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University of the Witwatersrand, Johannesburg

Faculty of Health Sciences

RESEARCH REPORT

A REVIEW OF CHRONIC LUNG DISEASE IN NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL FROM 1 JANUARY 2013 TO 31 DECEMBER 2014

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DECLARATION

I, Aripfani Veronica Mphaphuli, declare that this research report is my own original work.

It is being submitted for the degree of Master of Medicine in paediatrics at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

The research was accepted for publication as an article in South African Journal of Child Health on 01/11/2015.

…….

Date

DEDICATION

This humble work is dedicated to my family and my friends.

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I wish to express my sincere thanks to my supervisor Prof Daynia Ballot. I am extremely grateful and indebted to her for her expert, sincere and valuable guidance and encouragement extended to me.

I also thank Prof Cooper and the department of paediatrics and child health at the University of the Witwatersrand for the training.

I take this opportunity to record my sincere gratitude to all who, directly and indirectly have lent a helping hand in this venture.

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ABBREVIATIONS

CLD neonatal chronic lung disease

CMJAH Charlotte Maxeke Johannesburg Academic Hospital

PDA patent ductus arteriosus

PNCS Postnatal corticosteroids

NEC necrotizing enterocolitis

BPD bronchopulmonary dysplasia

PMA Post menstrual age

NIH National Institute of Health

GIT gastrointestinal

CP cerebral palsy

RCT Randomized controlled trial

AAP American academy of paediatrics

ELBW extreme low birth weight

VLBW very low birth weight

NBW normal birth weight

GA gestational age

VON Vermont oxford network

OP oral prednisolone

SD standard deviation

SGA small for gestational age

KMC kangaroo mother care

NCPAP nasal continuous positive airway- pressure ventilation

SVT surfactant

IPPV intermittent positive-pressure ventilation

PVL periventricular leukomalacia

A review of chronic lung disease in neonates at Charlotte Maxeke Johannesburg Academic Hospital from 1 January 2013 to 31 December 2014

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Background. Chronic lung disease (CLD) remains a significant morbidity in preterm babies despite advances in neonatal care. The use of postnatal corticosteroids (PNCS) to treat CLD remains controversial.
Objectives. To describe the clinical characteristics of babies with CLD at Charlotte Maxeke Johannesburg academic hospital (CMJAH) and to explore the use of PNCS for the prevention and treatment of CLD.
Methods. This was a 2-year retrospective review of neonates admitted to CMJAH. Neonates who were in hospital for ≥28 days were included. Comparisons were made between neonates with evolving CLD and those with no CLD.
Results. A total of 485 neonates were analysed, 237 had evolving CLD and 245 did not have CLD. Overall incidence of evolving CLD was 5%. More neonates with CLD needed resuscitation at birth (48.5% v. 39.8%; p=0.02) and had low 5 minutes Apgar scores (17.2% v.10.6%; p=0.001). Neonates with CLD had increased prevalence of patent ductus arteriosus (30.4% v. 7.7%; p=0.001) and late onset sepsis (56.5% v. 23.6%; p=0.001). The mortality rate was also higher in CLD babies (10.2 v. 2.4%; p=0.001). Necrotising enterocolitis (NEC) (29.2% v.8%; p=0.005) and sepsis (83.3% v. 53.8%; p=0.008) were associated with increased mortality. The use of PNCS was associated with less NEC (3.5% v. 17.2%; p=0.001) and improved survival (95.6% v. 81.7%; p=0.001).
Conclusions. CLD remains a common morbidity in neonates despite advances in neonatal care. The use of PNCS was shown to have short-term benefits. To get the most out of PNCS use for CLD, further studies need to be conducted to determine the safest type of steroid, the safe doses and the duration of treatment.

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Background

The clinical definition of neonatal chronic lung disease (CLD) also known as bronchopulmonary dysplasia (BPD) has evolved over time. It was first defined by Northway *et al*. in 1967 as persistent respiratory signs and symptoms along with the need for supplemental oxygen and an abnormal chest X-ray (CXR) at 28 days of age.[1] The definition of CLD was subsequently modified and defines BPD as oxygen dependence at 36 weeks post menstrual age (PMA) with or without the use of respiratory support and with or without the characteristic radiographic changes.[2] These definitions do not consider gestational age (GA) and do not indicate the level of oxygen dependence that can range from needing low-flow oxygen to being ventilator-dependent. To address this issue, the National Institute of Health has developed a consensus severity-based definition. This definition includes all babies born as needing more than 21% supplemental oxygen for at least 28 days. CLD is further classified into mild, moderate and severe, depending on the FiO_2 needed and the duration of oxygen therapy for preterm babies.[3] Because of the complexity of the definition, some units just use the need for oxygen on day 28 of life and often refer to this as evolving CLD. The incidence of CLD as defined by the need for oxygen supplementation at 36 weeks PMA is ~30% of premature infants with birth weight (BW) <1 000 g and is uncommon in infants born at >30 weeks of gestation or weight of >1 250 g.[3]

CLD has multifactorial aetiology and remains a major cause of morbidity in premature infants[1].Contributing factors include infection, exposure to high oxygen levels with the formation of toxic oxygen free radicals and ventilator-induced lung injury that results in arrested lung development and impaired lung function.[4] Several maternal risk factors including increasing age, hypertension, lack of antenatal steroid usage and chorioamnionitis have been associated with BPD.[4] Over the past few years, the pathophysiology and aetiology of BPD has changed. This pathophysiological and aetiological shift has been bought about by improved survival in extremely premature babies as a result of for instance, antenatal steroids and surfactant therapy. The classic BPD was characterized mainly by lung damage and fibrosis due to oxygen toxicity and mechanical ventilation. The new BPD is characterised by a disorder in lung development with fewer, larger and simplified alveoli.

