Role of c-reactive protein response to antibiotic therapy in children with a ventriculo-peritoneal shunt infection

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Declaration

I, Miss Kiara Rampershad, declare:

1. That the work described in this thesis has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

2. That my contribution to the project includes; the literature research conducted to prepare the research proposal and background knowledge of the thesis, writing of the research proposal, submission of the proposal to the Biomedical Research Ethics Committee (BREC) for approval, data collection conducted at the approved hospital (Inkosi Albert Luthuli Central Hospital) as well as analysis of the data collected and compilation of the final thesis, with further literature research supporting the data findings.

3. That the contributions of others to the project were as follows:

Dr ZNP Msibi, my primary supervisor, situated at the UKZN Physiology department, guided me throughout the writing process as well as provided critical feedback on the presented work

Dr B. Enicker, my co-supervisor situated at Inkosi Albert Luthuli Central Hospital, who assisted with the data collection procedure as well as the analysis of results.

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Acronyms and Abbreviations

Ab	Antibody
AIS	Antibiotic-impregnated shunt
ANOVA	Analysis of variance
BBB	Blood-brain barrier
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CVD	Cardiovascular diseases
E.coli	*Escherichia coli*
ELISA	Enzyme-Linked Immunosorbent Assays
EVD	External ventricular drain
G6PD	Glucose-6-phosphate dehydrogenase
GCS	Glasgow Coma Scale
GDM	Gestational diabetes mellitus
GOS	Glasgow Outcome Scale
GOSE	Extended Glasgow Outcome Scale
Hb	Haemoglobin
HCRN	Hydrocephalus Clinical Research Network
HIC	High-income countries
HRT	Hormone replacement therapy
IALCH	Inkosi Albert Luthuli Central Hospital
IFN	Interferons
IL-1β	Interleukin-1beta
IL-6	Interleukin-6
IQR	Interquartile range
IVH	Intraventricular haemorrhage
LMIC	Low and middle-income countries
MHC	Major Histocompatibility Complex
MMC	Myelomeningocele
Mtb	*Mycobacterium Tuberculosis*
NTD	Neural tube defects
PCh	Phosphocholine

PE	Phosphoethanolamine
PLT	Platelets
RBC	Red blood cells
SA	South Africa
SAP	Serum amyloid P-component
SBI	Serious bacterial infections
SNP	Single-nucleotide polymorphisms
TBI	Traumatic brain injury
TNF-α	Tumour Necrosis Factor alpha
UKZN	University of KwaZulu Natal
US	United States
VPS	Ventriculoperitoneal shunt
WCC	White cell count

Abstract

Hydrocephalus is a common neurosurgical condition in children, with a higher incidence in low and middle-income countries (LMIC). Ventriculoperitoneal (VP) shunt insertion remains the primary treatment, but postoperative infections are a major source of morbidity, leading to repeated surgeries and increased mortality. C-reactive protein (CRP) is a rapid, sensitive marker of inflammation that rises within hours of infection and declines quickly with effective treatment and correlates with bacterial burden. This makes it a practical, low-cost tool for monitoring VP shunt infections and determining the appropriate duration of antibiotic therapy in children. This study aims to evaluate whether CRP trends correlate with clinical improvement and can inform decisions regarding antibiotic treatment length. A total of 147 patients diagnosed with meningitis secondary to a VP shunt infection, from January 2018 to December 2024, were included in this retrospective study conducted at Inkosi Albert Luthuli Central Hospital (IALCH). Clinical presentation, serology results, and culture results were obtained and analysed. Of the 147 children included, more than half were infants (51.7%), presenting with the lowest mean CRP on admission (34.7 mg/L) and congenital hydrocephalus (48.3%). CRP levels were elevated at admission (mean 48.6 mg/L), peaked by day 3-5, and declined gradually to 29.4 mg/L by day 30, with a significant reduction from admission ($p = 0.02$). *Staphylococcus epidermidis* (25.9%) and *Staphylococcus aureus* (21.1%) were the most common organisms, with 58.6% showing antimicrobial resistance. Vancomycin ($n = 41$; 27.9%) was the most frequently used antibiotic, and mean treatment duration was 27 days, which aligned with a decrease in CRP at day 30. Persistent CRP elevation with no clear infection resolutions was associated with resistant organisms and a complicated infection. CRP is a valuable marker for monitoring treatment response in paediatric VP shunt infections, showcasing a decline with clinical improvement. However, its variability, particularly in infants and resistant infections, limits its use as the sole guide for antibiotic duration. The integration of CRP with clinical indicators, microbiological data, and shunt-related decision-making enhances therapy and supports better paediatric outcomes.

CHAPTER 1: INTRODUCTION

1.1.Background

Hydrocephalus is defined as the accumulation of cerebrospinal fluid (CSF) within the brain when the balance between regular CSF production and absorption is disrupted. This causes expansion of the ventricles, which leads to an increase in intracranial pressure and triggers symptoms such as headaches, nausea, vomiting, dizziness, and lowered visual perception. There is a higher incidence of paediatric hydrocephalus in lower and middle-income countries (LMIC), estimated at 123 cases per 100,000, compared to high-income countries (HIC), at 79 cases per 100,000 (1). In sub-Saharan Africa, the annual incidence is 225,000 for infant hydrocephalus cases, as a result of central nervous system (CNS) infections. This relates to 750 cases per 100,000 live births (2). If there is obstruction of CSF flow within the ventricles, it is categorised as obstructive or non-communicating hydrocephalus. When the CSF flow or absorption is obstructed in the subarachnoid space, it is classified as communicating hydrocephalus (3). Non-communicating (obstructive) hydrocephalus is caused by a physical blockage within the pathways that connect the ventricles. The aetiology of hydrocephalus can be either acquired or congenital. Congenital hydrocephalus is associated with neural tube defects (NTDs) such as myelomeningocele (MMC), aqueduct stenosis, and genetic abnormalities such as X-linked hydrocephalus. Congenital hydrocephalus originates when ependymal denudation and subcommisural organ failure leads to the closure of the foetal aqueduct individually or combined with other congenital malformations (4). Approximately 70-90% of infants with MMC develop hydrocephalus (3, 5-7). Acquired hydrocephalus results mainly from traumatic brain injury (TBI), brain tumours, CNS infections, and intraventricular haemorrhage related to pre-maturity.

A ventriculoperitoneal (VP) shunt is the most frequently performed neurosurgical procedure for the management of hydrocephalus (8, 9). The modern shunt consists of silastic tubing that runs subcutaneously from the head to the abdomen region with a valve placed between the ventricular and distal catheters. Flow-regulating valve mechanisms are added with antisiphon devices to hinder CSF overdrainage (4). Endoscopic third ventriculostomy is an alternative surgical procedure, particularly in patients with obstructive hydrocephalus. VP shunt complication rates are reported to range from 6% to 50% in developing countries (10). VP shunts have a failure rate of 30% within the first year of placement and 10% annually thereafter (3), with a reported mortality rate of 5-10% 30 years post-shunt procedure (4, 11). VP shunt complications include mechanical obstruction, overdrainage, intracranial haemorrhage, disconnection, bowel perforation, abdominal pseudocyst, shunt extrusion, and infections. Shunt failures due to a mechanical obstruction occur in 40% of paediatric patients within the first two years of placement (4) and can occur at the proximal or distal catheter or at the valve. This could be due to an intraventricular haemorrhage, subdural haematomas, or a shunt breakage. The international VP shunt infection rate ranges from 1% to 40% (1, 12). In high-income countries (HICs), shunt infection

rates range from 2% to 9%, while the range in LMICs is reported at 8.6% to 50% (13). A study conducted in Nigeria had a shunt infection rate of 7.2% with an overall complication rate of 30.4% (14), while a study from China reported rates of 6.98% (15). In the United States, shunt infection rates range from 1% to 11.7% (16). A South African study reported shunt infection rates of 9.6% over 20 years (3). The risk factors for shunt infection include patient characteristics, such as low birth weight, young age (including premature infants), nutritional status, low socioeconomic status, pre-existing CNS infections, late presentation, immunosuppression, and poverty. Other factors include surgeon experience, operating room traffic, lengthy procedures, multiple handling of the shunt, postoperative CSF leak, and not adhering to strict sterility protocols (8, 14, 16-19).

Over 98% of infections are caused by intraoperative contamination (20) with an infection rate of 5-9% per procedure, typically occurring within the first 5 weeks to 3 months post-surgery (8, 21, 22). VP shunt infections are the cause of 10-15% of shunt revisions (20, 23). Paediatric patients who develop a VP shunt infection have an increased risk of mortality and three times the risk of shunt revision-related operations (24, 25). VP shunt infection occurs when bacteria, often originating from the patient's skin, colonise the shunt during or after its insertion. Bacteria then form a biofilm on the shunt's surface as a protective mechanism to facilitate the propagation of infection. Bacteraemia can also lead to shunt infection (26). Infection confirmation is done via a positive microbiological CSF culture, with the common microorganisms being *coagulase-negative staphylococci* (CoNS) and *Staphylococcus aureus* (16, 21). Other isolated organisms include *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii,* and *Pseudomonas species*. The standard clinical features of patients with a VP shunt infection include signs of focal swelling and erythema over the shunt site, fever, vomiting, irritability, septic wound, poor feeding, and bulging fontanelle in infants (16).

The Hydrocephalus Clinical Research Network (HCRN) has advocated for standardising the perioperative care of children undergoing VP shunt procedures, with the implementation of knowledge-based perioperative protocols (22). These include hand washing and double gloving, perioperative antibiotics, patient positioning, use of the no-touch technique for the shunt equipment, cleaning with both alcohol-based and iodine solutions, and double draping in the operating room. These techniques have been shown to reduce the infection rate from 9.1% to 2.9% (10, 22, 27, 28). Another non-protocol technique includes the use of antibiotic-impregnated shunts (AIS), which significantly reduced the risk of infection (22, 29-31). Intraoperative practices include hair shaving when necessary, surgical site preparation, glove changing before handling the shunt, minimising shunt contact, limiting traffic in the operating room, and standardised shunt placement protocols (32). Further postoperative management protocols include appropriate wound care, regular follow-up appointments, educating patients about wound care, as well as the early detection of signs of infection. These include fever, wound erythema, and swelling (1, 16).

The initial intervention procedures for a severe infection include the removal of the infected shunt and placement of an external ventricular drain (EVD). This process allows for temporary CSF drainage during treatment. A new shunt can be placed after the CSF culture results return negative and after approximately 10-14 days of antibiotic therapy have been completed (55, 64, 65). The choice of antibiotic is based on culture results and consideration of blood-brain barrier penetration. When an infection is detected, antimicrobial therapy and removal of the shunt should commence promptly to prevent worsening of systemic sepsis, which increases the mortality rate. The shunt infection mortality rates are between 5.5% and 32.1% within the first year (1, 8, 33). This makes early detection of the infection vital for achieving favourable outcomes in paediatric patients and preventing recurrent shunt failures and infections (16, 18, 33). Antimicrobial therapy is used to combat bacterial meningitis in children. The common antibiotics used include Vancomycin, Cephalosporins, and Penicillin G (34). Before the prescription of antibiotics, blood cultures are conducted in order to identify the pathogens present. However, these results take 48-72 hours to generate in order to make a definite diagnosis. Blood culture results identify Gram-positive and Gram-negative bacteria present during infections. Due to the results not being available within a short period of time, empiric antibiotics are prescribed to the paediatric patient with uncertain results, which can lead to antibiotic resistance due to the extended or improper use of the medication (35-37). These challenges highlight the importance of the use of a biomarker, such as C-reactive protein (CRP), to monitor infection progression and antibiotic use.

CRP is an acute-phase reactant protein produced by liver hepatocytes and used to diagnose infections in the human body (18, 25, 34, 35, 38, 39). Serum CRP levels increase exponentially within the first hours of inflammation, after the first clinical symptoms are noted, and decrease immediately after the removal of the microbial stimulus (35, 36), due to its half-life of approximately 19 hours (8, 35, 36, 39). CRP levels usually peak 48-72 hours after initial infection and vary based on the severity or type of infection (40-42). CRP is the most commonly used parameter for determining the presence of an infection, especially in children, as CRP estimation is quick, straightforward and cost-effective, whilst also using ELISA techniques for detection and quantification (35). It, however, cannot distinguish between the different causes of inflammation but does correlate with bacterial load (39, 43). The CRP threshold for an infection varies and can be altered by factors such as gender, age, weight and blood pressure (44). Elevated CRP levels can detect various bacterial infections, such as meningitis, which can be caused by an infected VP shunt (8). CRP levels drop to normal within 3-7 days; however, patients with sepsis show persistently high CRP levels for at least 7 days or longer (40).

