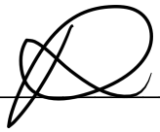
Incidence, Characteristics, Management and Outcomes of neonates with Patent Ductus Arteriosus (PDA) at Chris Hani Baragwanath Academic Hospital

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine in Paediatrics

DECLARATION

I, Delisha Naidoo, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____ Delisha Naidoo

July 2024 in Johannesburg

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DEDICATION:

I dedicate this MMED to:

To my husband Kiran Doorgapershad, for being my number one fan and always pushing me to be a better version of myself My parents, Sue and Ramoo Naidoo, for your unwavering support and encouragement throughout my career. To my sister and brother Herushka Chetty and Akhilon Naidoo for always being in my corner. To My nephew and nieces, Camron Naidoo, Aria Naidoo and Teia Naidoo for bringing so much joy into my life. To My family -The Naidoo's, the Doorgapershads, the Wardmans, the Naicks, the Premlals and the Ramsammys -they say it takes a village to raise a child, you have been my village throughout my life. To My consultants - Dr Nakwa, Dr Thomas and Prof Thandrayen - for all the advice, guidance and pushing me to be a better doctor. To the registrars in the Wits circuit, this journey would not have been possible without all of you especially: Mahtaab Khan.

Abstract:

Incidence, Characteristics, Management and Outcomes of Very Low Birth Weight Infants with Patent Ductus Arteriosus (PDA) at Chris Hani Baragwanath Academic Hospital

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Introduction:

Patent Ductus Arteriosus (PDA) accounts for 5-10% of congenital heart disease and is found in 300 per 1000 preterm infants. Significant morbidity and mortality have been associated with PDA. There is limited data available on PDA in low to middle income countries.

Methods:

This was a retrospective study carried out at Chris Hani Baragwanath Academic Hospital (CHBAH) between January to December 2017. Data on very low birth weight (VLBW) infants were extracted from the neonatal and paediatric cardiology unit's electronic databases and clinical records of patients with a diagnosis of PDA on echocardiography were retrieved for analysis.

Results

Of the 859 VLBW infants admitted during the study period, 54(6.2%) had a diagnosis of PDA on echocardiography. PDA was more common in low birthweight (p=0.001) and lower gestational age (p=0.005) infants. Forty (74%) presented with an ejection systolic murmur and 29 (54%) were deemed haemodynamically significant (>1.4mm). Thirty-one infants (57%) were managed with watchful waiting. There were 21(39%) patients managed medically of these, eighteen(86%) patients were managed using Ibuprofen (86%) making it the most common agent used among infants who were managed medically. Infants with a PDA had higher rates of intraventricular haemorrhage (IVH) [37% vs 12.4%; p-0.001], bronchopulmonary dysplasia (BPD) [42.6% vs 11.8%; p-0.001] and had a longer hospital stay (p=0.001). Risk factors for mortality were lower gestational age (OR 0.65, p<0.001, 0.6-0.71) and IVH (OR1.44, p<0.001, CI 1.17-2.18).

Conclusion

PDA is inversely proportional to gestational age and birth weight. Comorbidities in infants with PDA increased the hospital stay. Early identification and appropriate management are important as it may impact on these co-morbidities and length of hospital stay.

Keywords: PDA, VLBW, LMIC, Risk Factors, Management

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The Neonatal REDCap database (HREC number M220853)

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List of Abbreviations

BPD: Broncho-Pulmonary Dysplasia

CHBAH: Chris Hani Baragwanath Academic Hospital

ECHO: Echocardiogram

ELBW: Extremely Low Birthweight

ESM: Ejection systolic murmur

IPPV: Intermittent Positive Pressure Ventilation

IVH: Intraventricular Haemorrhage

LMIC: Low to Middle Income Countries

nCPAP: nasal Continuous Positive Airway Pressure

NEC: Necrotising Enterocolitis

PDA: Patent Ductus Arteriosus

VLBW: Very Low Birth Weight

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SAJCH author guidelines

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- 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); 'Department of Health' (DoH).
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
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- Units should be preceded by a space (except for % and ºC), e.g.40 kg and 20 cm but 50% and19ºC.
- 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.

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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

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- 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.

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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.

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 – 25 references

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.

Research Presentations:

1. Paediatrics Research Day Dec 2023
2. Priorities in Perinatal Care Mar 2024

Manuscript

Incidence, Characteristics, Management and Outcomes of Neonates with Patent Ductus Arteriosus (PDA) at Chris Hani Baragwanath Academic Hospital

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Introduction:

The patent ductus arteriosus (PDA) is reported to have an incidence of 300 per 1000 preterm infants and accounts for 5-10% of all congenital heart disease. (1) The PDA is associated with significant morbidity as well as mortality, with mortality rates reaching of about 30%.(2) Co-morbidities associated with PDA include intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and broncho-pulmonary dysplasia (BPD), which can result in both short- and long-term adverse consequences.(3)

Three strategies used in the management of PDA include watchful waiting, pharmacotherapy, and surgical closure. The strategy of watchful waiting involves fluid restriction and monitoring until the PDA closes.(4) The decision to treat the PDA pharmacologically is usually based on whether it is considered to be haemodynamically significant, both clinically as well as on echocardiography (ECHO). Pharmacotherapy with cyclooxygenase inhibitors, such as indomethacin and ibuprofen, or peroxidase inhibitors such as paracetamol, are commonly prescribed for medical closure.(4) Medical therapy has a 60-80% efficacy rate with recurrence and failure rates inversely proportional to gestational age.(4) Surgical ligation or dveice closure is usually reserved for patients with a haemodynamically significant PDA who have failed pharmacologic closure. The optimal management strategy, however, remains controversial, as pharmacologic therapy of the PDA carries the risk of drug-related adverse effects, and surgical ligation of the PDA reduces mortality however carries the risk of surgical complications, without necessarily reducing the risk of associated morbidities or mortality.(5,6)

Most data on PDA are from high income countries, with paucity of data from low to middle income countries (LMIC). This study aimed to describe the incidence, characteristics, management and outcomes of very low birth weight (VLBW) infants with a diagnosis of PDA from a public, tertiary hospital in a LMIC.

Methods:

Study design

This study was a single centre, retrospective, descriptive study of VLBW infants, weighing less than 1500g, admitted to the neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH) from January to December 2017 with a diagnosis of a PDA, confirmed on echocardiography (ECHO).

