ANTIBIOTIC USE IN A LEVEL III NICU IN SOUTH AFRICA

By

Dr Naana Ayiwa Wireko Brobby

Student Number WRKNAA001

SUBMITTED TO THE

UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the Degree

M. Phil Neonatology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of Submission: 19th February 2018

Supervisor: Dr Lloyd Tooke

Department of Neonatology

Groote Schuur Hospital

University of Cape Town

TABLE OF CONTENTS

DECLARATION

I, Dr Naana Ayiwa Wireko Brobby Student number WRKNAA001, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part of it has been, is being or is to be submitted for another degree in this or any other University.

I empower the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 19th February 2018

ABSTRACT

Background: Antibiotics are the most commonly used medications in the neonatal intensive care unit, and when used appropriately, can be lifesaving in the NICU. However, their inappropriate use has been found to be associated with certain adverse effects like Late Onset Sepsis, Necrotizing Enterocolitis, Chronic lung disease, Candidiasis, antibiotic resistance and death.

Objective: This study seeks to describe the current antibiotic practices and management of neonatal sepsis including antibiotic use in a level III Neonatal unit in South Africa

Method: The study was conducted at the Groote Schuur Hospital Neonatal Unit in South Africa which provides both emergency and continuous care for neonates in the Western Cape Province. All positive cultures as well as the duration of antibiotics within the period of 1st January 2016 to 31st December 2016 at the GSH Neonatal Unit were entered into a database. Data on infection and antibiotic use in Very Low Birth weight infants was extracted from the Vermont Oxford Network (VON) database. The GSH Neonatal Unit is one of the contributing units to the VON database. This was in addition to 2 Quality audits on antibiotic use in the unit done on 2 separate days in the months of February and November in 2016. The 10 month interval between the 2 audits was to allow for any policy changes to be implemented based on a series of educational webinars for staff that were organized during that period. Another audit was done in a randomly selected month collecting data of all infants on antibiotics for the entire month.

Results: The overall incidence rates of Early and Late onset sepsis among the VLBW infants were 1.0% and 5.2% respectively with the 24 – 26 week Gestational age category having the highest rates. GBS and Klebsiella pneumonia were the leading pathogens for EOS and LOS respectively. The incidence of sepsis among babies bigger than 1500g was 0.52%.The commonly used antibiotics were Ampicillin, Gentamycin and Meropenem, which were consistent with the Unit’s protocols. The major reasons for continued use of antibiotics beyond 48 hours were clinical signs concerning for risk of sepsis, pending culture results and laboratory results concerning for risk of sepsis. Regarding infants who received antibiotics for more than 48 hours,

a comparison of both audits showed GSH plotting below the lower quartile at 30% in the 1st audit, and at 67% between the median and the lower quartile in the 2nd audit.

Discussion: Gestational age has always been a universal risk factor for neonatal sepsis, and this was confirmed in this study. Inappropriate use of antibiotics in neonates arises on account of the difficulty clinicians face because of the nonspecific and vague nature of the signs of neonatal sepsis, especially in the VLBW category. Additional biomarkers for sepsis are increasingly being used to aid in the decision of whether or not to discontinue antibiotics after 36 - 48 hours.

Conclusion: There is the need for stricter antibiotic stewardship to reduce the inappropriate use of antibiotics among neonates. Antibiotics being used at GSH are appropriate for the prevailing organisms although there are some resistant organisms.

ACKNOWLEDGEMENTS

My sincere appreciation goes to the following people and organizations for their various contributions to this study:

- The African Paediatric Fellowship Programme (APFP) of the Department of Paediatrics of the University of Cape Town for the fellowship award which provided the platform for my fellowship training and for the opportunity for this study to be done. I am especially grateful to the Programme Administrator Avril Du Preez for her immense support.
- My Supervisor, Dr Lloyd Tooke who not only supported me throughout the entire Fellowship Programme but was also immensely and readily helpful with this study.
- The Consultants at the Department of Neonatology who were all very supportive and helpful during my Fellowship Programme
- The Nursing staff and Administrative Assistant of the Department of Neonatology of Groote Schuur Hospital who were especially very helpful during my data collection process
- The Vermont Oxford Network
- Mr Isaac Boakye of the Komfo Anokye Teaching Hospital, Ghana, who helped with the databases
- My family and friends for their moral support and encouragement throughout the period of my training and this study.

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

APP - Acute Phase Proteins

ASP – Antibiotic Stewardship Program

CBC – Complete Blood Count

CDC – Centers for Disease Control

CPAP – Continuous Positive Airway Pressure

CRP – C Reactive Protein

CSF – Cerebrospinal Fluid

ELBW – Extremely Low Birth Weight

EOS – Early Onset Sepsis

ESBL – Extended Spectrum Beta Lactamase

GSH – Groote Schuur Hospital

HREC – Human Research Ethics Committee

IDSA – Infectious Diseases Society of America

IAP – Intrapartum Antibiotics Prophylaxis

LOS – Late Onset Sepsis

NICHHD – National Institute of Child Health and Human Development

NICU – Neonatal Intensive Care Unit

PPROM – Preterm Premature Rupture of Membranes

PROM – Premature Rupture of Membranes

RDS – Respiratory Distress Syndrome

SPTL – Spontaneous Preterm Labour

UTI – Urinary Tract Infection

VON – Vermont Oxford Network

WCC – White Cell Count

WHO – World Health Organisation

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Antibiotics play a major role in the management of sepsis in neonatal units worldwide, and are the most commonly used medications in newborns, especially within the first 3 days of life (1). Neonatal sepsis can be defined as "a clinical syndrome characterized by systemic signs and symptoms of infection and bacteraemia during the first month of life" (2). It is the third leading cause of neonatal deaths globally, especially among the Very Low Birth Weight (VLBW) infants (3) and is known to cause about a million neonatal deaths worldwide annually (4).