CRP levels are also elevated three days post-surgical procedure, but persistently elevated levels indicate an infection (40, 45). A CRP level of less than 3 mg/L is considered normal and present in healthy individuals. Minor elevation is presented by 3-5 mg/L, with 6-10 mg/L showing moderate elevation, which is mostly associated with systemic inflammation and autoimmune diseases. CRP levels of >10 mg/L indicate significant elevation, present in bacterial or viral infections and major trauma. A level of

>50 mg/L indicates severe elevation in acute bacterial infections, such as VP shunt infections (National Library of Medicine, 2025). CRP levels show the balance between immunological status and microorganisms, which can help determine the duration of antibiotic therapy in children. CRP monitoring and guided antibiotic therapy can mitigate the adverse effects of prolonged antibiotic use and decrease morbidity and mortality rates in paediatric patients (35, 36).

1.2.Problem statement

Hydrocephalus management is achieved through surgical placement of a ventriculoperitoneal (VP) shunt in paediatric populations. Despite its common use, it carries significant postoperative risks. VP shunt infections largely contribute to morbidity in children with hydrocephalus, often resulting in extended hospital stays, the need for repeated surgical procedures, and substantial healthcare costs. Central nervous system (CNS) infections can negatively affect the quality of life for affected children and their families due to long-term neurological sequelae, developmental delays, behavioural difficulties, and cognitive impairment. Prompt detection and accurate monitoring of infection progression is therefore crucial for optimising outcomes. C-reactive protein (CRP) is a widely available, cost-effective, and sensitive biomarker of inflammation. It is commonly utilised in the management of paediatric infectious diseases; however, there is limited evidence regarding its specific use in neurosurgical infections, particularly VP shunts. Establishing whether CRP trends correlate with clinical improvement could support more precise decision-making in CNS infection management procedures.

The main challenge in VP shunt treatment is accurately determining the duration of antibiotic therapy. Clinicians often prescribe prolonged antibiotic courses due to uncertainty regarding infection resolution time, which contributes to excessive antibiotic use. Prolonged antibiotic administration is associated with an increased risk of adverse drug effects, disruption of the paediatric microbiome, and the increased threat of antimicrobial resistance. This research aims to ascertain whether CRP monitoring can serve as an effective supplement in VP shunt infection management by reducing antibiotic duration whilst prioritising paediatric patient safety. These findings can potentially lower mortality rates, positively impact recovery efforts, and contribute to the growing body of evidence supporting CRP-guided antibiotic therapy. This study seeks to strengthen clinical guidelines and enhance overall treatment strategies for children by contributing new evidence specific to paediatric neurosurgical infections.

1.3.Research Questions

Is CRP an effective biomarker for monitoring the response to antibiotic therapy in children with VP shunt infection-related meningitis?

1.4.Aim

To investigate the utility of CRP as a biomarker for assessing the response during combined medical-surgical management of paediatric VP shunt infections.

1.5.Objectives

- To characterise the demographic profile of paediatric patients diagnosed with VP shunt-associated bacterial meningitis at Inkosi Albert Luthuli Central Hospital (IALCH)
- To determine the aetiology of hydrocephalus associated with VP shunt infection at IALCH
- To assess the CRP levels at admission and analyse longitudinal trends during the course of antibiotic therapy
- To analyse the CSF biochemistry and identify the spectrum of cultured microorganisms in VP shunt-associated infections
- To compare the diagnostic performance of CRP with another inflammatory biomarker (white cell count) in monitoring therapeutic response.
- To determine the duration of hospitalisation and identify clinical and laboratory factors associated with prolonged length of hospital stay
- To determine the in-hospital mortality rate and predictors of mortality

1.6.Literature Review

1.6.1. C-reactive protein

C-reactive protein (CRP) is a homopentameric acute-phase inflammatory protein. This plasma protein was discovered in 1930 by Tillet and Francis while investigating patients suffering from the acute stage of Pneumococcus infection, and was named for its reaction with the capsular (C) polysaccharide of Pneumococcus (44, 46, 47). CRP is one of two acute-phase proteins, known as pentraxins, which are key components of the humoral arm of the innate immune system (47). They exhibit sequence and structural homology and are differentiated based on their function; those that bind best to phosphocholine (PCh) are CRP-like, while those that bind to phosphoethanolamine (PE) are serum amyloid P-component (SAP)-like. Only one is an acute-phase reactant; therefore, within hours after inflammation in humans, the blood CRP level increases exponentially, but SAP does not (39, 48). The human CRP gene is located on chromosome 1q23.2 on the long arm of chromosome 1 and has been associated with single-nucleotide polymorphisms (SNPs), which result in varying serum CRP levels (49). In the presence of calcium, CRP binds to polysaccharides, such as phosphocholine (PCh), on microorganisms, triggering the classical complement pathway of innate immunity by activating C1q (40, 44, 50). PCh is identified on some gram-positive bacteria, including Clostridium species and *Bacillus* species, and gram-negative bacteria, including *Haemophilus influenzae* and *Neisseria meningitides* (51). CRP acts as an opsonin for macrophages by initiating the classical complement pathway (52). Transcription of the CRP gene primarily occurs in liver hepatocytes in response to elevated levels of inflammatory cytokines, particularly interleukin-6 (IL-6) (18, 25, 37, 44, 53). IL-6 is a proinflammatory cytokine secreted by various cells, including inflammatory cells, keratinocytes, fibroblasts, and endothelial cells. It regulates the acute-phase response, with its primary role being the host's response to infection. A correlation exists between the increasing levels of IL-6 during inflammation and the corresponding increase in CRP levels (54, 55).

1.6.2. CRP analysis in the laboratory

CRP detection and levels are measured in the laboratory using sensitive Enzyme-Linked Immunosorbent Assays (ELISAs), as well as chemiluminescent, fluorescent, and electrochemical assays with a low detection sensitivity. ELISAs can be homogeneous or heterogeneous, with the former being more expensive and having low sensitivity, while heterogeneous methods are more sensitive and commonly used. Direct antigen screening has lower sensitivity and can yield false positives compared to the indirect ELISAs (51, 56). The conventional and widely used sandwich antibody-based ELISA format has been critically simplified and improved. The leach-proof binding of the capture antibody (Ab) through ionic and hydrophobic interactions is achieved. This results in highly sensitive ELISAs that are superior to conventional ELISAs and covalent Ab-immobilisation-based ELISAs. This procedure is exact and detects CRP in diluted whole blood, serum, or plasma with high specificity (57).

Disorders such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, diabetic ketoacidosis, alpha-thalassemia, lymphoma, and anaemia are characterised by the presence of Heinz bodies, which are groups of damaged haemoglobin found on the surface of red blood cells (RBCs). These have an impact on spectrophotometric measurements, falsely increasing the CRP results in relation to RBCs and haematocrit. Concerns about such interference have been reported for CRP diagnostics, and several CRP test kit manuals highlight this limitation in their specifications (58).

1.6.3. CRP per age group: neonates, infants, and toddlers

Newborns and infants have briefly elevated levels of CRP, which are higher than those present in older children and adults, mainly due to the adaptation process. The elevated CRP levels in newborns are due to physiological and immune responses during and after birth, with the baseline level of 5-10 mg/L. The process of labour and birth can cause mechanical stress, which is part of the normal inflammatory response and increases CRP levels, depending on the method of delivery. There has been an increase in neonatal CRP after instrument-assisted vaginal delivery, due to the underlying effects of extended labour periods, which increase stress (59). A study conducted by Bellieni et al. assessed the CRP levels of healthy newborns based on different types of delivery: vaginal delivery, emergency C-section, and elective C-section. They found that CRP levels were higher in babies born after vaginal delivery compared to those born after C-section, suggesting that the mechanical stress associated with vaginal delivery might contribute to elevated CRP levels (60). If a pregnancy is complicated by gestational diabetes mellitus (GDM), there is an increase in macrophages in the placenta, which also increases the expression of proinflammatory markers. The foetus, therefore, develops in an inflammatory environment (61). Antikainen and associates reported that prepubertal children from GDM conditions had more low-grade inflammation, as identified by increased levels of high-sensitivity C-reactive protein (62). Elevated CRP in the umbilical cord is reported to be related to neonatal sepsis or early onset sepsis, which typically occurs within the first 24 hours and is usually associated with *Escherichia coli* (E.coli) or a group B streptococcal infection (63). The current recommendation is that neonates with elevated CRP levels in umbilical blood may not require antimicrobials for more than 48 hours if the blood culture report is negative (64). The neonatal innate immune system is referred to as immature due to functional impairments in phagocytosis and bactericidal activity, which contribute to the susceptibility of newborns to infections (65). This suggests that minor infections or microbial exposures in the early days of life can lead to a heightened inflammatory response, leading to increased CRP production (65). Conditions such as neonatal sepsis, meningitis, or pneumonia can cause significant increases in CRP levels, which is a direct response to the infection. Neonatal sepsis forms only a portion of infected infants; however, mortality exceeds 1 million newborns a year (66). Even in the absence of overt infections, newborns can have slightly elevated CRP levels due to colonization with bacteria or viruses in the environment. CRP levels are also elevated in healthy term infants post-vaccination (Hepatitis B), which stabilise after 48-72 hours and should be taken into consideration when

differentiating from early neonatal sepsis (67). In toddlers, the primary cause of elevated CRP levels is infection, specifically bacterial infections such as urinary tract infections, meningitis, sepsis and pneumonia. Globally, 5.4 million children die before the age of 5 years, and approximately 50% of the mortality is caused by infectious diseases, many of which present with a fever, which is the common symptom related to infection identification (68).

1.6.4. CRP per age group: older children

In older children, CRP levels are usually low under healthy conditions but are sharply elevated during inflammatory conditions with a baseline level of 0.3-1 mg/L. Factors that affect CRP levels include acute infections, such as bacterial or viral infections; chronic inflammatory conditions, including autoimmune diseases; obesity and metabolic syndrome; trauma and injury; and allergic reactions (40). Bacterial infections are among the most common causes of elevated CRP levels in children. Once the pathogen invades the body, the immune system responds by producing cytokines that stimulate the release of CRP from the liver. Examples of bacterial infections include pneumonia, meningitis, sepsis and urinary tract infections. Elevated CRP can be an independent diagnostic marker for pneumonia in conjunction with suspected symptoms, but low concentrations do not rule out the condition. Therefore, prompt evaluation of the marker is needed in children with lower respiratory tract infections (69). In cases of extremely elevated CRP (>30 mg/L), bacterial infections are more prevalent (70). Some studies have shown that CRP values greater than 11 mg/L are associated with bacterial co-infection in children with moderate to severe bronchiolitis, in which CRP might be a prognostic marker of disease severity. However, other studies have reported that children with acute bronchiolitis have associated increased CRP concentrations regardless of bacterial co-infection (51, 71, 72). CRP levels also increase during viral infections, but to a lesser extent compared to bacterial infections. Common viral infections include influenza and gastroenteritis (51). CRP levels of >100 mg/L were reported to predict a bacterial superinfection in patients with influenza-like symptomatology. Pneumococci had the highest CRP levels, with Streptococci being the lowest (51, 73).