The management of CLD includes several preventive and therapeutic strategies that target several pathways and processes involved in pathogenesis of CLD. Some provide antioxidant protection; others minimise specific aspects of inflammation, reduce elastolytic and proteolytic injury or regulate growth. In addition, supportive pharmacological treatments that target the development of pulmonary oedema, bronchoconstriction and impaired gas exchange are used. The success of these interventions has been variable.[5]

Postnatal corticosteroids (PNCS) have been extensively studied and have been found to be effective in weaning infants off mechanical ventilation.[6-8] This effect has been proven for dexamethasone, which is the most widely studied PNCS in randomized controlled trials (RCTs). Despite the short-term benefits, dexamethasone has not been shown to reduce the total days of hospitalisation, duration of supplemental oxygen therapy, or incidence of CLD.[6-8] In the era before PNCS treatment, the long-term neurodevelopmental outcome for survivors with CLD was worse than that in similar infants without CLD.[9] Adverse effects of PNCS that includes hyperglycaemia, gastrointestinal (GIT) perforation, hypertension, infection, steroid-induced cardiomyopathy, long-term neurodevelopmental effects and growth retardation complicate the use of PNCS. The most worrisome long term effect is increased risk for poor neurological outcome including cerebral palsy (CP). Corticosteroids can have direct toxic effects on the developing brain, including neuronal necrosis, interference with healing and inhibition of brain growth.[9,10] A systematic review showed a significantly higher rate of CP after corticosteroid treatment and a non-significant reduction in mortality.[11] A multicentre double blinded RCT testing early postnatal dexamethasone therapy for prevention

of CLD had to be stopped before completion because of concern about serious side effects such as GIT perforation and periventricular leukomalacia (PVL).[12] The American Academy of Pediatrics (AAP) also recommended that alternative corticosteroids undergo studies and that all infants enrolled in RCTs for PNCS receive long-term neurodevelopmental follow up.[13]

Due to concern about the safety of PNCS, in 2002 the AAP released a policy statement regarding the use of PNCS for prevention or treatment of CLD stating that the routine use of dexamethasone could not be recommended.[13] The AAP recommended that dexamethasone use be limited to RCTs with long-term follow up. Since the publication of the AAP statement, postnatal use of dexamethasone for CLD has reduced; however the incidence of CLD has not diminished. Some reports have suggested that the incidence and severity of CLD may have actually increased.[14]

The data available for PNCS use in CLD are inconclusive and conflicting. As a result, clinicians are advised to use their own clinical judgment to balance potential adverse effects of CLD with the potential adverse effects of PNCS for each individual patient.

The incidence of CLD in very low birth weight (VLBW) babies at Charlotte Maxeke Johannesburg academic hospital (CMJAH) is lower than that reported in the Vermont Oxford network (VON).[15] At CMJAH, babies who are on supplemental O_2 for >28 days are given oral prednisolone (OP) for prevention/treatment of CLD. Babies who remain ventilator dependent are given dexamethasone.

Alternative PNCS include hydrocortisone, nebulised dexamethasone and oral prednisone.[5] One study looking at the effect of short course of oral prednisone (OP) in infants with O_2 dependent BPD provided evidence that OP is effective in a select patients with BPD.[16] Characteristics of babies with CLD and the use of PNCS have not been reviewed at CMJAH. This study aims to describe babies with evolving CLD and to explore the use of PNCS for evolving CLD at CMJAH.

Methods

This study is an institution-based retrospective audit conducted in the neonatal unit at CMJAH in Parktown, Gauteng Province. The objectives were to determine the incidence of CLD at CMJAH, to describe clinical and demographic characteristics and survival to discharge in babies with CLD and to compare these to those of babies without CLD. Evolving CLD was defined as oxygen use at 28 days of life and the need for supplemental oxygen at 36 weeks PMA was considered as definite CLD (VLBW babies only). Following approval by the Committee for Research in Human Subjects at the University of the Witwatersrand (Medical), the CEO and the HOD of Paediatrics at CMJAH, a 2-year (1 January 2013 to 30 December 2014) retrospective review of neonatal medical records was performed. Data from the existing CMJAH neonatal database (Research Electronic Data Capture hosted by the University of the Witwatersrand) was used for analysis. [17] The data are collected prospectively on an ongoing basis for the purpose of clinical audit from clinician completed hospital records. All babies admitted to the CMJAH neonatal unit within 72 hours of life (inborn and outborn), with BWs of ≥500 g, who were in hospital for ≥28 days were included. Babies with irretrievable data were excluded from the study. The group was divided into babies with evolving CLD and those without. The neonatal unit at CMJAH has 84 beds, 35 of which are high-care, 14 in paediatric/neonatal intensive care unit, 20 low-care beds and 15 kangaroo mother care beds. Respiratory support includes early rescue surfactant (SVT), supplemental oxygen via low-flow nasal cannulae (NPO_2), nasal continuous positive airway-pressure ventilation (NCPAP), intermittent positive-pressure ventilation (IPPV) and high frequency oscillatory ventilation. Due to limited resources ventilatory support in the form of NCPAP was only offered to babies with BW ≥750 g who showed signs of respiratory

