

Late onset neonatal sepsis in very low birth weight premature infants in the Neonatal High Care Unit, Pelonomi Hospital, Bloemfontein. A cohort study

MMED RESEARCH PROJECT

STUDY TITLE: Late onset neonatal sepsis in very low birth weight premature infants in the Neonatal High Care Unit, Pelonomi Hospital, Bloemfontein. A cohort study

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ABSTRACT

Background: Late onset neonatal sepsis (LOS) is a common problem in very low birth weight (VLBW) infants and is associated with increased mortality, morbidity and cost of care. Several known risk factors are reported in the literature, which may be maternal, host or healthcare related. Hygiene practices, overcrowding, staffing and healthcare interventions all play a role in the risk of LOS. Pelonomi Neonatal High Care is a 32-bed regional neonatal unit. The study period was from September 2015 to March 2016.

Methods: This was a prospective cohort study.

Study Population: All VLBW infants with birth weight between 1000g and 1499g excluding those referred to tertiary centers and those born with major congenital abnormalities were enrolled and followed up to 28 days of life.

Results: 117 infants were included. 43,6% of infants had at least one episode of LOS (incidence 435 per 1000 births per annum). There was a higher incidence of gram-negative (31%) and fungal infections (17%) than reported elsewhere. The use of invasive ventilation, nasal CPAP, nasal prong oxygen and surfactant were significantly associated with LOS as was increased duration of umbilical venous catheterisation. Longer periods to the initiation of feeding and the use of cefotaxime increased the risk of LOS. Breastfeeding appears to confer protection against LOS. Exposure to human immunonvirus and high maternal viral load may be a risk factor for LOS. LOS was present in 40% of deaths beyond 72hours of life and 10% of infants with LOS died. LOS was associated with increased morbidity in the form of increased length of stay, longer duration to full enteral feeding, longer duration of parenteral nutrition and increased necrotising enterocolitis. Only 50% of the infants received antenatal steroid therapy and 96.5% of infants experienced some degree of hypothermia. The unit was persistently overcrowded and key consumables for hand hygiene were frequently unavailable. Due to the persistence of overcrowding and the short duration of the study period a statistical relationship with LOS could not be proven.

Conclusion: LOS was significantly more frequent in this study population than reported in the literature with serious consequences for patients. Many identified risk factors are associated with routine practices in the care of VLBW infants in this unit. The unit was persistently overcrowded and there were several barriers to appropriate hand hygiene. Several factors such as role of genetic factors and HIV require investigation.

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INTRODUCTION

Late onset neonatal sepsis (LOS) is a common problem in very low birth weight (VLBW) infants admitted to neonatal units. It remains a significant cause of mortality and morbidity in Pelonomi Hospital Neonatal High Care Unit (Unpublished data collected for internal quality control). The scope of the problem and risk factors associated with LOS in this setting has not been studied adequately. Identifying the risk factors and circumstances contributing to LOS may contribute to planning strategies to reduce its occurrence in this setting.

1. Early vs. Late Onset Neonatal Sepsis:

Late onset sepsis (LOS) is defined as neonatal sepsis of onset at or beyond 72 hours of life and early onset sepsis (EOS) refers to the onset of sepsis before 72 hours of life.(1–3) This chronological division effectively differentiates early from late sepsis in terms of causative pathogens and route of infection. EOS implies vertical transmission via the transplacental route or via ascending maternal genitourinary infections and LOS implies community acquired or nosocomial infection. In the setting of neonatal units LOS is almost exclusively nosocomial(1,3)

2. Epidemiology:

2.1 Burden of Neonatal Mortality:

Annually, approximately four million infants die in the neonatal period globally. This is largely centred in the developing world and the highest rates of neonatal death still occur in Sub-Saharan Africa. Preterm birth and complications of prematurity are the leading cause of death in neonates and contribute to 28% of neonatal mortality.(4)

2.2 Burden of Neonatal Infections:

Late onset neonatal sepsis is a common clinical problem in neonatal units worldwide, although there is considerable variation between centres. The incidence of late onset neonatal sepsis is inversely related to the gestational age and birth weight of the infant and thus affects premature infants most frequently (16.5% in term infants; 17.5% in infants between 33 and 36 weeks gestation; 29.5% in infants between 29 and 32 weeks gestation; 36.3% in infants with gestational age less than 28 weeks). As a result, LOS is a problem of

increasing significance with increasing prematurity. This is further exaggerated by the increasing survival of ever more premature infants beyond the first days of life.(1,5)

In a study from Kuwait, where tertiary neonatal care is provided without strict measures to prevent nosocomial infections, the overall incidence of LOS was found to be 16.9 per 1000 live births across all gestational ages.(6) This may represent circumstances similar to Pelonomi hospital.

A large study of a wide variety of NICU's revealed that the incidence of both early and late onset neonatal sepsis had changed little in the decade leading up to 2012.(7)

There were 110 cases of confirmed neonatal sepsis and 346 cases of suspected sepsis in the Pelonomi Hospital Neonatal High Care Unit in 2014. This was, however, the rate over all weight categories. (Unpublished Data)

3. Consequences of Neonatal Infections:

3.1 Mortality:

Perinatal Problem Identification Program data from the 2010-2011 Saving Babies Report reflects that infection contributes to 1.89 early neonatal deaths per 1000 live births in South Africa.(8)

Several studies indicate a significantly increased risk of death for infants who develop late onset sepsis.(2,7,9–11) Mortality rates for infants with LOS vary from 5% - 21% in various studies.(2,5,10,12–14) One study found a mortality rate of 18% in those with LOS compared to 7% in those without LOS.(2) This may reflect differences in services rendered, local practices and resources available. Furthermore, recurrent episodes of LOS in particular are associated with increased mortality. Fungal infections and gram-negative infections are also associated with increased mortality.(6,10,14,15)

One study found that the need to investigate for late onset sepsis was associated with an increased risk of death.(16)

Independent predicting factors for sepsis-related mortality are reported as: need for intubation, necrotising enterocolitis, hypoglycaemia and thrombocytopenia.(9)

3.2 Morbidity:

3.2.1 Respiratory morbidity

Infants who develop LOS required longer duration of ventilator support compared to infants free of sepsis (33days vs. 10days).(2,11) LOS also increased the incidence of bronchopulmonary dysplasia to 43% as compared to the 21% in premature infants without LOS.(11)

3.2.2 Gastrointestinal morbidity

Several studies find necrotising enterocolitis to be more common in infants with late onset neonatal sepsis.(2,11,17) Patients with necrotising enterocolitis more frequently develop late onset neonatal sepsis.(2) Gram negative infections were more frequently associated with necrotising enterocolitis.(10) As discussed above, necrotising enterocolitis is an independent predictor of sepsis related death.(9)

3.2.3 Early central nervous system morbidity

Severe intraventricular haemorrhage occurs more commonly in infants with LOS (23% vs 21%)(11).

Incidences of meningitis in patients with LOS vary from 3 – 30%(18,19) Meningitis is more frequently associated with late onset sepsis than early onset neonatal sepsis(3,19) One study found fungal infections to be more commonly associated with meningitis(9) while another found gram negative infections to be more commonly causative.(6) Neonates with meningitis are at risk for short-term complications of meningitis including hydrocephalus, abscesses, ventriculitis and convulsions. (20) Long-term neurodevelopmental outcomes are also poorer in those patients with meningitis compared to those without.(18)

3.2.4 Neurodevelopmental impairment:

The National Institute of Child and Human Development (NICHD) undertakes long-term follow up of premature infants. Neurodevelopmental testing was provided between 18 and 22 months of postnatal life. Extremely low birth weight infants (<1000g) with LOS had significantly poorer neurodevelopmental scores than those who did not develop LOS. Neurodevelopmental impairment may take the form of delayed neurodevelopmental milestones, blindness, deafness and cerebral palsy.(1,2,15,21) The presence of meningitis further increases the risks of these deficits.(20)

A study of 38 preterm infants with LOS matched for gestational age compared neurodevelopment at 6-9 years of life. Infants who developed LOS had significantly lower IQ scores than their controls (89 vs 98) and had poorer performance in fine motor skills, verbal memory and attention.(22)

As mentioned above, the presence of comorbid meningitis further worsens neurodevelopmental outcomes.(18)

3.2.5 Growth impairment:

Long term follow up of ELBW infants revealed significantly impaired growth among infants with LOS compared with infants who were free of infection. This was predominantly in the parameters of length and head circumference with significantly more infants with infection being below the 10th centile for length (37% vs 30%) and head circumference (30% vs 20%)(21)

3.2.6 Increased duration of hospital stay

Length of hospital stay was prolonged in infants that developed LOS (79 vs. 60 days in one cohort and 98 vs. 58 days in another) (2,11)This has significant financial and care implications for institution, staff and patients.

3.2.7 Increased cost of healthcare

The treatment of patients with LOS incurs considerably increased medical costs. An episode of *Candida* sepsis was found to increase medical costs with US\$28000 during hospital admission.(23) The long-term cost of caring for children with neurodevelopmental delay and long-term morbidity has yet to be reported.