Autoimmune diseases also lead to chronically elevated CRP levels due to the immune system attacking the body tissue. This is common in juvenile idiopathic arthritis (74), systemic lupus erythematosus (75) and inflammatory bowel disease. It is also shown that teenagers with a higher body mass index (BMI) have significantly higher CRP levels (76). CRP levels are elevated to greater than 7 mg/L in allergic contact dermatitis and atopic dermatitis, with the potential to serve as a marker for disease severity (51, 77). Nutritional factors also contribute to elevated CRP levels. A study conducted by King et.al. showed elevated CRP levels were recorded in children aged 6-17 years old who had low magnesium intake (78)

1.6.5. The influence of sex on CRP levels

Levels of CRP differ between males and females and are highly influenced by physiological, hormonal, and lifestyle factors. In general, females tend to have higher CRP levels than males (79). Oestrogen, the primary female sex hormone, has been shown to have anti-inflammatory effects but also modulates the immune system to increase CRP under certain circumstances. Orally administered hormone replacement therapy (HRT) consistently increases CRP for both oestrogen and progesterone alone (79). There is emerging research that shows that oral HRT causes background levels of circulating CRP to increase in postmenopausal women, increasing the risk of thrombotic events such as clots (80). Changes in oestrogen and progesterone concentration are independently associated with changes in CRP concentration, indicating that progesterone increases CRP, oestrogen decreases CRP, and menstruation may increase CRP. The degree of elevation is dependent on the phase of the cycle (81). A ten-fold increase in oestrogen is associated with a 29% decrease in CRP, and menstruation is associated with a 17% increase in CRP (51, 79). A study conducted by Gaskins and colleagues showed a 10-fold increase in oestradiol was linked to a 24.3% decrease in CRP levels (82). Corcoran found that combining oestrogen and oxidised low-density lipoproteins increased CRP expression in a coronary heart disease model in older men and postmenopausal women; however, no effect on CRP expression was observed when oestrogen was replaced with testosterone (83). Oestrogen administration is also associated with increases in CRP among men being treated for prostate cancer (81). Testosterone in men, through its androgen receptors, regulates the expression of cytokines, providing a modulating role in the inflammatory response (84). It has an adverse effect on CRP levels and exhibits a more pronounced anti-inflammatory effect (85, 86). Low testosterone and increased CRP levels have been associated with increased mortality in men (84, 85, 87). In a cross-sectional study on non-diabetic Finnish men, results suggested metabolic syndrome as a great contributor to the high-CRP-low testosterone relationship (88). Elevated CRP and testosterone deficiency are associated with advanced age and chronic inflammatory diseases, such as cancer, obesity, diabetes, and cardiovascular disease (86)

Aside from hormonal differences that contribute to varying CRP levels in males and females, other factors, such as body composition and autoimmune diseases, also play a role. Females have a higher percentage of body fat compared to males, specifically subcutaneous fat. This is a source of proinflammatory cytokines, which stimulate the liver to release CRP, thereby increasing CRP levels. The quantity and distribution of body fat influence CRP to a greater extent in women compared with men (89, 90). In healthy middle-aged and older women, baseline levels of CRP are independent predictors of cardiovascular diseases (CVD) (91, 92). Postmenopausal women with CVD have higher CRP levels than males of the same age diagnosed with CVD. This is due to women developing CVD later in life, which is linked to the loss of protective effects of oestrogen, which assists in inflammatory regulation. The pre-menopausal state of younger women is protective against CVD in women, such that there is an approximate 10-year period for the first atherosclerotic cardiovascular event (91, 93). In a

study of 2,219 adults in the United States who had acute myocardial infarction, women younger than 55 years of age had higher levels of circulating CRP compared to men (94).

1.6.6. Benefits of CRP as a biomarker

CRP is a widely recognised and valuable biomarker that provides critical information in various clinical settings. Over the years, CRP concentrations have emerged as an essential tool for diagnosing, monitoring, and predicting outcomes in various diseases, making it one of the most commonly used inflammatory markers in clinical practice. This is due to CRP concentrations being broadly available, having good reproducibility, and being at a low cost (47, 95). It is essential when a diagnosis of sepsis is less obvious, as measurement of CRP is rapid and results have high sensitivity and specificity for sepsis, which range from 75-97% and 73-80% respectively (18, 96). This should be combined with clinical signs to diagnose sepsis (47). A variety of cutoff values for CRP suggest that the underlying inflammation depends on the primary pathophysiologic condition (96). The use of CRP for guided-antibiotic therapy is a safe method for determining the duration of antibiotic administration, as it was conducted on neonates, with no difference in mortality or relapse rates observed, compared to neonates not following the CRP-guided therapy (52). In a study conducted by P´ovoa and colleagues, CRP values correlated well with the severity of the infection. With a cutoff of 8.7 mg/L, the sensitivity and specificity of CRP for diagnosing infection were 93.4% and 86.1%, respectively. The specificity increased to 100% if CRP was combined with a temperature >38.2 ^{o}C (97). CRP is also advantageous for the diagnosis of postoperative infections, and various studies have shown that CRP levels of 190 mg/L on postoperative day 3 or greater than 140 mg/L on postoperative day 5 have a sensitivity of 66-82% and a specificity of 77-86% for infection (98, 99). The importance of utilising biomarkers, such as CRP, to guide antibiotic therapy lies in preventing further antibiotic resistance from occurring due to extended antibiotic use, as well as reducing mortality due to delayed antibiotic prescription during sepsis (40, 47, 100). The high risks associated with untreated infections in patients lower the threshold for prescribing of antibiotic treatment (101).

1.6.7. Limitations of CRP as a biomarker

CRP as a biomarker lacks specificity, due to CRP levels rising during burn injuries, cardiovascular disease, and malignancy, which limits the use of CRP as a sepsis biomarker (42, 102). It is useful in distinguishing between infection and inflammation if the levels are significantly elevated, but levels between 1 mg/L and 10 mg/L can be challenging to accurately interpret (National Library of Medicine, 2025). Questions remain regarding the predictive value, sensitivity, and specificity of CRP in diagnosing infection in ICU patients, especially in those receiving specific treatments such as glucocorticoids or statins (47, 103). There is often overlap in CRP levels between patients in the general hospital population with bacterial and non-bacterial infections, making it challenging to distinguish between them. However, CRP may be of greater use in distinguishing between critically ill populations (ICU

patients) (40, 96). False results are a possibility during CRP analysis in cases involving infections from multiple pathogens or those with more than one transformed bacterial colony. This will trigger false results for the direct pathogenic organism responsible for the infection, or in cases where the patient is vulnerable, more than one pathogen may be the cause of the final condition (42). False results are also triggered if there is a CRP single-nucleotide polymorphism, even though the CRP levels may have notable concentrations (51). CRP may not predict infections due to less virulent pathogens, and possibly in healthier individuals (104). Deirmengian et. al. demonstrated that the overall false-negative rate of the synovial fluid CRP test is reduced at lower diagnostic threshold levels of 3 mg/L. However, there was still a 15.6% possibility of false negative testing results in association with less-virulent organisms (104). Lowering the threshold level of any diagnostic test invariably increases the rate of false-positive testing and is unfavourable to test specificity (104). While CRP is often elevated in various diseases, its prognostic value can be limited in specific contexts, such as psychiatric disorders, where the relationship between CRP levels and clinical outcomes is still not fully understood (105). Dysregulated activation of the complement pathway, mediated by CRP, has been observed in some psychiatric disorders, such as schizophrenia and depression (105-107). CRP levels fluctuate with various underlying medical conditions or other factors that may result in a high serologic load as it is a non-specific marker. This suggests that CRP test results should be evaluated in conjunction with other potential critical biomarkers for the accurate diagnosis of a disease and not act as the sole factor for a diagnosis (51).

1.6.8. CRP in neurological conditions

CRP levels above 3 mg/L are an independent predictor of adverse outcomes one year post intracerebral haemorrhage (108). Elevated CRP and IL-6 have also been shown to be a marker for the development of white matter injury in preterm infants with a foetal inflammatory response (51). CSF CRP was discovered to be associated with motor and non-motor severity in Parkinson's disease as well as cognitive impairment in Alzheimer's disease (51). CSF CRP can differentiate between bacterial and viral central nervous system (CNS) infections, and is correlated to aggressive behaviour in individuals with a personality disorder (109, 110).

1.6.9. CRP in bacterial infections

A diagnosis of bacterial infections is confirmed with a positive blood culture result as well as elevated CRP levels. In various studies, a CRP level of greater than 40 mg/L is frequently cited as a useful cutoff for identifying bacterial infections (111). In paediatric emergency departments, CRP cutoffs varied by age group for identifying bacteraemia: 30 mg/L for ages 0 to 1 year, 45 mg/L for 1 to 3 years, and 50 mg/L for 12 to 18 years (112). Serious bacterial infections (SBIs) are caused by the invasion and multiplication of harmful bacteria within the body and can lead to life-threatening complications if not appropriately treated, which can cause highly elevated CRP levels. Categorisation of SBIs includes pneumonia, urinary tract infections, bacteraemia/bloodstream infections, intra-abdominal infections

and skin and soft tissue infections. SBIs can be caused by antibiotic-susceptible and antibiotic-resistant bacteria, thereby developing antimicrobial resistance which poses a threat for the successful treatment of SBIs. Common symptoms in children include breathlessness (80%), poor feeding (75%), irritability (75%), and weight loss (92%).

The majority of patients with culture-positive infections and serious bacterial infections typically require a more extended hospital stay to complete the antibiotic course and recover from other co-morbidities (113). If the patient had previous hospitalisation, this increases the risk for a severe bacterial infection by 3 up to 15-fold (113, 114). For differentiating bacterial pneumonia from non-bacterial pneumonia in children aged 1-5 years, a CRP cutoff of 36 mg/L was predictive of bacterial pneumonia with a sensitivity of 61.8% and specificity of 91.3% (115). Leboueny and colleagues found that the CRP levels in patients with TB corresponded with those of bacterial infection and decreased after four weeks following anti-TB treatment (116). The organism responsible was *Mycobacterium Tuberculosis* (*Mtb*), and CRP levels dropped with *Mtb* load. Various studies have shown CRP to have a good screening performance for active pulmonary tuberculosis in both HIV-positive and negative patients (116-119). Once the trigger for the bacterial infection is removed, CRP levels decrease rapidly (52, 120). CRP values are reliable to rule out bacterial infections when CRP has two values of less than 10 mg/L taken 8-12 hours apart (51).

1.6.10. CRP in viral infections

Common viral infections in children include the flu (Influenza virus), respiratory syncytial virus, bronchiolitis, and chickenpox, with symptoms such as a blocked or runny nose, a sore throat, vomiting, diarrhoea, and a loss of appetite, among others (Royal Children's Hospital Melbourne, 2025). In viral infections, CRP levels tend to be lower compared to those in bacterial infections, and in uncomplicated infections, CRP levels typically increase to approximately 20 mg/L (111). Interferons (IFNs) are part of a group of cytokines that are involved in upregulating the immune response. Interferons are essential in combating viral infections but also play a crucial role in tumour suppression, upregulation of Major Histocompatibility Complex (MHC) Class 1 and 2, signal transduction, and activation of immune cells, including natural killer cells and macrophages (121). Interferon-α may inhibit CRP production from hepatocytes which results in lower CRP levels compared to bacterial infections (40). A study conducted by Wang et. al. found that the presence of viral infections, such as human rotavirus, was associated with elevated CRP levels. Mixed infections were also noted, which could complicate the interpretation of CRP levels (122). In uncomplicated viral infections, CRP levels usually increase up to around 20 mg/L (111). Other inflammatory markers, such as interleukin-6 (IL-6) and serum amyloid A, were also elevated in children with viral infections, suggesting a broader inflammatory response that could influence CRP levels (123). Chow et. al. reported that a relatively elevated CRP level of 6-20 mg/L was more likely to be associated with a viral than non-viral upper respiratory tract infection, and a higher CRP level of 21-40 mg/L was more indicative of an influenza infection (124). Severe cases of COVID-

19 develop a hyperinflammatory response, leading to dysfunction of innate host defence systems, including cytokine release syndrome (cytokine storm) and multiple organ failure. Tan et. al. reported significantly elevated levels of CRP in the early stages of COVID-19 disease (10 and 20 mg/L), with levels correlating with the severity of the disease (125). If the levels increase further, this can lead to irreversible tissue damage related to the response to the viral infection.

1.6.11. CRP in fungal infections

There is limited data available for CRP in the context of fungal infections, and it usually affects immunocompromised patients, such as those undergoing chemotherapy or with hematologic malignancies (126). Candida species are common pathogens, with specific isolates, such as *Candida albicans,* frequently identified. A single-centre study of immunocompromised patients showed that CRP levels were elevated at 112–269 mg/L in the invasive fungal infections, but to a lesser degree than in patients with bacteraemia (CRP range 160–387 mg/L) (40, 127). A study by Martini et. al showed that a CRP cutoff of 100 mg/L helped distinguish bacterial from fungal infection, with a sensitivity of 82% and specificity of 53% for post-surgical patients at high risk of fungal infection (128).

