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Master of Medicine (Mmed) Paediatrics

Invasive Group B Streptococcal Disease in Newborns at Groote Schuur Hospital

University of Cape Town

January 2023

Declaration

The research reported in this dissertation is based on independent work performed by Bradley Browne, i.e. 'the candidate'. Neither the whole work, or any part of it, is being or has been submitted for a degree at any other university. This work is intended to be published in *The South African Journal of Child Health*, and has not been reported on or published prior to registration for the candidate's Mmed degree.

Plagiarism

This dissertation has been submitted to the Turnitin module and I confirm my supervisor, Prof. Lloyd Tooke, has seen my report and any concerns revealed by such have been resolved with my supervisor.

Bradley Browne

BRWBRA002

Signed by candidate

26 January 2023

Format

This dissertation is in the publication-ready format and is intended to be submitted the *The South African Journal of Child Health*, with the first author being Bradley Browne.
Word count: 2316 (exclusing abstract, tables, figures, references)

Contributions

Associate Professor Lloyd Tooke is the Mmed candidate's supervisor. He provided supervision and feedback in developing the study protocol, planning data analysis, and writing up of study results. Prof. Tooke is the final author on the journal submission.

Dr Amanda Khumalo is a provided access to The National Health Laboratory Services data to identify patients, as well as information regarding laboratory practices as relevant to this study. Dr Khumalo is the second authr on the journal submission.

Dr Bradley Browne, the candidate, independently performed the protocol development, data collection and analysis, and wrote up dissertation and publication-ready manuscript.

Acknowledgements

Firstly, I would like to acknowledge the young children and parents affected by Group B Streptococcus, that pass through our wards and trust us to care for them. This dissertation is dedicated to them.

Thank you to my supervisor, Prof. Lloyd Tooke for all the helpful discussions, for being readily-available at any time to support this work, and for encouraging me along. Thank you to Dr. Amanda Khumalo, for readily assisting with all matters 'microbiological', and for always being ready with a kind word.

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Abbreviations

GBS: Group B Streptococcus. iGBS: Invasive Group B Streptococcal disease. NDI: Neurodevelopmental impairment. EoD: Early-onset disease. LoD: Late-onset disease. ROM: Rupture of membranes. HIV: Human Immunodeficiency Virus. GSH: Groote Schuur Hospital. CRP: C-reactive Protein. SPTL: Spontaneous preterm labour. CSF: Cerebrospinal fluid. NHLS: National Health Laboratory Services. IQR: Inter-quartile range. NICU: Neonatal Intensive Care Unit. CPAP: Continuous positive airway pressure. CFM: Cerebral function monitoring. C/S: Caesarean section. NVP: Nevirapine. PCR: Polymerase chain reaction. NEC: Necrotising enterocolitis.

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Invasive Group B Streptococcal Disease in Newborns at Groote Schuur Hospital

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Abstract

Background. Group B Streptococcal disease is an important cause of morbidity and mortality in newborns globally, and is more common in Sub-Saharan Africa and South Africa. There are few studies reporting on the burden of invasive Group B Streptococcus disease (iGBS) in newborns in South Africa, especially in the Western Cape.

Objective. This study aims to describe a case series of newborns with iGBS in a tertiary hospital in the Western Cape.

Methods. A retrospective folder review was conducted between January 2015 and December 2020.

Results. Thirty five cases of invasive GBS disease were included in the study, 51% with early-onset disease (EoD) and 49% with late-onset disease (LoD). The median gestational age at birth was 27 and 31.5 weeks in the LoD and EoD groups respectively. The median birth weight was 900 g and 1812 g in the LoD and EoD group respectively. Meningits was more common in the LoD group, and pneumonia more common in the EoD group. The overall mortality rate was 23%, and GBS disease accounted for a cumulative 274 days in the intensive care unit.

Conclusion. Invasive GBS disease in newborns at GSH carries a high mortality rate with a similar burden of LoD and EoD. More studies of newborn iGBS are needed in the Western Cape and South Africa to better understand the burden of disease.