4. Pathogenic Bacteria:

4.1 Distribution of pathogens:

In most centres the most common causative pathogens of LOS are Gram-positive organisms (70%). The most common pathogenic gram-positive organism is coagulase negative staphylococcus (CoNS) (48%) followed by Group B streptococci and enterococcus species. Gram-negative organisms account for 18% and fungal infections for 12% of infections respectively. (2,5,17,24) *Gram-negative* bacteria responsible for LOS are most commonly *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. and *Pseudomonas* spp.(1)

4.2 Pathogen specific morbidity and mortality

CoNS are considerably less virulent than Gram-negative bacteria and fungi and thus contribute less to short term morbidity and mortality. The risk of neurodevelopmental impairment however is independent of pathogen and reflects the capacity of CoNS to exert long-term deleterious neurodevelopmental effects. (1,21)

Gram negative and fungal infections are more frequently associated with necrotising enterocolitis and meningitis. (6,9)

Infants with Gram-negative (32%) and fungal sepsis (52%) are considerably more likely to die than those with Gram-positive infection (18% in CoNS).(2,4,15)

5. Risk Factors for Late Onset Sepsis:

An understanding of the risk factors for late onset sepsis is critical to the guidance of strategies directed towards reducing the incidence of LOS.

5.1 Maternal factors and genetic factors:

Data from the NICHD network (6956 infants) and the Brazilian Neonatal Research Network Study (1507 infants) did not indicate that maternal factors strongly influence the incidence of LOS. A smaller study from Taiwan indicated only an association with antenatal maternal steroid use(2,13,17) There is however evidence in older studies that neutropaenic infants of pre-eclamptic mothers have increased risk of early and late neonatal sepsis.(25–27) A later, larger study from 2010 however contradicts these findings.(28)

Antenatal steroid administration is associated with reduced incidence of early onset sepsis but increased incidence of LOS.(5)

Exposure to antenatal antibiotics, frequently used in the management of preterm labour also increases the risk of LOS. (3,7,16)

Genetic polymorphisms in immunity may be implicated in susceptibility to infection but this has yet to be conclusively established with evidence from twin studies to the contrary.(29)

5.2 Patient factors:

Decreasing birth weight, decreasing gestational age and decreasing weight for gestational age (SGA) correlate with increasing incidences of LOS in VLBW infants.(2,5,11,12) Male gender predisposes to LOS (2)

5.3 Healthcare factors

5.3.1 *Invasive procedures*

Increasing durations of invasive positive pressure ventilation (IPPV) predispose to LOS (LOS also increases duration of mechanical ventilation as detailed above). Venous and arterial catheters increase the risk of LOS. The incidence of LOS also increases with increasing duration that catheters are in-situ.(2,30) Some studies however suggest that the use of percutaneously inserted central catheters may prevent some of the negative effects of total parenteral nutrition (TPN) via peripheral IV without increasing the risk of LOS.(31) A study of very low birth weight infants in Brazil found central venous catheters were an independent risk factor for LOS.(17)

5.3.2 *Pharmacotherapy*

H2 antagonist such as ranitidine and cimetidine increase gastric pH and predispose to bacterial overgrowth. This increases the risk of LOS.(5) H2 antagonists are however seldom used in Pelonomi Hospital NHCU and will thus not be evaluated.

5.3.3 *Antibiotic therapy*

Antibiotic therapy influences the normal colonisation of the infant intestine with the commensal microbiota.(32) The colonisation of the intestine with normal microflora is, in turn, an important factor in the development of normal intestinal immunity as well as humoral and cellular immunity.(33) The dysregulation of the normal symbiotic interaction between the gut microflora and the immune system predisposes to the development of inflammation and infection and should be considered in the examination of late onset sepsis.(34)

Most infants admitted to Neonatal High Care Unit are started empirically on broad-spectrum antibiotic therapy directed towards local vertically acquired organism sensitivities. Research however indicates that prolonged antibiotic therapy increases the risk of necrotising enterocolitis and death in extremely low birth weight infants.(35–37) The role of antibiotic

therapy and LOS needs to be investigated in our population on grounds of the empiric use of broad-spectrum antibiotic therapy in the majority of patients.

5.3.4 Nutrition

Nutrition of VLBW neonates represents a complex interaction between patient and healthcare factors. Delayed introduction of enteral feeding as compared to early introduction is associated with an increased risk of LOS.(2) Similarly faster progression to full enteral feeding as maintenance and earlier re-attainment of birth weight are protective against LOS.(2) Breastfeeding is also protective compared to formula feeding.(38) Longer durations of TPN use are associated with increased risk of LOS (particularly Gram negative infection).(14,17)

5.3.5 Hypothermia

Hypothermia is associated with increased mortality in very low birth weight infants.(39) A study of 5277 low birth weight infants found that there was an 11% increase in the rate of late onset sepsis for each degree Celsius decline in admission body temperature.(40) A larger study of 8872 infants initially suggested an increased risk of LOS in association with admission hypothermia but further statistical analysis led to a conclusion that this was not the case.(39)

5.3.6 Healthcare system factors

Overcrowding, understaffing and poor hygiene may lead to nosocomial infection outbreaks and contribute to increased risk of LOS. (41) Systemic hospital problems that most strongly correlate with nosocomial infections in PICU's are increasing patient density (reflected by total patient days) and decreasing nursing hours: patient day ratio. This is thought to be due to reduced attention to hygiene practises, lack of aseptic technique and reduced frequency of hand washing. A threshold does however exist above which increasing nursing hours increase the rate of nosocomial sepsis. This is thought to represent the effect of overcrowding.(42). Programs to improve hand hygiene have proven effective in reducing the transmission of nosocomial infections.(43) In South Africa existing guidelines recommend that the minimum requirements for nurses in a high care unit are one professional nurse per three patients but one to two is ideal. Alternatively one professional nurse and one experienced enrolled nurse may nurse four patients.(44) In the setting of neonatal intensive care higher nurse-to-patient ratios (more nurses per patient) are associated with reduced adverse events and mortality rates.(45)

In the developing world, systemic and health economics problems frequently contribute to infections in neonates. Overcrowding, over-regionalisation, shortage of basins, shortage of hand soap, shortage of disinfectant gel or hand rub and shortage of doctors and nurses are identified factors in neonatal infections including LOS.(38)

5.4 Human immunodeficiency virus

Antenatal and intrapartum exposure of infants to human immunonvirus (HIV) is highly prevalent in the population cared for at Pelonomi Hospital, affecting approximately 30% of infants (unpublished data used for internal quality control). Infants born to HIV infected mothers are at increased risk of mortality and morbidity.(46–48) The role of the maternal immune system and, by extension, HIV infection plays a critical role in the functioning of the newborn immune system. Reduced transplacental transfer of protective immunoglobins as well as measurably decreased populations of CD4⁺ subset T-lymphocytes are evident even in uninfected neonates. (46,47) Current evidence from South African studies is that HIV exposed neonates without perinatal infection are not at increased risk of early or late onset sepsis while infants who are infected in the perinatal period are at increased risk of early onset and late onset neonatal sepsis.(47) All low birth weight and very low birth weight infants exposed to HIV during the study period were tested for HIV by HIV polymerase chain reaction (PCR) after maternal consent was obtained. Since the onset of the study, national policy has changed to include a birth PCR for all infants exposed to HIV.

6. Clinical features and diagnosis

6.1 Clinical features

Clinical signs and features in infants with LOS are non-specific.(11,18,49) Fanaroff et al. found that increasing occurrences of apnoea and bradycardia most frequently alerted clinicians to the presence of LOS (65% of cases). Increasing requirement for respiratory support (oxygen requirement and ventilator support) was also a frequent finding (48% and 38% respectively). Gastrointestinal disturbance (enlarging gastric aspirates, poor tolerance of feeds, abdominal distension and blood in the stool) was present in 46% of cases. Lethargy and hypotonia were present in 37% of cases. Temperature instability was present in 10% of cases. Hypotension was present in 8% of cases. Hypotension was considered to be a drop in systolic or diastolic blood pressure of more than 10mmHg.(11,18)

Clinical features of late onset neonatal sepsis are important in that clinical signs of sepsis may be present in the absence of positive cultures(3,14,16,17). The prognosis and clinical outcomes of patients with clinical signs of sepsis are similar in those with negative cultures compared to those with positive cultures.(17) The requirement to investigate for sepsis significantly increases the risk of death and is thus of clinical significance.(16)

The non-specific features of sepsis overlap closely with those of neonatal meningitis and the two conditions cannot be differentiated on clinical grounds and must be distinguished by CSF analysis.(19)

6.2 Laboratory investigations.

6.2.1 Blood culture

Blood culture is the gold-standard diagnostic tool for the diagnosis of LOS.(1,18) The usefulness of this method is however limited by its time consuming nature and significant rates of false positive and false negative results.(1) Blood culture yields are significantly dependant on specimen size (at least 1ml of blood), technique of sampling, bacterial load and the presence of systemic antibiotics.(24,50) Improving automated techniques do allow for sensitivities of 74% in some settings.(18)

6.2.2 Haematological parameters

Haematological evaluation of LOS is predominantly centred around the evaluation of leukocyte and neutrophil indexes.(24) These tests are commonly used in practice but are most useful in excluding infection.(18)

Neutropenia is a strong indicator of sepsis although the absolute neutrophil count varies significantly with altitude, gestational age, sampling site and time from birth.(24)

Leukocytosis, leukopenia, high percentages of immature neutrophils (elevated I/T ratio) and low platelet counts are all associated with late onset neonatal sepsis. The I/T ratio (elevated when >0.2) is a superior marker compared to absolute immature neutrophil count and absolute neutrophil count. I/T ratio however has more utility in excluding infection (99% negative predictive value) as compared to identifying infection (25% positive predictive value).(24) Thrombocytopenia is associated with fungal aetiology LOS.(24)