failure. Babies with BW ≥900 g who showed signs of respiratory failure on NCPAP or became apnoeic were offered IPPV. Respiratory failure was defined as O_2 saturation <88% on 60% supplemental O_2, respiratory acidosis (pH <7.25 with $PaCO_2$ >60 mmHg) or markedly increased work of breathing.

Definitions

Maternal hypertension included both chronic and pregnancy induced hypertension. Chorioamnionitis was defined as premature and/or prolonged rupture of membranes, fever and foul smelling liquor in mothers. Resuscitation at birth was defined as the need for bag mask ventilation, chest compressions, or intubation and ventilation. The Ballard score was used to estimate gestational age (GA). Fenton growth charts (2013) were used to assess weight for gestational age.[18] The whole group of neonates was described and then stratified by BW category namely:

- ≥500-999 g, extreme low birth weight (ELBW)
- ≥1000 to 1499 g, very low birth weight (VLBW)
- ≥1500 to 2499 g, low birth weight (LBW)
- ≥2500 g, normal birth weight (NBW).

Babies were considered to be small for GA if the BW was <10^{th} percentile.[18] The 5 minute Apgar scores were categorised into two groups, namely Apgar score ≤5 and Apgar score >5. Babies were divided according to GA into two groups, namely <32 weeks and ≥32 weeks. PNCS was defined as steroids given in an attempt to facilitate weaning of patients off prolonged ventilation or supplemental oxygen. Dexamethasone is given to patients failing to wean off mechanical ventilation. NEC was considered as modified Bell's stage ≥2.[19] Sepsis was classified as culture-proven bacterial or fungal blood stream sepsis only.

Statistical analysis

The data was assessed for missing information and erroneous or suspicious entries. These entries were verified as far as possible with the original patient records. Information not available from the database was obtained from hospital files drawn from the hospital record archives. The database was then exported to IBM SPSS Statistics version 23.0 for analysis.
Babies with evolving CLD: Babies in different weight categories were compared in terms of therapeutic intervention and outcome. Babies who received PNCS were compared to those who did not, and babies who survived to discharge were compared to those who died. Finally the CLD group was then compared to the no CLD group. The data were normally distributed, so continuous variables were described using means and standard deviations (SD) while frequencies (percentages) were reported for categorical variables. For comparison Chi-square tests were used for categorical variables and independent t-tests for continuous variables. All analyses considered a value of $p<0.05$ as significant.

Results

There were 485 babies hospitalised for more than 28 days; records were not retrievable for 3 patients. Therefore, 482 patients were included, 237 with evolving CLD and 245 without CLD.

The overall incidence of evolving CLD was 237/4570 (5.1%). The incidence in the VLB)W babies was 206/1,302 (15.8%) and 31/3,268 (0.94%) in the >1 500 g babies (p<0.0001).The incidence of definite CLD was 98/1,302 (7.5%) in the VLBW babies.

Demographic and birth characteristics are shown in Table 1. There was no difference in the birth weight between babies with and without CLD (1017 grams (SD 101) vs 1041 grams (SD 104) p = 0.57). Similarly gestational age was not different between the two groups (CLD 28.2 weeks (SD1.9) vs no CLD 28.3 weeks (SD 1.9) p = 0.9). There were, however, more babies who were SGA in the no CLD group than in those with CLD (26.5% vs 12.9% p=0.03). The percentage of males with CLD was greater (50.2) than in the no CLD group (40.8%). There was no significant difference in maternal obstetric and labour room characteristics between CLD and no CLD babies (Table 1). There were more babies who had 5 minute Apgar scores ≤5 and needed resuscitation at birth in the CLD group.

Therapeutic interventions, morbidity and outcome are shown in Table 2. Neonates in the CLD group were more likely to be ventilated and to receive surfactant than those without CLD (see Table 2), The duration of ventilation was significantly longer in babies with CLD compared to those without CLD (15.7 days (SD 16.0) vs 6.1 days (SD 2.8) p =0.001). Similarly, CLD had an increased duration of NCPAP (5.4 days (SD 8.7) vs 2.9 days (SD 6.1) p = 0.001) and hospitalisation (56.0 days (SD 20.7) vs 42.2 days (SD 15.1) p=0.001) as compared to babies without CLD.

However very few (2.3%) of these neonates with CLD needed home oxygen therapy. Mortality was significantly higher in babies with CLD (10.2% v. 2.4%), (p=0.001) and those neonates with CLD were more likely to have a patent ductus arteriosus (PDA) (30.4% v. 7.7%), p=0.001 and late onset sepsis (LOS), (56.5% v. 23.6%), p=0.001.

