THE ROLE OF LUMBAR PUNCTURE IN YOUNG INFANTS WITH SEIZURES AND FEVER IN A RESOURCE-CONSTRAINED SETTING.

Ashton Coetzee

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Supervisor: Dr Liezl Smit
Co-Supervisor: Dr Regan Solomons

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: December 2016

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Date: December 2016

Signature: Dr AC Coetzee

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ABSTRACT

Background

Differentiating febrile seizures from serious infections like bacterial meningitis is essential but remains a clinical dilemma for many clinicians. This has lead to local guidelines advocating routine lumbar puncture (LP) in all infants less than 18 months of age presenting with fever-associated seizures irrespective of clinical findings. Recently revised American Academy of Pediatrics (AAP) guidelines for simple febrile seizures (SFS) recommends a LP only if there are 'clinical signs or symptoms of concern'. This guidance can however not necessarily be extrapolated to resource-constrained settings as studies chosen to inform these guidelines have deliberately excluded studies from developing countries. This study aim to evaluate the utility and outcome of LP, as a special investigation, in infants between the ages of 6 months and 18 months, presenting with seizures and associated fever, in a setting with uncertain immunization coverage and high burden of malnutrition, HIV and TB.

Methodology

A retrospective cohort review was conducted of infants aged 6 to 18 months admitted with fever and seizures to the Paediatric Emergency & Ambulatory unit at Tygerberg Children's Hospital over a 12 month period. Patients were identified using the admission records, patient admission notes and laboratory CSF results. Descriptive statistics was performed on demographic outcome variables. Univariate analysis for continuous variables were performed to determine adjusted associations between historical and/or clinical findings and CSF results.

Results

Fever and associated seizures were the presenting feature in 25% of infants between the ages of 6 to 18 month in our study. Infants included in our study were mostly well, with normal growth and development, none were HIV-infected and only 10% exposed to a known TB case. Immunizations were complete for age in 79% of infants.

62/84 (74%) of the infants eligible for the study underwent a lumbar puncture. The majority of infants were diagnosed as Febrile Seizures (75/84, 89%). Viral upper respiratory infection was the most common cause for fever (63%) in these infants. A clear source of fever was found to be statistically significant in differenciating between patients with normal and abnormal CSF results ($p < 0.001$).

Meningitis was diagnosed in 6/84 (7%) of infants; of whom 3 had abnormal neurological findings suggestive of meningitis at presentation. Based on CSF results, 3/62 (5%) were diagnosed as viral meningitis, 1/62 (2%) as tuberculous meningitis and 2/62 (3%) as presumed bacterial meningitis. No cases of meningitis were diagnosed in infants fulfilling the case definition of Simple Febrile Seizures in this study. Three children (3%) presenting with Complex Febrile Seizures and normal neurological findings were diagnosed and treated as meningitis (1 viral, 2 bacterial) following a LP.

Conclusion

Fever with associated seizures in infants between the ages of 6 to 18 month presented a significant burden of disease in our emergency unit; and underlines the need for evidence-based management guidelines. If American Academy of Pediatrics (AAP) guidelines for SFS had been applied to our study population, all cases of serious illness would have been investigated and identified. AAP guidelines could thus be applied to well infants between the ages of 6 and 18 months in resource-constrained settings; decreasing the use of LP with associated cost savings. Larger studies are required to identify clinical variables to guide best practice, especially in infants presenting with complex febrile seizures.

OPSOMMING

Agtergrond

Om koorsstuipe van ernstige infeksies soos bakteriële meningitis te differensieer is noodsaaklik, maar bly 'n kliniese dilemma vir baie dokters. Dit het gelei tot die plaaslike riglyne wat roetine lumbaalpunksie (LP) aanbeveel in alle babas minder as 18 maande wat met koors en konvulsies presenteer, ongeag die kliniese bevindinge. Onlangse hersiene 'American Academy of Pediatrics' (AAP) riglyne vir eenvoudige koorsstuipe (SFS) beveel 'n LP slegs aan indien daar kliniese tekens of simptome van kommer is. Hierdie aanbeveling kan egter nie noodwendig geëkstrapoleer word tot instellings met beperkte hulpbronne nie aangesien studies wat die riglyne toegelig het, doelbewus studies uitgesluit het van ontwikkelende lande. Hierdie studie het ten doel om die nut en uitkoms van LP, as 'n spesiale ondersoek, te evalueer in babas tussen die ouderdomme van 6 maande en 18 maande, wat presenteer met konvulsies en verwante koors in 'n omgewing met onseker immunisering dekking en 'n hoë las van wanvoeding, MIV en TB.

Metodiek

'n Retrospektiewe groep hersiening is gedoen van babas tussen die ouderdomme 6-18 maande wat toegelaat is met koors en konvulsies in die Pediatriese Nood & Ambulatoriese eenheid by Tygerberg Kinderhospitaal oor 'n tydperk van 12 maande. Pasiënte is geïdentifiseer mbv die toelatingsrekords, pasiënt toelatingsnotas en laboratorium SSV resultate. Beskrywende statistiek is uitgevoer op demografiese veranderlikes. Eenveranderlike analise vir kontinue veranderlikes is uitgevoer is om aangepaste assosiasies tussen historiese en / of kliniese bevindinge en SSV resultate te bepaal.

Resultate

Koors en verwante konvulsies was die presenterende klagte in 25% van babas tussen die ouderdomme van 6 tot 18 maande in ons studie. Babas in ons studie was meestal gesond, met 'n normale groei en ontwikkeling, niemand was MIV-geinfekteerd, en slegs 10% was blootgestel aan 'n bekende TB geval. Inentings was op datum vir ouderdom in 79% van gevalle.

62/84 (74%) van die babas wat gekwalifiseer het vir die studie het 'n lumbaalpunksie ondergaan. Die meerderheid van die babas is met ontslag gediagnoseer as koorsstuipe (75/84, 89%). Virale boonste respiratoriese infeksie was die mees algemene oorsaak vir koors (63%) in hierdie babas. 'n Duidelike bron van koors is

gevind om statisties beduidend te wees in die onderskeiding van pasiënte met normale en abnormale SSV resultate ($p < 0.001$).