1.7.Thesis Structure

This thesis contains three chapters as follows:

Chapter 1: Introduction consists of the background, rationale, research question, aims and objectives, literature review, methodology, and statistical analysis

Purpose: This section provides detailed information regarding hydrocephalus aetiologies, a ventriculoperitoneal (VP) shunt, the origin of the infection (meningitis), as well as the utilisation and characteristics of C-reactive protein (CRP) for monitoring purposes. Information regarding the use and importance of CRP is focused on in the literature review, which helps further the understanding of the importance of each objective. Chapter 1 introduces the study by outlining the research objectives and identifying the key areas of importance that form the foundation for the data collection process and the more detailed analysis

Chapter 2: Main manuscript following the specific layout and structure specified in the selected journal for publication (BMJ Paediatrics Open). Consisting of the abstract, introduction, methods, statistical analysis, results, discussion, and conclusion with recommendations.

Purpose: This chapter aims to provide answers to each of the objectives with the data collected and provide a comprehensive analysis of the information using literature to reach a viable conclusion. It served to identify whether CRP would be a valuable marker for antibiotic duration monitoring in children with a VP shunt infection

Chapter 3: Synthesis

Purpose: Summarises the overall aim and integrates the main findings of the manuscript to showcase the importance of the results and how each finding is linked to the overall aim and subsequent conclusion. It also includes recommendations for future studies. The synthesis highlights the conclusion that CRP can be used to monitor antibiotic administration duration. However, it is recommended that CRP levels be recorded over a longer period of time and monitored consistently in order to make an accurate deduction of antibiotic duration, as well as used in conjunction with other diagnostic factors.

CHAPTER 2: MANUSCRIPT

This manuscript has been submitted to the BMJ Paediatrics Open journal.

Manuscript ID: bmjpo-2025-004357

Chapter 1 included a literature review discussing the importance of CRP and its various roles in diagnosis and inflammatory monitoring in a variety of biological aspects. This chapter directly responds to the aims and objectives and utilises the literature to understand and interpret findings and present it comprehensively.

The manuscript titled “Role of C-reactive protein response to antibiotic therapy in children with a ventriculo-peritoneal shunt infection” follows the structural and content guidelines set out in the BMJ Paediatrics Open journal.

Role of C-reactive protein response to antibiotic therapy in children with a ventriculo-peritoneal shunt infection

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Abstract

Background: A ventriculoperitoneal (VP) shunt insertion is the main treatment involved in cerebrospinal fluid (CSF) management but is commonly associated with infectious complications, such as meningitis. Central nervous system (CNS) infections adversely impact the quality of life in children, increase healthcare costs, and may result in long-term neurological sequelae. C-reactive protein (CRP), an acute-phase biomarker that rises rapidly in response to inflammation, may present as a valuable indicator for monitoring VP shunt infections. The study aims to evaluate the utility of CRP in assessing the response to antibiotic therapy in paediatric VP shunt infections.

Methods: This retrospective study was conducted in the Neurosurgery department at Inkosi Albert Luthuli Central Hospital (IALCH) with data collected between January 2018 and December 2024. CSF biochemistry, culture results and clinical presentation was obtained from paediatric patients diagnosed with meningitis secondary to VP shunt sepsis.

Results: A total of 147 children were diagnosed, of which, 51.7% were infants with the lowest CRP at admission (34.7 mg/L). Boys (n = 84; 57.1%) were the majority, but they presented with lower mean CRP (43.4 mg/L, IQR= 4-53) compared to girls (54.5 mg/L, IQR = 4-90). Vancomycin was commonly used (27.9%) with a mean administration length of 27 days. When correlating antibiotic duration with mean CRP and WCC levels, the lowest points were at 21 and 30 days (24 mg/L and 8.4 $x10^9$/L respectively). The CRP and WCC decline after 14 days showed statistical significance between admission and day 30 (48.6 mg/L to 29.4 mg/L) ($p = 0.02$).

Conclusion: Although CRP-guided antibiotic management appears workable, the findings highlight the need for continued evaluation before CRP can be adopted as the main determinant of therapy duration. The study contributes to the expanding evidence base supporting CRP use in VP shunt infection management and associated reductions in infant mortality.

Key messages

What is already known on this topic: VP shunt insertions have a 30% infection rate with a 10-58% bacterial meningitis mortality rate. CRP levels rise relative to bacterial load, and levels exceeding 50 mg/L indicate an acute bacterial infection (VP shunt infection).

What this study adds: Supports that CRP monitoring can inform antibiotic decisions during combined management based on a consistent decline. The complicated nature of biofilm-forming bacteria and its role in prolonging CRP elevation. Illustrates the high-risk factors associated with unfavourable outcomes in paediatric meningitis.

How this study might affect research practice or policy: Highlights the practicality of biomarker-guided antibiotic therapy for promoting more objective and consistent treatment decisions. The findings

encourage the integration of biomarker-guided protocols into paediatric neurosurgical infection management guidelines, particularly in resource-limited settings, and highlight risk factors to be cautious of in future clinical settings/research.

Introduction

Pediatric hydrocephalus occurs due to disruption of cerebrospinal fluid (CSF) production or absorption, leading to ventricular enlargement and increased intracranial pressure [1]. It is often associated with congenital conditions such as neural tube defects, occurring in 70-90% of patients, or acquired causes including tumours, CNS infections, and intraventricular haemorrhage [2, 3]. Among neurosurgical options for hydrocephalus, ventriculoperitoneal (VP) shunt implantation continues to be the most widely used with alternative interventions, such as an endoscopic third ventriculostomy, used in selected cases of obstructive hydrocephalus [4, 5]. Modern shunts consist of subcutaneous tubing connecting the ventricles to the peritoneum via a valve, often with flow-regulating mechanisms to prevent overdrainage [6]. Despite their widespread use, VP shunts carry significant complication rates, reported between 6% and 50% in developing countries [7]. Mechanical failure is common, particularly in the first two years, with obstruction at the proximal or distal catheter. Long-term shunt failure occurs in 30% of cases within the first year, and 10% annually thereafter (3), and mortality rates of 5-10% have been reported up to 30 years post-shunt insertion [6].

Shunt infections remain a significant source of morbidity, accounting for 10-15% of revisions and contributing to extended hospital stays and inflated healthcare costs [8]. Infection rates vary globally, ranging from 4-12% in high-income countries to 3-30% in low and middle-income countries [7, 9, 10]. Most infections are caused by intraoperative contamination, with *Staphylococcus aureus* being the most common pathogen cultured, along with *Escherichia coli,* and *Staphylococcus pneumoniae* being present in 90% of infants and children in Africa [11]. Clinical manifestations include fever, vomiting, irritability, poor feeding, bulging fontanelle, or swelling over the shunt [11-13]. Management involves shunt removal, temporary external ventricular drainage, and culture-guided antibiotics, with mortality rates within the first year ranging from 5.5% to 32.1% [4, 14].

Optimising infection management is challenging due to uncertainty regarding the appropriate duration of antibiotic therapy. Prolonged empiric treatment increases the risk of adverse drug effects, disruption of the paediatric microbiome, and antimicrobial resistance [12, 15, 16]. C-reactive protein (CRP) is an acute-phase reactant produced by the liver that rises sharply following infection, peaks within 48-72 hours, and declines following infection resolution or improving inflammatory conditions [15, 17, 18]. CRP levels exceeding 10 mg/L indicate the presence of an infection, whilst levels >50 mg/L show signs of a severe acute bacterial infection, such as a VP shunt infection. CRP levels show the balance between immunological status and microorganism presence, which, therefore, can assist in determining the duration of antibiotic therapy in children. Persistently elevated CRP levels can indicate ongoing

infection or complications and may guide further antibiotic therapy [12, 15]. Although CRP is widely used in paediatric infectious diseases, evidence supporting its role in neurosurgical infections, particularly VP shunt infections, remains limited.

This study aims to evaluate the utility of CRP monitoring in children with VP shunt infections, to improve early detection, determine antibiotic duration, reduce morbidity, and inform clinical decision-making. By establishing CRP as a reliable biomarker for infection progression and antibiotic duration, this research could enhance paediatric outcomes, minimize unnecessary antibiotic exposure, and contribute to more effective, evidence-based management strategies in paediatric neurosurgery.

Methods

Study design and setting

This retrospective study was conducted in the Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital (IALCH). IALCH is a tertiary and quaternary hospital located in Durban, KwaZulu Natal. It serves as a specialised referral centre, servicing patients from KwaZulu Natal as well as referrals from the Eastern Cape. Routine healthcare data obtained from Meditech ® software between January 2018 and December 2024. A training course was held at IALCH for operation of the database. Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC/00006910/2024, BCA219/15). Informed consent was waived due to the retrospective design, with data analysed from existing medical records under secure conditions.

Case selection

The sampling technique used to determine the sample size was purposive sampling. Paediatric inpatients (0-18 years) diagnosed with meningitis secondary to VP shunt infection were included. Patients with shunt malfunction unrelated to infection or without clinical/laboratory evidence of meningitis were excluded. The patient codes were obtained from an already categorised Microsoft Excel datasheet containing patient diagnoses.

Data collection

Data was extracted from secure hospital information systems and coded into an Excel spreadsheet before analysis. This includes demographics, hydrocephalus aetiology, clinical presentation, symptom duration, haematology, biochemistry, CSF analysis, culture results, and CRP levels at admission and days 3, 5, 7, 14, 21, and 30. CRP <10 mg/L was considered normal (Annexure C). The extended Glasgow outcome scale (GOSE) was used to categorise patients at discharge.

Infection parameters

A VP shunt infection was defined by a positive CSF culture or organism identified on a gram stain, clinical signs (fever, irritability, neurological deficits), and typical biochemical findings (elevated WBC >10.6 x10^9/L, elevated CSF protein at >0.4 g/L, low CSF glucose <2.5 mmol/L). Infection resolution/clearance required negative CSF culture results, normal temperature (36.5–37.5°C), CRP <3 mg/L, WBC <3.9 ×10^9/L, and absence of new symptoms post-antibiotic therapy.

Statistical analysis

IBM SPSS Statistics software version 29.0 was used for data analysis. All data were normally distributed, aside from the continuous data (laboratory results), which suggested the optimal way to present the data was using the median. This method, however, did not show an accurate representation of the elevated laboratory results, specifically C-reactive protein levels; therefore, the mean values were utilised instead. Descriptive statistics were used to generate the IQR and mean values for continuous variables. Associations between continuous variables were assessed using one-way analysis of variance (ANOVA). Mean values were utilised to generate graphical representations of the laboratory results over the admission period. Mann-Whitney or Kruskal-Wallis tests were conducted to compare values for unequally distributed data, and a two-tailed independent samples t-test for normally distributed variables to test for statistical significance. Statistical significance was determined using Fisher's exact test for the analysis of categorical variables over the duration of the infection, and significance was represented by p <0,05. Correlation coefficients were generated to test the association between two variables, with the Pearson test used for equally distributed continuous data and the Spearman rank test for unequally distributed categorical data. The test was primarily used to observe any correlations between laboratory results, as well as the microorganisms cultured, and other factors suspected of being associated with extended infection resolution time or patient death. Multivariate analysis was utilised to identify factors associated with >30-day infection resolution at 95% CI.

Results

Demographics, aetiology and CRP in relation to infection characteristics

A total of 147 patients were diagnosed with shunt-related meningitis and met the inclusion criteria. In routine care, antibiotics and surgical source control co-occur; CRP trends are therefore interpreted as responses to combined management. The aetiology of hydrocephalus in children diagnosed with VPS infection is listed in Table 1. The majority (n = 76; 51.7%) of children were infants (age < 1 year), while the rest were aged 1 to 6 years (n = 45; 30.6%), 7 to 12 years (n = 14; 9.5%) and > 12 years (n =12; 8.2%). The mean admission CRP per age group is presented in Table 2. The admission CRP was lowest

in infants (p = 0.09) and highest in children > 12 years of age (p = 0.06). The p values show no statistical significance which indicates no correlation between age and elevated admission CRP levels.

Table 1: Aetiology of hydrocephalus in children diagnosed with VPS infection

Aetiology	n	%
Congenital	71	48.3
Infection	30	20.4
Intraventricular haemorrhage (IVH)	18	12.2
Brain tumour	17	11.6
Myelomeningocele	11	7.5

Table 2: Mean admission CRP level per age group

Age group (years)	n (%)	Mean CRP (IQR)	p value
<1	76 (51.7%)	34.7 (4 – 35.5)	0.09
1-6	45 (30.6%)	57.8 (4 - 108)	0.6
7-12	14 (9.5%)	55.1 (4 – 92.3)	0.6
>12	12 (8.2%)	93.2 (4 - 159)	0.06

IQR = interquartile range; CRP= mg/L

The majority of children were boys (n = 84; 57.1%), while the rest were girls (n = 63; 42.9%). Boys presented with a lower mean CRP (43.4 mg/L, IQR = 4-53) when compared to girls (54.5 mg/L, IQR = 4-90) p = 0.1.

