Ventriculostomy – Related Infections: Prognosis and Diagnosis in the Neurosurgical Intensive Care Unit

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Doctor of Philosophy

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Statement of Originality

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

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Authorship Attribution Statement

The content of this thesis has been produced by the author under the supervision of Associate Professor Anthony Delaney through the Northern Clinical School of the University of Sydney.

Chapters 2 and 4 comprise articles that have been published in scientific journals. The author was the lead and corresponding author for these articles, was jointly responsible for data collection and synthesis, and led drafting and revision of the final manuscripts.

Statistical analysis for Chapter 3 was performed by Alamgir Kabir, and for Chapter 4 by Joseph Alvin Santos.

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Ethical Clearance

Ethics approval was granted by the Northern Sydney Human Research Ethics Committee for the studies comprising chapter 3 (ref 2019/ETH08616) and chapter 4 (ref 2021/ETH00975).

Abstract

External ventricular drains (EVDs) are commonly used in the management of neurological disease such as subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), or intracerebral haemorrhage (ICH). Ventriculostomy – related infection (VRI) is a common complication associated with the presence of EVDs. Despite how common VRI is reported to be, there is minimal data regarding how a diagnosis of VRI affects long term outcomes in patients with EVDs.

Community acquired infections of the central nervous system (CNS) such as bacterial meningitis are associated with significant mortality and patients who survive these infections are at risk of seizures and cognitive dysfunction. However, VRI occurs in the setting of severe neurological illness. Neurological pathologies which require insertion of an EVD are often associated with high mortality, lengthy and complex hospital admissions, and poor functional neurological outcomes. Therefore, determining the effect of VRI on outcomes in these patients is difficult to separate from the effects of the complications of the primary neurological diagnosis.

Another confounding factor in determining outcomes associated with VRI is the lack of a consensus definition of VRI. Depending on the definition cited, different clinical features such as cerebrospinal fluid (CSF) culture, CSF white cell count, CSF glucose, CSF protein or fever will be used, and each definition will have different cut-offs for these clinical criteria. Most of these definitions are based on empirical clinical data and very few have been verified in follow up studies. With no consensus definition of ventriculostomy related infection, the reported incidence varies, complicating efforts to determine the contribution of ventriculostomy related infection to long term prognosis.

The difficulty agreeing upon a definition of VRI arises from the clinical context of these infections – the primary neurological diagnosis. Alongside the prognostic implications of diseases such as SAH, TBI, or ICH, these illnesses also cause derangements in clinical and CSF findings which may mimic CNS infection. This impairs the diagnostic utility of standard non-microbiological markers of CNS infection. Furthermore, traditional microbiological investigations such as CSF culture or gram stain lack sufficient sensitivity and may take days to yield a useful result. Modern molecular techniques such as polymerase chain reaction (PCR) may represent a useful diagnostic tool for timely recognition of infection, and studies suggest that PCR can improve the accuracy of VRI diagnosis.

To address some of these gaps in the literature, we first performed a systematic review to assess the relationship between a diagnosis of VRI and clinical outcomes. We searched several databases using search terms for VRI combined with a sensitive search strategy to identify studies related to prognosis and identified 18 cohort studies and 1 randomised controlled trial which reported data meeting our inclusion criteria. We found that a diagnosis of VRI was not associated with increased estimated mortality (pooled OR1.07, 95% CI 0.59 – 1.92) or functional neurological outcome (pooled OR for poor functional neurological outcome 1.42, 95% CI 0.36 – 5.56). A diagnosis of VRI was associated with an increased hospital length of stay (LOS) (pooled mean difference 16.87 days, 95% CI 12.19 to 21.56), increased intensive care LOS (pooled mean difference 8.4 days, 95% CI 2.51 – 14.29), increased duration of EVD insertion (pooled mean difference 5.24 days, 95% CI 3.05 – 7.43), and increased rate of permanent CSF shunt insertion (pooled OR 1.80, 95% CI 1.32 – 2.46).

The systematic review showed a lack of association between VRI and mortality or functional neurological outcome. There were limited data in the literature regarding functional neurological outcome, and no data reporting long term functional neurological outcome. To address this, we performed a retrospective registry study on 487 patients to assess the

association between VRI and clinical outcomes. Our primary outcome was functional neurological outcome at 6 months, with secondary outcome data extending to 24 months. We found that a diagnosis of VRI, as defined as the initiation of antibiotic treatment by the clinical team was not associated with poor functional neurological outcome (as defined by Glasgow outcome scale (extended) of 1-4) at 6 months (RR 0.78, 95% CI 0.55 – 1.08). VRI was not associated with worse functional neurological outcome at 12 months (RR 0.84, 95% CI 0.59 - 1.16) or 24 months (RR 0.73, 95% CI 0.49 - 1.04). Sensitivity analysis with pre-published definitions of VRI supported these findings. We found no adverse association between VRI and ICU mortality, hospital mortality, or 6-month mortality. VRI was associated with increased ICU and hospital length of stay. A diagnosis of VRI was associated with increased insertion of VP shunts.

Having found no clear association between VRI and adverse long-term neurological outcomes, the question was raised as to whether standard diagnostic methods in the clinical setting were adequate. Therefore, we performed a prospective study to investigate the incidence of VRI using 16S rRNA PCR, which we expected would represent a more accurate tool for detecting bacteria in the CSF. There were 237 CSF samples from 39 patients included in the study. We found that the incidence of VRI as defined by a positive 16S rRNA PCR was low (2.6% or 1/39 patients) and correlated best with diagnostic criteria which required a positive CSF culture. The incidence of VRI as defined by pre-published criteria varied widely (2.6% or 1/39 patients, to 41% or 16/39 patients). We also found no cases of “culture-negative VRI” (i.e. positive 16S rRNA PCR CSF samples with negative CSF culture). Instead, we found that in patients with culture-negative and PCR-negative CSF, the incidence of abnormal CSF findings was high (61.1% or 143/234 of CSF samples were associated with a body temperature >37.6°C, 47% or 95/202 of CSF samples had a red cell to white cell count ratio of 200 or less).

These studies contained in this thesis suggest that a diagnosis of VRI as defined by standard diagnostic criteria may not affect mortality or functional neurological outcomes. A diagnosis of VRI likely increases hospital and ICU length of stay, and rates of VP shunt insertion. It also shows that VRI is likely overdiagnosed and therefore overtreated, exposing patients to unnecessary antibiotics and associated side effects, and an increased risk of antibiotic resistance. Future research with multi-centre cohort studies would help to establish a more accurate definition of VRI, to help better direct treatment and prevention strategies.

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Manuscripts Arising from this Thesis

1. Chapter 2 has been published as:

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Abbreviations

APACHE II - Acute Physiology and Chronic Health Evaluation II

AUROC – Area Under the Receiver Operator Characteristic

BV – Bacterial Ventriculitis

CDC – Centre for Disease Control

CI – Confidence Interval

CNS – Central Nervous System

CoNS – Coagulase Negative Staphylococcus

CRI – Catheter Related Infection

CRP – C-Reactive Protein

CSF – Cerebrospinal Fluid

DRM – Drain Related Meningitis

ED-BM - External Drainage - Related Bacterial Meningitis

ERI – External Ventricular Drain Related Infection

EVD – External Ventricular Drain

EVDAI – External Ventricular Drainage Associated Infection

GCS – Glasgow Coma Scale

GOSE – Glasgow Outcome Scale (Extended)

ICH – Intracerebral Haemorrhage

ICP – Intracranial pressure

ICU – Intensive Care Unit

IVC – Intraventricular Catheter

LP – Linear Predictor

mNGS – Metagenomic Next Generation Sequencing

MV - Meningoventriculitis

NHSN – National Healthcare Safety Network

NOICE – Neuroscience Outcomes from Intensive Care database

PCR – Polymerase Chain Reaction

PCT – Procalcitonin

RASS – Richmond Agitation-Sedation Scale

REDCap - Research Electronic Data Capture database

RNSH – Royal North Shore Hospital

SAH – Subarachnoid Haemorrhage

TBI – Traumatic Brain Injury

VAI – Ventriculostomy Associated Infection, Ventriculostomy Associated Cerebrospinal Fluid Infection

VD-BM – Ventricular Drainage – related Bacterial Meningitis

VDRV – Ventricular Drain-Related Ventriculitis

VM – External Ventricular drain and lumbar catheter associated Ventriculitis and Meningitis

VRI – Ventriculostomy Related Infection

VRM – Ventriculostomy Related Meningitis

WFNS – World Federation of Neurological Societies

1. Introduction

1.1 Overview

A 65-year-old woman is currently intubated and sedated in intensive care (ICU). She presented to hospital via ambulance 6 days ago, after her family contacted emergency services when she became drowsy shortly after complaining of a severe headache. On arrival to the emergency department, she was opening her eyes to painful stimuli, only speaking in groans, and localising to painful stimuli with her left arm only. A CT angiogram of the cerebral arteries showed subarachnoid and intraventricular blood with hydrocephalus and an aneurysm of the right middle cerebral artery. She successfully underwent endovascular therapy to secure the aneurysm, and an external ventricular drain (EVD) was placed to manage her hydrocephalus. She was unable to be extubated post procedure due to depressed level of consciousness.

She has made slow neurological progress. Her admission is complicated by ongoing fevers. There has been no indication of respiratory or urinary source of infection. A cerebrospinal fluid (CSF) sample is taken from her EVD. On day 2, her CSF red cell count was 5,000x10^6 cells/L, and CSF white cell count was 20x10^6 cells/L (predominantly polymorphonuclear cells). Today, , her CSF white cell count has risen to 40 x10^6 cells/L, and her CSF red cell count is stable. Gram stain of her CSF is negative, and CSF and blood cultures are pending. Her CRP is 78. Her neurological status, and the fact that she is intubated, means a physical examination is limited and a history is impossible. The neurosurgical team is keen to start empirical therapy for ventriculostomy – related infection (VRI). The infectious diseases team is keen to await positive cultures prior to commencement of broad-spectrum antibiotics. The ICU team is keen to follow evidence-based guidelines for the diagnosis and treatment of ventriculostomy – related infection.

Ventriculostomy-Related Infection (VRI) is an infection of the cerebrospinal fluid (CSF) associated with the presence of an external ventricular drain (EVD). EVDs are neurosurgical devices commonly used in the management of acute hydrocephalus and suspected raised intracranial pressure, both potential complications of severe brain injury such as subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH) and traumatic brain injury (TBI)[1]. Because infections of the central nervous system (CNS) are associated with high morbidity and mortality, early diagnosis and treatment may improve prognosis [2,3]. However, there is substantial uncertainty about how to diagnose VRI.

In 2016, a review of definitions of VRI found 16 unique sets of diagnostic criteria. When applied to a set of culture positive CSF samples from patients with EVDs in place, VRI would have been diagnosed in 22% to 94% of the samples depending on the diagnostic criteria applied[4]. Another review in 2017 compared the rates of VRI between three published definitions, using the Centre for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) definition as the gold standard and found that in a cohort of 52 cases of VRI meeting the CDC/NHSN, the three definitions classified between 23% and 60% of the cases as VRI [5].

The variation in diagnostic criteria explains in part why it is unclear how commonly the infection occurs. The widest estimates of the incidence of VRI is from less than 1% to 45% [6-8], but two meta-analyses have estimated the pooled incidence at 8.8% per patient and 8.08% per EVD [9] or 11.4 infections per thousand EVD days [8]. However, both meta-analyses noted significant heterogeneity in the analysed literature, citing variations in definitions of VRI, methods of reporting incidence, study objectives and study methodology [8,9].

The poor clarity of the incidence of VRI influences our understanding of other epidemiological characteristics of these infections. For example, whilst it is generally

accepted that patients from the community presenting with CNS infections are at high risk of mortality or long term functional neurological deficit [3,10], this may not be extrapolatable to patients with VRI. Different studies suggest that patients diagnosed with VRI have worse or no difference in outcomes such as mortality, duration of EVD placement, or length of hospital stay [11-14]. Part of this discrepancy is due to different studies using different definitions of VRI to report outcomes.

The clinical context in which VRI occurs can explain some of this uncertainty. In an otherwise healthy individual, the clinical and laboratory findings associated with bacterial infections of the CNS are associated with a reasonable level of diagnostic certainty [15-17]. However, in patients who have suffered a brain injury necessitating the placement of an EVD, clinical and laboratory findings normally associated with CNS infections can also be attributed to neuronal damage, intrathecal blood, recent neurosurgery, or to sedatives and analgesia [18-22]. Therefore, the clinical status of patients who might contract VRI is already abnormal, compromising the diagnostic utility of clinical observations and laboratory parameters which would normally be used to diagnose a CNS infection.

Because most abnormal clinical and laboratory parameters in this population can be explained by recent brain injury or neurosurgery, greater importance is placed on microbiological testing. The two most used techniques are the gram stain and CSF culture. However, these investigations are limited by low sensitivity and time required to yield a result. In particular, CSF culture has a high false negative rate, especially in samples taken from patients who have recently received antibiotic therapy, and may require up to 48 – 72 hours for results [23-30]. This means clinicians may not be able to rely on a positive culture to make decisions about treatment.

To find quicker and more accurate ways of diagnosing VRI, modern molecular techniques have been studied, such as polymerase chain reaction (PCR). PCR has been demonstrated to have high sensitivity and specificity for the presence of bacteria in the CSF, able to detect the presence of bacterial genetic material in culture negative CSF samples [31,32]. However, the cost required to perform these techniques, combined with the lack of evidence-based guidelines in this context, precludes their use as part of standard practice in diagnosing VRI [33-35].

The studies comprising this thesis have two main goals. Firstly, to describe outcomes associated with VRI, both via a systematic review of existing literature and by using a cohort of prospectively collected data to measure outcomes associated with VRI. Secondly, to use 16S rRNA PCR to measure the incidence of VRI.

1.2 The External Ventricular Drain

An EVD is placed during a procedure called a ventriculostomy, which is the creation of a passage between the outer surface of the head and the cerebral ventricles. The most common indication for placement of an EVD is acute hydrocephalus, a common complication of subarachnoid haemorrhage (SAH) (in 20% of patients), intracerebral haemorrhage (ICH), traumatic brain injury (TBI) (in up to 29% of patients), infection, and brain tumours [1,36,37]. Although an EVD may be placed as a diagnostic tool for monitoring of intracranial pressure, placement of an EVD is a potentially life-saving procedure due to the severe consequences of acute hydrocephalus or untreated raised intracranial pressure [36,38].

The EVD is one of the most commonly performed neurosurgical procedures, with one study reporting approximately 25,000 ventriculostomies per year in the United States between 1997 and 2001, representing 14% of all neurosurgical procedures performed during the four years of the study [1,39,40]. The National Neurosurgical Procedural Statistics, published by the American Association of Neurological Surgeons, reported over 42,000 EVDs placed in 2006 (in a population of 300 million) [41,42]. The Australian Institute of Health and Welfare's measured incidence of EVD placement is 2,064 EVDs placed in 2015-16 in a population of 24 million[43]. Whilst this represents only 0.05% of all medical procedures on the nervous system in Australia, it was the 4th most commonly performed procedure involving the nervous system [44]. The placement of an EVD is common enough that it has been suggested that rates of infection associated with EVD placement could be used as a benchmark for service quality [18].

The first documented EVD was inserted in 1744, into a child suffering from congenital hydrocephalus. Claude-Nicolas Le Cat placed a trocar through the child's fontanelle. The child survived for 4 days after the procedure[45]. Since then, different materials have been used

(such as cat gut, horsehair, silk, and metal), different surgical insertion points tested, a closed drainage system has replaced the earlier open drains (which would empty directly onto the patient's bed), intracranial pressure monitors have been added, and the indications for EVD insertion have been expanded. But despite nearly 300 years of development, two important characteristics have persisted. Firstly, the device has essentially remained the same; a tube inserted into the cerebral ventricles, providing a conduit for CSF to leave the skull [39]. Secondly, despite its ubiquity in neurosurgical practice, there is considerable disagreement about what constitutes best practice in the management of a patient with an EVD.

In 2017, a survey was conducted which asked neurosurgeons about their practices in the placement and management of EVDs [46]. The investigators' hypothesis was that there would be no standard practices identified through the survey. This was supported by the results from the 1143 neurosurgeons who responded. Despite recommendations for the use of periprocedural antibiotics by the Neurocritical Care Society [1], the Infectious Diseases Society of America[47], and a Cochrane Review [48], 27.5% (314/1139) of respondents reported "never" or "not regularly" using periprocedural antibiotics[46]. The survey also queried neurosurgeons about their reported practices around continuous empirical antibiotic therapy while the EVD was in place; "Always" or "Whenever possible" accounted for 36% of responses. This practice is recommended against by both the neurocritical care society[1] and the Infectious Diseases Society of America[47].

Another survey published in 2017 investigating variations in strategies to prevent VRI showed that these variations in EVD management are not limited only to neurosurgeons. In a cohort of nurses, pharmacists and doctors, of which only 4% of the total cohort were neurosurgeons, 31% did not recommend perioperative antibiotics and 55% recommended prolonged prophylactic antibiotics [49].

Whilst the use of perioperative antibiotics and the type of EVD used are important modifying factors for a patient's risk of VRI[1], these surveys show similar variations with regard to the presence of an infection prevention protocol, the location of EVD insertion, antiseptic preparation and draping during EVD insertion, and indications and frequency of CSF sampling [46,49]. The explanation for poor consistency in this clinical context is likely to be multifactorial [50] but one reason involves the body of evidence upon which these decisions are based. At the core of this evidence base, there is a fundamental disagreement on how exactly VRI should be defined.

1.3 Definitions of Ventriculostomy-Related Infections

Although the description of VRI as an infection associated with the presence of an EVD is commonly accepted, it is widely reported that a formal definition of VRI does not exist [4,5,8,9,18,51-57], to the extent that even the name of the infection varies between studies. Infections associated with the presence of EVDs are referred to as ventriculitis [6,58-69], bacterial ventriculitis (BV) [70], meningitis [32,68], ventriculitis/meningitis [71], meningoventriculitis (MV) [72], CSF infection [73,74], secondary ventriculitis and meningitis [62], post-operative or neurosurgical ventriculitis/meningitis [71], EVD related ventriculitis [75], EVD-related CSF sepsis [76], ventriculostomy related infection (VRI) [4,9,28,49,53,56,77-83], intraventricular catheter (IVC) related infection [6,84], ventriculostomy related meningitis (VRM) [85], ventricular drain-related ventriculitis (VDRV) [86], ventricular drainage-related bacterial meningitis (VD-BM) [87], EVD related infection (ERI) [7,13,88], EVD related ventriculitis [89], catheter related infection (CRI) [90,91], catheter associated ventriculitis [92], CSF infection [93,94], external drainage-related bacterial meningitis (ED-BM) [29], drain related meningitis (DRM) [25,95], ventriculostomy associated infection (VAI) [5,51,54,96,97], EVD associated infection (EVDAI) [98],

ventriculostomy associated CSF infection (VAI) [8], and EVD and lumbar catheter associated ventriculitis and meningitis (VM) [20].

Alongside this exhausting variation in nomenclature, there are multiple diagnostic criteria for VRI, each with different domains, with each domain defining differing thresholds and descriptors for dictating what constitutes VRI [4,5]. A 2015 meta-analysis by Ramanan et al. [8] divided the definitions of the 35 included studies into four groups:

1. Positive CSF culture required
2. The CDC definition
3. Positive culture plus clinical or other microbiological criteria
4. Positive culture or clinical or other microbiological criteria.

By expanding Ramanan et al.'s idea to classify definitions by their respective requirements for culture, clinical and laboratory results, a rudimentary system of classification for definitions of VRI can be set out. Table 1-1 is a list of studies with definitions summarised in this manner, along with any qualifying factors. Any stated justification for the definition used in the study is noted (e.g. references to other definitions).

Table 1-1 - Descriptions of diagnostic criteria for Ventriculostomy-Related Infection from Lewis et al.[4] and Reyes et al.[5]

Study author/year	**Justification of Diagnostic Criteria**	**Classification of Strongest Definition**	**Additional Qualifiers and Levels of Diagnosis**
Arabi et al., 2005 [51]	References studies using positive culture and studies using clinical and laboratory criteria.	Positive culture, OR clinical AND laboratory criteria	- If culture is positive for commensal bacteria, additional clinical or laboratory signs required.
Bota et al., 2005 [82]	Uses definitions from Lozier et al., 2002 [9]	Positive culture AND clinical AND laboratory criteria	- Includes diagnostic criteria for Ventriculitis, VRI, suspected VRI, ventriculostomy colonization, contamination
Chi et al., 2001 [55]	References other studies using similar definitions	Positive culture	- Includes temporal restriction (infections recorded up until the first day of EVD placement were excluded). - CSF cultures taken if clinical suspicion of infection.
Citerio et al., 2015 [20]	Used modified CDC criteria, attempting to mitigate limitations of the criteria.	Positive culture, AND clinical AND laboratory criteria	- Includes criteria for "suspected infections" and "normal CSF findings".
Gozal et al., 2014 [54]	States definition is a refinement of Lozier et al's [9].	Positive culture, PLUS clinical OR laboratory criteria	- Includes temporal restrictions (exclude cultures at time of EVD placement, includes criteria up to 72 hours of EVD removal).
Holloway et al., 1996 [99]	No explicit justification given	Positive culture, OR clinical OR laboratory criteria	None
Hopkins et al., 2012 [77]	No explicit justification given	Positive culture, AND clinical OR laboratory criteria	- Includes criteria for definite peripheral infection or VRI, probable peripheral infection or VRI, unlikely, and no infection. - Includes temporal restrictions (infections that were present at study entry, diagnosed during collection of samples, or diagnosed up to 2 days post sampling were included). - In the absence of positive culture, commencement of appropriate antibiotics fulfilled the definition of VRI.
Lozier et al., 2002 [9]	States variation of definitions and proposes definitions to distinguish infection, colonisation and contamination. Declines to state thresholds for CSF parameters because of predictable abnormalities.	Positive culture, AND clinical AND laboratory criteria	- Includes definitions for ventriculitis, VRI, suspected VRI, EVD colonisation, and contamination.

Lyke et al., 2001 [6]	No explicit justification given	Positive culture	- Includes temporal restrictions (only positive cultures after 48 hours were included, positive cultures from up to 5 days after EVD removal were included). - If culture is positive for commensal bacteria, additional laboratory findings required. - CSF sample taken only if patient's clinical condition required further assessment
Mayhall et al., 1984 [78]	States lack of uniform criteria and therefore choosing to define infections microbiologically.	Positive culture only	- Includes temporal restrictions (EVD placement for at least 24 hours, and includes any CNS infection for up to two weeks after removal of the EVD). - Requires absence of other sources of infection. - Requires negative cultures at time of EVD placement.
McLaughlin et al., 2011 [79]	Uses CDC criteria [100]	Positive culture, OR clinical AND laboratory criteria	- Patients were followed up for 4 weeks post EVD removal.
Mikhaylov et al., 2014 [96]	No explicit justification given	Positive culture only	- Includes temporal restrictions (positive CSF culture within one week of EVD removal, if accompanied by clinical signs, was considered VRI)
Rath et al., 2014 [85]	Abnormal clinical and laboratory signs can be caused by post-operative local inflammation.	At least two of positive culture, clinical, or laboratory signs	- If culture is positive for commensal flora, more than one positive culture required to diagnose infection. - Contamination defined as single positive culture.
Schoch et al., 2008 [81]	No explicit justification given.	At least two of positive culture, clinical, or laboratory signs	- If culture is positive for commensal flora, more than one positive culture required to diagnose infection. - Contamination defined as single positive culture.
Stenager et al., 1986 [80]	No explicit justification given.	Positive culture only	- Includes thresholds for colony forming units per culture.
Tse et al., 2010 [56]	Definition based on positive culture and non-culture parameters from other referenced definitions.	Positive culture, AND clinical OR laboratory criteria.	- Requires exclusion of other sources of infection.
Wright et al., 2013 [101]	No explicit justification given.	Positive culture, AND clinical AND laboratory criteria.	- Includes criteria for definite, probable, and no infection.
Zabramski et al., 2003 [102]	No explicit justification given.	Positive culture only.	- Contamination criteria included; a culture was positive only if it grew on two different media.

1.3.1 "Positive Culture" Definitions

The most common definition of VRI is based on a positive CSF culture [8,9,51]. These definitions vary with regards to timing of culture, exclusion of non-CNS foci of infection, and considerations of contamination by commensal flora. Mayhall et al. [78] published a definition in 1984 which a 2002 review cited as the most commonly used criteria [9]. Their definition requires a positive CSF culture under the condition that CSF cultures at the time of EVD insertion are negative, there is no other detectable source of CNS infection (such as a CSF leak, a penetrating injury of the CNS, or a concurrent bacteraemia with the same organism), and the EVD has been in place for 24 hours or longer. CNS infections diagnosed within two weeks after the removal of the EVD were considered associated with the EVD.

Other definitions of VRI which rely on CSF culture results will qualify the diagnosis based on several factors. For example, if the bacteria grown is considered a commensal species, the definition may require other clinical factors (e.g. CSF glucose or white cell count) or may require repeat CSF cultures. The definition may exclude positive cultures within the first 24 hours of EVD placement. The definition may also extend the definition of VRI to include positive CSF samples taken up to 5 days after removal of the EVD [6,55,78].

The explanation for this variation, aside from changes in authorship or site-specific practice, may be attempts to compensate for an important limitation of exclusively using CSF culture results to define VRI; a positive CSF culture alone cannot distinguish infection, EVD colonisation, or sample contamination [20]. The use of CSF biochemistry and cell counts, and the extra criteria regarding commensal bacteria, may represent efforts to overcome this limitation.

1.3.2 The CDC Definition

The second most common definition for VRI is the CDC criteria [8,100], which requires either a positive CSF culture, or both a clinical and laboratory abnormality plus initiation of antibiotic treatment. This expands on "positive culture only" definitions because it accounts for patients' clinical and laboratory findings and allows for culture negative VRI [8,47]. However, there are still several shortcomings in the CDC's definition.

First, much like a definition relying on a positive culture, there is no distinction between infection, EVD colonisation, and sample contamination. The non-microbiological definition is additionally unable to distinguish infection from non-infective inflammation. Second, it has no timing criteria, which means it cannot distinguish between an infection already present upon EVD insertion, an infection associated with the EVD's placement, or an infection associated with the EVD's presence that only becomes clinically apparent after the EVD is removed. Third, by requiring a typical symptom of infection to define culture-negative VRI, the definition fails to consider that a patient admitted to intensive care may be sedated or intubated, meaning confusion or headache may not be reported. Furthermore, the classic symptoms of CNS infection (fever, headache, altered level of consciousness, and nuchal rigidity) are common in patients with severe neurological injury who have recently undergone neurosurgery [4,20,101]. For example, fever is a well described complication of TBI and SAH, and the ideal management of primary fever due to these pathologies is an area of ongoing research[103]. Fourth, there is no clear definition of 'appropriate antimicrobial therapy' and this may be defined differently between sites both with regards to agent and length of therapy. Finally, the CDC's criteria for VRI does not specifically address device-related CNS infections, unlike definitions for urinary tract infection, pneumonia, and sepsis, for which

there are separate definitions for catheter-related urinary tract infections, ventilator associated pneumonia, and central line-associated bloodstream infection [4,100].

1.3.3 Definitions Based on Clinical Criteria

To address the criticisms of both the "positive culture only" and CDC definitions, multiple authors have developed their own definitions for what constitutes VRI in a patient with an EVD in place. A 2016 review by Lewis et al. [4] found 16 novel definitions of VRI, each with their own inclusion and exclusion criteria and thresholds for abnormal clinical and laboratory parameters. A positive CSF culture was required to make a diagnosis of VRI in 50% of the included criteria and 50% allowed for CSF or clinical abnormalities in the absence of a positive culture. For some definitions, cultures taken immediately after EVD insertion were excluded (with a range from 0 – 48 hours) and some definitions allowed VRI to be diagnosed after removal of the EVD (ranging from 3 days to 4 weeks). The definitions that included CSF measurements (63%) used different quantitative thresholds for white cell count, glucose and protein and some used qualitative terminology like "abnormal CSF parameters". The majority of definitions used clinical signs and symptoms (69%), which included different both quantitative and qualitative descriptions of fever (38°C, 38.5°C, 38.6°C, "fever", "high-grade fever", and "increased patient temperature") and different clinical characteristics such as altered mental status, irritability, nuchal rigidity, or a "clinical picture of infection". Table 1-2 is a list of all definitions included in the Lewis et al. study, as well as a similar study by Reyes et al. [5]. The definition from a study by Honda et al. [84] is omitted because it is the same definition as published by Chi et al. [55].

Table 1-2 - Diagnostic criteria for ventriculitis from Lewis et al.[4] and Reyes et al.[5] as stated in their respective papers.

Study author/year	Stated Diagnostic Criteria
Arabi et al., 2005 [51]	"VAI was defined as culture of a recognised pathogen from the CSF after catheter insertion. If coagulase negative staphylococcus, diphteroides, Bacillus, Micrococcus, or Proprionibacterium species were isolated, at least 1 of the following criteria had to be identified: Positive Gram's stain, decrease in CSF glucose level, increase in CSF protein level, increased patient temperature, inflammation at the catheter site, altered mental status, or irritability. In exceptional cases the diagnosis of VAI was made on clinical grounds in the presence of altered mental status, fever, with CSF changes consistent with ventriculitis (high WBC, high protein, and low glucose). Exclusion criteria were as follows: (1) if CSF culture did not yield organisms but may have a positive Gram's stain, (2) if patient had meningitis or ventriculitis before the insertion of a catheter, and (3) if CSF became culture positive after 5 days of catheter removal."
Bota et al., 2005 [82]	"To define VRI, we used the criteria recently proposed by Lozier, et al., including fever (≥38.5°C, with/without clinical signs of meningitis) associated with at least one positive CSF culture and at least one element of CSF abnormality, including low CSF glucose levels (40 mg/dl, or 50% of serum glucose in patients with hyperglycemia), high CSF protein (50 mg/dl), or CSF pleocytosis (100/mm^3). Colonisation was considered to be present when several CSF cultures were positive without CSF abnormality. Contamination was defined as an isolated positive CSF culture without CSF abnormality."
Chi et al., 2001 [55]	"Ventriculostomy-associated infection was defined as culture of a pathogen from the CSF obtained either from the catheter or by lumbar puncture. An infection was considered as occurring on the day the CSF sample was obtained. However, infections documented before ventriculostomy or up to the first day after catheter insertion were not considered to be catheter-related and were not included in this analysis."
Citerio et al., 2015 [20]	"1. "Confirmed CSF infections" were defined as follows: a. A positive CSF culture and, b. An CSF/blood glucose ratio less than 0.5 and c. A neutrophilic CSF pleocytosis (> 5 cells/μL) and d. Fever (body temperature > 38°C). 2. Abnormal CSF findings with negative cultures were defined as "suspected infections." 3. No abnormal CSF findings with or without positive CSF cultures were classified as "normal CSF findings.""
Gozal et al., 2014 [54]	"VAI was defined as a single positive CSF culture in a patient with a ventriculostomy catheter, plus one or more of the following minor criteria: (1) Fever (recorded temperature exceeding 101.5℉), or (2) CSF glucose level either <50 mg/dL or <50 % of a serum glucose level drawn within 24 h of the CSF glucose. In order to maximize our sensitivity for VAI, a positive culture was determined by any reported bacterial growth. Institutional reporting included patients in whom the above criteria were met within 72 h of EVD removal. Excluded patients had a positive CSF culture obtained at the time of EVD insertion because these infections were not specifically catheter related. A specific patient could potentially have more than one VAI if multiple organisms were concomitantly isolated."

