Incidence, Aetiology and Short Term Outcomes of Extreme Hyperbilirubinaemia, in Term infants born in the Western Health subdistrict of Cape Town, South Africa between 2019 and 2020

By

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Presented in fulfilment of the requirements for the degree of
Master of Medicine (MMed): Paediatrics and Child Health
Faculty of Medicine and Health Sciences
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February 2024

Plagiarism Declaration

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Name: Carin Coraizin

Student number: CRZCAR002

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Date: 15/2/2024

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Declaration

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Acknowledgements and contributions

I would like to express my sincere gratitude to my supervisor, Dr Yaseen Joolay for his valuable guidance, commitment, and support throughout the research process. To my family, thank you for all the support, sacrifices and encouragement.

I would like to acknowledge further contributions to this thesis from Dr Heleen Vreede from the National Health Laboratory Service for assistance with data collection and Dr Cara Van Niekerk for assistance with data capturing.

Abbreviations

G6PD: Glucose-6-phosphate dehydrogenase

LMICs: Low and middle income countries

GA: Gestational age

NHLS: National Health Laboratory System

ECCR: Electronic continuity of care record

PIPP: Perinatal Problem Identification Program

MOU: Midwife obstetric unit

AAP: American Academy of Paediatrics

TCB: Transcutaneous bilirubin

Publication-ready manuscript

The following manuscript has been submitted to The Journal of Tropical Pediatrics. The journals aims, scope and author guidelines are given in appendix B.

Incidence, aetiology and short term outcomes of extreme hyperbilirubinaemia, in term infants born in the Western Health subdistrict of Cape Town, South Africa between 2019 and 2020.

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Abstract

Introduction: Extreme levels of bilirubin in the newborn is a major cause of lifelong neurodevelopmental impairment, which places a financial burden on healthcare resources and caregivers.

Objective: To determine the incidence, aetiology and short term outcomes of extreme hyperbilirubinaemia in term infants born in a resource-limited setting.

Methods: This is a retrospective observational study looking at term neonates with a birth weight ≥ 2500g, born in the Western health subdistrict of Cape Town, South Africa, between 1 January 2019 and 31 December 2020, who were exposed to a serum bilirubin level of ≥ 430 μmol/L in the first week of life and received care in the public health system.

Results: Extreme hyperbilirubinaemia occurred in 59 term infants. The incidence was 74 cases per 100 000 (<0.01%) live births equating to 1 case in every 1345 live births. The cause of hyperbilirubinaemia was identified in 51 of the cases (86%), the most common being ABO incompatibility (31/51, 61%), followed by glucose-6-phosphate dehydrogenase deficiency (11/51, 22%). Twelve infants (20 %) underwent an exchange transfusion. Six infants were encephalopathic. Forty-seven infants (80%) were readmitted after initial post-natal discharge, with a mean age of readmission of 113 hours old (SD 31 hours).

Conclusion: The incidence of extreme hyperbilirubinaemia in the Western health subdistrict of Cape Town is higher than in high-income settings. Further work should focus on training of healthcare workers and education of caregivers, for the early detection of significant hyperbilirubinaemia to prevent neurological complications caused by bilirubin toxicity.

Introduction

Hyperbilirubinaemia in term infants is common, with up to 65% of newborn infants developing jaundice in the first week of life. This is a normal physiological response in the newborn's transition to extrauterine life. [1] Most cases of neonatal hyperbilirubinaemia do not have serious consequences, but it is known that toxic levels of bilirubin is a major cause of lifelong neurodevelopmental impairment. [2] Although there is no single threshold at which bilirubin becomes neurotoxic [3], Bhutani et al. and Olusanya et al. proposed definitions for the severity of hyperbilirubinaemia, which is presented in Table 1. [4, 5]

The commonest causes of neonatal hyperbilirubinaemia worldwide include haemolytic diseases like ABO incompatibility, glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency and rhesus disease, perinatal infections, sepsis and exclusive breastfeeding. The primary aim in the management of neonatal hyperbilirubinemia is to prevent bilirubin induced mortality and neurotoxicity. [4] Treatment modalities for hyperbilirubinaemia include phototherapy, intravenous immunoglobulin and exchange transfusion, with phototherapy being the first line choice of treatment.[6] Most infants who receive these treatments survive and recover from the acute phase of bilirubin encephalopathy but despite early recovery, these infants may go on to develop permanent neurological sequelae. [7]