Meningitis is gediagnoseer in 6/84 (7%) van babas; waarvan 3 met abnormale neurologiese bevindings suggestief van meningitis presenteer het by aanbieding. Op grond van SSV resultate, is 3/62 (5%) gediagnoseer as virale meningitis, 1/62 (2%) as tuberkuleuse meningitis en 2/62 (3%) as vermoedelike bakteriële meningitis. Geen gevalle van meningitis is gediagnoseer in babas wat aan die gevalsdefinisie van eenvoudige koorsstuipe voldoen het in hierdie studie nie. Drie kinders (3%) wat met kompleks koorsstuipe en normale neurologiese bevindings presenteer het, is gediagnoseer en behandel as meningitis (1 virale, 2 bakteriële) nav die LP ondersoek.

Gevolgtrekking

Koors met gepaardgaande konvulsies in babas tussen die ouderdomme van 6 tot 18 maande maak 'n beduidende deel uit van siektetoestande in ons noodeenheid; en beklemtoon die noodsaaklikheid vir bewysgebaseerde behandelingsriglyne. As die ‘American Academy of Pediatrics’ (AAP) riglyne vir SFS toegepas was op ons studie populasie, sou alle gevalle van ernstige siekte korrek ondersoek en geïdentifiseer wees. AAP riglyne kan dus toegepas word in gesonde babas tussen die ouderdomme van 6 en 18 maande in beperkte hulpbron instellings; met gevolglike vermindering van die gebruik van LPs en gepaardgaande kostebesparings. Groter studies is nodig om die kliniese veranderlikes te identifiseer wat tot beste praktyk kan lei, veral in babas wat presenteer met komplekse koorsstuipe.

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List of Abbreviations

Acute Gastroenteritis (AGE)
American Academy of Paediatrics (AAP)
Bacterial Meningitis (BM)
Central Nervous System (CNS)
Complex Febrile Seizures (CFS)
Case Report Form (CRF)
Chest X-Ray (CXR)
Computed Tomography (CT)
Electronic Content Management System (ECM)
Febrile seizures (FS)
Human Immunodeficiency Virus (HIV)
International Classification of Diseases 10th revision (ICD 10)
Lower Respiratory Tract Infection (LRTI)
Lumbar Puncture (LP)
Magnetic Resonance Imaging (MRI)
National Health Laboratory Service (NHLS)
Polymerase Chain Reaction (PCR)
Polymorphonuclear Leukocytes (PMN)
Tuberculosis (TB)
Simple Febrile Seizures (SFS)
Upper Respiratory Tract Infection (URTI)
Urinary Tract Infection (UTI)
World Health Organisation (WHO)

List of Tables and illustrations

Chapter 1: INTRODUCTION

Seizures occur in the context of many childhood illnesses, and account for approximately 1-5% of all emergency department visits[1 2]. Simple febrile seizures (SFS), which carry a fairly benign prognosis, are the most common form of childhood seizures[3].

Differentiating febrile seizures from serious infections like bacterial meningitis is essential, but remains a clinical dilemma for many clinicians in the emergency care setting. Children between the ages of 6 and 18 months are especially problematic as the specific localizing signs and symptoms of meningitis may not manifest or be minimal[4].

The fear of missing bacterial meningitis (BM) has thus led some authors to advocate for routine lumbar puncture (LP) in infants presenting with fever-associated seizures even if the clinical examination points to a febrile seizure[5 6 7.8] .

In 2011, the American Academy of Pediatrics (AAP) revised their guidelines for simple febrile seizures, and recommends a lumbar puncture (LP) to exclude meningitis only if there are 'clinical signs or symptoms of concern'. A LP is only recommended as optional in a child between 6 and 12 months of age who are not fully immunized with Haemophilus influenza type B (HiB) and Pneumococcal vaccines, and in those who have received antibiotics in the days preceding the seizure. A LP is not recommended in a child older than 12 months if there are no signs or symptoms suggestive of meningitis[12]. These recommendations were further informed by the global decline in the incidence of bacterial meningitis in areas with good immunization coverage[8].

This guidance can however not necessarily be extrapolated to our resource-constrained setting as studies chosen to inform these guidelines have deliberately excluded studies from developing countries because of the "higher prevalence of bacterial meningitis and the different spectrum of diseases encountered such as malaria, HIV-related CNS infections and CNS Tuberculosis." [1]. No AAP or other guidelines exists for children presenting with complex febrile seizures.

To our knowledge, no studies have examined the role of LP in infants presenting with febrile seizures in the South African context; with a high burden of malnutrition, HIV

and TB. This study aimed to evaluate the utility and outcome of LP, as a special investigation, in infants between the ages of 6 months and 18 months, presenting to the Tygerberg Hospital Paediatric Ambulatory Unit with seizures and associated fever.

Chapter 2: LITERATURE REVIEW

Febrile seizures (FS) are the most common form of childhood seizures, affecting 2 to 5% of all children[9]. The median age of onset is 18 months, and half of children present between 12 and 30 months[10].

The diagnosis of a FS can be made in children between the ages of 6 months and 6 years if the seizure is associated with a febrile illness and a clear source of the fever is found on clinical examination. The diagnosis of a febrile seizure excludes any central nervous system (CNS) infection, metabolic abnormality, underlying seizure disorder or neurological abnormality[2,11,12].

Febrile seizures are classified as either simple or complex. Simple febrile seizures (SFS) are generalised tonic-clonic seizures, lasting less than 15 minutes with a full return to normal neurological function and no further seizures within 24 hrs[2]. Complex febrile seizures (CFS) who represent 20-30%of febrile seizures, are less well-defined, comprising prolonged seizures (> 15 minutes) and/or focal seizures and/or recurrent seizures and/or residual post-ictal neurological deficit[13].

The most common underlying etiology for FS (including both SFS and CFS) is viral upper respiratory tract infections[14]. A multi-center retrospective review studied the causes of infection in 455 children who presented with SFS; while no source of infection was found in 34% of cases,, otitis media accounted for 34%, upper respiratory infection for 12%, viral syndrome for 6% and pneumonia for 6% of underlying causes of fever[15].

Simple febrile seizures carry a fairly benign prognosis[3]. Children with SFS have no increased risk of mortality, hemiplegia or mental retardation. The risk of epilepsy after a SFS is slightly higher than that of the general population[3]. The main risk associated with SFS is a 30% risk of recurrence[16], with 65-90% occurring within one year of the first SFS[7, 17].Complex febrile seizures have a more guarded prognosis and requires more intensive evaluation in comparison to SFS. The risks of developing unprovoked seizures with complex febrile seizures is higher at 6-8%[18].