Study setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary, public, academic hospital which lies on the outskirts of Soweto, Johannesburg, South Africa. The hospital and its cluster conduct approximately 30000 deliveries with an average of 4500 admissions to the CHBAH neonatal unit per year. Preterm deliveries account for 20% of all deliveries. The hospital is a major referral centre for surrounding regional and district hospitals, maternal obstetric units (MOUs) and clinics. The neonatal unit at CHBAH has 185 neonatal beds consisting of 18 intensive care beds (level 3 nursery), 48 high care beds (level 2 nursery), 100 standard care beds (level 2 and 1 nursery) and 19 kangaroo mother care (KMC) beds (level 1 nursery). The paediatric department at CHBAH also offers paediatric cardiology services run by specialist paediatric cardiologists and cardiology fellows.

Infants who are suspected of having a PDA on clinical grounds, or who require an ECHO for any other clinical indication, are referred to the paediatric cardiologists. If the diagnosis of a PDA is confirmed, infants are managed according to the neonatal unit's protocol, which includes watchful waiting for non-haemodynamically significant PDA and medical management with ibuprofen in those that are haemodynamically significant (PDA with the following ECHO characteristics: size > 1,4mm/kg, left atrium to aortic ratio is >1,4, the PDA to left pulmonary artery ratios >1, left ventricular dysfunction and reversal of end diastolic flow) . Where ibuprofen is contraindicated, paracetamol is prescribed.

Data collection

Data on all VLBW infants born at CHBAH and admitted to the neonatal unit during the study period, including data on VLBW infants with confirmed isolated PDA, were extracted from the neonatal unit's and paediatric cardiology unit's electronic databases. All VLBW neonates who had major underlying congenital malformations or genetic syndromes, or who were not expected to survive were excluded.

Clinical records of patients with ECHO confirmed PDA and those without a PDA were retrieved for detailed analysis. The two groups of patients were than compared by looking at the infants' demographic and clinical characteristics, clinical presentation at the time of PDA diagnosis, ECHO findings, management and associated adverse effects (need for ventilation, death, length of stay) and co-morbidities, including NEC, BPD and IVH. Outcome at hospital discharge was also collected. Data was entered onto an Excel spreadsheet and analysed using STATISTICA (version 13).

Study definitions

Very Low Birth Weight: birth weight less than 1500g

Patent ductus arteriosus: persistence of the DA after birth, diagnosed on ECHO.

Haemodynamically significant PDA: PDA with the following ECHO characteristics: size > 1,4mm/kg, left atrium to aortic ratio is >1,4, the PDA to left pulmonary artery ratios >1, left ventricular dysfunction and reversal of end diastolic flow.

Bronchopulmonary dysplasia: the need for supplemental oxygen for more than 28 days can be mild, moderate, and severe (Appendix A)

Necrotizing enterocolitis is ischaemic necrosis of the intestinal mucosa, presenting with clinical and radiological signs according to the modified Bell's staging (Appendix B)

Intraventricular haemorrhage is bleeding into the cerebral ventricular system, graded according to the Papille classification (Appendix C)

Retinopathy of prematurity are insults that disrupt neurovascular growth. (Appendix D)

Statistical analysis

Categorical data are presented as proportions and percentages, continuous variables as means (SD) or medians (IQR) depending on the distribution of the data. Comparative and logistic regression analysis was performed using a Chi-squared test of Fisher's exact test or the Mann-Whitney U test depending on the distribution of the data.

Ethical considerations

Patient consent was waivered as this was a retrospective study. Ethics clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC M220238). The Neonatal Unit Ethics REDCap number (M151196).

Results

Incidence and baseline characteristics

There were 878 (4.2%) VLBW of the 20575 total live births at CHBAH in 2017 as per hospital records. Of these, 12 (1.4%) died in the first 72 hours of life and 7 (0.79%) had missing electronic records, leaving 859 VLBW infants that were included in the study. (Figure 1) Eight hundred and five infants (93.7%) either did not have an ECHO performed or had an ECHO which did not confirm a PDA. Fifty-four infants (6.2%) had an ECHO confirmed PDA, with an incidence of 62 per 1000 VLBW. There were more infants with a birth weight between 1000g - 1500g with a PDA diagnosis, compared to those < 1000g (with a prevalence of 4.8% vs 1.4%). The mean gestational age and birthweight were 29 weeks (SD ± 2.8) and 1140g (±255.3) respectively. Lower gestational age (OR 0.65, 95% CI 0.60-0.70; p-0.001) and birthweight (OR 0.99, 95% [CI 0.993-0.995, p-0.001]) were associated with a PDA. There were no significant

differences in sex, mode of delivery, 5 minute APGAR scores, HIV exposure and antenatal steroid exposure between VLBW infants with and without PDA. More infants with PDA received intermittent positive pressure ventilation (IPPV) compared to those without a PDA (13% vs 4%; p=0.009). There was no difference between groups regarding the need for nCPAP (p=0,25). Table 1

Clinical presentation and ECHO diagnosis

Among infants with a PDA diagnosis, an audible ejection systolic murmur (ESM) on precordial auscultation was the most frequent clinical presenting feature, accounting for 40.7% (n=22) of infants, followed by increased oxygen requirements and oxygen dependence at 25.9% (n=14) and 9.3% (n=5) respectively (Figure 2). Other clinical findings that warranted the ECHO confirming the PDA included a haemangioma and persistent tachycardia. PDA in 29 (54%) infants were found to be haemodynamically significant on ECHO.

Management

Thirty-one (57%) infants with PDA were managed with watchful waiting, while 21 (39%) infants were managed with medical treatment. Of those who were medically treated, the majority of patients were treated with Ibuprofen (n=18; 85.7%), followed by paracetamol in 2 (9.5%) infants, and indomethacin in 1 (4.8%) infant. Anti-failure therapy with diuretics was commenced in 18 (33%) infants. Two infants required device closure (4%). Figure 3

Outcomes

Infants with PDA were more likely to develop BPD (aOR 4.2; CI 95% [1.8- 9.6]; p=0.001) as well as IVH (aOR 1.59; 95% CI [1.17- 2.18]; p=0.001) when compared to those without PDA. PDA was not associated with an increased risk of NEC. Infants with PDA had a significantly longer hospital stay than those without PDA. All-cause mortality rate was similar between both groups. Table 2

Risk factors associated with mortality, among infants with a PDA, included a lower gestational age (p<0.001), lower birthweight (p<0.001), and the presence of IVH (p<0.001), Protective factors included a diagnosis of BPD (p<0.001), and the need for IPPV (p-0.028). Table 3

Discussion

This study reported an incidence of 6.2% ECHO confirmed PDAs in VLBW infants, with a higher prevalence in the 1000-1500g weight band. VLBW infants with PDAs were of lower birthweight and gestational age. More than half had a haemodynamically significant PDA. There was an increased need for mechanical ventilation in those with a PDA. Watchful waiting was the most frequent management strategy, and if treated, Ibuprofen was the drug of choice. Comorbidities of BPD and IVH were seen in those with a PDA. Lower gestational age and IVH were associated with mortality.