Neonatal hyperbilirubinemia accounted for 1309 deaths per 100 000 live births in 2016 and ranked seventh globally among all causes of neonatal deaths in the first week of life. [4]. Evidence suggests that low- and middle-income countries (LMICs) have a greater burden of hyperbilirubinaemia when compared to high-income countries. In a systematic review the overall incidence of severe jaundice globally was reported as 99 cases per 100 000 (<0.1%) live births with the highest incidence of 6678 cases per 100 000 (6.7 %) live births reported in Africa and the lowest of 37 cases per 100 000 live births in Europe (<0.1%). [8] In South Africa, the incidence of severe hyperbilirubinaemia revealed a rate of 13.5% and a rate of exchange transfusion of 5% in a study done four decades ago.[9] In studies done in high-resourced countries like Denmark, Sweden and Australia the incidence of extreme hyperbilirubinaemia ranged from 9.4 to 50 per 100 000 live births. [2, 10, 11] There is a

paucity of information regarding extreme hyperbilirubinaemia, especially in LMICs, with no publications found in South Africa.

We conducted this study to determine the incidence of extreme neonatal hyperbilirubinemia in the Western health subdistrict of Cape Town, South Africa, as the largest burden of disease is in Africa and South-east Asia, but most of the literature on significant hyperbilirubinaemia emanates from high-income countries. [8] The information from this study will improve knowledge in LMICs, that would be valuable in strategies for risk reduction.

Methods

This is a retrospective observational study looking at term neonates with a gestational age (GA) of ≥ 38 weeks and a birth weight ≥ 2500 g, born in the Western health subdistrict of Cape Town between 1 January 2019 and 31 December 2020, who were exposed to a total serum bilirubin (TSB) level of ≥ 430 μmol/L in the first week of life. A bilirubin level of more than 430 μmol/L was chosen to define extreme hyperbilirubinemia as this is the exchange transfusion threshold used for term infants at 120 hours in South Africa [6]. The primary objective of the study was to determine the incidence of infants with extreme hyperbilirubinaemia in the first week of life. Secondary outcomes were to describe the aetiology and short-term outcomes of these infants, specifically looking at mortality and morbidity, specifically looking at treatment received, complications and signs of encephalopathy. Ethical approval was obtained from the University of Cape Town Health Sciences Faculty Research Ethics Committee on 8 April 2021 and the approval number is 210/2021 and consent for the study was obtained from the Western Cape Department of Health. Cases were extracted from the National Health Laboratory System (NHLS) who were born in this period, who were < 8 days old and had a blood TSB ≥ 430 μmol/L, that was taken at public health facilities tending to newborns in the Western health subdistrict of Cape Town. NHLS is one central laboratory system used by public health facilities in South Africa and a total of 14 health facilities were included in this study from the Western health subdistrict. Medical records for cases identified were obtained in the form of the electronic continuity of care record (ECCR) system and where ECCR records did not provide the required information a physical folder review was done. The data was then collected and

entered into a confidential REDCap database. Data were summarized using descriptive statistics, specifically the mean, median, standard deviation, and interquartile range. Statistic tests were done using IBM SPSS Version 28.0.1.0. released in 2021, Armonk NY: IBM Corp. Continuous variables were analyzed using the Student's t-test a and Mann Whitney U tests were used for skewed data. Chi square and Fisher's exact test was used for categorical data. Data on live births were obtained from the Perinatal Problem Identification Program (PPIP). A p-value of less than or equal to 0.05 was used to denote statistical significance.

Results

One hundred thirty-seven tests were found with a value of ≥ 430 µmol/L from a total of 81 patients over the two-year period. Of the 81 patients, 59 met the inclusion criteria for this study (Figure 1). During the period studied PPIP reported a total of 79321 live births of infants with a birthweight of more than 2500 g. The incidence of extreme hyperbilirubinaemia was calculated to be 74 cases per 100 000 live births (<0.1%) equating to 1 case in every 1345 live births.

