A Prospective Study of Neonatal Sepsis at the Charlotte Maxeke Johannesburg Academic Hospital's Paediatric Emergency Department

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DECLARATION

I, Tchouambou Simo Nelly Clotilde, hereby declare that this research report is my own work and has not been submitted or presented for any other degree or professional qualification at this or any other Institute. This research was undertaken in the Division of Emergency Medicine, University of the Witwatersrand, Johannesburg.

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SUBMISSION FORMAT OF THIS RESEARCH REPORT

As per University of the Witwatersrand Faculty of Health Sciences guidelines, this research report is being submitted in the publication ready format. The article has been submitted to The African Journal of Emergency Medicine and is currently under publication consideration.

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The author hereby certifies that this submission is not under publication consideration elsewhere and that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

AUTHOR CONTRIBUTIONS

TC – Primary author, study design, data collection, data analysis, manuscript write up and approval of the final manuscript and corresponding author

AL – Assisted with study design, data analysis, interpretation of results, editing of manuscript and approval of the final manuscript

FM – Assisted with data analysis, interpretation of results, preparation of manuscript, approval of the final manuscript

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DISSEMINATION OF RESULTS

Findings of this research study will be presented to clinical staff employed at the Charlotte Maxeke Johannesburg Academic Hospital Emergency Department.

AFRICAN RELEVANCE

- The incidence of neonatal sepsis in low- and middle-income countries is estimated at 3930 cases per 100 000 live births
- Neonatal sepsis accounts for a third of neonatal deaths in low-income countries
- A history of preterm birth, low birth weight, being HIV-exposed, not being breast fed and presentation with lethargy, dehydration, poor feeding, irritability, fever, vomiting, and respiratory distress are associated with a significantly higher likelihood of neonatal sepsis
- ED clinicians must adopt a high index of suspicion when attending to neonates presenting with these features

ABSTRACT

Background: Despite a significant reduction in the prevalence of neonatal sepsis over the last three decades, the prevalence still remains high, especially in low- and middle-income countries. The aim of this study was to determine the prevalence and presenting features of neonatal sepsis at a paediatric emergency department (ED).

Methods: Medical records of all neonates presenting to an academic hospital paediatric ED over a six-month period were analysed. Data was compared between neonates with and without sepsis. The odds ratio was calculated to determine factors associated with neonatal sepsis.

Results: Of the 210 neonates that were included, 43 (20.5%) were diagnosed with sepsis. Of these, 19 (44.2%) presented within the first 72 hours of life (early-onset neonatal sepsis) and 4 (9.3%) died prior to hospital discharge. A history of maternal employment (odds ratio (OR) 2.38, p=0.021), preterm birth (OR 3.24, p=0.019), low birth weight (<2.5kg) (OR 2.67, p=0.026), being human immunodeficiency virus-exposed (OR 3.35, p=0.002), not being breast fed (OR 4.36, p=0.001), and signs of lethargy (OR 14.01, p<0.001), dehydration (or 11.14, p<0.001), poor feeding (OR 7.20, p<0.001), irritability (OR 6.93, p<0.001), fever (OR 5.50, p<0.001), vomiting (OR 4.14, p<0.001) and respiratory distress (OR 4.12, p<0.001) at presentation were significantly associated with neonatal sepsis.

Conclusion: Among neonates presenting to the paediatric ED, various clinical features on history and examination may be useful in predicting the diagnosis of neonatal sepsis. Clinicians working in the paediatric ED must adopt a high index of suspicion when attending to neonates presenting with these features.

KEYWORDS

neonatal sepsis; emergency department; HIV exposed; preterm birth; low birth weight; breast feeding

INTRODUCTION

Neonatal sepsis can be defined as a clinical syndrome presenting with non-specific signs and symptoms secondary to an underlying bloodstream bacterial infection that manifests within the first 28 days of life [1]. Despite a significant reduction in global neonatal mortality over the past three decades, the burden remains high, with there being 18 neonatal deaths per 1000 live births reported in 2017. It is projected that 27.8 million children will die in their first month of life between 2018 and 2030. [2]. Neonatal sepsis has been shown to be responsible for approximately a third of neonatal deaths in low-income countries [3].