Differentiation of febrile seizures from serious infections like bacterial meningitis, septicaemia, or seizures triggered by fever in children with underlying epilepsy, is

essential. Bacterial meningitis remains a disease with a 7% mortality rate and the importance of early recognition and treatment remains high[19].

Seizures represent a common presenting complaint in bacterial meningitis(BM)[20 21] but it is uncommon for first-time SFS to be the sole manifestation of bacterial meningitis in the absence of other clinical signs[2]. In a review of 115 patients with confirmed bacterial meningitis by Kimia et al., 91% were either comatose or obtunded at presentation, with the remaining 9% having a normal level of consciousness but with other clinical signs of meningitis. Seizures were present in 23%.

The exclusion of serious illness in children between 6 and 18 months presenting with seizures and associated fevers remain problematic however, as at this age specific localizing signs and symptoms of meningitis may not be apparent on clinical examination[22].

The fear of missing BM has thus led some authors to advocate routine lumbar puncture (LP) in all infants presenting with febrile seizures, irrespective of clinical findings[1 8 23]. The 1996 American Academy of Pediatrics (AAP) consensus statement reflected this sentiment and recommended clinicians to 'strongly consider' doing a lumbar puncture for cerebrospinal fluid analysis in infants from 6-12 months of age presenting with first SFS, and to 'consider' it in infants from 12-18 months of age[24]. The Italian League Against Epilepsy also recommended a LP in children under 18 months as "clinical signs and symptoms for meningitis may be minimal." [25]

The management guidelines for SFS have since evolved. In 2011, the AAP revised their guideline and now advises clinicians to determine the aetiology of the fever, and to perform a lumbar puncture to exclude meningitis only if there are 'clinical signs or symptoms of concern'. An LP is recommended as optional in a child between 6 and 12 months of age not fully immunized with Haemophilus influenza type B (HiB) and Pneumococcal vaccines, and in those who have received antibiotics in the days preceding the seizure. The subcommittee felt that clinicians would recognize symptoms of meningitis in children older than 12 months and that a LP is not warranted in a child older than 18 months if there are no signs and symptoms suggestive of meningitis[12].

These recommendations are further supported by the global decline in the incidence of bacterial meningitis in areas with good immunization coverage [26]. Since the introduction of HiB and Pneumococcal vaccines, the incidence of BM has dramatically decreased in the United States. Reported risk of bacterial meningitis in children presenting as first SFS in the absence of other clinical signs ranges from 0% to 0.2%[15,27-28].

A ten-year retrospective review of 704 infants aged 6 to 18 months presenting with first SFS to the Boston Children's Hospital Emergency Centre did not identify any patients with bacterial meningitis[2]. Hom et al. found the risk of bacterial meningitis to be 0% (CI 0.0-3.0) in 150 infants aged 6 to 18 months presenting with SFS[29].

Even though the AAP consensus statement is only for children presenting with SFS, studies report a similarly low risk of bacterial meningitis in children presenting with complex febrile seizures (CFS). In a retrospective study of 71 children between 6 months and 6 years of age presenting with a CFS to an Emergency Centre in Los Angeles over a four-year period, 93% underwent a LP as part of the evaluation. In one case (1.5%), bacterial meningitis was diagnosed. All of these children also underwent a computed tomography (CT) scan as well as magnetic resonance imaging (MRI) of the brain; with abnormality only reported in one case of bacterial meningitis.[30]. Kimia et al. similarly described low risk of BM in their cohort. Of infants between the ages of 6 and 60 months who presented with a CFS, 64% (90/526) received a lumbar puncture and bacterial meningitis was diagnosed in 1% (95% CI 0.2 - 2.8) of cases[31].

This evidence can however not necessarily be extrapolated to inform management guidelines in resource-constrained settings with often unknown or low immunization coverage rates and the additional burden of malnutrition, HIV and TB.

In all the recent systematic reviews and meta-analysis on the risk of BM in young children with first SFS, only studies from resource-sufficient countries were included. Studies from resourced-constrained countries were excluded because of the "higher prevalence of bacterial meningitis and the different spectrum of diseases, such as malaria, HIV related CNS infections and CNS Tuberculosis." [1, 22]. Kimia et al further excluded all immune-compromised children or any child with a chronic illness in their study[2, 22].

Most management guidelines in developing countries, including our Ambulatory Unit, recommend an extensive workup of all children below the age of 18 months presenting with seizures and associated fever, based on the high disease burden of HIV, TB and malnutrition.

Limited data assessing the role of LP in young infants presenting with fever and associated seizures in developing countries is available. In a prospective study of 377 children aged 2 months to 10 years from Papua New Guinea where local guidelines strongly recommend that an LP be performed in all febrile children after a seizure, no children presenting with a single seizure and normal physical examination were diagnosed with bacterial meningitis. Cerebral malaria was diagnosed in 24.5% of children presenting with a single seizure, and 47.6% of children presenting with multiple seizures[32].

In a study from Iran, 254 previously healthy children aged 6 months to 5 years presenting with a first fever-associated-seizure were studied. All received lumbar punctures and only 4.7% cases were diagnosed with meningitis. Risk factors significantly associated with meningitis were age <12 months, lethargy, irritability, vomiting, neck stiffness, bulging fontanel, headache, drowsiness, coma, complex seizures, and prior antibiotic use. All children diagnosed with meningitis had at least one of the above-mentioned risk factors[33].

In a retrospective study of 497 children aged 6 to 18 months presenting with a first febrile seizure to a tertiary hospital in India, LP was performed in 40% of cases. The incidence of bacterial meningitis was only 0.86% in infants presenting with SFS, but 4.8% in children presenting with CFS[34]. Seizures persisting for longer than 30 minutes, prolonged post-ictal drowsiness and the presence of neurological abnormalities were the most reliable predictors of bacterial meningitis.

To our knowledge, no studies have examined the role of LP in infants presenting with febrile seizures in the South African context. The extent of immunization coverage in South Africa is uncertain, adding further complexity to the evaluation and clinical decision-making in this group of patients. According to the South African Department of Health, immunization coverage is 96%; even though the World Health Organisation (WHO) estimates it at only 64%[35,36].