Holloway et al., 1996 [99]	"Infection was defined as a positive culture, or in the absence of a positive culture, infection was defined as greater than 50% polymorphonuclear leukocytes on CSF count with a minimum of 50 cells counted or CSF glucose less than 15 mg/100 ml."
Hopkins et al., 2012 [77]	"Definition of infection was divided into: (1) Definite…VRI a positive culture with a clinical picture of infection or commencement of intrathecal antibiotics was necessary; (2) Probable: …For VRI this was raised CSF WCC: red cell count ratio (>1:700), in the absence of positive culture or starting intrathecal antibiotics, but with a clinical picture of infection; (3) Unlikely: very limited documentation suggesting infection; and (4) No infection: no documentation suggesting infection, or documentation that excluded infection."
Lozier et al., 2002 [9]	"A contaminant constitutes an isolated positive CSF culture and/or Gram's stain, an expected CSF glucose and protein profile, and an expected CSF cell count. Ventriculostomy colonisation is defined by multiple positive CSF cultures and/or Gram's stains with expected CSF profiles and cell counts and lack of clinical symptoms other than fever. Progressively declining CSF glucose and increasing CSF protein profiles accompanied by advancing CSF pleocytosis in the absence of positive CSF cultures or Gram's stains characterize suspected VRIs. The addition of a positive CSF culture or Gram's stain with a paucity of clinical symptoms other than fever defines VRI. VRI progresses to ventriculitis when it is accompanied by high-grade fever and clinical signs of meningitis, including nuchal rigidity, photophobia, decreased mental status, seizures, or moribund appearance."
Lyke et al., 2001 [6]	""Nosocomial ventriculitis" was defined as culture of a recognised pathogen from the CSF either at the time of or 2 days after IVC insertion. The day of insertion was defined as "day 0". In addition, if common skin flora, such as coagulase-negative Staphylococcus, Corynebacterium, Bacillus, Micrococcus, or Propionibacterium species were isolated, then ≥1 of the following criteria had to be identified: a Gram stain of the original CSF sample that produced a finding consistent with the organism cultured, a decrease in the CSF glucose level (≤25 mg/dL), an increase in the CSF protein level (≥50 mg/dL), or a finding of neutrophilic pleocytosis (≥10 cells/mm3). We excluded the following patients: (1) those whose CSF culture did not yield organisms but who had organisms identified on a smear of the original CSF sample or had only laboratory parameters that were consistent with ventriculitis, (2) those who were given a principal diagnosis of meningitis or ventriculitis before the insertion of an IVC, and (3) those whose CSF culture yielded pathogens ≥5 days after the IVC was removed."
Mayhall et al., 1984 [78]	"For a diagnosis of ventriculitis or meningitis related to ventriculostomy, the following criteria had to be met: (1) no other detectable source of central nervous system infection such as CSF leak, concurrent bacteremia with the same organism isolated from CSF, or penetrating injury of the central nervous system; (2) negative cultures of CSF obtained at time of ventriculostomy; (3) ventricular catheterization for 24 hours or longer; and (4) documentation of ventricular or meningeal infection by positive cultures of CSF obtained by aspiration from the ventricular catheter or lumbar puncture"

McLaughlin et al., 2011 [79]	"…meningitis or ventriculitis must meet one of the following criteria: (1) organism isolated from culture of CSF; or (2) one of the following with no other recognised cause: fever >38°C, headache, nuchal rigidity, meningeal signs, irritability, AND physician prescribed appropriate antimicrobial treatment AND any of the following: (a) organism seen on Gram stain of CSF; (b) increased white cells, elevated protein, and/or decreased glucose in CSF; (c) organism isolated from blood cultures."
Mikhaylov et al., 2014 [96]	"A positive CSF culture within 1 week of removal of the EVD with clinical evidence of ventriculitis was treated with a full course of antibiotics and was also considered to represent a VAI."
Rath et al., 2014 [85]	"A diagnosis of EVD-related ventriculo-meningitis was made if at least two of the following three criteria were met: (1) one or more new clinical signs of the disease, such as nuchal rigidity, headache, fever, or neurological deterioration (difference of ≥1 point in short form of the Scandinavian Stroke Scale with exclusion of deterioration due to primary disease); (2) increase of 100% or more in CSF cell count; or (3) detection of bacteria or fungi by CSF culture or PCR."
Schoch et al., 2008 [81]	"VRI was diagnosed if at least two of the following three criteria were met: (i) one of more new clinical signs such as nuchal rigidity, headache, fever or neurological deterioration (SSS difference ≥1 point with exclusion of causes due to primary disease); (ii) CSF cell count increased by more than 100% over the previous day; (iii) bacteria detected in CSF gram staining and/or culture. If a culture tested positive for common skin pathogens, especially for Staphylococcus epidermidis, repeated evidence in two different samples was required to prove CSF infection; in the event of only one positive CSF culture the result was deemed to be contamination."
Stenager et al., 1986 [80]	"A diagnosis of probable ventricular infection (PVI) was made when 1) one culture showed ≥100 colony forming units (c.f.u.)/0.1 ml CSF or 2) growth of < 100 c.f.u./0.1 ml in 2 or more cultures."
Tse et al., 2010 [56]	"…defined ventriculostomy-related infection as a positive bacteria culture together with any two of the below mentioned individual factors from different subgroups. Factors considered according to subgroups: 1. Clinical features: fever, nuchal rigidity, photophobia, seizures, alteration of conscious level or turbid sampled CSF appearance. 2. Biochemical test results: increase of CSF protein level, decrease of CSF glucose level or increase of serum inflammatory markers of C-reactive protein level. 3. Haematological test results: raised of CSF or blood white cell count. 4. Exclusion of other foci of infection: absent clinical features related to other sites of infection and insignificant culture from other possibility infected systems."
Wright et al., 2013 [101]	"A VRI was defined as definite if there were clinical signs and symptoms of infection, abnormal CSF parameters, and a positive CSF culture; a VRI was defined as probable if clinical signs and symptoms and abnormal CSF parameters were present but the culture was negative; and no infection was defined as having no CSF abnormalities and a negative CSF culture."
Zabramski et al., 2003 [102]	"Infection was defined as a positive CSF culture. For the purposes of the this study, cultures were considered positive only if the same organism grew of two different media (for example, broth and blood agar) or on the same medium twice."

The primary objective of the Lewis et al. study [4] was to apply these definitions to a cohort of only 18 culture positive CSF samples taken as part of the care of patients with EVDs admitted to two American hospitals. The medical records associated with these samples were retrospectively examined by two neurointensivists. Depending on which diagnostic criteria was used, the incidence of VRI in this cohort ranged from 22% to 94%. In this study, the gold standard was treatment with antibiotics for longer than 7 days, which occurred in 67% of the cohort. When compared to the study's gold standard, the diagnostic criteria with the highest sensitivity, specificity, and concordance with adequate antibiotic therapy was the diagnostic criteria by Hopkins et al. [77], which included "clinical picture of infection" as part of the definition. One limitation of the study is the gold standard of antibiotic therapy, which would introduce bias due to site-specific variations in thresholds for commencing antibiotics[5].

A similar study by Reyes et al.[5] performed a retrospective analysis to assess the value of the CDC/NHSN criteria as a surveillance tool for the guidance of reimbursement through Medicare/Medicaid. The study included 52 CSF samples from a single centre which met the CDC/NHSN criteria and measured the incidence of VRI compared to three previously published definitions[20,54,84]. In contrast to the study by Lewis et al., this study included culture-negative CSF samples. In this cohort, the incidence of VRI was measured between 23% and 60%.

Several studies have included different classifications to account for colonisation, contamination, and culture negative infection. The most thorough definition was published in a 2002 review by Lozier et al. [9], which suggested that efforts must be made to distinguish clinically relevant infections. The study proposed diagnostic criteria for 5 clinical entities: contamination, ventriculostomy colonisation, suspected ventriculostomy-related infection, ventriculostomy-related infection, and VRI. These definitions have different requirements for culture, clinical and laboratory results.

What is left unclear about these definitions is the justification for their diagnostic accuracy. Lozier et al. [9] made an important point in attempting to identify clinical relevance but the diagnostic criteria seem to be based on expert opinion rather than evidence. In fact, all of the definitions from the reviews comparing diagnostic criteria [4,5] appear to either reference or expand upon existing criteria, sometimes without a clear evidence base to justify the original definition, or their modified version, or the new definition they have devised – all while noting the lack of a consistent definition [6,9,20,51,54-56,77-82,84,85,96,99,101,102].

1.3.4 Proposed Diagnostic Approaches

The anecdotal nature of definitions for VRI has led to researchers combining test results to produce screening and prediction tools to diagnose the infection. The advantage of these criteria over the definitions as described by Lewis et al. and Reyes et al. [4,5] is that these definitions are produced as the results of collected data, rather than as a priori guidelines based on expert opinion.

The most recent of these diagnostic criteria were designed by Hernández Ortiz et al. in 2018 [27]. The study recruited 320 patients with a recent history of neurosurgery (with or without EVDs), who developed fever and elevations in serum leukocytes or CRP. The study proposed a score out of 10 (with 1 point assigned for a diagnosis of SAH, raised CRP, and low CSF: serum glucose <0.4, 1.5 points for CSF neutrophils >50% of total CSF white cells and CSF leak, and 4 points for a CSF lactate >4mmol/L) and suggested that a patient with a score of 6 or greater should receive antibiotics. Apart from a lack of external validation[104], there are limitations of this study specifically related to patients with EVDs in place. Because an aneurysmal subarachnoid haemorrhage is scored one point, and 50% of cases of VRI have a CSF lactate less than 4mmol/L [47,105] (which would account for 4 points), a large number of

patients with VRI will not have a score greater than five. The prediction rule may also have reduced accuracy in patients with an EVD because only a proportion of patients in this study had an EVD. However, despite its limitations, this study represents a step forward; a definition of VRI as an outcome instead of expert opinion.

$$Z - Blood = 0.009 * age + 0.06 * Operation\ duration + 0.03 * serum\ leukocyte\ count + 0.017$$
$$* serum\ neutrophil\ percentage + 0.006 * serum\ platelet\ count + 0.11$$
$$* Postoperative\ days - 0.062 * serum\ sodium\ concentration + 3.467$$

$$ZcLact = 0.145 * Operation\ duration + 0.423 * CSF\ lactate + 0.085 * Postoperative\ days - 3.089$$

Figure 1-1 - Algorithms 1 and 2 from Zhang et al., 2017 [106], based on clinical factors with blood and CSF parameters, respectively

Two research groups have proposed elaborate algorithms to diagnose VRI. Zhang et al. developed an integrative prediction tool in 2017 [106], as did van Mourik et al. in 2011, which was subsequently validated in 2012 and 2015 [25,95,107]. The algorithms are shown in Figures 1-1 and 1-2. Both models used large cohorts of neurosurgical patients and accounted for several important variables. The reliability of the algorithms varied. For example, ZcLact (as shown in figure 1-1) from the paper by Zhang et al.[106] had a sensitivity of 86.67% and a specificity of 85% compared to a definition by Li et al.[108]. A validation of the algorithms published by van Mourik et al.[107] showed sensitivity of 65 – 85% for predicting a positive CSF culture or gram stain and a positive predictive value of 50 – 55%, compared to the CDC definition. However, there is no guarantee that a hospital or health district's electronic medical records system will facilitate the use of automated and intricate algorithms, precluding their use in certain healthcare settings.

$$P(DRM) = 1/(1 + e^{-LP})$$

Where;

$$LP = -8.014 + 0.713 * \text{Number of drains} + 1.659 * \text{if EVD} + 0.017 * CRP + -0.015 * \left(\frac{CRP}{10}\right)^2 + 0.233 * \left(\frac{CRP}{100}\right)^3 + 0.077 * \text{leukocytes(blood)} + 0.350 * ln(\text{CSF leukocyte}) + 2.617 * \text{if positive culture} + 0.281 * \text{number antibiotics started} + 1.466 * \text{if empiric therapy}$$

Figure 1-2 - Predictive model for drain related meningitis (DRM) from van Mourik et al., 2012[25]. A linear predictor (LP) is a set of coefficients and independent variables used to predict a dependent variable.

There is one common theme throughout these three diagnostic models; the prediction is based on a definition of VRI, and these definitions are based on tenuous grounds. For example, van Mourik et al.'s studies use the CDC definition [25,95,107], which is problematic for reasons described above [4,20,100,101]. The Hernandez Ortiz et al. [27] study based their model on a definition proposed by Lieb et al. in 1999 [109] which, much like many definitions, has no expressed justification. The Zhang et al. study [106] based their definition on a study by Li et al. [108] from 2015, citing a 1992 article by Gray et al. called "Laboratory Diagnosis of Bacterial Meningitis" [110], which compiled a suggested diagnostic criteria for bacterial meningitis based on a compilation of 8 other studies, none of which addressed neurosurgical patients. Therefore, there is a strong argument that these models are not effective for predicting or diagnosing VRI. Instead, they detect a set of clinical abnormalities that may represent VRI but without objective evidence to support their accuracy.

The lack of a validated definition for VRI has several consequences. Clinically, a sensitive and specific definition is required to avoid both overtreatment (with implications regarding hospital costs, antibiotic stewardship, and delayed diagnosis of alternate foci of infection) and

undertreatment (with implications regarding prognosis and potential sequelae of delayed treatment) [20]. Furthermore, the lack of a standardised definition affects the development of quality control programs and impairs assessments of interventions to reduce the risk of developing VRI. But the lack of a consensus definition leaves a more basic question unanswered: how many patients with EVDs in place get VRI?

1.4 The Incidence of Ventriculostomy-Related Infections

When defining any disease, the variation in definition determines which elements of a patient's clinical picture contribute to a definitive diagnosis. Depending on the study (and therefore the definition), the incidence of VRI is between <1% and 45% [6-8,58,111]. There are relatively few pooled estimates of incidence [8,9,112,113] and even these vary vastly in reported incidence of VRI (between 8.8% to 23% of patients). As with many meta-analyses, these studies report methodological heterogeneity as a limitation, with variations in the definition of VRI specifically noted as a source of heterogeneity.

Lozier et al. [9] published one of the earliest comparisons of how definitions affect measurements of the incidence of VRI. The paper performed a literature review which included 32 papers published between 1941 and 2001. From 25 studies including 5,261 patients, the pooled incidence using their proposed definition was 8.80% of patients and 8.08% of EVDs. However, by applying the definition of Sundbarg et al. (which required a positive CSF culture plus laboratory results) [114] on the 4 studies reporting clinical data (comprising 1,762 patients), the rate dropped to 6.62% of patients or 6.10% of EVDs.

Ramanan et al. [8] performed a more recent analysis of definition and incidence. By analysing their four categories of VRI definitions separately (culture positive only, CDC criteria,

positive culture AND clinical or other microbiological criteria, positive culture OR clinical or other microbiological criteria), four different measures of incidence were reported. Culture-only definitions showed an incidence rate of 11.5/1000 EVD days, the CDC definition showed 8.8/1000 EVD days, positive culture plus clinical or microbiological criteria showed 9.1/1000 EVD days and positive culture or clinical or microbiological criteria showed 17/1000 EVD days. To some extent these variations are to be expected; the highest incidence is in the definition which allows for any abnormality (culture or clinical or microbiological), and if both a positive culture plus a clinical or microbiological test is required, the incidence falls.

More recent primary studies show similar variability. A large multicentre observational study by Woo et al.[18] measured the incidence of VRI in a cohort of 2,575 patients using 5 different diagnostic criteria. Using a positive culture only definition[55], the incidence of VRI was 4.7% of patients. When a definition also required inclusion of clinical features[54], the incidence dropped to 2.2%. More restrictive definitions (for example requiring a positive culture, a complete set of CSF abnormalities, and fever[9], or additional CSF or clinical criteria when a culture shows commensal bacteria[6]) again reduced the incidence to 0.6% and 0.8% respectively. However, using the CDC criteria as published in Scheithauer et al.[115], the incidence was 2.8% - nearly half that of the positive culture only criteria. But while the CDC criteria have no contingency for contamination, Scheithauer et al. included exclusion criteria, stating "meningitis cases were excluded if meningitis followed a systemic infection (eg, central venous line sepsis)" and;

> *"…to ascertain whether the frequency of isolating (coagulase negative staphylococcus (CoNS)) allows us to distinguish true infections from contaminations we subdivided patients with regard to the number of positive CSF results. Only cases in which a positive CSF specimen was followed by at least one negative one were*

documented as "isolation once". We found that isolating CoNS twice or more seemed to be indicative of meningitis infection whereas isolating CoNS in only one sample seemed to be indicative of contamination only." [115]

Thus, the CDC definition included in Woo et al.'s [18] analysis is distinct from the original CDC definition for VRI because it adds criteria to exclude contaminants[100]. Although this amendment may be reasonable, it shows the somewhat arbitrary way in which definitions of VRI are proposed.

These studies demonstrate one effect of poorly defined a disease – there is no clear baseline incidence. But whether one chooses to refer to Ramanan et al.'s 11.4/1000 EVD days [8] or Lozier et al.'s 8.80% of patients [9] or any other large estimate of incidence as the true incidence of VRI, it will inevitably be clouded by the lack of a consensus definition.

This uncertainty partly explains the variation shown in Baum et al.'s and Lewis et al.'s surveys on neurosurgical EVD management practices[46,49]. In addition, numerous studies have examined the effects of infection prevention bundles in neurosurgical ICUs [11,112,116-118] but the cost-benefit analysis of individual measures taken to prevent VRI is difficult to assess without a clear and agreed-upon definition [119]. Without this definition, there is no reliable baseline of the incidence of VRI. Because no reliable baseline exists, it is difficult to assess the impact of clinical practice on the incidence of VRI, leading to variations in clinical practice that are difficult to justify or refute[46,49]. Furthermore, because there is no broad consensus for what clinical features constitute VRI, it is difficult to assess the effect of VRI on patient outcomes.

1.5 The Clinical Diagnosis of Ventriculostomy-Related Infections

We have described several important elements of the uncertainty regarding VRI, such as variations in clinical practice, the absence of a validated definition, and discrepancies in measured incidence. The next major contributing factor to be discussed here is the difficulty in clinically diagnosing VRI, due to an already abnormal clinical picture upon which a bacterial infection may be imposed.

Community-acquired infections of the CNS have well described symptomatology [15,16,120] and CSF investigation is considered the diagnostic gold standard [17,121]. Well validated diagnostic scoring systems have been developed to diagnose bacterial meningitis[122,123]. However, it is not clear as to whether the diagnostic approach to community-acquired CNS infections can be extrapolated to the diagnosis of VRI.

1.5.1 Clinical Signs and Symptoms

In the context of a patient who has suffered severe brain injury requiring placement of an EVD, the standard clinical and laboratory indicators of infection lose their diagnostic accuracy. The blood and products of haemolysis mixed with CSF after stroke or trauma irritates the meninges, as does the bone dust and implants from neurosurgery, leading to an aseptic meningitis[21,22,106]. As a result, patients with recent neurosurgery who have an uncomplicated course of recovery will frequently experience headache, fever, and neck stiffness[9,18-20].

Unfortunately, the data examining the sensitivity and specificity of clinical indicators of infection have failed to find them reliable for the early diagnosis of VRI. A 2019 systematic review and meta-analysis by Dorresteijn et al.[113] analysed the data from 42 articles including 3,035 patients with EVDs, with an incidence of 23% (697 cases of VRI). When patients with VRI were compared to patients without VRI, the two groups had similar proportions of

decreased level of consciousness and meningeal irritation. Incidence of headache in patients without VRI was not reported. Fever was the most useful clinical indicator reported in the meta-analysis – fever was found in 72% of patients with VRI and 29% of patients without VRI.

It should be noted that the limitations of the Dorresteijn meta-analysis are similar to limitations described previously in this review; a heterogenous group of studies with small sample sizes and variable definitions of VRI. The study notes that of the 42 studies included in the analysis, 7 did not describe diagnostic criteria for VRI.

Although fever may be a sensitive indicator of infection, it likely has low specificity – patients at risk of VRI are also at risk of other causes of fever, such as extra-cranial infections or venous thromboembolic disease[124]. Furthermore, the confounding effects of sedation, plus the aseptic inflammation from haemorrhage and trauma, mean the chances are low that clinical signs are diagnostic parameters with high sensitivity and specificity. Therefore, there is greater importance on the utility of laboratory analysis in the early diagnosis of VRI.

1.5.2 CSF Cell and Biochemical Markers

A 1998 review of the immune response to insertion of a neurosurgical device described the response as follows:

> *"At the time of the initial insertion of a ventricular catheter (or any other implant), brain cells are destroyed, tissues are displaced, and blood vessels are disrupted. The immediate results are focal hemorrhage and edema that spread into surrounding tissues. Platelets can adhere to silicone rubber, and any that enter the catheter could bind to and alter the function of more distal shunt components (e.g., the valve mechanism). Serum proteins, including*

immunoglobulins, albumin, fibronectin, and fibrinogen, also adhere to the shunt surface. These adsorbed proteins can act as opsonins, which stimulate macrophages and monocytes to produce growth factors (which can cause proliferation of cells, including astrocytes) and other cytokines (which in turn potentiate the inflammatory response).''[125]

Whilst the review is now more than 2 decades old, there is more recent evidence that the insertion of an EVD causes local haemorrhage and oedema and leads to increased levels of brain derived proteins in the spinal fluid associated with stroke or neurotrauma[126,127]. Therefore, in an otherwise healthy patient, the placement of an EVD has potential to cause CSF abnormalities.

However, patients with acute hydrocephalus, cerebral oedema, or raised intracranial pressure are not otherwise healthy. The aseptic meningitis caused by haemorrhagic CSF and neurosurgical trauma can lead to elevated CSF leukocyte counts, in addition to the leukocytes accounted for by blood moving into the CSF or leukocytes recruited to heal damaged brain parenchyma. The brain damage from the primary injury or the neurosurgery to prevent sequelae of acute hydrocephalus or raised intracranial pressures or the turnover of red blood cells can lead to elevated CSF protein. The increased cellular content of the CSF and the immune response due to aseptic meningitis and the primary neurological injury can lead to decreased CSF glucose [9,19,57,125,128]. Therefore, the standard approach to CSF analysis for bacterial CNS infection (i.e. raised leukocytes, raised protein, and decreased glucose in the CSF) may not be useful in diagnosing CNS infections in people requiring an EVD.

The Dorresteijn et al. meta-analysis [113] demonstrated that whilst the mean values for CSF parameters of infection in patients with VRI deviated from baseline in an expected fashion

(i.e. elevated CSF protein and leukocytes, decreased CSF glucose), the magnitude of change from baseline was not significant enough to allow for accurate and reliable diagnosis of VRI.

Another proposed approach to using standard CSF parameters to diagnosing VRI is the cell index, proposed by Pfausler et al. in 2004 [57]. The cell index is defined as follows:

$$\frac{(Leukocytes\ in\ CSF / Erythrocytes\ in\ CSF)}{(Leukocytes\ in\ Serum / Erythrocytes\ in\ Serum)}$$

This approach is theoretically promising because it takes into account the white blood cells brought into the CSF by bleeding – if all CSF white blood cells can be accounted for by haemorrhage, then the cell index will equal 1[57,128]. Pfausler et al.'s original study analysing the utility of the cell index found it to be a useful early diagnostic tool for VRI. However, the study was only a pilot study, with 13 patients in the cohort. The cell index was validated in 2017 by Lunardi et al.[68] who suggested a threshold of 2.9 for patients with TBI and haemorrhage stroke. On the other hand, at least two other studies have failed to establish a clinically useful threshold for the cell index[29,88].

An opposing view to the establishment of a threshold value for the cell index was proposed by Beer et al. in their 2008 review of nosocomial CNS infections[128]. They suggested that trying to find an absolute cut-off to prove infection is futile because the clearance of blood from the CSF involves the immigration of white blood cells, and therefore the cell index is subject to fluctuations. The emphasis of a lack of physiological norm in this patient population might suggest that changes in parameters over time are more important than cut-off values.

Another argument against the use of cell index is the finding that serum leukocyte counts can be elevated in post-neurosurgical bacterial meningitis which would lower the cell index. A 2013 study by Choi et al.[129] attempted to find a useful predictive tool for post-neurosurgical

bacterial meningitis and of the clinical parameters the study collected, the only measurement which reached statistical significance between infected and non-infected patients was serum leukocyte count greater than 9,500/mm^3. However, 50% of non-infected patients also had elevated serum leukocyte counts above the defined threshold.

The lack of encouraging data for standard CSF parameters in diagnosing VRI has led to research into other biomarkers for CNS infection. Yet, studies looking at the diagnostic utility of lactate [22,130,131], procalcitonin [108,129], CRP [88,132,133], or other more exotic inflammatory markers [29,59,66] have not produced convincing data supporting their use in the routine diagnosis of VRI. The reasons for the lack of diagnostic accuracy in these markers are similar to those explaining the lack of diagnostic accuracy in conventional markers of CNS infection. For example, sedation may suppress CSF lactate, lactate can rise with the withdrawal of sedation[134], and the CSF lactate of patients with and without VRI overlap significantly[135].

1.5.3 Microbiological Tests

In patients with an EVD in place, the standard microbiological tests are the gram stain and culture. A gram stain of the CSF is the quicker and cheaper of the two but it has very poor specificity[28,30,136], with a large study of patients with EVDs finding a sensitivity of 39.8% for gram stain compared to culture[29]. Nevertheless, it is generally agreed that a positive culture establishes a diagnosis of VRI which is why it is the most used definition[8,9,59]. Culture results can also provide antibiotic susceptibility, making it a crucial part of the investigation process in a patient with suspected VRI[52,137].

CSF culture has important limitations. The false negative rate of CSF culture has been reported at between 20% to 70%[25-27,106]. This is to be expected in patients with prior exposure to antibiotics, which often occurs before culture results are available as early intervention

may improve prognosis[30,35,138,139]. A false negative rate is also to be expected in patients with antibiotic impregnated EVDs[140]. However, culture results may also be falsely negative in the presence of a biofilm, produced by many pathogens implicated in VRI[141,142]. For example, a case study published in 2010[143] describes a patient with multiple negative CSF cultures who was subsequently found to have a *Staphylococcus aureus* biofilm coating their EVD. Because the formation of a biofilm is recognised as a potential precursor to VRI, the inefficacy of culture in these patients is cause for concern[62,144,145].

1.5.4 Polymerase Chain Reaction

Polymerase chain reaction (PCR) is a commonly performed genetic test which increases the number of copies of genetic material in a sample. This process involves heating DNA to separate the strands (denaturing), the attachment of primers designed to attach upstream to the locus of interest (annealing), and generation of the locus of interest with a thermostable DNA polymerase (extension). This cycle leads to exponential amplification of genetic material, allowing the production of millions of copies of DNA from as few as 1 – 100 cells[146,147]. Different primers allow for the detection of different genetic sequences. For example, the 16S ribosomal RNA (rRNA) PCR allows for detection of a widely conserved genetic sequence in bacteria. Sequencing of hypervariable regions can then allow for identification of particular species of bacteria[148].

In several studies of bacterial infections of the CNS, PCR has been shown to have a superior rate of detection when compared to culture[139,149-151]. Some studies show a three-fold increase in rate of diagnosis[33,34] and a significant number of culture negative CSF samples yield positive results with molecular techniques[136,138,152]. One advantage of these techniques may be the detection of microbial genetic products in patients who have already received

antibiotics because some studies have shown that with prior antibiotics administration, PCR may be superior to culture[87,153,154].

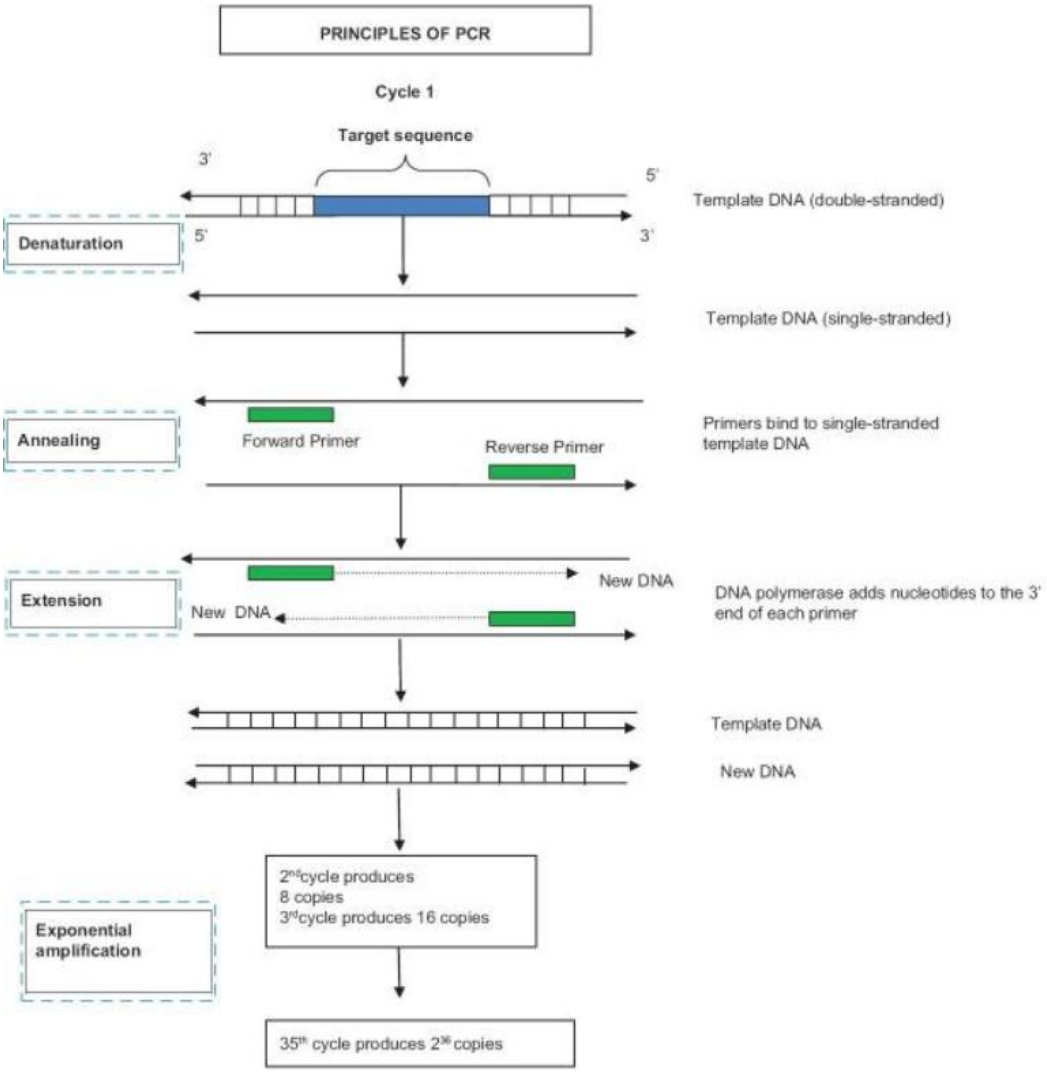

Figure 1-3 – Polymerase chain reaction. Reproduced from an article by Maheaswari et al. 2016[146]

In the context of neurosurgical patients, who commonly have derangements in clinical or laboratory parameters consistent with infection, even when no bacterial infection is present,

and who have a potentially increased rate of false negative culture results due to prophylactic or empiric antibiotics or antibiotic impregnated catheters, techniques like PCR may allow more accurate diagnosis of VRI.