Between 2009 and 2018, the incidence of neonatal sepsis in low- and middle-income countries was estimated as 3930 cases per 100 000 live births [4]. In sub-Saharan Africa, it is estimated that neonatal sepsis is associated with a loss of 5.29 to 8.73 million disability-adjusted life years (DALYs), which translates to an annual economic burden of 10 to 469 billion US dollars [5]. Every year, a million neonates die from neonatal sepsis, with approximately 42% of these deaths occurring within the first seven days of life [6]. The overall mortality associated with neonatal sepsis has been estimated at 17.6% [4].

The clinical presentation of neonatal sepsis is predominantly non-specific and includes a myriad of signs and symptoms such as lethargy, dehydration, poor feeding, irritability, fever, vomiting, diarrhoea, respiratory distress, jaundice, seizures, hypothermia, and haemodynamic shock. This coupled with the low yield of true positive laboratory culture findings renders the diagnosis of neonatal sepsis challenging [7].

Although there are multitudes of publications relating to the subject of neonatal sepsis, there is a paucity of data on the prevalence and presenting features of neonatal sepsis in the paediatric emergency department (ED) setting in South Africa and other Low and Middle-

Income Countries (LMIC). Hence, the aim of this study was to determine the prevalence and presenting features of neonatal sepsis at a paediatric emergency department in Johannesburg, South Africa.

METHODS

This prospective cross-sectional study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) paediatric ED between 01 January and 30 June 2018. The hospital is a 1088 bed facility with approximately 220 paediatric beds that cater for a comprehensive range of paediatric medical and surgical subspecialities. Permission to conduct the study and ethics approval were obtained from the hospital manager and the Human Research Ethics Committee of the University of the Witwatersrand (certificate no M160608) respectively. The study enrolled all neonates that presented during the data collection period and in whom consent for study participation was obtained.

For the purpose of this study, neonatal sepsis was defined as presentation within the first 28 days of life and either a laboratory culture confirmed diagnosis of sepsis or presentation with clinical and/ or other laboratory features (combination of C-reactive protein (CRP), procalcitonin (PCT) and neutrophil count) that the attending specialist paediatrician attributed to the presence of neonatal sepsis and treated as such [7]. Early-onset neonatal sepsis was defined as presentation of sepsis within 72 hours of birth, while late-onset neonatal sepsis was defined as presentation with sepsis after 72 hours of birth [8]. Preterm birth was defined as birth before the completion of 37 weeks of pregnancy [9], while low birth weight was defined as weight at birth of less than 2.5kg [10]. Neonates who initially received empiric antibiotic therapy for possible neonatal sepsis, but in whom the diagnosis was later reviewed to a non-sepsis diagnosis, were categorised as not presenting with sepsis.

Doctors and nurses employed at the paediatric ED were briefed regarding the study protocol and requested to inform the primary investigator of all neonates (≤28 days of age) that presented over the data collection period. The primary investigator also reviewed the paediatric ED patient register to identify potential study subjects that were not identified by the unit staff. Informed consent for study participation was obtained from the primary caregiver of the neonate. Data from hospital records were collected daily by the primary investigator over the entire duration of hospital stay and entered into a standardised data collection sheet. Where necessary, additional information relevant to the study but not found in the patient's hospital records was directly obtained from the participant, the participants laboratory records, or the primary caregiver. Collected data included demographic details (sex, nationality, maternal employment), patient referral, preterm birth status, birth weight, HIV exposure status at birth, method of delivery, feeding method, in-hospital mortality, and clinical features at presentation. Subjects were followed up until data collection was completed. Inter-rater reliability was assessed by an independent researcher who re-extracted data from a random sample of 21 medical records and compared these to data obtained by the primary investigator. The overall Cohen's kappa coefficient (κ) was 0.82, indicating that the degree of inter-rater reliability was acceptable.

The data was thereafter entered into Microsoft® Excel® (Microsoft 365, Version 16.0.13029.20232) and exported to Stata version 16 (StataCorp Limited, Texas, United States of America) for statistical analysis. Frequency and percentage were determined for each of the variables. The chi-square test was utilized to determine if there were significant differences between neonates with sepsis and those without sepsis The odds ratio (OR) and 95% confidence interval (CI) were also calculated to determine the likelihood of neonatal sepsis for each of the included variables. A p-value of less than 0.05 was regarded as

significant. Study reporting conformed with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [11].