6.2.3. Acute phase reagents

C-reactive protein (CRP) is produced by the liver as part of the host response to bacterial infection and provides good specificity in the diagnosis of sepsis compared to procalcitonin. Values reach a peak within 24 hours of infection (92% sensitivity) but begin to rise within 8 hours of infection. CRP values must however be interpreted within the context of host characteristics such as gestational age and immune status.(18,24,51)

Procalcitonin (PCT) has better sensitivity (87 -100%) for bacterial sepsis than CRP. PCT also exhibits an earlier rise (within 2 hours) compared to CRP.(18,24,51)

6.2.4. Cerebrospinal fluid analysis

Incidences of meningitis in patients with LOS vary from 3 – 30%.(18,19) Provided no contraindication to lumbar puncture exists, CSF should be obtained for analysis in neonates with suspected sepsis or positive blood cultures.(24) This is for purposes of diagnosing bacterial meningitis.(24) Furthermore organisms are frequently cultured from CSF in the absence of positive blood cultures (38%).(52,53)

Wide variability in cytological parameters in the cerebrospinal fluid of neonates and the high incidence of traumatic lumbar punctures complicates the diagnosis of meningitis.(54)

6.2.5. Urine analysis

Urine cultures are seldom positive (7%) in LOS.(18)

ELBW infants with candiduria (positive growth of candida species in urine) are at increased risk of neurodevelopmental impairment and death. Thus the culture of urine is of use in the evaluation of LOS.(24)

6.2.6 Acid-base analysis

Fanaroff et al. found that otherwise unexplained metabolic acidosis was present in 11% of cases of LOS.(11)

6.2.7 Hyperglycaemia

The same study found that hyperglycaemia was present in 9% of cases of LOS.(11)

6.2.8 Novel investigations.

Several new methods for the diagnosis of LOS are under investigation. These include polymerase chain reaction, cytokine levels (tumour necrosis factor and interleukin 6), toll-like receptor and nuclear factor kappa-beta.(18) These are not available in our service and will not form part of the scope of this study.

PROBLEM STATEMENT

Pelonomi Hospital is the largest regional healthcare centre in the Free State and is as such responsible for the management of a large number of very low birth weight neonates. Late onset neonatal sepsis is a common problem in VLBW infants and is associated with increased mortality and morbidity. Medical interventions, overcrowding, understaffing and poor hygiene practices may increase the incidence of LOS.

Considerable variations in rates and consequences of LOS are found in the literature. This implies that factors related to the characteristics of individual units and patient groups influence the incidence and effect of LOS. Individual units must thus collect reliable data pertaining to their patients so as to identify factors that can be improved to reduce LOS in their unique setting.

The risk factors that promote the onset of LOS have not been studied in VLBW infants at Pelonomi Hospital. Identifying risk factors for LOS may be used to plan strategies for the reduction of LOS in the medium term and ensure prompt diagnosis when LOS occurs. The overall incidence of LOS needs to be measured so as to evaluate trends over time and monitor performance and efficacy of interventions. The determination of local organism profiles is required to compile local antibiotic protocols and promote antibiotic stewardship.

AIMS AND OBJECTIVES

1. Aim:

The aim of this study was to describe the incidence, risk factors, outcomes and pathogen profile of late onset neonatal sepsis in very low birth weight premature infants at Pelonomi Hospital Neonatal High Care Unit in the first 28 days of life. These infants were admitted over a six month period from 11 September 2015 to 9 March 2016

2. Objectives:

1. The incidence of LOS was measured during the study period.
2. Various risk factors were identified and their effect on the risk of LOS was measured.
3. Nursing hours, patient days and the ratio of these two variables to one another were measured over the study period and its effect on the incidence of LOS was determined. The availability of key consumables in hand hygiene was monitored during the study period.
4. The causative organisms in episodes of culture positive LOS were recorded, and where possible the effect of specific organisms on mortality and morbidity was measured.
5. LOS associated mortality and morbidity was recorded during the study period and determinants of these were investigated.

METHODS

1. Study site:

Pelonomi Hospital Neonatal High Care Unit, situated in Bloemfontein in the Free State Province.

2. Study design:

This was a prospective, observational-descriptive cohort study.

3. Study population and sampling

Preterm infants (under 37 completed weeks gestational age) with birth weights from 1000g to 1499g admitted to the Pelonomi Hospital Neonatal High Care Unit from 11 September 2015 to 9 March 2016. 117 infants were enrolled in the cohort once inclusion and exclusion criteria were applied. All eligible infants were included in the study. There were no withdrawals in this period.

4. Study period

The study period spanned the period from 11 September 2015 to 9 March 2016.

5. Inclusion and Exclusion Criteria

Inclusion:

Infants weighing 1000g to 1499g at birth and below 37 weeks gestation admitted to the Neonatal High Care Unit were included. Infants were admitted to the High Care Unit within 24 hours of birth.

Exclusion:

Infants with major congenital abnormalities other than patent ductus arteriosus were not included. Infants referred to Universitas Tertiary Hospital before day 28 were excluded from the study. Infants that were older than 72h on admission were excluded, as it was impossible to differentiate late and early onset sepsis in these cases.

6. Measurement

Data was collected on an on-going basis during the study period and was reviewed periodically. Data was collected on a standardised data form (Appendix 1).

The following protocol was followed:

- Day 1-3:** Infants enrolled in study on admission to NHCU.
 Data form placed in patient record.
 Maternal consent obtained by registrar responsible for infant care.

Day 3 – 28: Infants were monitored for the development of LOS.

Data was collected on risk factors being investigated..

Data collected on the occurrence of IVH, NEC and oxygen dependence at day 28 of life.

Data included demographics, anthropometry and clinical data used in the diagnosis of LOS as detailed in the literature review. This included vital signs, clinical signs, blood results and blood culture results.

Data regarding risk factors for LOS as detailed in the literature study were collected on a continuing basis. This included maternal, patient and healthcare factors.

At discharge, death or 28 days of life the file was audited to determine if at any point the infant had suffered from a patent ductus arteriosus or necrotising enterocolitis. The results of any cranial ultrasounds were recorded.

A second data form (Appendix 2) was completed once a day with regards to nursing hours, bed occupancy and availability of hand soap, hand sanitising rub, hand towels, hand towel dispensers and soap dispensers.

Data forms for each infant were collected at discharge, death or at 28 days.

7. Definition of terms and case definition

Late onset sepsis – Neonatal sepsis occurring after 72 hours of life.

Confirmed LOS – Clinical and laboratory evidence of LOS as well as a positive blood culture obtained during an episode of sepsis.(17)

Clinical LOS – Clinical and laboratory evidence of LOS without growth on blood culture during a period of sepsis.(17)

Very low birth weight - A birth weight of 1000g to 1499g

Preterm birth/Prematurity – Birth less than 37 completed weeks gestational age. For purposes of this study this was guided by the best obstetric assessment (weeks since last normal menstrual period or sonographic assessment) or Ballard score.

Nursing Hours: The sum total hours worked by all nurses in one calendar month in the neonatal unit. (42)

Bed occupancy: The total number of patients admitted in the neonatal unit

Patient Days: The sum total of the days all patients were admitted in the unit. This is the sum of the total bed occupancy of every day in the calendar month.

Nursing Hours: Patient Days ratio: The ratio of nursing hours to patient days

Mild hypothermia: Surface body temperature 36.0°C to 36.4°C³¹

Moderate hypothermia: Surface body temperature 32.0°C to 35.9°C³¹

Severe hypothermia: Surface body temperature <32°C³¹

Core body temperature is not routinely monitored at Pelonomi Hospital.

8. Patient management:

Patients were managed as per local treatment protocols and practices and no alteration was made to their treatment by the investigator.

9. Data analysis:

Statistical analysis was done by the Department of Biostatistics of the University of the Free State. Categorical data are presented below using frequencies and percentages, while continuous data are presented using means with standard deviations (SDs), medians with ranges, and 95% confidence intervals (CIs). For categorical variables, comparison of measurements between those infants who did and did not develop LOS were conducted using cross tabulation with Chi-square analysis, or the calculation of odds ratios or relative risk

for the two groups. For continuous variables, differences between the two groups (presence/absence of LOS) were calculated by means of Student's t-tests.

ETHICAL CONSIDERATIONS

1. Ethical approval:

Ethical approval was obtained from the Ethics Committee of the Faculty of Health Sciences, University of the Free State. Permission was obtained from the Free State Department of Health as well as the Department of Paediatrics and Child Health of the University of the Free State.

2. Consent:

The purpose, details and implications of the study were explained to the parents of enrolled infants verbally and with a plain-language information leaflet. Consent was explained and it was made clear that it can be withdrawn at any stage. It was made clear that refusal to participate or request to withdraw would not influence treatment of the patient. Each mother or guardian signed a written consent form and was supplied with an information leaflet that was available in English, Afrikaans and SeSotho. The option of interpreter was available to the parents at their request.

3. Implications for patient and parents

There were no additional cost implications for the patient or parents. The participation in the study is beneficial for the parents in that improved practices would be of benefit in subsequent births should those infants require admission to the unit.

RESULTS

1. Study Population

During the study period 123 infants were admitted that fell within the gestational age and weight criteria for inclusion. Six were excluded from the study, three due to transfer to higher level of care and three due to presentation beyond 72h of life.

