

There is no standard definition for EVD infections and therefore it is difficult to diagnose. This limits the study, surveillance and comparison of practices for EVD infections. Lewis *et al*. found sixteen different definitions for EVD infections of which nine were subjective. After applying these definitions to a test cohort, the frequency of infection ranged from 22% to 94%, thereby showing a large variability in defining EVD infections.[7]

Most studies consider high CSF white cell count, low glucose levels and high protein levels as important parameters used concurrently with microbiology results when diagnosing EVD infections, however; abnormalities in CSF cell count, glucose, and/or protein may not be reliable to diagnose healthcare-associated ventriculitis and meningitis. Normal CSF cell count, glucose, and protein may not reliably exclude infection in patients with healthcare-associated ventriculitis and meningitis. In addition, a negative CSF Gram stain does not exclude the absence of infection, particularly in those who have received antimicrobial therapy.[9]

Schade *et al*. has defined an EVD infection as the presence of one positive CSF culture with clinical manifestations of meningitis such as headache, fever, nuchal rigidity and a reduced level of consciousness. He also defined colonisation as having two or more positive CSF cultures with the same pathogen in the absence of clinical manifestations. Contamination was defined as a single positive CSF culture with a common skin pathogen with no further positive cultures and no clinical manifestations.[10]

IDSA does not provide a definition but rather guidelines on identifying EVD infections. The following recommendations are given: an elevated CSF white cell count and/or low CSF: serum glucose ratio with ≥ 1 positive cultures, or an increasing white cell count with clinical manifestations of infection suggest infection. A low CSF: serum glucose ratio and a high CSF protein concentration are also suggestive of EVD-related infections. CSF cultures that grow *Staphylococcus aureus,* aerobic gram-negative bacilli or fungal pathogens are also indicative of infection.[3]

If a microorganism is considered a common contaminant cultured from an enrichment broth only or from just 1 of multiple cultures with normal CSF parameters and no clinical manifestations, this is not considered infection. CSF cultures with multiple organisms from a single sample may be contaminants in patients with no symptoms of infection or an elevated CSF white cell count.[3]

According to IDSA, contamination should be considered when there is an isolated CSF culture or Gram stain with normal CSF parameters and in the absence of clinical manifestations. Colonisation should be considered in the presence of multiple positive CSF cultures or Gram stain, with normal CSF parameters in the absence of clinical manifestations.[3]

According to the Centres for Disease Control (CDC) and Prevention, healthcare-associated ventriculitis or meningitis includes the following criteria: microorganisms cultured from CSF, or 2 or more symptoms with no other cause found in each of the 2 groups of patients. These include patients >1 year-old with headache, focal neurological signs and fever >38°C, or patients ≤1 year-old with apnoea, hypothermia or fever >38°C, irritability or bradycardia. In the criteria there must also be at least 1 of the following findings: Elevated CSF white cell count and protein and a low CSF: serum ratio, organisms visualised on the Gram stain of CSF or organisms cultured from blood culture.[3]

Clinical manifestations of meningitis and ventriculitis include headache, fever, nausea and vomiting, new or worsening altered mental status, nuchal rigidity and focal neurological deficit. However, clinical manifestations of EVD infections are not specific and may overlap with signs and symptoms caused by the underlying neurosurgical condition.[5]

Most studies found that EVD-related infections occur if the catheter has been in situ for more than 5 days. In a study conducted by Walti *et al*, EVD-associated infections occurred 6 days after insertion with a range of 1 – 17 days. Meningitis occurred 1 – 10 days after EVD removal in 47% of patients.[11] Jamjoom *et al*, found that the risk of EVD-related infections occurred after a catheter dwelling time of ≥ 8 days.[4] In a study conducted by Khalaveh *et al*, infections occurred at a mean duration of 25.6 days with a wide range of 7 to 163 days, thereby indicating that prolonged use of EVDs increases the risk of acquiring infection.[12]

3. AIMS AND OBJECTIVES

3.1. Aims:

- To retrospectively analyse the clinical and laboratory characteristics of EVD-related infections at a central referral hospital in KwaZulu-Natal from 2019 – 2021

3.2. Objectives:

- To describe the demographic profile of patients with suspected EVD-related sepsis

- To assess the length of external ventricular drain dwelling time and its correlation with infection, colonisation and contamination
- To correlate clinical criteria and CSF cell count and chemistry with positive CSF cultures in patients suspected of having EVD-related infections, colonisation or contamination
- To analyse the microbial aetiology of EVD-related infections, colonisation and contamination
- To determine the antimicrobial susceptibility patterns of the major causative microorganisms of EVD-related infections, colonisation and contamination

4. METHODS

4.1. Study Design

- Retrospective, observational, descriptive cohort study of external ventricular drain infections at Inkosi Albert Luthuli Central Hospital for the period of 2019 - 2021.

4.2. Study population

- The study population will include all patients admitted to IALCH neurosurgery wards with external ventricular drains in situ who have had positive CSF cultures from 1 January 2019 to 31 December 2021.
- Demographic data will include age groups and gender.