The effect of BW in the CLD babies is shown in Table 3. In hospital mortality (overall 10%) and morbidity in CLD babies was not influenced by BW category. There was however a significant difference in the duration of ventilation, with NBW babies staying the longest on the ventilator and VLBW the shortest (31 $\pm$ 21 v. 12 $\pm$ 12 days). Duration of hospitalisation was longest among the ELBW infants (Table 3).

The use of PNCS v. no PNCS in babies with evolving CLD is shown in Table 4. The overall usage of PNCS was high (55%). PNCS was associated with less NEC and a lower mortality, however the duration of ventilation tended to be longer in babies who received PNCS.

The effect of morbidity and ventilatory support in babies with evolving CLD is shown in Table 5. The incidence of late onset sepsis and NEC were significantly higher in the patients who died. The use of early rescue surfactant (SVT) and NCPAP did not improve survival (Table 5), but IPPV was associated with increased mortality, 70.8% v. 39.7% in the non CLD group.

Table 1. Demographic, obstetric and labour room characteristics				
	CLD ***n* (%)**	**no CLD** ***n* (%)**	Chi square	*p*-value
GA for BW SGA	30/232 (12.9)	65/243 (26.5)	5.911	0.030
Gender Male	118/235 (50.2)	100/245 (40.8)	5.911	0.016
Maternal characteristics				
Race Black	221/234 (94.4)	237/244 (97.1)	0.038	0.845
Antenatal steroids	93/185 (50.2)	116/219 (52.9)	0.658	0.429
Maternal hypertension	51/206 (24.7)	64/220 (29.0)	1.014	0.328
Chorioamnionitis	7/188 (3.7)	9/223 (4.0)	0.150	0.801
Mode of delivery CS	133/205 (64.8)	160/241 (66.3)	0.017	0.896
Apgar score at 5 minutes ≤5	37/214 (17.2)	26/230 (10.6)	85.448	0.001
Resuscitation at birth	100/197 (48.5)	92/231 (39.8)	5.139	0.025

Table 2. Therapeutic intervention, morbidity and outcome characteristics				
	CLD	No CLD		
	n (%)	*n* (%)	Chi square	*p*-value
Therapeutic intervention				
NCPAP	120/205 (58.5)	149/237 (62.8)	0.09	0.696
Ventilation	100/233 (42.9)	29/226 (12.8)	15.20	0.001
Postnatal corticosteroids	114/193 (59.0)	13/230 (5.6)	129.07	0.001
Surfactant at anytime	201/232 (86.6)	174/243 (71.6)	16.138	0.001
Morbidity				
Necrotising enterocolitis	23/235 (9.4)	14/244 (5.7)	3.323	0.090
Late onset therapy	133/206 (56.5)	58/245 (23.6)	54.934	0.001
PDA	69/220 (30.4)	19/244 (7.7)	41.508	0.001
Periventricular leukomalacia	3/187 (1.5)	1/131 (0.5)		
Outcome				
Mortality	24/236 (10.2)	6/245 (2.4)	12.252	0.001
Need for home oxygen	5/219 (2.2)	0 (0.0)		
NCPAP = nasal continuous positive airway pressure ventilation				

Table 3. The effect of BW in babies with evolving CLD							
	ELBW *n* = 90	VLBW *n* = 116	LBW *n* = 21	NBW *n* = 10	Total *n* = 237	Chi square	*p*-value
		n (%)					
Mortality	10 (11.1)	10 (8.6)	2 (9.5)	2 (20)	24 (10.2)	1.450	0.690
Need for home O_2	1/90 (1.1)	3/108 (2.6)	0 (0.0)	1/9 (7.1)	5/219 (2.2)	4.310	0.229
Necrotising enterocolitis	7/89 (7.8)	11 (9.5)	4/20 (20)	2 (20)	24 (10.2)	3.797	0.284
Patent Ductus Arteriosus	30 (33.3)	38 (32.8)	0	1/5 (7.1)	69/220 (30.4)	5.147	0.161
Late Onset Sepsis	59/90 (65.4)	57/116 (49.1)	13/20 (65)	5/10 (35.7)	133/206 (56.5)	6.323	0.970
*Duration of hospitalisation	62 (17)	53 (23)	44 (13)	44 (16)			0.001
*Duration of ventilation	17 (19)	12 (12)	15 (12)	31 (21)			0.007
For *continuous variables, *n* (SD) and *p*-values are given.							

Table 4. The effect of PNCS v. No PNCS use in the evolving CLD				
	PNCS *n*=114	**No PNCS *n*=93**		
			Chi square	*p-value*
Mortality	5 (4.4)	17 (18.3)	10.409	0.001
Late onset sepsis	67 (58.8)	4 (50.5)	1.404	0.148
Necrotising enterocolitis	4 (3.5)	16 (17.2)	11.006	0.001
Patent ductus arteriosus	43 (37.7)	22 (23.7)	4.703	0.350
Home oxygen	3 (2.6)	1 (1.0)	0.530	0.637
NCPAP	104 (91.2)	76 (82.6)	3.430	0.09
Ventilation	43 (38.1)	39 (42.9)	0.484	0.566
***Duration of hospitalisation**	62 (23.6)	49 (16.2)		0.12
***Duration of ventilation**	17 (18.1)	10 (10.9)		0.029
For *continuous variables, *n* (SD) and *p*-values are given.				