The reported incidence of PDA in preterm infants ranges between 20-60%, depending on the geographic area and diagnostic criteria used .(8,9) There is paucity of data in LMIC regarding the incidence of PDA. This may be due to the underdiagnosis of PDA due to lack of cardiology services, or healthcare priorities may focus on other diseases. In this study we found a much lower incidence of 6.2% of VLBW infants. There were more PDAs seen in patients in the weight category of 1000g – 1500g compared to the group of less than 1000g. In our limited resource setting ELBW infants weighing less than 900 grams who are not offered invasive mechanical ventilation may have demised before the diagnosis could be made. Secondly, a screening ECHO is not performed in our setting, and is only performed if the diagnosis is suspected clinically. Therefore, many neonates with asymptomatic PDAs, may have been missed.

In high income countries (HIC) the incidence of PDA is reported to be higher, at 40-80%, in the smaller birthweight categories likely attributable to advances in neonatal care with more ELBW infants surviving.(1,10) A study in Vietnam reported an incidence of 70-90% in infants born at less than 28 weeks.(11) Another study done in South Africa by Mwandla et al reported an incidence of 11.9% in ELBW with symptomatic PDA.(12)

This study showed no difference in the PDA group in the receipt of antenatal steroids compared to those without PDA. Two non-randomised control trials suggested that antenatal steroid administration may be protective against the development of a PDA.(13,14) Another study found that administration of steroids at least 24 hours before birth greatly reduced clinically significant PDA.(15) In our setting, many women are un-booked and/or arrive late at hospital for delivery and antenatal steroids before 24hrs of delivery are not received. Our sample size may be too small to accurately report on differences.

The most frequent clinical presentation was an ESM, followed by increased oxygen requirements and oxygen dependence. These presenting signs/symptoms have also been found to be the most common clinical presentations in other studies(16)

There were no differences between the infants with PDA and those without PDA and the need for nCPAP, however, more of those with a PDA required invasive mechanical ventilation. There is a paucity of data regarding the association between PDA and the increased need for ventilation. One study did show that moderate to large sized PDA increased the need for ventilation as well as the duration of ventilation when compared to patients without PDA.(17)

The majority (61%) of infants in our study were managed conservatively, and 39% received medical management. Within the medical management group, the majority of patients were treated with ibuprofen at 18 (85.7%). Anti-failure therapy (furosemide) was commenced in 18 (33%) of the study population. Device closure (vascular plugs) was used in 2 (3.7%) of the study population.

In our setting a very small percentage of patients received device closure as a form of management after failing medical management. There is a great deal of debate as to whether to treat or not treat PDA. This largely results from the side effect profile of the drugs used to treat PDA, as well as the lack of evidence showing long term benefits to closing a PDA.(9) Many other centres have used indomethacin as first line treatment, this differs from this study as the current protocol encourages the usage of ibuprofen in our setting due to a better side effect profile.(18)

With regards to complications, this study did find an increased risk of developing both IVH and BPD which has been previously reported.(19) (20)However, this study did not find an increased risk for the development of NEC despite other studies finding a correlation. This could be due to our small sample size and small numbers of infants with NEC in the study.(21,22) In this study infants with a PDA had a longer duration of in-hospital care compared to their non-PDA counterparts but there was no difference in mortality. Logistic regression analysis reported a lower gestational age, lower birth weight, IVH and BPD as risk factors for mortality. In our setting many ELBW infants demise before a PDA is diagnosed due to sepsis and limited invasive

respiratory support being offered due to resource constraints. Thus, a strong correlation with death could not be established.

In conclusion, in this study we found a low incidence of ECHO confirmed PDA in VLBW infants with clinical signs/symptoms. Infants with a PDA had and increased risk of morbidity. Although mortality was unchanged, some of the associated morbidities increased the risk of death. Therefore, it is important that these infants are diagnosed timeously, managed appropriately, and monitored for associated co-morbidities.

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This study had no funding.

Author contributions

A special thank you to Dr F. L. Nakwa and Dr R. Thomas for providing access to the neonatal data base as well as all the advice and guidance with the research all the contributions to the paper.

Conflict of interests:

Authors had no conflicts of interest.

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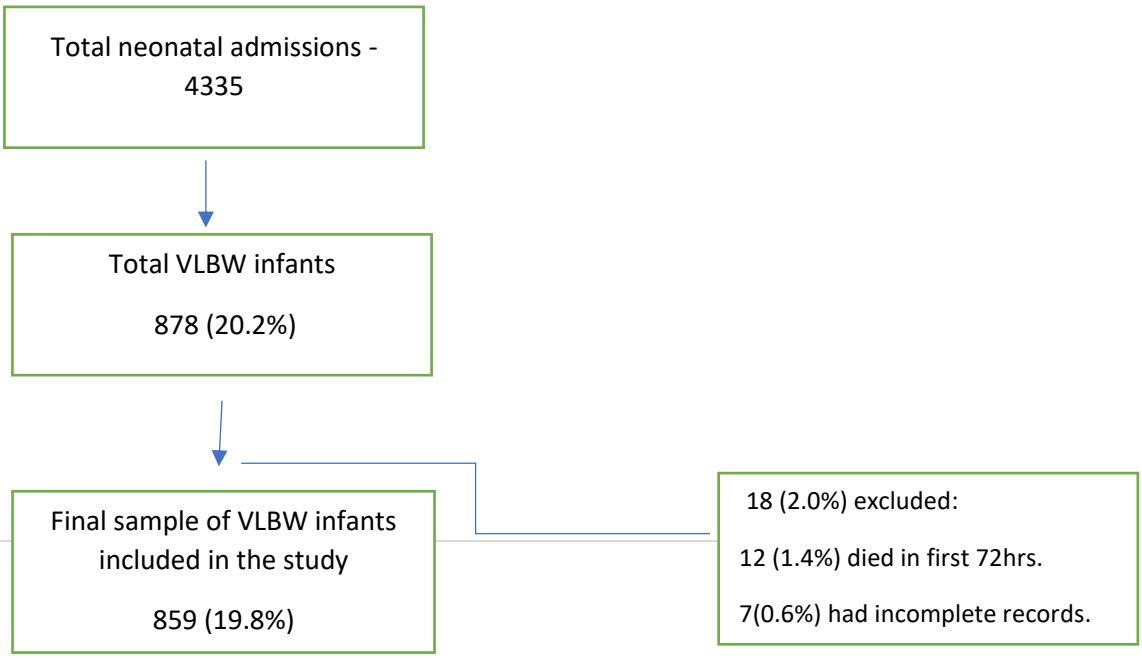

Total neonatal admissions - 4335
Total VLBW infants
878 (20.2%)
Final sample of VLBW infants included in the study
859 (19.8%)
18 (2.0%) excluded:
12 (1.4%) died in first 72hrs.
7(0.6%) had incomplete records.