As early as the mid-90's, studies have consistently shown that using PCR can increase the rate of detection of bacteria in the CSF of neurosurgical patients. Salord et al. published one of the first studies of PCR in neurosurgical patients in 1995[155]. The prospective cohort study used 16S rRNA PCR on the CSF of 27 patients who had either positive CSF culture or CSF neutrophils greater than 100 cells/mm^3. As control, they also enrolled 43 control patients without clinical evidence of VRI and inoculated 16 of these specimens with a known concentration of bacteria. Using PCR, the research team found bacterial DNA in all 7 culture positive patients and in 19 of the 20 culture negative patients.

A similar study from 1996 by Druel et al.[32] included 27 patients with laboratory signs of meningitis (7 with positive CSF culture, and 20 with elevated CSF leukocyte count, RCC:WCC <200, and a predominance of polymorphonuclear cells). CSF samples were cultures and tested with 16S rRNA PCR in parallel. Only 7 of the 27 patients had a positive culture, but all patients meeting criteria for VRI according to cell counts had a positive 16S rRNA PCR. None of the 30 control patients had a positive 16S rRNA PCR of the CSF. The conclusion of both studies was the suggestion that aseptic meningitis may have a bacterial origin.

Further studies have shown similarly encouraging results for the role of PCR. A 2005 prospective cohort study using 16S rRNA PCR on 86 CSF samples collected from patients with post-neurosurgical meningitis (with or without EVDs) found that 50% of culture negative samples tested positive for PCR [31]. The three other studies found in this review

which examined PCR in neurosurgical populations found a proportion of culture negative patients who were positive for PCR [83,85,87].

One limitation of many of these studies is that only samples at high risk of infection were selected and some of the studies did not have strict definitions for what constituted a high-risk sample[31,32,155]. This represents a selection bias which would increase the false negative rate of CSF cultures. This also limits the generalisability of the results by only including samples with an inflammatory profile because the use of PCR in the management of VRI may have benefits in non-inflammatory CSF (e.g. for early detection of bacteria before the onset of an inflammatory process). These earlier studies have limited generalisability to the modern context due to advances in PCR and nucleic acid amplification technology[156].

Although these results indicate an important role for PCR in diagnosing VRI and a sensitivity which supersedes the gram stain and culture, it is not a perfect substitute. These techniques are expensive, and the equipment and personnel may not be available at smaller or more remote sites[34]. Secondly, a multiplex PCR designed to amplify the gene segments responsible for antimicrobial resistance in a broad range of species does not exist to the extent that it could replace CSF culture results, thereby leaving CSF culture as still the best test to guide antimicrobial therapy.

Two studies found during this review attempted to correlate clinical and laboratory findings other than CSF culture results to PCR results. The earlier of the papers, from 2014, compared standard CSF parameters, as well as CSF IL-6 and CSF lactate, to the results of multiplex PCR in 62 CSF samples from 42 patients with VRI[85]. Whilst the authors reported that the multiplex PCR would be a useful test to confirm VRI with CSF abnormalities, their data did not include a control group, so a set of CSF parameters could not be established which would differentiate VRI from aseptic meningitis. When comparing the PCR positive and PCR

negative groups there was a large crossover between the standard deviations for CSF leukocytes, glucose, protein, lactate, and IL-6 for these groups. There was no report of statistical significance of the crossover.

The most recent of these studies is a 2017 prospective cohort study published by Dabrowski et al.[157]. This study recruited 50 patients (30 with EVDs, 20 with external lumbar drains) and a total of 276 CSF samples. VRI was defined according to the definition published by Schade et al[158] (positive CSF culture plus one of fever/headache/neck stiffness/altered mental status; colonisation was defined by two or more consecutive CSF samples without clinical features of infection, and contamination was defined as a single CSF culture without clinical features of infection). 16S rRNA PCR was performed concurrently with CSF culture. Of the 50 patients, 8 patients met criteria for VRI (16%), 6 patients met criteria for EVD colonisation (12%), and 7 patients met criteria for sample contamination (14%). A positive 16S rRNA PCR, with a negative CSF culture and the presence of clinical features as defined by Schade et al. was present in 5 patients (10%). EVD colonisation according to 16S rRNA PCR was found in eight patients (16%), and 3 patients (8%) were defined as having sample contamination. When comparing the results of CSF culture and 16S rRNA PCR to non-microbiological parameters of infection, the authors found significant crossover in CSF leukocytes, glucose and protein, and serum leukocytes and CRP. Although the Area Under the Receiver Operating Characteristic (AUROC) suggested a 100% negative predictive value for CSF leukocytes, CSF protein, and CSF glucose, the reported mean values and ranges suggested there were cases of VRI without rises in CSF leukocytes, protein, or glucose.

The Dabrowski study[157] is one of few studies which compare CSF culture and 16S rRNA PCR to non-microbiological indicators of CNS infection. The authors suggest a cut-off of >512 cells/μL in CSF provide a sensitivity of 100% and specificity of 90.5% for VRI but this is in contrast to the large systematic review by Dorresteijn et al.[113] which suggests no

difference in CSF leukocyte counts between patients with and without VRI. Other studies using PCR to diagnose VRI have not shown CSF leukocytes to be a distinguishing characteristic[85]. Furthermore, like other studies examining the use of PCR in VRI, there is no attempt to compare the diagnostic utility of PCR with other diagnostic criteria for VRI.

1.6 The Prognosis of Ventriculostomy-Related Infections

Community acquired infections of the CNS are associated with significant morbidity and mortality. In Australia and New Zealand, bacterial meningitis is estimated to have a mortality rate approaching 20%[159] and patients who survive bacterial meningitis have high rates of neurological sequelae such as hearing loss, seizures, and cognitive impairment[160]. These outcomes explain clinical concerns regarding VRI, but it is unclear as to whether the data for bacterial meningitis can be extrapolated to VRI.

A diagnosis of VRI occurs in the context of EVD placement, which is commonly used in the setting of acute severe neurological injury. For example SAH, which is a common indication for EVD insertion, is associated with a mortality rate of 20 – 50%[161]. Furthermore, severe brain injury is associated with an immunosuppressed state[162]. These patients' primary neurological diagnosis, coupled with immunological sequelae and subsequent hospital-acquired or disease-specific complications, can lead to lengthy hospital admissions with numerous accumulating reasons for poor patient outcome.

A further layer of complexity is added when considering the interplay between the complications these patients suffer, risk factors for VRI, and a diagnosis of VRI. For example, VRI may be associated with bacteraemia[13], but patients with severe brain injury are at increased risk of early ventilator acquired pneumonia, which can lead to bacteraemia[163].

Furthermore, severe head injury may require prolonged intubation (which increases the risk of ventilator-acquired pneumonia) or prolonged EVD placement (which is associated with VRI[9]). For these relationships, cause and effect is difficult to establish.

In this setting, secondary brain injury may develop. This refers to a process in which a cycle of continuing brain injury beyond the primary pathology is triggered by processes such as inflammation, excitotoxicity, hypoxia or oedema. The immunological underpinnings of this process are complex, but they drive a pathology which clinicians aim to interrupt[164,165].

VRI may represent a trigger for the immunological cascade of secondary brain injury, which would support the hypothesis that early treatment can prevent progressive brain injury (aside from the benefits of early treatment of infection). However, the febrile patient with progressive CSF pleocytosis after their brain injury may meet diagnostic criteria for VRI, but instead represent a patient with secondary brain injury.

Over the past decades, advances in the management of patients with brain injury have led to improved survival in this patient population. Consequently, there has become a greater interest in how patients fare after the acute phase of their neurological injury[166]. Survivors after aneurysmal SAH often have seizures or cognitive impairment [161,167] and the incidence of dementia after ICH is estimated to range from 20 – 40%[168].

Although it would be expected that CNS infection in the setting of acute brain injury would have an additive prognostic effect in this patient population, studies reporting outcomes associated with VRI are varied. Some suggest an increased risk of patient centred outcomes (such as death, seizures, or sepsis)[169], but not all could confirm an increased risk of mortality[13]. Other outcomes are more consistent, for example duration of EVD insertion or length of stay in hospital or ICU, with both being correlated with risk of VRI[13,169].

1.7 Summary

The insertion of an EVD is a common procedure used in the management of patients with acute brain injury. While it can be a life-saving procedure, it is associated with complications such as infection, known a ventriculostomy – related infection or VRI. VRI is reported to be common and would be expected to have a deleterious effect on patient prognosis. However, in contrast to community acquired CNS infections, there are few studies that have reported the association between a diagnosis of VRI and prognosis in this population. Measurements of incidence or prognosis of VRI are confounded by variations in diagnostic criteria for VRI. A consensus definition of VRI is made difficult because of the abnormal clinical and laboratory findings caused by the primary neurological diagnosis. The use of microbiological molecular diagnostic techniques such as PCR may improve diagnosis of VRI.

1.8 Objectives and Hypotheses

This thesis is comprised of three studies which seek to address some of the issues described in this chapter. The objectives of the following research are as follows:

1. Evaluate the association between a diagnosis of VRI and clinical outcomes, especially long-term functional neurological outcome
2. Evaluate the diagnostic accuracy of existing diagnostic criteria for VRI when compared to a modern standard (16S rRNA PCR).

Our hypothesis was that a diagnosis of VRI would be associated with worse long term functional outcome. We also hypothesised that PCR would have a higher sensitivity for diagnosing VRI when compared to current diagnostic methods (i.e. published diagnostic criteria or clinical diagnosis of VRI).

2. The Association Between Ventriculostomy - Related Infection and Clinical Outcomes: A Systematic Review and Meta-Analysis

The study comprising this chapter was published as an article titled “The Association Between Ventriculostomy - Related Infection and Clinical Outcomes: A Systematic Review and Meta-Analysis”[170].

Although community acquired infections of the CNS are associated with significant morbidity and mortality, it is not clear the same can be said of VRI. To address this uncertainty, we performed a systematic review of studies reporting outcomes associated with VRI. Our primary objective was to evaluate the association between VRI and mortality. In addition, we evaluated the association between VRI and poor neurological outcome, duration of intensive care admission, duration of hospital admission, duration of EVD placement, and requirement for placement of a permanent CSF shunt.

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Original Research

The association between ventriculostomy – Related infection and clinical outcomes: A systematic review and meta-analysis

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ABSTRACT

Background: Ventriculostomy – related infection (VRI) is a common complication of patients who require placement of an external ventricular drain (EVD). The clinical outcomes of people who are diagnosed with VRI is poorly characterised. We performed a systematic review and meta-analysis to assess the association between VRI, and clinical outcomes and resource use, in patients treated with an EVD.

Methods: We searched MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of clinical trials to identify clinical trial and cohort studies that reported outcomes including mortality, functional outcome, duration of EVD insertion, and intensive care and hospital length of stay. Inclusion criteria and data extraction were conducted in duplicate. Where sufficient data were available, data synthesis was conducted using a random effects model to provide a pooled estimate of the association between VRI and clinical outcomes and resource use. We also pooled data to provide an estimate of the incidence of VRI in this population.

Results: Nineteen studies including 38,247 patients were included in the meta-analysis. There were twelve different definitions of VRI in the included studies. The pooled estimate of the incidence of VRI was 11 % (95 % confidence interval (CI), 9 % to 14 %). A diagnosis of VRI was not associated with an increase in the estimated odds ratio (OR) for mortality (OR 1.07, 95 % CI 0.59 to 1.92, $p = 0.83$ $I^2 = 83.5$ %), nor was a diagnosis of VRI associated with changes in neurological outcome (OR 1.42, 95 % CI 0.36 to 5.56, $p = 0.89$, $I^2 = 0.3$ %). Those diagnosed with VRI had longer intensive care unit length of stay (estimated pooled mean difference 8.4 days 95 % CI 3.4 to 13.4 days, $p = 0.0009$, $I^2 = 78.7$ %) an increase in hospital length of stay (estimated mean difference 16.4 days. 95 % CI 11.6 to 21.2 days, $p < 0.0005$, $I^2 = 76.6$ %), a prolonged duration of EVD placement (mean difference 5.24 days, 95 % CI 3.05 to 7.43, $I^2 = 78.2$ %, $p < 0.01$), and an increased requirement for an internal ventricular shunt (OR 1.80, 95 % CI 1.32 to 2.46, $I^2 = 8.92$ %, $p < 0.01$).

Conclusions: Ventriculostomy related infection is not associated with increased mortality or an increased risk of poor neurological outcome, but is associated with prolonged duration of EVD placement, prolonged duration of ICU and hospital admission, and an increased rate of internal ventricular shunt placement.

1. Introduction

External ventricular drains (EVDs) are commonly used to manage hydrocephalus or raised intracranial pressures in the context of severe acute brain injury such as subarachnoid hemorrhage, traumatic brain injury, and intracerebral hemorrhage [1]. While they can be life-saving tools, and provide valuable information for the management of patients with severe brain injury [2], they are also associated with a number of

Abbreviations: CNS, Central Nervous System; CSF, Cerebrospinal fluid; EVD, External Ventricular Drain; GOS, Glasgow Outcome Scale; LOS, Length of Stay; mRS, modified Rankin Scale; NOS, Newcastle Ottawa Scale; RoB2, Revised Cochrane Risk of Bias scale; VRI, Ventriculostomy-related infection.

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complications, including infection.

Ventriculostomy – related infection (VRI) is an infection of the cerebrospinal fluid, and is reported to be a common complication of EVD use [3]. Furthermore, a primary neurological illness requiring the insertion of an EVD often portends poor prognosis from the perspective of both short-term and long-term outcomes. However, whilst community acquired infections of the central nervous system are associated with poor outcomes [4], and individual studies indicate that a diagnosis of VRI may be associated with worse prognosis in patients with EVDs [5], there are inconsistent data regarding outcomes in this patient population.

We performed a systematic review to assess the reported incidence of VRI in patients with EVDs, and to assess the association between a diagnosis of VRI and clinical outcomes including mortality and poor neurological outcome. In addition, measures of resource use such as duration of intensive care admission, duration of hospital admission, duration of EVD placement, and requirement for placement of an internal ventricular shunt were reported.

2. Methods

This investigator-funded review was undertaken according to a pre-planned protocol (PROSPERO registration CRD 42019134778) and is reported according to current standards (as per the PRISMA statement [6], the PRISMA checklist is attached in Supplementary Document 1).

2.1. Eligibility criteria

We included data from randomized controlled trials or cohort studies that included adult patients who had placement of an EVD, where there was an exposure group who had VRI and a control group without VRI, and at least one outcome of interest was reported. A diagnosis of VRI was defined as per individual studies. The primary outcome for this review was in-hospital mortality, with measure of effect as recorded by the individual studies. Additional outcomes included functional neurological outcome at longest recorded length of follow-up (with good functional neurological outcome defined as a Glasgow Outcome Scale (GOS) of 5 to 6, or a modified Rankin Scale (mRS) of 0 to 2), mortality at longest follow-up, duration of intensive care unit (ICU) admission, duration of hospital admission, duration of EVD placement, and incidence of other infective and non-infective complications.

2.2. Information sources

We searched MEDLINE using the PubMed interface, as well as EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews using the OVID interface. We also searched reference lists from included trials and relevant review articles.

2.3. Search strategy

We used combinations of search terms for ventriculostomy related infection combined with a sensitive search strategy to identify studies related to prognosis [7]. The full details of the search strategy are included in Supplementary Document 2.

2.4. Selection process

The titles and abstracts of all reports were downloaded into a reference management software system [8], and duplicates were removed. Two authors independently screened the titles and abstracts, and full text manuscripts were obtained of all studies that might potentially meet the eligibility criteria. Two authors then independently applied the inclusion criteria, with disagreements resolved by consensus, or by a third reviewer if required.

2.5. Data collection process and data items

Data were extracted from the full text manuscripts by two authors, with disputes resolved by discussion or in consultation with a third reviewer. We extracted data regarding details of the included studies (first author, year of publication, number of centers included in the study, study design, patient population, length of follow up, number of study participants with an EVD, number of patients diagnosed with VRI). We collected data regarding the criteria used to diagnose VRI as well as the number of study participants with and without a diagnosis of VRI. We collected data regarding the outcomes as detailed above.

2.6. Risk of bias assessment

We used the Newcastle-Ottawa scale [9] to assess risk of bias in the included observational studies, and version 2 of the Cochrane risk-of-bias tool (RoB2) for randomized trials [10] to assess of risk of bias in the randomized clinical trials. Risk of bias was assessed independently by two authors, with disputes resolved by discussion or by consultation with a third reviewer.

2.7. Data synthesis and effect measures

When sufficient data were available to allow pooling, we used a Sidik-Jonkman random effects model [11] to provide a pooled estimate of the odds ratio (OR) or risk ratio (RR) (with 95 % confidence intervals (CI)) for binary outcomes such as mortality, and a pooled estimate of standard mean difference (MD) (with 95 % CI) for continuous outcomes. Continuous data reported in metrics other than mean and standard deviation were converted to mean and standard deviation according to standard methods [12]. A random effects model was chosen as the primary analytical method due to expected variations in effect measures from variations in diagnostic criteria for VRI. As per the Cochrane Handbook for Systematic Reviews of Interventions, sensitivity analysis for the primary outcome was performed using a fixed effect model [12]. We also used data on the proportion of study participants diagnosed with VRI in each study to estimate a pooled incidence of VRI, also with 95 % CI. Heterogeneity was estimated using the I^2 statistic [12]. Analyses were undertaken using the *meta*-analysis package and metaprop_one commands in STATA 16.1.

2.8. Assessment of reporting bias

We assessed for the possibility of small study bias by visual inspection of contour enhanced funnel plots and using the Egger test [13].

3. Results

3.1. Study selection

There was a total of 1,642 records identified by the search. After removal of duplicates and screening of abstracts, 54 studies and 16 abstracts were selected for full-text review. 51 of these articles were excluded; 11 did not report outcomes in patients with VRI, 26 reported outcomes in a manner inappropriate for meta-analysis (e.g. qualitatively), 11 did not report EVD use specifically (e.g. cohorts included lumbar drainage), 2 were not published in English, and 1 was a duplicated result. After applicated of the inclusion criteria, 19 studies (18 observational studies and one randomized controlled trial) including a total of 38,247 participants were included in the review. The searches were performed in February 2020 and July 2021. The study selection process is shown in Fig. 1.

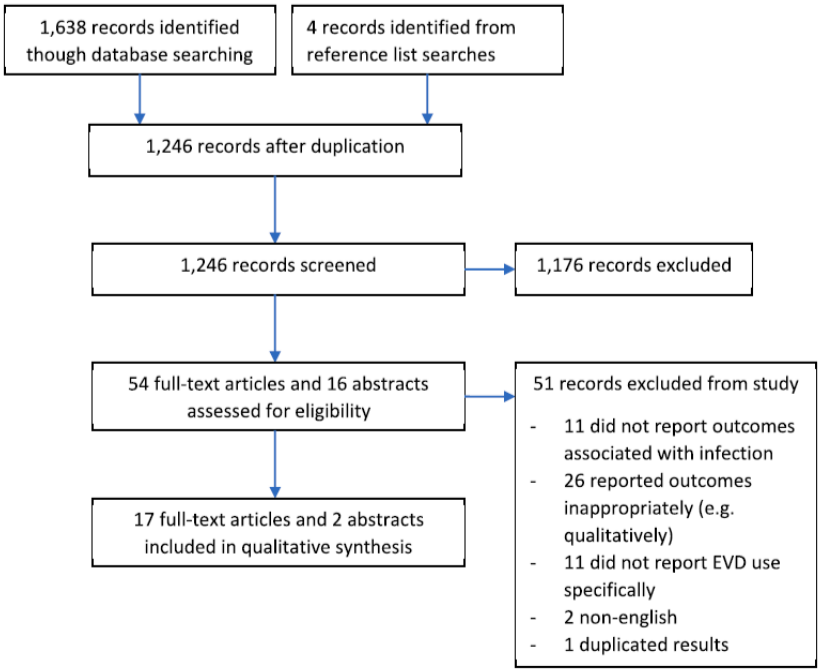

Fig. 1. PRISMA flow diagram.

3.2. Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. Two studies [14–15] reported before and after cohorts related to the implementation of interventions to reduce the incidence of VRI. The before and after cohorts were analyzed separately. Both studies reported significant differences in the incidence of VRI following the intervention. One study [16] which used administrative data accounted for the majority of patients in this systematic review (34,238 from a total of 38,247 patients).

3.3. Diagnostic criteria of VRI

The definition of VRI used to define cases of VRI in each of the included studies is shown in Table 2. Twelve different definitions were identified. The most commonly used diagnostic criteria was a positive CSF culture without clinical criteria (five studies [14,17–20]). Three studies [15,21–22] used the definition outlined by the Centre for Disease Control. One study [23] did not include a definition of VRI. One study [16] used International Classification of Diseases coding. Two papers [24–25] explicitly distinguished VRI from EVD colonisation. Two papers [26–27] required additional clinical criteria to diagnose VRI in the setting of CSF cultures positive for commensal species.

3.4. Interventions for VRI

Documented interventions for VRI included intravenous antibiotics (for either the duration of EVD placement [19,23,27–29], at least 21 days [21], or an undefined duration[15,18,24,25,30]), EVD exchange [22,31], and intrathecal antibiotics [25–26,30]. Five papers listed no treatments for VRI [14,16–17,20,32]. One study [22] reported outcomes in patients after the introduction of a new EVD removal policy. However, the study did not compare patient outcomes in patients with and without a diagnosis of VRI, other than as an outcome pooled from both EVD removal policies. Another study [31] reported the incidence of EVD replacement in patients with VRI, but did not specifically report outcomes associated with timing of EVD removal.

One paper [29] reported an increase in mortality in patients with VRI who were treated with continuous prophylactic antibiotics for the duration of EVD placement, but had small sample sizes and did not report formal statistical analysis. No other studies quantitively analysed interventions in patients with and without a diagnosis of VRI in a manner appropriate for meta-analysis.

3.5. Microbiology of VRI

Sixteen studies discussed microbiology of VRI [15,17–22,24–32]. Five of these studies reported outcomes associated with microbiology of infection [21,24,27,29–30]. One study [24] described an increased rate of co-infection in patients with gram negative infection, but did not quantitively report this outcome. One study [21] reported no significant difference in mortality in patients with VRI due to gram-positive versus gram-negative infection. Three studies [27,29–30] qualitatively reported outcomes in patients with a positive CSF culture, but drew no formal conclusions regarding the impact of microbiology on outcomes in patients with VRI. None of the studies reported the impact of microbiology on patients with VRI when compared to patients without VRI.

3.6. Risk of bias

The details of the risk of bias assessments are shown in Supplementary Tables 2 and 3. Of the 18 cohort studies only one [16] provided analysis controlling for known confounders (such as severity of primary neurological diagnosis). Conflict of interest statements were included in 10 studies [31,15–16,18–22], all of whom declared no conflict of interest. The remaining 9 studies had no statement regarding conflict of interest [17,23–30].

3.7. Incidence of VRI

The proportion of study participants in the included studies who were diagnosed with VRI ranged from 0.03 to 0.34. The overall pooled

Table 1
Characteristics of the studies included in systematic review (Abbreviations: CNS – Central Nervous System; CSF – Cerebrospinal Fluid; EVD – External Ventricular Drain; ICH – Intracerebral Haemorrhage; ICU – Intensive Care Unit; IVH – Intraventricular Haemorrhage; SDH – Subdural Haematoma; VP shunt – Ventriculoperitoneal shunt; VRI – Ventriculostomy – Related Infection).

Author	Year	Design	Centres	Population	Age of Population (years)	Gender of Population	Primary Neurological Diagnosis/ Indication for EVD Insertion	Duration of follow up	Number of patients with EVDs	Number of patients diagnosed with VRI
Arabi et al.	2005	Retrospective cohort study	Single	All patients with an EVD. Patients with CNS infection prior to EVD insertion were excluded.	For all patients: 35 ± 15	For all patients: Male: 79 % Female: 21 %	For all patients: Trauma 63 %; Non-trauma 37 %; Craniotomy 35 %	Until discharge from hospital	84	12
Batista et al.	2015	Retrospective cohort study	Single	All patients with an EVD	For all patients: 58 (mean)	For all patients: Male: 37 % Female: 63 %	"Main diagnosis were intracerebral haemorrhage (ICH), spontaneous subarachnoid haemorrhage (SAH) and traumatic brain injury (TBI)."	Until discharge from ICU	30	5
Bota et al.	2005	Retrospective cohort study	Single	All patients with an EVD. Patients with CNS infection prior to EVD insertion were excluded.	For patients not diagnosed with VRI: 41 (mean), 18–84 (range) For patients diagnosed with VRI: 44 (mean), 18–85 (range)	For patients not diagnosed with VRI: Male: 56 % Female: 44 % For patients diagnosed with VRI: Male: 63 % Female: 37 %	For patients not diagnosed with VRI: SAH 33 %; ICH 12 %; IVH 16 %; brain tumour 15 %; neurotrauma 18 %; basilar cranial fracture 6 %; craniotomy 69 % For patients diagnosed with VRI: SAH 47 %; ICH 9 %; IVH 22 %; brain tumour 12 %; neurotrauma 7 %; basilar cranial fracture 3 %; craniotomy 84 %	Until discharge from hospital	638	58
Camacho et al.	2010	Prospective cohort study	Single	All patients with an EVD. Patients with CNS infection, open skull fracture, CSF leakage, or congenital hydrocephalus prior to EVD insertion were excluded.	For patients not diagnosed with VRI: 44.18 (mean) 5–83 (range) For patients diagnosed with VRI: 45.18 (mean), 8–88 (range)	For patients not diagnosed with VRI: Male: 45 % Female 55 % For patients diagnosed with VRI: Male: 63 % Female: 37 %	For patients not diagnosed with VRI: SAH 42 %; Trauma 27 %; Stroke 12 %; Tumour 12 % For patients diagnosed with VRI: SAH 36 %; Trauma 27 %; Stroke 14 %; Tumour 18 %	Until 30 days after EVD removal	119	22
Hagel et al.	2014	Retrospective cohort study	Single	All patients with an EVD. Patients with open skull fracture and CSF leakage, or CNS infection prior to EVD insertion were excluded.	For patients not diagnosed with VRI: 61 (mean) 18–86 (range) For patients diagnosed with VRI: 51 (mean), 18–81 (range)	For patients not diagnosed with VRI: Male: 56 % Female: 44 % For patients diagnosed with VRI: Male: 44 % Female: 56 %	For patients not diagnosed with VRI: SAH, nontraumatic 60 %; SAH, traumatic 18 %; tumour, malignant 8 %; tumour, benign 4 %; hydrocephalus 2 %; contusion/ oedema 8 % For patients diagnosed with VRI: SAH, nontraumatic 71 %; SAH, traumatic 11 %; tumour, benign 6 %;	Until 7 days after discharge from ICU	218	18

(continued on next page)

Table 1 (*continued*)

Author	Year	Design	Centres	Population	Age of Population (years)	Gender of Population	Primary Neurological Diagnosis/ Indication for EVD Insertion	Duration of follow up	Number of patients with EVDs	Number of patients diagnosed with VRI
							hydrocephalus 6 %; contusion/ oedema 6 %			
Hersh et al.	2019	Retrospective cohort study	Single	All patients with an EVD.	For patients not diagnosed with VRI: 57 (median), 44–66 (IQR) For patients diagnosed with VRI: 51 (median), 44.5–62 (IQR)	For patients not diagnosed with VRI: Male: 52 % Female: 48 % For patients diagnosed with VRI: Male: 62 % Female: 38 %	For patients not diagnosed with VRI: ICH 25 %; SAH 47 %; Trauma 2 %; Tumour 13 %; Other 14 % For patients diagnosed with VRI: ICH 21 %; SAH 50 %; Trauma 0 %; Tumor 13 %; Other 17 %	Until discharge from hospital	243	24
Katzir et al.	2019	Retrospective cohort study	Single	All patients with an EVD for longer than 5 days. Patients with CNS infection prior to EVD insertion, or CSF leak before or during EVD insertion, were excluded.	For patient not diagnosed with VRI: 52 ± 17 For patients diagnosed with VRI: 48 ± 19	For patient not diagnosed with VRI: Male: 56 % Female: 44 % For patients diagnosed with VRI: Male: 64 % Female: 36 %	For patient not diagnosed with VRI: Head injury 18 %; Shunt malfunction 6 %; Aneurysmal SAH 28 %; IVH 1 %; ICH 16 %; Tumour 13 % Stroke 3 %; Obstructive hydrocephalus 5 % For patients diagnosed with VRI: Head injury 32 %; Shunt malfunction 18 %; Aneurysmal SAH 9 %; IVH 9 %; ICH 14 %; Tumour 14 %; Stroke 5 %; Obstructive hydrocephalus 0 %	For 6 months after diagnosis	142	22
Kim et al.	2012	Retrospective cohort study	Single	All patients with an EVD. Patients with CNS infection prior to EVD insertion were excluded.	For patient not diagnosed with VRI: 54 ± 16 For patients diagnosed with VRI: 57 ± 16	For patient not diagnosed with VRI: Male: 42 % Female: 58 % For patients diagnosed with VRI: Male: 50 % Female: 50 %	For patient not diagnosed with VRI: SAH 57 %; ICH 14 %; Neoplasm 13 %; Other 15 % For patients diagnosed with VRI: SAH 58 %; ICH 17 %; Neoplasm 17 %; Other 8 %	Until discharge from hospital	343	12
Kohli et al.	2018	Retrospective cohort study	Single	All patients with an EVD. Patients with any infection prior to EVD insertion, or previous EVD insertion, were excluded.	For patient not diagnosed with VRI: 49 (mean) For patients diagnosed with VRI: 49 (mean)	For patient not diagnosed with VRI: Male: 54 % Female: 46 % For patients diagnosed with VRI: Male: 50 % Female: 50 %	For patient not diagnosed with VRI: ICH 33 %; SDH 9 %; SAH 14 %; Neoplasm 17 %; Stroke 5 %; Traume 9 %; Primary Hydrocephalus 14 % For patients diagnosed with VRI: ICH 50 %; SDH 0 %; SAH 10 %; Neoplasm 20 %; Stroke 0 %; Trauma 0 %;	Not specified	163	10