Neonates especially the VLBW infants, are more prone to infections due to their low immunity, and the many invasive procedures they undergo in the nursery / Neonatal Intensive Care Unit (NICU) (5).

The National Institute of Child Health and Human Development (NICHHD) and the Vermont Oxford Network (VON) define Early Onset Sepsis (EOS) as the onset of signs accompanied by a positive culture within the first 72 hours of life, whilst Late Onset Sepsis (LOS) is characterized by the presence of signs and a positive culture after 72 hours of life (6).

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis – 3) recently updated the definition of sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection" (7).

"Suspected / Presumed Sepsis" is a common diagnosis in the neonatal unit. This typically refers to the presence of risk factors for neonatal sepsis in the history and or clinical signs that could be due to neonatal sepsis. There is usually the absence of a positive culture (8).

Early Onset Neonatal Sepsis

EOS is typically caused by organisms transmitted vertically from the mother either in utero or during delivery. The diagnosis of EOS can be especially challenging since the signs are nonspecific and can easily be confused with any of the other multiple non-infectious conditions in the newborn that present like sepsis. Hence empiric treatment of EOS is often dependent more on perinatal risk factors than signs (3). Several factors have been associated with the development of EOS. These include maternal colonization with GBS, previous sibling with a GBS infection, maternal chorioamnionitis, prematurity, black race, and vaginal delivery (9–11). A study done in South Africa found preterm delivery, VLBW, first birth and meconium stained amniotic fluid to be risk factors for EOS (12).

Typical organisms associated with EOS are usually from the maternal vaginal flora (13). Group B Streptococcus (GBS) is still one of the leading causes of EOS worldwide, even though the institution of the Intrapartum Antibiotic Prophylaxis (IAP) has seen a remarkable drop in its incidence (14,15). Weston et al found Escherichia coli (E. coli) to be the second most common pathogen after GBS causing EOS, and the commonest cause of mortality (9). However, Stoll et al found E. coli to be more common in VLBW infants than GBS (16). The causative pathogens however continue to change with time (17). Klebsiella spp., Enterococcus spp., H influenzae, L. monocytogenes, and S. aureus are also possible causative organisms of EOS (18).

The rate of EOS has risen from 2.4% to 3.3% within a 4 year period from 2012 to 2015 across the Vermont Oxford Network of neonatal units, though a drop in rate from 2.5% to 1.5% was recorded at Groote Schuur Hospital (GSH), a tertiary hospital with a level III NICU in South Africa over the same period of time (19).

Late Onset Neonatal Sepsis

Improved neonatal care and the increase in the survival of premature infants, especially among the VLBW category, have resulted in an increase in the incidence of LOS in the past decade (17). LOS is usually acquired from the care-giving environment of the infant. Preterm infants / VLBW infants are more prone to LOS due to their immature immune systems, and common risk factors include mechanical ventilation, invasive procedures and prolonged hospitalization (20).

The lower the gestational age and the birth weight, the higher the risk of LOS. Other factors associated with an increased risk of LOS include Necrotizing Enterocolitis (NEC), Patent Ductus Arteriosus, Bronchopulmonary Dysplasia (BPD) (21), and Meconium stained amniotic fluid (12).

The NICHHD Neonatal Research Network found that about 70% of all organisms causing LOS were Gram positive; with coagulase negative Staphylococcus (CoNS) contributing almost 50% of infections. S. aureus and GBS were also identified. Gram negative organisms and fungi contributed 18% and 12% of infections respectively. E. coli, Klebsiella, Pseudomonas and Serratia were the common Gram negative organisms whereas Candida albicans was the most frequently isolated fungus (21).

Data collected by VON shows that the rate of LOS between 2012 and 2015 did not change much from 12.6% to 12.7% among the VON networks, whereas GSH Neonatal unit in South Africa recorded a drop from 10.4% to 7.8% within the same period of time (19).

Antibiotic Use in the NICU

The significant morbidity and mortality associated with Neonatal Sepsis, coupled with the vague and protean signs and symptoms, tends to justify the liberal use of empiric antibiotics, especially in EOS (20,21). The choice of antibiotics is dependent on the prevalent organisms and their susceptibility patterns in that particular environment (1). In the past 10 – 15 years, the incidence of culture-proven EOS has been low, especially after the introduction of IAP for GBS (22,23). Despite this, most high risk infants are still put on antibiotics on account of the dire consequences should the diagnosis be “missed” (24). One study identified 63% of all neonates receiving antibiotics for up to 48 hours, and 26% on antibiotics for 5 days or more despite both groups having negative cultures (25). Schulman et al found a 40 – fold variation in the prescribing of antibiotics across 127 NICUs in California (26). Spitzer et al revealed a “great deal of variation among neonatologists” in the management of suspected neonatal sepsis among term infants, with 17% and 12% of neonates receiving antibiotics for 4 – 6 days and 7 – 10 days respectively even though none of them had a positive culture (27). A point prevalence study done in 29 NICUs revealed almost 44% of all patients receiving antibiotics at the time, and on a median number of 2 antimicrobials at a time (28). The Centers for Disease Control and Prevention reported that about 50% of all prescribed antibiotics were either unnecessary or ineffective, with about 23000 people dying yearly in the United States alone from Antibiotic resistant infections (29). Despite the fact that antibiotics play a phenomenal role in NICUs worldwide, its use and misuse in neonates, especially in the VLBW infants could be associated with adverse effects, like increased incidence of NEC, chronic lung disease, LOS, invasive candidiasis and death (30–33). Another major concern associated with the use of antibiotics is the development of antibiotic resistant infections, especially in a group as vulnerable as newborns. India is facing such a burden where about 58,000 infants are said to have died due to antibiotic resistant infections in 2013 (34). Studies have revealed strong associations between antibiotic use and the development of not only short-term complications like NEC and nosocomial infections, but childhood obesity and wheezing conditions later in life (34,35). Clark et al found an increased risk of neonatal mortality associated with the use of Cefotaxime

(1). A Canadian study found that among VLBW infants without NEC or culture-proven sepsis, higher antibiotic use rates were associated with increased risks of chronic lung disease, periventricular leukomalacia and retinopathy of prematurity (36).