As previously stated, the protocol for children presenting with seizures and fever at the Tygerberg Hospital Paediatric Emergency & Ambulatory Unit recommends a LP for all children less than 18 months of age. These infants are admitted to the short-stay ward and treated with intravenous antibiotics for presumed bacterial meningitis until results become available.

The increased medical costs of empiric inpatient management and LPs in infants presenting with FS in a resource-constrained setting do not seem justified in patients with a possible low risk of bacterial meningitis [18]. Furhermore, lumbar puncture is an invasive and painful procedure and not without complications. The value of a lumbar puncture in infants presenting with seizures and associated fever in young infants is however poorly-defined in our setting, complicated by uncertain immunization coverage and a high burden of malnutrition, HIV and TB.

This study aims to evaluate the utility and outcome of lumbar puncture in infants between the ages of 6 months and 18 months presenting with seizures and associated fever to the Tygerberg Hospital Paediatric Emergency & Ambulatory Unit. The study further aims to examine potential clinical risk-factors associated with abnormal cerebrospinal fluid findings. Being able to identify those with low risk for serious illness will limit unnecessary investigations and reduce costs in an already overburdened healthcare system. Conversely, infants at high risk of meningitis should be identified by the management guidelines.

Chapter 3: RESEARCH DESIGN AND METHODOLOGY

A. Research Question

What is the role of a lumbar puncture in the evaluation of infants between the ages of 6 months and 18 months presenting with seizures and associated fever to a Pediatric Ambulatory Unit in a setting with uncertain immunization coverage and high burden of malnutrition, HIV and TB?

B. Aim and Objectives

The overall aim of the study was to determine the role of lumbar puncture in excluding meningitis in infants between 6 and 18 months of age admitted with seizures and associated fever to the Paediatric Emergency & Ambulatory Unit at Tygerberg Hospital over a one year period; January till December 2013.

Objectives

Primary Outcome measures

1. To describe the prevalence of seizures and associated fever as presenting complaints in infants between 6 and 18 months of age.
2. To describe the utilization of lumbar puncture in infants between 6 and 18 months of age presenting with seizures and associated fever.
3. To describe the yield of lumbar puncture in infants between 6 and 18 months of age presenting with seizures and associated fever.
4. To describe the aetiology of seizures and associated fever in infants between 6 and 18 months of age.

Secondary Outcome measures

1. To determine clinical risk factors associated with abnormal lumbar puncture findings in infants between 6 and 18 months of age presenting with seizures and associated fever.

C. Study design

We conducted a retrospective cohort review of infants 6 - 18 months of age who presented to the Pediatric Emergency & Ambulatory Unit with seizures and associated fever over a one-year period. Initially our aim was to review the period January till December 2013. Due to inability to access the admission records for September and October 2013, September and October 2014 were substituted to

complete 12 months of data collection, to adjust for seasonal variation in disease patterns.

D. Setting

Tygerberg Hospital is a major referral centre in Cape Town, South Africa. This hospital serves the immediate surrounding areas, providing primary and secondary healthcare to children, as well as tertiary healthcare to all paediatric patients in Metro East (the East half of the Cape Town metropolitan area), as well as the Northern and Eastern rural districts of the Western Cape Province of South Africa. Paediatric patients with primary and secondary healthcare problems are managed in the Paediatric Ambulatory Unit, which is combined with acute referrals and 24hr emergency care, as well as a 24-bed short stay in-patient ward. Seizures are one of the most common presenting complaints. The Paediatric Ambulatory Unit sees approximately 1000 children per month; with about a third admitted to the short-stay in-patient ward.

E. Target population, Study Population and Sampling

The target population comprised all children accessing ambulatory and emergency paediatric care services. The study population included infants between 6 and 18 month of age admitted to the Tygerberg Hospital Paediatric Ambulatory Unit short stay ward with seizures and associated fever.

Inclusion criteria:

- All infants between (and inclusive of) the ages of 6 months and 18 months presenting and subsequently admitted with a history of seizure(s) and associated fever.

Exclusion criteria:

- Seizure without fever.
- Fever without seizure.
- Known epilepsy, ventriculo-peritoneal shunt, chronic neurological disease (e.g. cerebral palsy, neurocutaneous syndrome), or systemic metabolic disease that may produce seizures.

A. Data collection & analysis

Study participants were systematically identified from the routine Paediatric Ambulatory Unit short stay in-patient ward admission registers from January 1, 2013 to December 31, 2013 (see amendment to included months above).

No formal sample size was calculated since all primary outcome measures were descriptive in nature.

Sources of Data

The primary sources of data :

- Paediatric Ambulatory Unit short stay inpatient Admissions Register:
  All children who are seen in the Paediatric Ambulatory Unit Outpatients and Resuscitation area and require admission to either the Paediatric Ambulatory Unit or secondary ward within Tygerberg Hospital are entered into the ward admissions register. At discharge or transfer the destination and final discharge diagnosis and ICD 10 code is recorded.
- The Tygerberg Hospital Clinicom database:
  Hospital administration and clerks use this patient management system to manage admission, discharge and movement of patients within the hospital. Basic demographic information is collected as well as age at presentation, admission, discharge and movement of patients between wards. An ICD 10 code is recorded at discharge. This system will be used to cross check with the admissions register that all infants diagnosed with 'febrile convulsions' (R56.0), 'bacterial meningitis' (G00.9), 'TB meningitis' (A17.0), 'viral meningitis' (A87.9), 'convulsions' (G40.6), 'status epilepticus' (G41.0), or 'HIV encephalopathy' (B22.0) on ICD 10 coding have been included in the study if the inclusion criteria applies.
- Routine health information as captured on the electronic management system (ECM)
- CSF laboratory results will be obtained using the National Health Laboratory Service (NHLS) database.

Data Collection Methods

Routine Health Information, ages and discharge diagnosis, as captured in the Ward Admissions register was used to collect quantitative data.

Each patient enrolled in the study was assigned a unique patient identifier number and a paper-based case report form (CRF) was used to collect the data from the Electronic Content Management system (ECM). This data was entered into an electronic database. Patient names, hospital numbers and physical addresses were not entered into the paper or electronic database.