4.3. Methodology:

- Patients' clinical diagnosis and clinical manifestations (fever, headache, nausea and vomiting, reduced level of consciousness, nuchal rigidity) and demographics (age and gender) will be accessed from the IALCH Meditech system.
- Laboratory and microbiological data will be accessed from the NHLS laboratory information system.
- A spreadsheet consisting of standardised data fields will be used
- Only patient hospital numbers and NHLS specimen episode numbers will be documented to identify patients thereby ensuring confidentiality

- NHLS data will be reviewed to establish the aetiology and antimicrobial susceptibility patterns of EVD-related infections. The antimicrobials that will be assessed are tabulated below:

Gram positive microorganisms	**Gram negative microorganisms**
▪ Ampicillin/Penicillin ▪ Cloxacillin ▪ Third generation cephalosporins ▪ Vancomycin ▪ Linezolid ▪ Rifampicin	▪ Third generation cephalosporins ▪ Carbapenems ▪ Aminoglycosides ▪ Ciprofloxacin ▪ Trimethoprim-sulfamethoxazole ▪ Colistin ▪ Tigecycline

- CSF chemistry and cell count (with reference to table 1), microbiological data and patient's clinical manifestations will be analysed to attempt to distinguish infection from colonisation and contamination:
  - Infection criteria: ≥ 1 positive CSF cultures with clinical manifestations and/or abnormal CSF parameters (white cell count, glucose, protein)
  - Colonisation: multiple positive CSF cultures with the same microorganism without clinical manifestations and normal CSF parameters
  - Contamination: a single positive CSF culture or culture only from the enrichment broth without clinical manifestations and normal CSF parameters

- Other variables to be documented include:
  - Age and date of birth
  - Gender
  - Date of CSF specimen collection
  - Dwelling time of the external ventricular drain

Table 1: Normal values for CSF glucose, protein and leukocyte count [13]

Tests	< 1 month	1– 3 months	4 – 24 months	>2 years
CSF/Serum Glucose	Ratio not useful	>0.66	>0.66	>0.6
Protein (g/dl)	< 1 (term) < 1.5 (preterm)	< 0.55	< 0.35	< 0.58
Leukocytes (cells/mm^3)	< 20	< 10	< 5 (100% lymphocytes)	< 5 (100% lymphocytes)

5. EXCLUSION CRITERIA:

- Patients who were admitted with blocked or infected ventriculoperitoneal shunts and for those patients for who new shunts were inserted prior to the use of an external ventricular drain.
- Patients who developed meningitis due to their primary condition prior to insertion of an external ventricular drain.

6. STATISTICAL ANALYSIS:

Descriptive Statistics will be used to describe the data. Frequencies and percentages will be used for categorical data. Frequency distributions of numeric data will be examined for normality and means (SD) or medians (IQR) used as appropriate. Categorical characteristics will be compared among the three groups using chi square tests. Numeric data will be compared using ANOVA or Kruskal Wallis tests. Factors with a p value < 0.3 will be included in a multi variable logistic model using the contaminated group as a reference. P values, odds ratios and 95% confidence intervals will be reports. Stata V17.1 will be used for statistical analysis.

7. ETHICAL CONSIDERATIONS:

- The study will be submitted to the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu Natal for review and approval

- Consent will be obtained for Inkosi Albert Luthuli Central Hospital management and the National Health Laboratory Service (NHLS) for use of patients' clinical and laboratory data. The NHLS microbiology department at Inkosi Albert Luthuli Central Hospital has class approval for laboratory data (BE:085/12)
- Confidentiality will be maintained when collecting data by using hospital numbers only, therefore no names and surnames will be used. Patient samples will be identified using episode numbers only.
- There will be no work done with clinical specimens and live cultures, therefore no biosafety risks are posed.
- The collected data will be securely stored on a single, password protected computer which is only used by the principal investigator and supervisor and the data will be destroyed upon completion of the project and/or publication

8. REFERENCES:

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APPENDIX B

Approval Letter:

Biomedical Research Ethics Committee at the University of KwaZulu-Natal

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

22 July 2022

Dr Jenine Naomi De Meyer (993215908)
School of Lab Med & Medical Sc
Medical School

Dear Dr De Meyer,

Protocol reference number: BREC/00004111/2022
Project title: External ventricular drain infections: a retrospective analysis at a central referral hospital in KwaZulu-Natal, South Africa
Degree: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 22 July 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 22 July 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 16 August 2022.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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INSPIRING GREATNESS

APPENDIX C

Approval Letter:

KZN Department of Health

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

Postal Address: Private Bag X9051
Physical Address: 330 Langalibalele Str; PM Burg; 3201
Tel: 0333953189/3123/2805 Fax: 033-3943782
Email address: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Health Research & Knowledge Management Unit

NHRD Ref: KZ_202206_029

Dear Dr J de Meyer
(UKZN)

Approval of research

1. The research proposal titled **'External ventricular drain infections: a retrospective analysis at a central referral hospital in KwaZulu-Natal, South Africa'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central hospital.