1. Introduction

1.1. Global burden of disease

Streptococcus agalactiae, also known as Lancefield's group B streptococcus (GBS), is a leading cause of severe illness in infants.[1,2] Globally, invasive GBS disease (iGBS) accounted for approximately 57 000 stillbirths, 90 000 infant deaths, and 3.5 million preterm births in 2015.[2,3] In surviving children, GBS septicaemia and meningitis increases risk for neurodevelopmental impairment (NDI).[2] Sub-Saharan Africa carries a disproportionately high burden of iGBS compared to the rest of the world.[4]

Invasive GBS disease in newborns is divided into early-onset disease (EoD) and late-onset disease (LoD), which occurs between day 0 and 6 of life and day 7 and 90 of life respectively. Early-onset disease is acquired vertically and commonly results in septicaemia or pneumonia. Late-onset disease frequently causes septicaemia and meningitis.[2] Important risk factors in infants include maternal GBS colonisation of the gastrointestinal and genitourinary tract, preterm birth, very low birth weight, prolonged rupture of membranes (ROM) and maternal infection with human immunodeficiency virus (HIV).[2,4,5] Effective vaccinations to prevent iGBS in newborns are anticipated but not yet available.[4] Routine antenatal testing by means of a vaginal swab for maternal GBS colonisation, combined with intra-partum antibiotic administration to those who test positive, is an effective but expensive strategy to prevent EoD in newborns.[6]

1.2. GBS in South Africa

There are few studies describing the burden of iGBS in South African infants, and no recently published studies outside of Gauteng Province. Surveillance in Soweto reports an incidence (per 1000 live births) of 2.4 – 3, which is higher than the estimated incidence of 1.1 in Sub-Saharan Africa, and 0.53 globally.[7–9] Mortality due to iGBS in South Africa is high, with one Gauteng cohort reporting a fatality rate of 18%, almost double that of global estimates.[9,10] In addition, survivors in South Africa and other low and middle Income Countries have an increased risk of NDI.[11]

The combined risk factors of a high HIV prevalence of 30% among pregnant women in South Africa,[12] a high GBS carriage rate, and sub-optimal intrapartum antibiotic prophylaxis, are likely key drivers of GBS disease in South Africa.[13]

There are no recently published studies describing iGBS in newborns in the Western Cape Province of South Africa. Therefore this study aims to describe a case series of newborns with iGBS at Groote Schuur Hospital (GSH), a tertiary hospital in the Western Cape.

1.3. Standard of care at GSH

Universal antenatal testing for maternal GBS colonisation is not performed at GSH. However, GBS bacteruria is frequently picked up incidentally on urinalysis. Newborns who are born with risk factors for sepsis are identified according to hospital protocols, and blood cultures are performed on all of these infants along with a C-reactive protein (CRP) between 36 and 48 hours after antibiotic initiation. Risk factors for early-onset sepsis include GBS exposure (including maternal GBS bacteruria and a previous baby with iGBS), spontaneous preterm labour (SPTL), prolonged ROM greater than 18 hours, maternal septicaemia or chorioamnionitis, and suspected or confirmed sepsis in a twin. Postnatal risk factors include respiratory distress, apnoeas, neonatal encephalopathy, glucose or temperature abnormalities, feed intolerance, and metabolic acidosis. Cerebrospinal fluid analysis is conducted on all surviving infants with blood culture-confirmed sepsis or where there is clinical suspicion of meningitis.

2. Methods

2.1. Study Design

A retrospective folder review was conducted for all cases of newborn iGBS between January 2015 and December 2020 at Groote Schuur Hospital (GSH). An iGBS case was defined as any infant less than 90 days old with a positive blood or cerebrospinal fluid (CSF) culture for GBS. Data from National Health Laboratory Services (NHLS) laboratory information system were used to identify all iGBS cases at GSH during the study period.

The NHLS uses the BacT/Alert (Organon Teknika Corp., Durham, N.C.) instrument, an automated microbial detection system, to incubate and flag positive blood cultures. Positive cultures are then Gram stained and subcultured onto appropriate media. Further organism identification and susceptibility testing is performed using Vitek 2 (BioMérieux). CSF specimens are Gram stained and cultured onto appropriate media according to laboratory standard operating procedures. Microorganisms are further identified using Lancefield's grouping and Vitek 2 (BioMérieux) for susceptibility testing.

Once cases were identified, data were collected on a case report form using Microsoft Excel. Data analysis was descriptive, using graphs and tables to analyse categorical and numerical data. Results are presented as medians with associated inter-quarile ranges (IQR). Where relevant, R (version 4.05) was used to conduct the Mann Whitney and Fisher's exact tests to assess for statistical significance for continuous and categorical variables respectively.