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Design	Centres	Population	Age of Population (years)	Gender of Population	Primary Neurological Diagnosis/ Indication for EVD Insertion	Duration of follow up	Number of patients with EVDs	Number of patients diagnosed with VRI
							Primary Hydrocephalus 20 %			
Lyke et al.	2001	Prospective cohort study	Single	All patients with an EVD. Patients with CNS infection prior to EVD insertion were excluded.	For patient not diagnosed with VRI: 55 (mean) 22–93 (range) For patients diagnosed with VRI: 52 (mean) 22–69 (range)	For patient not diagnosed with VRI: Male: 43 % Female: 57 % For patients diagnosed with VRI: Male: 36 % Female: 64 %	For EVDs not associated with VRI: Tumour 16 %; ICH 68 %; Closed head trauma 3 %; Open head trauma 3 %; Previous neurosurgical procedure 72 % For EVDs associated with VRI: Tumour 36 %; ICH 55 %; Closed head trauma 0 %; Open head trauma 0 %; Previous neurosurgical procedure 82 %	Until discharge from hospital	157	11
Moon et al.	2007	Retrospective cohort study	Single	All patients with an EVD. Patients with CSF leakage unrelated to EVD insertion, concurrent bacteremia with the same pathogen, or penetrating injury to the brain were excluded.	For all patients: 48.5 (mean) 1–82 (range)	For all patients; Male: 63 % Female: 37 %	For all patients: Trauma 63 %; Tumour 4 %; Vascular Disease 27 %; Hydrocephalus 6 %	Not specified	112	15
Murthy et al.	2016	Retrospective cohort study	Multiple (data extracted from national database)	Patients with non-traumatic ICH requiring EVD insertion. Patients who died within 48 h of ICU admission, or those with initiation of a palliative care code, were excluded.	For patient not diagnosed with VRI: 18–64: 61 % 65–79: 30 % >80: 10 % For patients diagnosed with VRI: 18–64: 69 % 65–79: 26 % >80: 5 %	For patient not diagnosed with VRI: Male: 56 % Female: 45 % For patients diagnosed with VRI: Male: 63 % Female: 37 %	Only patients with ICH were included.	Until discharge from hospital	34,238	1934
Poon et al.	1998	Randomised controlled trial	Not stated	All patients with an EVD.	For patients in group I (as defined by the study): 44 ± 19 For patients in group II (as defined by the study): 46 ± 17	For patients in group I (as defined by the study): Male: 61 % Female: 39 % For patients in group II (as defined by the study): Male: 61 % Female: 39 %	For patients in group I (as defined by the study): Head injury 9 %; Brain tumour 45 %; Vascular 29 % For patients in group II (as defined by the study): Head injury 10 %; Brain Tumour 46 %; Vascular 30 %	Not specified	228	15
Segura Pensado et al.	2019	Retrospective cohort study	Not stated	All patients with an EVD.	For all patients: 58 ± 13	For all patients: Male: 51 % Female: 49 %	Not reported.	Until discharge from hospital	51	17
Sweid et al.	2020	Retrospective cohort study	Single	All patients with an EVD. Patients with a systemic infection prior to or during	For patient not diagnosed with VRI:	For patient not diagnosed with VRI:	For patient not diagnosed with VRI: SAH 35 %; ICH 22	Until discharge from hospital	389	12

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Design	Centres	Population	Age of Population (years)	Gender of Population	Primary Neurological Diagnosis/ Indication for EVD Insertion	Duration of follow up	Number of patients with EVDs	Number of patients diagnosed with VRI
				EVD placement, CNS infection before or during EVD insertion, death within 5 days of ventriculostomy insertion, EVD inserted at an outside hospital, prior CSF leak, and an open scalp laceration, were excluded.	57 ± 16 For patients diagnosed with VRI: 51 ± 16	Male: 45 % Female: 55 % For patients diagnosed with VRI: Male: 25 % Female: 75 %	%; Tumour 16 %; Hydrocephalus 22 %; Other 9 % For patients diagnosed with VRI: SAH 42 %; ICH 33 %; Tumour 0 %; Hydrocephalus; 8 %; Other 17 %			
Talibi et al.	2020	Prospective/ Retrospective cohort study	Single	All patients with an EVD. Patients with previous EVDs, or CNS infection prior to EVD insertion were excluded.	For patients pre-EVD care bundle: 53 (median) 43–64 (IQR) For patients post-EVD care bundle: 56 (median) 44–67 (IQR)	For patients pre-EVD care bundle: Male: 58 % Female: 42 % For patients post-EVD care bundle: Male: 55 % Female: 45 %	Not reported.	Not specified	275	48
Williamson et al.	2014	Retrospective cohort study	Single	Patients with an EVD and at least one CSF sample sent. Patients with VP shunts, lumbar drains, or CNS infection prior to EVD insertion were excluded.	For patient not diagnosed with VRI: 51 ± 17 For patients diagnosed with VRI: 47 ± 15	For patient not diagnosed with VRI: Male: 51 % Female: 49 % For patients diagnosed with VRI: Male: 67 % Female: 33 %	Not reported.	Until discharge from hospital	410	43
Wright et al.	2013	Retrospective cohort study	Single	All patients with an EVD. Patients with previous EVDs, or CNS infection prior to EVD insertion were excluded.	For patient not diagnosed with VRI: 53 ± 18 For patients diagnosed with VRI: 59 ± 15	For patient not diagnosed with VRI: Male: 52 % Female: 48 % For patients diagnosed with VRI: Male: 14 % Female: 86 %	For patient not diagnosed with VRI: SAH 38 %; ICH 30 %; Tumour 24 %; Trauma 3 %; Hydrocephalus 3 %; Infectious 1 %; Other 2 % For patients diagnosed with VRI: SAH 76 %; ICH 19 %; Tumour 5 %; Trauma 0 %; Hydrocephalus 0 %; Infectious 0 %; Other 0 %	Not specified	141	21
Zakaria et al.	2013	Prospective/ Retrospective cohort study	Single	All patients with an EVD. Patients with CNS infection prior to EVD insertion were excluded.	For patients pre-EVD care bundle: Without VRI: 53 (mean) With VRI: 50 (mean) For patients post-EVD care bundle: Without VRI: 51 (mean) With VRI: 45 (mean)	For patients pre-EVD care bundle: Male: 52 % Female: 48 % For patients post-EVD care bundle: Male: 49 % Female: 51 %	For patients pre-EVD care bundle, without VRI: SAH/IVH 41 %; CSF leak 13 %; Trauma 11 %; Tumour 23 %; Other 11 % For patients pre-EVD care bundle, with VRI: SAH/IVH 50 %; CSF leak 6 %; Trauma 11 %; Tumour 19 %; Other 15 %	Until discharge from hospital	266	72

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Design	Centres	Population	Age of Population (years)	Gender of Population	Primary Neurological Diagnosis/ Indication for EVD Insertion	Duration of follow up	Number of patients with EVDs	Number of patients diagnosed with VRI
							For patients post-EVD care bundle, without VRI: SAH/IVH 35 %; Trauma 12 %; Tumour 28 %; Other 25 % For patients post-EVD care bundle, with VRI: SAH/IVH 33 %; Trauma 6 %; Tumour 22 %; Other 39 %			

estimate of the incidence of VRI in the included studies was 0.11 (95 % CI 0.09 to 0.14, $I^2 = 90.0$ %), as shown in Fig. 2.

3.8. Association between VRI and mortality

Mortality data were reported in 13 cohorts [14,16–17,26,29,31,21–24]. Data from 12 cohorts, including 36,266 participants, were presented in a format that permitted pooling [14,16–17,26,29,31,22–24]. The pooled estimate of the OR for mortality was 1.07 (95 % CI 0.59 to 1.92, $p = 0.83$, $I^2 = 83.5$ %), as shown in Fig. 3. There was no evidence of small study bias on Egger's test ($p = 0.68$). The contour enhanced funnel plot is included as Supplementary Fig. 1. When data were pooled using a fixed effect model, a diagnosis of VRI was associated with an increased risk of death (estimated OR for mortality 1.19, 95 % CI 1.08 to 1.30, $I^2 = 65.1$ %, $p < 0.01$) (Supplementary Fig. 2), with a single retrospective study [16] that used administrative data contributing 89.8 % of the data to the analysis.

Association between VRI and Functional Outcome.

Functional outcome was reported in five studies [19–20,22,27,32], with data from two studies [22,32] including 385 participants in a format that permitted pooling. The pooled estimated of the OR for a good outcome was 1.42 (95 % CI 0.36 to 5.56, $I^2 = 0.26$ %, $p = 0.37$) (Table 3 and Supplementary Fig. 3). Of the other three studies, one [27] reported a statistically significant incidence of poor neurological outcome, and two [19–20] reported no difference (Supplementary Table 1). Duration of follow-up was until hospital discharge [19–20,27,32], or at 6 months [22]. The study which reported functional neurological outcome at 6 months reported no significant difference in functional outcome, and was able to be included in the meta-analysis.

3.9. Association between VRI and duration of EVD placement

Duration of EVD placement was reported in fifteen studies [14–15,18,19,21–28,30–32]. Data from twelve studies including 2,643 patients was able to be pooled [18,28,21–26,30–32]. A diagnosis of VRI was associated with a longer duration of EVD placement (mean difference 5.24 days, 95 % CI 3.05 to 7.43, $I^2 = 78.2$ %, $p < 0.01$) (Table 3 and Supplementary Fig. 4). Of the three studies not included in pooled analysis, one reported no effect of a diagnosis of VRI on duration of EVD placement [14], and two reported an increased duration of EVD placement in patients with a diagnosis of VRI [15,27] (Supplementary Table 1).

3.10. Association between VRI and ICU or hospital length of stay

Six studies including 1,745 patients reported ICU length of stay (LOS) in a format permitting pooled analysis [20,22,24,26,31–32]. A diagnosis of VRI was associated with a longer ICU admission (mean 8.4 days, 95 % CI 2.5 to 14.3, $I^2 = 78.7$ %, $p = 0.01$) (Table 3 and Supplementary Fig. 5). Eleven studies including 36,679 patients reported hospital LOS in a format permitting pooled analysis [16,18,31,21–23,25–27]. A diagnosis of VRI was associated with prolonged hospital LOS (mean 16.9 days, 95 % CI 12.3 to 21.6, $I^2 = 81.4$ %, $p < 0.01$) (Table 3 and Supplementary Fig. 6). One study including two cohorts [14] reported LOS in a format not appropriate for pooled analysis, and reported increased LOS in patients with a diagnosis of VRI in both cohorts (Supplementary Table 1).

3.11. Association between VRI and placement of an internal ventricular shunt

Incidence of internal ventricular shunt insertion was reported in four studies [16,18–20]. Three papers [18–20] reported outcomes associated with insertion of a ventriculoperitoneal shunt. One paper [16] reported outcomes associated with "permanent CSF shunt" insertion. No papers reported insertion of ventriculoatrial or other specific types of internal ventricular shunts as an outcome. No papers described policies regarding insertion of internal ventricular shunts in patients diagnosed with VRI. Three studies [16,19–20] including 34,821 patients were pooled for analysis. The pooled estimate of the OR for internal ventricular shunt placement was 1.80 (95 % CI 1.32 to 2.46, $I^2 = 8.92$ %, $p < 0.01$) (Table 3 and Supplementary Fig. 7). The results of the remaining study [18] are described in Supplementary Table 1.

3.12. Other outcomes

Number of EVDs per patient was reported in two studies [22,26]. Both studies reported a higher number of EVDs in patients with a diagnosis of VRI. A higher incidence of venous thromboembolism and seizures in patients diagnosed with VRI was reported in one study [16].

Five studies reported incidence of non-CNS infections in patients with EVDs [15–16,18,24,31]. The results of these data were conflicting, and are described in Supplementary Table 1.

4. Discussion

We performed a systematic review and meta-analysis to assess the association between a diagnosis of VRI and clinical outcomes. We found no association between VRI and increased mortality or functional outcome, although there was an association with increased mortality in the sensitivity analysis. We found a significant association between a diagnosis of VRI and resource use as defined by prolonged duration of EVD insertion, and increased LOS in both hospital and ICU. We also

Table 2
Definitions for VRI in the included studies (Abbreviations: CDC – Centers for Disease Control and Prevention; CNS – Central Nervous System; CSF – Cerebrospinal Fluid; EVD – External Ventricular Drain; IVC – Intraventricular Catheter; VAI – Ventriculostomy – Associated Infection; VRI – Ventriculostomy – Related Infection; WBC – White Blood Cell).

Study Author and Year	Definition of VRI
[26]	"VAI was defined as culture of a recognized pathogen from the CSF after catheter insertion. If coagulasenegative staphylococcus; diphteroides; Bacillus, Micrococcus, or Proprionibacterium species were isolated, at least 1 of the following criteria had to be identified: Positive Gram's stain, decrease in CSF glucose level, increase in CSF protein level, increased patient temperature, inflammation at the catheter site, altered mental status, or irritability. In exceptional cases the diagnosis of VAI was made on clinical grounds in the presence of altered mental status, fever, with CSF changes consistent with ventriculitis (high WBC, high protein, and low glucose). Exclusion criteria were as follows: (1) if CSF culture did not yield organisms but may have a positive Gram's stain, (2) if patient had meningitis or ventriculitis before the insertion of a catheter, and (3) if CSF became culture positive after 5 days of catheter removal."
Batista et al. 2015	"Infection was defined as a positive CSF culture"
[24]	As per Lozier et. al
Camacho et al. 2010	CDC criteria
[31]	"We defined EVD-related infection as positive CSF culture result plus clinical symptoms or CNS pleocytosis/cell count increase, or in the case of negative CSF culture, clinical symptoms, and CNS pleocytosis/cell count increase."
[32]	"…ventriculostomy-associated ventriculitis was defined as a positive cerebrospinal fluid (CSF) gram stain plus the isolation of CSF culture with concurrent clinical symptoms of fever, seizure, or altered mental status."
[22]	CDC criteria
[18]	"A CSF infection was defined as a positive CSF culture and documented to have occurred on the same day that the CSF culture was obtained."
[19]	"A positive infection was defined as a positive CSF culture after EVD placement."
[27]	""Nosocomial ventriculitis" was defined as culture of a recognized pathogen from the CSF either at the time of or 2 days after IVC insertion. The day of insertion was defined as "day 0". In addition, if common skin flora, such as coagulase-negative Staphylococcus, Corynebacterium, Bacillus, Micrococcus, or Propionibacterium species were isolated, then 1 of the following criteria had to be identified: a Gram stain of the original CSF sample that produced a finding consistent with the organism cultured, a decrease in the CSF glucose level (<25 mg/dL), an increase in the CSF protein level (>50 mg/dL), or a finding of neutrophilic pleocytosis > 10 cells/mm3)."
[30]	"1) a febrile conditions with temperature above 38.5C° at the time of >2 days after EVD catheter insertion, and 2) a positive CSF culture. However, when CSF cultures were negative, the term "suspicious ventriculititis" was used if CSF pleocytosis (above 15cells/mm3) and CSF/plasma glucose ratio of <0.5 were noted in CSF laboratory results. We excluded the following patients who have other detectable sources for infection; 1) CSF leakage unrelated with EVD, 2) concurrent bacteremia with the same pathogens, and 3) penetrating injury of the brain."
[16]	"VAI was defined as any patient with ventriculostomy who developed meningitis (ICD-9-CM 320.x, 321.x, 322.x)."
[29]	"…as defined by CSF culture and/or CSF white cell count > 50/cu mm…"
[23]	Not stated
[25]	"VAI was defined as fever (38 °C for 30 min or 38.3 °C) at least 24 h after EVD placement associated with CSF leucocytosis >10 cells/mm3 (500 red blood cells equivalent to 1 white blood cell), increased proteins (>50 mg/dl), and decreased glucose (<50 % of serum glucose) with positive CSF culture. To differentiate colonization from infection, an infection was determined when the Gram stain of the original CSF sample that produced a finding was consistent with the organism cultured in addition to the aforementioned criteria."
[14]	Positive CSF culture
[20]	Positive CSF culture
[28]	"A VRI was defined as definite if there were clinical signs and symptoms of infection, abnormal CSF parameters, and a positive CSF culture; a VRI was defined as probable if clinical signs and symptoms and abnormal CSF parameters were present but the culture was negative; and no infection was defined as having no CSF abnormalities and a negative CSF culture."
[15]	CDC criteria

found an association between a diagnosis of VRI and incidence of internal ventricular shunt insertion. Our analyses indicate high heterogeneity between the included studies, and should be interpreted with caution.

The lack of association between VRI and mortality or neurological outcome is unexpected, especially considering the morbidity and mortality associated with community acquired CNS infections [4]. One explanation may be the clinical vigilance associated with a critically ill patient with an EVD in place admitted to an ICU, in whom the risk of a CNS infection would be presciently recognized. In this context, the poor outcomes associated with delayed initiation of antibiotics in patients with community acquired meningitis [33–34] may be mitigated by early intervention. Furthermore, the increased resource use we have found in patients diagnosed with VRI suggests an additive effect of CNS infection in patients with severe brain injury.

Another possible explanation for this lack of association between VRI and mortality or functional neurological outcome is the effect of heterogenous definitions. Diversity in diagnostic criteria of VRI is a well-recognized source of uncertainty, and the incidence of VRI in a cohort will change depending on which definition is used [35]. Definitions which require a positive CSF culture often do not distinguish infection from sample contamination or EVD colonization [15,17,19–22,28–32]. Other definitions are based on cerebrospinal fluid (CSF) analysis and require no evidence of microbiological disease [15,21–22,24,29,31], which may not distinguish VRI from aseptic meningitis [36–37]. Therefore, bias in definitions of VRI may lead to a diagnosis of infection in patients with EVD colonization, sample contamination, or aseptic meningitis. This means that studies may underestimate the prognostic implications of VRI due to an unreliable denominator, as a number of patients meeting diagnostic criteria for VRI will have outcomes commensurate with brain injury without infection.

Potential confounders for outcomes associated with VRI were not reported in the eligible studies in a fashion allowing for pooled analysis. Treatments included intrathecal and intravenous antibiotics (with durations varying between a minimum of 21 days, or until resolution of clinical evidence of infection), and EVD exchange. Only one study [29] reported outcomes in patients with and without VRI in different treatment groups, but did not report statistical analysis of outcomes. Outcomes related to bacterial epidemiology of VRI compared to patients without VRI was not quantitively reported in any of the studies.

The strengths of this study include robust methodological design and reporting format, consistent with best practice for systematic reviews as outlined by the PRISMA statement [6]. Our review included data from a large number of patients, and our pooled estimate of the incidence of ventriculitis is consistent with other pooled estimates [3]. The limitations of this study include the heterogeneity of the included studies, as evidenced by high I^2 values and wide confidence intervals. Identified sources of heterogeneity include variations in diagnostic criteria for VRI (twelve different definitions were used in the studies included in this review), and methodological heterogeneity (for example due to variations in site-specific treatments and length of patient follow-up). Many of the studies we found which reported outcomes of interest had small

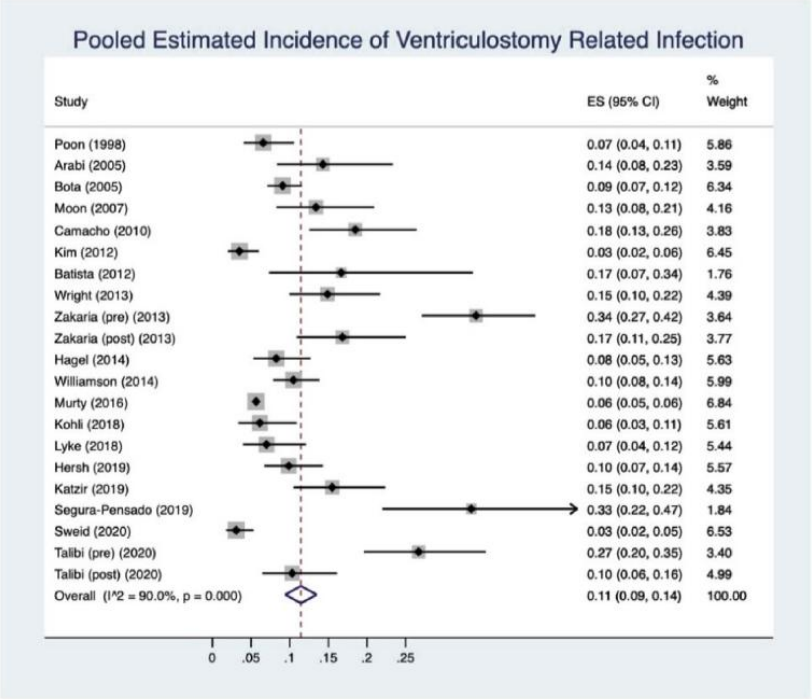

Fig. 2. Pooled estimate of the incidence of Ventriculostomy-Related Infection.

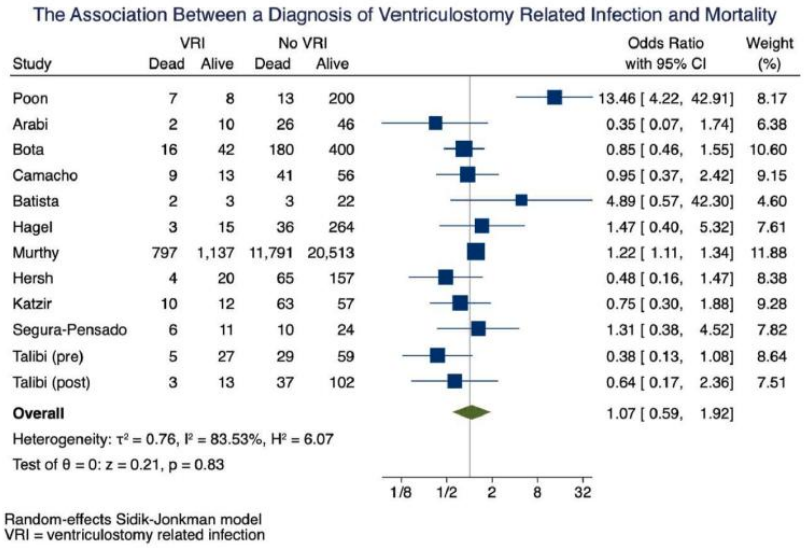

Fig. 3. Association between Ventriculostomy – Related Infection and mortality (Abbreviations: VRI - Ventriculostomy – Related Infection).

sample sizes which, in addition to study heterogeneity, could have masked an impact of VRI on outcomes. Furthermore, the study with the largest sample size used ICD-10 codes for the diagnosis of VRI [16], and using administrative data has been shown to introduce substantial variability in the diagnosis of sepsis [38,39]. Some of our outcomes of interest, such as functional neurological outcome or insertion of an internal ventricular shunt, were only reported in a small number of eligible studies.

This meta-analysis highlights a significant association between a diagnosis of VRI and healthcare resource use, indicating that prevention of VRI may reduce healthcare costs. Although VRI should not be dismissed as a serious complication, the absence of a clear association between VRI and patient-centred outcomes can inform clinicians in the management of patients and in discussions with patients and their families; for example, that although a patient may require a longer hospital admission, a diagnosis of VRI may not have an effect on a

Table 3
Results of pooled analysis for outcomes (Abbreviations: CI – Confidence Interval; EVD – External Ventricular Drain; ICU – Intensive Care Unit; LOS – Length of Stay; OR – Odds Ratio).

	Cohorts	Participants	Outcome	95 % CI	I2	p value
Mortality	12	36,266	OR 1.07	0.59 to 1.92	83.53 %	0.83
Mortality (fixed effects model)	12	36,266	OR 1.19	1.08 to 1.30	65.10 %	<0.01
Functional outcome	2	385	OR 1.42	0.36 to 5.56	0.26 %	0.37
Duration of EVD insertion (days)	12	2,643	Mean difference 5.24 days	3.05 to 7.43	78.15 %	<0.01
ICU LOS (days)	6	1,745	Mean difference 8.4 days	2.51 to 14.29	78.74 %	0.01
Hospital LOS (days)	13	36,679	Mean difference 16.87 days	12.19 to 21.56	81.42 %	<0.01
Receipt of internal ventricular shunt	3	34,821	OR 1.80	1.32 to 2.46	8.92 %	<0.01

patient's functional outcome. However, variation in definitions of VRI is a potential confounder for diagnosing, treating, and preventing VRI. Multidisciplinary consensus is required to devise a set of diagnostic criteria with sufficient sensitivity and specificity to distinguish VRI from aseptic inflammation. With a consistent set of diagnostic criteria, future research into outcomes associated with VRI can not only assess patient-centred outcomes, but also the impact of factors such as bacterial epidemiology or clinical interventions for VRI.

5. Conclusion

VRI is an infection associated with the presence of an EVD. In this meta-analysis, we have shown that a diagnosis of VRI was not associated with increased mortality or worse functional neurological outcome. VRI is associated with longer stays in ICU and hospital, increased length of EVD insertion, and increased incidence of internal ventricular shunt insertion. These conclusions should be interpreted with caution due to heterogeneity and risk of bias in the included studies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2023.02.005.

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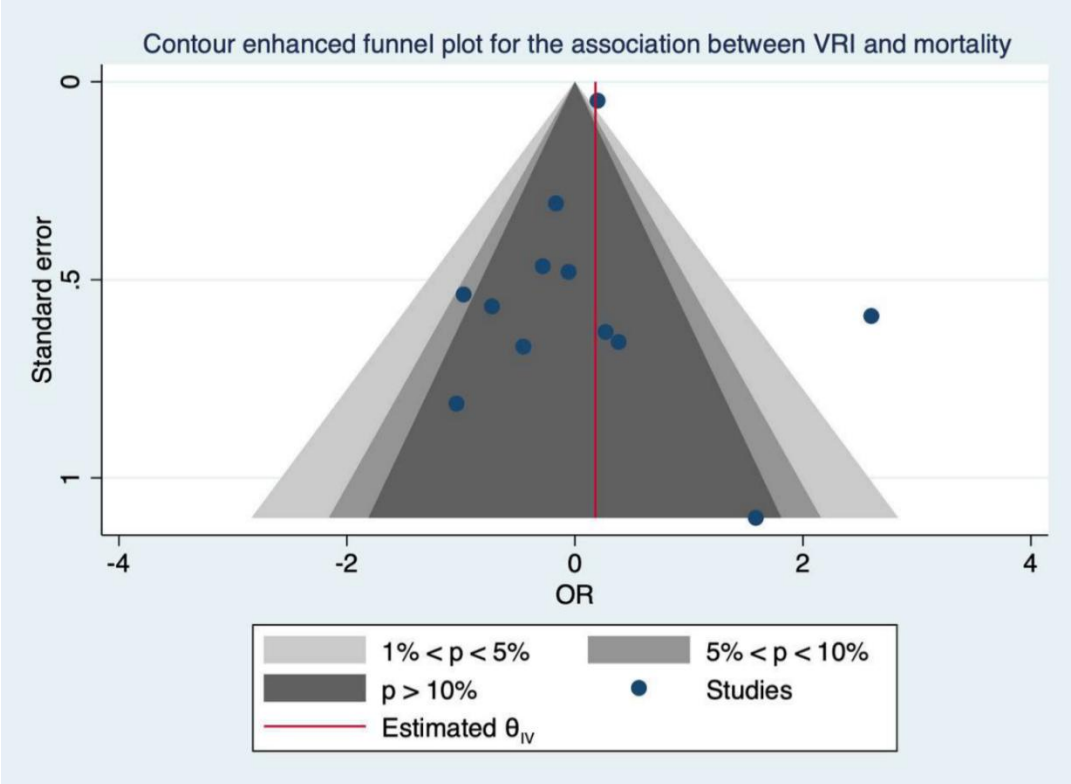

Figure 2-4 (published as Supplementary Figure 1) - Contour enhanced funnel plot for the association between Ventriculostomy – Related Infection and mortality

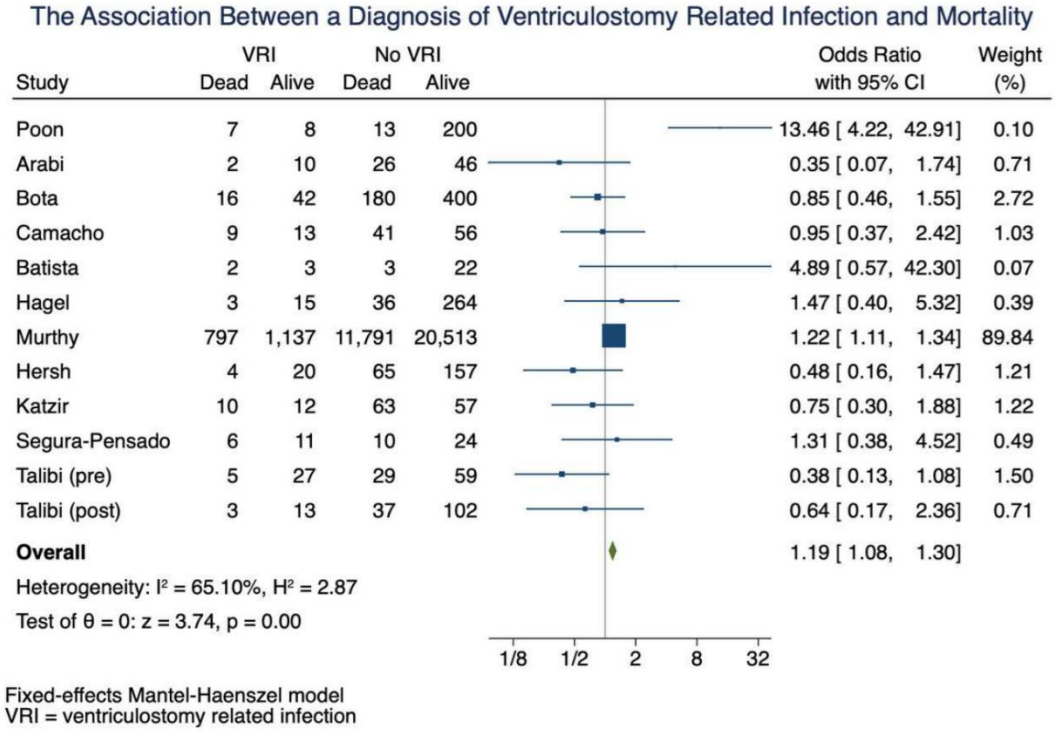

Figure 2-5 (published as Supplementary Figure 2) ‑ Association between Ventriculostomy ‑ Related Infection and mortality: a fixed effects model