Variables collected included (see Appendix 1, *Data Collection sheet*):
Personal identifier, age at presentation (months), sex, weight, nutritional category, fever, source of fever, type of seizure, duration of seizure, recurrent seizures in the same illness, previous febrile seizure history, preceding antibiotic exposure, level of consciousness, focal or localizing signs, presence of meningism, lumbar puncture done, CSF results (microbiology and biochemistry), immunisation status, TB contact or concern, HIV status, developmental history and diagnosis at discharge (ICD 10 coding).

Operational definitions used (see Appendix 2, *Coding sheet*)
For the purpose of the study, the following definitions were used:

- Sex: male or female
- Age: months
- Nutritional status: categorized based on World Health Organisation (WHO) weight for age classification (Normal nutrition = weight for age > -2 z score, Moderate malnutrition = weight for age < -2 but > -3 z score, Severe malnutrition = weight for age < -3 z score)
- Fever: documented temperature > 38°C or history of fever as a presenting complaint
- Simple febrile seizure: self-limiting, duration less than 15 minutes, tonic-clonic features, no reoccurrence within 24 hrs, no postictal pathology. [37]
- Complex febrile seizure: duration longer than 15 minutes, may present as multiple seizures within 24 hrs, focal seizures with possible features of clonic and/or tonic movements, loss of muscle tone, seizure activity followed by transient unilateral paralysis. [35]
- Source of fever: documented site of infection e.g. otitis media, urinary tract infection etc.
- Preceding Antibiotics: any oral or parental antibiotics given to the infant within 72 hours of presentation
- History of previous febrile seizure: documented febrile seizure in history on presentation or as documented in previous patient records
- Abnormal Development: developmental milestones delayed/regressed compared to norm for age group.
- Abnormal neurological examination: depressed level of consciousness, post-ictal for longer than 1 hour, focal or localizing signs, meningism, bulging fontanel, signs of raised intracranial pressure, or irritability.

- Lumbar puncture results: cerebrospinal fluid (CSF) microbiology and biochemistry results.
    - Normal CSF being defined as less than 5 leukocytes per mm^3 , protein levels between 0.2 – 0.45 g/l and glucose >50% of serum levels (as serum glucose was not always readily avaialble the NHLS reference range of 2.2 – 3.9 mmol/l was used) [38].
    - Bacterial meningitis was defined by either 1) microscopy and/or culture confirmation of a bacterial pathogen on CSF or 2) Purulent CSF with or without culture confirmation of a bacterial pathogen on blood. A PMN predominant cellular picture, with 5 – 10000 cells per mm^3, protein between 1.0 and 5.0 g/l and a decreased glucose level, with a positive gram stain being confirmatory[38 39].
    - Viral meningitis was defined as having a lymphocyte predominant cellular picture with less than 1000 cells, raised protein between 0.5 and 2.0 g/l and generally normal CSF glucose levels. With CSF viral polymerase chain reaction (PCR) detected, or the clinical outcome was favourable with only supportive care and other causes of meningitis excluded[38 40].
    - TB meningitis may have a mixed cellular picture depending on the timing of CSF samples taken, with 10 – 500 cells, highly elevated protein levels of between >1.0 g/L and low CSF glucose levels <2.2 mmol/L or CSF:serum glucose ration 0.5. Acid fast bacilli are rarely detected but may be cultured or detected by PCR means[38 41].
- Immunization history: according to the South African immunization schedule as documented in patient records
- TB contact or concern: close contact with an adult diagnosed with pulmonary TB in the past 2 years; or TB workup done (Mantoux, Chest X-ray, gastric aspirates) as documented in patient records
- HIV status: as documented in patient records at presentation with seizure and associated fever (unknown, negative, exposed, infected)
- ICD-10 coding: The International Classification of Disease tenth revision (ICD-10) is the World Health Organization system of coding that notes various medical records including diseases, symptoms, abnormal findings and external causes of injury.

Data management and statistical analysis

Routine Health Information was used to collect quantitative data and laboratory reports were obtained for each patient using the unique hospital number.

Each patient enrolled in the study was assigned a unique patient identifier number and a paper-based case report form (CRF) was used to collect the data from the clinical records. The data was entered into an electronic database. Patient names, hospital numbers and physical addresses were not entered in the paper or electronic database. All paper documents will be kept in a locked cupboard for 5 years.

Data Analysis

Data were analysed using Stata. Descriptive statistics was performed on demographic outcome variables. Univariate analysis was based on Chi-square with calculation of Odds Ratios and 95% confidence limits as well as t-tests for continuous variables. Multivariable logistic regression analysis was performed to determine adjusted associations between historical and/or clinical findings and CSF results.