RESULTS

A total of 221 neonates presented to the paediatric ED during the period of data collection. Consent for study participation could not be obtained for 11 neonates, hence, a total of 210 neonates were included in the final study sample. Of these, 43 (20.5%) were diagnosed with sepsis, which comprised 19 (44.2%) neonates presenting with early-onset neonatal sepsis and 24 (55.8%) neonates presenting with late-onset neonatal sepsis. Laboratory culture confirmed sepsis was present in 9 (20.9%) neonate. All 43 subjects with neonatal sepsis received empiric antibiotic therapy at ED presentation and also required hospital admission. Among the 167 (79.5%) subjects without neonatal sepsis, 51 (30.5%) received empiric antibiotic therapy at ED presentation and 25 (15.0%) required hospital admission.

Table 1 compares data pertaining to patient demographics, clinical history findings and in-hospital mortality between neonates that presented with and without sepsis. Of note, the likelihood of sepsis was more than two times higher among neonates whose mothers were employed (OR 2.38, p =0.021) and neonates with a low birth weight (<2.5kg) (OR 2.67, p=0.026), the likelihood of sepsis was more than three times higher among neonates with a history of prematurity (OR 3.24, p =0.019) and neonates who were HIV-exposed (OR 3.35, p=0.002), and the likelihood of sepsis was more than four times higher among neonates that died during hospital admission (OR 4.18, p =0.049) and neonates that were formulae fed (OR 4.36, p =0.001). There were no significant differences with regards to sex, nationality, and method of delivery.

Table 1: Comparison of demographic data, clinical history findings and in-hospital mortality between neonates presenting with and without sepsis

Variable	Neonatal sepsis		OR (95% CI)	P-Value
	Yes (n=43)	No (n=167)		
Sex				
Male	24 (55.8)	74 (44.3)	1.00 (reference)	0.179
Female	19 (44.2)	93 (55.7)	1.59 (0.81-3.12)	
Nationality				
South African	31 (72.1)	116 (69.5)	1.00 (reference)	0.737
Non-South African	12 (27.9)	51 (30.5)	1.14 (0.54-2.39)	
Maternal employment	31 (72.1)	87 (52.1)	2.38 (1.14-4.94)	0.021
Self-referral	12 (27.9)	34 (20.3)	1.54 (0.72-3.31	0.271
Preterm birth	8 (18.6)	11 (6.6)	3.24 (1.21-8.65)	0.019
Low birth weight (<2.5kg)	10 (23.2)	17 (10.2)	2.67 (1.12-6.36)	0.026
HIV-exposed	15 (34.9)	23 (13.8)	3.35 (1.56-7.23)	0.002
Method of birth delivery				
Normal vaginal delivery	34 (79.1)	123 (73.7)	1.00 (reference)	0.467
Caesarean section	9 (20.9)	44 (26.3)	1.35 (0.60-3.04)	
Feeding				
Formulae feeds	21 (48.8)	30 (18.0)	1.00 (reference)	0.001
Breast fed	22 (51.2)	137 (82.0)	4.36 (2.12-8.93)	
In-hospital mortality	**4 (9.3)**	**4 (2.4)**	**4.18 (1.00-17.45)**	**0.049**

OR – odds ratio; CI – confidence interval; ED – emergency department

Table 2 compares clinical features between neonates that presented with and without sepsis. Of note, the likelihood of sepsis was significantly higher among neonates that presented with lethargy (OR 14.01, p < 0.001), dehydration (OR 11.14, p <0.001), poor feeding (OR 7.20, p <0.001), irritability (OR 6.93, p <0.001), fever (OR 5.50, p <0.001), vomiting (OR 4.14, p <0.001) and respiratory distress (OR 4.12, p <0.001), while the likelihood of sepsis was significantly lower (OR 0.37, p =0.012) among neonates that presented with jaundice.