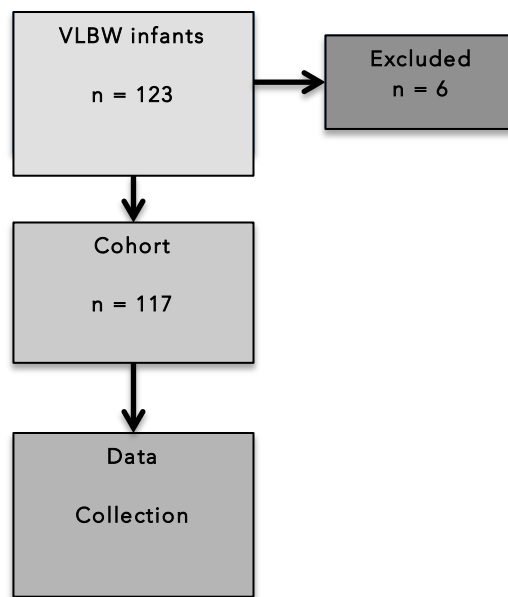


Figure 1: Study population

Males and females were equally represented in this population. The majority of patients were black, followed by coloured as detailed in table 1 below.

Population characteristic		Number (n)	Percentage (%)
Sex	Male	58	49.5
	Female	59	50.5
Race	Black	95	82.6
	Coloured	18	15.6
	Other	2	1.8
	Missing data	2	1.78

Table 1: Population Characteristics

The mean gestational age was 30 weeks (SD 20.3; 95% CI 30.03 to 30.78) and the mean birth weight was 1258g (SD 140.38; 95% CI 1232.60 to 1284.01). Most patients in the cohort were appropriate weight for gestational age (69.2%) while only 30.8% were small for gestational age.

2. Late onset sepsis

Of the enrolled infants, 43.6% had at least one episode of late onset sepsis. The incidence of LOS during the study period was 436 per 1000 per annum, assuming a constant spread for the year. Furthermore, 8.5% of the included infants had multiple episodes of LOS. There were 57 positive blood cultures during the study period. The organism distribution is described in the figure below. Gram negative organisms cultured were: Klebsiella species (4), Serratia species (5), Pseudomonas species (5) and Acinetobacter baumannii (1). Gram positive cultures were: Coagulase negative staphylococci (12), Streptococcus viridans (2), group B streptococci and enterococcus species (9). There were six cultures of various Candida species.

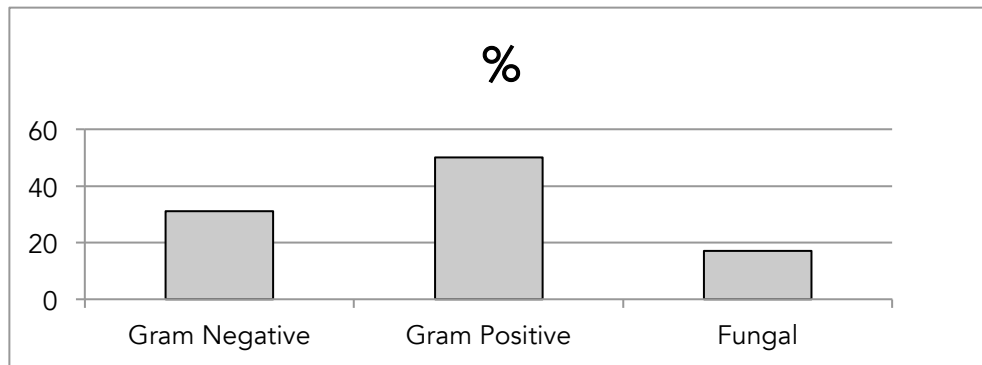


Figure 2. Organism distribution

3. Risk Factors for LOS

The risk of LOS was not found to be altered by gender in this population (odds ratio 0.86, CI 0.413 to 1.795) Black infants had an increased frequency of LOS compared to coloured infants. (48.9% vs 22.2%; P-value 0.06). The mean birth weight of those with LOS (1230g; SD 149.3; 95% CI 1188 to 1272) was similar to those who did not develop LOS (1280g; SD 130.9; 95% CI 1284.4 to 1313.2). (t=1.83: df=114: P-value: 0.0537). The mean gestational age was 30 weeks in both those affected and unaffected by LOS (t =1.58, df=114, P-value: 0.119)

Pre-eclampsia affected the pregnancy of 44 patients in this cohort (37.61%). The infants of mothers with pre-eclampsia had a lower mean admission neutrophil count than those of mothers without pre-eclampsia (2.6 vs. 3.7 x 10³ per µl; t=2.22; P-value: 0.0282). Lower admission neutrophil counts were associated with increased frequency of LOS although the statistical significance is not proven (p-value 0.09) as in table 2.

Neutrophil Count (n x 10 ³ per µl)	LOS (n) (%)	No LOS (n) (%)
<1.0	6 85.7	1 14.3
1.0 – 1.49	2 33.3	4 66.7
1.5 – 1.99	3 60	2 40
>= 2	9 36	16 64

Table 2: Neutropoenaia and LOS

Fifty-two of the mothers were infected with HIV (44.5%); 8 of these mothers were not on any form of antiretroviral therapy at the time of delivery. More cases of LOS occurred in infants exposed to HIV compared to the infants of HIV negative mothers but the p-value is too high to prove statistical significance (54.5% vs 35.94%; p-value 0.1345). Thirty eight mothers infected by HIV had a measured or documented HIV viral load at the time of delivery. HIV positive mothers of infants with LOS had a higher mean viral load (12981.4) than the mothers of the infants that did not develop LOS (1109.7) but again the p-value is not significant (p-value 0.104; t=1.70; df = 20.51). When mothers were grouped into virologically suppressed (VL < 1000) or non-suppressed (VL >= 1000), infants of suppressed mothers had less LOS although this was not statistically significant (p-value 0.148; Odds ratio 3.84) The mean CD4+ count of mothers of infants without LOS was 417.1 cells per mm³ (95% CI 329.4 to 504.8 cells per mm³; SD 202,7). The mean CD4+ count of mothers of infants who developed LOS was 399,6 cells per mm³ (95% CI 307,2 to 492,1; SD 208,5) (P-value 0,77)

Three of the infants exposed to HIV were found to be infected with HIV by HIV - polymerase chain reaction (6%).

Regarding birth, 62 (53.45%) of the enrolled patients were delivered by the vaginal route, of which four required assisted delivery (3.45%). 54 of the enrolled infants were delivered by caesarean section (46.55%). Incidence of LOS was similar between these groups 44.8% of infants born by vaginal route developed LOS and 41.51% delivered by caesarean section developed LOS. (P-value: 0.489)

The use of several interventions was monitored during the 28-day follow-up period as detailed in table 3 below. The use of a number of interventions was associated with an increased occurrence of LOS.

Intervention	Number exposed	LOS (%)	P-value	Odds ratio (Confidence Interval)
IPPV	23	IPPV: 68.2 No IPPV: 38.3	0.0162	3.45 (1.28 to 9.28)
NCPAP	71	NCPAP: 56.3 No NCPAP: 24.4	0.0010	3.98 (1.74 to 9.10)
Nasal Prong O₂	85	NPO ₂ : 50.6 No NPO ₂ 25.8	0.0206	2.94 (1.18 to 7.31)
UVC	111	UVC: 45.8 No UVC 14.3	0.1329	5.08 0.59 to 43.66)
UAC	17	UAC: 68.8 No UAC: 40.0	0.03	3.30 (1.07 to 10.22)
TPN	32	TPN: 75.0 No TPN: 32.1	<0.0001	6.33 (2.51 to 15.92)

Table 3: Frequency of procedures and LOS

The effect of the duration of use of the above interventions as well as the effect of the duration of each on the risk of LOS is reflected in table 4 below.

Intervention	Mean Duration *Std deviation †95% CI	P-value
IPPV	LOS: 3.13 1.64* 2.22 to 4.04 † No LOS: 3.00 1.73* 1.39 to 4.60 †	P-value 0.863 Pooled t-value 0.17 Degree of freedom 20
NCPAP	LOS: 4.17 2.58* 3.34 to 5.00 † No LOS: 2.48 1.34* 1.99 to 2.97 †	0.0007 Satterthwaite t-value 3.57 Degree of freedom 61.18
Nasal Prong O₂	LOS: 4.64 4.64* 4.48 to 7.34 No LOS: 3.60	P – value 0.0206 Pooled t-value 3.22 Degree of freedom 83
UVC	LOS: 6.74 2.31* 6.08 to 7.40 † No LOS: 5.47 2.03* 4.94 to 6.00 †	P – value 0.0030 Pooled t-value 3.03 Degree of freedom 107
UAC	LOS: 3.63 1.43* 2.67 to 4.6 † No LOS: 3.80 2.28* 0.97 to 6.63 †	P – value 0.862 Pooled t-value -0.18 Degree of freedom 14
Admission IV cannula	LOS: 3.55 1.63* 2.98 – 4.12 † No LOS: 3.44 1.69* 2.74 to 4.14 †	P- value 0.78 Pooled t-value 0.27 Degree of freedom 57
TPN	LOS: 2.90 3.88* 2.9 – 6.18 † No LOS: 1.23 1.51* 1.23 to 3.76 †	P –value 0.041 Satterthwaite t-value 2.13 Degree of freedom 29