Table 3 highlights the time to VPS infection presentation and mean CRP levels, which is also depicted graphically in Figure 1. A correlation analysis was conducted to determine whether the time to infection from a previous shunt insertion had an effect on elevated CRP levels at admission. There was no statistical significance identified (p > 0.05).

Table 3: Time to VPS infection and median CRP

Time to infection (days)	n (%)	Mean CRP (IQR)	p value
< 14	83 (56.5%)	46 (4 - 70)	0.6
14 – 30	39 (26.5%)	63 (4 – 79)	0.3
31 – 90	19 (12.9%)	27.6 (4 - 33)	0.9
>90	6 (4.1%)	45.8 (4 - 84)	1

IQR= interquartile range

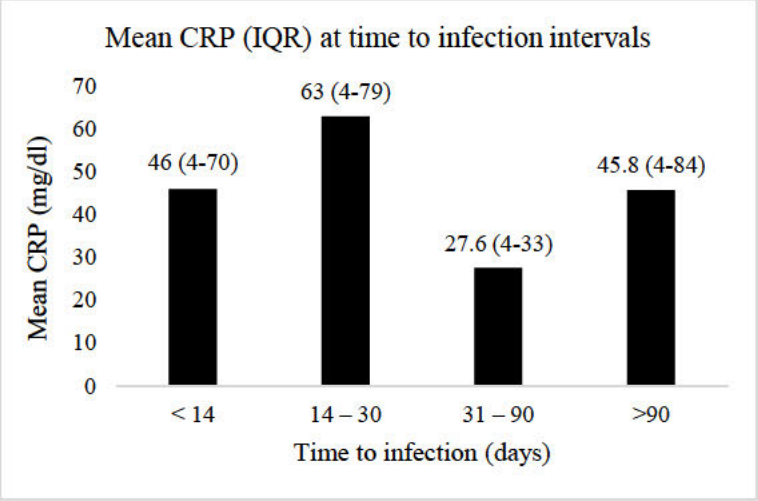

Figure 1: Mean CRP (mg/L) and IQR for each time to infection interval

Table 4 describes the duration of VPS infection symptoms and mean admission CRP, showing elevated CRP levels in children with VPS infection symptoms of >30 days. The p values of 0.9 and 0.8 indicate statistically that the CRP levels did not significantly differ across the different time intervals for duration of symptoms ($p > 0.05$).

Table 4: Duration of VPS infection symptoms and mean CRP levels

Duration of symptoms (days)	n (%)	Mean CRP (IQR)	p value
<7	78 (53.1%)	48.5 (4 – 77)	0.2
7-30	59 (40.1%)	46.8 (4 – 58.5)	0.2
>30	10 (6.8%)	52.9 (3.5 – 96.8)	0.8

IQR= interquartile range; p values >0.05 show no correlation between elevated CRP levels and the time taken for symptoms to appear

Patient clinical and biochemical profile

The commonest clinical presentation of children with VPS infection was vomiting (n = 44; 29.9%) and seizures (n = 25; 17%). The rest of the clinical symptoms are presented in Table 5.

Table 5: Clinical symptoms associated with VPS infection

Clinical symptom	n	%
Vomiting	44	29.9
Seizures	25	17
Poor feeding	20	13.6
Irritability	19	12.9
Headache	19	12.9
Fever	12	8.2
Neck stiffness (meningism)	6	4.1
Other	28	19

Other = abdominal pain (2), body weakness (5), unsteady gait (9), abdominal distension (3), lethargy (7), occipital ulcer (1), hemiparesis (1)

The biochemical profile of children diagnosed with VPS infection is presented in Table 6.

Table 6: The admission biochemical profile of children diagnosed with VPS infection

Variable	n	%	Mean CRP (IQR)	p value
WCC				
Mean (IQR)	12 (8.1- 15.2)			
< 3.9	6	4.1	47.6 (4 – 121.5)	0.8
3.90 – 12.6	89	60.5	49 (4 – 33.5)	0.7
>12.6	52	35.4	47.5 (4 – 112.5)	0.7
Haemoglobin				
Mean (IQR)	10.8 (9 – 11.9)			
<8	17	11.6	40.2 (14-157)	0.5
8-10	40	27.2	53 (4 – 83.5)	0.3

>10	65	44.2	46.6 (4 – 38.3)	0.2
PLT				
Mean (IQR)	477 (334-609)			
<150	5	3.4	44.6 (4-157)	0.9
150 – 450	66	44.9	49.1 (4 – 34.5)	0.9
>450	76	51.7	47.6 (4 – 83.5)	0.9
Sodium				
Mean (IQR)	136.4 (133-140)			
<135	54	36.7	61.3 (4-92)	0.3
135-145	87	59.2	42.7 (4 – 39.5)	0.5
>145	6	4.1	8.3 (3.2 - 16)	0.2
Potassium				
Mean (IQR)	4.8 (4.4-5.3)			
<3.5	5	3.4	25.6 (4-16)	0.7
3.5-5.1	94	63.9	45.2 (4 – 54.5)	0.6
>5.1	48	32.7	57.5 (4 – 73.8)	0.5
Urea				
Mean (IQR)	3.3 (2.2-4)			
<1.5	4	2.7	33.3 (6 – 64.8)	0.9
1.5-5.5	129	87.8	48 (4 – 66)	0.9
>5.5	14	9.5	52.9 (4 – 105.8)	0.9
Creatinine				
Mean (IQR)	27.3 (17-33)			
<40	124	84.4	48.6 (4 – 72.5)	0.7
40-80	22	15	47.6 (4 – 58.5)	0.8

>80	1	0.7	4 (156 - 156)	0.4

**WCC = white cell count (x10^9/L); HB=Haemoglobin(g/dL); PLT= Platelets (x10 9 /L); Sodium (mg/L); Potassium (mmol/L); Urea (mmol/L); Creatinine (umol/L); CRP= C-Reactive Protein (mg/L)*

The CSF results are presented in Table 7. The biochemical factors had p values >0.05 which indicates statistically that the categories above did not result in any significant difference in CRP levels at admission.

Table 7: Admission CSF results of children presenting with VPS infection

Variable	n	%	Mean CRP (IQR)	p value
CSF Glucose				
Mean	2.6 (1.8 – 3.5)			
<2.5	70	47.6%	42 (4 – 98.5)	0.8
2.5-4	61	41.5%	52.7 (4 – 33.5)	1
>4	12	8.2%	57 (4 – 140.5)	1
CSF protein				
Mean	2.2 (0.2 – 2.2)			
<0.15	22	15	68 (4 – 34)	0.5
0.15-0.4	26	17.7	38.9 (4 – 50)	0.9
>0.4	95	64.6	45.5 (4 – 79)	0.6

** Glucose (mmol/l); Protein (g/L)*

Microbiology, antibiotic therapy and inflammatory marker trends

The commonest organism cultured from the CSF was *Staphylococcus epidermidis* (n = 38; 25.9%). The rest of the organisms responsible for VPS infection are presented in Table 8.

Table 8: Organisms cultured from the CSF of children with VPS infection

Organism	n	%
Staphylococcus epidermidis	38	25.9
Staphylococcus aureus	31	21.1
Klebsiella pneumoniae	12	8.2

Staphylococcus species	11	7.5
Acinetobacter baumannii	8	5.4
Staphylococcus haemolyticus	8	5.4
Staphylococcus capitis	6	4.1
Enterococcus faecium	6	4.1
Pseudomonas aeruginosa	5	3.4
Candida species	3	2
Enterococcus faecalis	3	2
Enterobacter clocae complex	2	1.4
Staphylococcus xylosus	2	1.4
Staphylococcus saprophyticus	2	1.4
Corynebacterium species	2	1.4
Streptococcus agalacticiae	1	0.7
Sphingomonas pacimobilis	1	0.7
Proteus mirabilis	1	0.7
Escherichia coli	1	0.7
Rhizobium radiobacter	1	0.7
Staphylococcus pseudointermedius	1	0.7
Stenotrophomonas maltophilia	1	0.7
Streptococcus pneumoniae	1	0.7

Figure 2 shows a box plot of the CRP per organism cultured from the CSF of children with VPS infection. *Sphingomonas pacimobilis* had the highest mean CRP levels (198 mg/L; IQR = 198 - 198) whilst *Proteus mirabilis* had the lowest median CRP levels (4 mg/L; IQR = 4-4), followed by *Enterococcus faecium* (7.5 mg/L; IQR = 4-9.3).

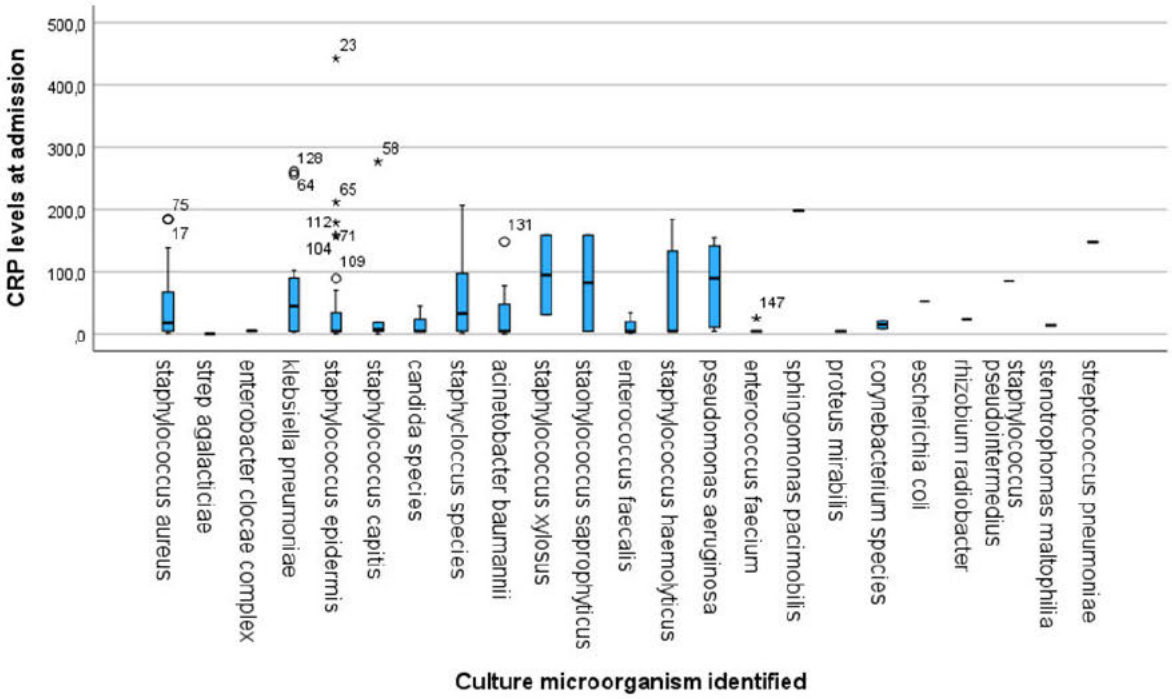

Figure 2: Boxplot graph of the CRP per organism cultured from the CSF of children with VPS infection

The most frequently used antibiotic was Vancomycin (27.9%). Table 9 presents the frequency of antibiotics used to treat infection and the mean CRP per day of antibiotic treatment. Eighty-six (58.5%) children were diagnosed with multidrug resistant organisms, while in 61 (41.5%) cases the culture was negative for resistance.