The ethnic demographic for this region as per consensus data in 2022 is Mixed race (42 %), Black African (39%), White (16%), Indian/Asian (1%) and other (2%). A description of the patient demographic characteristics is given in Table 2. Thirty-three (56%) of the infants were male and 26 (44%) of the infants were female. Thirty (51%) of the infants were born at a midwife obstetric unit (MOU), 25 (42%) infants were born at a regional or district hospital, 3 infants (5%) were born at a tertiary level hospital and 1 infant (2 %) was born before arrival to a facility. The mean maternal age was 26 years (standard deviation [SD] 5.1), and 20 mothers (34%) were primiparous. Forty-three cases had a confirmed GA ≥ 38, of the 43 the mean GA was 39. Sixteen cases were noted to be term, but the actual GA was not specified. The mean birth weight was 3339 g (SD 436 g). The median peak bilirubin level reported was 476 µmol/L (IQR 449 - 530 µmol/L). The highest recorded bilirubin level was 761 µmol/L.

Characteristics of infants with extreme hyperbilirubinemia identified before and after discharge from hospital is presented in Table 3. Extreme neonatal hyperbilirubinemia was

identified in 12 infants (20%) before they were discharged from hospital. The remaining 47 infants (80%) were readmitted with hyperbilirubinemia from home. The mean age of readmission was 113 hours old (SD 31 hours). Five infants (8 %) had lost more than 10% of their birth weight at the time of readmission. The mean weight at readmission was 3190 g (SD 443) and the median weight difference since birth and readmission was 70 g (IQR 0 – 225 g).

A cause for extreme hyperbilirubinemia was identified in 51 of the cases (86%). ABO incompatibility was the most common cause (61%), followed by G6PD deficiency (22%), rhesus isoimmunization (2%), sepsis (2%) and no causes were found in 8 of the cases (16%).

All 59 infants received phototherapy. Twelve infants (20%) underwent an exchange transfusion with 1 out of the 12 (2%) infants received a second exchange transfusion. The characteristics of infants who received exchange transfusions are presented in Table 4. No complications were reported for those who underwent an exchange transfusion. Six infants (10%) were treated with intravenous immune globulin, three of whom also received exchange transfusions. The mean bilirubin-induced neurologic dysfunction score was 5.8 (SD). At the time of presentation 6 infants (10%) had abnormal neurological signs and symptoms suggestive of encephalopathy such as poor feeding, high pitched cry, opisthotonos or seizures. Five (8%) out of the six who were encephalopathic received exchange transfusions. Causes were identified in 4 out of the six infants. Five (8%) out of the six infants were readmitted to hospital.

All 59 infants survived to be discharged home. The median age of discharge was 8 days old (IQR 7 - 10). The 6 infants who were encephalopathic had a median age of discharge of 11 days (IQR 9 - 13) versus a median of 8 days (IQR 7 - 10) who were not encephalopathic ($p = 0.018$).