Table 5. The effect morbidity and ventilatory support on survival for babies with evolving CLD				
	Survived *n* (%)	Died *n* (%)	Chi square	*p*-value
PDA	62/199 (31.2)	7/22 (31.8)	0.04	1.00
Necrotising enterocolitis	17/212 (8.0)	7/24 (29.2)	10.555	0.005
Late onset sepsis	114/212 (53.8)	20/24 (83.3)	7.676	0.008
Surfactant	183/209 (87.6)	18/23 (78.3)	1.548	0.206
Ventilation	83/209 (39.7)	17/24 (70.8)	8.510	0.004
NCPAP	178/211 (84.4)	19/24 (79.2)	0.429	0.557
*Duration ventilation	15.0 (16.4)	19.1 (13.6)		0.805
*Duration of NCPAP	5.0 (8.0)	9.0 (13.2)		0.0001
*Duration of hospitalisation	57.3 (20.9)	44.4 (15.1)		0.271
For *continuous variables, *n* (SD) and *p*-values are given.				

Discussion

Our study findings show that evolving CLD in neonates remains a common morbidity in babies at CMJAH with an overall incidence of 5.1%. The incidence was much higher in the VLBW babies (15.8%). Data from the 2013 and 2014 Vermont Oxford Network show rates of CLD between 10.8% - 30.7% among different centres. Vermont Oxford Network only reports VLBW data and this explains the apparently low incidence of CLD at CMJAH. Although it was not possible to grade the severity of CLD, most babies were not discharged on oxygen suggesting that there were few with severe disease. More than 50% of neonates with CLD at CMJAH received PNCS and the use of PNCS for CLD was associated with improved survival and less NEC. This is contrary to studies that have shown no significant different in NEC incidence between PNCS and no PNCS use[15] and surprisingly studies have not shown an association between PNCS and improved survival.[15] The use of PNCS at CMJAH was 9.1% of all VLBW infants, which was comparable to that reported in the VON for the same period (2013) at 9.1%.

Our study findings show that within the group of babies with evolving CLD, BW did not influence survival reflecting that at CMJAH most babies who die, do so within the first week of life or after 28 days of life when BW has less effect on survival. More ELBW babies are being offered ventilatory support now and those who survive are at higher risk of developing CLD due to severe prematurity. Our study shows that among these CLD patients there was a significantly increased rate of late onset sepsis and PDAs. These findings are in agreement with a study done by Trembath *et al.* who outlined the risk factors for CLD. [20]

There is a lot of concern surrounding the use of PNCS, including sepsis and poor neurological outcome (especially PVL and CP). However there was no significant difference

in LOS in the group that received PNCS compared to those who did not. Studies have shown an association between use of PNCS for CLD and PVL.[8, 9] The incidence of PVL was very low in the current study and so comparison could not be done. This study only looked at short-term outcome of neonates with CLD and use of PNCS. Follow up to evaluate neurodevelopmental outcome in neonates who received PNCS is necessary. The use of PNCS for the prevention and treatment of CLD remains controversial. This requires investigation with the aim of improving management (prevention and treatment) of CLD in preterm babies.

Limitations

This was a retrospective analysis from an existing database. Information not routinely collected in the database was not readily available. FiO_2 is not recorded, so severity of CLD could not be graded. GA is determined by the attending clinicians and may not be accurate, so the definition of 36 weeks PMA may be inaccurate. LOS was classified as culture-proven bacterial or fungal blood stream sepsis only, endotracheal or induced sputa were not available in the database, thus the incidence of sepsis may have been underestimated. The definition of CLD requires that the need for oxygen therapy be for a cumulative ≥28 days and not an acute event. Due to the retrospective nature of the study, it was not possible to distinguish between babies who have been on O_2 for a cumulative 28 days and those who had been acutely placed on O_2. The type of steroid administered was not recorded and neither was the timing e.g. early vs late.

Conclusions

CLD remains a common morbidity in VLBW babies and is associated with higher mortality despite advances in neonatal care. More and more ELBW/VLBW babies are surviving and the incidence of CLD is higher in this BW group. The use of PNCS has shown short-term benefits in terms of its association with improved survival and reduced NEC. Further studies need to be conducted to determine the safest type of steroid, safe doses and duration of treatment to get the most out of PNCS use for CLD.

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APPENDIX ONE: AUTHOR GUIDELINES FOR SAJCH

Author guidelines for South African Journal of Child Health

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.
AUTHORSHIP Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**). **CONFLICT OF INTEREST** Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest. **RESEARCH ETHICS COMMITTEE APPROVAL** Provide evidence of Research Ethics Committee approval of the research where relevant. **PROTECTION OF PATIENT'S RIGHTS TO PRIVACY** Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.
ETHNIC CLASSIFICATION References to ethnic classification must indicate the rationale for this. **MANUSCRIPTS** Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences. ***Original articles*** not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to child health. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.* ***Scientific letters***/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words. ***Editorials***, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJCH peer review process. ***Review articles*** are rarely accepted unless invited. ***Letters to the editor***, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address. ***Obituaries*** should be about 400 words and may be accompanied by a photograph.
MANUSCRIPT PREPARATION Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**. **Qualification, affiliation 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 a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'. **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. **General formatting** The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).
ILLUSTRATIONS AND TABLES If tables or illustrations submitted have been published

elsewhere, the author(s) should provide consent to republication obtained from the copyright holder. **Tables** may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc. **Figures** must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook. **REFERENCES** Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. 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. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. **Journal references:** Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753] **Book references:** Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472. **Internet references:** World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010). **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)'. **PROOFS** A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled. **CHANGES OF ADDRESS** Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication. **CPD POINTS** Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested