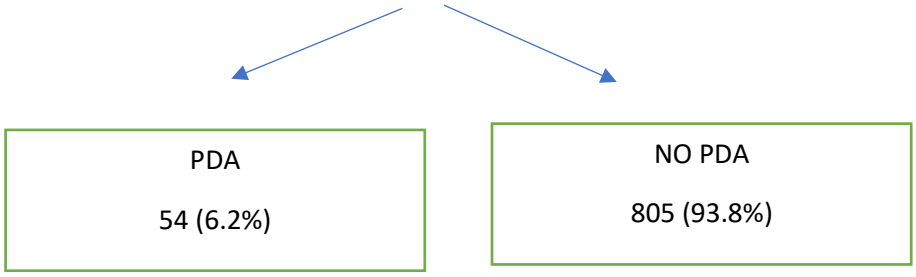


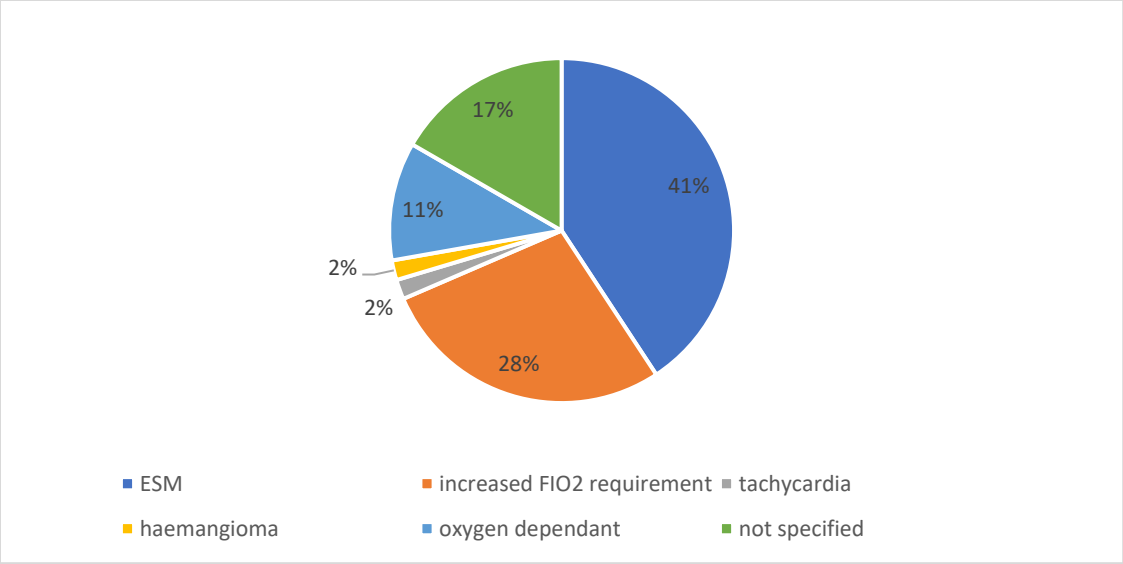
Figure 1: Consort Diagram

Table 1: Demographic and Clinical Characteristics of VLBW Infants with and without PDA.

Characteristic	**Total patients N=859 n (%)**	**With PDA N=54 n (%)**	**Without PDA N=805 n (%)**	**p-value**
Gender Male Female	 409 (47.4) 450 (51.6)	 26 (48.1) 28 (51.9)	 383 (47.6) 422 (52.4)	0.935
Gestational Age*	29±2.84	28.83 (±1.9)	29.4(±2.9)	0.005
<30 weeks >30 weeks Unknown	443 (51.6) 410 (47.7) 6 (0.7)	36 (66.7) 17 (31.4) 1 (0.9)	407 (50.6) 393 (48.9) 5 (0.5)	

Birthweight *	1140±255.34	1145 (±195.2)	1140 (±258.4)	0.001
<1000g 1000g- 1500g	246 (28.6) 613 (71.4)	12 (22.2) {1.4%} 42(77.8) {4.9%}	234 (29.1) 571 (70.9)	
Mode of delivery				0.859
Caesarean section Normal vaginal delivery Unknown	489(56.9) 364(42.4) 6(0.7%)	31(57.4) 22 (40.7) 1 (1.9)	458 (56.9) 342(42.5) 5(0.6%)	
HIV Exposed Hiv unexposed or unkown	220 (25.6) 639(74.4)	13 (24.1) 41(75.9)	207(25.7)	0.784
Antenatal steroids Received Not received unknown	 386(44.9) 469(54.6) 4(0.5)	 22 (40.7) 30 (55.6) 2(3.7)	 364 (45.2) 439 (54.5) 2(0.3)	0.671
5-minute APGAR #	8 (3 – 10)	8 (1 –9)	8 (3 –10)	0.00
Ventilation nCPAP IPPV None	 593 (69) 36 (4) 230 (27)	 41 (76) 7(13) 6 (11)	 552 (68) 29 (4) 224 (28)	 0.257 0.009 0.07

* Mean (SD), #Median (IQR) * {}- prevalence
nCPAP – nasal continuous positive airway pressure, IPPV – intermittent positive pressure ventilation