Blood cultures

Blood culture (or the culture of another body fluid like cerebrospinal fluid) is the gold standard (37) for diagnosing sepsis in neonates.

One major drawback with blood cultures is the time to positivity since this influences the duration of antibiotics in the event of a negative result. A 4 month prospective study comparing conventional neonatal blood culture with 16S rRNA PCR found that the diagnosis of sepsis by PCR provided a 100% sensitivity, 95.4% specificity, 77.2% positive predictive value and 100% negative predictive value (38). One study identified that improved technology integrated into automated blood culture systems could shorten time to positivity. The study revealed that 77%, 89% and 94% of all microorganisms could be identified at 24, 36 and 48 hours of incubation in aerobic cultures respectively (39). The current recommendation is that empirical antibiotics be stopped within 36 - 48 hours as soon as blood culture results are confirmed to be negative and the baby is showing no clinical features of sepsis. Sivanandan et al identified about 50% of all Extremely Low Birth Weight (ELBW) infants received more than 5 days of antibiotics in spite of negative blood culture results within the first 48 hours (24). However, in EOS, the interpretation of a negative blood culture result is dependent on several factors; such as, the adequacy of the amount of blood used for the culturing, the previous use of antibiotics by the mother in the intrapartum period, or previous exposure to antibiotics by the neonate and whether the organism grows in that particular culture medium, among other factors (37,40).

The dependence of blood cultures on the volume of blood required is a major challenge. Getting at least 1ml of blood for culture, especially in the preterm infants, which is the recommended volume in order to increase the likelihood of microorganism recovery (41), can be difficult in the neonatal setting. Studies confirm that 1 out every 4 cases of neonatal sepsis have 4 or less colony forming units/ml making it difficult for the organism to be isolated in culture, especially if the sample is less than 1ml (41,42). Most blood samples are commonly taken from peripheral veins, though it could also be taken from heel pricks, arteries and central veins (43). There is not much published data on the use of the umbilical cord for the collection of blood for culture in EOS. However this method potentially has several advantages; the procedure would enable an adequate volume of blood to be taken with ease, and it would be painless for the newborn. There is however a higher risk of contamination if not done under extremely sterile conditions (44,45). Another challenge with blood cultures is whether or not certain microorganisms should be considered as contaminants or pathogens. One such microorganism is CoNS, which was initially considered to be a contaminant but seems to be fast gaining grounds as a pathogen in recent years. Bodonaik and Moonah found in their study that, of the 60 patients with CoNS isolated in their blood 5 (8.3%) out of these patients had the CoNS being considered as actual pathogens (46).

Simple methods like strict hand washing, simple educational tools and the use of a clinical performance dashboard indicator have been proven to significantly reduce not only the incidence of neonatal sepsis, but the rates of contaminations in blood cultures (47).

Biomarkers for Sepsis

Even though blood culture remains the gold standard in the diagnosis of neonatal sepsis (6), other laboratory sepsis markers are steadily gaining grounds alongside culture results, and many of these markers have and are still being extensively studied. An ideal septic marker, especially in neonates should require only a small volume of blood for testing, a short laboratory feedback time, and have a very high sensitivity as well as a high negative predictive value. This enables the marker to be able to identify all the ill ones and sufficiently rule out the non-ill ones respectively (48,49).

Haematological indices like White Cell Count (WCC), Platelets, and Immature to Total (IT) Neutrophil ratio were initially relied upon, but in recent years, the Acute Phase Proteins (APP) like C – Reactive Protein (CRP) and Procalcitonin, are fast becoming popular among clinicians. One study found the total WCC was found to have a poor positive predictive value for neonatal sepsis. Even though neutropenia was found to have a better specificity for neonatal sepsis than an elevated neutrophil count, the IT neutrophil was adjudged to have the best sensitivity among all the neutrophil indices. A single IT ratio measurement was found to have a 99% negative predictive value, however, the value was also found to rise in almost 50% in uninfected infants (8). WCC, platelets and neutrophils were found to have high specificity for EOS but not sensitive enough to adequately rule out EOS in the neonate. High and low WCC, high absolute neutrophil counts, low platelets and high IT ratios have also been found to be associated more with LOS than EOS (50).

Currently some of the most promising neonatal sepsis markers include CRP, Tumor Necrosis Factor α, Interleukins 6 & 8, and Procalcitonin (37).

APPs are usually produced by the liver immediately in reaction to an inflammatory process caused by an injury or an infection. The CRP has been found to be part of a humoral response to an infection, rising by 6 – 8 hours, and peaking by 24 hours following the onset of the infection (6). CRP was found to perform better in LOS compared to EOS, especially when serial measurements are taken (51). Most clinicians are now adopting the practice of monitoring the trends of these APPs, especially the CRP, to make the decision of whether or not to discontinue antibiotics after 48 – 72 hours of antibiotics. Unfortunately, in situations where the CRP values are consistently > 1.0mg /dl, there is not enough data to conclude on the duration the antibiotics should be given for (52). A recent study looked at the roles of CRP and the Complete Blood Count (CBC) in LOS. A combination of the CBC at the time of the first blood culture, and the CRP at 24 hours provided a sensitivity of 88% and a negative predictive value of 93% (53). Even though Procalcitonin has been found to be more sensitive than CRP, it has less specificity in identifying neonates with sepsis, and it also tends to be elevated even in conditions with non-infectious etiologies like respiratory distress syndrome and immediately after delivery (54). Despite this, there is still controversy as to which is better, CRP or Procalcitonin in the aiding of diagnosis of neonatal sepsis (55,56)