Table 9: Antibiotics administered to children with VPS infection and CRP levels over 30 day period

Antibiotic	n	%	CRP Day1	CRP Day 3	CRP Day 5	CRP Day 7	CRP Day 14	CRP Day 21	CRP Day 30	p value
Vancomycin	41	27.9	52.9	51.6	48.8	45.8	30.9	22.3	25.5	0.7
Ceftriaxone	12	8.2	57.7	72	157.5	53.6	15.5	22.5	35.8	0.7
Vancomycin & Ceftriaxone	26	17.7	31.4	40.2	25.6	20.3	24.1	32.8	26.9	0.6
Meropenem	13	8.8	59.2	47.9	53.6	51.1	42	22.2	39.4	0.6
Meropenem & Vancomycin	31	21.1	47.9	42.8	37.5	18.6	45.4	18.8	37.8	0.5

Meropenem & Ceftriaxone	4	2.7	58.5	5	20	10.8	88.7	38	46.6	0.9
Ampicillin	1	0.7	4	4	4	4	4	4	4	0.7
Ceftriaxone & Ampicillin	1	0.7	85.2	40.6	90.2	82.6	56.8	22.3	12.6	0.6
Cefotaxime	3	2	8.7	144.5	117.5	67.7	46	23.5	27.3	0.7
Fluconazole	2	1.4	4	49	67	4	4	7.5	4	0.8
Amoxicillin	3	2	68.7	150	86	38	52.3	33.7	22.5	0.9
Amikacin	1	0.7	4	4	4	4	30	9	15	0.7

Given right-skew and outliers, paired Wilcoxon signed-rank tests and median paired differences will complement parametric estimates. CRP distributions were right-skewed with outliers; paired inferences may be sensitive to these features, and we therefore interpret p-values with caution. The admission-to-day 30 comparison did not model repeated measures or adjust for missingness; thus the observed decline should be interpreted circumspectly. The mean length of antibiotic use was 27 days (IQR = 8 - 30). When correlated with the mean CRP and WCC (Figure 4), the CRP was at the lowest point at 21 days followed by WCC lowest level at day 30. Between admission and day 30, CRP decreased (48.6 to 29.4 mg/L); given skewed distributions and outliers, we interpret this reduction cautiously. A complete-case paired samples test indicated a difference between admission and day 30 CRP ($p = 0.02$). A complementary Wilcoxon signed-rank test performed on complete cases did not demonstrate a statistically significant median difference ($Z = -1.57$, $p = 0.117$), reflecting the skewed distribution of CRP values. To address non-normality, a paired t-test was also performed on log-transformed CRP values, which confirmed a significant decline over time ($p = 0.04$). CRP measurements at both admission and day 30 were available for n = 106 patients

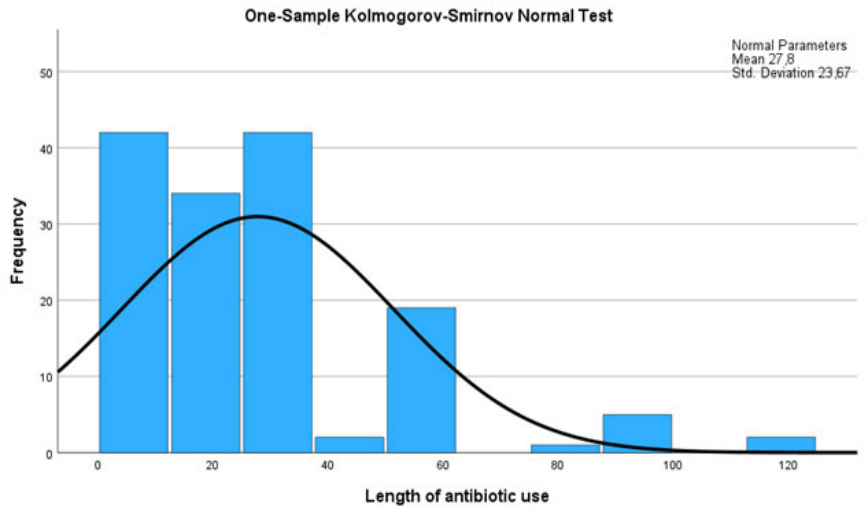

Figure 3: Distribution graph for length of antibiotic administration (days)

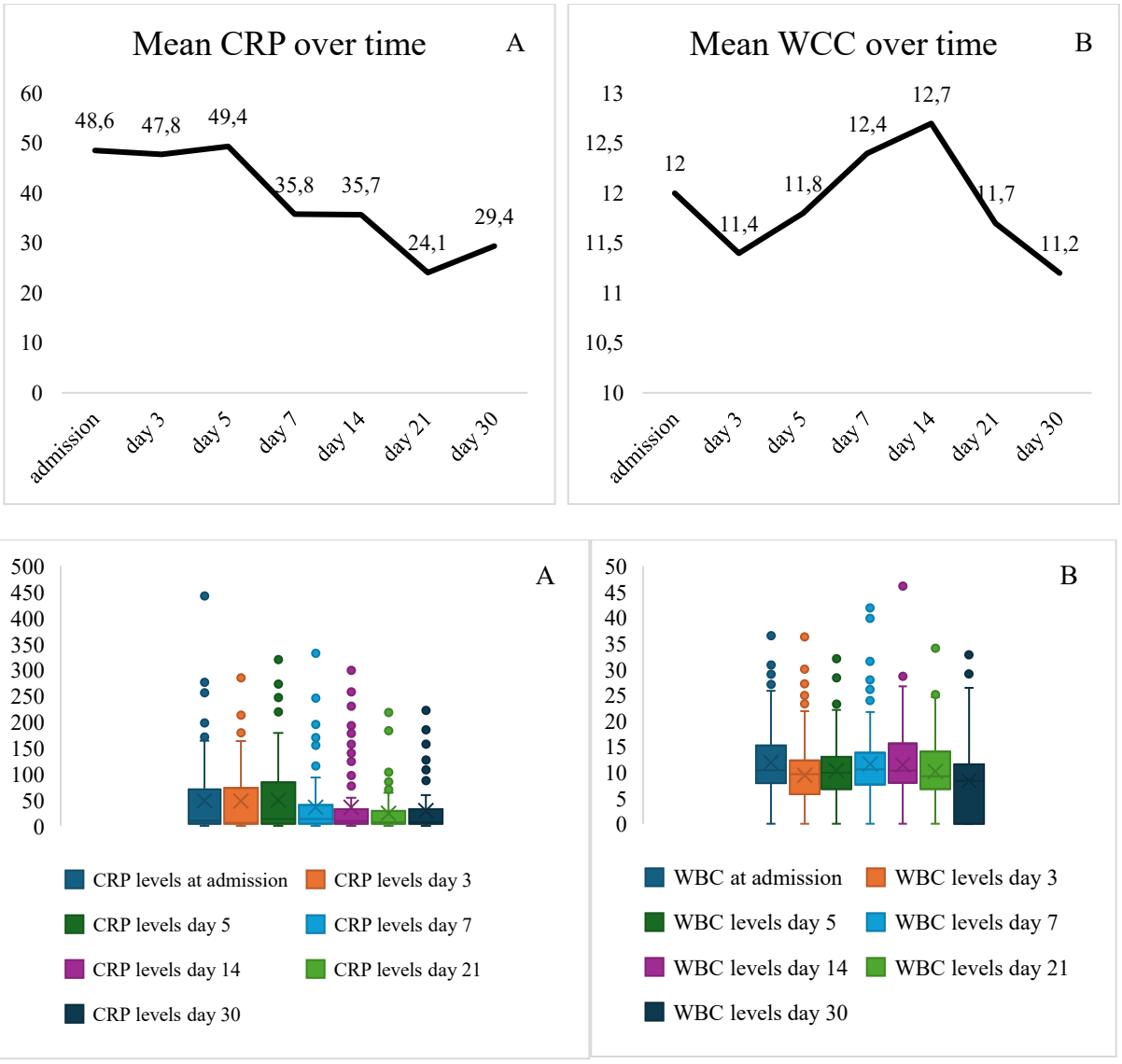

Figure 4: Line graph and boxplot showing CRP (A) and WCC (B) levels over 30 days

Patient mortality

Twenty-five (17%) children diagnosed with a shunt infection died. The mean admission CRP was 41.4 mg/L (IQR 2.5 - 60.5). The majority (48%) of children had CRP greater than 10 mg/L.

Table 10 highlights the deceased children and shows that majority had elevated CRP levels (>10 mg/L) at admission and remained high at the time of death as well as having 7-30 days of symptoms being a predictor of mortality ($p = 0.05$). Table 11 shows the factors that place patients at higher risk of death in the study, based off $p < 0.05$ from a binary logistic regression analysis. In both tables, patients aged >12 years old is highlighted as a factor that can be associated with a higher risk of death (odds ratio = 8; 95% CI).

Table 10: Details of children who died

Variable	n = 25 (%)	Mean CRP at admission (IQR)	Mean CRP at death (IQR)	p value
CRP				0.06
< 10	13 (52%)	3.5 (0.9 – 6.5)	71.6 (27 - 144)	
10- 50	4 (16%)	27.8 (16 – 42.3)	87.1 (23.8 – 201)	
>50	8 (32%)	109 (56.8 – 172)	94 (21.5 – 126.3)	
Age				
<1	11 (44%)	10.5 (2 - 16)	116 (26 - 211)	0.2
1-6	4 (16%)	71 (11.5 – 150.5)	50.8 (11 – 106.8)	0.5
7-12	3 (12%)	17.6 (4 - 47)	30.7 (28 - 32)	0.2
>12	7 (28%)	83.1 (10 - 155)	88 (41 - 127)	0.03
Sex				
Male	14 (56%)	39.5 (3.8 – 56.8)	81 (28.5 – 137.8)	0.9
Female	11 (44%)	43.6 (1 - 92)	95.5 (26 - 206)	0.3
Time to infection (days)				
< 14	14 (56%)	24.4 (1.8 – 52.3)	95.4 (25 – 180.5)	0.9
14 – 30	8 (32%)	78.4 (1.6 – 172.3)	65.9 (20.5 - 87)	0.6
31 - 90	2 (8%)	10 (4 - 28)	60 (55 - 127)	0.9

91 - 180	1 (4%)	45 (45 - 45)	206 (206 - 206)	0.9
Duration of symptoms (days)				
< 7	4 (16%)	103(20.5 – 182.5)	26.8 (11 – 53.2)	0.9
7 – 30	18 (72%)	28.8 (1 – 52.3)	108 (33.5–190.3)	0.05
>30	3 (12%)	34.7 (34 - 79)	45 (22 - 87)	0.2
Organism cultured from CSF				
Staph. epidermidis	4 (16%)	48.8 (1.8 - 136)	133 (23 - 240)	0.3
Staph. aureus	6 (24%)	51 (4.7 - 115)	50 (24 – 80.5)	0.9
Klebsiella pneumoniae	4 (16%)	26.3 (3.3 - 51)	129 (60.5 – 199)	0.3
Staph. species	3 (12%)	23.7 (4 - 10)	52.3 (11 - 124)	0.6
Acinetobacter baumannii	2 (8%)	8 (47 - 159)	108.5 (32 - 185)	0.7
Staph. haemolyticus	2 (8%)	49.5 (34 - 211)	149 (87 - 211)	0.7
Pseudomonas aeruginosa	1 (4%)	155 (155 - 155)	87 (87 - 87)	1
Enterococcus faecalis	2 (8%)	17.5 (1 - 23)	25.5 (10 - 41)	0.1
Escherichia coli	1 (4%)	52 (52 - 52)	32 (32 - 32)	1
WCC				
<3.9	1 (4%)	10 (10 - 10)	50 (50 - 50)	0.9
3.9 – 12.6	16 (64%)	58.6 (3.8 – 94.3)	81 (20.5 – 126.3)	0.7
>12.6	7 (28%)	4 (4 - 16)	65 (26 - 211)	1
HB				
<8	1 (4%)	4 (4 - 4)	55 (55 - 55)	0.6
8-10	8 (32%)	42.6 (4.5 – 64.3)	91.8 (28 – 165.3)	0.4
>10	16 (64%)	43 (1 - 82)	87.5 (23.5 – 171)	0.3
PLT				
<150	2 (32%)	100 (4 - 159)	101.5 (18 - 185)	0.1
150-450	14 (56%)	37 (1 - 74)	81 (31 – 124.8)	0.3
>450	9 (36%)	34.5 (6.5 – 43.5)	94 (20 – 200.5)	0.1
Na				

<135	8 (32%)	36 (4.5 – 47.5)	80 (17 – 180.3)	0.1
135 – 145	14 (56%)	27.5 (1.8 – 92.8)	82 (29.5 – 140)	0.8
>145	3 (12%)	16 (147 - 159)	65 (65 - 185)	0.05
K				
<3.5	6 (24%)	7 (3.8 - 16)	107(53.8–191.5)	0.002
3.5 – 5.1	14 (56%)	56.3 (1.8 – 92.8)	72.8 (25 – 124.8)	0.001
>5.1	5 (20%)	38 (0.5 – 92.6)	105 (12.5 - 234)	0.001
Urea				
<1.5	0	0	0	1
1.5 – 5.5	21 (84%)	27.9 (1.5 – 48.5)	90.1 (27 - 182)	0.3
>5.5	4 (16%)	111.8 (35 – 177)	74.3(29.8 - 117)	0.5
Creatinine				
<40	17 (68%)	7 (3.5 – 43.5)	55 (22 - 182)	0.002
40 – 80	6 (24%)	48.5 (1.7 – 92.8)	59.5 (26.5 - 147)	0.001
>80	2 (8%)	78 (1 - 156)	65 (41 - 156)	1
CSF glucose				
<2.5	14 (56%)	27 (3.8 – 36.8)	90 (20 – 190.3)	0.4
2.5 – 4	9 (36%)	54 (0.9 – 93.5)	90 (30 - 153)	0.8
>4	2 (8%)	77.5 (4 - 159)	59.5 (32 - 87)	1
CSF protein				
<0.15	5 (20%)	80.8 (31 - 125)	76.6 (41 - 107)	1
0.15 – 0.4	5 (20%)	38.6 (2 – 95.5)	108 (20 - 234)	1
>0.4	15 (60%)	29 (3 - 45)	84 (26 - 179)	0.9

*****Staph. = staphylococcus*

Table 11 presents factors associated with mortality after a multiple regression analysis. An odds ratio of 8.3 indicates that children older than 12 years are at greater odds of dying due to a VP shunt infection.