ESM - ejection systolic murmur, FIO2 - fractional inspired oxygen concentration

Figure 2: Clinical Presentation of Infants Diagnosed with a PDA

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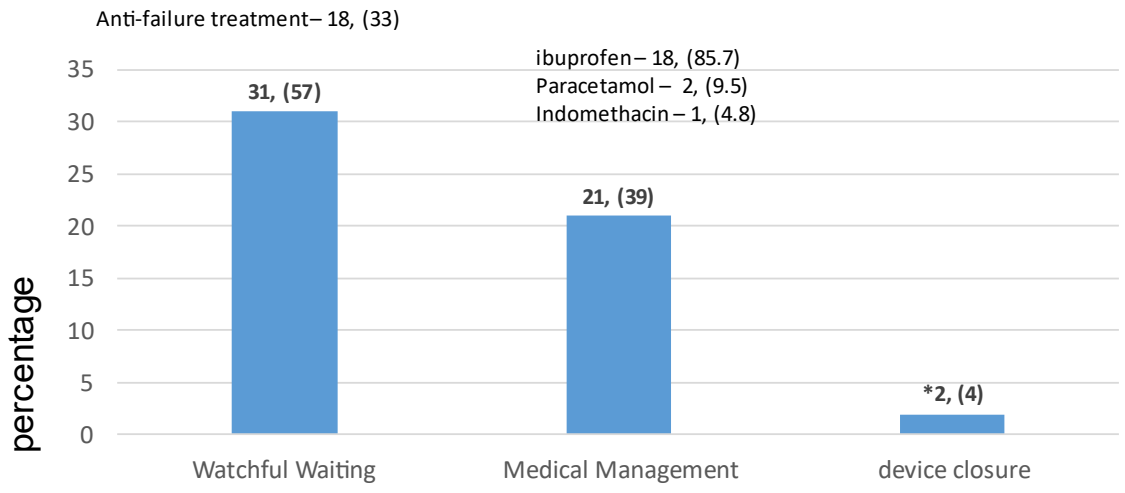

Figure 3: Management of Infants with a PDA

*percentages in brackets

Table 2: Complications and Outcomes in Infants with and without a PDA

	Total N=859 n (%)	**PDA N=54 n (%)**	**No PDA N=805 n (%)**	**p-value**	**OR**	**CI**
NEC	48 (5.6)	1 (1.9)	47 (5.8)	0.39	0.888	0.68-1.17
IVH	120 (13.9)	20 (37)	100 (12.4)	0,001	1.59	1.17-2.18
BPD	118 (13.7)	23 (42.6)	95 (11.8)	0,001	4.2	1.8-9.6
Length of stay 1-30 days 31-60 days >61 days	 460 (53.50 243 (28.2) 140 (16.2)	 13 (24.1) 21 (38.9) 17 (31.5)	 447 (55.5) 222 (27.6) 123 (15.3)	 0,001 0,001 0,018	1.01	1.01-1.02
Discharged	618 (71.9)	38 (70.4)	580 (72.2)	0,19	0.07	0.05-0.09
Demised	222 (25.8)	15 (27.8)	207 (25.7)	0.32	0.07	0.04-0.12
Unknown outcome	19(2.2)	1(1.8)	18(2.1)			

NEC – necrotising enterocolitis, IVH – intraventricular haemorrhage, BPD – bronchopulmonary dysplasia

Table 3: Risk factors for mortality in VLBW infants with PDA*

	aOR	**95% CI**	**p-value**
GA	0.65	0.6-0.71	<0.001
Sex	0.65	0.47-0.88	0.07
Birth weight	1.00	0.99-1.0	<0.001
Antenatal steroids	0.8	0.37-1.75	0.58
IVH	1.44	1.21-1.71	<0.001
BPD	0.07	0.02- 0.23	<0.001
NEC	0.89	0.68-1.17	0.4
Need for ventilation	0.71	0.52-0.93	0.028
Length of stay	1.00	0.99-1.01	0.09

GA – gestational age, IVH – intraventricular haemorrhage, BPD – Bronchopulmonary dysplasia, NEC – necrotising enterocolitis

*Multivariable logistic regression analysis (variables with a with a p-value >0.1 included in the model)

Appendix A

Bronchopulmonary Dysplasia (BPD) definition

Table 1. Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Jobe, A.H.; Bancalari, E. Bronchopulmonary Dysplasia. *Am. J. Respir. Crit. Care Med.* 2001, 163, 1723–1729. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Gestational Age	<32 wk	≥32 wk
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	>28 d but <56 d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen > 21% for at least 28 d **plus**	
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need * for <30% oxygen at 36 wk PMA or discharge, whichever comes first	Need * for <30% oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need * for ≥30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need * for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = post menstrual age; PPV = positive pressure ventilation. * A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical feature of respiratory distress. A day of treatment with oxygen > 21% means that the infant received oxygen > 21% for more than 12 h on that day. Treatment with oxygen > 21% and/or positive pressure at 36 wk PMA, or at 56 d postnatal age or discharge, should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and following 36 wk PMA, 56 d postnatal age, or discharge.

Davidson LM, Berkelhamer SK. Bronchopulmonary Dysplasia: Chronic Lung Disease of Infancy and Long-Term Pulmonary Outcomes. J Clin Med. 2017 Jan 6;6(1):4. doi: 10.3390/jcm6010004. PMID: 28067830; PMCID: PMC5294957

Appendix B

Modified Bell's staging.

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs
IA	**Suspected**	Temperature instability, apnoea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus
IB			Grossly bloody stool	
IIA	**Definite** Mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopaenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA	**Advanced, severely ill**, Intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnoea, combined respiratory and metabolic acidosis, DIC, and neutropaenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites
IIIB	Perforated bowel			Same as above, plus pneumoperitoneum

Appendix C (23)

Papile classification

Grading of IVH

- Grade I Germinal matrix haemorrhage.
- Grade II Blood within ventricular system without distension
- Grade III Blood within ventricular system with distension
- Grade IV/ III+IPE Intra-ventricular and -parenchymal bleed (echodensity)

Appendix D

Retinopathy of Prematurity ROP Staging

Stage	Definition	Description
1	Demarcation line	Thin flat white line between vascular and avascular retina
2	Ridge	White or pink line with height extending above the plane of the retina
3	Extraretinal fibrovascular proliferation	Neovascularisation extending into the vitreous makes ridge appear ragged
4	Partial retinal detachment	Extra-foveal (4A) or Foveal (4B)
5	Complete retinal detachment	Funnel-shaped usually
Plus, Disease	Arterial tortuosity of posterior retinal vessels and venous dilatation	
Aggressive Posterior (AP-ROP or Rush disease)	Severe form of ROP with with rapid progression. Posterior prominence of plus disease that does not always follow the usual stepwise progression in severity	

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University of the Witwatersrand

Faculty of Health Sciences

Incidence, Characteristics, Management and Outcomes of Neonates with Patent Ductus Arteriosus (PDA) at Chris Hani Baragwanath Academic Hospital

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Introduction

The ductus arteriosus (DA) is a vascular structure essential for foetal circulation that joins the descending proximal aorta to the pulmonary artery.(1) During the embryological period, the sixth pair of the embryonic arch persists as the proximal branch pulmonary arteries and the distal portion persists as the DA connecting the left pulmonary artery and the left dorsal aorta. (24)