Antibiotic Stewardship in the NICU

Antibiotic stewardship refers to interventions put in place to improve and promote the appropriate selection, dose, route of administration, and duration of antibiotic therapy. The aims are to improve quality of patient care, promote cost effectiveness, and to help curb the level of antibiotic resistance (57,58). So far there is no consensus on the best means of antibiotic use even though a lot of programs have been researched and put in place. The only programs that seem to have produced some kind of significant improvement in the use of antibiotics are those that focus on the prudent use of antibiotics in the hospital setting (59). A guideline published by the Infectious Diseases Society of America (IDSA) in 2007 categorizes Antibiotic Stewardship Programs (ASP) into two main broad categories, the Prospective Audit with feedback Strategy and the Prior Approval Strategy. The Prospective audit strategy requires the ASP team to review the use of selected antibiotics at a predetermined time and give feedback to clinicians as to whether to continue after the set time, or to stop. The Prior

Approval strategy requires the clinical team to gain approval from the ASP team before initiating antibiotics (60). Provision of guidelines, frequent training and education of staff, dose optimization and conversion of parenteral to oral antibiotics also serve as additional strategies (60,61). The general recommendation is that a combination of these strategies increases the chances of improving antibiotic use in the hospital setting as opposed to the use of single strategy approaches (62). Several studies have revealed the positive impact ASPs have had on the use of antibiotics in the hospital setting, but setting up of ASPs comes with their own challenges. A survey done among Infectious Disease specialists in North America found that only about a third had managed to set up an ASP in their hospitals, with 18% still in the planning stages (63).

However, with the signs of neonatal sepsis being so non-specific and similar to other common non – infectious neonatal conditions (20), it is often difficult for the clinician to strictly adhere to the prevailing antibiotic guidelines. This serves as a major challenge for antibiotic stewardship programs in the neonatal setting.

The Surveillance and Correction of Unnecessary Antibiotic Therapy (SCOUT) study revealed that when appropriate quality improvement processes are put in place, antibiotic use can be reduced significantly in the NICU. In this instance, the study reported a reduction of 27% in the use of antibiotics in the NICU. This was after employing an electronic "hard stop" on empirical antimicrobial therapy after 48 hours (25). The "hard stop" ensured that it would be impossible for the Clinician to extend the duration of antibiotics beyond the 48 hour set time without justifying the need.

Many attempts have been made towards the establishment of risk scores and systems to enable the clinician readily identify those who need antibiotics and safely exclude those who do not. But so far, no system is sufficiently sensitive and specific enough for use in the neonate (40). The EOS algorithm based on the CDC 2010 GBS guidelines however has produced some promising results, as Mukhopadhyay et al managed to show a 25% reduction in EOS evaluations among infants of 36 weeks gestation or more (64).

This study seeks to describe the current practices and management of neonatal sepsis including antibiotic use in a level III Neonatal unit.

Specific objectives

- To investigate which antibiotics are being used, their duration of use and determine if the GSH Neonatal Unit protocols are being followed
- To identify the pathogens causing sepsis and to determine if the GSH antibiotic protocol is appropriate for these organisms and describe the clinical signs and laboratory values of the babies with sepsis
- To determine the incidence rates of EOS and LOS in the unit

CHAPTER 2: METHODS

The study was conducted at the Groote Schuur Hospital (GSH) Neonatal Unit. The GSH has a level III Neonatal Unit located in Cape Town, South Africa, one of 2 centers in the Western Cape Province that provides tertiary neonatal services. It serves as both an emergency and continuous care setting for babies. Babies admitted there are mostly from the GSH Obstetrics Department, as well as referrals from surrounding hospitals in the province. On the average, the unit has about 2000 admissions per year, with more than 500 of them belonging to the VLBW category.

The Antibiotic policy for the Unit is as follows:

EOS: Gentamycin and Penicillin G (or Ampicillin)

LOS: Meropenem.

Vancomycin is added if baby has or has had a central line in situ.

Antibiotics to be stopped after 36 – 48 hours if the baby is no longer exhibiting clinical features of sepsis, there are negative cultures and laboratory values are within normal range. CRP is the most commonly used sepsis biomarker in determining the duration of antibiotics, in addition to the blood culture. The cut off value is 10mg/dl.

If a positive culture is obtained antibiotics are changed or downscaled appropriately in line with the sensitivity pattern.

To investigate antibiotic use and sepsis rates in the Unit, 3 sub studies were performed:

1. Blood culture database: All babies who were admitted at the GSH neonatal unit from 1st January 2016 to 31st December 2016 and had a blood culture done were entered in a Database. Data on all blood cultures done were correlated with that from the National Health Laboratory System (NHLS). All positive cultures were followed up, the babies' folders drawn, information such as clinical signs as well as what antibiotics were given and their duration extracted. Babies were followed up until discharge from the unit or transferred to a step down facility. This was a retrospective folder review.

The incidence rates for VLBW infants were obtained from the VON database; Sepsis incidence rates for bigger babies (> 1500g) and for the overall number of babies were calculated using admission data for the unit.

2. Antibiotic usage database: The month of February 2016 was randomly chosen and data was collected on all babies admitted to the GSH neonatal unit who were started on antibiotics. Data was collected on daily basis including weekends and was then entered into a database. Information collected included any antenatal septic risk factors that the mother might have had, signs of sepsis in the baby, what antimicrobial agents were started and their duration, what cultures were done and isolated pathogens if any. The data was collected prospectively from the baby's folder. This was a nested study from the Blood culture Database, since according to the unit's protocols; all babies who are put on antibiotics must have a blood culture done first.
3. VON Quality Audits: GSH participated in the "Vermont Oxford Network (VON) Day Quality Audits: Choosing Antibiotics Wisely" which took place on the 9th of February and 8th of November 2016 at GSH. Data was extracted from the VON Database as well as via folder reviews. VON is a collaborative international database incorporating demographic and admission data from over a thousand neonatal units around the world. GSH is one of the contributing neonatal units. Data on all VLBW infants admitted to the unit are entered into the VON database all year round. Data entered include the gestational age, birthweight, clinical features and diagnoses, duration of hospitalization and outcome. For the audits, the folders of all babies in the unit regardless of birthweight who were on antibiotics were identified. A questionnaire was used to collect the data which included gestational age and birth weight, respiratory support required, indication for initiating antibiotics including antenatal risk factors, reasons why babies received more than 48 hours of antibiotics, and what cultures were done and what isolates were obtained. Data from the unit was compared to information from the over 1000 centers also participating. This was a point prevalence study.