Table 4: Duration of procedures and LOS

The majority of infants experienced hypothermia in the first 24 hours of life. The mean lowest temperature recorded in the first 24 hours was 34.7°C (SD 0.84). Only two patients did not experience hypothermia in the first 24h of life. 88.89% had moderate hypothermia and 7.69% had mild hypothermia. Almost half (46.15%) of patients with moderate hypothermia developed LOS. Thirty-three point three (33.3%) percent of patients with mild hypothermia and no patients with normothermia developed LOS (p-value 0.49)

The mean duration of initial antibiotic therapy was 3.9 days (SD 1.45). The majority of patients received a combination of ampicillin and amikacin as their first line antibiotic (88%) while the remainder received cefotaxime. The mean duration of initial antibiotic therapy in patients who developed LOS was 4.17 days compared to 3.78 days in those who did not develop LOS (t=1.47; df=114; P-value 0.1451). Those treated with cefotaxime as their first line antibiotic had more LOS than those who were treated with ampicillin and amikacin (78.57% vs. 39.22%; Odds ratio 5.6 with a CI of 1.49 to 21.64; p-value: 0.0083)

Only 50% of patients in this study were provided with antenatal steroids. Of those who had antenatal steroids 40.35% developed LOS while 46.5% of those who did not receive antenatal steroids developed LOS (p- value 0.574)

Less than a quarter (23.93%) of infants evaluated were provided with surfactant therapy. There was an increase in LOS in those exposed to surfactant (66.67%) compared to those who did not receive surfactant (37.08%)(P-value 0.008; Odds ratio 3.39 with a CI of 1.36 to 8.418)

The mean number of hours to initiating enteral feeding was 36.57 hours (SD 20.61 hours; 95% CI 32.67 – 40.46). Shorter intervals from birth to the initiation of breastfeeding were seen in infants who did not develop LOS (Mean: 29.53 hours; SD 13.32; 95% CI 8.20 to 22.79) compared to those who did develop LOS (Mean :45.02 hours; SD 24.44; 95% confidence limit 38.07 to 51.98); (Pooled t-value: 4.21; P –value <0.0001).

Exclusive breastfeeding was the most frequently used feeding strategy. 72.65% of mothers used exclusive breastfeeding followed by mixed feeding (19.66%) and exclusive formula feeding (7.69%). The frequency of LOS was lower in those infants who received breast milk. 42.8% of exclusively breastfed, 66.67% of exclusively formula fed and 34.78% of mixed feeding infants developed LOS.

The statistical significance of this is however low with a P-value of 0.259.

4. Clinical Presentation

The clinical presentation of LOS was variable and non-specific as detailed in table 5 below.

Clinical Feature	Number of patients (n)	Percentage of patients with LOS (%)
Temperature instability	31	60.8
<i>Hypothermia</i>	28	54
<i>Hyperthermia</i>	3	6.8
Cardiovascular disturbance	27	52.9
<i>Tachycardia</i>	11	21.4
<i>Poor perfusion</i>	16	31.5
GIT disturbance	23	45
<i>Ileus</i>	4	7.8
<i>Abdominal distension</i>	16	31.8
<i>Vomiting</i>	6	9.7
<i>Bloody stools</i>	2	4
<i>Diarrhoea</i>	1	2
Respiratory disturbance	25	49
<i>Respiratory distress</i>	18	35.3
<i>Apnoea</i>	9	17.6
Glucose disturbance	9	17.5
<i>Hypoglycaemia</i>	9	17.5
<i>Hyperglycaemia</i>	1	2

Table 5: Clinical presentation of LOS

Laboratory parameters that were used in the diagnosis of late onset neonatal sepsis are listed in table 6.

Parameter	Mean	95% CI
CRP	20.2	10.2 – 30.2
White cell count	8.7	6.8 – 10.7
Neutrophil count	3.9	2.7 – 5.2
I/T ratio	0.3	0.27 – 0.35

Table 6: Laboratory values in diagnosis of LOS

5. Outcomes of patients who developed LOS

The mean number of days to attainment of full enteral feeding was 9.85 days (SD 5.34; 95% CI 8.79 to 10.91). The mean number of days to attain full enteral feeding was greater in those who developed LOS (12.95 days; SD 6.42; 95% CI 10.97 to 14.93) compared to those who did not develop LOS (7.5 days; SD 2.55; 95% CI 6.83 to 8.18) ($t=5.35$; degree of freedom 52.01; P-value <0.0001). Infants with multiple episodes of LOS took longer to obtain full enteral feeding than those who had one episode of LOS. (Difference between means 4.41 by ANOVA procedure, significant below the 0.05 level; 95% CI 0.22 to 8.60)

There was an increased risk of necrotising enterocolitis in infants who developed late onset neonatal sepsis. 16 infants with LOS developed NEC (31.37%) while only 2 children without LOS developed NEC (3.08%). (Odds ratio 14.4; 95% CI 3.1277 to 66.29; P-value <0.0001). Accurate data regarding IVH was not possible as very few patients had head ultrasounds performed after 72 hours of life.

Only 11 of the infants who developed LOS had CSF analysis performed. 5 of these had CSF analyses indicative of meningitis. There was one positive CSF culture of *Serratia marcescens* although 80% of the infants with meningitis had positive blood cultures.

Only 4 of the infants who developed LOS had specimens obtained for urine MCS of which three were positive.

Of the infants with LOS, 10% died during the study period. LOS contributed to 38% of the overall mortality and 40% of the mortality affecting the VLBW group once deaths before 72 hours were excluded. When infants who died before 72 hours of age were excluded there was an increased frequency of death in infants who developed LOS compared to those who did not 10% vs 4.84% (P-value 0.4631; Odds Ratio 2.18; 95% CI 0.49 to 9.68).

Five infants were still on nasal prong oxygen at 28 days of life. Eight percent of infants who had LOS were still oxygen therapy compared to the 1.52% of infants who did not develop LOS. (P-value 0.11)

Of the Infants with LOS, 93.48% were still admitted to the unit on day 28. This is much higher than 62.07% of infants who did not develop LOS and were still admitted on day 28. (Odds ratio 8.79; CI 2.42 to 31.66; p- value 0.0002)

6. Effect of hospital conditions on LOS

There was not adequate data to demonstrate a relationship between patient density and nursing staff and LOS or between the availability of consumables and LOS.

The mean bed occupancy during the study period was 37.011(SD 5.149; 95% CI 36.25 to 37.76). The mean number of nursing staff per day was 31.17 (SD 3.77; 95% CI 30.61 to 31.72). This is the total number of staff over day and night duty. The daily nursing hours were determined. The mean nursing hours were 345.89 hours (SD 41.39; 95% CI 339.81 to 351.96). Nursing included professional nurses, enrolled nurses and staff nurses. The mean nursing hours to patient days ratio was 9.52 (SD 1.61; 95% CI 9.275 to 9.794). When bed occupancy, nursing staff numbers, nursing hours and the nursing hours patient days ratio are related to the incidence of LOS the graphs below are the result.

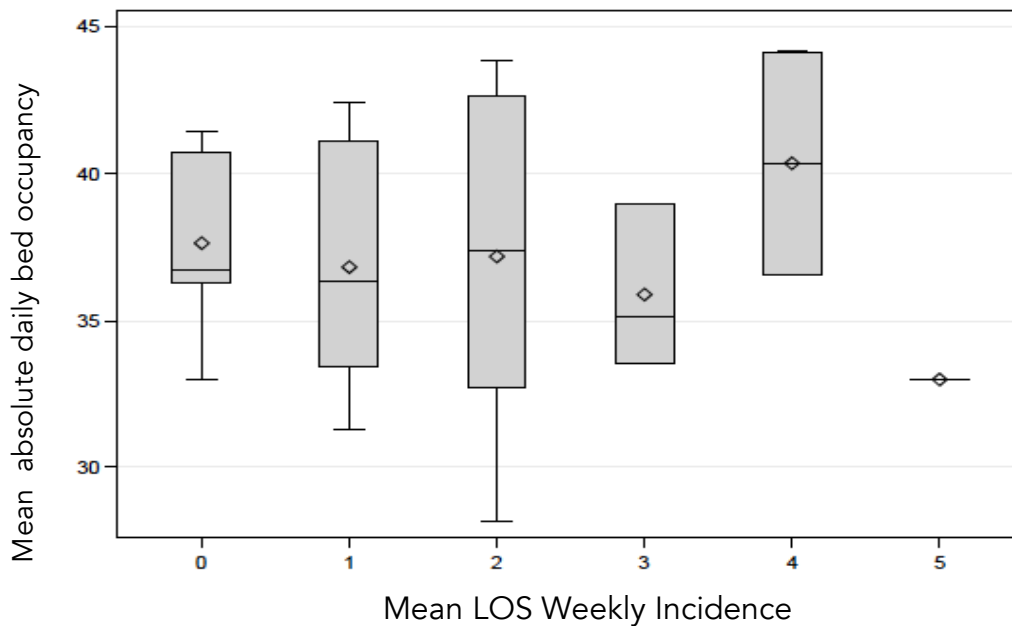


Figure 3: Mean daily bed occupancy and LOS

None of the differences in the above analysis were significant below the 0.05 level. (Alpha 0.05; error degrees of freedom 20; error mean squared 21.15; critical value 2.71.)