Table 11: Multiple regression analysis showing factors associated with mortality

Factor for mortality	n (%)	p value	Exp(B)	95% CI
Age >12	7 (58.3%)	0.002	8.3	[2.2; 30.8]
TB meningitis comorbidity	3 (75%)	0.03	5.7	[1.1; 28.1]
CRP >10mg/L at admission	12 (48%)	0.04	0.2	[0.06; 0.9]
Sodium >145 at admission	3 (50%)	0.05	5.8	[0.9; 33.7]

**Exp (B) = odds ratio; CI = confidence interval*

Discussion

This study focuses on the behaviour of C-reactive protein (CRP) during the antibiotic response in children diagnosed with a ventriculoperitoneal shunt (VPS) infection, particularly focusing on its diagnostic and monitoring value. Given the retrospective design and carriable follow-up, we prioritised simple, interpretable complete-case comparisons as an initial feasibility assessment. CRP peaks between 2 and 4 days and returns to normal within 7 days. White cell count (WCC) peaks within 24-48 hours after an infection has begun and remains elevated for a more extended period of time. For VP shunt infections, CRP rises to >50 mg/L, which is typically associated with severe acute bacterial infections and can take over a week or more to return to normal (<10 mg/L) [19]. The overall mean CRP admission level in this study is lower than that reported in other studies (48.6 mg/L). Schumann et. al. recorded a mean CRP level of 91.8 ± 70.2 mg/L in children with an infected shunt. The presence of the infection (meningitis) is confirmed by the elevated WCC correlating with elevated CRP levels (WCC>12.6 µmol/L; mean CRP = 47.5 mg/L) as well as elevated CSF protein levels (CSF protein >0.4 mg/L; mean CRP = 45.5 mg/L). Ahmed and colleagues also noted elevated CSF protein levels at 94.65 mg/L [20]. While both markers are useful, CRP showed earlier downward movement, suggesting it may be a more responsive indicator of improvement in the inflammatory process. CRP levels were elevated at admission (48.6 mg/L) and day 5 (49.4 mg/L) and proceeded to decline afterwards across the remainder of the admission period (day 30 = 29.4 mg/L). WCC followed a similar pattern whereby levels were elevated at admission (12 $x10^9$/L) but only had a steady decline after day 14 (day 30 = 11.2 $x10^9$/L). These levels did not, however, decrease drastically enough to levels that indicate bacterial infection clearance and took a longer time to return to normal levels (CRP <10 mg/L; WBC <3.9 $x10^6$/L). When an infection is detected, there is a rapid release of CRP. CRP functions as an acute-phase reactant, mainly induced by an inflammatory stimulus signal, mediated by interleukin-6 (IL-6) acting on the hepatic gene responsible for CRP transcription. CRP activates the C1q molecule in the fluid phase classical complement pathway to promote opsonisation of the pathogens. It also initiates cell-mediated pathways by engaging phagocytic cells via Fc receptors of IgG immune complexes to expedite the removal of pathogens [21]. The patient's hepatocytes consistently transcribe CRP due to the delayed clearance of the infection, as well as the complicated nature of the microorganism.

CRP is still elevated at day 5, which could be due to the peak immune response not occurring as yet (48-96 hours after the onset of the infection), with delayed astrocyte activation (22) as well as the antibiotic course not being administered yet. The reason for the slow decline in this study could be attributed to a complicated infection, individual immune system responsiveness, shunt replacement/temporary removal, or antibiotic resistance. Of the organisms cultured, the majority were resistant to one or more antibiotics (n = 86; 58.6%), with 59 (40.1%) being resistant to Cloxacillin. If the patient did not undergo a shunt revision/temporary removal and was only prescribed antibiotics, the

source of the infection remained, which would result in persistently high CRP levels, as seen in these findings. The mean length of antibiotic use is 27 days, and the majority of patients receive less than 40 days of antibiotic administration, indicated by the distribution graph. Given the skewed distribution of CRP values, complementary analyses were performed to assess the robustness of the findings. While the non-parametric Wilcoxon signed-rank test did not demonstrate statistical significance, analysis of log-transformed CRP values confirmed a significant decline over time. These findings suggest that the observed reduction in CRP is broadly consistent across analytical approaches, although variability and skewness in inflammatory marker data should be considered when interpreting the magnitude of change. The ANOVA analysis showed a statistical difference between the mean CRP at admission and day 30 ($p = 0.02$). This indicates that the inflammatory conditions have improved, evidenced by the significant decline in CRP levels from admission, although the decline does not necessarily indicate complete infection clearance. The duration of the decline is also supported by the generally accepted duration of antibiotics for infection, which are typically given for 14 days. Antibiotic administration on days 3 and 5 would result in a decline in CRP by day 21, which is close to the duration depicted in the distribution graph. These findings suggest that CRP levels can be used to predict the approximate duration of antibiotic use but cannot be the sole factor that determines the duration. CRP levels would need to be recorded consistently to accurately determine the antibiotic administration period, especially in cases involving more severe organisms or the possibility of resistance/inappropriate antibiotics being administered. Inappropriate/ineffective antibiotics could also be the reason for a spike in CRP/WCC during the admission period, followed by a prolonged decrease.

CRP levels at admission were generally elevated above the standard threshold for bacterial infection (CRP >10 mg/L). However, admission levels were lower than the common threshold for severe acute bacterial infections (CRP >50 mg/L), particularly among infants (age <1 year; n = 76; 51.7%), who made up more than half of the cohort. These levels do, however, increase by day 3 (mean = 51.7 mg/L; IQR = 4-70). Admission levels were lower than the CRP threshold for severe acute bacterial infection diagnosis but higher than the threshold for a bacterial infection diagnosis, confirming the role of CRP as a sensitive marker of inflammation. The slightly lower CRP levels upon admission does not rule out the presence of a VP shunt infection, as infant CRP levels fluctuate at birth due to physiological stresses, an immature immune system, as well as post-vaccination [23-25]. The reduced expression of complement and antimicrobial proteins and peptides likely contribute to a newborn's susceptibility to pyogenic bacteria [25]. These age-related characteristics likely contributed to the modest elevations in CRP seen at presentation. The CRP levels were paired with culture results and symptoms to confirm the diagnosis of the infection. Older children (>12 years) had the highest mean CRP levels at admission (93.2 mg/L; IQR= 4 - 159) as well as presented with a longer time to infection from last VPS insertion (mean = 29 days; IQR = 7-30). This aligns with recent findings stating that the greater the time to postoperative infection (within 30 days post-surgery), the higher the CRP levels [25]. This duration also

falls within the average timeframe for an early shunt complication to occur (0-2 months) [8]. These findings suggest that higher CRP levels at admission reflects the duration and progression of the infection and heightened inflammatory activity.

The significant presence of congenital hydrocephalus (n = 71; 48.3%) in this study correlates with the majority of the participants being infants and is a common finding in multiple studies [26, 27]. The development of the blood-brain barrier (BBB) begins in late gestation and continues through the postnatal period. It is a period of time of increased permeability that renders the developing brain more vulnerable. Developing cerebral vessels are more fragile and susceptible to drugs, toxins and pathological conditions, thus contributing to cerebral damage and neurological disorders later on [28]. Zaniel et. al. states a 7% incidence of hydrocephalus in children with an infection (meningitis), specifically neonates and infants, (29) which is higher in this study at 20.4%. A greater majority of the cohort were boys (n = 84; 57.1%); however, the girls had higher mean CRP levels at admission (54.5 mg/L, IQR = 4-90), but this showed no statistical difference. For young children, a systematic analysis conducted stated that the difference in CRP levels between boys and girls was negligible (30), a finding supported by the results of this study. Children who were admitted 14-30 days after the initial VPS insertion had the highest CRP levels upon admission (mean = 63 mg/L). This indicates a more immediate postoperative complication and is a typical timeframe for a VP shunt complication after insertion [32, 33]. Factors that influence a VP shunt infection include the younger age at which the shunt was placed, with congenital hydrocephalus patients having an increased chance of developing an infection [32, 33]. This association may be due to the underdeveloped humoral and cellular immune systems in infants, the immaturity of the skin barrier, and characteristics of the bacterial flora in this specific age group.

The most common symptom in this study was vomiting, especially diagnosed in infants (n = 21; 47.7%), followed by seizures and poor feeding, also common amongst the infant patients (n = 9; 36%, n = 11; 55% respectively). The occurrence of seizures in the study is lower than the overall rate of 37.4% in children with bacterial meningitis [34]. The mean CRP of 52.9 mg/L was the highest for children who had >30 days of symptoms before presenting for admission. Early intervention is crucial. For extended symptom duration, beyond 30 days, comprehensive shunt management becomes increasingly important, accompanied by increased risk of other complications [19]. Biofilm-forming bacteria, such as *Staphylococcus epidermidi*s and *Staphylococcus aureus*, attach to the surface of implanted devices and can evade the host immune defences whilst also being more resistant to antimicrobial treatment [22]. Polysaccharide intercellular adhesion (PIA) is one of the molecules involved in attachment and is a significant virulence factor, rendering staphylococcal strains better able to form biofilms and be more resistant to phagocytosis by neutrophils and antibacterial peptides. Microglia and astrocytes are responsible for recognising these threats in the CNS and secreting proinflammatory mediators such as TNF-α, IL-1β, and nitric oxide. Proinflammatory mediators are necessary to control infection, but they

can also cause neuronal damage. Chronic inflammation has been associated with neurodegeneration, behavioural disorders, seizures, and cognitive impairment [22, 28].

Staphylococcus epidermidis was cultured in 25.9% of children and was most common among the infant patients (n = 21; 55%). A study conducted in a children's hospital in California, United States, also cultured *Staphylococcus epidermidis* as the organism causing the infection [32]. In South Africa, *Acinetobacter baumannii, Klebsiella pneumoniae* and *Streptococcus pneumoniae* were the prominent microorganisms identified in infants diagnosed with bacterial meningitis between 2014 and 2018 [35]. *Staphylococcus aureus* was commonly cultured in children older than 1 month [36]. Among the children with *Staphylococcus aureus* infections, 19 (61.3%) had elevated CRP levels (>10 mg/L but <50 mg/L) at admission, whilst 9 (29%) remained elevated after 30 days. *Staphylococcus aureus* infections cause serious illness, prolonged hospital stays, higher risk of death, and significantly higher treatment costs [37]. *Staphylococcus epidermidis* had 10 (26.3%) patients with elevated CRP levels remaining after 30 days. This reflects the organism's strong biofilm-forming capacity and the challenges associated with elimination without shunt removal.

The metabolic and structural characteristics of biofilms make infections less susceptible to antibiotic treatment. The extracellular matrix characteristic of biofilm growth can limit antibiotic treatment through binding of the antimicrobial compounds or by degradation of these compounds by enzymes and other by-products. The growth and nutrient adaptations of the biofilm also limit the efficacy of many antibiotics, as their mechanism of action targets the growth of the organism [22]. In correlation with literature, vancomycin was commonly used to treat VPS infections, particularly caused by Staphylococcus organisms [36]. A combination of meropenem and other antibiotics, specifically vancomycin, did not show improvement in CRP levels between admission and day 30 and had the highest number of patients with elevated CRP levels at day 30 (n =13; 41.9%). This course is particularly administered to patients with a more severe or resistant infection, and the slow decline in CRP can reflect illness severity. This highlights the need for further monitoring of patients given meropenem in terms of the risk factors, such as a higher risk of seizures in patients with pre-existing renal impairment. Fifty-three percent (53%) of children were admitted for less than 30 days (n = 78; 53.1%), with 49 (62.8%) having no readmissions. This indicates positive antibiotic outcomes, along with shunt replacement and monitoring.