Table 2: Comparison of clinical features between neonates presenting with and without sepsis

Variable	Neonatal sepsis		OR (95% CI)	P-Value
	Yes (n=43)	No (n=167)		
Lethargy	11 (25.6)	4 (2.4)	14.01 (4.19-46.76)	**<0.001**
Dehydration	11 (25.6)	5 (2.9)	11.14 (3.62-34.24)	**<0.001**
Poor feeding	20 (46.5)	18 (10.8)	7.20 (3.32-15.60)	**<0.001**
Irritability	10 (23.2)	7 (4.1)	6.93 (2.46-19.52)	**<0.001**
Fever	19 (44.2)	21 (12.6)	5.50 (2.58-11.72)	**<0.001**
Vomiting	20 (46.5)	29 (17.4)	4.14 (2.01-8.51)	**<0.001**
Respiratory distress	16 (37.2)	21 (12.6)	4.12 (1.91-8.89)	**<0.001**
Jaundice	10 (23.2)	75 (44.9)	0.37 (0.17-0.80)	**0.012**
Seizures	2 (4.6)	0	20.18 (0.95-428.42)	0.054
Hypothermia	3 (6.9)	3 (1.8)	4.1 (0.80-21.08)	0.091
Shock	1 (2.3)	1 (0.6)	3.95 (0.24-64.51)	0.335
Rash	7 (12.3)	12 (7.2)	2.51 (0.92-6.83)	0.071
Cough	12 (27.9)	30 (17.9)	1.77 (0.81-3.84)	0.149

Diarrhoea	6 (13.9)	17 (10.2)	1.43 (0.53-3.88)	0.482

DISCUSSION

To our knowledge, this is the first study to describe the prevalence and characteristics of patients presenting with neonatal sepsis to a paediatric ED setting in Southern Africa. In this study, neonatal sepsis was diagnosed in approximately one-fifth (20.5%) of all neonates presenting to the ED. Comparatively, a systematic review and meta-analysis comprising 14 683 neonates across 22 studies that were conducted in Iran, reported that the pooled national prevalence of neonatal sepsis in Iran was 15.98%, with there being a slightly higher prevalence in boys [12]. In another study that was conducted at a tertiary level hospital in North West Nigeria, the reported prevalence of neonatal sepsis was much higher at 37.6% [13].

In this study, the prevalence of early neonatal sepsis was 44.2%. Comparatively, a systematic review and metanalysis of 18 studies that were conducted in Ethiopia, reported a much higher prevalence of early onset-neonatal sepsis of 75.4% [14]. The study conducted in North West Nigeria also reported a high prevalence of early onset-neonatal sepsis of 78.2% [13]. A possible reason for the higher reported prevalence in these two studies is that both studies defined early-onset neonatal sepsis as onset of sepsis within the first seven days of life, whereas we defined it as onset within the first three days of life. In stark contrast to our study findings, an earlier study conducted between 2001 and 2003 at the neonatal unit of the same hospital as this study, reported that only five of ninety-six (5.2%) neonates presented with early-onset sepsis. The study however only enrolled neonates with a laboratory culture positive sepsis [15].

A study conducted in Southern Ethiopia reported that the likelihood of neonatal sepsis was 2.76 times higher in neonates who were born to mothers with lower income compared to

those who were born to mother with higher income [16]. Another study reported that every year approximately one millions neonates die from infections in low income households in Pakistan [17]. In contrast, in our study, the likelihood of developing neonatal sepsis was 2.38 times higher in neonates whose mothers were employed in comparison to neonates whose mothers were unemployed. Although we did not determine total household income and reasons for this rather surprising finding, a possible reason may be that total household income could have been low, hence these mothers were forced to seek employment. This finding should be further investigated in future studies.

A systematic review and metanalysis comprising of eight studies that were all conducted in Ethiopia, reported that compared to normal birthweight neonates, those with a low birth weight (<2.5kg) were 1.42 times more likely to develop sepsis [18]. Comparatively, in this study, a low birth weight (<2.5kg) was associated with a 2.67 times higher likelihood of neonatal sepsis.

The prevalence of neonatal sepsis was significantly higher among HIV exposed neonates in this study. Similarly other studies also reported a higher incidence of sepsis among HIV exposed but uninfected infants that were <3 months old [19–22]. Group B streptococcus was the causative organism in most of these studies. In comparison to breastfed neonates, the likelihood of presentation with neonatal sepsis was 4.36 times higher among formulae fed neonates in this study. A study conducted in Bangladesh reported that compared to neonates in whom breastfeeding was initiated within an hour of birth, those in whom there was a >48-hour delay in initiating breastfeeding and those that were not breastfed, respectively had a 4.13- and 4.7-times higher likelihood of developing severe illness in the first seven days of life [23]**.** Another study showed that even among partially breastfed neonates, the likelihood of neonatal sepsis was 18 times lower [24]**.**

In this study, presentation with lethargy (OR 14.01), dehydration (OR 11.14), poor feeding (OR 7.20), irritability (OR 6.93), fever (OR 5.50), vomiting (OR 4.24) and respiratory distress (OR 4.12) were associated with a significantly higher likelihood of being diagnosed with neonatal sepsis. Comparatively, a study that investigated the predictors of neonatal sepsis in four developing countries reported that a bulging fontanel (OR 10.0), poor feeding (OR 5.1), a history of convulsions (OR 4.2), hypothermia (OR 3.7), fever (OR 3.6) and a decrease in the level of consciousness (OR 3.0) were significantly associated with a higher likelihood of sepsis [25].