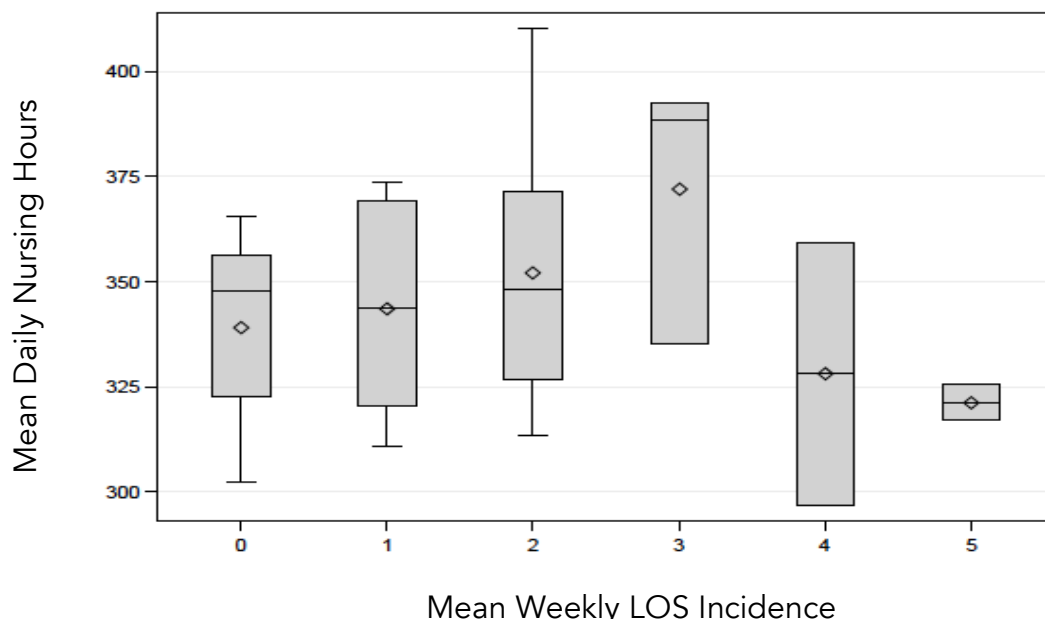


Figure 4: Mean daily nursing hours and mean incidence of LOS

None of the differences in the above analysis were significant below the 0.05 level. (Alpha 0.05; error degrees of freedom 20; error mean squared 893.796; critical value of F 2.71.)

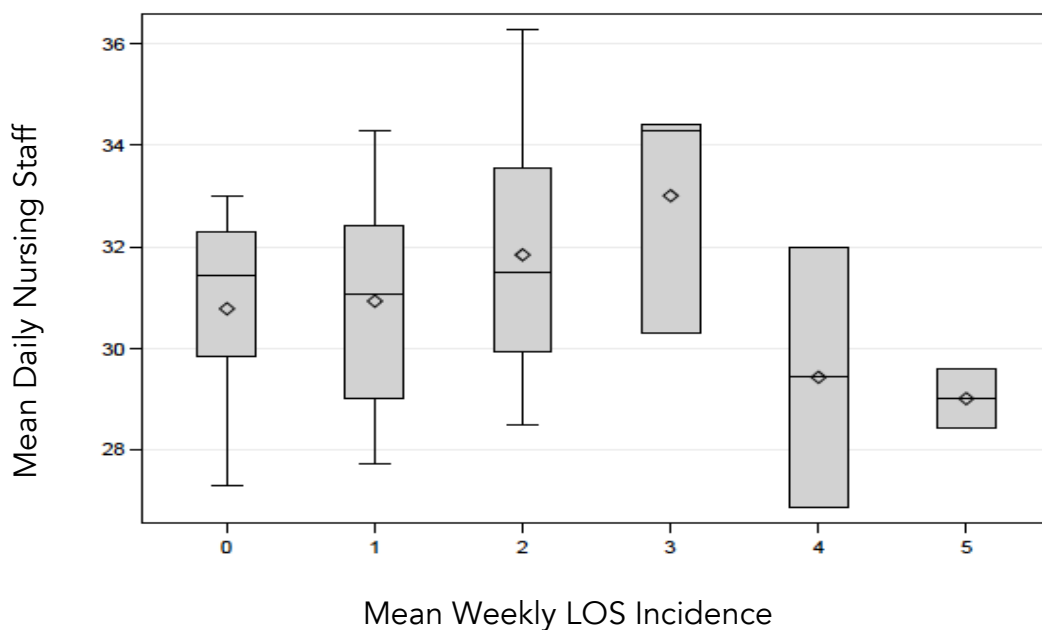


Figure 5. Mean daily nursing numbers and mean incidence of LOS: Note: This is the total number of nursing staff over 24h and does not reflect the absolute number of staff on duty at any given time which is lower.

None of the differences in this analysis were significant below the 0.05 level. (Alpha 0.05; error degrees of freedom 20; error mean squared 6.275; critical value of F 2.71.)

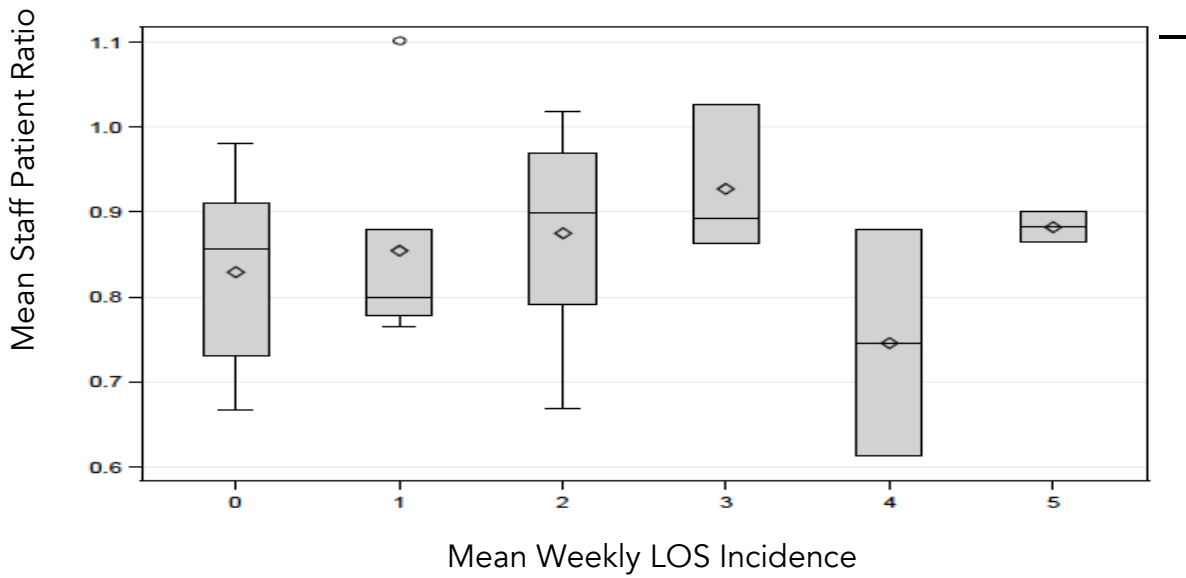


Figure 6: Mean Staff Patient Ratio and Incidence of LOS: Note this is the ratio over a 24h period but does not indicate the absolute nurse patient ratio at any given moment as the nursing numbers are divided over shifts

None of the differences in this analysis were significant below the 0.05 level. (Alpha 0.05; error degrees of freedom 20; error mean squared 0.015; critical value of F 2.71.)

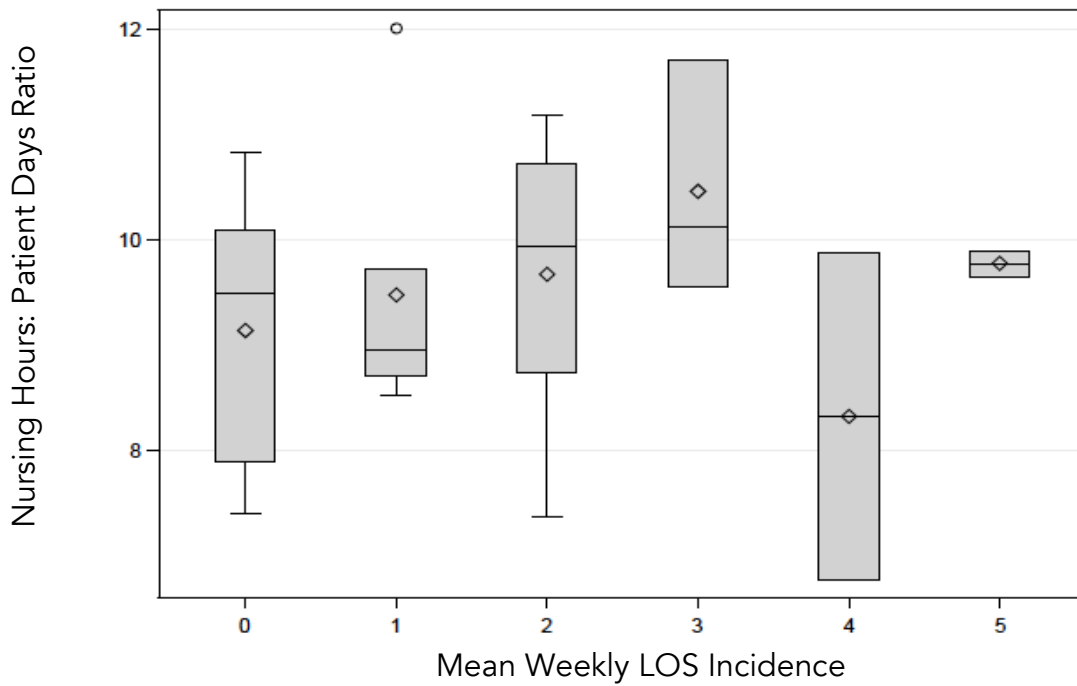


Figure 7: Nursing Hours Patient Days Ratio and Incidence of LOS:

None of the differences in this analysis were significant below the 0.05 level. (Alpha 0.05; error degrees of freedom 20; error mean squared 1,867; critical value of F 2.71.)