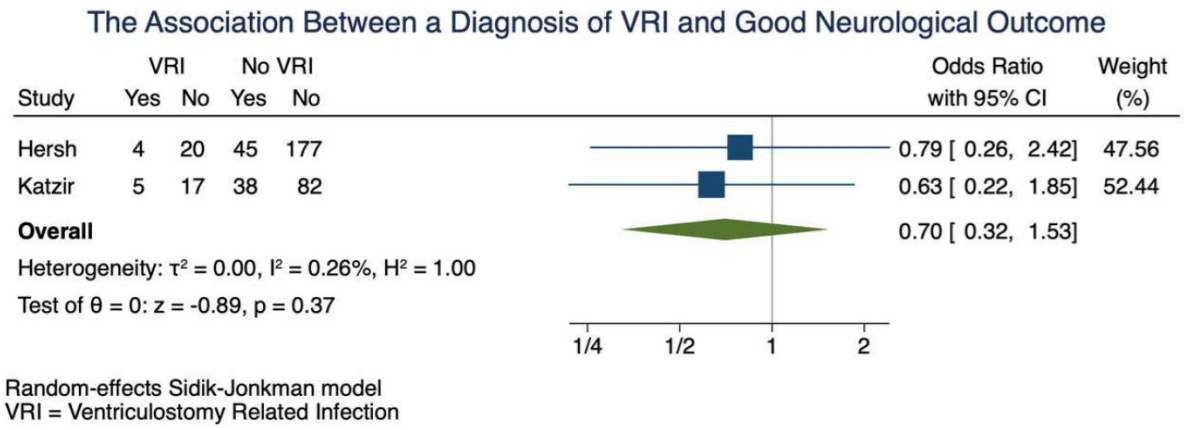

Figure 2-6 (published as Supplementary Figure 3) – Association between Ventriculostomy – Related Infection and good neurological outcome

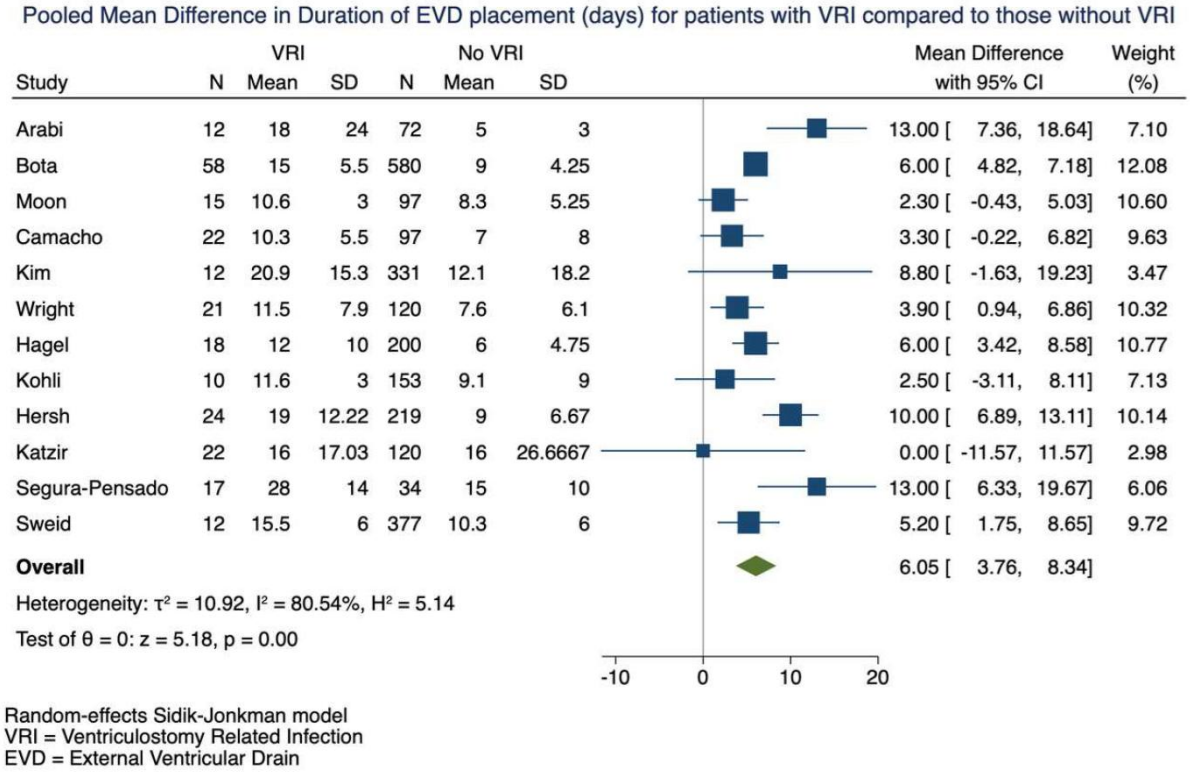

Figure 2-7 - Supplementary Figure 4 – Pooled mean difference in duration of External Ventricular Device placement for patients with a diagnosis of Ventriculostomy – Related Infection compared to patients without Ventriculostomy – Related Infection

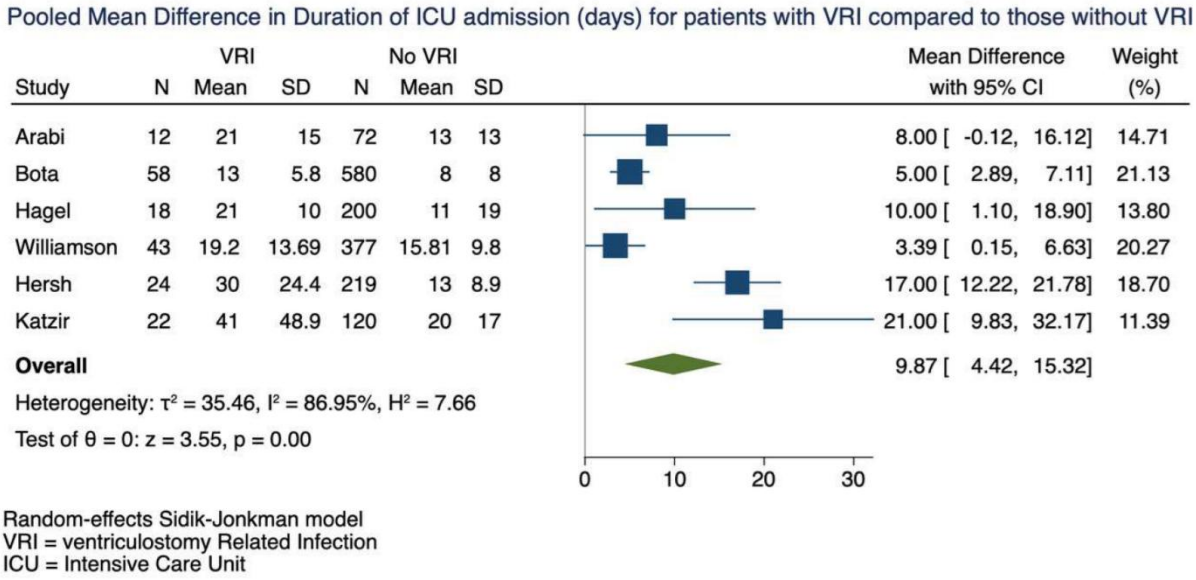

Figure 2-8 (published as Supplementary Figure 5) - Pooled mean difference in Intensive Care Unit length of stay (days) for patients with Ventriculostomy ‐ Related Infection compared to those without Ventriculostomy ‐ Related Infection

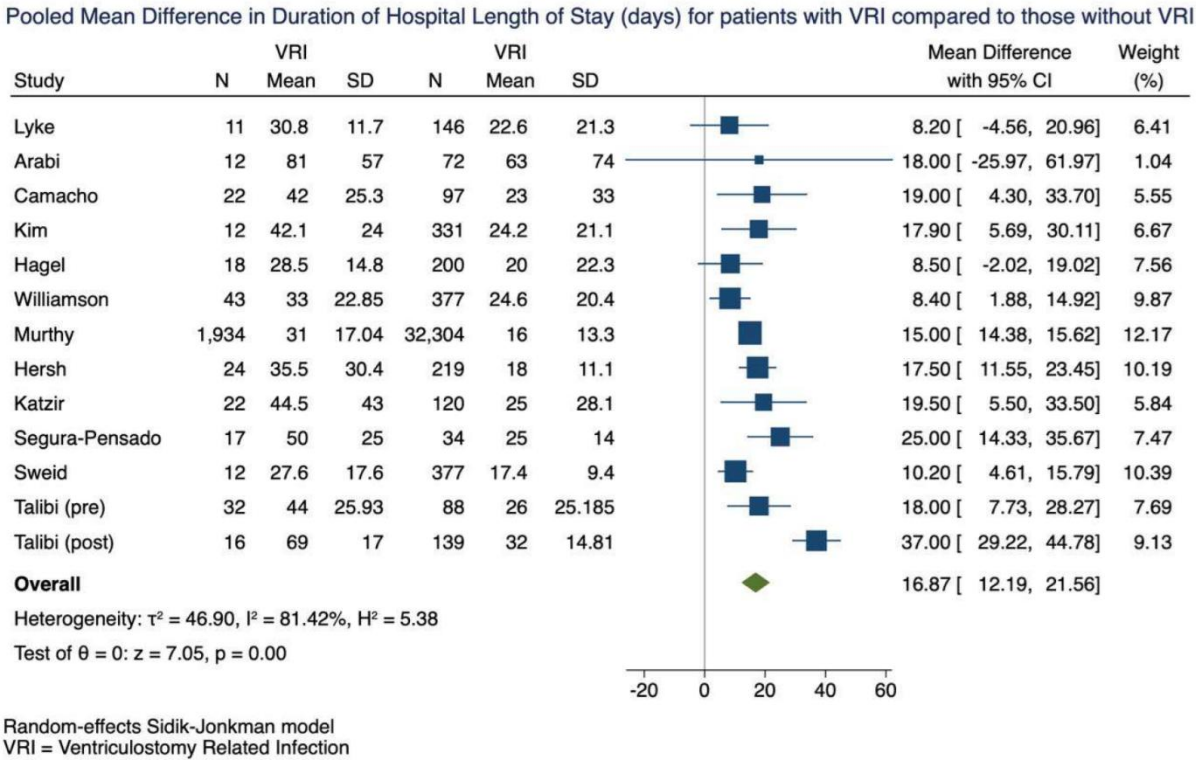

Figure 2-9 (published as Supplementary Figure 6) ‑ Pooled mean difference in hospital length of stay (days) for patients with Ventriculostomy ‑ Related Infection compared to those without Ventriculostomy ‑ Related Infection

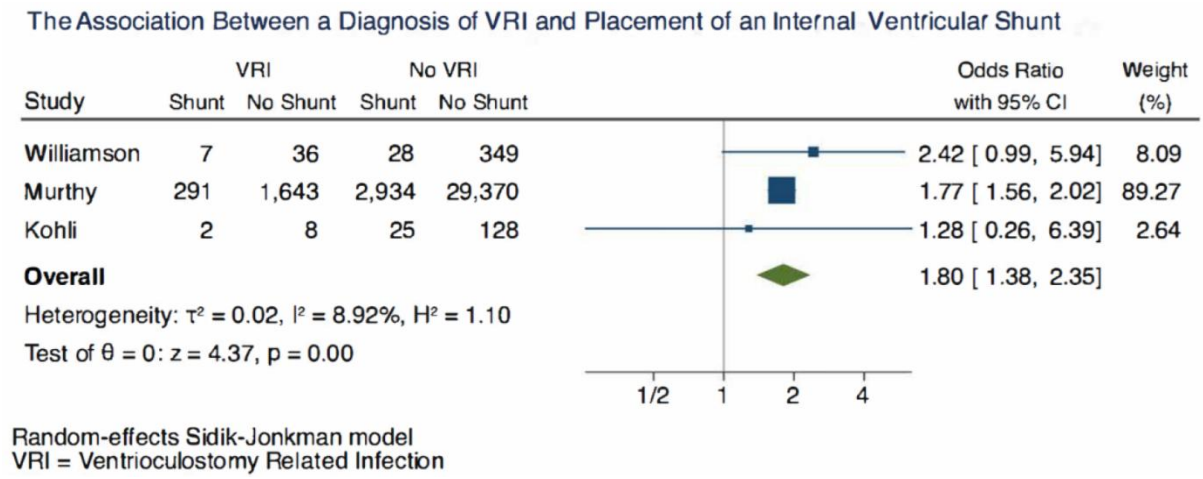

Figure 2-10 (published as Supplementary Figure 7) – Association between Ventriculostomy – Related Infection and Placement of an Internal ventricular shunt

Table 2-4 (published as Supplementary Table 1) – Descriptive summary of outcomes not appropriate for pooled analysis

Outcome	Author and year	Result reported	VRI	No VRI	Summary Statistic
Mortality	Williamson et al. 2014	Death or hospice	11.63% (5/43)	21.49%(81/377)	p=0.13
Functional outcome	Kohli et al. 2018	GOS 1 or 2	30% (3/10)	33.3% (51/153)	p=0.8282
	Lyke et al. 2001	More severe neurological impairment	N/A	N/A	RR 5.33 (95% CI 1.18 to 32.5)
	Williamson et al. 2014	Death or hospice	11.63% (5/43)	21.49%(81/377)	p=0.13
	Williamson et al. 2014	mRS, mean (SD)	4.20 (1.28)	4.43 (1.17)	p=0.08
	Williamson et al. 2014	GOS, mean (SD)	2.91 (1.04)	2.76 (1.03)	p=0.09
Duration of EVD insertion	Lyke et al. 2001	Average duration of EVD insertion (until removal or diagnosis of infection), mean (range)	8.45 days (2 to 23)	5.07 days (1 to 23)	p=0.007
	Talibi et al. 2020	Duration of EVD (until removal, infection, or death) pre-EVD care bundle, days (range)	9 (5 to 14)	7 (5 to 15)	p=0.673
	Talibi et al. 2020	Duration of EVD (until removal, infection, or death) post-EVD care bundle, days (range)	13 (9 to 16)	11 (6 to 16)	p=0.206
	Zakaria et al. 2013	Duration of drainage in retrospective cohort, mean days	22.1	9.7	OR 1.15 (95% CI 1.09 to 1.22, p<0.05)
	Zakaria et al. 2013	Duration of drainage in prospective cohort, mean days	22.6	10.2	OR 1.20 (95% CI 1.10 - 1.31, p<0.05)
Length of stay	Talibi et al. 2020	LOS pre-EVD care bundle cohort, excluding patients that died in hospital (days)	44 (33 to 68)	26 (20 to 54)	p=0.013
	Talibi et al. 2020	LOS post-EVD care bundle cohort, excluding patients that died in hospital (days)	11 (6–16)	13 (9 to 16)	p=0.206
Placement of a VP shunt	Kim et al. 2012	Insertion of a VP shunt	33% (4/12)	N/A	N/A
Number of EVDs	Arabi et al. 2005	Number of EVDs = 1	58% (7/12)	97% (70/72)	N/A
	Arabi et al. 2005	Number of EVDs ≥ 2	42% (5/12)	3% (2/72)	p<0.001
	Katzir et al. 2019	>1 EVD	63% (14/22)	24% (29/120)	Univariate analysis: OR 5.5 (95% CI 2.1 to 14.4, p=0.001) Multivariate analysis: OR 4.64 (95% CI 1.7 - 12.6,

					p=0.003)
	Katzir et al. 2019	EVDs replaced	3.3 ± 2.9	1.3 ± 0.56	<0.0001
Incidence of venous thromboembolism	Murthy et al. 2016	Venous thromboembolism	8.6% (166/1934)	4.6% (1484/32304)	p<0.001
Incidence of seizures	Murthy et al. 2016	Seizures	13.7% (265/1934)	10.8% (3482/32304)	p<0.001
Incidence of non-CNS infection	Bota et al. 2005	Presence of a co-infection	12% (7/58)	7% (42/580)	p=0.03
	Hagel et al. 2014	Presence of any concomitant infection	44% (8/18)	23% (45/200)	p<0.01
	Hagel et al. 2014	Lower respiratory tract infection	33% (6/18)	21% (42/200)	p=0.23
	Hagel et al. 2014	Surgical site infection	11% (2/18)	1% (1/200)	p=0.02
	Hagel et al. 2014	Urinary tract infection	6% (1/18)	0% (0/200)	p=0.08
	Hagel et al. 2014	Central line-associated bloodstream infection	11% (2/18)	1% (2/200)	p=0.05
	Hagel et al. 2014	Presence of any other concomitant infection	0% (0/18)	1% (1/200)	p=1.0
	Kim et al. 2012	Presence of a concomitant systemic infection	83.3% (10/12)	61% (202/331)	p=0.12
	Murthy et al. 2016	Pneumonia	29.2% (565/1934)	23.8% (7679/32304)	p<0.001
	Murthy et al. 2016	Urinary tract infection	23.7% (459/1934)	19% (6122/32304)	p<0.001
	Murthy et al. 2016	Sepsis	21.3% (412/1934)	9.7% (3137/32304)	p<0.001
	Zakaria et al. 2013	Presence of wound/chest/urine infection	44% (8/18)	35% (31/89)	OR 1.50 (95% CI 0.54 to 4.18, p=0.44)

Table 2-5 (published as Supplementary Table 2) – Risk of bias assessment using the Newcastle Ottawa Scale[171] for observational cohort studies included in this study

Author and Year	Selection	Comparability	Outcome
Arabi et al. 2005	☆☆☆☆	No stars	☆☆☆
Batista et al. 2015	☆☆☆☆	No stars	☆☆☆
Bota et al. 2005	☆☆☆☆	No stars	☆☆☆
Camacho et al. 2010	☆☆☆☆	No stars	☆☆☆
Hagel et al. 2014	☆☆☆☆	No stars	☆☆☆
Hersh et al 2019	☆☆☆	No stars	☆☆☆
Katzir et al. 2019	☆☆☆☆	No stars	☆☆☆
Kohli et al. 2018	☆☆☆☆	No stars	☆☆☆
Lyke et al. 2001	☆☆☆☆	No stars	☆☆☆
Moon et al. 2007	☆☆☆	No stars	☆☆☆
Murthy et al. 2016	☆☆☆	☆	☆☆☆
Segura Pensado et al. 2019	☆☆	No stars	☆☆☆
Sweid et al. 2020	☆☆☆☆	No stars	☆☆☆
Talibi et al. 2020	☆☆☆☆	No stars	☆☆☆
Williamson et al. 2014	☆☆☆☆	No stars	☆☆☆
Wright et al. 2013	☆☆☆	No stars	☆☆☆
Zakaria et al. 2013	☆☆☆☆	No stars	☆☆☆

Table legend – Quality of studies in the Newcastle Ottawa scale is based on the number of stars assigned. Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Table 2-6 (published as Supplementary Table 3) – Risk of bias assessment using the Cochrane risk-of-bias tool for randomized trials for randomized controlled trials in this study

Author and Year	**Domain 1: Risk of bias arising from the randomization process**	**Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**	**Domain 3: Risk of bias due to missing outcome data**	**Domain 4: Risk of bias in measurement of the outcome**	**Domain 5: Risk of bias in selection of the reported result**	**Overall risk of bias**
Poon et al. 1998	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns

Supplementary Document (Published as Supplementary Document 2): Search Strategy for "The Association between Ventriculostomy Related Infection and Clinical Outcomes: A Systematic Review and Meta-analysis"

For each database, two search strategies were used.
The first search strategy was:

- (Ventriculitis) OR ((Ventriculostomy OR "external ventricular drain*") AND infection)

AND

- incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]

The second search strategy was:

- (Ventriculitis) OR ((Ventriculostomy OR "external ventricular drain*") AND infection)

AND

- ((prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])

3. Ventriculostomy-Related Infections and Functional Neurological Outcomes: A Retrospective Observational Study

3.1 Introduction

The EVD is a commonly used neurosurgical device in the management of severe brain injury. Patients with EVDs are commonly diagnosed with VRI. However, the incidence of VRI is difficult to accurately measure due to variations in diagnostic criteria[4]. The lack of a consensus definition of VRI also impacts assessments of prevention, treatment, and prognosis. It is well established that community acquired CNS infections are associated with poor morbidity and mortality[10,159], so it makes sense that an infectious complication of a device used in this setting would contribute to the morbidity and mortality of patients with acute brain injury.

The results of the systematic review in chapter 2 challenge this assertion. Our pooled analysis suggested no association between a diagnosis of VRI and mortality and a paucity of data assessing long term functional neurological outcome. Only one of the nineteen studies included long term follow up and this was limited to 6 months[14]. Otherwise, follow up was either at hospital discharge, ICU discharge, 30 days after EVD removal, or not specified[170].

The most commonly used tool to assess functional outcome after brain injury is the Glasgow Outcome Scale (extended) (GOSE)[166]. The original Glasgow Outcome Scale was proposed in 1974, at a time when mortality from severe neurological injury was decreasing due to advances in critical care. The Glasgow Outcome Scale and the GOSE, first published in 1981[172] and shown in table 3-1, were research tools developed to describe the quality of life experienced by survivors of brain injury, with a focus on a patient's ability to function

independently[166]. The short and long-term outcomes associated with severe brain injury due to SAH, TBI and ICH are poor[161]. The long-term prognosis of patients with severe brain injury should be worse for patients who contract VRI, as data for community acquired bacterial meningitis suggests that functional deficits are present for at least several years after the primary infection[10]. Therefore, longer term follow – up of functional neurological status is warranted in patients diagnosed with VRI.

Another source of heterogeneity was the thirteen different definitions of VRI (with one study not defining VRI), a commonly cited issue in research regarding VRI[4,5,8]. A positive CSF culture is the most common definition of VRI[8] but on its own, a positive CSF culture cannot distinguish infection from contamination or colonisation[9]. Furthermore, CSF cell counts and biochemistry, or symptoms of CNS infection (fever, nuchal rigidity, headache, and altered level of consciousness), may not distinguish infection from aseptic meningeal inflammation due to the primary neurological diagnosis or may be difficult to detect in an intubated and sedated patient[52,113]. To address this, different studies propose a variety of combinations of clinical, laboratory and microbiological parameters to define VRI[4]. Whilst varying definitions of VRI affect measurements of the incidence of VRI[4,18], there are limited data directly comparing how these variations in diagnostic criteria affect measurements of clinical outcomes in patients with VRI.

Therefore, we sought to assess the association between a clinical diagnosis of VRI (as defined by commencement of treatment by the clinical team) and poor functional neurological outcomes as defined by a Glasgow Outcome Scale – Extended (GOSE) of 1 – 4 at 6 months. Secondary outcomes were GOSE at 12 and 24 months, mortality, hospital and ICU length of stay (LOS), duration of EVD insertion, and incidence of ventriculoperitoneal (VP) shunt insertion.

Table 3-1 - Overview of the Glasgow Outcome Scale and Glasgow Outcome Scale (extended). Reproduced from Wilson et al. 2021[173]

Glasgow Outcome Scale	**Glasgow Outcome Scale (extended)**	**Domain**	**Criteria**
Dead	1. Dead		
Vegetative State	2. Vegetative State	Consciousness	
Severe Disability (SD) Conscious but dependent	3. Lower SD	Function in Home	Unable to look after themselves for 8 h
	4. Upper SD	Function in Home Function Outside the Home	Unable to look after themselves for 24 h OR Unable to shop OR Unable to travel
Moderate Disability (MD) Independent but with limitations in one or more activities	5. Lower MD	Work/Study Social and Leisure Activities Family and Friendships	Unable to work/study OR Unable to participate OR Constant problems
	6. Upper MD	Work Social and Leisure Activities Family and Friendships	Reduced work capacity OR Participate much less OR Frequent problems
Good Recovery (GR) Return to normal life	7. Lower GR	Social and Leisure Activities Family and Friendships Symptoms	Participate a bit less OR Occasional problems OR Some symptoms affecting daily life
	8. Upper GR		No problems

Abbreviations: GR – Good recovery; MD – Moderate Disability; SD – Severe Disability

3.2 Methods

This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[174]. Ethics approval for this study was granted by the Northern Sydney Local Health District Human Research Ethics Committee (2021/ETH00975).

3.2.1 Study Design and Setting

This prospective cohort study was conducted at a 13-bed neurosurgical intensive care unit (ICU) at Royal North Shore Hospital (RNSH) in Sydney, Australia. Patients admitted to the unit who met inclusion criteria between January 2015 and January 2023 were included in a prospective database called the Neurological Outcomes from Intensive CarE (NOICE), which enrolled patients admitted to ICU with a primary diagnosis of SAH, TBI, or ICH. Patients enrolled in NOICE are followed during their ICU stay, then at 6, 12 and 24 months after discharge from ICU[175].

3.2.2 Participants

Patients admitted to ICU with a primary diagnosis of SAH, TBI, or ICH were enrolled prospectively in NOICE using an opt-out approach. The clinical progress of patients enrolled in NOICE was followed during their ICU admission and then by follow up phone calls at 6, 12 and 24 months to assess functional neurological outcomes. The complete inclusion and exclusion criteria for NOICE are included in table 3-2. For this study, participant data was

extracted from NOICE. Patients were included if they had an EVD inserted as treatment for their primary neurological diagnosis and had at least one CSF sample taken from their EVD. Patients with evidence of pre-existing central nervous system infection were excluded from this study.

Table 3-2 – Patient enrolment criteria for the NOICE database

Inclusion Criteria	• All patients admitted to Royal North Shore Hospital Intensive Care Unit (ICU) under the care of a Neurosurgeon, Neurologist or Interventional Neuroradiologist with a primary diagnosis of subarachnoid haemorrhage (SAH) including aneurysmal and non-aneurysmal cause, spontaneous intracranial haemorrhage (ICH) or traumatic brain injury (TBI) should be enrolled into the NOICE database.
Exclusion criteria	• Patients admitted to the ICU with a secondary diagnosis of TBI, SAH or ICH not under the care of a Neurosurgeon, Neurologist or Interventional Neuroradiologist; e.g. a multi-trauma patient with a minor TBI admitted under the orthopaedic surgeons. An exception to this would be patients admitted with a secondary diagnosis of TBI, SAH or ICH, which later becomes their primary reason for ICU admission; e.g. a multi-trauma patient found to have a diffuse axonal injury on MRI, 3 days post admission. • Patients admitted with haemorrhagic transformation of acute an ischaemic stroke. • Patients admitted with a spontaneous subdural haemorrhage. • Patients admitted with a chronic subdural haemorrhage with no precipitating head injury. • Patients admitted with an ICH as a complication of thrombolysis. • Patients admitted with an ICH as a post-operative complication; e.g. an ICH due to external ventricular drain insertion for obstructive hydrocephalus. • Patients admitted with an ICH as a complication of a known or newly diagnosed neoplasm; e.g. a patient who has an ICH into a metastasis. • Patients admitted to ICU for less than 24 hours or admitted due to a documented lack of available step down beds. Step-down patients who remain in ICU for greater than 24hrs, solely due to bed block, remain excluded. • Patients who are admitted to the ICU and transferred to a private hospital within 24 hours of admission • Patients who are transferred from another ICU after significant period of time receiving treatment in that ICU (e.g. 7 days or more).

Abbreviations: ICU – Intensive Care Unit; ICH – Intracerebral Haemorrhage; SAH – Subarachnoid Haemorrhage; TBI – Traumatic Brain Injury

3.2.3 Variables and Data Sources

Information about patient demographic, disease severity scoring (according to the World Federation of Neurosurgical Societies (WFNS) grading system for SAH[176], the Marshall score for TBI[177], and the ICH score for ICH[178]), clinical, and follow up data were extracted from NOICE. Data recorded in NOICE are collected prospectively. Information about CSF samples was collected retrospectively from the electronic medical record. At this centre, CSF samples were routinely collected twice a week, additional samples may be taken if considered clinically indicated by the treating ICU or neurosurgical teams. Information about VP shunt insertion and date of death were extracted from NOICE if these events occurred during ICU admission and otherwise from the electronic medical record.

Treatment of VRI was extracted from NOICE, which defines treated VRI as the initiation of antibiotics by the clinical team with a documented indication for VRI. Clinical diagnosis of VRI was chosen as the primary outcome because the lack of consensus regarding definitions of VRI[4] means clinicians are not using a standard set of criteria. We also used four pre-published definitions[54,55,99,179], listed in table 3-3. The Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN) definition contains subjective criteria (e.g. meningeal signs), which were excluded from the definition used for this study because they may not be reliably reported in patients who are intubated or sedated. The use of antibody titres was also excluded from the definition because they are not routinely performed at this centre. Normal ranges of CSF parameters were defined according to the Royal College of Pathologists of Australasia [180].

Patients were contacted by NOICE coordinators at 6, 12 and 24 months after ICU discharge. Functional neurological outcome was recorded using the GOSE[173]. Good functional neurological outcome was defined as a GOSE of 5 – 8 and poor functional neurological outcome was defined as a GOSE of 1 – 4. Our primary outcome was poor functional

neurological outcome at 6 months, with VRI defined as initiation of treatment by the clinical team. Secondary outcomes were functional neurological outcome at 12 and 24 months, mortality at ICU discharge, hospital discharge, and 6 months, VP shunt insertion, LOS in hospital and ICU, duration of EVD insertion, and number of EVDs.

Table 3-3 – Pre-published Definitions of Ventriculostomy-Related Infections (VRI)

Author, Year	Definition
Chi, 2010[55]	Ventriculostomy-associated infection is defined as a positive cerebrospinal fluid (CSF) culture obtained from the external ventricular drain (EVD) or via lumbar puncture, excluding positive cultures obtained prior to one day after EVD placement
Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN), 2023 [179]	Meningitis or ventriculitis must meet at least one of the following criteria: 1. Patient has organism(s) identified from CSF by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment for example, not Active Surveillance Culture/Testing 2. Patient has fever (>38.0°C) and at least one of the following: a. increased white cells, elevated protein and decreased glucose in CSF (per reporting laboratory's reference range) b. organism(s) seen on Gram stain of CSF c. organism(s) identified from blood by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing
Gozal, 2014[54]	Ventriculostomy-associated infection is defined as a positive CSF culture in a patient with a ventriculostomy within 72 hours of removal plus one or more of the following: a) fever (recorded temperature exceeding 101.5 degrees Fahrenheit (38.6 degrees Celsius), or b) CSF glucose level either < 50 mg/dL or < 50% of a serum glucose level drawn within 24 hours of the CSF glucose
Holloway, 1996 [99]	Ventriculostomy-related ventriculitis is diagnosed if a CSF culture from a ventriculostomy is positive, excluding cultures taken immediately after ventriculostomy placement. In the absence of a positive culture, a diagnosis can be made if there are greater than 50 white blood cells in the CSF, greater than 50% of which are neutrophils, or CSF glucose less than 15 mg/100 ml

Abbreviations; CDC/NHSN - Centre for Disease Control/ National Healthcare Safety Network, CSF - Cerebrospinal Fluid, EVD – External Ventricular Drain, VRI – Ventriculostomy – Related Infection.

3.2.4 Statistical Methods

The study population was described using frequencies and percentages for categorical variables and means with standard deviations for continuous variables. We calculated the cumulative incidence of VRI along with their 95% confidence intervals (CIs) for all five definitions of VRI. We also calculated the cumulative incidence of poor functional neurological outcomes among patients with and without VRI. The relative risk (RR) was calculated to assess the association between VRI and poor functional neurological outcomes. A Poisson regression model with a log link function was employed to estimate the RR and its 95% CI. These RRs were adjusted for age and sex using a multivariable Poisson model. The same method was applied to mortality at ICU and hospital discharge, as well as at the 6-month follow-up. For mortality, we used the term "mortality ratio (MR)" instead of RR.