2. You are requested to take note of the following
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 07/07/2022.

APPENDIX D:

Approval Letter: Inkosi Albert Luthuli Central Hospital

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL — **OFFICE OF THE MEDICAL MANAGER**

Private Bag X03, Mayville, 4058

800 Vusi Mzimela (Bellair) Road, Mayville, 4091

Tel. 031 240 1059 Fax: 031 240 1006 Email: Ursula.john@ialch.co.za

Reference: BREC/00004111/2022
Enquiries: Medical Management

15 June 2022

Dr J N De Meyer (993215908)
School of Laboratory Medicine & Medical Science
Medical School

Dear Dr De Meyer

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **External ventricular drain infections: a retrospective analysis at a central referral hospital in KwaZulu-Natal, South Africa.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr A Harrichandparsad
Clinical Care Manager

GROWING KWAZULU-NATAL TOGETHER

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville, 4091
Tel: 031 240 1059 Fax: 031 240 1050 Email: Ursula.john@ialch.co.za

OFFICE OF THE MEDICAL MANAGER

15 June 2022

Dr J N De Meyer (993215908)
School of Laboratory Medicine & Medical Science
Medical School

Dear Dr J N De Meyer

Re: Approved Research: Ref No: BREC/00004111/2022: External ventricular drain infections: a retrospective analysis at a central referral hospital in KwaZulu-Natal, South Africa.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr A [redacted]dparsad
Clinical Care Manager

GROWING KWAZULU-NATAL TOGETHER

APPENDIX E:

Approval Letter:

Department of Neurosurgery

Inkosi Albert Luthuli Central Hospital

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1134 Email: : **basileni@ialch.co.za**

DEPARTMENT OF NEUROSURGERY

800 Vusi Mzimela Road
Cato Manor
Durban
4138

To Dr Jenini Naomi De Meyer

LETTER OF SUPPORT FOR STUDY TITLED: EXTERNAL VENTRICULAR DRAIN INFECTIONS: A RETROSPECTIVE ANALYSIS AT A CENTRAL REFERRAL HOSPITAL IN KWAZULU-NATAL, SOUTH AFRICA

Dear Dr De Meyer

I have the pleasure to inform you that the Neurosurgery Department at Inkosi Albert Luthuli Central Hospital is in support of your request to perform a retrospective study involving data from patients admitted in the Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital.

I would like to take this opportunity to wish you the best of luck with your research.

Thank you

[redacted]

Dr Basil Enicker

____

Head of Department
Date: 3 June 2022

APPENDIX F:

Approval Letter:

National Health Laboratory Service

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI
COLLEGE OF HEALTH SCIENCES

ACADEMIC COMPLEX BUSINESS UNIT
DEPARTMENT OF MEDICAL MICROBIOLOGY
SCHOOL OF LMMS, CHS, UKZN & NHLS
Level 4, Pathology Laboratory Building
Inkosi Albert Luthuli Central Hospital
800 Vusi Mzimela (Bellair) Road, Mayville, 4091
Tel: +27 (0)31 240 2787
Reference:

NATIONAL HEALTH LABORATORY SERVICE
Practice No: 5200296

Permission letter from Medical Microbiology Department
Inkosi Albert Luthuli Academic complex
Microbiology Laboratory
NHLS/ KZN

Date: 14 September 2022

RE: The title of my Dissertation: External ventricular drain infections: a retrospective analysis at a central hospital in KwaZulu-Natal, South Africa
Student name: Dr J. de Meyer
Student number: 993215908
School of Laboratory Medicine and Medical Sciences (LMMS)
College of Health Sciences
University of KwaZulu-Natal
Supervisors: Dr Yesho Mahabeer (Pathologist, Microbiology) and Dr Khine Swe Swe-Han (HOD)

In my capacity as the Academic Head of Department, the Discipline of Medical Microbiology at the National Health Laboratory Services (NHLS)/ University of KwaZulu -Natal (UKZN), KZN, permission is granted for the Dr J. de Meyer to perform laboratory work in the IALCH Academic complex - Microbiology. The title of her study is, "External ventricular drain infections: a retrospective analysis at a central hospital in KwaZulu-Natal, South Africa".
She will be working under supervision of microbiology pathologist, Dr Yesho Mahabeer .

[redacted]4/09/2022

Dr Khine Swe Swe/Han (MB,BS; DTMH; PDIC; FC Path; MMed; PhD(Med Micro)
Head of Academic Department (HOD)
Medical Microbiology Department-KZN
Inkosi Albert Luthuli Central Hospital Academic Complex
Univ of KwaZulu-Natal & National Health Laboratory Services
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dr.khine85@gmail.com
Practice Number: 5200296

NATIONAL HEALTH LABORATORY SERVICE
ALBERT LUTHULI MICRO LABORATORY
800 Vusi Mzimela Road
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Tel: 031 240 2787

APPENDIX G:

Turnitin Report

EVD sepsis

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