LIMITATIONS

There are some limitations to this study. Firstly, this was a single centre study, hence, our findings may differ to that of other facilities where triage criteria and management protocols may vary. Secondly, due to the low yield associated with obtaining a positive laboratory cultures in neonates with sepsis, it is possible that the true prevalence of neonatal sepsis may have been under- or over-reported, thereby influencing our study findings. However, this limitation is applicable to all studies that relate to neonatal sepsis. Thirdly, due to the relatively small sample size, our data was not amenable to multivariate analysis. Hence, we were unable to determine which of the studied variables are independent predictors of neonatal sepsis and related mortality. Nevertheless, it is hoped that findings of this study will encourage others to conduct similar but larger scale studies that will aim to determine variables that will serve as independent predictors of neonatal sepsis.

CONCLUSION

Among neonates presenting to the CMJAH paediatric ED, a history of maternal employment, preterm birth, low birth weight, being HIV exposed, not being breast fed, poor feeding and signs of lethargy, dehydration, irritability, fever, vomiting, and respiratory distress were significantly associated with a diagnosis of neonatal sepsis. Due to the non-specific presentation of neonatal sepsis and the consequences associated with missing the diagnosis, clinicians working in the paediatric ED must adopt a high index of suspicion when attending to neonates presenting with these features.

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RESEARCH PROTOCOL

A prospective study of neonatal sepsis at the Charlotte Maxeke Johannesburg Academic Hospital's Paediatric Emergency Department

Research protocol in partial fulfilment of the degree for Master of Science in Medicine (Emergency Medicine)

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INTRODUCTION

Predominantly due to its non-specific nature of presentation, the definition of neonatal sepsis is controversial, inconsistent and often confounded [1]. Neonatal sepsis can be defined as a myriad of clinical signs and symptoms characterized by an exaggerated inflammatory response secondary to a bacterial invasion of the bloodstream of the newborn infant within the first month of life [2]. Although the distinction between early-onset neonatal sepsis and the late-onset neonatal sepsis is variable most clinicians divide neonatal sepsis in these two categories. Early-onset neonatal sepsis is usually defined as the onset of sepsis before 3 days of life, whereas late-onset neonatal sepsis refers to the onset of sepsis from >3 until 28 days of life [3].

The presenting features of sepsis in the newborn infant may vary from mild to severe depending on the degree of maturity of the host immune system, the virulence of the causative agent and the duration of the infection. Signs and symptoms of neonatal sepsis are often insidious, nonspecific and may include respiratory distress, cyanosis, apnoea, poor feeding, lethargy, irritability, fever, hypothermia, vomiting, diarrhoea, unexplained jaundice, bulging fontanel, poor perfusion and skin manifestations including the presence of abscesses and petechia [4]. Term newborns are more like to present with fever, while preterm newborns are more likely to present with hypothermia [5]. Pyrexia is also a non-specific finding and may be secondary to other aetiologies including environmental causes, dehydration, and the presence of a hematoma. However, a sustained temperature elevation (>39˚C) longer than one hour is highly predictive of bacterial infection [6].

The causative organisms in neonatal sepsis are related to the age of onset of sepsis. In early neonatal sepsis, microorganisms are acquired either via the transplacental route or during passage through the colonized birth canal at delivery. Before the antibiotic era, gram-positive cocci were the most common pathogens causing neonatal infection. With the widespread use of intrapartum prophylaxis against Group B *Streptococcus*, there has since been an increase in the prevalence of gram–negative organisms; specially *Escherichia Coli* [7]. In a population-based observational study that was conducted in Israel, the authors reported that *Escherichia Coli*, Coagulase-negative *Staphylococcus*, *Haemophilus influenza* and *Listeria monocytogenes* were the microorganism most associated with the early-onset neonatal sepsis [8]. In contrast a study conducted in San Francisco reported that the most common etiologic agents of early-onset neonatal sepsis were Group B Streptococcus, *Streptococcus Viridians* and *Escherichia Coli, whereas Candida Albicans*, *Staphylococcus Aureus* and Coagulase-negative Staphylococci were the most common pathogens associated with late-onset neonatal sepsis [9].