Eligibility Criteria

Inclusion criteria

- All babies admitted to the GSH neonatal unit who had a positive blood culture in 2016
- All babies at GSH in the month of February and on the 8^{th} of November 2016 who received intravenous antibiotics

Exclusion criteria

- Babies whose folders could not be traced or had insufficient data
- Babies whose parents refused consent to partake in the study

Data Analysis

Data was extracted from patients' folders and entered into a database in Microsoft Access. The data was exported to STATA/MP 13.0 (StataCorp. 4905 Lakeway Drive Station, Texas 77845, USA) for analysis. Descriptive statistics determining percentages for categorical variables and summary statistics for continuous variables were done. The results were presented in the form of tables and charts.

Data retrieved from the VON database had already been analysed by the VON team.

Ethics

Ethical clearance to keep databases for the antibiotic usage and blood culture audits (HREC R002/2016) and the VON database (HREC R040/2013) were obtained from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town.

Confidentiality

All identifying markers were removed from the database. All the data was stored on a password protected computer. All hard copies were stored in a filing cabinet in a locked room.

Consent

For the VON quality audits, verbal consent was taken from the parents.

As the folder review was retrospective in nature and did not pose any risks to the patients or their parents, consent was not required.

CHAPTER 3: RESULTS

Sub study I: Blood Culture database

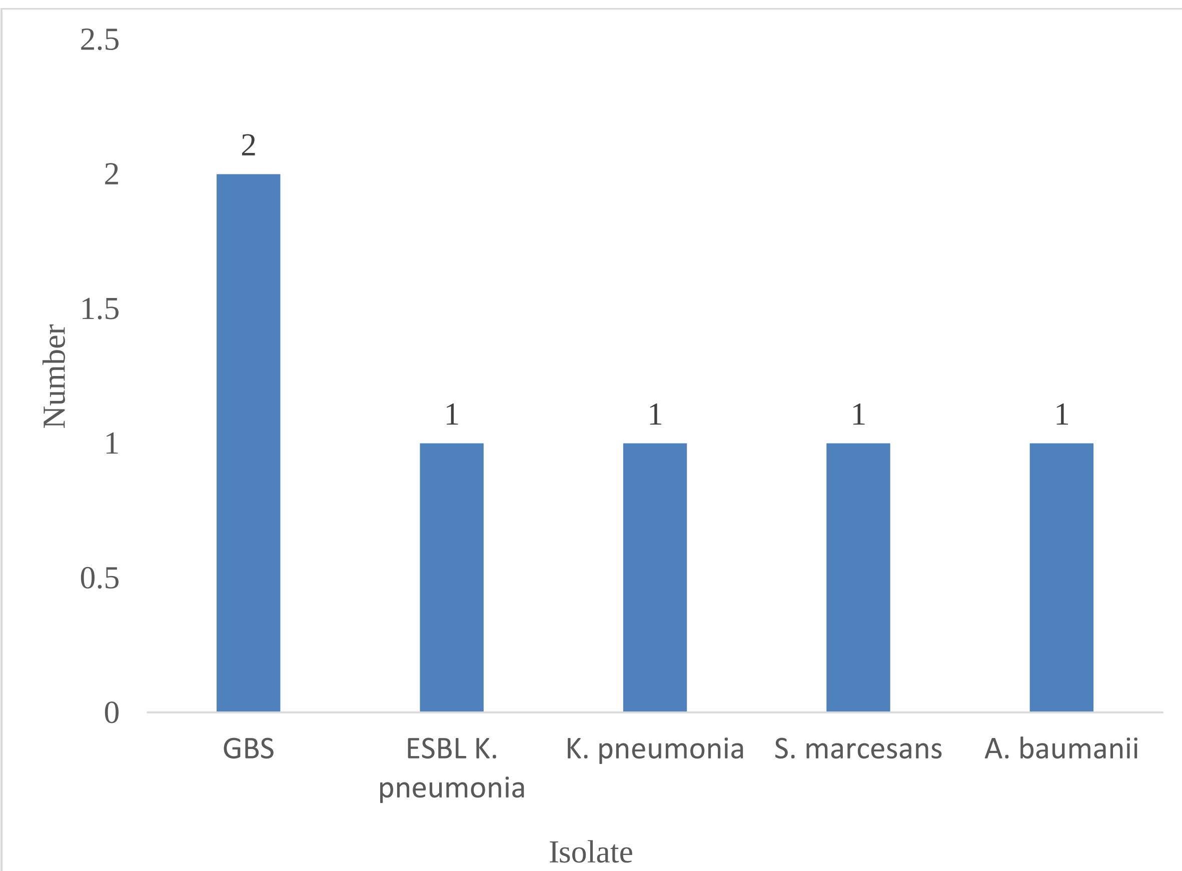
There were a total of 2031 admissions at GSH in the year 2016, including 493 VLBW infants with the remaining 1538 being bigger babies (> 1500g). 43 babies had positive blood cultures from a total of 874 blood cultures. Of the 43 babies with the positive blood culture isolates, 32 were VLBW infants with the remaining 11 being bigger babies.

There were incomplete data for 2 babies and a missing folder for 1 baby. This left a total of 40 babies for the blood culture audit.

Early Onset Sepsis

There were 11 babies who had positive blood cultures, with one baby growing more than one organism in the blood, making a total of 12 isolates. Out of the 12 isolates, 6 were considered to be contaminants, and these were CoNS (4), Bacillus species (1), and S. warneri (1). This left 6 babies for the study.