During foetal circulation only 5-10% of blood from the right ventricle flows through the lungs, the remainder passes through the DA to the aorta.(25) Foetal patency of the ductus arteriosus is controlled by a variety of factors such as low oxygen tension and the cyclooxygenase mediated products of arachidonic acid metabolism, prostaglandin, and prostacyclin. Prostaglandin levels are higher in the foetus due to placental production and reduced metabolism by the lung. The smooth muscle cell of the DA is the site of oxygen-sensing and the endothelium is responsible for releasing vasoactive substances that affect vascular tone.(24)

At birth there is an abrupt increase in oxygen tension which results in inhibition of ductal smooth muscle voltage-dependant potassium channels. The former results in cell membrane depolarization leading to an influx of calcium and ductal constriction. Oxygen also causes the release of endothelin 1, which is a potent vasoconstrictor. Endothelin-1 causes G-protein coupling which results in increasing intracellular calcium.(26) Prostaglandin levels also fall due to increased metabolism by lungs and decreased production because of elimination of the placenta. The medial smooth muscle then contracts resulting in wall thickening, lumen obliteration and reduction in the length of the ductus arteriosus. The constriction leads to the formation of a hypoxic zone. This triggers cell death and also induces the production of the vascular endothelial growth factor and transforming growth factor which results in vascular remodelling and as a result, anatomical closure of the DA.(24)

The patent ductus arteriosus (PDA) accounts for approximately 5-10% of all congenital heart disease. Patent ductus arteriosus has an incidence of 1 in 2000 live births in term infants and an incidence of 300 per 1000 in preterm infants. The reported incidence of symptomatic PDAS is 11 to 36% with higher numbers in neonates born at <30 weeks.(20) The rate is inversely proportional to gestational age, hence, it is seen in about 20% of infants greater than 32 weeks and 60% of infants less than 28 weeks.(27) However, in term infants it is associated with a structural abnormality and is frequently seen in genetic syndromes such as the trisomies. Risk factors associated with PDAs are prematurity, respiratory distress syndrome (RDS), antenatal steroids, female gender and

sepsis.(22) There is also an association with rubella infection in the first 4 weeks of pregnancy.(26)

The PDA occurs more frequently in preterm infants due to multiple immaturity mechanisms.(24) Premature infants fail to produce the hypoxic zone because of reduced sensitivity to oxygen and increased sensitivity to prostaglandin E1 (PGE1), nitric oxide and endothelin-1. This results in suboptimal constriction of the DA and therefore predisposes preterm infants to have a PDA.(7) The potassium and calcium channels don't function optimally yet which results in suboptimal oxygen mediated constriction in the preterm rabbit DA.(6,7) Preterm infants also have a decreased sensitivity to oxygen and an increased sensitivity PGE2, nitric oxide and endothelin-1 which acts to dilate and relax vascular smooth muscle.(24)

Patients with a PDA may have a multitude of clinical presentations. Clinically, PDA can present with respiratory distress or failure, have bounding pulses, a widened pulse pressure and a murmur found at the upper left sternal border. This murmur is often referred to as a "machinery" murmur as there is a both a systolic and diastolic component. In neonates the murmur is an ejection systolic murmur due to the high pulmonary pressures which prevent the diastolic run off from being heard. Infrequently, a diastolic rumble is audible at the cardiac apex when the duct is greater than 1,5mm in size (classified as a moderate to large PDA).(28)

The diagnosis of a PDA starts based on clinical suspicion. A cohort study of preterm infants by Skelton and associates indicated that clinical signs had a high specificity but low sensitivity. (18) Most significant PDAs did not have clinical signs. (18) The gold standard to diagnose a PDA is on echocardiogram (ECHO). Colour doppler during an ECHO is used to detect the presence of a PDA. A colour flow signal is seen entering the pulmonary artery near the origin of the left pulmonary artery. Echocardiography is extremely sensitive in detecting even an extremely tiny patent ductus arteriosus. (17)

A PDA is considered to be haemodynamically significant if it has the following features on ECHO: DA diameter of 1.4 mm/kg body weight, left atrium (LA): aorta (Ao) ratio of 1:1.4, holo-diastolic flow reversal in the descending aorta as well as enlargement of the left ventricle.(29) As a result of the holo-diastolic flow reversal, some neonatologists consider a resistance index of 0.9 on cerebral doppler examination of the anterior cerebral artery a sign of significant ductal shunting with adverse cerebral steal effect.(17)

Patent ductus arteriosus has significant clinical consequences for neonates. The left to right shunt causes pulmonary over circulation and volume overload to the left side of the heart. This results in

various long and short term complications including intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), pulmonary oedema and congestive cardiac failure (CCF) (30). Long term complications are pulmonary hypertension, bronchopulmonary dysplasia (BPD), Eisenmenger's syndrome and death (11,12).

Treatment of a PDA currently is based on whether it is haemodynamically significant, either clinically or on ECHO. The treatment of PDA, however, remains controversial. Studies have found that 60% of PDAs will close spontaneously. (4,17) There are currently three main management strategies: watchful waiting, medical closure, and surgical management. The strategy of watchful waiting involves fluid restriction and monitoring until the PDA closes.(31) Pharmacotherapy with cyclooxygenase inhibitors like indomethacin and ibuprofen or peroxidase inhibitors like paracetamol are prescribed for medical closure. Cyclooxygenase inhibitors act by inhibiting prostaglandin thereby facilitating closure of the PDA. However, primary duct closure with either ibuprofen or indomethacin ranges between 60-80%, with decreasing efficacy and higher recurrence rates with more premature infants.(31) Cyclooxygenase inhibitors are associated with adverse effects like acute kidney injury (AKI), NEC, gastrointestinal haemorrhage and intestinal perforation when used in conjunction with steroids. Cyclooxygenase inhibitors affect renal, cerebral and gastrointestinal perfusion and are contraindicated with renal dysfunction and NEC.(32) Though the efficacy rates remain similar more side effects are seen with indomethacin than with ibuprofen use.(10,13) A study by Dang et al showed that closure rates with paracetamol were similar to that of ibuprofen at 81% and 79% respectively, but treatment with paracetamol had fewer side effects. Usage of paracetamol is indicated as an alternative to cyclooxygenase inhibitors in patients with AKI, thrombocytopaenia or NEC. (10)

Surgical ligation of the PDA is considered in patients with haemodynamically significant PDA where medical management has failed or when there are contraindications to medical management.(33) Ligation of the PDA is usually indicated when there is associated profound pulmonary haemorrhage, deteriorating respiratory status, inability to extubate or wean an infant on ventilatory support and cardiac failure with associated failure to thrive.(34) Surgical intervention is only considered after 4 weeks of age as at this point medical management success rates fall due to maturation of ductal tissue which subsequently becomes less responsive to prostaglandins. Short term side effects associated with surgical ligation include recurrent laryngeal nerve damage, injury to the thoracic duct, pneumothorax and left ventricular dysfunction for a period after PDA ligation and death. The mortality rate is 0-2% with surgical ligation of the PDA.(34)

Patent ductus arteriosus contributes to significant morbidity and mortality in the neonate and is dependent on the anatomy of the DA. It is imperative to identify a neonate with a PDA and to manage timeously. There is paucity of data on PDA in low to middle income countries (LMIC). This study aims to determine the incidence, clinical course, treatment, and outcomes of very low birth weight (VLBW) neonates diagnosed with PDA in the neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH).