Late-onset neonatal sepsis is generally associated with community-acquired or nosocomial pathogens. A study reported that 36% of 9 575 extremely low birth weight infants developed late-onset neonatal sepsis [10]. Another reported that Gram-positive organisms accounted for 70% of infections among very low birth weight infants. Coagulase-negative staphylococci, gram negative organisms and fungi accounted for 48%, 18%, and 12% of infections in this study respectively, with more than one organism being isolated in some cases [11]. More recent studies have also reported an increasing incidence of Gram-negative pathogens such as Escherichia Coli, Klebsiella spp., Enterobacter spp. and Pseudomonas spp. as causative organisms for late-onset neonatal sepsis [12].

The mortality rate for sepsis in the neonatal period is greater than any other period of life. In 2010, the Child Health Epidemiology Reference Group (CHERG) of The World Health Organization (WHO) and the United Nation Children's Fund (UNICEF) stated that globally 7.6 million children had died before their fifth birthday with approximately 40% (3.072 million) of these deaths occurring within the neonatal period and 5.2% (0.393 million) due to neonatal sepsis [13].

Community-based studies conducted in developing countries in Africa, Asia, South Asia and the Pacific found that the mortality rate of neonatal sepsis in newborns varied from 49 to 170 per 1000 live births while the incidence of blood-culture confirmed cases was about 5.5 per 1000 live births [14]. In Africa, neonatal sepsis accounts for 4% of neonatal deaths [13]. In Sub-Saharan Africa, the morbidity and the mortality from neonatal sepsis reflects a continuous burden of the disease [6]. A study conducted in 2005 in South Africa reported that the incidence of cultured-proven sepsis among patients included in the study was 8.5%. The

overall mortality rate of neonatal sepsis was 1.7% with the majority comprising low birth weight babies [15].

Maternal risks factors such as premature birth (<37 weeks), premature rupture of membranes (PROM), prolonged rupture of membranes (ROM >18 h), chorioamnionitis, maternal Group B streptococcal colonization and a septic or traumatic delivery were found to be associated with early-onset neonatal sepsis [6,16]. Babies of HIV-infected mothers are also more predisposed to developing both early- and as late-onset neonatal sepsis [17,18].

Numerous studies have addressed the continuing burden of neonatal sepsis [2,6,12,16]. Although, due to advances in neonatal care, there has been a significant global improvement in the survival of preterm infants, continued efforts to gather high quality data, especially in developing countries are essential to improve the outcomes of the neonatal sepsis.

For the purpose of this study neonatal sepsis will be defined as either a culture-confirmed diagnosis of sepsis or presentation with clinical and/ or laboratory features that the attending specialist paediatrician attributed to the presence of neonatal sepsis and treated as such [19].

STUDY AIM AND OBJECTIVES

Study aim

To determine the clinical profile of neonate with sepsis presenting to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Paediatric Emergency Department (PED).

Study objectives

1. To determine the prevalence of neonates with neonatal sepsis presenting to the CMJAH PED.

2. To describe the demographic and clinical characteristics of neonates with and neonates without sepsis
3. To determine the odds ratio and compare demographic and clinical characteristics of neonates with and neonates without sepsis

METHODS

Study design

Prospective, descriptive, and comparative cross-sectional study.

Study population

Neonates (≤28 days of age).

Study Site

The study will be conducted at the Charlotte Maxeke Johannesburg Academic Hospital, Paediatric Emergency Department, Area 161.

Inclusion criteria

All neonates, ≤28 days of life, that will present to the CMJAH PED, Area 161 over the 6-month data collection period.

Sample size

Convenience sample that will include all neonates presenting over a 6-month period. As per past unit registers, approximately 200 neonates are expected to present over the data collection period.