In all of the analyses above it is important to note that these are the ratios over a whole day. The true instantaneous ratios of nurses to patients may be considerably higher and is expected to be well in excess of what is acceptable.

Alcohol hand rub was unavailable on 50 days, soap on 23 days and hand towels on 20 days. There were 4 days where there were malfunctioning automated soap dispensers.

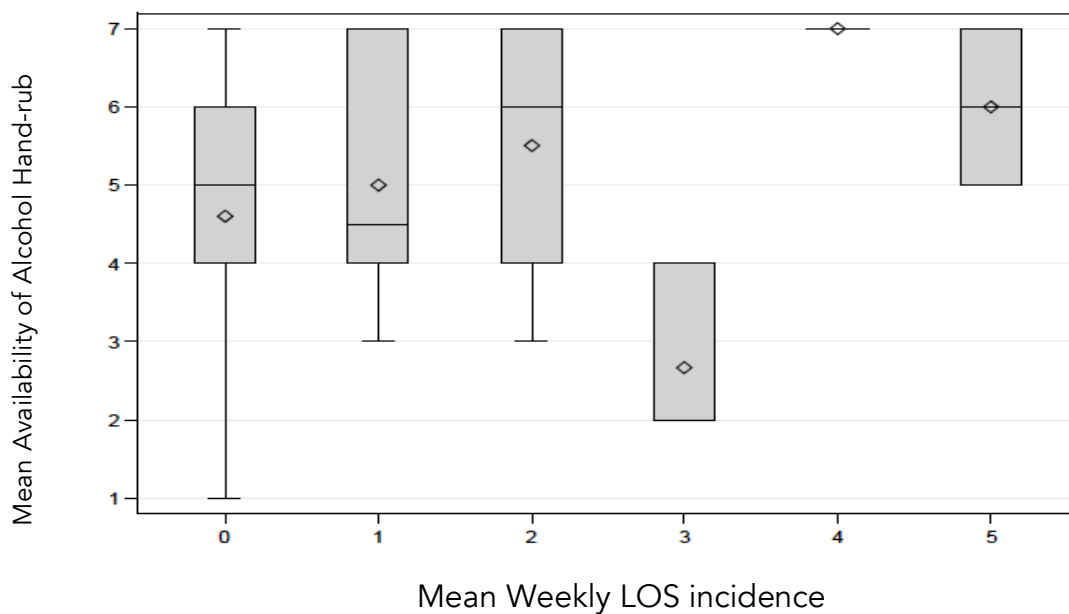


Figure 8: Mean Availability of Alcohol Hand-rub and Incidence of LOS:
The y axis in this analysis reflects the number of days in the week that alcohol hand rub was available

None of the analyses above were significant below the 0.05 level. (Alpha 0.05; Error degrees of freedom 20; Error mean square 2.893; Critical value of F 2.71)

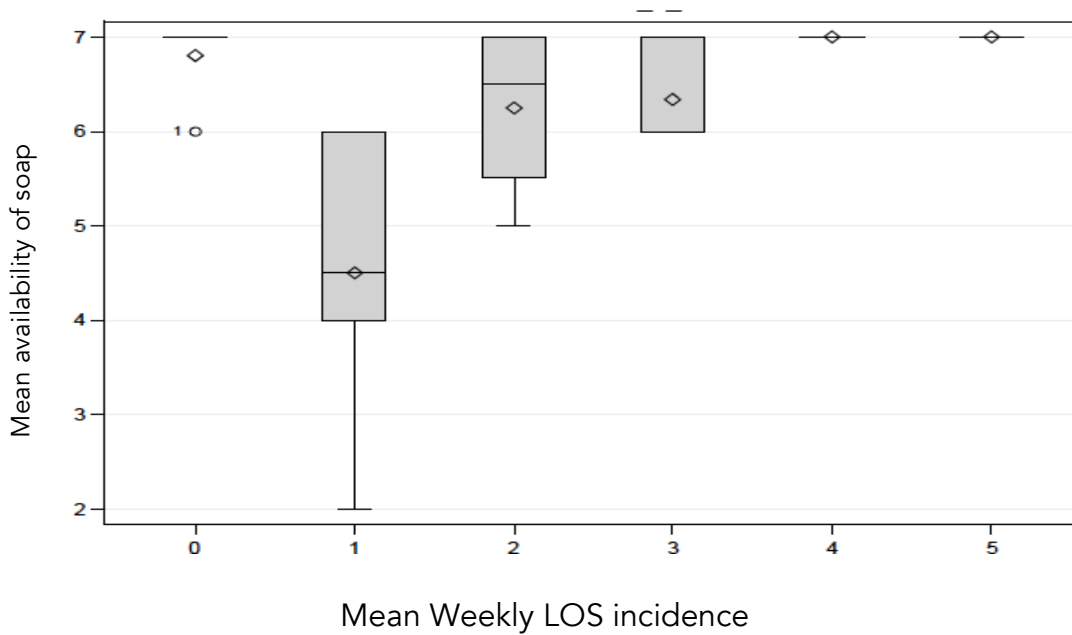


Figure 9: Mean Availability of Soap and Incidence of LOS: The y-axis in this figure reflects the number of days in a week that soap was available

None of the analyses with regards to the availability of soap were significant below the 0.05 level. (Alpha 0.05; Error degrees of freedom 20; Error mean square 0.923; Critical value of F 2.71)

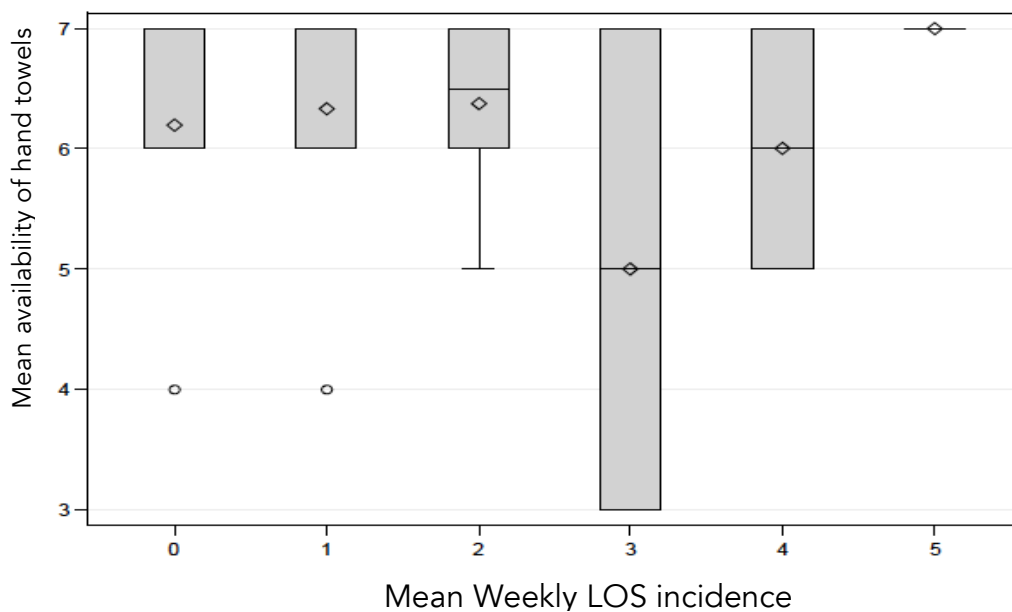


Figure 10: Mean Availability of Hand Towels and Incidence of LOS: The y-axis reflects the number of days in a week that hand towels were available

None of the analyses with regards to the availability of hand towels were significant below the 0.05 level. (Alpha 0.05; Error degrees of freedom 20; Error mean square 1,400; Critical value of F 2.71)

The relationships above were duplicated with the comparison staggered by a week to adjust for the possibility of a delayed effect. Similarly no significant comparisons were found and it was concluded that a larger data set would be required to analyse this relationship.

DISCUSSION

The frequency of LOS was significantly higher in this population than what is reported in the reviewed literature. Furthermore the pathogen distribution in this study differs from the literature with a significantly higher percentage of gram negative and fungal infections. The reason for this could not be established during this study.

While the statistical significance of the increased frequency of LOS in black infants is not high, the role of genetic and host factors in LOS is the topic of on-going study(1,29). Research into the role of these factors in our population should be considered in future research. The effect of decreasing birth weight and gestational age on LOS reflected in literature review is not found in this study population. This may reflect the relatively narrow weight range selected in this population (1000 to 1499g).

The finding of lower absolute neutrophil counts in the infants of pre-eclamptic mothers on admission concurs with the findings in the literature(25,28). While the statistical significance of the increased frequency of LOS found in this cohort is limited, larger case-control studies of infants affected by pre-eclampsia are required, considering the existing equipoise in the literature.

Infants exposed to HIV may have an increased frequency of LOS and there may be a correlation between maternal viral load and LOS. While statistical significance could not be established, this finding may be in line with other studies regarding the effect of maternal HIV infection on infant immunity(46–48) but this is not conclusive.