Figure 1: Isolates for positive blood cultures < 72 hours



5 (83.3%) out of the 6 confirmed EOS had antenatal risk factors with Spontaneous Preterm Labour (SPTL) being the most common. (Table 1) The 6th baby developed signs of sepsis within 24 hours of birth.

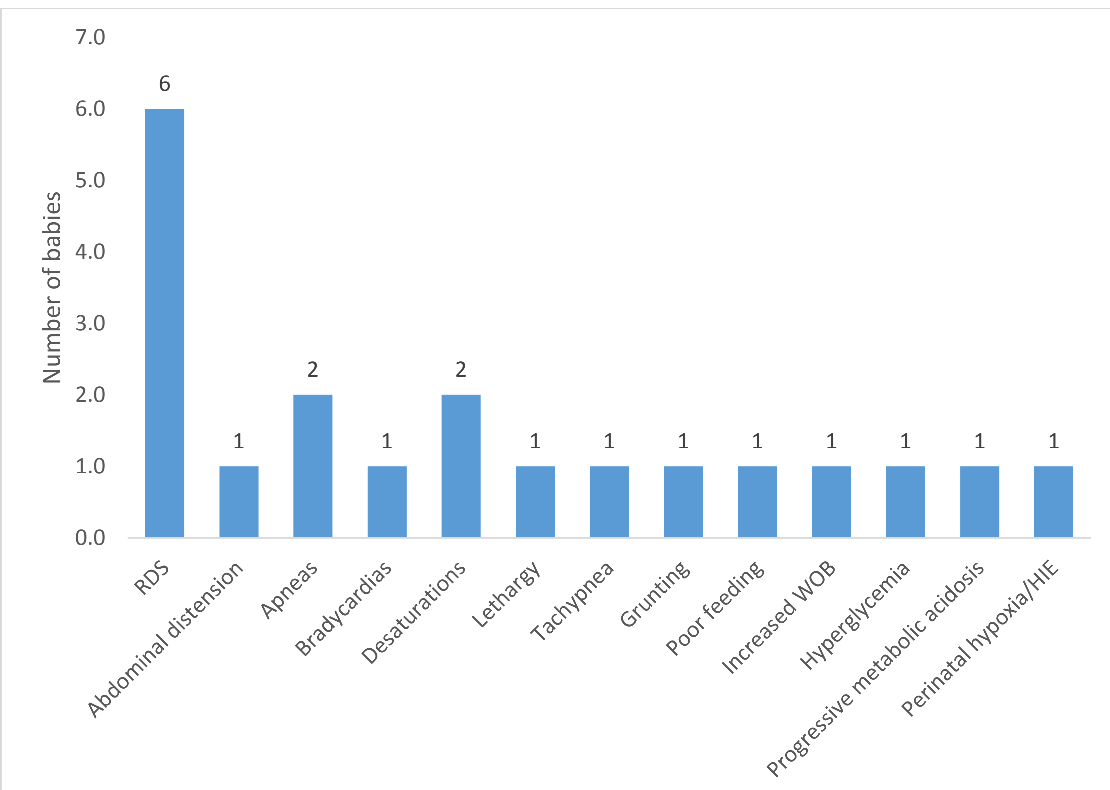
Maternal Chorioamnionitis, maternal fever and Preterm Premature Rupture of Membranes (PPROM) were absent

Table 1: Antenatal Risk factors

Antenatal Risk factors	**Number (%)**
SPTL	4(66.7)
Maternal UTI	1(16.7)
None	1(16.7)

The leading clinical features for EOS were RDS, apneas and desaturations. (Figure 2)

Figure 2: Signs of EOS



*WOB - Amount of effort used to expand the lungs

5 (83.3%) out of the 6 EOS cases had a CRP done, and 3 (50%) each had a Lumbar puncture and a Complete Blood Count (CBC) done. (Table 2) All CSF results were normal. All 3 CBCs had low white cell counts. Only 3 of them had all 3 investigations done.

Table 2: Additional Sepsis Biomarkers for EOS

Variable	**Number**	**Total**
CRP	5	6
CSF	3	6
CBC	3	6

5 babies had CRPs done before initiation of antibiotics, with 4(80%) out of the 5 having CRPs $\geq$10g/dl. The CRPs ranged from <1mg/dl (A. baumanii) to101mg/dl (GBS). 50% of the babies with confirmed EOS died including the baby who did not have a CRP done. (Table 3) Not all deaths were primarily due to the EOS.

Table 3: Isolated Pathogens for EOS and CRP values

Pathogens	CRP at initiation of antibiotics	Outcome
GBS	101	Discharge
GBS	31	Discharge
K. pneumonia	36	Death
ESBL Klebsiella	10	Death
A. baumanii	<1	Discharge
S. marcesans	Not done	Death

5(83.3%) out of the 6 babies with confirmed EOS received Ampicillin – Gentamycin. (Table 4) Reason for 1 baby receiving Ampicillin only is not clear.