2.2. Case Definitions

Case definitions for meningitis, pneumonia, and septicaemia are as follows; Pneumonia was diagnosed based on chest X-ray findings and/or a suggestive clinical picture as assessed by the treating neonatologist. Meningitis was diagnosed based on CSF studies that were culture-positive for GBS or had CSF cell count, protein, and glucose values in keeping with meningitis, as assessed by the treating neonatologist. Septicaemia was diagnosed when GBS bacteraemia was detected in the absence of a clear focus of infection. A case was described as 'required intensive care' if the treating neonatalologist admitted the infant to the Neonatal Intensive Care Unit (NICU) for at least one of the following reasons; close monitoring, endotracheal intubation and ventilation, continuous positive airway pressure (CPAP) respiratory support, inotropic support, or Cerebral Function Monitoring (CFM).

2.3. Ethical Approval

Ethics approval was obtained from the University of Cape Town Departmental Research Committee (see appendix 2). There are no conflicts of interest to declare.

3. Results

There were 36 cases of iGBS during the study period. Complete records were not available for one case, which was excluded from the analysis. Of the remaining 35 cases, 18 (51%). were EoD and 17 (49%) were LoD. The average time to culture positivity was 9.2 hours in the EoD group, and 6.8 hours in the LoD group. All of the cultures were sensitive to penicillin and ampicillin. Eleven (31%) cases were born at primary and secondary centres and referred to GSH for tertiary care. See *table 1* for a comparison of characteristics in the EoD and LoD groups.

3.1. Early Onset Disease

All 18 EoD cases were diagnosed in the first 24 hours of life, except for one diagnosed at 72 hours. The median birth weight and gestational age in the EoD group was 1960 g and 32 weeks respectively *(Figure 1)*. Fourteen cases (78%) were born prematurely (before 37 completed weeks gestation). Four mothers received no antenatal care, and 4 mothers cultured GBS in urine specimens collected prior to delivery.

Thirteen cases (72%) delivered vaginally and 5 (28%) via caesarean section (C/S). Of the 5 C/S, 3 were performed on mothers who had both SPTL and spontaneous ROM, and two were performed on mothers who were not in labour with no ROM and no other risk factors. Of the 13 vaginal-delivered cases, 10 had SPTL and 2 had prolonged ROM. None of the cases in the EoD group received intra-partum ampicillin prophylaxis.

3.2. Late-Onset Disease

All cases in the LoD group were diagnosed between week 2 and 11 of life *(Figure 2)*. The median birth weight and gestational age was was 942 g and 27 weeks respectively. All of the cases were born very preterm (less than 32 completed weeks gestation). Eleven cases (65%) delivered vaginally and 6 cases (35%) by caesarean section. Four cases (24%) received no antenatal care.