Aim

To determine the incidence, clinical characteristics, risk factors, diagnosis, and outcomes of VLBW with PDA at Chris Hani Baragwanath hospital (CHBAH).

Objectives

1. To determine the incidence of PDA in VLBW neonates.

2. To describe the demographic and clinical characteristics of VLBW neonates diagnosed with a PDA and compare them to those without PDA.

3. To determine the risk factors associated with PDA.

4. To describe the ECHO findings in VLBW neonates diagnosed with a PDA.

5. To describe the pharmacological management of VLBW neonates diagnosed with a PDA, as well as complications associated with management.

6. To describe co-morbidities in VLBW neonates diagnosed with a PDA.

7. To determine all-cause mortality rates in VLBW neonates diagnosed with a PDA and compare the survivors to non-survivors.

8. To compare outcomes of VLBW neonates with PDA to those without a PDA.

Study Methods

Study design

This will be a single centre, retrospective, descriptive study of VLBW neonates, with a birth weight less than 1500g, admitted in the neonatal unit at CHBAH from January 2017 to December 2017 with a diagnosis of a PDA.

Study setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary, public, academic hospital which lies on the outskirts of Soweto, Johannesburg, South Africa. The hospital and its cluster conduct approximately 30000 deliveries with an average of 4500 admissions to the CHBAH neonatal unit per year. Preterm deliveries account for 20% of all deliveries. The hospital is a major referral centre for surrounding regional and district hospitals and maternal obstetric units (MOUs) and clinics. The neonatal unit at CHBAH has 185 neonatal beds consisting of 18 intensive care beds (level 3 nursery), 48 high care beds (level 2 nursery), 100 standard care beds (level 2 and 1 nursery) and 19 kangaroo mother care (KMC) beds (level 1 nursery). The paediatric department at CHBAH also offers paediatric cardiology services run by specialist paediatric cardiologists and cardiology fellows. Neonates who are suspected of having a PDA on clinical grounds, or who require an ECHO for any other clinical indication, are referred to the paediatric cardiologists for this investigation.

Study participants

All VLBW neonates admitted to the neonatal unit at CHBAH, during the year 2017, will be included in the study. Only VLBW infants with an ECHO confirmed PDA will be included for the description of PDA in this cohort.

Exclusion criteria:

1. All VLBW neonates who have major underlying congenital malformations or genetic syndromes, or who are not expected to survive.
2. Neonates weighing 1500 grams or more.

Study procedures

Data on all VLBW neonates born during the study period will be extracted from the neonatal units REDCap database, including data on VLBW infants with a PDA. To augment any missing information on the database, clinical records of these patients will be retrieved where necessary. Data collected will include demographic and clinical characteristics of the neonate, clinical presentation at time of PDA diagnosis, ECHO findings, pharmacotherapy used and associated adverse effects such has thrombocytopaenia, AKI, NEC, respiratory failure and IVH, if any, associated morbidities and outcomes (Appendix A). This data will then be entered onto an Excel spreadsheet and each patient will be assigned a unique study number, therefore keeping the patient identity anonymous. A separate sheet will be kept with the patient identifiers and the unique study number. The data will be kept on a password protected computer and only the investigator and the supervisors will have access to this data.

Study Definitions

Very Low Birth Weight: birth weight less than 1500g

Patent ductus arteriosus: persistence of the DA after birth, diagnosed on ECHO.

Haemodynamically significant PDA: PDA with the following ECHO characteristics: size > 1,4mm/kg, left atrium to aortic ratio is >1,4, the PDA to left pulmonary artery ratios >1, left ventricular dysfunction and reversal of end diastolic flow.

Bronchopulmonary dysplasia: the need for supplemental oxygen for more than 28 days can be mild, moderate, and severe (Appendix B)

Necrotizing enterocolitis is ischaemic necrosis of the intestinal mucosa, presenting with clinical and radiological signs according to the modified Bell's staging (Appendix C)

Intraventricular haemorrhage is bleeding into the cerebral ventricular system, graded according to the Papille classification (Appendix D)

Retinopathy of prematurity are insults that disrupt neurovascular growth. (Appendix E,23)

Sample size calculation

With approximately 20000 annual deliveries, and a VLBW rate of 5%, we estimate a sample size of around 1000 VLBW neonates. With the reported incidence of symptomatic PDA of approximately 11 to 36 %we calculated a sample size of 110 - 360 VLBW infants a with PDA. Due to the

retrospective nature of the study, we anticipate missing data in approximately 10% of patients, giving us a final estimated sample size of 99 - 324 patients with PDA for analysis.

Data analysis:

Data will be collected and entered on an Excel spread sheet and analysed using the statistical package Stata, version 15. Means and standard deviations will be used to describe continuous variables with normal distribution, and medians and ranges will be used to describe continuous variables that are not normally distributed. Frequencies and proportions will be used to describe categorical variables. To compare survivors to non-survivors, and to compare VLBW neonates with PDA to those without PDA, the student t-test will be used when comparing parametric data and a Mann-Whitney U test to compare non-parametric data and the Pearson Chi-square test to compare categorical variables. Differences between the two groups will be statistically significant when the p-value is less than 0.05.

Ethics

Patient identifiers will be anonymized and be represented by a study number on the data sheet. As this is a retrospective study and patient confidentiality maintained, patient consent will not be obtained. The protocol will be submitted for ethics approval to the human research ethics committee (HREC), University of the Witwatersrand. Approval will also be obtained from the Head of Department of Paediatrics, Head of Neonatology, and the CEO at Chris Hani Baragwanath Academic hospital. The protocol will be registered on the National Research database.

Limitations

Clinical presentations vary and asymptomatic PDAs during this time may not be picked up as there isn't universal cardiac screening. Due to the retrospective nature of the study, we anticipate that there may be some missing data due to missing hospital records as well as incomplete record keeping.