Data collection

- Data collection will commence once the protocol has been approved and ethics clearance obtained.
- Data will be collected by the primary investigator.
- Doctors and nurses employed at the CMJAH PED will be briefed regarding the study protocol and thereafter requested to inform the primary investigator of all neonates (≤28 days of age) that will presented over the data collection period.
- The primary investigator also review the PED patient register to identify potential study subjects that were missed by the unit staff.
- The primary investigator will obtain informed consent for study participation from the primary caregiver of the neonate.
- Data from hospital records were collected daily by the primary investigator over the entire duration of hospital stay and entered into a standardised data collection form (appendix A).
- Where necessary, additional information that may be required but not found in the patient's hospital records will be directly obtained from the participant, the participants laboratory records, or the primary caregiver.
- Collected data will include demographic details (sex, nationality, maternal employment), patient referral, preterm birth status, HIV exposure at birth, method of birth delivery, feeding method and clinical features at presentation.
- Inter-rater reliability will be assessed by an independent researcher who will be asked to re-extract data from a random sample of 21 medical records and these will be compared to data obtained by the primary investigator.

Data analysis

The data will be entered into Microsoft® Excel® and exported to Stata version 16 (StataCorp Limited, Texas, United States of America) for statistical analysis. Data will mostly be categorical in nature and will be described using frequency and percentage. The chi-square test will be utilized to determine if there are any significant differences between neonates presenting with sepsis and those without sepsis. The data will thereafter be subjected to binary logistic regression to determine which variables are associated with a higher likelihood

of neonatal sepsis. Findings will be reported as crude odds ratio (OR) with 95% confidence interval (CI) and p-value. Study reporting conformed will conform with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [20].

ETHICAL CONSIDERATIONS

Patients will be enrolled in the study only once written informed consent is obtained from the parent / caregiver (appendix B). Patient confidentiality will be respected at all times. Data collection sheets will not include personal data. Only relevant demographic data will be included. The information gathered will be protected by a coded numbering system, which will be stored in a password protected computer that will only be accessible to the researchers. Permission to conduct the study will be obtained from the head of the PED and hospital management (appendix C). Ethics clearance will be obtained from the Human Research Ethics Committee of the University of the Witwatersrand. Care givers will be given an information sheet explaining details of the study (appendix D).

TIMING

January-March 2016: Prepare protocol

April 2016: Protocol assessment

May 2016: Ethics

January-June 2018: Data collection

July-December 2018: Data Analysis and writing-up of report

FUNDING

This research project will be self-funded with an estimated cost as follows:

Stationery and printing – R500.00

Travel expenses (petrol) – R3000.00

Total cost – R3500.00

LIMITATIONS

Firstly, since this will be a single centre study, hence our findings may differ to that of other facilities due to possible differences in triage criteria and management protocols. Secondly, due to the difficulty associated with confirming a diagnosis of neonatal sepsis, it is possible that this may be under- or over-diagnosed, thereby resulting in under- or over-reporting of the actual prevalence and characteristics of neonatal sepsis.

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APPENDICES

Appendix A: Data collection sheet

Patient Identification Number (PIN):					
Demographic data					
Age (Date of birth)			**Sex**: F/M		
Race	Black	Asian	White	Coloured	Other
Socio-economic status (Mother)					
Employment		Employed		Unemployed	
Referring centres	Self	Clinics	Peripheral hospital	Private	Other
Maternal RVD Status	+ve		-ve	unknown	
Preterm	Y		N		
Delivery method	NVD		Caesarean section		
Invasive procedures (specify)					
Birth weight: _____g			**Gestational Age**: ____weeks		
Feeding	Exclusive breast		Exclusive formulae	Mixed Feeding	
Presenting features					
Lethargy		Fever		Hypothermia	
Respiratory distress		Vomiting		Diarrhoea	
Jaundice		Poor feeding		Rash	
Dehydration		Seizures		Decreased LOC	
Shock		Irritability		Apnoea	
Other (specify)					

Appendix B: Request for permission from hospital clinical director and head of PED to conduct research study

To**:** **Dr Mofokeng (Clinical Director, CMJAH)**
Prof Motara (H.O.D, CMJAH Emergency Department)

I am a postgraduate student currently registered at the University of Witwatersrand. I hereby request permission to carry out a research study, which is a part requirement of my MSc Med degree in Emergency Medicine. My proposed research study is entitled: ***A prospective study of neonatal sepsis at Charlotte Maxeke Johannesburg Academic Hospital's Paediatric Emergency Department*** (see attached protocol proposal)

If granted permission, the study will take place at the Charlotte Maxeke Johannesburg Academic Hospital on neonate who will be attending the Paediatric Emergency Department (Area 161). Informed consent will be obtained before enrolment in the study. At all times patient anonymity and confidentiality will be respected. There will be no risks or side effects involved. The study will all neonates (≤28 days of age) that will present from 01 January 2018 to 30 June 2018). The study will not interfere with the normal service delivery of the Paediatric Emergency Department. There will be no major expense involved. All minor expenses for the study will be borne by me. While undertaking this study I will ensure that my work and patient responsibilities will not be compromised.