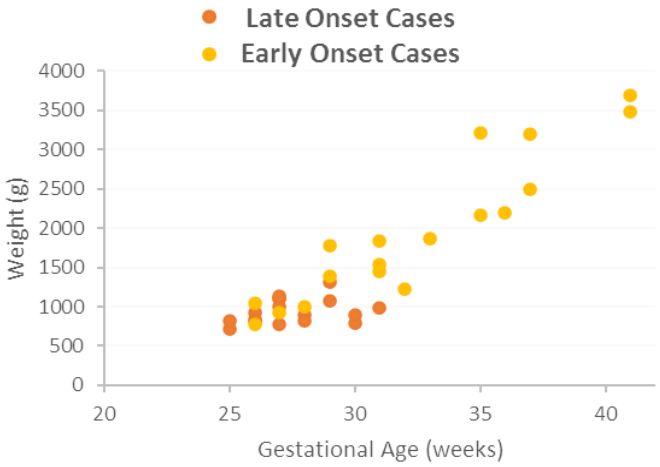

Figure 1: Gestational Age and Birth Weight of EoD and LoD cases

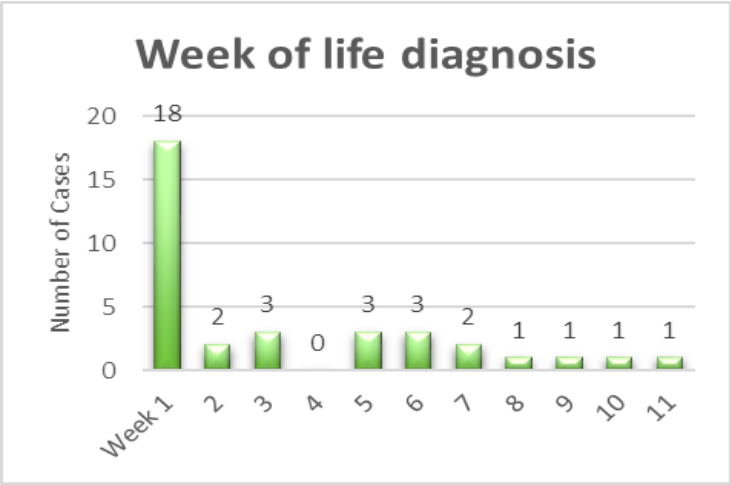

Figure 2: Week of life of iGBS diagnosis in EoD and LoD cases

3.3. HIV Exposure

Maternal HIV infection status and recent viral loads (within 12 weeks prior to delivery) were available for all cases. Seven (20%) cases were HIV exposed, 3 in the EoD group and 4 in the LoD group. In 2 cases exposure was considered ‘high risk’ due to a recent maternal HIV viral load of >1000 copies/mL. All HIV-exposed newborns received post-exposure prophylaxis with nevirapine (NVP), and the two high risk cases received NVP and zidovudine. All cases tested HIV Polymerase chain reaction (PCR) negative at birth, and all survivors were negative at repeat testing carried out between 6 and 10 weeks life. HIV exposure was not significantly associated with LoD, meningitis, or death.

3.4. Focus of Infection and Mortality

The predominant presentation in the EoD group was septicaemia (11 cases, 61%), and pneumonia (7 cases, 39%). One of the pneumonia cases also had meningitis. The predominant presentation in the LoD group was septicaemia (8 cases, 47%), followed by meningitis (5 cases, 29%), pneumonia (3 cases, 18%), and 1 case (6%) presented with necrotizing enterocolitis (NEC). Two cases of LoD meningitis cultured GBS on CSF and the remaining 3 had suggestive CSF cell counts. The prevalence of meningitis was 5.3 times greater in the LoD group compared to the EoD group (95% CI: 0.69 – 40.8).

Four cases (22%) in the EoD group demised as a result of iGBS, 2 of which had pneumonia and 2 septicaemia. Three of these demised in the first 24 hours of life, and one on day 9. Four cases (24%) in the LoD group demised as a result of iGBS of which 1 had pneumonia, 1 had NEC, and 2 had septicaemia. Of the 8 deaths, 2 cases were HIV exposed, one with EoD and one with LoD. Early onset disease versus LoD, HIV exposure, focus of infection, and not receiving antenatal care were not significantly associated with mortality.

The LoD case with NEC had a gestational age of 31 weeks and birth weight of 985 g. The patient deteriorated on day 11 of life with a clinical and radiological picture consistent with NEC as assessed by the treating neonatologist. The case was managed medically. They developed a coagulopathy and a large intra-cranial parenchymal haemorrhage 24 hours after deterioration, and demised 6 hours later. Furthermore, 2 other cases with EoD and 1 with LoD later developed NEC after recovering from iGBS on day 8,17, and 67 of life respectively. One case with LoD diagnosed on day 37 of life, recovered from iGBS but demised 7 weeks later in hospital with no clear cause (sudden unexpected death in infancy).

Table 1. Characteristics and risk factors of iGBS EoD and LoD cases

Description	All Cases (n=35), n (%)	Early-onset disease (n=18), n (%)	Late-onset disease (n=17), n (%)
Patient Characteristics			
Median Birthweight (g)(IQR)	1100 (900 - 1812)	1812 (1261 – 2425)	900 (820 – 1075)
Median Gestational age at birth (weeks)(IQR)	29 (27 – 31.5)	31.5 (29 – 35.75)	27 (26 – 29)
Male	17 (48)	9 (50)	8 (47)
Female	18 (52)	9 (50)	9 (53)
Risk Factors			
HIV Exposed	7 (20)	3 (17)	4 (24)
No Antenatal Care	8 (22)	4 (22)	4 (23)
GBS on maternal urine culture	4 (11)	4 (22)	0
Prolonged rupture of membranes (>18 hours)	7 (20)	4 (22)	3 (18)
Spontaneous preterm labour	25 (71)	13 (72)	12 (71)
Perinatal / Delivery			
Caesarean Section	11 (31)	5 (28)	6 (35)
Vaginal Delivery	24 (68)	13 (72)	11 (65)
Born outside GSH	11 (31)	6 (33)	5 (29)
Postnatal Outcomes			
Demised	8 (23)	4 (22)	4 (24)
Septicaemia	19 (54)	11 (61)	8 (47)
Pneumonia	10 (29)	7 (39)	3 (18)
Meningitis (confirmed and probable)	6 (17)	1 (6)	5 (29)
Necrotizing enterocolitis	1 (3)	0	1 (6)
Ventilated	18 (51)	9 (50) (4 demised)	9 (53) (4 demised)
Inotropes	9 (26)	7 (39)	2 (12)
C-reactive Protein (median)(mg/dL)	69 (n = 24)	31 (n = 11) (5 – 72)	81.5 (n = 13) (32 – 101)