A significant design flaw discovered after completion of data collection is the difficulty in resolving whether the use of respiratory support and TPN are increasing the risk of LOS or was required in the treatment of LOS.

IPPV, NCPAP and NPO₂ were used more frequently in patients who developed LOS. The use of these however is not limited to the first 72h of life and it may be that some required some form of respiratory support in the management of LOS. Further research focused on determining the role of respiratory support in the development of nosocomial infection is required although in the NICHD cohort, IPPV was associated with LOS as was the duration of IPPV(2). Similarly patients who develop LOS may not tolerate their feeds and require parenteral nutrition, however the use of TPN is reported as a risk factor for LOS in the medical literature (14,17). Hygiene practices during the use of these modalities may also increase the risk of LOS and need to be considered. Similarly longer durations of use of these modalities in patients may be either or both cause and consequence of LOS and need to be studied individually and in greater numbers to draw a final conclusion. The increased days of use found in patients with LOS still indicate an increased burden of care and cost implication and should encourage stricter hygiene practices when using these modalities.

It was not possible to establish statistical significance regarding the use of umbilical venous lines due to the fact that the great majority of infants were provided with this as their first venous access. A longer duration of UVC use was found to be significantly associated with LOS and may implicate UVC usage in LOS.

The high frequency of hypothermia in this cohort is concerning considering the independent effect of hypothermia on mortality.(39) In terms of the effect on LOS, a similar correlation between the severity of hypothermia and the frequency of LOS reported in the literature was also found although statistical significance could not be proven(40).

The longer mean duration of first line antibiotic use found in infants with LOS, although not statistically significant, is in keeping with the findings of Hansen, Sanchez and Ambalavan.(35) Furthermore the use of cefotaxime as first line antibiotic was associated with an increased risk of late onset sepsis, which was statistically and clinically significant. This is in line with concerns that third generation cephalosporins contribute to colonisation and infection with resistant organisms.(55–57)

There was not adequate coverage with antenatal steroids considering the proven benefit they provide.

Infants that received surfactant therapy had an increased risk of LOS that was not reported in the medical literature reviewed. No conclusion could be made regarding minimally invasive vs. conventional methods. In addition to encouraging good hygiene practices during this procedure, this finding would support recent recommendations that surfactant use is most beneficial in those patients who fail to respond to NCPAP.(58)

Longer durations to the initiation of enteral feeding was found in infants affected by LOS correlating with the finding that early initiation of enteral feeding is a protective factor.(2) The reason for delay was not documented in this study.

Infants with LOS experienced considerable morbidity and mortality. Although statistical significance could not be proven with regards to increased mortality, the findings in this group are clinically significant and concur with other studies.(2) There was an increased risk of necrotising enterocolitis in this group as well as a significantly longer duration required to achieve enteral feeding. The findings regarding meningitis support the findings in the literature that meningitis is frequently the site of infection in LOS. The number of infants who developed LOS but did not have a lumbar puncture was far greater than what is suggested in the literature. The fact that a significant portion of the CSF analyses that were performed indicated meningitis reinforces this. This is most likely due to excessive workloads on doctors, but lumbar puncture should be mandatory in new cases of LOS. Infants who developed LOS took considerably longer to achieve full enteral feeding than their peers who did not develop LOS and had longer durations of parenteral nutrition. As mentioned above the duration of ventilation and parenteral nutrition was longer in patients with LOS although it could not be clearly demonstrated that there was a difference in respiratory support at 28 days of age. Infants who developed LOS were much less likely to be discharged by day 28 compared to those who did not develop LOS. These all contribute to an increased burden of care and financial costs in infants affected by LOS.

Bed occupancy remained high throughout the study period and the mean bed occupancy is in excess of 100% for the unit's intended capacity of 32 patients (mean bed occupancy 115.6%). The distinction between professional nurses, enrolled nurses, staff nurses and student nurses was not made. All nurses handle and feed infants while professional nurses have the added tasks of administration of intravenous medications and fluids and the care of critically ill infants.

Even when nurses are considered as a whole the nursing hours to patient days ratio is lower than what is reported in the reviewed literature.(42) Considering that the reflected data is over a 24h period, it is likely that the nurse-patient ratios especially of professional nurses was outside the recommended range for considerable periods.(44) While statistical significance of the analyses performed could not be established the reflected relationship is not optimal. A further study of longer duration and higher power is required to demonstrate this further.

Key consumables for hand hygiene were frequently unavailable during the study period. While we were unable to establish a statistically significant relationship between the availability of these and the incidence of LOS, the effectiveness of good hand hygiene in preventing nosocomial infections is well documented.(43)

CONCLUSION

Late onset neonatal sepsis was a common problem among the infants included in this study with serious consequences for those affected and the Neonatal High Care Unit as a whole. Late onset neonatal sepsis was frequently present in infants who died. Infants with LOS were less likely to be discharged by day 28 of life. Infants with LOS took longer to achieve full enteral feeding and required longer durations of parenteral nutrition. Necrotising enterocolitis was more common in infants with LOS. Meningitis is a common problem in infants with LOS and was detected when investigated for, but inadequate numbers of infants with LOS underwent lumbar puncture for CSF examination.

Black infants may be at increased risk of LOS but this must be investigated further. The use of IPPV, NCPAP, nasal prong oxygen, surfactant, TPN, and UAC are associated with LOS. Longer durations of UVC, IPPV and TPN usage were associated with LOS but causality could not be established. Delay in the initiation of enteral feeding was associated with LOS. Infants treated with cefotaxime as their first line antibiotic were at increased risk of LOS. Maternal HIV infection may increase the risk of LOS and infants of mothers who are not virologically suppressed may be at increased risk of LOS but further research is required to prove this with statistical significance.

Bed occupancy was high during the study period and was frequently in excess of the capacity for which the unit was designed. The nursing hours to patient days ratio was low during the study period. Key consumables for hand hygiene were frequently unavailable during the study period. No conclusion could be drawn regarding the relationship between these factors and sepsis from the collected data but the conditions reflected are not conducive to good infection control practices.

Other useful findings from the data bare mentioning. There was poor coverage with antenatal steroids in this patient cohort. Exposure to hypothermia was pervasive. Considering the high rates of LOS in this unit, the number of lumbar punctures for CSF analysis performed was low. There is a high incidence of HIV infection in the mothers of VLBW patients in our setting but the role of HIV infection, maternal viral load and maternal immune status in LOS requires investigation.

It is critical that meaningful interventions stemming from these findings and from the published literature be implemented urgently.

RECOMMENDATIONS

It is recommended that a hospital-wide program for the reporting of nosocomial infections be established and that a database of nosocomial infections be established and maintained.

Written policies for hygiene practices in the handling of infants, performance of procedures (venous and arterial access and the provision of surfactant therapy), preparation of TPN, preparation of ventilator and NCPAP circuits and respiratory therapy (such as suctioning) and administration of medications.

The adherence to these measures should be monitored intensively until full adherence is achieved and then on a periodic basis.

The use and duration of use of IPPV, NCPAP, nasal prong oxygen, TPN, first line antibiotics, UVC and UAC should be limited to the minimum necessary.

Early initiation of enteral feeding, protocol driven progression of enteral feeding and active support of lactation should be encouraged. The activities of the donor breast milk bank should be supported and improved. It is suggested that decisions regarding feeding plans be made antenatally and include obtaining consent for the use of banked donor breast milk for infants of mothers with threatening preterm labour.

Antibiotic stewardship must be supported. The use of third generation cephalosporins should be limited to where contra-indications exist to penicillins and aminoglycosides.

Measures should be put in place to increase capacity and decrease bed occupancy. It is recommended that other centres on levels one, two and three be expanded to allow down referral, decrease admissions at this level 2 facility and increase ease of referral to higher levels of care better suited to the needs of VLBW infants. Uninterrupted supply of necessary consumables required for correct hand hygiene practices must be ensured at all time.

This should include daily checklists of supplies in the unit as well as redundant inventory to ensure that supply is not interrupted at any stage.

Nursing numbers should be increased and career development and further training should be actively supported for nurses caring for ill neonates.

Efforts should be made on a national level to reduce the prevalence of HIV in the general population as well as pregnant mothers. Mothers who are infected with HIV should receive intensive support and access to appropriate anti-retroviral therapy to ensure that they are virologically suppressed at the time of delivery.

Vigilance for non-specific signs of LOS should be maintained. In infants that develop LOS, the performance of CSF analysis should be mandatory in the absence of contraindications.

A high index of suspicion should be maintained for meningitis and the development of necrotising enterocolitis in these infants.

Evidence based practices in the management of preterm neonates should be supported. In the context of the findings of this study it is imperative that efforts be made to prevent hypothermia and ensure that all mothers who present with preterm labour be provided with

the benefit of antenatal steroids.

Further research is recommended in the following areas:

1. The effect of neutropaenia related to pre-eclampsia as a risk factor for LOS.
2. The effect of race on LOS in South African populations as well as attempts to identify genetic polymorphisms that increase the risk of LOS in South Africa.
3. The effect of maternal HIV infection, the effect of infant HIV infection, the effect of maternal viral load and maternal immune status should be investigated as a larger study.
4. More detailed studies designed to determine if surfactant use increases the risk of LOS.
5. Studies designed to determine more exactly whether longer durations of ventilation and other therapies are the cause or consequence of LOS.
6. A larger study designed exclusively to measure the effect of nursing numbers, patient density and hygiene practices in LOS is recommended.

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