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Influence of HIV status on outcomes of children admitted with sepsis at a paediatric hospital in Zambia: protocol for a prospective longitudinal study

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ABSTRACT

Introduction Sepsis, a condition of global public health concern, is a major cause of morbidity and mortality, especially in patients with underlying HIV infection. This study aims to determine outcomes, aetiology and antibiotic resistance patterns among children with HIV exposure or infection admitted with a clinical presentation suggestive of sepsis who have confirmed bloodstream infections at Arthur Davison Children's Hospital (ADCH) in Ndola, Zambia.

Methods and analysis This will be a prospective longitudinal study of 200 children aged <2 years admitted with sepsis at ADCH with two of the following conditions: temperature of 38.0°C, respiratory rate ≥20 breaths per minute and pulse rate ≥90 beats per minute. About 2–5 mL of blood collected from each participant will be inoculated into BACTEC culture bottles and incubated for 5–7 days. Positive cultures will be inoculated onto culture media for subculture followed by species identification followed by antibiotic susceptibility testing. Time-to-event outcomes such as hospital readmission and mortality will be analysed using Kaplan-Meier and Cox proportional hazards. Predictors will be identified using regression methods. All statistical tests will use a 5% significance level with a 95% confidence level. STATA V.16 will be used for statistical analysis.

Ethics and dissemination Ethical clearance and approval have been granted by the Tropical Diseases Research Centre Ethics Committee (TDRC-EC 092/07/23). Caregiver consent will be obtained verbally for participants presenting as medical emergencies, and written informed consent will be obtained once stable. Findings from this study will be shared with the Ministry of Health Zambia and will be disseminated to the scientific community through peer-reviewed scientific journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will investigate sepsis in children infected with HIV and exposed to HIV, a high-risk population.
⇒ This study will generate critical data on antibiotics suitable for children exposed to HIV, infected with HIV or not infected with HIV, information that is currently lacking in our setting.
⇒ To enable targeted interventions, our study will investigate risk factors for resistant bacterial species causing bloodstream infections in children at Arthur Davison Children's Hospital (ADCH).
⇒ Due to the integration of this study into the routine operations of the facility, study staff may be limited in their control of participants and clinicians who will be responsible for interventions and clinical outcomes in this population.
⇒ Despite the selection of a referral facility for this study, our generalisation of this data may be limited to only the catchment population ADCH.

INTRODUCTION

Background

Sepsis, a condition of global public health concern,[1] is a major cause of morbidity and mortality, especially in patients with underlying HIV infection.[2] Sepsis can be defined as a life-threatening organ dysfunction caused by an infectious agent.[3] The defining features of sepsis include at least two of the following: a white blood cell count of more than 12x ×109/L or less than 4 x 10^9/L, temperature equal to or more than 38°C, heart rate more than 90 beats per minute and a respiratory rate more than 20 breaths per minute.[4] Bacterial organisms, the major causes of sepsis, can enter the bloodstream via the nasopharynx, lungs, gastrointestinal tracts and genitourinary tracts.[5] Sepsis is among the most common opportunistic infections in children infected with HIV.[6] Sepsis in children infected with HIV results from the invasion of extrinsic-resistant bacterial normal flora.[7] Despite microorganisms differing from place to place, clinical syndromes rather than specific bacteria are managed in the absence of an accompanying microbiological profile.[8]

In recent years, sepsis has increasingly been caused by multi-drug-resistant (MDR) bacteria,[9] resulting from antibiotic misuse, low-dose prescriptions and the incomplete