Table 4: Antibiotics for EOS

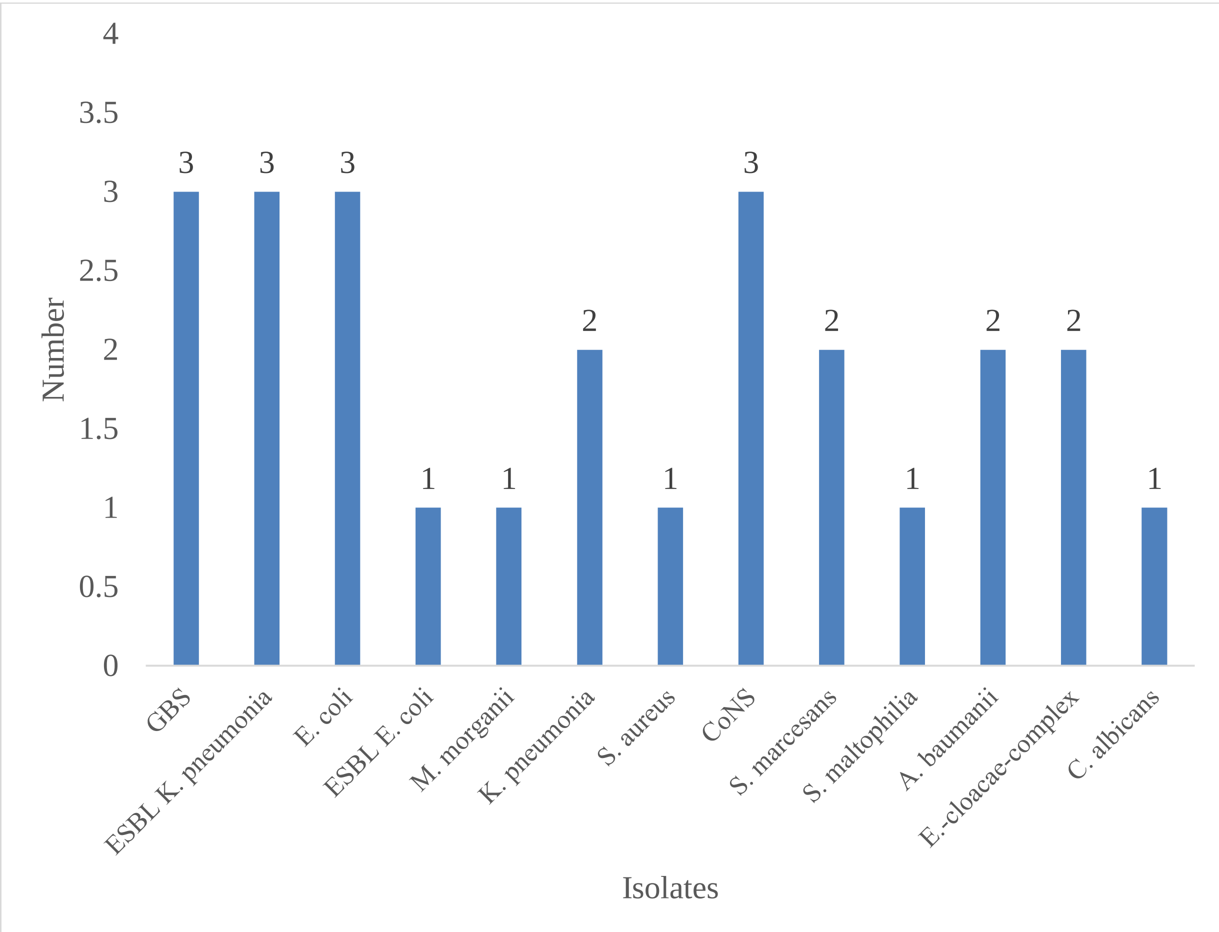
Antibiotic (n = 6)	Number
Ampicillin – Gentamycin	5
Ampicillin Only	1

Late Onset Sepsis

There were a total of 29 cases of positive blood cultures among 29 babies.

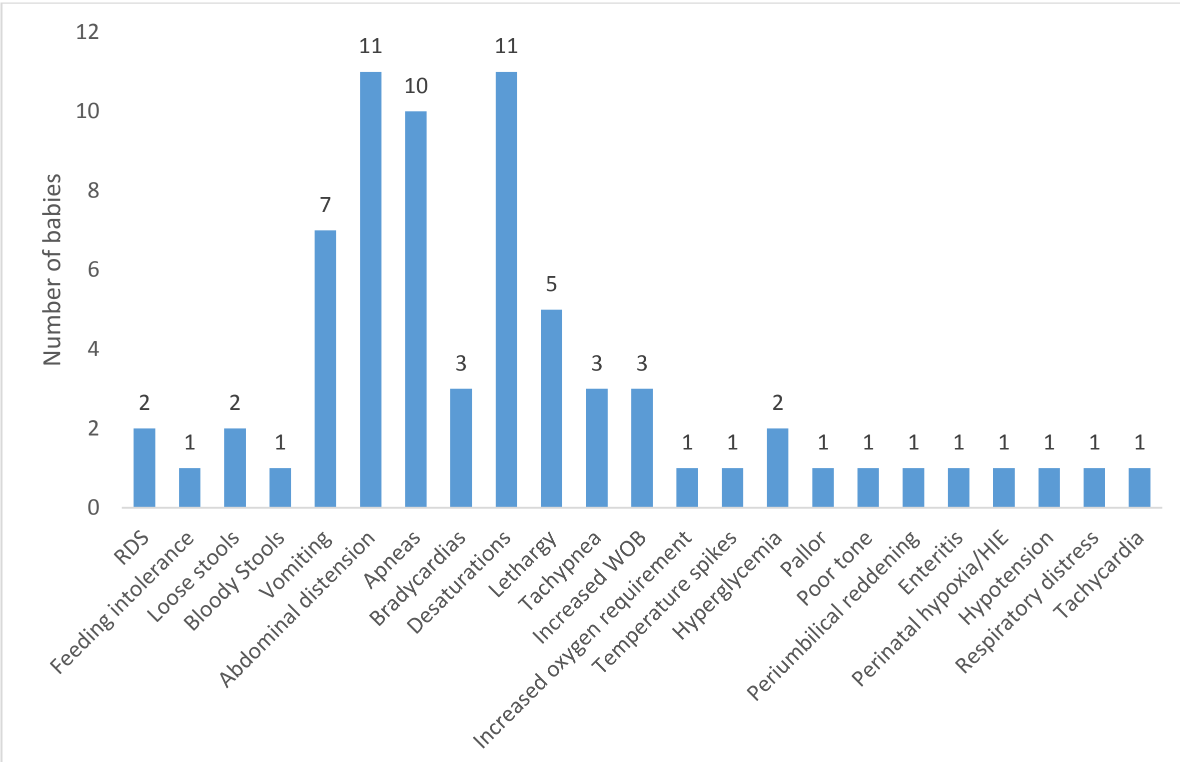
K. pneumonia (including ESBL), E. coli (including ESBL), CoNS and GBS were the most common pathogens isolated for LOS at GSH. (Figure 3) Bacillus species and C. indologenes were considered to be contaminants, on account of their low CRPs and stable clinical states. Of the 5 CoNS infections, 3 were considered pathogens due to their deteriorating clinical condition and high CRP values. This left a total of 25 babies.