The mortality rate of this study was 17% which is lower than the mortality rate linked to *Staphylococcus aureus* bacteraemia at 29 - 63% [38]. It is, however, within the paediatric range of mortality due to bacterial meningitis, at 10-58% (39) and aligns with the South African infant mortality rate (16.6%) [24]. A study conducted in Angola showed an overall inpatient mortality of 20% [39]. The common symptoms noted in mortality patients were vomiting (n = 9; 36%), seizures (n = 6; 24%), and poor feeding (n = 5; 20%). A multiple regression analysis showed children aged >12 years to be at a higher

risk of death. This is linked to the group having the highest CRP levels at admission as well as the longest duration of symptoms before admission (mean = 21 days; IQR = 7-30). The children were admitted for an extended period of time to monitor the progression of the infection. The frequent microorganism present in the demised children was also *Staphylococcus aureus* (n = 6; 24%), which is linked to poorer outcomes in literature [38, 40].

Limitations of this study include the retrospective approach, heterogeneity of organisms and resistance patterns and that procalcitonin, a potentially valuable inflammatory marker, was not included due to incomplete data in patient records. Immunosuppressed patients were not highlighted, which limits the generalisability of the results for the South African/broader African population. CRP trajectories were not stratified by shunt externalisation/revision or EVD placement, precluding attribution of changes to antibiotics alone.

Conclusion

This study provides insight regarding the monitoring of CRP levels in children with a VP shunt infection over the course of antibiotic administration, within KZN. The CRP-guided antibiotic strategy is feasible; however, this study highlights the need for further evaluation regarding the use of CRP as the leading indicator for duration of antibiotic use and VP shunt infection monitoring, while adding to the existing body of knowledge of CRP utilisation. Overall, the CRP patterns observed demonstrate that while CRP remains a useful marker of inflammation, its interpretation in VP shunt infections requires careful consideration of patient age, timing of infection relative to shunt insertion, and organism characteristics, specifically biofilm-forming bacteria. It is recommended that CRP levels be recorded over a more extended period of time and monitored consistently in order to make an accurate deduction of antibiotic duration and infection resolution, along with the consideration of previously highlighted high-risk factors to avoid adverse outcomes and reduce the infant mortality rate.

Contributors

KR completed the literature search, data collection and analysis as well as compiled the final manuscript. ZNPM was responsible for reviewing the manuscript and providing feedback for areas of improvement. BE assisted with the data analysis and understanding as well as corrections provided. I acknowledge the use of artificial intelligence (AI) in the initial planning and research phase to consolidate key points from literature to understand the topic at hand. AI was not utilised for data generation or large bodies of intellectual content inserted directly into the content. This preserves the authenticity of the information and maintains integrity. AI utilised: Grammarly, Evidence Hunt, Phind

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Competing interests

None to declare

Data availability statement

No external data available

Ethical approval

Permission to conduct this study was granted by the Biomedical Research Ethics Committee (BREC). Reference number BREC/00006910/2024

Patient and public involvement

No patients were involved in the data collection process as this was a retrospective study design.

Patient consent for publication

Not applicable

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CHAPTER 3: SYNTHESIS

Hydrocephalus is a major contributor to paediatric neurosurgical morbidity worldwide, with particularly high incidence and complication rates in low and middle-income countries (LMICs) (1). The underlying causes vary, from congenital to acquired (infections), but the CSF diversion strategies are consistent (5). A ventriculoperitoneal (VP) shunt insertion is standard treatment; however, its effectiveness is hindered by the high rates of shunt failure (30% within the first year of placement) and infections, resulting in repeated surgical interventions, prolonged hospitalisation, long-term neurological sequelae, and mortality (3). Majority of VP shunt infections arise as an immediate postoperative complication caused by skin flora during the insertion of the shunt. The organisms proceed to form a biofilm on the shunt components, making infections difficult to clear, often resulting in shunt removal and extended antibiotic therapy. The diagnosis can be complicated by non-specific symptoms, postoperative inflammatory changes, as well as delayed microorganism confirmation (20, 26). As a result, clinicians resort to empiric antibiotics, which contribute to prolonged antibiotic courses and antimicrobial resistance. In order to address these challenges, accessible inflammatory biomarkers such as C-reactive protein (CRP) can provide valuable support in monitoring treatment. CRP is widely used in paediatrics due to its low cost and sensitivity; however, its role in VP shunt-related meningitis requires further investigation. Utilising and understanding whether CRP trends reflect infection progression and resolution could improve clinical decision-making as well as the duration of antibiotic therapy (35, 36, 40). This study highlights the potential utilisation of CRP as a monitoring tool in paediatric VP shunt infections to guide future management strategies.

This study demonstrated that CRP was elevated in almost all children at admission, confirming its sensitivity as an inflammatory marker. The admission levels were lower than expected for a severe bacterial infection diagnosis (>50 mg/L); however, the levels did elevate by day 5 (mean = 49.4 mg/L). This was most noticeable among the infant majority, who presented with characteristically lower CRP responses due to developmental immune immaturity and altered neonatal inflammatory physiology. CRP showed a consistent pattern over the admission period, despite the variations due to age. This involved early elevation, peak at days 3-5 followed by a gradual decline. CRP began decreasing earlier than white cell count (WCC), supporting the findings as a more responsive marker of improving inflammation. The statistically significant decline between admission CRP and day 30 ($p = 0,02$) shows a link between CRP dynamics and progressive clinical recovery. CRP did not return to normal levels (CRP <10 mg/L) within the admission period as a VP shunt infection is more severe and can be complicated by resistant organisms and varying patient immune responses. Patients with congenital hydrocephalus were already predisposed to infection due to blood-brain barrier (BBB) immaturity, fragile cerebral vasculature, and an impaired immune response. The significant number of patients with

congenital hydrocephalus aligns with global epidemiology (129) and underscores the need for more careful postoperative monitoring of this cohort.

The prolonged CRP elevation observed in many patients underscores the complexity of VP shunt infections. Over half of the cultured organisms showed antibiotic resistance (58.6%) and biofilm-forming bacteria, particularly *Staphylococcus epidermidis* and *Staphylococcus aureus.* Biofilm formation prevents the entering of antibiotics and leads to persistent inflammatory signalling (26) which is consistent with the longer CRP elevation amongst the children infected with these organisms. The delayed CRP decline was also associated with longer symptom duration before admission, infections occurring in the common immediate post-op timeframe, as well as delayed shunt removal/revision. This indicates that CRP reflects the presence of the infection as well as its chronic nature and pathogen virulence. The group of patients diagnosed with *Staphylococcus aureus* (21.1%) aligns with international literature and trends, whilst the presence of *Acinetobacter* and *Klebsiella* reflects local paediatric infection patterns (130). The CRP levels varied by pathogen, with biofilm organisms being associated with more persistent inflammation and a lesser decline. This presents a link between biofilm physiology and a prolonged inflammatory response.

The average antibiotic duration of 27 days aligns with the durations set by clinicians for neurosurgical infections but, also highlights the likelihood of extended use when infection clearance is uncertain. The overall trend in CRP corresponds with standardised treatment timelines, which suggests that CRP monitoring may support more accurate decisions regarding antibiotic duration. However, its use as a sole determinant of treatment length is insufficient, specifically in cases where resistant and biofilm-forming pathogens are involved. The finding regarding vancomycin and meropenem ineffectiveness supports the role of CRP as an additional diagnostic tool rather than a definitive marker. These patients showed limited CRP improvement and show a greater need for monitoring in severe infectious cases. The mortality rate of 17% falls within the existing range for paediatric bacterial meningitis (131). Older children (>12 years) exhibited a higher risk of death, correlating with both higher admission CRP levels and prolonged symptom duration. This suggests delayed recognition and a more serious infection present. These findings further reiterate the need for early diagnosis, prompt shunt removal, and careful monitoring in both older and younger children with delayed presentations.

Conclusion

Overall, the findings indicate that CRP is a sensitive, accessible biomarker that correlates with infection severity and clinical improvement in VP shunt infections. CRP trends reflect pathogen characteristics, particularly biofilm formation, and antimicrobial resistance. Age, time relative to shunt insertion and the underlying hydrocephalus aetiology, are all significant factors that influence CRP fluctuations and forms part of the attentive factors taken into consideration during the treatment process. CRP can support infection monitoring and may supplement antibiotic stewardship but used within clinical and

microbiological considerations to prevent further antibiotic resistance. These results reinforce the potential of CRP-guided antibiotic therapy to enhance paediatric neurosurgical infection management, whilst highlighting the need for further research into biomarker-guided antibiotic strategies, specifically in patients with a VP shunt infection.

Recommendations

Recommendations include the regular monitoring of CRP, specifically in patients diagnosed with high-risk organisms, prioritise early shunt revisions and extended postoperative care in biofilm or resistant infections. Future directions of this research area could involve prospective studies comparing CRP, WCC, and procalcitonin to accurately determine the most significant biomarker for VP shunt infections in children. Further research could also be conducted among immunosuppressed populations to determine if the trends are consistent and to enhance the generalisability of the results.

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Annexure

Annexure A – Ethical clearance

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

20 May 2025

Miss Kiara Rampershad (220003631)
School of Laboratory Medicine & Medical Science
Westville

Dear Miss Rampershad,

Protocol reference number: BREC/00006910/2024
Project title: The role of C-reactive protein determining response to antibiotic therapy in children diagnosed with Ventriculoperitoneal shunt infections
Degree: Masters

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**15 May 2025**
Expiration of Ethical Approval:	**14 May 2026**

I wish to advise you that your application for recertification for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC). The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 10 June 2025.

Yours sincerely

[redacted]

.....
Ms A Marimuthu
(for) Prof S Singh
Chair: Biomedical Research Ethics Committee

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

Annexure B – BMJ Paediatrics Open journal submission confirmation

Dear Miss Rampershad:

Your manuscript entitled "Role of C-reactive protein response to antibiotic therapy in children with a ventriculoperitoneal shunt infection: a retrospective study" has been successfully submitted online and is presently being given full consideration for publication in BMJ Paediatrics Open.

Your manuscript ID is bmjpo-2025-004357.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://mc.manuscriptcentral.com/bmjpo and edit your user information as appropriate.

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Thank you for submitting your manuscript to BMJ Paediatrics Open.

Annexure C – Data collection sheet

Factor	**Categories**
Gender	Male
	Female
Age Groups	0 - <1
	1 - 6
	7 - 12
	>12
Patient Address	
Referring hospital	
Age at admission	
Time to VPS infection from last shunt	
Birth weight	
Aetiology of hydrocephalus	Infection
	Brain tumour
	Myelomeningocele
	Encephalocele
	Trauma
	IVH prematurity
	Subarachnoid haemorrhage
	Arachnoid cyst
	Congenital
	Aqueduct stenosis
	Dandy-walker malformation
	Idiopathic or unknown
Clinical presentation	Fever
	Increased intracranial pressure
	Meningeal irritation
	Vomiting
	Headaches
	Irritability
	Poor appetite
	Neck stiffness

	Sensitivity to light
Laboratory tests	C-reactive protein levels: - Admission - Day 3 - Day 5 - Day 7 - Day 14 - Day 21 - Day 30
	Procalcitonin Admission – Day 30
	Glucose concentration in CSF Admission – Day 30
	Protein concentration in CSF Admission – Day 30
	White blood cell count Admission – Day 30
	Serum glucose Admission – Day 30
	Platelet count Admission – Day 30
	Haemoglobin levels Admission – Day 30
	Sodium Admission – Day 30
	Potassium Admission – Day 30
	Urea Admission – Day 30
	Creatinine levels Admission – Day 30
Antibiotic administered	
Length of antibiotic use	

Mode of antibiotic administration	Intravenous
	Intraventricular
Patient diagnosis (CT scan features)	
Culture microorganism identified	
GCS at admission	
GCS at discharge	
GOS at admission	
GOS at discharge	
Length of hospital stay	
Follow-up (months)	Including GOS after 6 months
Mortality	