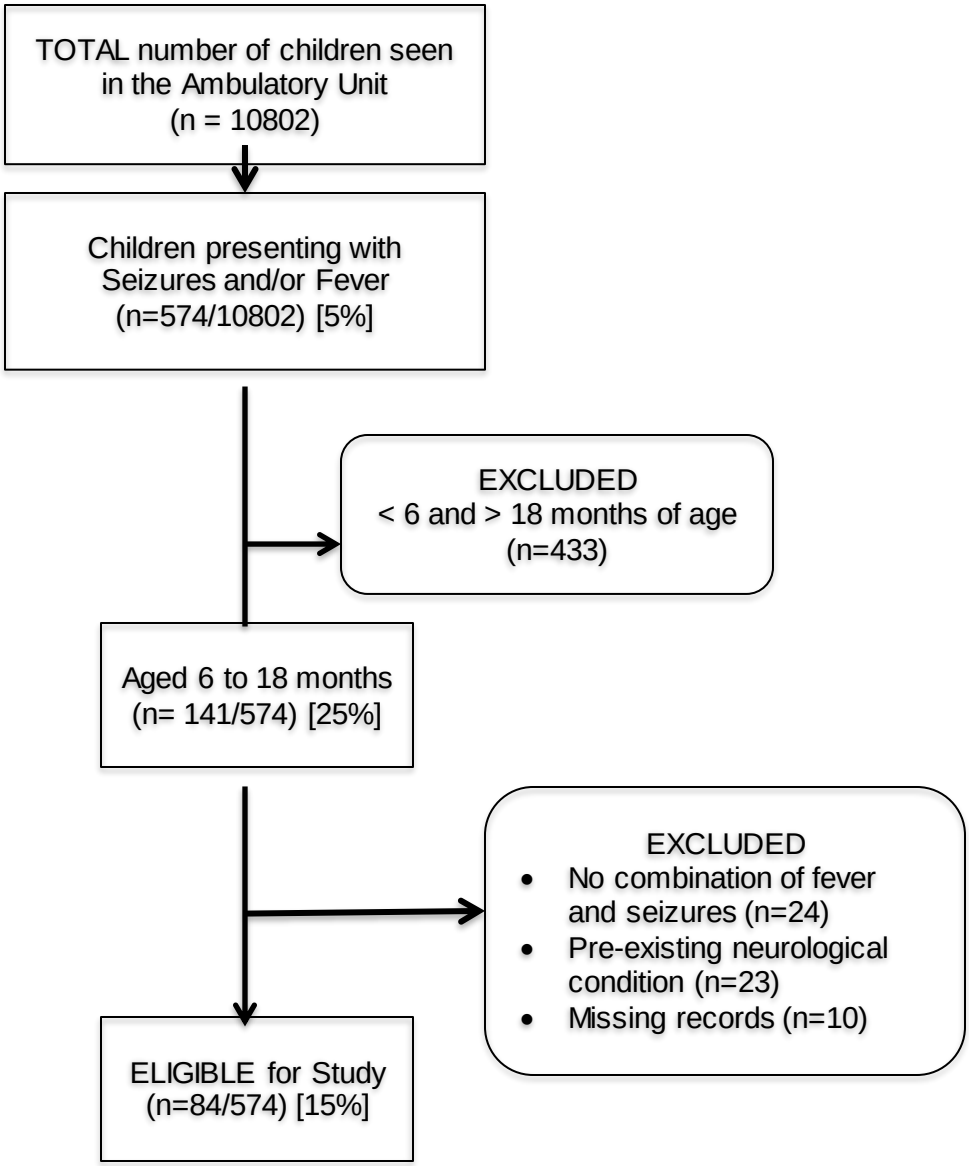
B. Ethical considerations

This study was approved by the Health Research Ethics Committee of Stellenbosch University (protocol number S14/06/138).

Chapter 4: RESULTS

During the study period a total of 10 802 children were admitted to the Paediatric Ambulatory Unit of whom 574/10 802 (5%) presented with seizures and/or associated fever. 141/574 (25%) of these infants were between the ages of 6 and 18 months, with 84/574 (15%) infants included in the retrospective review after exclusion criteria were applied (Figure 1).

Figure 1. Flow Diagram of Systematic Identification of Study Population.



A. Study Population Characteristics

Infants included in our study were mostly well, with normal growth and development. None were HIV-infected and only 9/84 (10%) were exposed to a known TB case. Immunizations were complete for age in 66/84 (79%) of infants and 9/84 (10%) have been started on a course of oral antibiotics prior to presentation.

A history of previous febrile seizures were given in 17/84 (20%) of infants. 73/84 (87%) of infants had a clear source of the fever outside of the central nervous system at presentation.

Table 1. Summary of Study Population Characteristics, History and Clinical Findings

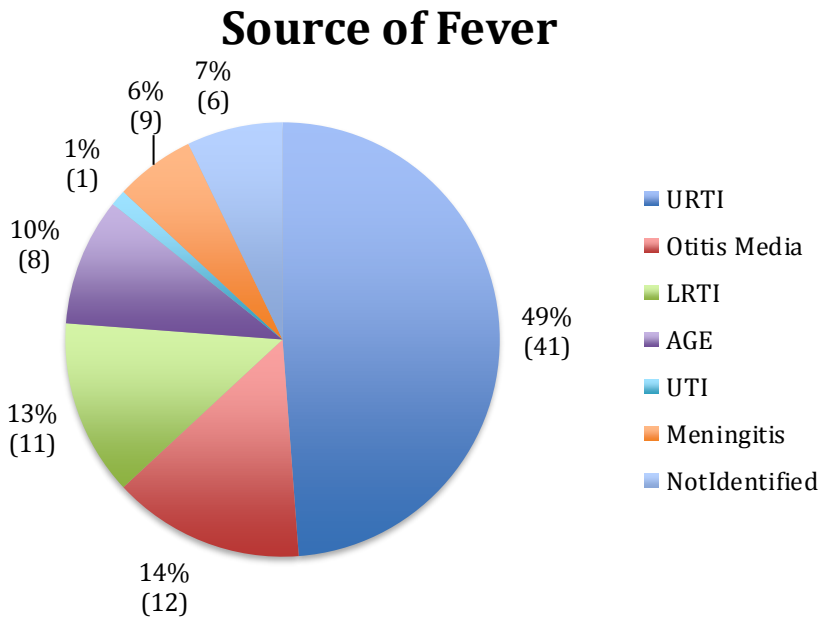
Variable	***n/N (%)***
Male Sex	42/84 (50%)
Age (months)	12.2 (range 6-17)
Nutritional Category based on weight for age z-scores	
Normal growth	79/84 (94%)
Moderate malnutrition	3/84 (3.6%)
Severe malnutrition	2/84 (2%)
Weight unknown	0/84 (0%)
Completed Immunization schedule for age	66/84 (79%)
HIV status	
HIV infected (tested)	0/84 (0%)
Not exposed to HIV	54/84 (64%)
HIV negative (tested)	11/84 (13%)
Unknown status	19/84 (22%)
Known TB exposure	9/84 (10%)
Preceding Antibiotic exposure	9/84 (10%)
Previous Febrile Seizures	17/84 (20%)
Development	
Normal milestones	70/84 (83%)
Delayed milestones	1/84 (2%)
Not documented	13/84 (16%)

Fever	
Documented as above 40'C	1/84 (2%)
Documented as between 38-40'C	42/84 (50%)
History of fever	39/84 (46%)
Seizure type	
Generalized Tonic-Clonic	68/84 (80%)
Focal	16/84 (20%)
Seizure Duration	
< 15 minutes	51/84 (60%)
> 30 minutes (Status epilepticus)	6/84 (6%)
Recurrence of seizures in same febrile illness	33/84 (39%)
Not documented	16/84 (20%)
Findings on Neurological examination	
Normal	69/84 (82%)
Localising signs	8/84 (10%)
Depressed level of consciousness	6/84 (7%)
Meningism	8/84 (10%)
Incomplete examination records	4/84 (5%)

B. *Documented Aetiology of Seizures and Associated Fever*

The most common source of fever was upper respiratory tract infection (URTI) 41/84 (49%), followed by lower respiratory tract infection (LRTI), 11/84 (13%), and acute gastro enteritis (AGE), 8/84 (10%). No identifiable source of fever were documented in 6/84 (7%) of the patients with meningitis documented as source of fever in 5/84 (6%) of cases (Figure 2).