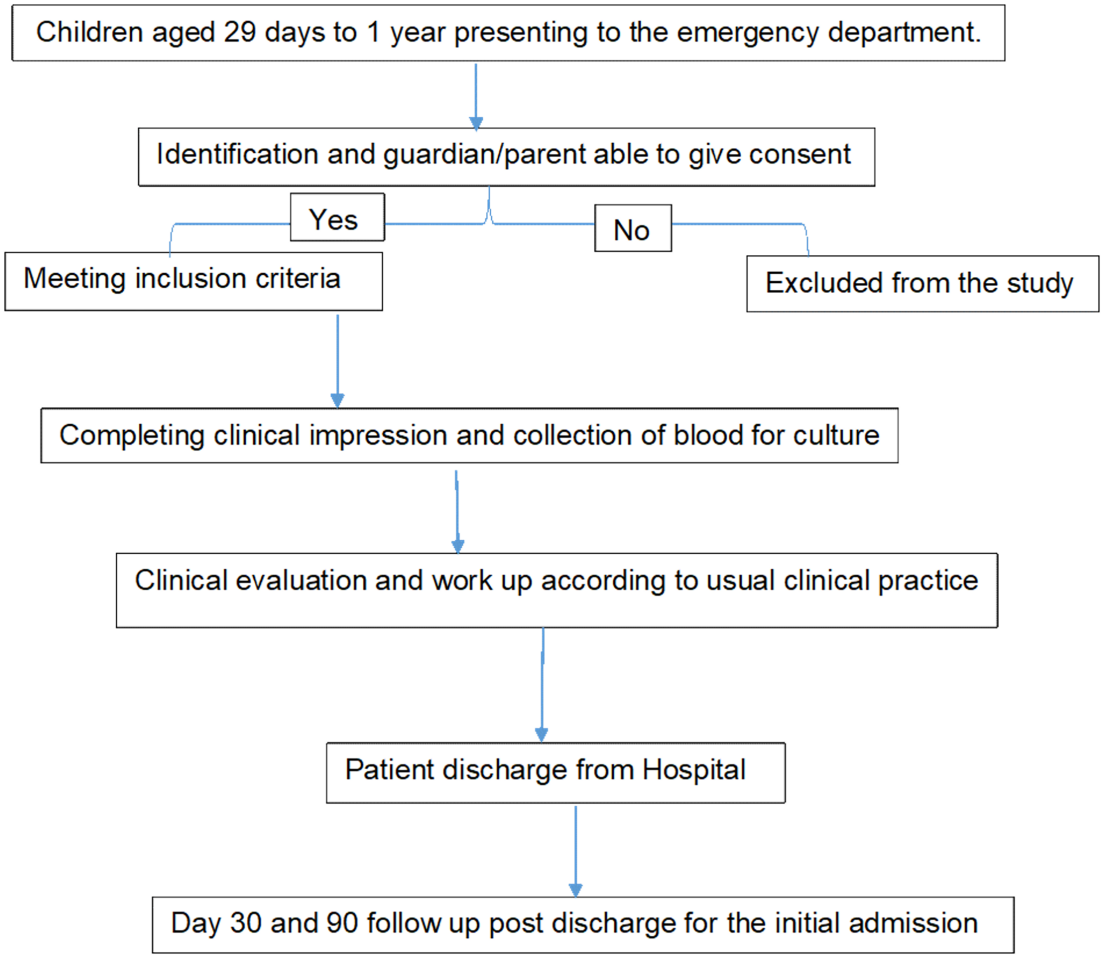

Figure 1 Sampling strategy.

intake of a prescribed dosage.[10] Bacteraemia is becoming more prevalent in patients infected with HIV.[11] Antibiotic administration in patients suspected of sepsis is encouraged, ideally immediately after blood collection for culture to determine the causative agent.[12] However, sepsis diagnosis is provisional in most children infected with HIV in many low- and middle-income countries,[13] and antibiotics are administered empirically at admission prior to blood culture.[14] The types of bacteria causing sepsis depend on the patient's age and premorbid conditions such as HIV.[15] The prevalence of HIV in Zambian children is approximately 1.1%,[16] with about 64% of children infected with HIV being on antiretroviral therapy.[17]

According to the Zambia Demographic Health Survey 2020 (ZDHS), over 30% of children presenting with fever are administered antibiotics despite not knowing the cause.[18] There is little known about the epidemiology and outcomes of sepsis and antibacterial resistance among infants infected with HIV.[19] A previous study done at ADCH in neonates showed resistance to the first-line and second-line treatments used as empirical treatment in children exposed to HIV and not exposed to HIV.[20] However, if no action is taken towards resistant bacteria, there will be continuous pressure on broad-spectrum antibiotics, increasing the likelihood of bacteria becoming resistant and causing sepsis in children.[21] While the ultimate cause of death is not identified in these patients, it is likely that a large proportion will succumb to severe sepsis.[19]

Despite a high mortality rate in childhood associated with sepsis, there is limited evidence on the causes and outcomes of paediatric bloodstream infections (BSI), especially in the context of HIV infection. In addition, there is a paucity of data on antibiotic susceptibility patterns in children infected with HIV admitted to hospitals with sepsis in Zambia.