Cost and funding

The investigator will privately fund the cost of stationery and printing, with an estimated cost of R300

Gant chart

	2021					2022					
	Aug	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**June**
Assignment 0f topic	X										
Protocol preparation		X	X	X	X						
Assessment of protocol						X	X				
Data collection								X			
Write up									X	X	
Submission											X

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Appendix A

Data collection sheet

Incidence, Characteristics, Management and Outcomes of Neonates with Patent Ductus Arteriosus at Chris Hani Baragwanath Academic Hospital

SECTION A: PATIENT DETAILS	
PATIENT STUDY ID	
POST NATAL AGE	
SEX	
BIRTH WEIGHT	
GESTATIONAL AGE AT DELIVERY	
SECTION B: ANTENATAL HISTORY	
MATERNAL AGE	
PARITY AT DELIVERY	
IS BABY HIV EXPOSED	YES ☐ NO ☐ UNKNOWN ☐
WAS MOTHER ON ANTENATAL ART	YES ☐ NO ☐ UNKNOWN ☐ N/A☐
DID MUM RECEIVE ANTENATAL STEROIDS	YES ☐ NO ☐ UNKNOWN ☐ N/A☐
SECTION C: BIRTH HISTORY	
MODE OF DELIVERY	NVD ☐ C/S ☐
1 MIN APGAR SCORE	
5 MIN APGAR SCORE	
SECTION D: CLINICAL INFORMATION	
ECHO CONFIRMED PDA	YES ☐ NO ☐
IF YES, CLINICAL PRESENTATION AT TIME OF PDA DIAGNOSIS	
GENETIC CONDITIONS	
ECHO findings at diagnosis and any repeat examinations	
RENAL FUNCTION test (U&E), prior to pharmacologic treatment and after pharmacologic treatment, if available	
PLATELET COUNT prior to pharmacologic treatment and after pharmacologic treatment, if available	
RESPIRATORY SUPPORT AT TIME OF PDA DIAGNOSIS IF IPPV, DATE INTUBATED:	ROOM AIR ☐ NASAL PRONGS ☐ CPAP ☐ IPPV ☐ HFOV ☐

MAXIMUM RESPIRATORY SUPPORT	
SECTION E: ASSOCIATED MORBIDITIES	
NEC If yes, grading:	YES ☐ NO ☐
IVH If yes, grading:	YES ☐ NO ☐
BPD If yes, grading:	YES ☐ NO ☐
OTHER UNDERLYING MORBIDITIES	
Management	
IBUPROFEN If yes, date started, dose and duration per course	YES ☐ NO ☐
INDOMETHACIN If yes, date started, dose and duration per course	YES ☐ NO ☐
PARACETAMOL If yes, date started, dose and duration per course	YES ☐ NO ☐
FUROSEMIDE	YES ☐ NO ☐
Surgical management	
Outcomes	
OUTCOME AT DISCHARGE	SURVIVED ☐ DIED ☐
IF DIED, CAUSE OF DEATH	
LENGTH OF HOSPITAL STAY	

Appendix B

Bronchopulmonary Dysplasia (BPD) definition

Table 1. Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Jobe, A.H.; Bancalari, E. Bronchopulmonary Dysplasia. *Am. J. Respir. Crit. Care Med.* 2001, 163, 1723–1729. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Gestational Age	<32 wk	≥32 wk
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	>28 d but <56 d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen > 21% for at least 28 d **plus**	
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need * for <30% oxygen at 36 wk PMA or discharge, whichever comes first	Need * for <30% oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need * for ≥30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need * for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = post menstrual age; PPV = positive pressure ventilation. * A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical feature of respiratory distress. A day of treatment with oxygen > 21% means that the infant received oxygen > 21% for more than 12 h on that day. Treatment with oxygen > 21% and/or positive pressure at 36 wk PMA, or at 56 d postnatal age or discharge, should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and following 36 wk PMA, 56 d postnatal age, or discharge.

Davidson LM, Berkelhamer SK. Bronchopulmonary Dysplasia: Chronic Lung Disease of Infancy and Long-Term Pulmonary Outcomes. J Clin Med. 2017 Jan 6;6(1):4. doi: 10.3390/jcm6010004. PMID: 28067830; PMCID: PMC5294957.

Appendix C

Modified Bell's staging

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs
IA	**Suspected**	Temperature instability, apnoea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus
IB			Grossly bloody stool	
IIA	**Definite** Mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopaenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA	**Advanced, severely ill**, Intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnoea, combined respiratory and metabolic acidosis, DIC, and neutropaenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites
IIIB	Perforated bowel			Same as above, plus pneumoperitoneum

Appendix D

Papile classification

Grading of IVH

- Grade I Germinal matrix haemorrhage
- Grade II Blood within ventricular system without distension
- Grade III Blood within ventricular system with distension
- Grade IV/ III+IPE Intra-ventricular and -parenchymal bleed (echodensity)

Appendix E (23)

Retinopathy of Prematurity ROP Staging

Stage	Definition	Description
1	Demarcation line	Thin flat white line between vascular and avascular retina
2	Ridge	White or pink line with height extending above the plane of the retina
3	Extraretinal fibrovascular proliferation	Neovascularisation extending into the vitreous makes ridge appear ragged
4	Partial retinal detachment	Extra-foveal (4A) or Foveal (4B)
5	Complete retinal detachment	Funnel-shaped usually
Plus, Disease	Arterial tortuosity of posterior retinal vessels and venous dilatation	
Aggressive Posterior (AP-ROP or Rush disease)	Severe form of ROP with with rapid progression. Posterior prominence of plus disease that does not always follow the usual stepwise progression in severity	

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FROM: Mr Iain Burns

Human Research Ethics Committee (Medical) Tel: 011 717 1252

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R49 Dr D Naidoo

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NAME:	Dr D Naidoo
(Principal Investigator)	
DEPARTNENT:	School of Clinical Medicine Department of Paediatrics and Child Health Division of Neonatology Medical School University
PROJECT TITLE:	*Incidence,* characterise/cs, *management and outcomes of neonates with Patent Ductus Arteriosus at Chris Hani Baragwanath Academic Hospital*
DATE CONSIDERED:	2022/02/25
DECISION: CONDITIONS:	Approved unconditionally
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen. Potgieter@wits.ac.za>
SUPERVISOR:	Drs F Nakwa and R Thomas Dr CB P enny, Chairperson, HREC (Medical)
APPROVED BY:	2022/03/30
DATE OF APPROVAL:	

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of lhe Witwatersrand, Johannesburg.

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 submit details to the Committee. I agree to submit a yearly **progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed **in February** and therefore reports and re-certification will be due in the month of February each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

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