3.5. Clinical Presentation and Care

The most common presenting clinical features were respiratory distress (88.6%), Shock (28.6%), and apnoea (22.9%). Seventeen cases (94%) in the EoD group required intensive care, for a cumulative 158 days. Fifteen cases (88%) in the LoD group required intensive care, for a cumulative 116 days. Eighteen cases (51%) required invasive ventilation, and 9 (26%) required inotropic support.

The cohort included one set of twins (monochorionic diamnionotic) with LoD who were born at 30 weeks gestation with twin A and B weighing 795 g and 900 g respectively. They presented on day 35 and 36 of life with pneumonia and septicaemia. Twin A required invasive positive pressure ventilation for 5 days, and both survived to discharge.

3.6. Laboratory Investigations

C-reactive protein measurements were taken in survivors between 36 and 48 hours life. In the EoD group 11 cases had a CRP measurement, with a mean of 53 mg/dL. Four (36%) of the CRPs were below 10 mg/dL. In the LoD group, 13 (76%) cases had a CRP measurement, with a mean of 83 mg/dL and no CRP's below 10 mg/dL. The difference between the CRPs in the EoD and LoD groups is not statistically significant (P-value = 0.104). For those in the LoD group with meningitis, 4 of the 5 cases had CRPs with mean of 67.5 mg/dL.

4. Discussion

This study describes a high case fatality rate of 22.8% in newborns with iGBS, which is higher than previously reported in Johannesburg (18%) and Soweto (16.9%).[5,10] The higher fatality rate may be partly explained by the high prevalence of very preterm babies in this cohort. Our findings of an increased prevalence of meningitis in newborns with LoD compared to EoD is in keeping with previous studies.[10] The HIV exposure prevalence in our cohort (17%) is similar to the reported antenatal HIV prevalence in the Western Cape (17.9%),[12] but we did not find an association between HIV exposure LoD which is well-described in other South African studies.[5]

Recent studies conducted in LMIC's indicate a high risk for NDI in newborns with iGBS, particularly in those with septicaemia or meningitis as the focus of infection.[11] A Focus of

septicaemia and / or meningitis occurred in 71% of cases in our cohort. Further studies are needed to assess the risk for NDI in iGBS survivors in our setting. Furthermore, 91% of iGBS cases required NICU admission for a cumulative 274 days. This is important for a country with limited resources for intensive care facilities.

A correlation between iGBS and NEC has been previously described,[14] and in our study one case with LoD presented with NEC and 3 cases developed NEC 1 – 4 weeks after diagnosis of iGBS. Further studies are needed to explore this association in our setting.

In this cohort, CRP values were higher in LoD compared to EoD. Although not statistically significant, there is a described link between CRP kinetics and gestational age which may account for higher CRP values in the LoD group.[15] Furthermore, CRP measurements were less than 10 mg/dL in 36% of EoD cases, but not in any LoD cases. This is in keeping with previous studies indicating that CRP has reduced sensitivity in newborns with early onset sepsis,[15] and may have clinical implications for the use of CRP to rule out EoD.

Limitations in this study include a relatively small number of iGBS cases, although it is a complete sample for the time period. Furthermore, cases in this study are limited to those admitted in a single teritary unit. The addition of iGBS descriptive studies from other neonatal units in the Western Cape would offer a more complete overview of the impact of iGBS in the province.

5. Conclusion

Invasive GBS disease in this case series of mostly preterm and low birth weight newborns at GSH carries a high mortality rate, with a similar burden of LoD and EoD. To our knowledge, no other studies have described the impact of GBS in such small newborns in South Africa, and there are no recent studies describing newborn iGBS in the Western Cape Province. Further studies are needed to describe the prevalence of iGBS in term and preterm newborns in the Western Cape, and identify risk factors for poor outcomes that may guide interventions.