Figure 1. Flow chart of the study selection

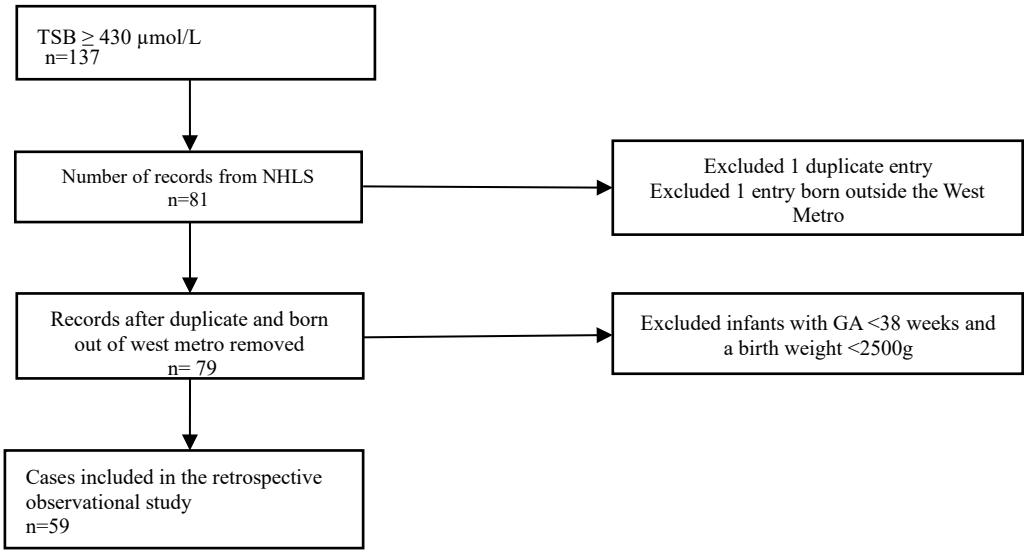

Table 1: Severity of Hyperbilirubinaemia

Severity of Hyperbilirubinaemia	Bilirubin Value
Significant	291 - 341µmol/L
Severe	342 - 426 µmol/L
Extreme	427- 513 µmol/L
Hazardous	≥513 µmol/L

Table 2: Demographic characteristics

Characteristic **Infant**	**No. (%) of infants** **n=59**
Sex, male	33 (55.9)
Birth weight, g, mean (SD)	3339 (436)
Readmission	47 (80)
Peak total bilirubin, µmol/L, median (IQR)	476 (449-530)
Readmission age, hours, mean (SD)	113 (31)
Weight loss of > 10 %	5 (8.5)

Maternal	
Maternal age, years, mean (SD)	26 (5)
Primigravida	20 (34 %)
Place of birth	
MOU	30 (51%)
Regional or district hospital	25 (42%)
Tertiary Hospital	3 (5%)
Home	1 (2%)

Table 3: Characteristics of infants with extreme hyperbilirubinemia identified before and after discharge from hospital

Characteristic	**Identified before discharge n=12**	**Readmitted to hospital n=47**	p value
Birth weight, g, mean (SD)	3468 (322)	3306 (458)	0.253
Sex, male, no (%)	6 (50%)	27 (57%)	0.643
Peak total bilirubin level, median (IQR)	470 (446-528)	476 (452-530)	0.504
Causes of jaundice, no. (%) ABO incompatibility BF jaundice G6PD def Sepsis Rh iso immunisation Unknown	 9 (75%) 0 1 (8%) 0 1 (8%) 1 (8%)	 22 (46,8%) 7 (15%) 10 (21%) 1 (2%) 0 7 (15%)	0.183
Haemolytic cause no. (%)	11 (91%)	32 (68%)	0.151

Exchange transfusion no. (%)	4 (33%)	8 (17%)	0.240
Intravenous immune globulin no. (%)	2 (17%)	4 (9%)	0.591
Encephalopathy no. (%)	1 (8%)	5 (11%)	1.000
Age at discharge, days, median (IQR)	7 (6-9)	8 (7-10)	0.018

p-value ≤ 0.05 is statistically significant

Table 4: Characteristics of infants who received exchange transfusion

Characteristic	Exchange transfusion N= 12	No exchange transfusion N= 47	p-value
Sex, male	6 (50%)	27 (58%)	0.643
Birth weight, g, mean (SD)	3255 (389)	3360 (449)	0.460
Peak total bilirubin level, median (IQR)	536 (474-605)	472 (445-507)	***0.015***
Readmission	8 (67%)	39 (83%)	0.240
Readmission age, hours, mean (SD)	107 (29)	113 (32)	0.666
Haemolytic cause	9 (75 %)	27 (58.7)	0.530
Encephalopathy	5 (42%)	1 (2%)	***0.001***
Intravenous immune globulin	3 (25%)	3 (6%)	0.092
Age at discharge, days, median (IQR)	8 (7-10)	8 (7-10)	0.723

p-value ≤ 0.05 is statistically significant

Discussion

This study highlights that extreme hyperbilirubinaemia is an important neonatal condition in South Africa. In the two-year study period, the incidence of extreme hyperbilirubinaemia in the Western health subdistrict of Cape Town was 74 cases per 100 000 live births (<0.1%). Authors are currently not aware of any studies that document the incidence of extreme hyperbilirubinaemia in sub-Saharan Africa. Twenty-two of the infants had hazardous hyperbilirubinaemia (TSB ≥513 μmol/L), which calculates to an incidence of 24 in 100 000 (<0.05%). The incidence in the Western health subdistrict of Cape Town, South Africa is 74 cases per 100 000 live births (<0.1%), which is statistically significantly high in comparison to high-income countries, where it ranges from 9.4 to 50 per 100 000 live births (0.01-0.05%)