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1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
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4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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APPENDIX TWO : PROTOCOL

A REVIEW OF CHRONIC LUNG DISEASE IN NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL FROM 1 JANUARY 2013 TO 30 SEPTEMBER 2014

Candidate: Dr Aripfani Veronica Mphaphuli

Student No: 0201182J

Qualification: MBBCH (Wits), DCH (SA)

Degree protocol is submitted for: MMed (Paed)

Supervisor: Prof Daynia Ballot

Glossary

CMJAH Charlotte Maxeke Johannesburg Academic Hospital

PNCS Postnatal corticosteroids

CS corticosteroids

CLD neonatal chronic lung disease

BPD bronchopulmonary dysplasia

PMA Post menstrual age

RCT Randomized controlled trial

AAP American academy of paediatrics

PDA patent ductus arteriosus

PVL periventricular leukomalacia

1. Introduction

The clinical definition of Neonatal chronic lung disease (CLD) also known as Bronchopulmonary dysplasia (BPD) has evolved overtime, it was first defined by Northway et al in 1967 as persistent respiratory signs and symptoms along with the need for supplemental oxygen and an abnormal CXR at 28 days of age[1] This definition did not take into account the gestational age of the patient. The modern and widely used physiological definition takes this into account and defines BPD as oxygen dependence at 36 weeks PMA (post menstrual age) with or without the use of respiratory support and with or without the characteristic radiographic changes [2] .The above mentioned definitions do not indicate the level of oxygen dependence which can range from needing low-flow oxygen to being ventilator-dependent. To address this issue the NIH (National Institute of Health) has developed a consensus severity-based definition. This definition includes babies born at ≤32 weeks of gestation and needing more than 21% oxygen for at least 28 days. A second assessment at 36 weeks PMA is required in order to assign severity and classify them into mild, moderate and severe BPD[3].

	MILD Supplemental O_2 (for 28 days) and	MODERATE Supplemental O_2(for 28 days) and	SEVERE Supplemental O_2(for 28 days) and
<32 weeks GA at birth	RA at 36 weeks PMA or at discharge(whichever comes first)	<0.3 FiO_2 at 36 weeks PMA or discharge	≥0.3 FiO_2 ± positive pressure support at 36 weeks PMA or at discharge
≥32 weeks GA at birth	RA by postnatal day 56 or at discharge	<0.3 FiO_2 by postnatal day 56 or at discharge	≥0.3 FiO_2 ±positive pressure support by postnatal day 56 or at discharge

For the purpose of this study the definition of BPD will be the need of supplemental oxygen at 28 days postnatal age and at 36 weeks PMA as defined by Vermont-Oxford Network (VON).

The incidence of CLD as defined by need for oxygen supplement at 36 weeks PMA is ~30% of premature infants with birth weight <1000grams and is uncommon in infants born at >30 weeks of gestation or weight of >1250grams[3].

CLD is a complex disease with multifactorial aetiology. It remains a major cause of morbidity in premature infants[1].Contributing factors include infection, exposure to toxic oxygen levels with formation of toxic oxygen free radicals and ventilator-induced lung injury which result in arrested lung development and impaired lung function. Inflammation plays a major role. Injury at the early developmental stage of the lung results in an arrest of both alveolar and vascular growth. Histopathological findings show alveolar simplification (fewer, larger alveoli and fewer capillaries) [3]. Several maternal risk factors including age, hypertensions, lack of antenatal steroid usage and chorioamnionitis have been associated with BPD[14].

Several preventive and therapeutic strategies have been employed; these target several pathways and processes involved in pathogenesis of CLD. Some provide antioxidant protection; others minimize specific aspects of inflammation reduce elastolytic and proteolytic injury or regulate growth. In addition, supportive pharmacological treatments that target development of pulmonary oedema, bronchoconstriction and impaired gas exchange are used. Their success has been variable.[7]

Post natal corticosteroids (PNCS) have been extensively studied and have been found to be effective in weaning infants off mechanical ventilation when given moderately early or late[4,-

[6.] This effect has been proven for dexamethasone which is the most widely studied PNCS in RCTs. Despite this effect dexamethasone has not been shown to reduce the total days of hospitalization, duration of supplemental oxygen therapy, or incidence of CLD[4, 5, 6]

Corticosteroids are potent anti-inflammatory agents. Systemic steroid administrations reduces the inflammatory response, produces a rapid improvement in pulmonary function with better gas exchange and facilitate weaning from mechanical ventilation. Steroids also enhance surfactant production, decrease airway oedema, stabilize capillary leakage, augment β adrenergic activity and decrease overall lung fibrosis[7]. For these reasons PNCS offer a great promise in the management of CLD. In the era before PNCS treatment, the long term neurodevelopmental outcome for survivors with CLD was worse than that in similar infants without CLD[8]. However adverse effects such as hyperglycaemia, GIT perforation, hypertension, Infection, steroid-induced cardiomyopathy, long term neurodevelopmental effects and growth retardation complicate the treatment. The most worrisome long term effect is increased risk for poor neurological outcome including cerebral palsy. A systematic review showed a significantly higher rate of CP after corticosteroid treatment and a non-significant reduction in mortality[10]. Corticosteroids can have direct toxic effects on the developing brain, including neuronal necrosis, interference with healing and inhibition of brain growth[8, 9].A multicentre double blinded RCT testing early postnatal dexamethasone therapy for prevention of CLD had to be stopped before completion because of concern about serious side effects such as gastrointestinal perforation and periventricular leukomalacia.[13.]