Figure 2. Documented sources of fever in infants between 6 and 18 months of age presenting with seizures as percentage of the total patients seen (number of cases)



C. Lumbar Puncture Utility and Yield

Only 62/84 (74%) infants underwent a Lumbar Puncture (LP) to exclude Meningitis. The reasons for not following the treatment guidelines is unclear from the clinical records. However, none of these infants had any neurological abnormalities suggestive of meningitis on examination at the time of admission.

Meningitis or serious illness was diagnosed in 6/84 (7%) of infants based on CSF results. Review of the abnormal CSF results indicate that viral meningits, 3/62 (5%); both confirmed and presumptive, represent the main causative agent of meningitis in this review. There were no confirmed bacterial cultures, although 2/62 (3%) patients were treated for presumed bacterial meningitis . Only one infant had CSF suggestive of TB meningitis with an abnormal neurological examination and other risk factors that warranted further investigations.

Clinical variables of the 6 patients diagnosed with meningitis are summarised in Table 2. The mean age of this sub-group was 11.3 months and none were known with previous febrile seizures.

Table 2. Historical and Clinical variables of Infants with Abnormal CSF results

Variables	***Patient***					
	1	***2***	***3***	***4***	***5***	***6***
Malnutrition			X			
Preceding antibiotics		X				
Focal Seizure					X	
Reccurent seizures same illness	X	X			X	X
Prolonged depressed LOC	X		X			
Localising signs			X			
Meningism	X			X		
Incomplete immunisations			X			

On further analysis of the CSF results of these 6 patients, the following was found:

- *Patients 1 and 2* were treated as presumptive viral meningitis with lymphocyte-predominant CSF cell counts, normal CSF protein and CSF glucose levels. Bacterial and TB cultures were negative, however no viral PCR panels were done on their CSF samples.
- *Patient 3* had a lymphocyte-predominant cell count, with raised polymorphonuclear leukocytes (PMN), raised CSF protein and low CSF glucose levels suggestive of TB meningitis. CSF TB cultures were negative, but subsequent gastric washings were positive for acid-fast bacilli. No CSF TB PCR was performed.
- *Patient 4* had a lymphocyte-predominant cell count, with a raised PMN count. The viral PCR panel was positive for Herpes virus. The CSF sample was sent from an outside centre with no results available for CSF protein or glucose levels.
- *Patients 5 and 6* were treated as presumptive bacterial meningitis. Patient 5 had a bloody CSF sample with raised PMN and low CSF glucose levels. Patient 6 had a mixed cellular picture. Both patients' CSF bacterial cultures were negative.

No serious infection was thus diagnosed in children presenting with a SF in this study population. Three percent (3/84) of children presenting with CFS, and normal neurological findings, were diagnosed and treated as meningitis following a LP.

D. Clinical variables (risk factors) associated with abnormal lumbar puncture findings

Clinical variables of the 62 infants who underwent LP were analysed (Table 3). Univariate analysis for continuous variables and multivariate logistic regression analysis to determine adjusted associations between findings on history and/or clinical examination and CSF results did not yield statistically-significant data because of the small sample size. A clear source of fever outside of the central nervous system (CNS) was however statistically-significant in predicting a normal cerebrospinal fluid (CSF) result.

Table 3. Comparison of clinical variables of normal and abnormal CSF findings.

Variable	***Normal CSF (n=56)***	***Abnormal CSF (n=6)***	***Statistical Relevance***
Sex			
Female	27	5	p=0.197
Male	29	1	
Age (months)	12.3 (3.5 SD)	11.3 (2.9 SD)	p=0.511
Prior Febrile seizures	11	0	p=0.580
Nutrition			p=0.141
Normal	54	5	
Moderate malnutrition	1	1	
Severe Malnutrition	1	0	
Incomplete immunizations	14	1	p=0.509
Prior Antibiotics	5	1	p=0.472
HIV-infected	0	0	*
TB exposure	5	2	p=0.101
Fever characteristics			p=0.140
> 40'C	0	0	
38-40'C	26	2	
Fever on history only	29	3	
Seizure Type			p=1.00
Generalised tonic-clonic	45	5	
Focal	11	1	

Duration of Seizure			p=0.255
< 15 min	34	3	
> 15 min	8	0	
Status epilepticus	4	0	
Recurrent seizures	22	4	p=0.227
Clear extraneural infection site	51	1	p<0.001
Abnormal Neurological findings			
Localising signs	6	1	p=0.866
Depressed level of consciousness	4	2	p=0.112
Meningism	6	2	p=0.264

* p-value impossible to calculate as both categories are either negative, unexposed or unknown

E. Diagnosis at Discharge

At discharge, 89% (75/84) infants were diagnosed with FS, 60% (51/84) as SFS and 29% (24/84) as CFS. The incidence of FS in infants between 6 and 18 months presenting with seizures and fever was thus 13% (75/574) in this study. A further 6/84 (7%) were diagnosed with meningitis, and 3/84 (3%) subsequently with an underlying seizure or neurological disorder based on additional clinical features and investigations.

Chapter 5: DISCUSSION

The overall aim of this study was to determine the role of lumbar puncture in excluding meningitis in infants between 6 and 18 months of age admitted with seizures and associated fever to the Paediatric Emergency & Ambulatory Unit in a resource constrained setting.

Our study confirmed that seizures occur in the context of many childhood illnesses and accounted for 5% of Emergency Department visits. Fever and associated seizures were the presenting feature in 25% of infants between the ages of 6 to 18 month in our study; presenting a significant burden of disease and underlining the need for evidence-based management guidelines.

The utilization of LP in patients in this age group was 74% in our study, compared to 40-100% utilization of LP to exclude meningitis in other studies[28 29 31 32]. This may further reflect the uncertainty of clear indications for a LP in these children as well as changing guidelines over time.

FS were the most common final diagnosis in our study, with the overall incidence of FS in this age group higher at 13% than the reported 2-5% in the literature[9]. This is most likely due to other studies reporting on incidence in all children, compared to our study focusing on a specific age group. Nevertheless, it underlines the frequent clinical dilemma faced by clinicians to exclude meningitis or other serious illness in this particular age group.