For other continuous outcomes, such as length of stay (LOS) in ICU or hospital, number of EVD insertions, and duration of EVD, we calculated the mean and standard deviation for patients with and without VRI. The mean difference was used to measure the association for all continuous outcomes. Univariate and multivariable linear regression models were utilised to estimate unadjusted and adjusted (for age and sex) mean differences and their 95% CIs. Statistical significance was set at $p<0.05$. All statistical analyses were performed using R version 4.4.1.

As we considered the possibility of immortal time bias as a potential source of bias, we conducted an exploratory time-to-event analysis for the mortality outcome. Due to the lack of date of death information for all cases, we were unable to perform a time-to-event analysis in the main analysis. In this sensitivity analysis, we constructed Kaplan-Meier survival curves to compare the survival probabilities between patients with and without VRI.

1.9 Results

3.2.5 Participants

Data of 558 patients with EVDs inserted as part of their routine clinical care were included in the study. Of these patients, 3 had SAH due to mycotic aneurysm and 68 patients had no CSF samples taken during their admission. These patients were excluded, leaving 487 patients for analysis. Demographics and admissions data for these patients are shown in table 3-4.

Table 3-4 – Characteristics of the study population

Characteristic	**N = 487**
Age (years) (median, range)	59 (16 – 88)
Female sex (no., %)	251 / 487 (51.8%)
Primary neurological diagnosis	
Subarachnoid Haemorrhage (n, %)	251 (51.5%)
WFNS score	
1	107 / 251 (42.6%)
2	59 / 251 (23.5%)
3	12 / 251 (4.8%)
4	33 / 251 (13.1%)
5	38 / 251 (15.1%)
Not recorded	2 / 251 (0.8%)
Traumatic Brain Injury	128 (26.3%)
Marshall score	
1	2 / 128 (1.6%)
2	58 / 128 (45.3%)
3	19 / 128 (14.8%)
4	6 / 128 (4.7%)
6	43 / 128 (33.6%)
Intracerebral Haemorrhage	102 (20.9%)
ICH score	
0	2 / 102 (2.0%)
1	22 / 102 (21.6%)
2	35 / 102 (34.3%)
3	29 / 102 (28.4%)
4	10 / 102 (9.8%)
5	1 / 102 (1.0%)
Not Recorded	3 / 102 (2.9%)

Abbreviations; ICH – Intracerebral Haemorrhage, WFNS – World Federation of Neurosurgical Societies

3.2.6 The Incidence of VRI

As defined as treatment by the clinical team, VRI occurred in 17% (83 of 487) of patients. The incidence of VRI as defined by treatment by the clinical team and as defined by four pre-published diagnostic criteria (shown in table 3-2) is shown in table 3-5. VRI as defined by pre-published criteria occurred in between 1.8% (9 of 487) and 48.0% (234 of 487) of patients. The median time to diagnosis of VRI as defined by treatment by the clinical team was 7 days after insertion of EVD (IQR 5, 9).

Table 3-5 – Incidence of Ventriculostomy – Related Infection (VRI)

Diagnostic criteria	**No of patient with VRI**	**Incidence (%, 95% CI)**
Treated for VRI	83/487	17.0 (13.9, 20.7)
Chi et al. 2010[55]	11/487	2.3 (1.2, 4.1)
CDC/NHSN 2023[179]	234/487	48.0 (43.5, 52.6)
Gozal et al. 2014[54]	9/487	1.8 (0.9, 3.6)
Holloway et al. 1996[99]	196/487	40.2 (35.9, 44.8)

Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, VRI – Ventriculostomy – Related Infection

3.2.7 VRI and functional neurological outcome

When using the clinical diagnosis of VRI, the adjusted estimated risk ratio for unfavourable neurological outcome at 6 months associated with a diagnosis of VRI was 0.78 (95% CI 0.55 to 1.08). As shown in table 3-6, this result was consistent when using alternative diagnostic criteria for VRI.

A diagnosis of VRI as defined by pre-published diagnostic criteria or by treatment of VRI by the clinical team had no association with poor functional neurological outcome at 6 months, as defined as a GOSE of 1 – 4. These results are shown in table 3-6. A diagnosis of VRI was not associated with poor functional neurological outcome at 12 months or 24 months, shown in table 3-7.

3.2.8 VRI and mortality

The association between a diagnosis of VRI and mortality is shown in table 3-8. At ICU discharge, hospital discharge, and 6, 12, and 24 months, the association of VRI with mortality varied based on the definition employed. Using the definitions published by Chi[55] or Gozal[54] (which required positive cultures), there was no association between VRI and mortality at any of these time points. Patients diagnosed with VRI according to the criteria published by the CDC[179] and Holloway et al.[99], had lower mortality rates at ICU discharge, hospital discharge, and 6-month follow-up.

Sensitivity analysis was performed with Kaplan-Meier curves for 6-month mortality of all participants and exclusion of patients who died within 5 days of EVD insertion. Visual inspection of Kaplan-Meier curves of 6-month mortality of participants who were treated for VRI by the clinical team (figure 3-1) and who met the CDC and Holloway definitions of VRI (figures 3-2 and 3-3), showed an early rise in mortality in patients who did not meet these definitions. When participants who died in the first 5 days after EVD insertion were excluded (as shown in table 3-9), a diagnosis of VRI according to the CDC[179] or Holloway et al.[99] criteria was not associated with higher mortality.

Table 3-6 - Association between ventriculostomy - related infection (VRI) and poor functional neurological outcome at six months

Diagnosis methods	Poor GOSE score (1-4) among patients without VRI n/N (%)	Poor GOSE score (1-4) among patients with VRI n/N (%)	Unadj. RR (95% CI)	Adj. RR (95% CI)*	p-value
Treated for VRI	247/390 (63.3)	39/81 (48.1)	0.76 (0.53, 1.05)	0.78 (0.55, 1.08)	0.14
Chi 2010[55]	280/461 (60.7)	6/10 (60.0)	0.99 (0.39, 2.02)	1.05 (0.41, 2.15)	0.91
CDC/NHSN 2023[179]	150/244 (61.5)	136/227 (59.9)	0.97 (0.77, 1.23)	1.01 (0.80, 1.27)	0.96
Gozal et al. 2014[54]	280/463 (60.5)	6/8 (75.0)	1.24 (0.49, 2.54)	1.22 (0.48, 2.50)	0.64
Holloway et al. 1996[99]	182/281 (64.8)	104/190 (54.7)	0.85 (0.66, 1.07)	0.84 (0.65, 1.06)	0.15

*(*Adjusted for age and sex) Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, GOSE – Glasgow Outcome Scale (Extended), VRI – Ventriculostomy – Related Infection.*

Table 3-7 - Association between ventriculostomy – related infection (VRI) and poor neurological outcome at 12 and 24 months

Outcome	Diagnosis methods	Poor GOSE score (1-4) among patients without VRI n/N (%)	Poor GOSE score (1-4) among patients with VRI n/N (%)	Unadj. RR (95% CI)	Adj. RR (95% CI)*	p-value
Poor functional neurological outcome at 12 months	Treated for VRI	234/384 (60.9)	40/80 (50.0)	0.82 (0.58, 1.13)	0.84 (0.59, 1.16)	0.32
	Chi 2010[55]	266/453 (58.7)	8/11 (72.7)	1.24 (0.56, 2.34)	1.36 (0.61, 2.56)	0.40
	CDC/NHSN 2023[179]	148/242 (61.2)	126/222 (56.8)	0.93 (0.73, 1.18)	0.96 (0.75, 1.21)	0.72
	Gozal et al. 2014[54]	267/455 (58.7)	7/9 (77.8)	1.33 (0.57, 2.59)	1.36 (0.58, 2.66)	0.43
	Holloway et al. 1996[99]	175/277 (63.2)	99/187 (52.9)	0.84 (0.65, 1.07)	0.83 (0.64, 1.06)	0.14
Poor functional neurological outcome at 24 months	Treated for VRI	217/357 (60.8)	32/74 (43.2)	0.71 (0.48, 1.01)	0.73 (0.49, 1.04)	0.10
	Chi 2010[55]	242/420 (57.6)	7/11 (63.6)	1.10 (0.47, 2.16)	1.22 (0.52, 2.39)	0.68
	CDC/NHSN 2023[179]	138/227 (60.8)	111/204 (54.4)	0.90 (0.70, 1.15)	0.93 (0.72, 1.19)	0.55
	Gozal et al. 2014[54]	243/422 (57.6)	6/9 (66.7)	1.16 (0.46, 2.38)	1.19 (0.47, 2.45)	0.67
	Holloway et al. 1996[99]	160/257 (62.3)	89/174 (51.1)	0.82 (0.63, 1.06)	0.81 (0.63, 1.05)	0.12

*(*adjusted for age and sex) Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, GOSE – Glasgow Outcome Scale (Extended), VRI – Ventriculostomy – Related Infection.*

3.2.9 VRI and length of stay in ICU and hospital

As defined by initiation of treatment by the clinical team, VRI was associated with an increased ICU LOS (adjusted mean difference 6.3 days, 95% CI 4.0 – 8.5 days) and hospital LOS (adjusted mean difference 12.0 days, 95% CI 5.9 – 18.0 days). This result was supported by the ICU LOS and hospital LOS when VRI was defined by any of the published diagnostic criteria. These results are shown in table 3-10.

The lowest mean difference of both ICU and hospital LOS was shown when VRI was defined by the diagnostic criteria of Holloway et al.[99] (adjusted mean difference of ICU LOS 4.9 days, $p < 0.01$, 95% CI 5.9 – 18.0 days; adjusted mean difference of hospital LOS 6.0 days, $p = 0.01$, 95% CI 1.4 – 10.7 days). The highest mean difference of both ICU and hospital LOS was shown when VRI was defined by the diagnostic criteria of Gozal et al.[54] (adjusted mean difference of ICU LOS 14.5 days, $p < 0.01$, 95% CI 8.1 – 21.0; adjusted mean difference of hospital LOS 26.3 days, $p = 0.01$, 95% CI 9.4 – 43.2).

3.2.10 VRI and CSF drainage device usage

The association between a diagnosis of VRI and outcomes related to EVDs and ventriculoperitoneal shunts are shown in Table 3-11.

A diagnosis of VRI as defined by treatment of the clinical team was associated with an increased duration of EVD insertion (adjusted mean difference 6.3 days, $p <0.01$, 95% CI 4.3 – 8.3 days). This result was supported by increased duration of EVD insertion when VRI was defined by published criteria. The mean difference of duration of EVD insertion and diagnosis of VRI was similar to the primary definition of this study when VRI was defined

according to the CDC[179] or Holloway et al.[99] diagnostic criteria (which emphasise non-microbiological criteria to diagnose VRI). When VRI was defined according to positive CSF culture results (as per Chi et al.[55] or Gozal et al.[54]), VRI was associated with a longer duration of EVD insertion (for Gozal et al., adjusted mean difference 17.7 days, p <0.01, 95% CI 12.2 – 23.2 days).

A clinical diagnosis of VRI was associated with increased incidence of VP shunt insertion (adjusted RR 2.5, p < 0.01, 95% CI 1.6 – 3.8). The definitions which used non-microbiological criteria (published by the CDC[179] and Holloway et al.[99]) supported this result. Diagnostic criteria reliant upon a positive CSF culture (as published by Chi et al.[55] and Gozal et al.[54]) did not show an association between a diagnosis of VRI and insertion of a VP shunt (for Gozal et al., adjusted RR 2.5, p = 0.08, 95% CI 0.8 – 6.0).

There was a statistically significant (but not clinically significant) association between VRI and increased number of EVDs inserted during the period of enrolment (adjusted mean difference 0.4, p < 0.01, 95% CI 0.2 – 0.5). These findings were supported by the number of EVDs inserted when VRI was defined by published diagnostic criteria.

Table 3-8 – Association between ventriculostomy-related infection (VRI) and intensive care unit (ICU) mortality, hospital mortality, and 6-month mortality

Outcome	Diagnosis methods	Mortality among patients without VRI n/N (%)	Mortality among patients with VRI n/N (%)	Unadj. MR (95% CI)	Adj. MR (95% CI)*	p-value
Death in ICU	Treated for VRI	87/404 (21.5)	1/83 (1.2)	0.06 (0.00, 0.25)	0.06 (0.00, 0.26)	0.01
	Chi et al. 2010[55]	87/476 (18.3)	1/11 (9.1)	0.50 (0.03, 2.23)	0.53 (0.03, 2.40)	0.53
	CDC/NHSN 2023[179]	59/253 (23.3)	29/234 (12.4)	0.53 (0.34, 0.82)	0.55 (0.35, 0.86)	0.01
	Gozal et al. 2014[54]	88/478 (18.4)	0/9 (0.0)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.98
	Holloway et al. 1996[99]	66/291 (22.7)	22/196 (11.2)	0.49 (0.30, 0.79)	0.49 (0.29, 0.78)	<0.01
Death in hospital	Treated for VRI	110/404 (27.2)	4/83 (4.8)	0.18 (0.05, 0.42)	0.18 (0.06, 0.44)	<0.01
	Chi et al. 2010[55]	113/476 (23.7)	1/11 (9.1)	0.38 (0.02, 1.71)	0.43 (0.02, 1.94)	0.41
	CDC/NHSN 2023[179]	75/253 (29.6)	39/234 (16.7)	0.56 (0.38, 0.82)	0.58 (0.39, 0.85)	0.01
	Gozal et al. 2014[54]	113/478 (23.6)	1/9 (11.1)	0.47 (0.03, 2.10)	0.49 (0.03, 2.19)	0.48
	Holloway et al. 1996[99]	81/291 (27.8)	33/196 (16.8)	0.60 (0.40, 0.90)	0.61 (0.40, 0.91)	0.02
Six-month mortality	Treated for VRI	125/390 (32.1)	6/81 (7.4)	0.23 (0.09, 0.48)	0.24 (0.09, 0.50)	<0.01
	Chi et al. 2010[55]	130/461 (28.2)	1/10 (10.0)	0.35 (0.02, 1.58)	0.39 (0.02, 1.76)	0.35
	CDC/NHSN 2023[179]	82/244 (33.6)	49/227 (21.6)	0.64 (0.45, 0.91)	0.67 (0.47, 0.95)	0.03
	Gozal et al. 2014[54]	130/463 (28.1)	1/8 (12.5)	0.45 (0.03, 1.98)	0.44 (0.03, 1.96)	0.41
	Holloway et al. 1996[99]	91/281 (32.4)	40/190 (21.1)	0.65 (0.44, 0.94)	0.66 (0.45, 0.95)	0.03

**Adjusted for age and sex. Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, ICU – Intensive Care Unit, MR - Mortality Ratio, VRI – Ventriculostomy – Related Infection.*

Table 3-9 – Association between ventriculostomy-related infection (VRI) and intensive care unit (ICU) mortality, hospital mortality, and 6-month mortality, excluding patients who died within 5 days of EVD insertion.

Outcome	Diagnosis methods	Mortality among patients without VRI n/N (%)	Mortality among patients with VRI n/N (%)	Unadj. MR (95% CI)	Adj. MR (95% CI)*	p-value
Death in ICU	Treated for VRI	49/365 (13.4)	1/83 (1.2)	0.09 (0.01, 0.41)	0.09 (0.01, 0.41)	0.02
	Chi et al. 2010[55]	49/437 (11.2)	1/11 (9.1)	0.81 (0.05, 3.69)	0.85 (0.05, 3.91)	0.88
	CDC/NHSN 2023[179]	26/219 (11.9)	24/229 (10.5)	0.88 (0.50, 1.54)	0.91 (0.52, 1.59)	0.73
	Gozal et al. 2014[54]	50/439 (11.4)	0/9 (0.0)	-	-	-
	Holloway et al. 1996[99]	31/255 (12.2)	19/193 (9.8)	0.81 (0.45, 1.42)	0.78 (0.43, 1.38)	0.40
Death in hospital	Treated for VRI	71/365 (19.5)	4/83 (4.8)	0.25 (0.08, 0.60)	0.25 (0.08, 0.61)	0.01
	Chi et al. 2010[55]	74/437 (16.9)	1/11 (9.1)	0.54 (0.03, 2.42)	0.61 (0.03, 2.77)	0.63
	CDC/NHSN 2023[179]	41/219 (18.7)	34/229 (14.8)	0.79 (0.50, 1.25)	0.80 (0.51, 1.27)	0.35
	Gozal et al. 2014[54]	74/439 (16.9)	1/9 (11.1)	0.66 (0.04, 2.97)	0.69 (0.04, 3.10)	0.71
	Holloway et al. 1996[99]	45/255 (17.6)	30/193 (15.5)	0.88 (0.55, 1.39)	0.89 (0.55, 1.41)	0.62
Six-month mortality	Treated for VRI	86/351 (24.5)	6/81 (7.4)	0.30 (0.12, 0.63)	0.31 (0.12, 0.65)	0.01
	Chi et al. 2010[55]	91/422 (21.6)	1/10 (10.0)	0.46 (0.03, 2.08)	0.52 (0.03, 2.32)	0.51
	CDC/NHSN 2023[179]	48/210 (22.9)	44/222 (19.8)	0.87 (0.57, 1.31)	0.89 (0.59, 1.34)	0.58
	Gozal et al. 2014[54]	91/424 (21.5)	1/8 (12.5)	0.58 (0.03, 2.61)	0.57 (0.03, 2.54)	0.57
	Holloway et al. 1996[99]	55/245 (22.4)	37/187 (19.8)	0.88 (0.58, 1.33)	0.89 (0.58, 1.34)	0.58

**Adjusted for age and sex. Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, ICU – Intensive Care Unit, MR - Mortality Ratio, VRI – Ventriculostomy – Related Infection.*

Table 3-10 – Association between diagnosis of Ventriculostomy – Related Infection (VRI) and length of stay (LOS) in Intensive Care (ICU) and hospital

Outcome	Diagnosis methods	Mean (SD) among patients without VRI	Mean (SD) among patients with VRI	Unadj. beta (95% CI)	Adj. beta (95% CI)*	p-value
ICU LOS (days)	Treated for VRI	16.1 (9.5)	22.5 (10.7)	6.4 (4.1, 8.7)	6.3 (4.0, 8.5)	<0.01
	Chi et al. 2010[55]	16.9 (9.9)	28.1 (11.8)	11.2 (5.2, 17.1)	10.6 (4.7, 16.4)	<0.01
	CDC/NHSN 2023[179]	13.6 (9.5)	21.0 (9.2)	7.3 (5.6, 9.0)	7.2 (5.5, 8.8)	<0.01
	Gozal et al. 2014[54]	16.9 (9.7)	31.5 (15.5)	14.6 (8.1, 21.1)	14.5 (8.1, 21.0)	<0.01
	Holloway et al. 1996[99]	15.2 (10.3)	20.0 (8.9)	4.8 (3.1, 6.6)	4.9 (3.1, 6.7)	<0.01
Hospital LOS (days)	Treated for VRI	30.3 (23.1)	42.4 (34.9)	12.0 (6.0, 18.1)	12.0 (5.9, 18.0)	<0.01
	Chi et al. 2010[55]	32.0 (25.8)	47.9 (22.0)	15.9 (0.4, 31.3)	15.5 (0.1, 30.8)	0.05
	CDC/NHSN 2023[179]	26.5 (20.5)	38.8 (29.3)	12.3 (7.9, 16.8)	11.9 (7.4, 16.4)	<0.01
	Gozal et al. 2014[54]	32.0 (25.5)	57.7 (30.8)	25.8 (8.8, 42.7)	26.3 (9.4, 43.2)	0.01
	Holloway et al. 1996[99]	30.2 (23.4)	35.7 (28.8)	5.5 (0.9, 10.2)	6.0 (1.4, 10.7)	0.01

**Adjusted for age and sex. Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, ICU – Intensive Care Unit, LOS – Length of Stay, VRI – Ventriculostomy – Related Infection.*

Table 3-11 - Association between VRI and duration of EVD insertion, number of EVDs inserted, and incidence of ventriculoperitoneal (VP) shunt insertion.

Outcome	Diagnosis methods	Mean (SD) or incidence (%) among patients without VRI	Mean (SD) or incidence (%) among patients with VRI	Unadj. beta or RR (95% CI)	Adj. beta or RR (95% CI)*	p-value
Number of EVDs	Treated for VRI	1.2 (0.6)	1.6 (1.0)	0.4 (0.2, 0.5)	0.4 (0.2, 0.5)	<0.01
	Chi et al. 2010[55]	1.3 (0.6)	2.0 (1.4)	0.8 (0.4, 1.1)	0.7 (0.3, 1.1)	<0.01
	CDC/NHSN 2023[179]	1.2 (0.5)	1.4 (0.8)	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	<0.01
	Gozal et al. 2014[54]	1.2 (0.6)	2.7 (1.5)	1.4 (1.0, 1.9)	1.4 (1.0, 1.8)	<0.01
	Holloway et al. 1996[99]	1.1 (0.4)	1.5 (0.9)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	<0.01
Duration of EVD insertion (days)	Treated for VRI	12.7 (8.1)	19.1 (9.4)	6.4 (4.4, 8.4)	6.3 (4.3, 8.3)	<0.01
	Chi et al. 2010[55]	13.6 (8.4)	25.4 (12.5)	11.8 (6.7, 16.9)	11.3 (6.3, 16.4)	<0.01
	CDC/NHSN 2023[179]	10.8 (8.0)	17.1 (8.3)	6.2 (4.8, 7.7)	6.3 (4.9, 7.7)	<0.01
	Gozal et al. 2014[54]	13.5 (8.2)	31.6 (15.3)	18.1 (12.6, 23.6)	17.7 (12.2, 23.2)	<0.01
	Holloway et al. 1996[99]	11.7 (8.6)	17.0 (7.9)	5.3 (3.8, 6.8)	5.2 (3.6, 6.7)	<0.01
VP shunt inserted	Treated for VRI	58/404 (14.4)	29/83 (34.9)	2.43 (1.54, 3.77)	2.46 (1.55, 3.81)	<0.01
	Chi et al. 2010[55]	83/476 (17.4)	4/11 (36.4)	2.09 (0.64, 5.00)	2.16 (0.66, 5.21)	0.13
	CDC/NHSN 2023[179]	36/253 (14.2)	51/234 (21.8)	1.53 (1.00, 2.36)	1.59 (1.04, 2.45)	0.04
	Gozal et al. 2014[54]	83/478 (17.4)	4/9 (44.4)	2.56 (0.78, 6.14)	2.48 (0.76, 5.96)	0.08
	Holloway et al. 1996[99]	39/291 (13.4)	48/196 (24.5)	1.83 (1.20, 2.80)	1.77 (1.16, 2.72)	0.01

**Adjusted for age and sex. Abbreviations; CDC/NHSN – Centre for Disease Control/National Healthcare Safety Network, EVD – External Ventricular Drain, ICU – Intensive Care Unit, LOS – Length of Stay, VP shunt – Ventriculoperitoneal shunt, VRI – Ventriculostomy – Related Infection.*

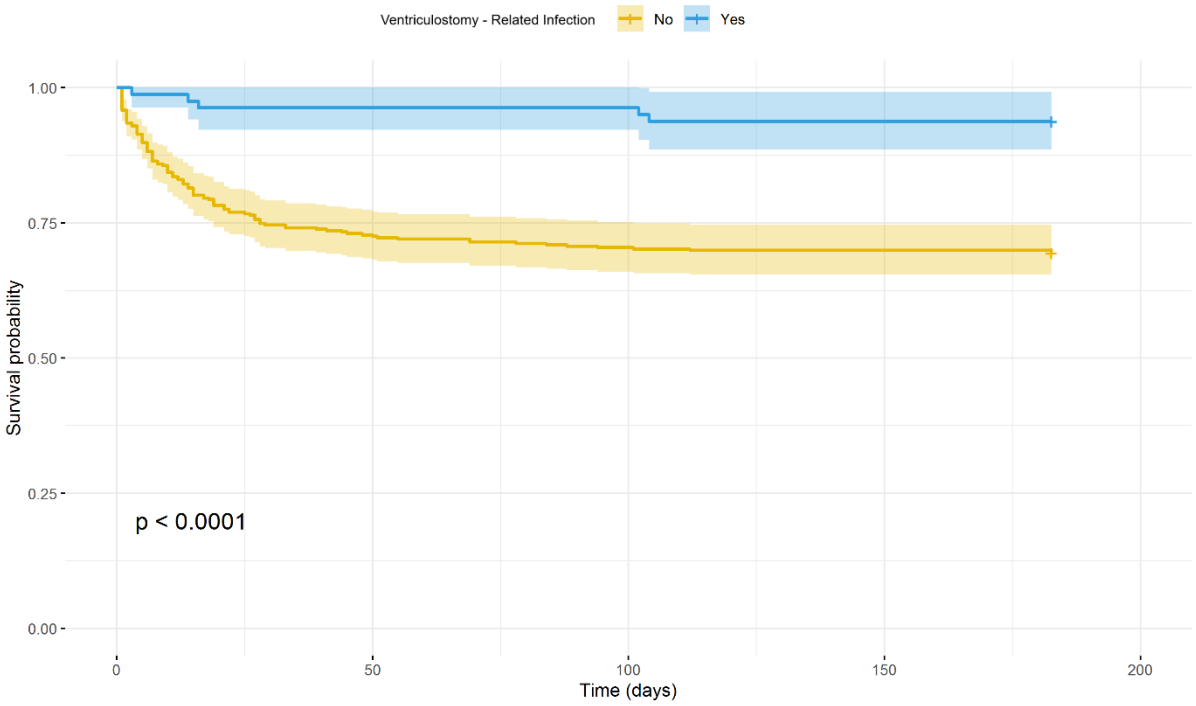

Figure 3-1 - Kaplan-Meier curve representing 6-month mortality in patients treated for ventriculostomy – related infection (VRI) compared to patients who were not treated for VRI. The median time to diagnosis was 7 days (IQR 5 – 9 days).

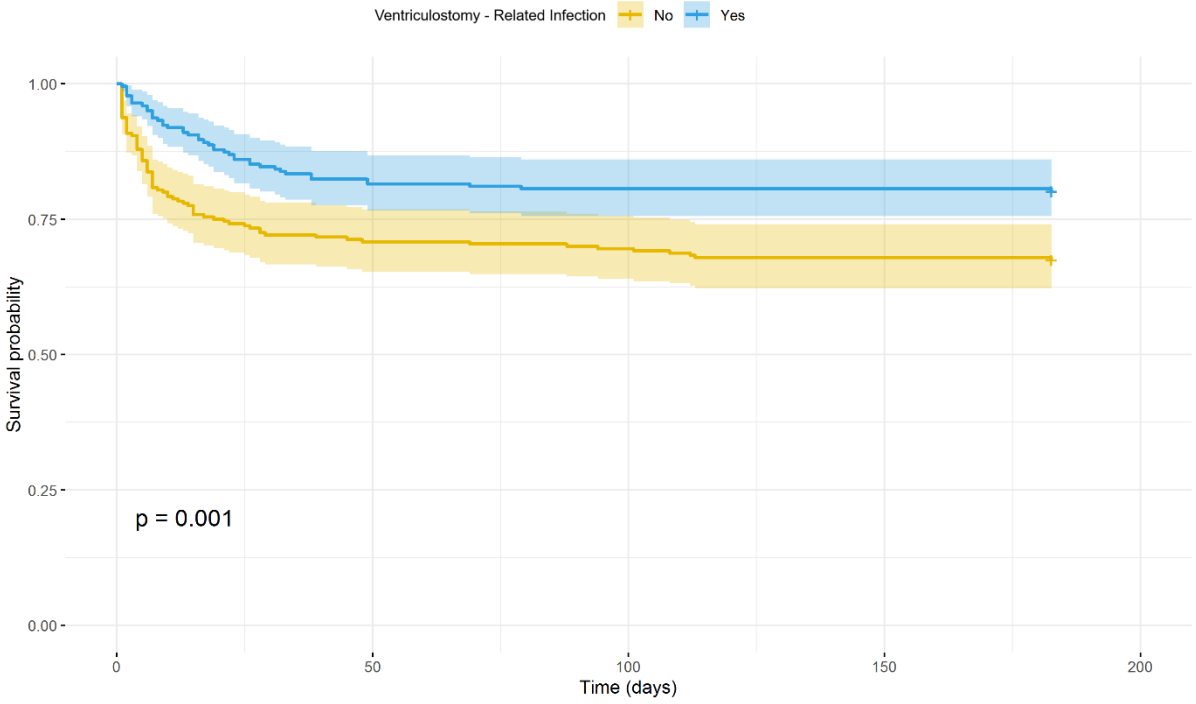

Figure 3-2 - Kaplan-Meier curve representing 6-month mortality in patients diagnosed with ventriculostomy – related infection as defined by the Centre for Disease Control/National Healthcare Safety Network[179] compared to patients who did not meet this definition

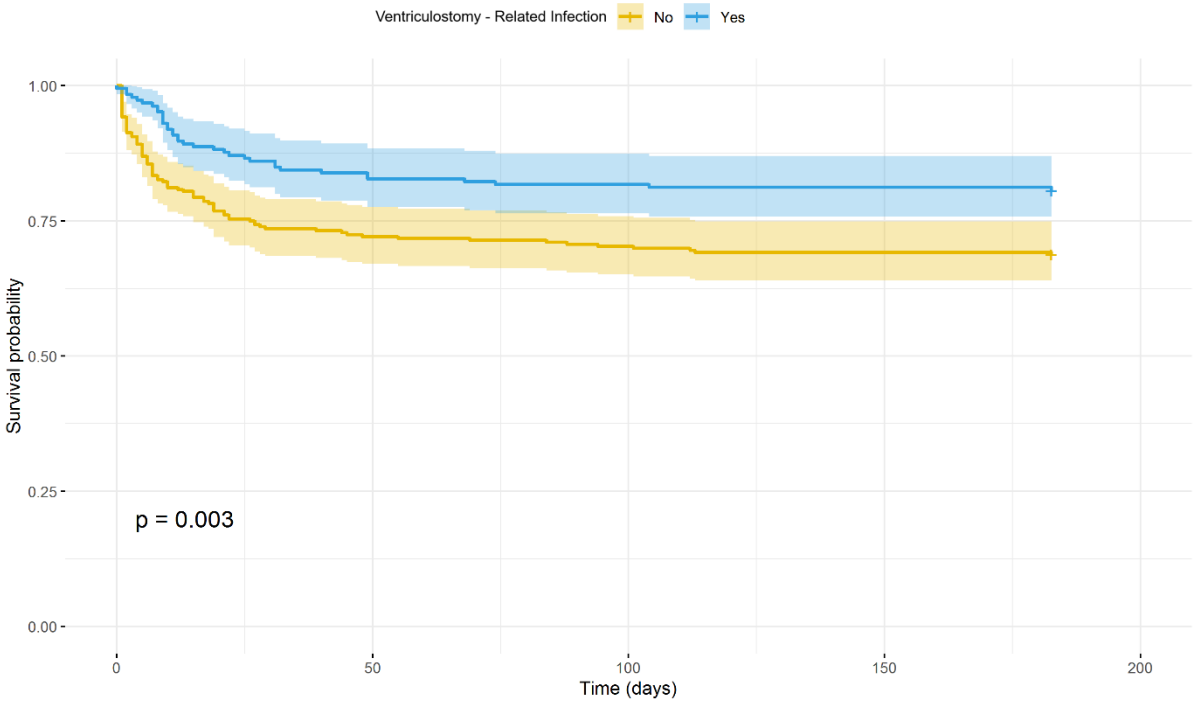

Figure 3-3 - Kaplan-Meier curve representing 6-month mortality in patients diagnosed with ventriculostomy – related infection as defined by Holloway et al.[99] compared to patients who did not meet this definition

3.3 Discussion

3.3.1 Key Results

We performed a retrospective cohort study to assess the association between a diagnosis of VRI (as defined by initiation of treatment by the clinical team) and poor functional neurological outcome at 6 months. We also assessed the association between a clinical diagnosis of VRI and other outcomes including poor functional neurological outcome at 12 and 24 months, inpatient mortality, mortality at 6 months, duration of EVD insertion, length of stay in ICU and hospital, and incidence of VP shunt insertion.