As a result in 2002, the American Academy of pediatrics (AAP) in a policy statement regarding the use of PNCS for prevention or treatment of CLD concluded that the routine use of dexamethasone could not be recommended. Instead they recommended that dexamethasone use be limited to RCTs with long-term follow up. They also recommended that alternative corticosteroids undergo studies and that all infants enrolled in RCTs for PNCS receive long-term neurodevelopmental follow up[11]. Since the publication of the AAP statement, postnatal use of dexamethasone for CLD has reduced; however the incidence of CLD has not reduced. Some reports have suggested that the incidence or severity of CLD may have increased[12]

Hydrocortisone is the other corticosteroid that has been studied and proven to work in treatment and prevention of CLD. Several RCTs showed that hydrocortisone was beneficial and was not associated with poor neurodevelopmental outcome[7]. No RCTs of other corticosteroids such as prednisone or methyl-prednisolone have been published.

The data available for PNCS use in CLD are inconclusive and conflicting; as a result clinicians are advised to their own clinical judgment to balance potential adverse effects of CLD with the potential adverse effects of PNCS for each individual patient. The use of PNCS for prevention and treatment of CLD remains controversial. These issues warrant investigation with the aim of improving management (prevention and treatment) of CLD in preterm babies. The is a need to identify the most efficacious corticosteroid, safe dosages and timing of administration to get the most out of PNCS use in CLD.

These study aims to describe neonates with CLD at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and explore the use of PNCS for treatment and prevention of CLD in these patients.

2. Purpose of the study

2.1 Aim

To describe babies with CLD and to explore the use of postnatal corticosteroids for CLD in preterm babies in the neonatal unit at CMJAH from 1 January 2013 to 30 September 2014.

2.1.1 Definition

Both definitions of CLD – namely oxygen at 28 days of life and at 36 weeks PMA will be considered.

2.2 Objectives

2.2.1 To determine incidence of CLD at CMJAH

2.2.2 To describe the demographics and clinical characteristics of patients with CLD in neonatal unit

2.2.3Todetermine the outcome of babies with CLD in terms of, survival to hospital discharge and use of home oxygen

2.2.4 To compare the outcome of infants who received PNCS versus those who didn't

3. Methodology

3.1 Study design

This study is an institution-based descriptive review; it will include a retrospective review of neonatal medical records of neonates who received oxygen therapy at 28 days of life and / or 36 weeks PMA and analysis of secondary data

3.2 Site of study

This study will be conducted in the Neonatal Unit at CMJAH Parktown, Gauteng Province.

3.3 Study population

The study population will include all neonates (weighing > 500 grams at birth) admitted within 72 hours of life to the neonatal unit at CMJAH from 1 January 2013 to 30 September 2014

3.4 Inclusion criteria

All babies who received oxygen therapy at 28 days of life and / or at 36 weeks PMA

3.5 Exclusion criteria

3.5.1 Patients with unobtainable information

3.5.2 Babies who are transferred to CMJAH for ventilation and then transferred back to their hospital of origin

3.6 Measurement

3.6.1 Variable

The data collected will be categorized into obstetric and labour room, demographic, therapeutic and outcome factors in accordance with the objectives of the study. Variables and source are outlined in table 1

Table 1: Variables

TYPE	VARIABLE	SOURCE
Obstetric and labour room	Maternal age	Neonatal database
	Antenatal steroids	
	Maternal Hypertension	
	Ante partum haemorrhage	
	HIV exposure	
	Syphilis exposure	
	Chorioamnionitis	
	Mode of delivery	
	5 minute Apgar score	
	Resuscitation at birth	
Demographic factors	Gestational age(weeks) by Ballard score	Neonatal database
	Birth weight(grams)	
	Appropriate for gestational age	
	Gender	
	Race	
Therapeutic factors	Timing of PNCS administration (early, moderately early or late) Dosage and duration of treatment Surfactant administration Ventilation type and duration -NCPAP -IPPV	Hospital records and Neonatal Database

	-HFOV Necrotizing enterocolitis(NEC)	
	Late onset sepsis	
	Patent ductus arteriosus	
	Periventricular leukomalacia	

Outcome factors		
	Need for home oxygen therapy	
	Death	
	Duration of hospitalization	

3.6.2 Measurement tool

A data collection tool (attached) was developed to capture data from the database. This tool was designed using data from published literature on the chosen topic.