Overall, meningitis was diagnosed in 7% of infants presenting with fever and seizures in our study; this is higher than reported in studies from both resource-rich settings[2 29 30 31] and resource constrained countries[33 34], but unfortunately these studies used different inclusion criteria and different age groups, making it difficult for direct comparisons.

In keeping with studies from resource rich countries[15 27 28], no meningitis was diagnosed in children presenting with a SF in this study population and a definite clinical diagnosis of a source of fever outside of the CNS was statistically-significant to differentiate between normal and abnormal CSF findings.

The 6 patients diagnosed with meningitis in this review did not meet the definition of SFS with clear indications for LP independent of age. Abnormal neurological findings were present in half of the children with abnormal CSF results, although not statistically-significant. This questions the assumption that infants younger than 18 months are more difficult to diagnose on clinical examination with meningitis.

The two (3%) cases of presumed bacterial meningitis identified in our study is higher compared to reports from resource-rich countries (0-1.5%)[15, 25-29], but lower than studies from resource-constrained countries (4.7-4.8%) [31, 32]. These children presented with complex febrile seizures and normal neurological findings; suggesting more careful assessment in children presenting with CFS in the emergency setting.

Similar to other studies[13], viral infections were the most common cause (> 60%) for fever and seizure in our study. Acute gastroenteritis accounted for 10% of the cause of fever, which hasn't previously been described in the literature. This may be in keeping with the lower incidence of acute gastroentritis in resource-rich countries and the introduction of the rota virus vaccine[42].

Our study population comprised of generally well infants with normal growth and development and no immune suppression; more in keeping with characteristics described in studies from resource rich countries, although the 78% complete immunization coverage were lower than described in these countries.

In view of the low risk of meningitis in well children presenting with SF and a clear source of fever outside of the central nervous system described in this study, it can be argued that the current American Academy of Peadiatric (AAP) guidelines for SF can be adopted in our setting. Applying these guidelines to our study population would have detected all cases of meningits.

Limitations

This study looked at retrospective routinely collected paper-based data in a busy short-stay inpatient ward with the possibility of incomplete data. Due to limited patients the study was not powered to calculate clinical variables (risk factors) associated with abnormal lumbar puncture findings in infants between 6 and 18 months of age presenting with seizures and associated fever. Furthermore, this was a single-center review and findings may not be transferable to other settings. Other

resource-poor settings may have larger burdens of malnutrition, HIV and TB in their populations.

Chapter 6: CONCLUSIONS AND RECOMMENDATIONS

Fever with associated seizures in infants between the ages of 6 to 18 month presented a significant burden of disease in our emergency unit; and underlines the need for evidence-based management guidelines.

Currently our institutional protocol on investigations needed for fever-associated seizures are based on older versions of American and European guidelines, which use age as a determining factor in those meeting the definition of SFS. The age cut-off of 18 months has been used based on the assumption that meningitis is difficult to detect in this age group. There is however little reliable evidence to support this long-held notion. Recent updates to the AAP guidelines have questioned this age paramenter, lowering the age cut-off to 12 months, with the proviso of a well-grown, fully-immunized and relatively HIV naïve population.

Our study suggests that despite our resource-constrained setting with malnutrition, HIV, and TB exposure, AAP guidelines for Simple Febrile seizures may be applied to healthy infants between the ages of 6 and 18 months; decreasing the use of LP with associated saving of costs.

Larger studies are required to identify clinical variables to guide best practice, especially in infants presenting with Complex Febrile seizures.

Appendix

1. Coding Sheet
2. Case Report Form (CRF)

1. CODING SHEET

1. AGE –

   in months (range 6 – 72 months)

2. SEX –

   1= male

   2= female

3. WEIGHT –

   1= normal for age

   2= failure to thrive

   3= severe malnutrition

   9= unknown

4. FEVER -

   1= 38 – 40 degrees

   2= > 40 degrees

   3= history of fever

5. SEIZURE -

   1= generalized tonic-clonic

   2= focal seizure

6. DURATION -

   1= <15 minutes duration

   2= 15-30 minutes

   3= status epilepticus

   9= unknown

7. PRECEDING ANTIBIOTIC EXPOSURE -

   1 = yes

   2 = no

   9 = unknown

8. RECURRENT SEIZURE IN SAME ILLNESS –

   1= yes

   2= no

9. PREVIOUS FEBRILE SEIZURE HISTORY –

   1= yes

   2= no

   9 = unknown

10. LEVEL OF CONSCIOUSNESS –

    1= normal level of consciousness

    2= depressed level of consciousness / GCS < 12

9 = unknown

11. FOCAL or LOCALISING SIGNS –

1= yes

2= no

12. PRESCENCE OF MENINGISM –

1 = yes

2 = no

13. LUMBAR PUNCTURE –

1= normal

2= abnormal

9= not performed

14. SOURCE OF FEVER –

1= upper respiratory tract infection

2= otitis media

3= lower respiratory tract infection

4= acute gastroenteritis

5= urinary tract infection

6= meningitis

7= septicemia

9= not identified

15. IMMUNISATION HISTORY –

1= up to date

2= not up to date

9= unknown

16. TB CONTACT HISTORY –

1= yes

2= no

9= unknown

17. HIV -

1= positive

2= negative (confirmed)

3= exposed

4= unexposed

9= unknown

18. DEVELOPMENTAL HISTORY –

1= appropriate for age

2= developmental delay

9= unknown

19. DIAGNOSIS AT DISCHARGE –

1= simple febrile seizure

2 = complex febrile seizure

3= meningitis / septicaemia

4= underlying seizure / central nervous system disorder

5= other

2. Data collection sheet

CODING SHEET

Unique coding number -	1. Age ☐
2. Sex ☐	3. Weight ☐
4. Fever ☐	5. Seizure type ☐
6. Duration of seizure ☐	7. Preceding antibiotic exposure ☐
8. Recurrent seizures ☐	9. Previous febrile seizure history ☐
10. Level of consciousness ☐	11. Focal or Localising signs ☐
12. Presence of Meningism ☐	13. Lumbar puncture ☐
14. Source of fever ☐	15. Immunisation status ☐
16. TB contact ☐	17. HIV status ☐
18. Developmental history ☐	19. Diagnosis at discharge ☐

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