[12-14]. Our higher rates can be attributed to a combination of factors such as resource constraints, delays in treatment due to lack of recognition, knowledge and management of hyperbilirubinaemia by both healthcare workers and caregivers, as well as risk factors such as ABO incompatibility, G6PD deficiency and septicaemia. Twelve infants (20%) underwent an exchange transfusion over the two-year study period and 6 infants were noted to be encephalopathic. Our current exchange transfusion protocol is to exchange infants who are above the exchange transfusion threshold and who are not responding adequately to intensive phototherapy or who have signs of encephalopathy. Although our study did not aim to assess the long-term neurologic disease a further study looking at these patients would be helpful. The limitations of our study were that our study only reflects data from the public sector of the Western health subdistrict and did not include data from the private sector, and that a weight ≥ 2500 g was used as a proxy for term babies.

In South Africa, healthy newborns are discharged with their mothers within 24 hours after an uncomplicated vaginal delivery and within 48hrs following an uncomplicated Caesarean section delivery. At discharge, mothers are advised to bring their newborns for a follow-up evaluation at their local clinic within one week. [15] In this study the majority of infants (n=47, 80 %) were readmitted from home. The mean age of readmission was 113 hours (<5 days old). Although not statistically significant, there were higher exchange transfusion rates in those readmitted, compared to those identified in hospital as well as higher rates of encephalopathy. Infants 72 hours and older have a higher chance of being diagnosed with neonatal jaundice, which is in accordance with the natural progression of physiological jaundice that peaks between days 3 and 5. [15] In our setting follow up at 48-72 hours is often a challenge for parents, due to distance from hospital and finances. As most of the patients were readmitted, it raises the concern that there is under-recognition of infants with jaundice or at risk of developing jaundice and highlights the importance of identifying at-risk newborns before they are discharged home as well as arranging earlier follow-up at the local clinic for those at risk.

It has been shown that visual inspection of jaundice is not accurate in predicting the presence or severity of hyperbilirubinaemia.[17] Okuwundu et al. have demonstrated that measuring the transcutaneous bilirubin (TCB) level on all infants before discharge from hospital is helpful in predicting which infants will experience severe hyperbilirubinaemia and may

reduce hyperbilirubinaemia-related morbidity and mortality.[18] The latest American Academy of Pediatrics (AAP) guidelines also recommends that all infants should have at least one TCB or TSB measured prior to discharge.[16] We recommend implementing TCB screening on all infants during the hospital stay and subsequent clinic visit in our own system. We recommend that other similar hospital systems make these changes if they are experiencing similarly high incidence of extreme hyperbilirubinaemia and exchange transfusions but recognize that universal TCB screening is a challenge in our resource limited setting as many public health facilities in South Africa don't have access to TCB devices and rely on blood draws which can have delays in getting results and starting treatment. TCB devices are utilized in larger regional and tertiary hospitals in this region and at the time of the study was not commonly available at primary healthcare level. The devices are costly, between $5000 and $8000 per device however, device breakdown, global supply chain delay and lack of consumable items all contribute to the limited use of TCB devices in the community.

ABO incompatibility and G6PD deficiency were the leading causes for extreme hyperbilirubinaemia in this study, which is in keeping with aetiology found in other studies. [2, 10, 14]. For all babies, it is important to know the mother's blood group and to screen for jaundice, especially if they are born to mothers with type O blood. This will help in identifying infants at risk for developing hyperbilirubinaemia and who will need sooner follow-up and repeat screening. G6PD deficiency is recognized as one of the important causes of hyperbilirubinemia leading to kernicterus and it is a condition that is prevalent in sub-Saharan Africa.[14] Currently, G6PD screening in South Africa is not routinely performed. Although, the World Health Organization recommends G6PD screening among populations where 3-5% of males are affected, the AAP only recommends testing in jaundiced newborns receiving phototherapy with family history, ethnicity or a geographic origin suggestive of G6PD deficiency. [16]

Emphasis should be made on educating both families and healthcare workers on neonatal jaundice and other signs of hyperbilirubinaemia to ensure early identification and prompt treatment of hyperbilirubinaemia. Mothers should be educated on neonatal jaundice in the antenatal period and counselled on the benefits of early detection, timely follow-up and

appropriate treatment and educated on the possible consequences of hyperbilirubinaemia. This is an important aspect of the primary prevention of significant hyperbilirubinaemia.

