PLOS ONE

RESEARCH ARTICLE

# Neonatal sepsis at Mulago national referral hospital in Uganda: Etiology, antimicrobial resistance, associated factors and case fatality risk

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**Citation:** Tumuhamye J, Sommerfelt H, Bwanga F, Ndeezi G, Mukunya D, Napyo A, et al. (2020) Neonatal sepsis at Mulago national referral hospital in Uganda: Etiology, antimicrobial resistance, associated factors and case fatality risk. PLoS ONE 15(8): e0237085. https://doi.org/10.1371/journal.pone.0237085

**Editor:** Patrick Butaye, Ross University School of Veterinary Medicine, SAINT KITTS AND NEVIS

**Received:** December 29, 2019

**Accepted:** July 20, 2020

**Published:** August 10, 2020



**Data Availability Statement:** All relevant data are within the manuscript and its Supporting Information files.

**Funding:** This work was funded by the Norwegian programme for capacity development in higher education and research for development (NORHED) through the Survival Pluss project (Project Number; UGA-13-0030). JKT received the grant. URL: https://norad.no/en/front/funding/norhed/projects/norhed-project-in-south-sudan-

## Abstract

### Background

Sepsis is the third most common cause of death among neonates, with about 225,000 newborns dying every year globally. Data concerning the microbial etiology of neonatal sepsis and antimicrobial resistance profiles of its causative agents are necessary to inform targeted and effective treatment and prevention strategies.

### Objective

To determine the proportion of newborns with symptoms and signs of sepsis who had a positive blood culture, its bacterial etiology, the antimicrobial resistance patterns as well as the factors associated with culture-positivity and case fatality at Mulago national referral hospital in Uganda.

### Methods

We conducted a cross-sectional study among 359 neonates with symptoms and signs of sepsis who presented to the pediatric emergency care unit of Mulago national referral hospital from mid-January to end of December 2018. We performed blood culture and antimicrobial susceptibility testing, and conducted polymerase chain reaction to identify methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. We used multivariable logistic regression to estimate the association between potential risk factors and culture-positive neonatal sepsis.

### Findings

Of the 359 neonates recruited, 46 (12.8%; 95% CI 9.5%, 16.7%) had a positive blood culture. The predominant isolated bacteria were *Staphylococcus aureus* in 29 (63.0%),

and-uganda/. The NORHED played no role in design, analysis or interpretation of the study findings. The contribution by VN and HS was supported by the Centre for Intervention Science in Maternal and Child Health (CISMAC; project number 223269), which is funded by the Research Council of Norway through its Centres of Excellence scheme and the University of Bergen (UiB), Norway.

**Competing interests:** The authors have declared that no competing interests exist.

*Escherichia coli* in seven (15.2%), and *Klebsiella pneumoniae* in five (10.9%). Of the 46 pathogens, 73.9% were resistant to ampicillin, 23.9% to gentamicin and 8.7% to ceftriaxone. We isolated MRSA from the blood specimens of 19 (5.3%) of the 359 neonates, while 3 (0.8%) grew extended spectrum beta lactamase producers. The case fatality risk among neonates with neonatal sepsis was 9.5% (95% CI: 6.6%, 13.0%). Cesarean section delivery was strongly associated with culture-positive sepsis (adjusted odds ratio 3.45, 95% CI: 1.2, 10.1).

## Conclusion

One in eight neonates with clinical signs of sepsis grew a likely causative bacterial pathogen. *S. aureus* was the main pathogen isolated and a third of these isolates were MRSA. A significant proportion of the isolated bacterial pathogens were resistant to the first and second line antibiotics used for the treatment of neonatal sepsis. There is need to revisit the current treatment guidelines for neonatal sepsis.

## Introduction

The mortality among children less than 5 years of age has declined considerably over the last two decades, but neonatal mortality remains high, accounting for 2.6 million annual deaths[1]. Uganda has a neonatal mortality of 22.3 deaths per 1,000 live births which is one of the highest in the world[2]. Severe infections are the leading cause and accounts for approximately one-third of newborn deaths in sub-Saharan Africa[3]. Among survivors, neonatal sepsis may be accompanied by long-term complications such as neurodevelopmental impairment[4]. To achieve the third sustainable development goal of reducing neonatal mortality to under 12 deaths per 1,000 live births, a better understanding of the etiology of neonatal sepsis is needed.

Important signs and symptoms of neonatal sepsis include inability to breastfeed, convulsions, fast breathing, severe lower chest wall in-drawing, lethargy, fever and hypothermia[5]. Neonatal sepsis is a clinical syndrome including septicemia and meningitis that is classified according to disease onset[6]. Early-onset sepsis (EOS) is defined as disease among neonates aged 72 hours or less while late-onset sepsis occurs from 4 to 28 days[6]. Early-onset sepsis usually results from an infection acquired *in utero* or during the birth process and group B *Streptococcus*(GBS) is the most common pathogen causing EOS in high income countries whereas *Staphylococcus aureus*, *Klebsiella species* and *Escherichia coli* are the most common causes in low and middle income-countries[7–9]. In low and middle income countries, late-onset sepsis is usually a result of infection from the surrounding environment (hospital or community) and the incriminated pathogens are majorly gram negative bacteria including *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Pseudomonas aeruginosa*; as well as *S. aureus* [10–12]. However, the pathogen profile differs depending on the region. There is a predominance of gram negative pathogens and low prevalence of GBS in south Asia and sub-Saharan African compared to the high GBS prevalence in high income countries[10, 11, 13]. Surveillance of the etiology of neonatal sepsis and resistance patterns of the causative bacteria is critically important in informing the empirical treatment of neonatal sepsis and in guiding the development of preventive strategies, including the development and deployment of vaccines. This information is particularly important in resource-limited settings where access to blood cultures is limited and if available, often unaffordable.