Study rationale

The identification of pathogens in blood cultures has great diagnostic and prognostic value. Frequent information on common microorganisms and their antimicrobial susceptibility patterns is essential in formulating treatment guidelines for patients. According to WHO 2018 surveillance data, there are high levels of antibiotic resistance to a number of serious bacterial infections in both high- and low-income countries.[22]

This study will determine whether the antibiotics administered to children empirically for suspected sepsis in the HIV-infected, the HIV-exposed (children born to mothers infected with HIV) and the HIV-non-exposed

Table 1 Schedule of study activities

Field procedures and activities	At admission	At discharge	Day 30 follow-up visit	Day 90 follow-up visit
Secure informed consent	■			
Collect demographic and clinical information	■			
Collect blood for culture	■			
Record antibiotics administered during admission		■		
Antibiotics at discharge		■		
Phone interview for follow-up visit			■	■

and not infected are likely to be effective based on bacterial culture and sensitivity testing and, if not, to develop improved empiric treatment algorithms. The study will highlight the current status of antibiotic resistance in the infant population, bacterial resistance to commonly used antibiotics and the most common bacteria causing infections in infants infected with HIV, exposed to HIV or infants not exposed to or infected with HIV seen at ADCH.

METHODS AND ANALYSIS

Main objective

To determine the outcome, aetiology and antibiotic resistance patterns among children with HIV exposure or infection and those without HIV exposure or infection admitted to Arthur Davison Children's Hospital (ADCH) in Ndola, Zambia, with sepsis.

Specific objectives

1. To evaluate adverse outcomes (duration of hospitalisation, complications of hospitalisation and mortality) among children exposed to or infected with HIV and those without exposure to or infected with HIV admitted with sepsis.
2. To investigate the common bacteria responsible for BSIs among children admitted with sepsis who are exposed to or infected with HIV and those without exposure to or infected with HIV.
3. To determine patterns of antibiotic susceptibility among children exposed to or infected with HIV and those who are not exposed to or infected, admitted with sepsis.
4. To determine factors associated with MDR bacterial infections among children exposed to or infected with HIV and those without exposure or infected with HIV, admitted with sepsis.
5. To determine factors associated with adverse outcomes in children admitted with sepsis among children exposed to or infected with HIV and those without exposure or infected with HIV, admitted with sepsis.

Hypothesis

We hypothesise that there is no difference in children with BSI, MDR bacteria and adverse outcomes (defined as prolonged hospitalisation and/or rehospitalisation during the follow-up period) identified among HIV exposed, HIV infected and HIV uninfected and unexposed.

Study design and time period

This will be a prospective longitudinal study of all infants admitted with suspected sepsis from November 2023 to June 2024 at ADCH in Ndola, Zambia.

Study site

ADCH is the largest tertiary hospital in the Copperbelt Province of Zambia, with a bed capacity of about 250–300 beds, and it is the only specialised paediatric hospital in the Northern region of Zambia. The majority of infants needing critical medical attention in the province as well as in the nearby provinces of North Western, Luapula, Muchinga and Northern provinces are referred to ADCH. More than 10 infants are admitted to ADCH daily and the majority of the admissions are due to infectious causes.

Study population

The study will be conducted on all infants admitted to ADCH with suspected sepsis.

Inclusion criteria

For infants to be included in the study, they will need to meet the following criteria:

1. Less than 2 years of age presenting with a temperature of ≥38.0°C and either a heart rate ≥90 beats per minute or a respiratory rate ≥20 breaths per minute.
2. Signs and symptoms of a possible bacterial infection according to WHO IMNCI criteria.

Exclusion criteria

Children whose parents will not provide consent for their child to participate in the study will be excluded.

Outcomes

Primary outcomes

1. All-cause mortality (both in and out of the hospital during the 90-day follow-up).
2. Blood culture and drug sensitivity results at admission

Secondary outcomes

1. Length of hospital stay >72 hours.
2. Mortality for days 30 and 90
3. Unplanned readmission within 30 days and 90 days after discharge

4. Bacteria causing bloodstream infections.

Sample size

To calculate the sample size, we assumed to detect about 53.0% of confirmed bloodstream infection in children exposed to or infected with HIV[23] and about 26.0% in children not exposed to or infected with HIV.[24] A 95% CI was used with a ratio of 1:1 between the exposed and the unexposed group with the outcome being a positive blood culture for bacteria. Taking a potential loss to follow-up rate of 20% into consideration and 80% power, a sample size of 200 participants was calculated using Stata V.16.

Sampling strategy

Due to the success of option B+ for the prevention of mother-to-child transmission, many fewer children in Zambia are HIV infected. Although we originally planned to have differential recruitment (with recruitment of HIV-positive children only on Mondays and Wednesdays), the protocol has been amended to have daily recruitment of all three categories of children. The sampling strategy is shown in figure 1.