3.7 Data collection

Data will be collected by a single researcher using the data collection tool. Data from the existing CMJAH neonatal database will be used for analysis. This data is collected prospectively on an ongoing basis for the purposes of clinical audit from clinician completed hospital records and entered into REDCAP database. Neonatal records are kept in a database system and will be accessible to the researcher. Information will be de-identified to maintain confidentiality. Information that is not available from the database will be obtained from hospital files drawn from the hospital record archives.

Data will be coded and entered onto Microsoft Excel. The data will be assessed for missing information and erroneous or suspicious entries. These entries will be verified as far as possible with the original patient records. Database will then be exported to STATISTICA for analysis.

3.8 Data Analysis

For descriptive purposes, means and standard deviations (SD) or median (range) will be reported for continuous variables while frequencies (percentages) will be reported for categorical variables. Where data is skewed, median and range will be reported. The whole group of neonates will be described and then stratified by birth weight category – namely < 1000 grams, 1000 to 1500 grams, 1500 to 2500 grams and > 2500 grams. Babies who received PCNS will be compared with those who did not and babies who survived to discharge will be compared to those who died. For comparison Chi-square tests will be used for categorical variables and student t-test or Mann Whitney U test for continuous variables as appropriate. All analyses will consider a value of $p<0.05$ as significant with 95% confidence intervals reported for estimates.

4. ETHICAL CONSIDERATIONS

The protocol will be submitted for approval to the Committee for Research in Human Subjects at the University of the Witwatersrand (Medical). Permission for the study will then be obtained from the CEO of Charlotte Maxeke Johannesburg Academic Hospital and the HOD of paediatrics.As this is a retrospective audit; no consent will need to be obtained from individual patients. The neonatal database at CMJAH, to be used for this study is confidential and has limited accessibility.

No identifying data fields (name, patient number) will be included in the data sheets thereby preventing the possible linkage of a questionnaire to a particular patient. Data sheets will only contain a study number. The study numbers will allow for the matching of data sheets to the particular patients.

5. LIMITATIONS

The hospital archive system is not complete and reliable, so information not routinely collected in the database may not be readily available. Gestational age is determined by the attending clinicians and may not be accurate, so the definition of 36 weeks PMA may be inaccurate.

6. COST

The cost involved in the study is for stationery, printing and binding estimated at R500 which will be borne by the investigator as there is no funding for this study.

7. TIME FRAME

Year	2014										2015					
Activity	march	April	May	Jun	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	March	April	May	June
Literature review																
Preparation of protocol																
Submission of protocol																
Submission to Ethics																
Data Collection																
Data analysis																
Write up of research report																

9. References

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DATA COLLECTION TOOL:

A REVIEW OF CHRONIC LUNG DISEASE IN NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL FROM 1 JANUARY 2013 TO 30 SEPTEMBER 2014

Obstetric and labour room	Maternal age			
	Antenatal steroids	Yes	No	
	Maternal Hypertension	Yes	No	
	Ante partum haemorrhage	Yes	No	
	HIV exposure	Yes	No	
	Syphilis exposure	Yes	No	
	Chorioamnionitis	Yes	No	
	Mode of delivery			
	5 minute Apgar score			
	Resuscitation at birth			
Demographic factors	Gestational age(weeks) by Ballard score			
	Birth weight(grams)			
	Appropriate for gestational age			
	Gender	male	Female	intersex
	Race			
Therapeutic factors:	Timing of PNCS administration(early, moderately early or late)	early	Moderately early	late
	Dosage and duration of treatment			
	Surfactant administration	Yes	No	

	Ventilation type and duration -NCPAP -IPPV -HFOV		
Other factors	Late onset sepsis	Yes	No
	Patent ductus arteriosus	Yes	No
	Periventricular leukomalacia	Yes	No
	Necrotizing enterocolitis	yes	No
Outcome factors :	Need for home oxygen therapy	Yes	No
	Death	Yes	No
	Duration of hospitalization		

APPENDIX THREE: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Aripfani Veronica Mphaphuli

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150206

NAME: (Principal Investigator)	Dr Aripfani Veronica Mphaphuli
DEPARTMENT:	Paediatric and Child Health Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Chronic Lung Disease in Neonates at Charlotte Maxeke Johannesburg Academic Hospital from 1 January 2013 to 30 September 2014
DATE CONSIDERED:	27/02/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/09/2015

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX FOUR: TURNITIN REPORT

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ORIGINALITY REPORT

11%	0%	11%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	K. L. Watterberg. "Postnatal Corticosteroids to Prevent or Treat Bronchopulmonary Dysplasia", PEDIATRICS, 10/01/2010 Publication	3%
2	Baveja, R.. "Pharmacological Strategies in the Prevention and Management of Bronchopulmonary Dysplasia", Seminars in Perinatology, 200608 Publication	3%
3	Ballot, Daynia E, Tobias Chirwa, Tanusha Ramdin, Lea Chirwa, Irma Mare, Victor A Davies, and Peter A Cooper. "Comparison of morbidity and mortality of very low birth weight infants in a Central Hospital in Johannesburg between 2006/2007 and 2013", BMC Pediatrics, 2015. Publication	2%
4	N. Hussain. "Effect of a Short Course of Prednisolone in Infants With Oxygen-Dependent Bronchopulmonary Dysplasia", PEDIATRICS, 01/28/2008 Publication	2%