Conclusion

The incidence of extreme hyperbilirubinaemia in the Western health subdistrict of Cape Town, South Africa is higher than in high-income settings. Most infants were readmitted soon after discharge from hospital. Further work should focus on immediate advocacy throughout the region for adequate training of healthcare workers for early detection of significant hyperbilirubinaemia and identifying at-risk newborns before they are discharged to prevent neurological complications caused by bilirubin toxicity. Further immediate research is also needed to see if this problem is prevalent in other regions of South Africa or the African continent as well.

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Appendix A: Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 April 2021

HREC REF: 210/2021

Dr Y Joolay
Division of Neonatology
Red Cross Children's Hospital
Email: yaseen.joolay@uct.ac.za
Student: carincoraizin@gmail.com

Dear Dr Joolay

PROJECT TITLE: INCIDENCE, AETIOLOGY AND SHORT-TERM OUTCOMES OF SEVERE HYPERBILIRUBINEMIA IN TERM INFANTS BORN IN THE WEST METRO AREA OF CAPE TOWN-MMED CANDIDATE-DR CARIN CORAIZIN.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 April 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Carin Coraizin will also be involved in this study.

Please quote the HREC REF 210/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

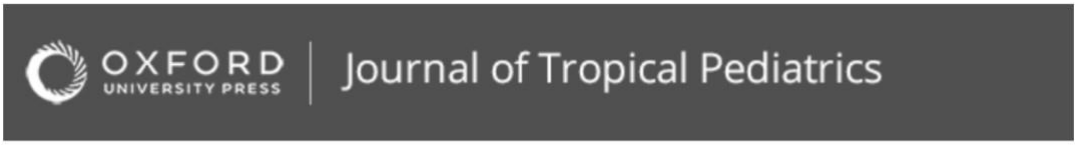
PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/REF 210/2021sa

Appendix B: Proof of submission to Journal of Tropical Paediatrics

Manuscript ID: JTP-2023-368-0P

Manuscripts submitted to Journal of Tropical Pediatrics



Incidence, Aetiology and Short Term Outcomes of Extreme Hyperbilirubinaemia in term infants in the West health subdistrict of Cape Town, South Africa between 2019 and 2020

Journal:	*Journal of Tropical Pediatrics*
Manuscript ID	JTP-2023-368-OP.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	02-Mar-2024
Complete List of Authors:	Coraizin, Carin; University of Cape Town, Paediatrics and Child Health Vreede, Helena; University of Cape Town Faculty of Health Sciences, Department of Chemical Pathology Van Niekerk, Cara; University of Cape Town Department of Paediatrics and Child Health, Department of Paediatrics and Child Health Joolay, Yaseen; University of Cape Town Department of Paediatrics and Child Health, Neonatal Medicine, Department of Paediatrics
Keywords:	Hyperbilirubinaemia, Newborns, Extreme hyperbilirubinaemia, Low and middle income countries

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- All sources of funding for the research in the submitted manuscript have been disclosed.
- All authors meet the authorship criteria described by the International Committee of Medical Journal Editors (ICMJE) at http://www.icmje.org/recommendations/browse/roles-andresponsibilities/defining-the-role-of-authors-and-contributors.html and excerpted here:

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- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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3. Manners T, Jones R, Riley M. Relationship of overweight to haitus hernia and reflux oesophagitis. In: Newman W (ed). The Obesity Conundrum. Amsterdam: Elsevier Science, 1997,352–74.
4. Hou Y, Qiu Y, Vo NH et al. 23-O derivatives of OMT: highly active against H. influenzae. In: Programs and Abstracts of the Forty-third Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2003. Abstract F-1187, p.242. American Society for Microbiology, Washington, DC, USA.
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