We found that a diagnosis of VRI as defined by the initiation of treatment by the clinical team was not associated with an increase in the risk of poor functional neurological outcome at 6 months. This was supported by sensitivity analysis using four pre-published diagnostic

criteria included in this study. A diagnosis of VRI was not associated with increased risk of poor functional neurological outcome at 12 or 24 months. A diagnosis of VRI as defined by initiation of treatment by the clinical team, or as defined by the CDC[179] or Holloway et al.[99], was associated with decreased mortality. However, sensitivity analysis to account for the immortal time bias suggested that a diagnosis of VRI by any of the included definitions was not associated with increased ICU mortality, in-hospital mortality, or 6-month mortality. A diagnosis of VRI was associated with increased ICU and hospital LOS, and increased duration of EVD insertion. A diagnosis of VRI as defined by initiation of treatment by the clinical team was associated with increased VP shunt insertion. This was supported when VRI was defined by non-microbiological criteria (as per the CDC[179] or Holloway et al.[99] definitions), but diagnostic criteria for VRI which required a positive CSF culture (as per the Chi et al.[55] or Gozal et al.[54] definitions) were not associated with increased VP shunt insertion.

3.3.2 Strengths and Limitations

The strengths of this study include a large patient cohort with prospectively collected data up to 24 months after admission to ICU. The results of the systematic review[170] comprising chapter 2 shows that follow up beyond 6 months was not reported in the literature, meaning this outcome represents a novel contribution to the literature. Another strength was the robustness of the data as demonstrated by concordance of outcomes associated with VRI as defined by treatment by the clinical team with sensitivity analysis using multiple pre-published diagnostic criteria.

A limitation of this study was the low number of positive CSF cultures which reduces the generalisability of the outcomes associated with VRI as defined by the diagnostic criteria

published by Chi[55] or Gozal[54]. The low numbers of patients who met these diagnostic criteria reduces the statistical power associated with outcomes in these groups.

Another limitation is the confounding effect of the heterogeneity of the study population. We didn't account for severity of illness in the three primary neurological diagnoses (SAH, TBI, and ICH) due to the lack of a common metric for disease severity across the three diagnoses meant analysis of the study population and the lack of a simple statistical approach to modelling severity of illness under this constraint. This is a common source of confounding in studies reporting outcomes associated with VRI – in the systematic review comprising chapter 2, only one[169] of the 18 studies included only one diagnosis and controlled for disease severity. We chose to keep our study methodologically consistent with the majority of academic literature reporting outcomes associated with VRI. Therefore, we enrolled participants with several primary neurological diagnoses and reporting outcomes of the whole cohort. The trial's single-centre design is another noted limitation.

The protective association against mortality of VRI as defined by treatment by the clinical team, or by the diagnostic criteria published by the CDC[179] or Holloway et al.[99], is an unexpected finding. Inflammation in the serum or CSF of patients with SAH, ICH and TBI is considered a poor prognostic indicator[181-183]. These results may be explained by two types of bias: the immortal time bias or misclassification bias. Misclassification bias, whether differential or non-differential, is difficult to account for, can have unpredictable effects on the direction of bias (though non-differential misclassification is generally considered to bias towards the null), and is a notable source of bias in the setting of a poorly defined illness[184,185]. The immortal time bias can be examined using Kaplan-Meier curves[186], and in our study, exclusion of patients with early mortality. The shift of mortality ratios towards the null hypothesis with these sensitivity analyses shows that the immortal time bias likely accounts for some of the measured protective effect of VRI.

Exclusion of patients who died within 5 days of their primary neurological injury was chosen because the median time to initiation of treatment by the clinical team (7 days, IQR 5 – 9), suggests that most treatment for VRI occurred after 5 days. Although there are patients who were treated for VRI within the first five days of their admission to ICU, it is unlikely that mortality within this time frame was due to VRI. Instead, mortality within this time frame is more likely to be secondary to the primary neurological diagnosis. However, this sensitivity analysis is not intended as a robust investigation of early mortality in brain injury. Instead, it serves to demonstrate the effect on mortality due to VRI from patients who died shortly after suffering a severe neurological injury.

3.3.3 Interpretation

This study reveals that the findings of the systematic review hold true when follow-up is extended to a longer duration (24 months, compared to the longest follow up of 6 months in the systematic review[14]); a diagnosis of VRI was associated with increased ICU LOS, hospital LOS and increased rates of VP shunt insertion but was not associated with worse functional neurological outcome or mortality. This study shows this with a sample size amongst the largest studies in the systematic review the third largest sample size of the studies in the systematic review (487 participants, with the larger sample sizes being 34,238 participants[169] and 638 participants[82]. Both studies only followed participants until discharge from hospital).

Another limitation of the systematic review was variety in definitions for VRI, which is a well described phenomenon in the academic literature[4,8]. Whilst the definitions used in this paper are only a sample of the diagnostic criteria in the literature, they represent the largest categories of commonly used definitions[8]; positive CSF culture (represented by the definition

published by Chi et al[55]), the CDC criteria[179], both positive CSF culture and clinical criteria (Gozal et al[54]), and either positive CSF culture or clinical criteria (Holloway et al[99]).

Although non-microbiological criteria are often used to diagnose VRI, there is evidence to suggest that these parameters may not sufficiently distinguish VRI from aseptic inflammation[113], and recent studies using PCR suggest that the incidence of culture – negative VRI is very low[156,187]. In this study, the low rate of positive CSF cultures is both a limitation and an observation of interest. If CSF culture results are the best indicator of the presence of VRI, then a low incidence of positive CSF cultures means a low incidence of VRI. Therefore, the results of this study may not be generalisable to indicate the association between VRI (as defined by a positive CSF culture) and clinical outcomes. However, this also indicates that the true incidence of VRI is low (1.8% of patients when defined by Chi et al.[55], compared to 17% of patients when defined by treatment by the clinical team) and the low mortality in the cohort is because either VRI is easily treated or does not have the clinical impact we fear.

On the other hand, definitions of VRI which relied on the presence of non-microbiological markers of infection (such as the CDC definition[179], the Holloway et al. definition[99], or VRI as defined by the initiation of treatment by the clinical team) were associated with lower mortality. This finding is unexpected and may be explained by the immortal time bias or misclassification bias.

3.3.4 Generalisability

The cohort of this study is a representative sample of patients with severe brain injury who require an EVD. However, this study occurred at a centre with a dedicated high volume neuroscience ICU, with specialised nursing staff trained in the management of EVDs. This

may limit generalisability due to site-specific practices regarding the maintenance of EVDs and the management of VRI. This may also affect the incidence of positive CSF cultures.

Multicentre trials with larger cohorts and an increased incidence of positive CSF cultures would improve the generalisability of these results. Other avenues of investigation may assess approaches to treatment – for example, the initiation of antibiotics only in the presence of microbiological evidence of VRI (either culture or PCR) or early cessation of empirical treatment of VRI based on negative microbiological tests.

In conclusion, we performed an analysis of prospectively collected data to assess the outcomes associated with VRI. We found that VRI was not associated with worse functional outcome at 6 months. We found that VRI was not associated with worse functional neurological outcome at 12 or 24 months. We found that VRI was not associated with increased mortality when performing sensitivity analysis to account for the immortal time bias. VRI as defined by treatment by the clinical team but not by the included pre-published diagnostic criteria was associated with a higher rate of VP shunt insertion. VRI was associated with increased ICU and hospital LOS and increased duration of EVD insertion.

4. The Incidence of Ventriculostomy-Related Infections as Diagnosed by 16S rRNA Polymerase Chain Reaction: A Prospective Observational Study

This chapter was published as “The Incidence of Ventriculostomy-Related Infections as Diagnosed by 16S rRNA Polymerase Chain Reaction: A Prospective Observational Study”[187].

The data from the systematic review comprising chapter 2 shows that a diagnosis of VRI was not associated with worse mortality or functional neurological outcome but was associated with increased duration of EVD placement, longer length of stay in hospital and ICU, and an increased rate of EVD placement. However, the study was limited by low number of cohorts (for some outcomes) and variations in the diagnostic criteria for VRI.

Subsequently, we analysed data from a prospective database of long-term follow-up of patients admitted to a neurosurgical ICU, shown in chapter 3. The results of this study were similar to the systematic review – a diagnosis of VRI was not associated with increased patient mortality or poor functional neurological outcome but was associated with increased length of stay in ICU and hospital and longer duration of EVD insertion. These outcomes were not affected by which definition of VRI was used. Definitions requiring inflammatory CSF findings, as well as VRI diagnosed by the clinical team, were associated with increased incidence of VP shunt insertion.

Given these studies did not clearly demonstrate an association between a diagnosis of VRI and poor clinical outcomes, we considered that this may have been due to inaccuracy of diagnostic methods. We undertook a prospective cohort study to compare the diagnostic accuracy of commonly used diagnostic criteria to a modern diagnostic technique, 16S rRNA PCR.

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Original Research

The incidence of ventriculostomy-related infections as diagnosed by 16S rRNA polymerase chain reaction: A prospective observational study

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ABSTRACT

Background: Ventriculostomy-related infections (VRIs) are reported in about 10 % of patients with external ventricular drains (EVDs). VRIs are difficult to diagnose due to clinical and laboratory abnormalities caused by the primary neurological injury which led to insertion of the EVD. Polymerase chain reaction (PCR) of the cerebrospinal fluid (CSF) may enable more accurate diagnosis of VRI. We performed a prospective cohort study to measure the incidence of VRI as diagnosed by 16S rRNA PCR.

Methods: Patients admitted to intensive care with a primary diagnosis of subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), or intracerebral haemorrhage (ICH), who required an EVD, were assessed for inclusion in this study. Data were extracted from the electronic medical record, bedside charts, or from a prospectively collected database, the Neuroscience Outcomes in Intensive CarE database (NOICE). 16S rRNA PCR was performed on routinely collected CSF as per laboratory protocol. VRI was also diagnosed based on pre-existing definitions.

Results: 237 CSF samples from 39 patients were enrolled in the study. The mean patient age was 55.7 years, and 56.4 % were female. The most common primary neurological diagnosis was SAH (61.5 %). The incidence of a positive PCR was 2.6 % of patients (1 in 39) and 0.8 % of CSF samples (2 in 237). The incidence of VRI according to pre-published diagnostic criteria was 2.6 % – 41 % of patients and 0.4 % – 17.6 % of CSF samples. 28.2 % of patients were treated for VRI. Pre-published definitions which relied on CSF culture results had higher specificity and lower false positive rates for predicting a PCR result when compared to definitions incorporating non-microbiological markers of VRI. In CSF samples with a negative 16S rRNA PCR, there was a high proportion of non-microbiological markers of infection, and a high incidence of fever on the day the CSF sample was taken.

Conclusions: The incidence of VRI as defined as a positive PCR was lower than the incidence of VRI according to several published definitions, and lower than the incidence of VRI as defined as treatment by the clinical team. Non-microbiological markers of VRI may be less reliable than a positive CSF culture in diagnosing VRI.

1. Introduction

External ventricular drains (EVDs) are one of the most common neurosurgical devices used in modern practice [1]. Ventriculostomy – related infections (VRIs) are diagnosed in approximately 10 % of patients with an EVD [2,3]. These infections are commonly diagnosed using routine microbiological tests (e.g. culture or gram stain of the cerebrospinal fluid (CSF)), analysis of the cytology or biochemistry of the CSF, or clinical parameters such as fever. However, primary neurological injuries which require the placement of an EVD may cause

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aberrations in clinical findings consistent with central nervous system (CNS) infection, such as raised CSF white cell counts, raised CSF protein, and low CSF glucose [4]. Therefore, although these findings would typically indicate a CNS infection, they may not distinguish patients with VRI from patients without infection [5], and has led to uncertainty about how to best diagnose VRI [6].

Molecular diagnostic techniques such as polymerase chain reaction (PCR) may be useful for the diagnosis of VRI. PCR uses DNA primers to amplify target genes, for example the highly preserved 16S rRNA gene in bacterial species [7]. The amplification process produces millions of copies of the target gene. Studies comparing PCR to conventional diagnostic parameters suggest PCR may detect bacterial DNA in the CSF of patients with negative CSF culture [8], and may outperform standard clinical and laboratory markers of CNS infection [9]. Therefore, because non-microbiological markers of infection are difficult to interpret in the setting of acute neurological injury, PCR may be a more time-efficient microbiological technique when compared to CSF culture.

We performed a prospective observational cohort study to measure the incidence of VRI as defined as a positive 16S rRNA PCR in patients with subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), and intracerebral haemorrhage (ICH), who required placement of an EVD. We also compared the incidence of VRI as diagnosed by 16S rRNA PCR to pre-published definitions of VRI and describe diagnostic parameters of VRI in this cohort.

2. Methods

This manuscript has been structured according to the STROBE guidelines [10]. Ethics approval for this study was granted by the Northern Sydney Local Health District Human Research Ethics Committee (RESP/18/099). Funding for the 16S rRNA PCR testing was provided by a grant from the Northcare foundation.

2.1. Study design and setting

This prospective observational cohort study was conducted in the Neurosciences Intensive Care Unit (ICU) at Royal North Shore Hospital, a tertiary referral centre in Sydney, Australia. This is a 13 bed ICU which specialises in the management of neurosurgical patients. Patient recruitment occurred from August 2018 until June 2019. Due to the COVID-19 outbreak and consequent redirection of laboratory resources, sample analysis was delayed until 2023.

2.2. Participants

Patients admitted to the ICU with a primary diagnosis of SAH, TBI, or ICH, who required placement of an EVD for their primary diagnosis, and had at least one CSF sample taken, were eligible to consent for this study. Patients were excluded if they had evidence of CNS infection prior to EVD insertion. If the eligible patient was unable to be consented, a person responsible was approached for consent. Patients were followed until 2 weeks after removal of their EVD.

2.3. Variables and data sources

Variables collected for this study included demographics, primary neurological diagnosis, illness severity scoring [11–15], and daily clinical and laboratory data. 16S rRNA PCR was performed in batches by the RNSH microbiology lab on stored CSF samples taken as part of routine clinical practice – at this centre, CSF samples were taken twice a week, and when clinically indicated. An in-house 16S rRNA in vitro diagnostics method has been validated for use at RNSH New South Wales Health Pathology National Association of Testing Authorities accredited laboratory, using the MagNA Pure96 (MP96) Extraction Platform and Thermal Cycler BioRad CT1000 Touch.

A volume of 200 μL CSF drain samples was used for extraction on the Roche MagNA Pure automated extractor. The CSF drain samples were run in duplicate with a spiked control to monitor for inhibition to ensure no false negative results were issued. An in-house positive control, negative control and no-template control were included in each run. Two set of primers were used in this protocol, and each patient had two sets of master mix. Primer sets 1 and 2 were (forward) 5′-GAC TCC TAC GGG AGG CAG CAG-3′ and (reverse) 5′-CTG ATC CGC GAT TAC TAG CGA TTC-3′. Primer sets 1 and 2 generate 1020 base pairs [16]. Primer sets 3 and 4 were (forward) 5′-CCT AAC ACA TGC AAG TCG ARCG-3′ and (reverse) 5′-CGT ATT ACC GCG GCT GCT-3′. Primer sets 3 and 4 generate 490 base pairs [17,18].

5 μL of extracted DNA samples was mixed with 20 μL of master mix and amplified in the thermal cycler. The obtained amplicon was purified by using a Qiaquick PCR Purification Kit, sequenced with the Applied Biosystems Hitachi 3500 Genetic Analyzer with Big Dye protocol, and compared to a public DNA database [19]. When multiple CSF samples were taken in a day, the first CSF sample was included in analysis. Samples were frozen at −80 degrees Celsius between collection and PCR analysis.

Clinical data from eligible patients were prospectively collected in a registry called the Neurological Outcomes in Intensive CarE (NOICE) registry [20], which was accessed for this study. Data not included in NOICE such as CSF cytology and biochemistry were extracted separately from the electronic medical record.

Four pre-published definitions [21–24] were selected to measure the incidence of VRI. These definitions are shown in Supplementary Table 1. The Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN) criteria [22] contains subjective criteria (i.e. meningeal signs, headache) which were excluded from the definition used for this study, because these findings may not be reliably reported in an intubated or sedated patient. Antibody titres were excluded as they are not routinely measured at this site. Normal ranges of CSF criteria were defined according to the Royal College of Pathologists of Australasia [25]. Treatment of VRI was extracted from NOICE, and was defined as initiation of antibiotic therapy for VRI based on the clinical team's judgement. The clinical teams involved in the care of the patient were not involved in this study.

2.4. Statistical methods

Demographics data are presented as mean and standard deviation for normally distributed data, and median and interquartile interval for non-normally distributed data. Nominal data, such as the incidence of VRI, is presented as counts and proportions. For each definition of VRI, the diagnostic accuracy was calculated both by patient and by CSF sample. For the latter, diagnostic accuracy was calculated only on samples where 16 s rRNA PCR was done AND samples where it was possible to assess the presence or absence of VRI based on available data. Receiver operating characteristic (ROC) analysis was used to obtain the measures of diagnostic accuracy (sensitivity, specificity, area under the ROC (AuROC) curve, and percentage of correctly classified patients/CSF samples) of the four definitions of VRI against the reference, 16 s rRNA PCR. Diagnostic markers for VRI were presented as mean and standard deviation, and as proportions of CSF samples with diagnostic markers between specific thresholds. 16S rRNA PCR is not a test routinely performed at RNSH, so sample size was limited by funding provided from a grant from the Northcare Foundation. Statistical analyses were conducted using Stata BE V17.0 for Windows (StataCorp LLC, College Station, TX).

3. Results

3.1. Participants

There were 42 patients admitted to ICU who met inclusion criteria during the enrolment period, and 39 patients consented to be included

in the study. 16 s rRNA PCR was performed on 237 CSF samples. Demographics data for enrolled patients is included in Table 1.

3.2. The incidence of VRI

The incidence of VRI as measured by 16S rRNA PCR, clinician-initiated treatment of VRI, and four pre-published definitions of VRI, is described in Table 2.

The clinical team initiated treatment for VRI in 11 of 39 patients (28.2 %). VRI as defined as a positive 16S rRNA PCR was diagnosed in 2.6 % of patients (1 of 39 patients). The incidence of VRI according to the pre-published definitions ranged from 2.6 % of patients to 41 % of patients. The incidence of VRI according to diagnostic criteria relying on CSF culture results [21,23] was closest to the incidence of VRI as defined as a positive 16S rRNA PCR. Definitions incorporating non-microbiological criteria [22,24] measured a higher incidence of VRI compared to 16S rRNA PCR.

Table 1
Patient characteristics.

	Total
	N = 39
Age, years (mean, SD)	55.7 (16.2)
Sex (n, %)	
Male	17 (43.6 %)
Female	22 (56.4 %)
Origin of patient (n, %)	
Emergency department	37 (94.9 %)
Transfer from external intensive care unit	2 (5.1 %)
Pre-admission level of function (n, %)	
Independent	37 (94.9 %)
Some help required	2 (5.1 %)
Charlson Comorbidity Index (n, %)	
0	31 (79.5 %)
1	3 (7.7 %)
2	3 (7.7 %)
3	2 (5.1 %)
Primary neurological diagnosis (n, %)	
Subarachnoid hemorrhage	24 (61.5 %)
Traumatic brain injury	11 (28.2 %)
Intracerebral hemorrhage (ICH)	4 (10.3 %)
Duration of intensive care admission, days (median, IQR)	19.3 (13.5–26.7)
Duration of hospital admission, days (median, IQR)	29.9 (20.9–44.9)
Duration of external ventricular drain insertion, days (median, IQR)	15.0 (11.0–19.0)
Number of cerebrospinal fluid samples per patient, count (median, IQR)	6.0 (3.0–8.0)
Disease severity	
Subarachnoid hemorrhage (N = 24)	
World Federation of Neurosurgical Societies (WFNS) grade [11] (median, IQR)	2.0 (1.0–4.0)
Fisher grade (median, IQR) [12]	4.0 (4.0–4.0)
Claassen grade (median, IQR) [13]	5.0 (4.0–5.0)
First documented Glasgow coma scale (GCS) (median, IQR)	13.5 (7.0–14.5)
Traumatic brain injury (N = 11)	
Marshall score (median, IQR) [14]	2.0 (2.0–6.0)
First documented GCS (median, IQR)	3.0 (3.0–6.0)
Intracerebral hemorrhage (N = 4)	
ICH score (median, IQR) [15]	2.5 (2.0–3.0)
First documented GCS (median, IQR)	9.0 (6.5–13.0)

GCS = Glasgow Coma Scale; ICH = Intracerebral Haemorrhage; IQR = Interquartile Range; SD = Standard Deviation; WFNS = World Federation of Neurosurgical Societies.

Table 2
Number of positive results from 16S rRNA polymerase chain reaction (PCR) test and existing definitions of ventriculostomy-related infection (VRI), by cerebrospinal fluid (CSF) sample and by patient.

	By CSF sample	By patient
16 s rRNA PCR test	2/237 (0.8 %)	1/39 (2.6 %)
Chi 2010 [21]	2/216 (0.9 %)	1/39 (2.6 %)
Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN) 2023 [22]	11/243 (4.5 %)	9/39 (23.1 %)
Gozal 2014 [23]	1/243 (0.4 %)	1/39 (2.6 %)
Holloway 1996 [24]	38/216 (17.6 %)	16/39 (41.0 %)
Treated for VRI		11/39 (28.2 %)

CDC = Centre for Disease Control; CSF = Cerebrospinal Fluid; NHSN = National Healthcare Safety Network; PCR = Polymerase Chain Reaction; VRI = Ventriculostomy-Related Infection

3.3. The accuracy of published definitions of VRI

Measures of diagnostic utility for pre-published definitions of VRI when compared to 16S rRNA PCR are described in Table 3 (by patient) and Table 4 (by sample).

When compared to 16S rRNA PCR, the definitions by Chi et al. [21] and Gozal et al. [23], which relied on CSF culture results, correctly classified >99 % of patients and CSF samples. The definitions which included non-microbiological criteria were less accurate at predicting a positive 16S rRNA PCR. The definition published by the CDC/NHSN [22] correctly classified 79.49 % of patients and 96.17 % of CSF samples. The definition published by Holloway et al. [24] correctly classified 61.54 % of patients and 82.69 % of CSF samples. The definitions published by the CDC/NHSN and Holloway et al. had lower specificity and higher false positive rates than the definitions by Chi et al. and Gozal et al.

3.4. Diagnostic parameters of VRI

Diagnostic parameters of VRI in CSF samples with a negative 16S rRNA PCR are described in Table 5. One CSF sample with a positive CSF culture was PCR negative. A fever of 37.6 °C or greater was measured on the same day as 61.1 % of CSF samples. The red cell count to white cell count ratio (RCC:WCC) in 202 PCR negative CSF samples was 200 or less and 47 % of samples. An elevated protein was measured in 64 % of CSF samples, and a CSF:blood glucose ratio was less than 0.5 in 25.9 % of CSF samples. Of 32 CSF samples in which a lactate was measured, lactate was greater than 2.0 mmol/L in 81.2 % of samples.

4. Conclusions

We performed a prospective cohort study to measure the incidence of VRI as defined as a positive 16 s rRNA PCR in patients admitted to ICU with a diagnosis of SAH, TBI or ICH. We found that the incidence of VRI as defined as a positive PCR was less than the incidence of VRI diagnosed by the treating team. The incidence of VRI according to pre-published definitions ranged from 2.6 % to 41 % of patients. A positive 16S rRNA PCR was best predicted by diagnostic criteria which required a positive CSF culture. The diagnostic parameters described in Tables 3 and 4 should be interpreted with caution due to the low incidence of VRI in this cohort. We also found that high numbers of CSF samples with a

Table 3
Measures of diagnostic accuracy for pre-existing definitions of ventriculostomy-related infection (VRI) when compared with 16S rRNA polymerase chain reaction (PCR) (by patient).

Definition	N patients	AuROC (95 % CI)	Sensitivity	Specificity	False negative	False positive	Correctly classified
Chi 2010 [21]	39	1.000 (0.910 to 1.000)	100.00	100.00	0.00	0.00	100.00
Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN) 2023 [22]	39	0.895 (0.758 to 0.971)	100.00	78.95	0.00	21.05	79.49
Gozal 2014 [23]	39	1.000 (0.910 to 1.000)	100.00	100.00	0.00	0.00	100.00
Holloway 1996 [24]	39	0.803 (0.635 to 0.907)	100.00	60.53	0.00	39.47	61.54
Treated for VRI	39	0.868 (0.726 to 0.957)	100.00	73.68	0.00	26.32	74.36

AuROC = Area Under Receiver Operating Characteristic; CDC = Centre for Disease Control; CSF = Cerebrospinal Fluid; NHSN = National Healthcare Safety Network; PCR = Polymerase Chain Reaction; VRI = Ventriculostomy-Related Infection

Table 4
Measures of diagnostic accuracy for pre-existing definitions of ventriculostomy-related infection (VRI) when compared with 16S rRNA polymerase chain reaction (PCR) (by CSF sample).

Definition	N matched samples	AuROC (95 % CI)	Sensitivity	Specificity	False negative	False positive	Correctly classified
Chi 2010 [21]	208	1.000 (0.982 to 1.000)	100.00	100.00	0.00	0.00	100.00
Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN) 2023 [22]	235	0.981 (0.951 to 0.993)	100.00	96.14	0.00	3.86	96.17
Gozal 2014 [23]	235	0.750 (0.688 to 0.803)	50.00	100.00	50.00	0.00	99.57
Holloway 1996 [24]	208	0.913 (0.867 to 0.948)	100.00	82.52	0.00	17.48	82.69

AuROC = Area Under Receiver Operating Characteristic; CDC = Centre for Disease Control; CSF = Cerebrospinal Fluid; NHSN = National Healthcare Safety Network; PCR = Polymerase Chain Reaction; VRI = Ventriculostomy-Related Infection.

negative PCR had abnormal CSF parameters consistent with CSF infection. These data suggest that VRI is over-diagnosed.

Variations in the incidence of VRI based on different definitions is a well described phenomenon. One systematic review [6] found 17 different definitions of VRI, and studies which compare the incidence of VRI based on different definitions find different results based on the diagnostic criteria in use [6,26,27]. In part, this stems from the absence of a validated gold standard diagnostic tool for VRI. For example, CSF cultures have been reported to have a false negative rate of between 20–70 % [28–31], which is further confounded by the use of antibiotic impregnated EVDs [32]. Molecular microbiological technologies such as PCR or metagenomic sequencing may have potential as gold standard diagnostic tools, but their use in clinical practice has yet to be validated in a large enough cohort.

Although PCR has been purported to diagnose culture negative VRI [8], there were no cases of culture negative VRI in this study. Whilst only one patient had a positive 16S rRNA PCR result, 11 patients were treated for VRI by the clinical team, and 16 patients met the definition for VRI as published by Holloway et al. [24], which allowed for culture negative VRI. On the other hand, a positive PCR was best predicted by the definition which relied exclusively on a positive CSF culture taken after the first 24 h of EVD placement [21]. This is reflected by the high specificity and low false positive rates in the definitions relying on CSF culture results.

The compromised diagnostic utility of definitions which use non-microbiological markers is consistent with previous studies demonstrating limited utility of these markers of CNS infection for the diagnosis of VRI [4,5]. CSF samples with a negative PCR had a high incidence of results commensurate with CNS infection, such as increased white cells, decreased RCC:WCC ratio, or increased protein. These samples were also associated with a high incidence of fever on the day the sample was taken. On the other hand, the incidence of positive gram stain or culture was low in these samples. In this study, the single PCR-negative CSF sample with a positive culture was taken at the time of EVD insertion. Both PCR and repeat culture of the culprit sample were negative, suggesting that the positive culture was a contaminant. However, because the positive culture led to commencement of treatment for VRI in this patient, the culture has been considered positive in the study analysis. This accounts for the reduced diagnostic accuracy of the definition published by Gozal et al. [23].

The high incidence of clinical markers suggestive of infection, and the low incidence of positive gram stain or culture in PCR-negative CSF samples, indicates that a positive CSF culture is the most reliable marker of VRI. It also suggests that reliance on routine non-microbiological markers of CNS infection may lead to overdiagnosis of VRI. In a 2016 systematic review of definitions of VRI [6], 13 of 16 definitions included clinical or laboratory criteria, and 8 of 16 did not include a CSF culture result. The earliest definition in this systematic review is from a 1984 paper [33] which used prospective data to conclude that VRI should be diagnosed on the basis of a positive CSF culture due to the low predictive value of CSF white cell counts or fever. 40 years later, our findings support this assertion.

The lack of a consensus definition, the variability demonstrated by different diagnostic criteria, and the lack of a gold standard diagnostic tool, have consequences on accuracy of diagnosis and treatment of VRI. Whilst CNS infections in patients presenting from the community have poor morbidity and mortality [34], the same has not been clearly demonstrated in patients with VRI [3]. One explanation for this is that a patient admitted to ICU, who is at risk of VRI, will have more prompt recognition and treatment of CNS infection compared to an undifferentiated patient presenting from the community. This would reduce delays in treatment. Therefore, the impact of CNS infection on mortality and functional neurological outcome would be minimised. However, another explanation is that VRI is over diagnosed, and patients with aseptic CNS inflammation in the setting of severe neurologic pathology are being analysed in the same group as patients with true CNS infection.

Table 5
Analysis of diagnostic markers of ventriculostomy-related infection from cerebrospinal fluid (CSF) samples with a negative 16 s-rRNA polymerase chain reaction (PCR).