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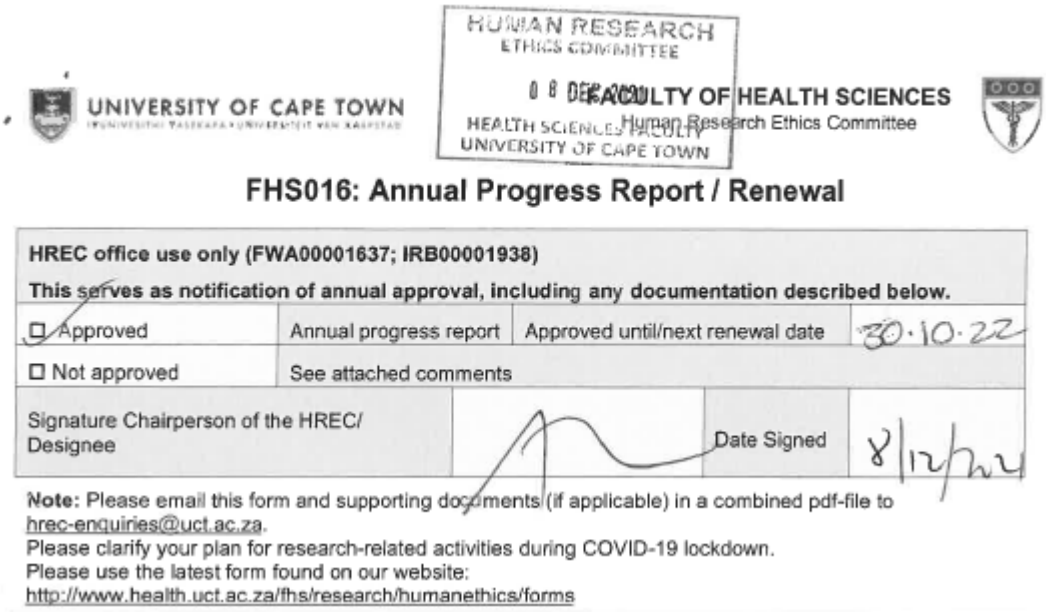
7. Appendices

Appendix 1. Data Capture Form

Patient		**initial management**	
Summary		Early Diagnoses (<72 hours)	
		initial antibiotic (full detail + time between dx + AB)	
Folder / Name / mother FN		resp	
Date of birth / discharge / death		CVS	
GA		CNS	
birth weight		GIT	
Sex		feeds + fluids	
length		Clinical Course	
Head Circumference		Investigations	
Twin?		other management	
HIV exposure / risk		regained birth weight	
HIV PCR			
		Deterioration (if GBS later)	
Maternal		later Diagnoses	
gravidity, age, booked. Blood group.		Time of deterioration	
HIV, Tx, VL, CD4		level of care before deterioration	
RPR		presentation	
Co-morbidities		Septic work up	
substance use		investigations	
Colonized (GSB Screen?)		initial antibiotic (full detail + time between dx + AB)	
urine		change in antibiotic	
antibiotics (intrapartum)		clinical course	
medications		resp	
prev newborn morbidity / GBS		CVS	
previous NND / ID		CNS	
social		GIT	
USS:		Other management	
		Notes	
Perinatal			
Spont labour / steroids		**Sepsis**	
ROM duration		BC time + indication	
Mode of delivery		time to positivity	
CTG		other organisms	
Meconium		sensitivity	
chorioamnionitis + placenta		focus of infection	
other mat morbidity		septic markers	
apgars		duration of AB	
delivery complications		time to stabilisation	
present at delivery		LP result	
peripartum condition			
resus required		**Outcome**	
cord gas / encephalopathy		clinical course	
Intrapartum antibiotics		Death	
		comorbidity	
Nursery admission (birth)		length of stay	
admitted?		days in ICU	
septic RF		days on resp support	
Define resp distress (timing / severity)		other episodes of sepsis	
congenital abn / diaphragm		Cranial USS	
time deterioration		HIE or CFM	
differential			
other diagnoses / morbidities			
other (++detail)			
Medications			

Appendix 2. Ethics Approval Letter



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HUMAN RESEARCH ETHICS COMMITTEE
0 8 DEC 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.10.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	8/12/21

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Appendix 3. South African Journal of Child Health Author Guidelines

http://www.sajch.org.za/index.php/SAJCH/about/submissions#authorGuidelines

MANUSCRIPT PREPARATION

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 3 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
    - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
    - Do not include any references in the abstracts.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.

- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.