Data collection procedure

Confirmation of HIV infection in exposed children is done at 6 weeks of age by DNA PCR.[25] However, the HIV status of the child will be obtained from the under-five card and confirmation will be done with the guardian or caregiver. After obtaining written informed consent from the child's caregiver, demographic and clinical information obtained at admission will be entered in electronic case report forms on a mobile application installed with REDCap. The phone number of the guardian or caregiver for the participant will be obtained for follow-up contact. The duration of hospitalisation will be determined for all children from the date of admission to an outcome event, which can either be discharge or death.[26] Discharged participants will be contacted at day 30 after discharge via a phone interview to determine the well-being of the child and whether the child was later re-hospitalised or died. Table 1 outlines the schedule of activities during the course of the study.

Sample collection

To determine the causative bacteria and antibiotic susceptibilities, blood samples will be collected at admission for bacterial culture. The skin will be cleaned with a disinfectant solution before the withdrawal of blood. Thereafter, 3–5 mL of blood will be drawn aseptically from a peripheral vein and injected into a BACTEC Peds Plus (Becton Dickinson, Ireland) culture bottle.

Sample analysis

The blood sample will be sent to the microbiology laboratory at ADCH. Incubation in an automated machine at 37°C will be done immediately on receipt of the specimen for 5–7 days. After the automated BACTEC machine detects a positive culture within 24–72 hours, inoculation onto different culture media for subculture and organism identification will be performed using gram stain and biochemical tests. Thereafter, antibiotic susceptibility testing will be done using the Kirby-Bauer disc diffusion method, as per the Clinical and Laboratory Standards Institute guidelines.[27] Commonly used antibiotics, namely amoxicillin, cotrimoxazole, ceftriaxone and erythromycin, will be used for antibiotic susceptibility testing depending on the gram stain and biochemical results. The growth of multiple bacterial organisms will be considered contaminants.[28] However, if a pathogen and a common contaminant are isolated from the same culture, this will be classified as BSI with the pathogen.[29]

Data management and analysis

Collected data will be cleaned using data cleaning scripts in REDCap and then exported to STATA software V.16 SE (STATA Corp) for statistical analysis. Continuous variables will be compared univariably between HIV infected (n=67), HIV exposed (n=66), and HIV non-infected or non-exposed (n=67) in children admitted with sepsis using means and SDs (or median and IQR where non-normal), and categorical variables using χ^2 or Fisher's exact tests. To test for any difference in means between two continuous variables, a t test will be used for normally distributed data and a non-parametric Wilcoxon rank-sum (Mann-Whitney) test will be used for skewed data to find differences between medians. Time-to-event outcomes such as hospital readmission and mortality will be analysed and compared between HIV infected, HIV exposed, and HIV non-exposed or non-infected using Kaplan-Meier and Cox proportional hazards. Predictors of these outcomes will be identified using regression methods to identify an exploratory model with adequate control of confounding. The interpretation of effects will focus on those with $p<0.05$. Survival and logistic regression methods will be used to determine the relationship between the outcome and explanatory variables. All statistical tests will be tested at a 5% significance level with a 95% confidence level.

Patient and public involvement

The study results will be shared with ADCH management to bridge the gap between the study findings and the management of the patients. Patients and the public will not be directly involved in the conduct of the study.

ETHICS AND DISSEMINATION

Ethical clearance and approval for the study have been granted by the Tropical Diseases Research Centre Ethics Committee (TDRC-EC 092/07/23) and the National Health Research Authority. Permission to carry out the study and access patient information at ADCH has been obtained from ADCH hospital management. Confidentiality of patient information will be maintained as study data will be restricted to the principal investigator or designated study staff. Names of study participants will

not be displayed on the data collection tool; instead, serial numbers will be used to identify the patients.

Consent

Verbal consent will be sought from parents or guardians whose children present as emergencies and written informed consent obtained once the child is stabilised. Written consent will be sought from the parent or guardian after they have been given information about the study, an information leaflet offered or read out and time allowed for consideration. The right of the participant to refuse to participate without giving reasons will be respected. All participants will be free to withdraw at any time from the study without giving reasons and without prejudicing further management or treatment.

Publication policy and dissemination plans

All publications and presentations relating to the study will be authorised by the principal investigator (PI) and will include at least the study PI, local mentor and international mentor. The PI will be the custodian of the data and specimens generated from the study. Study data will not be the property of the participating healthcare facility where the data were generated but upon request, the data can be shared with the respective institutions. Study findings will be presented at ADCH and at local and international conference or scientific symposia. Additionally, the findings from the study will be shared with the Ministry of Health and will be disseminated to the scientific community through peer-reviewed scientific journals.

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Contributors JG conceptualised the study, wrote the first draft and acted as the guarantor. VD and RLM reviewed and edited the manuscript. CJ and DH performed the editing, reviewed the manuscript and supervised the conduct of the study.

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Competing interests None declared.

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