Yours Sincerely

_____ _____
Dr T Clotilde (Researcher) Date

Pending University of the Witwatersrand ethics review board approval, I hereby grant permission to Dr N Simo to carry out the research study outlined above.

_____ _____
H.O.D Emergency Department Date

_____ _____
Clinical Director (CMJAH) Date

Appendix C: Parent / legal guardian information sheet

Good day, my name is Dr Tchouambou NS Clotilde. I am a student at the University of Witwatersrand conducting a research project for my master's degree in science in Emergency Medicine. Thank you for taking the time to read this information sheet.

Invitation to participate: Since you are the parent / legal guardian of _____, I am inviting you to voluntarily take part in this research project on behalf of him / her.

Introduction: _____ (name of patient) presented to the hospital and is receiving treatment as per standard treatment guidelines. This is a study involving research and not routine care. Research is just the way we learn the answer to a question. In this study we want to learn more about the illness of your relative.

What is involved in the study: Information for the study will be collected from the hospital records of _____ (name of patient), who is your son / daughter / other (specify): _____. I may also ask you a few questions as well as examine _____ (name of patient). Information that will be collected relates to demographic details, medical findings, laboratory / other test findings and discharge / final outcome details.

Benefits: The information obtained may be useful for future patients as we may then be able to better understand his / her illness. This may also result in improved care for other patients living with his / her illness.
Risks: This study would take approximately 15 minutes of your time. It is completely safe; there is no pain, no cost and no side effects or risk of any harm to you or the patient.

Confidentiality: All information is anonymous and cannot be later linked to you or the patients. Every effort will be made to keep all information confidential.

Participation is voluntary: You may choose to withdraw him / her from the study at any time. His / her treatment will not be affected by taking part, not take part or at any time deciding to no longer want to take part in the study.

Reimbursements: There will be no money paid to you or the patients for participating in the study. The results of the study will be available to the patient once the study has been completed.

Ethics: This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Any queries may be directed to the chair; Professor P Cleaton-Jones on 011 717-1234.The results of the study will be submitted for publication once the study has been completed.

I really appreciate your time and help if you choose to volunteer for my research project on behalf of _____. Please feel free to contact me if you have any questions on 073 486 8623 or email me: nellysimo@yahoo.com

Sincerely yours
Dr Tchouambou NS Clotilde

Appendix D: Consent form (parent / legal guardian)

Consent from parent / legal representative for participant in research

I, _____, consent / do not consent to participate in the research project entitled: **A prospective study of neonatal sepsis at Charlotte Maxeke Johannesburg Academic Hospital's Paediatric Emergency Department** on behalf of: _____

The procedures have been explained to me and I understand and appreciate their purpose, and the extent of my involvement. I have read and understand the attached study information leaflet. I understand that the research forms part of a research project and may not provide any direct benefit to me or the patient. This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Any queries may be directed to the chair; Professor P Cleaton-Jones on 011 717-1234. I am aware that participation is voluntary, and that I am free to withdraw from the project at any time without any consequences.

_____	_____
Date	Date
_____	_____
Parent / patient representative Name	Researcher
_____	_____
Parent / patient representative Signature	Researcher Signature

ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Tchouambou Simo Nelly Clotile

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160608

NAME: (Principal Investigator)	Dr Tchouambou Simo Nelly Clotile
DEPARTMENT:	Emergency Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Prospective Study of Neonatal Sepsis at the Charlotte Maxeke Johannesburg Academic Hospital's Pediatric Emergency Department
DATE CONSIDERED:	24/06/2016
DECISION:	Approved unconditonally
CONDITIONS:	
SUPERVISOR:	Dr Abdullah Laher and Dr Feroza Motara
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/08/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

TURN-IT-IN REPORT

Tcouambou SN Clotilde.docx

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