Characteristic	N samples (%)
Body temperature (N = 234)	
<36.5 °C	9 (3.8 %)
36.5 °C –37.5 °C	82 (35.0 %)
37.6–38.3 °C	77 (32.9 %)
>38.3 °C	66 (28.2 %)
CSF culture result (N = 233)	
Negative	232 (99.6 %)
Positive	1 (0.4 %)
CSF gram stain (N = 234)	
Negative	234 (100.0 %)
Positive	0 (0.0 %)
CSF white cell count (N = 229)	
0–5 × 10^6/L	80 (34.9 %)
5–50 × 10^6/L	104 (45.4 %)
51–100 × 10^6/L	21 (9.2 %)
101–500 × 10^6/L	18 (7.9 %)
>500 × 10^6/L	6 (2.6 %)
CSF neutrophil count (N = 229)	
0–5 × 10^6/L	113 (49.3 %)
5–50 × 10^6/L	85 (37.1 %)
51–100 × 10^6/L	16 (7.0 %)
101–500 × 10^6/L	10 (4.4 %)
>500 × 10^6/L	5 (2.2 %)
CSF red cell count: white cell count ratio (RCC:WCC) (N = 202)	
CSF RCC:WCC > 1000	34 (16.8 %)
CSF RCC:WCC 501–1000	29 (14.4 %)
CSF RCC:WCC 201–500	44 (21.8 %)
CSF RCC:WCC ≤200	95 (47.0 %)
Cell index [1] (N = 222)	
0–1	105 (47.3 %)
1.1–5	62 (27.9 %)
5.1–10	23 (10.4 %)
10.1–20	10 (4.5 %)
>20	22 (9.9 %)
CSF protein (N = 161)	
<0.15 g/L	11 (6.8 %)
0.15–0.45 g/L	47 (29.2 %)
0.46–0.80 g/L	46 (28.6 %)
0.81–1.00 g/L	17 (10.6 %)
>1.00 g/L	40 (24.8 %)
CSF glucose (N = 164)	
<2.8 mmol/L	10 (6.1 %)
2.8–4.5 mmol/L	81 (49.4 %)
4.6–6.0 mmol/L	55 (33.5 %)
>6,0 mmol/L	18 (11.0 %)
CSF: serum glucose ratio (N = 147)	
0–0.25	2 (1.4 %)
0.26–0.50	36 (24.5 %)
0.51–0.75	91 (61.9 %)
>0.75	18 (12.2 %)
CSF lactate (N = 32)	
CSF lactate 0–1.9	6 (18.8 %)
CSF lactate 2.0–3.9	19 (59.4 %)
CSF lactate 4.0–5.9	5 (15.6 %)
CSF lactate ≥6.0	2 (6.2 %)

CSF = Cerebrospinal Fluid; PCR = Polymerase Chain Reaction; RCC: WCC = Red Cell Count: White Cell Count ratio.

This would create a bias in analysis due to the formation of an unreliable denominator. Therefore, any studies examining the incidence, treatment, prevention, or prognosis of patients with VRI are more difficult to design or interpret.

Moreover, these diagnostic uncertainties have direct effects on patient care. Overdiagnosis of VRI will necessarily lead to overtreatment with broad spectrum antibiotics, exposing a vulnerable patient group to potential adverse reactions associated with these medications, and increasing the risk of antibiotics resistance in our communities. Overdiagnosis of VRI may also lead to delayed diagnosis and treatment of alternative pathology which explains the patient's clinical findings.

Although we acknowledge the small cohort size as a limitation of this study, this study represents a contribution to our understanding of the value of PCR in the diagnosis of VRI which is comparable to other similar studies [8,9,35,36]. The four studies found during our literature review which used PCR on CSF samples only from EVDs included between 28 and 67 patients and between 24 and 86 CSF samples (our study included 39 patients and 237 CSF samples). Other limitations of this study include the low incidence of a positive 16S rRNA PCR (which makes the AUROC, sensitivity, and false negative rates in Tables 3 and 4 less reliable, although they are included for completion), and that the precise reasons for initiating treatment for VRI by the clinical teams in these patients was not available from the NOICE database. This study recruited patients from a specialised ICU in a major tertiary centre with a high neurosurgical patient load and nursing staff specifically trained in the management of patients with EVDs, so these findings may not be generalisable to centres with less exposure to patients with EVDs. Further research would involve multi-centre studies to detect more cases of VRI, and to increase the generalisability of the study.

In this prospective cohort study, the incidence of VRI as diagnosed by 16S rRNA PCR was 2.6 % of patients and 0.8 % of CSF samples. This is closest to the incidence measured by diagnostic criteria relying on a positive CSF culture. Diagnostic criteria for VRI using non-microbiological markers of CNS infection had a lower specificity and higher false positive rate compared to definitions relying on a positive CSF culture. The incidence of abnormal CSF results and fevers associated with CSF samples with a negative PCR was high. These findings suggest that the incidence of VRI is lower than currently estimated.

5. Statements and declarations

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CRediT authorship contribution statement

Simon Chadwick: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation. **Pierre Janin:** Writing – review & editing, Methodology. **Archie Darbar:** Writing – review & editing, Resources, Methodology. **Oliver Flower:** Writing – review & editing, Project administration, Methodology. **Naomi Hammond:** Writing – review & editing, Methodology. **Frances Bass:** Writing – review & editing, Resources. **Kelly Harbour:** Writing – review & editing, Resources, Methodology. **Leonie Chan:** Writing – review & editing, Resources. **Katerina Mitsakos:** Writing – review & editing, Resources. **Jonathon Parkinson:** Writing – review & editing, Methodology. **Joseph Alvin Santos:** Writing – review & editing, Formal analysis. **Anthony Delaney:** Writing – review & editing, Writing – original draft, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2024.05.034.

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Table 4-6 (published as Supplementary Table 1) – Pre-published Definitions of Ventriculostomy-Related Infections.

Author, Year	Definition
Chi, 2010[55]	Ventriculostomy-associated infection is defined as a positive cerebrospinal fluid (CSF) culture obtained from the external ventricular drain (EVD) or via lumbar puncture, excluding positive cultures obtained prior to one day after EVD placement
Centre for Disease Control/National Healthcare Safety Network (CDC/NHSN), 2023 [179]	Meningitis or ventriculitis must meet at least one of the following criteria: 1. Patient has organism(s) identified from CSF by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment for example, not Active Surveillance Culture/Testing 2. Patient has fever (>38.0°C) and at least one of the following: a. increased white cells, elevated protein, and decreased glucose in CSF (per reporting laboratory's reference range) b. organism(s) seen on Gram stain of CSF c. organism(s) identified from blood by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing
Gozal, 2014[54]	Ventriculostomy-associated infection is defined as a positive CSF culture in a patient with a ventriculostomy within 72 hours of removal plus one or more of the following: a) fever (recorded temperature exceeding 101.5 degrees Fahrenheit (38.6 degrees Celsius), or b) CSF glucose level either < 50 mg/dL or < 50% of a serum glucose level drawn within 24 hours of the CSF glucose
Holloway, 1996 [99]	Ventriculostomy-related ventriculitis is diagnosed if a CSF culture from a ventriculostomy is positive, excluding cultures taken immediately after ventriculostomy placement. In the absence of a positive culture, a diagnosis can be made if there are greater than 50 white blood cells in the CSF, greater than 50% of which are neutrophils, or CSF glucose less than 15 mg/100 ml

5. Discussion and Conclusions

5.1 Summary and Key Findings

5.1.1 Background

Acute brain injury due to SAH, TBI, and ICH is associated with high morbidity and mortality[161,167]. As part of the management of their brain injury, patients may have an EVD inserted to treat hydrocephalus or measure intracranial pressure. The EVD, as a foreign body inserted into a patient, represents a potential nidus of infection which connects directly to the cerebral ventricles. It is well recognised that community acquired bacterial infections of the CNS are associated with high mortality, and survivors are at high risk of neurological sequelae[159,160]. Therefore, it would stand to reason that VRI would combine the poor outcomes of community-acquired CNS infections with the poor outcomes associated with severe brain injury.

The assessment of this logic is made difficult by the absence of a widely agreed-upon and validated definition of VRI[4]. Different studies use varying permutations of CSF culture (which may specify, for example, species of organism or number of positive cultures), CSF white cell count, CSF protein, CSF glucose, serum:CSF glucose ratios, fever, or symptoms of CNS infection (headache, nuchal rigidity, or altered level of consciousness).

There are limitations to these diagnostic tools. For example, CSF cultures may take 24 – 48 hours to yield a result, and longer for sensitivities to be available. However, the utility of non-microbiological parameters of infection is impaired by the presence of CNS inflammation due to the primary brain injury (leading to clinical and laboratory findings similar to infection), and treatments associated with the management of acute brain injury (such as

sedation or intubation, which may mask features of CNS infection – an intubated patient may have difficulty in reporting a worsening headache).

Molecular microbiological diagnostic techniques such as PCR may overcome the time constraints associated with CSF cultures but with higher specificity than non-microbiological markers of infection. Studies assessing the diagnostic utility of PCR have reported high rates of detection of bacterial DNA in culture-negative CSF samples[85,157].

The goals of this thesis were as follows:

1. To evaluate the association between a diagnosis of VRI and clinical outcomes. Our hypothesis was that a diagnosis of VRI would be associated with worse long term functional outcome
2. To evaluate the diagnostic accuracy of existing diagnostic criteria for VRI when compared to a modern standard (16S rRNA PCR). Our hypothesis was that PCR would have a higher sensitivity when compared to CSF culture.

5.1.2 Systematic Review of Outcomes Associated with VRI

We performed a systematic review to assess outcomes associated with a diagnosis of VRI. We included studies of cohorts of adult patients requiring EVD placement, who compared outcomes between patients with and without a diagnosis of VRI (as defined by the individual study). There were 18 cohort studies and one randomised controlled trial which met our inclusion criteria, including 38,427 participants. The primary objective of the study was inpatient mortality. Secondary objectives included functional neurological outcome, mortality at longest follow up, duration of ICU admission, duration of hospital admission, duration of EVD placement, and the incidence of other infectious and non-infectious complications.

In this systematic review, a diagnosis of VRI was not associated with increased mortality or worse functional neurological outcome. However, a diagnosis of VRI was associated with longer duration of hospital and ICU length of stay, increased duration of EVD insertion, and increased rates of VP shunt insertion.

The strengths of this study were robust methodological design and a large number of included patients. However, the systematic review was limited by heterogeneity of the included studies, notably due to variations in definitions of VRI, represented by high I^2 values and wide confidence intervals. Some of the secondary outcomes had small numbers of cohorts for pooled analysis. Importantly, only one study reported 6 month follow up[14]. The remaining studies followed patients until hospital discharge, for a short period after EVD removal, or did not specify duration of follow up.

Another gap in the literature was that none of the studies attempted to account for variability in definitions of VRI when assessing outcomes. The incidence of VRI varies depending on the diagnostic criteria applied[4,8] and variations in incidence may lead to variations in measurements of outcomes association with VRI.

In conclusion, the findings of this systematic review indicate that a diagnosis of VRI is not associated with worse mortality or functional neurological outcome. We were led to perform the next study due to a paucity of data regarding long term outcomes and an absence of data examining the effect of different definitions of VRI on assessment of outcomes.

5.1.3 Retrospective Cohort Study

The retrospective cohort study included in chapter 3 aimed to address two important limitations of the systematic review – the lack of long-term follow-up in the included studies and the heterogeneity of studies due to variations in the definition of VRI. Therefore, we

performed a retrospective cohort study to assess the association between a diagnosis of VRI and clinical outcomes.

Data from 487 participants with EVDs inserted was extracted from a database of patients admitted to ICU with a primary neurological diagnosis of SAH, ICH, or TBI, who were followed for up to 24 months after ICU admission. VRI was not associated with worse functional neurological outcome at 6, 12, or 24 months. When evaluating the association between VRI and mortality, sensitivity analysis was performed by excluding patients who died in the first five days of admission and by creating Kaplan-Meier curves. These sensitivity analyses showed that VRI was not associated with increased mortality in ICU, hospital, or at 6 months. VRI was associated with increased hospital and ICU LOS, and increased duration of VP shunt insertion. Participants diagnosed with VRI as defined by non-microbiological criteria were more likely to undergo VP shunt insertion.

The measured association between a diagnosis of VRI and reduced mortality is unexpected. Explanation for this finding include a protective effect of antibiotics, or an increased exposure to clinicians in ICU leading to earlier recognition and management of clinical issues (due to lower clinician:patient ratio with respect to both medical and nursing staff compared to the ward).

Another explanation may be that a diagnosis of VRI confounds assessment of prognosis due to the primary neurological injury, and clinicians would treat VRI to remove it as a confounding factor. This gives patients extra time to recover. Therefore, when clinicians decide the time is right for neurological prognostication, assessment of the patient is such that life supporting treatment is continued. Supporting this is that the most significant mortality benefit occurring when VRI was defined as initiation of treatment by the clinical team.

However, it would seem unlikely that that contracting a CNS infection while recovering from an acute brain injury would reduce a patient's chance of death. Instead, we suspect that these results are due to bias, specifically the immortal time bias and differential or non-differential misclassification bias.

Immortal Time Bias

The immortal time bias refers to a bias caused by misclassification of exposure status due to periods of time in which an outcome may occur with a patient remaining unexposed[188]. A simple relevant example was offered in a 2012 editorial[186], which described the "tea and crumpet" study. In this study, all patients admitted to ICU are offered tea and crumpets on day 3 of admission. The results of this study would show that such a treat would improve ICU mortality. However, by offering the exposure only to patients on day 3, we have selected for patients who both survive the first 72 hours of ICU admission and who are well enough to voluntarily accept tea and crumpets.

In this study, participants dying before meeting diagnostic criteria for VRI increase the mortality rate of patients who are not diagnosed with VRI. This confers a measured protective association of a diagnosis of VRI. Exclusion of participants who died within the first five days after EVD insertion shifted the mortality ratios and 95% confidence intervals towards the null for VRI as diagnosed by treatment by the clinical team and as defined by the CDC[179] and Holloway[99] diagnostic criteria. This was also observed for the definitions published by Chi et al.[55] and Gozal et al.[54], although the confidence intervals for those diagnostic criteria already included a mortality ratio of 1.0 prior to exclusion of participants who died within the first 5 days.

Another technique to address immortal time bias is by using Kaplan-Meier curves because these graphs document the survival of the exposed group from the time of exposure and the

unexposed group from the time of enrolment[186]. The 6-month Kaplan-Meier curves for VRI as defined by CDC[179] or Holloway[99] criteria show early mortality in participants who did not meet these diagnostic criteria for VRI. This suggests that the measured association between a diagnosis of VRI and mortality is partly explained by the immortal time bias.

Misclassification Bias

Misclassification bias is due to inaccurate assignment of exposure to a cohort. It can be non-differential (in which the degree of misclassification of exposure is similar throughout the cohort) or differential (in which the degree of misclassification is not equally distributed throughout a cohort)[184]. As a heuristic, non-differential bias is considered to bias results towards the null[184] but there are several methodological examples in which this heuristic does not hold[185,189]. Furthermore, in most real-world examples it is difficult to confidently state that misclassification is equally likely throughout a cohort[189,190], which means the direction of bias can be difficult to predict. Differential misclassification can bias outcomes in either direction[184] and judgement of the likely direction of bias is required to properly interpret the data.

It could be argued that this study may be affected by either non-differential or differential misclassification bias. VRI is not a consistently defined disease[4], therefore a patient with an EVD may have equal probability of being diagnosed with VRI or not being diagnosed with VRI (non-differential misclassification). However, part of the uncertainty regarding the diagnosis of VRI is the use of microbiological versus non-microbiological parameters. Non-microbiological definitions of VRI are common[4,8] but they may not sufficiently distinguish infection from aseptic inflammation[113]. Therefore, a cohort of patients with EVDs, who have

a propensity towards developing an inflammatory CSF profile, are more likely to be diagnosed with VRI than they are to contract VRI (differential misclassification).

The degree to which misclassification bias affects these results is likely highest in the outcomes for VRI as defined by treatment by the clinical team. NOICE does not record the clinical reasoning for commencing treatment for VRI, so it is difficult to precisely assess the effect misclassification bias in the measured outcomes of VRI as defined by clinical treatment of VRI. Nevertheless, we can infer that many of these diagnoses were based on non-microbiological data due to the low rate of positive CSF cultures in our cohort.

With this study showing no clear association between a diagnosis of VRI and mortality or functional neurological outcome, we decided to compare commonly used diagnostic methods for VRI against 16S rRNA PCR.

5.1.4 Prospective Cohort Study

With the results of the retrospective cohort study concordant with the results of the systematic review, the next objective was to assess whether 16S rRNA PCR added value to the diagnosis of VRI. The primary objective of the study was to measure the incidence of VRI as defined by a positive 16S rRNA PCR. We also compared the incidence of VRI as defined by four published diagnostic criteria and as defined by treatment by the clinical team. Finally, we reported the ranges of non-microbiological parameters of infection on the same day of a CSF sample with a negative 16S rRNA PCR.

We included 39 patients admitted to ICU with a primary diagnosis of SAH, TBI, or ICH, who required EVD insertion as part of their management. We prospectively performed PCR on the

237 CSF samples taken from their EVDs as part of routine care and recorded test results related to definitions of VRI.

We found that the incidence of VRI as defined as a positive 16S rRNA PCR was low (2.6% of patients (1 in 39) and 0.8% of CSF samples (2 in 237)). Using different diagnostic criteria, the incidence of VRI ranged from 2.6% to 41% of patients (1/39 – 16/39). The incidence of VRI as defined by treatment by the clinical team was 28.2% (11/39). There were no CSF samples that were 16S rRNA PCR positive and culture negative. In CSF samples with a negative CSF, there was a high incidence of findings consistent with CNS infection such as fever, high CSF leukocyte count, high CSF protein count, and low CSF glucose.

This study had sample sizes comparable to other similar studies[31,32,85] but had a lower rate of positive CSF cultures. The reduced incidence of positive CSF cultures limits the diagnostic value of 16S rRNA PCR, particularly with regard to sensitivity and false negative rate.

Consequences of the low incidence of positive CSF PCR

The low incidence of positive 16S rRNA PCR was an unexpected finding in this study. Initially, our study design assumed that there would be a high rate of positive PCR due to the sensitivity of the test. Studies identified via the literature review comprising chapter 1 of this thesis which assessed the use of PCR as a diagnostic tool for VRI suggested a high incidence of culture negative VRI identified by PCR[31,85]. To distinguish culture negative VRI from a false positive PCR (e.g. due to sample contamination), we planned fortnightly meetings including an intensivist and an infectious diseases physician to contextualise participants' PCR results in the setting of their clinical findings and laboratory results. The goal of these meetings would be adjudication of positive PCR results as either suggestive of true infection

or false positives. The low incidence of positive 16S rRNA PCR meant that these meetings were not necessary.

Another consequence of the low number of positive 16S rRNA PCR was a pivot of study objectives. Originally, one of the secondary outcomes of the study was to compare the clinical and laboratory findings of patients on days with a positive CSF 16S rRNA PCR to patients with a negative PCR. We had hoped that this would allow the development of a set of diagnostic criteria using routine markers of infection that would predict a positive CSF PCR. As the PCR results came available, it became clear that a new *a posteriori* definition of VRI would not eventuate from this study. Instead, we decided to report the clinical parameters associated with negative 16S rRNA PCR of the CSF. This data was still useful as it demonstrated a high incidence of abnormal diagnostic parameters in patients with both culture- and PCR-negative CSF.

The SARS-CoV-2 Pandemic

Recruitment for this study began in mid-2018 and ended in late 2019. Samples were stored at -80ºC within 72 hours of collection in the microbiology laboratory at Royal North Shore Hospital. The outbreak of SARS-CoV-2 in New South Wales led to a necessary redirection of resources towards diagnosis of this new illness. These resources included both personnel and reagents required for the PCR. This led to significant delays in performing the PCR.

The CSF samples remained in storage during this time, until analysis was completed in 2023. This led to concerns from reviewers regarding the stability of samples during prolonged storage. The half-life of DNA is just over 520 years[191] and nucleic acids have been shown to be stable at -80ºC for up to 16 months[192]. Whilst it is possible that some of the bacterial nucleic acid degraded during this time, the long half-life and the prompt storage of the

samples means that any bacterial DNA which had degraded enough to yield a negative CSF PCR would be unlikely to represent an infection. Additionally, our findings are consistent with more modern studies assessing the use of PCR to diagnose VRI[156,193]. These studies indicate that with modern assays, the incidence of CSF culture-negative VRI is low.

5.1.5 Key Findings

The pertinent findings of the research contained in this thesis are as follows:

1. A diagnosis of VRI based on non-microbiological criteria is not associated with increased mortality or reduced functional neurological outcome
2. A diagnosis of VRI based on any criteria is associated with an increase in ICU and hospital length of stay, and an increased duration of EVD insertion
3. None of the definitions used to define VRI in our studies were associated with worse mortality or poor functional outcome
4. In our cohort, the incidence of VRI as defined as a positive 16S rRNA PCR was low
5. Definitions of VRI requiring a positive CSF culture were most closely associated with a positive 16S rRNA PCR
6. Definitions of VRI which allow for culture-negative infections over-estimate the incidence of VRI compared to 16S rRNA PCR, as does VRI as defined by initiation of treatment by the clinical team.

5.2 Implications and Context of the Research

Although logic might suggest an additive effect of VRI on outcomes associated with acute CNS pathology such as SAH, TBI, or ICH, the research comprising this thesis suggests that a

diagnosis of VRI is not associated with differences in mortality or poor neurological outcome. This begs the question as to whether the way VRI is defined would affect measurements of outcome. However, the study comprising chapter 3 of this thesis suggests that this is independent of whether VRI is defined by CSF culture or by raised CSF cell counts or biochemistry. The incidence of patients meeting diagnostic criteria based on non-microbiological criteria[99,100] was higher than the incidence of positive CSF cultures. We can therefore state with some confidence that fulfilling these diagnostic criteria is not associated with higher mortality or poor functional neurological outcome.

This needs to be interpreted in the context of a low incidence of CSF cultures. Although our data suggests no significant association between a positive CSF culture and worse mortality or functional neurological outcome, the incidence of VRI as defined by a positive CSF culture was around 2% (11/487 patients in chapter 3 and 1/39 patients in chapter 4). There are several conclusions that may be drawn from this. Based on the study in chapter 4 (which suggests a positive CSF culture may be the most accurate conventional marker of VRI), the incidence of VRI is likely much lower than would be suggested by definitions using non-microbiological criteria and is overtreated by clinicians. Therefore, the lack of association between positive cultures and mortality or functional neurological outcome suggests that either 1) VRI is being effectively treated, 2) the bacterial isolates are more commonly representative of contamination or EVD colonisation (for example due to the presence of a biofilm), or 3) the incidence of positive CSF cultures in this cohort are too low.

Another (less likely) interpretation is that VRI is of limited clinical consequence. However, a 2022 retrospective cohort study[194] from 21 neurosurgical units in the United Kingdom challenges this assertion. The study identified 46 cases of VRI from 495 EVD insertions and separated them into 26 cases of confirmed VRI (as defined by clinical suspicion plus a positive CSF culture) and 20 cases of suspected VRI (as defined by clinical suspicion plus a

negative CSF culture). The study found that although any case of VRI had longer duration of EVD insertion (concordant with our findings), patients with suspected VRI compared to confirmed VRI had lower 30-day mortality (suspected 0% vs confirmed 23.1%, p = .03) and lower modified Rankin Scale (mRS) (suspected median mRS 2.5 [IQR, 1–4] vs confirmed mRS 4.5 [IQR, 3–5]; p = .03).

Another study by Pietrzko et al.[193], published months before the study in chapter 4, used 16S rRNA PCR as part of the diagnostic workup for VRI in a cohort of 193 patients. PCR was used if patients met clinical criteria for VRI[47] but had a negative gram stain. Patients with a positive CSF culture or positive CSF PCR were defined as having confirmed VRI (12 patients) whereas patients with a negative CSF culture or PCR, who met the clinical criteria, were defined as having suspected VRI (66 patients). Confirmed VRI was associated with higher rates of poor functional neurological outcome (as defined as a GOSE of 1 – 4) at 3 months compared to patients with patients with suspected VRI (60%, 40/66 patients in suspected VRI compared to 100%, 12/12 patients in confirmed VRI, p = 0.016). The 3-month mortality in patients with confirmed versus suspected VRI was not different.

The diagnostic criteria selected for the studies in chapters 3 and 4 are representative of the variety of commonly used published definitions for VRI: CSF culture only[55], CDC/NHSN criteria[100], CSF culture plus clinical/laboratory criteria[54], and CSF culture or clinical/laboratory criteria[99]. Considering the breadth of definitions of VRI[4,27,106,107], there are some limitations of using a sample of definitions. For example, a patient with fever and "increased white cells…in CSF" meets diagnostic criteria for VRI according to the CDC criteria[100] but does not state the numerical cut off for normal. Therefore, we defined "increased white cells" in the CSF according to the Royal College of Pathologists Australia's manual[180], which defines increased white cells as 5 or greater mononuclear cells and zero neutrophils. In the setting of severe brain injury, this definition may be overly liberal, leading

to overestimation of the incidence of VRI. However, the definition published by Holloway et al.[99] defines VRI according to a CSF white cell count >50, and measured a higher incidence of VRI compared to the CDC criteria in one of the studies[187] (perhaps due to omission of fever as a defining criteria).

The results of the prospective cohort study in chapter 4 suggest that extensive deliberation about how to define cut offs for non-microbiological definitions for VRI may not be productive. We found that a positive 16S rRNA PCR was best predicted by a positive CSF culture and that CSF samples with a negative PCR and a negative culture were associated with abnormalities consistent with CNS infection. The poor diagnostic efficacy of non-microbiological findings is consistent with the results of a 2019 systematic review by Dorresteijn et al.[113] which included 3,305 patients with EVDs. This study found limited discriminatory benefit of non-microbiological markers of infection for the diagnosis of VRI.

Our findings of a low incidence of culture-negative VRI (as defined by negative CSF culture and positive CSF PCR) is supported by a study published within a few months of our study in chapter 4, written by Widén et al.[156]. This study assessed the use of real-time PCR and nanopore sequencing in the diagnosis of VRI. The study included 84 CSF samples from patients with EVDs inserted. Of these samples, 22 had positive CSF cultures and 62 had negative CSF cultures (44 treated with antibiotics, 18 had not received antibiotics). 61 of the 62 CSF samples with a negative culture had a negative real-time PCR and had nanopore sequence read numbers below control. This provides additional evidence against the hypothesis of culture-negative VRI being a common diagnosis.

It should be noted that this thesis does not discount culture-negative VRI as a clinical entity. Instead, clinicians should have a more rigorous benchmark for non-microbiological criteria to justify a clinical diagnosis of VRI. This is supported by the high incidence of clinical

abnormalities in culture-negative and PCR-negative patients in chapter 4. This research also suggests that for large studies looking at clinical metrics associated with VRI, cases should be defined by positive microbiological investigations such as CSF culture results. Although this would lead to a small number of patients with culture-negative VRI being incorrectly categorised, the overall effect of misclassification bias would be minimised, leading to more accurate assessments of outcomes associated with VRI.

5.3 Directions for Future Research

Although this thesis aims to address some of the uncertainty regarding the diagnosis and prognosis of VRI, there are still numerous unanswered questions about VRI regarding topics such as risk factors and treatment for VRI. As discussed at length during this thesis, there are variations in diagnostic criteria for VRI[4] and the varying definitions make consistent measurements of outcomes difficult. However, there is a growing body of evidence, to which this thesis contributes, that relying on non-microbiological criteria to diagnose VRI should be discouraged. Therefore, further research on VRI should define VRI according to CSF culture results or other microbiological diagnostic techniques (e.g. PCR) and systematic reviews looking at VRI should only include studies which define VRI in this way.

In finding a standard definition for VRI, another question remains regarding defining positive CSF cultures as “infection” versus “colonisation” versus “contamination”. The use of non-microbiological diagnostic criteria alongside a positive CSF culture is less likely to be fruitful given the increasing body of evidence that parameters such as CSF leukocytes/protein have limited ability for detecting VRI[113,187]. One approach could be the requirement of more than one positive CSF culture to establish VRI if common commensal organisms are identified[51,81]. However, the ability of these definitions to predict mortality or functional

neurological outcome would need to be assessed in large multi-centre trials with high numbers of positive CSF cultures.

If CSF culture results are important for accurate diagnosis of VRI, then technical aspects of CSF culture protocols should be optimised. For example, the use of blood culture bottles prior to plating is used to increase the yield of pleural[195] or ascitic[196] fluid cultures, but is not as well established for CSF samples[197]. Our lab used blood culture bottles to improve yield of CSF cultures if CSF samples had abnormal cell counts or if the patient was on antibiotics. This is supported by some small studies of CSF cultures[197,198], and the effects may be extrapolated from data on practices using samples of different body fluids[195,196]. Further research is needed to establish best practice for the technical approach to CSF culture.

Given the lack of association between VRI and increased mortality, another avenue of research could involve the timing of initiation of treatment for VRI. One outcome of interest from the study by Pietrzko et al.[193] was that the use of PCR as an early investigation reduced the mean duration of antibiotic days from 14 to 5.5. Validation of these results would substantially reduce the antibiotic use in patients with EVDs. Another possible approach would be to withhold antibiotics until definitive diagnosis of VRI, especially at sites where the baseline incidence of positive CSF cultures is low. Either superior or non-inferior randomized controlled trials comparing CSF PCR-guided algorithm with conventional criteria to initiate antibiotic therapy in patients with suspected VRI will be pivotal in defining the best strategy in dealing with the complexity of issues related to VRI in neurosurgical patients in the intensive care units.

The increased use of molecular diagnostic techniques means PCR may become a routine part of the diagnosis of VRI. This raises questions about its use from both technical and clinical perspectives. The conflicting outcomes of studies assessing the diagnostic utility of PCR for

VRI suggest that local laboratory protocols can affect the sensitivity of these assays[156]. Another explanation for a low rate of culture negative VRI in our study compared to others may be advances in technology. In earlier studies[32,83,85,151,155], higher rates of positive PCR in patients with a negative CSF culture may be due to less sophisticated assays when compared to those used in more recent studies[156].

Other molecular diagnostic techniques such as metagenomic next-generation sequencing (mNGS) may prove useful in the diagnosis of VRI[199]. Whilst recent research[200,201] has demonstrated added value of mNGS in the diagnosis of CNS infections, there is only one study examining the use of this test in the setting of VRI[199]. More research is needed to standardise PCR assays for VRI and to investigate the use of mNGS for diagnosing VRI.

5.4 Conclusion

The research in this thesis shows that a diagnosis of VRI is not associated with increased mortality or worse functional outcome but is associated with increased duration of ICU and hospital length of stay, and duration of EVD insertion. Our cohort studies had a low incidence of positive CSF culture, which makes some of the outcomes difficult to generalise. The incidence of VRI as defined by a positive 16S rRNA PCR correlated best with positive CSF culture, was found to be overestimated by VRI defined by non-microbiological criteria, and was over diagnosed by clinicians.

6. References

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