Figure 3: Isolates for positive blood cultures > 72 hours



Abdominal distension, desaturation, apneas and vomiting were the top clinical features in LOS. (Figure 4)

Figure 4: Signs of LOS



23 babies out of the 25 with confirmed LOS had CRPs done, 9 and 21 had Lumbar punctures and CBCs done respectively. (Table 5) 8 of them had all 3 investigations done.

Table 5: Additional Sepsis Biomarkers for LOS

Variable	Number
CRP	23
CSF	9
CBC	21

The CRP values ranged from 0 to 126mg/dl. (Table 6) Out of the 25 babies with positive cultures, there were 7(28%) deaths. Not all deaths were primarily due to the LOS.

Table 6: Isolated Pathogens for LOS and CRP values

Pathogen	CRP at initiation of antibiotics	Outcome
GBS	28	Discharge
GBS	0	Discharge
GBS	1	Discharge
ESBL Klebsiella	46	Discharge
ESBL Klebsiella*	2	Discharge
ESBL Klebsiella	21	Death
K. pneumoniae	22	Death
K. pneumoniae	23	Death
ESBL E. coli	0	Death
E. coli	2	Discharge
E. coli	122	Discharge
E. coli	0	Death
S. maltophilia	23	Discharge
S. marcesans	9	Discharge
S. marcesans	111	Death
A. baumanii	9	Discharge
A. baumanii	126	Death
E. cloacae complex	12	Discharge
E. cloacae complex	91	Discharge
M. morganii	2	Discharge
CoNS	29	Discharge
CoNS	86	Discharge
CoNS	0	Discharge
C. Albicans*	2	Discharge

25 babies were managed for LOS. All babies with LOS received Meropenem; making it the most commonly used antibiotic for LOS. (Table 7) Some babies received a combination of medications. *C. albicans was isolated in a baby that had ESBL K. pneumonia and baby was placed on Fluconazole. (Table 6)

Table 7: Antibiotics for LOS

Antibiotic (n = 25)	**Number**
Meropenem	25
Vancomycin	2
Ampicillin	1
Ciprofloxacin	1
Cefotaxime	1
Cefepime	1
Fluconazole	1

Sepsis Incidence rates for VLBW and Bigger infants

Out of the 2031 total admissions at GSH in 2016, 493 were VLBW infants. The total number of positive cultures was 40, including 10 contaminants. Of the 30 true pathogens, 8 were isolated from babies bigger than 1500g.

This put the incidence of sepsis among babies weighing greater than 1500g at GSH at 0.52%.

The overall sepsis at GSH rate was 1.5%.

The rates for EOS and LOS among VLBW infants are displayed below.

There were 5 VLBW babies with confirmed EOS, with an overall EOS rate of 1.0% Out of these, 3 belonged to the 27 – 29 gestational age category. The global VON rate for EOS was 2.4%, with the highest EOS rate among infants < 24 weeks gestation. (Table 8)

Table 8: EOS among the VLBW infants for 2016

GSH (1052) and Network Values
Infection-All VLBW Infants

	GSH (2016)			Network (2016)	
GA Category	Cases	N	%	N	%
<24 Weeks	0	1	0.0%	2,872	4.9%
24-26 Weeks	1	58	1.7%	14,287	3.8%
27-29 Weeks	3	218	1.4%	23,014	2.1%
30-32 Weeks	1	159	0.6%	16,284	1.5%
>32 Weeks	0	51	0.0%	4,871	1.2%
All	5	487	1.0%	61,235	2.4%

There were 23 VLBW babies with confirmed LOS, making a rate of 5.2% at GSH. 47.8% belonged to the 27 – 29 gestational age group. The rates reduced with gestational age both at GSH and in the global VON survey which revealed a total rate of 12.1%. (Table 9)

Table 9: LOS among the VLBW infants for 2016

GSH (1052) and Network Values
Infection-All VLBW Infants

	GSH (2016)			Network (2016)	
GA Category	Cases	N	%	N	%
<24 Weeks	0	0		2,241	35.6%
24-26 Weeks	4	32	12.5%	13,145	23.8%
27-29 Weeks	11	203	5.4%	22,416	10.0%
30-32 Weeks	7	154	4.5%	16,047	4.9%
>32 Weeks	1	50	2.0%	4,766	3.4%
All	23	439	5.2%	58,615	12.1%

Sub study II: Antibiotic Usage audit

During the month of February 2016, a total of 44 babies received antibiotics out of 148 total number of admissions. Data for this audit was retrieved from the babies' folders. 4 of the folders could not be traced, leaving a total of 40 for the audit.

There were a total of 41 cases of suspected sepsis among 40 babies; 30 cases of presumed EOS, 11 presumed LOS with 1 baby having more than one episode of suspected LOS.

E. coli was the only pathogen isolated from one baby for suspected EOS during the audit. CoNS and 2 Bacillus spp were isolated from 3 babies and considered as contaminants.

Suspected EOS

28 babies had antenatal risk factors out of the total of 30 who had suspected EOS. SPTL (64.3%) and PPROM (21.4%) and were the commonest antenatal risk factors. (Table 10) The baby with confirmed E. coli EOS had SPTL as an antenatal risk factor.

Table 10: Antenatal risk factors for suspected EOS

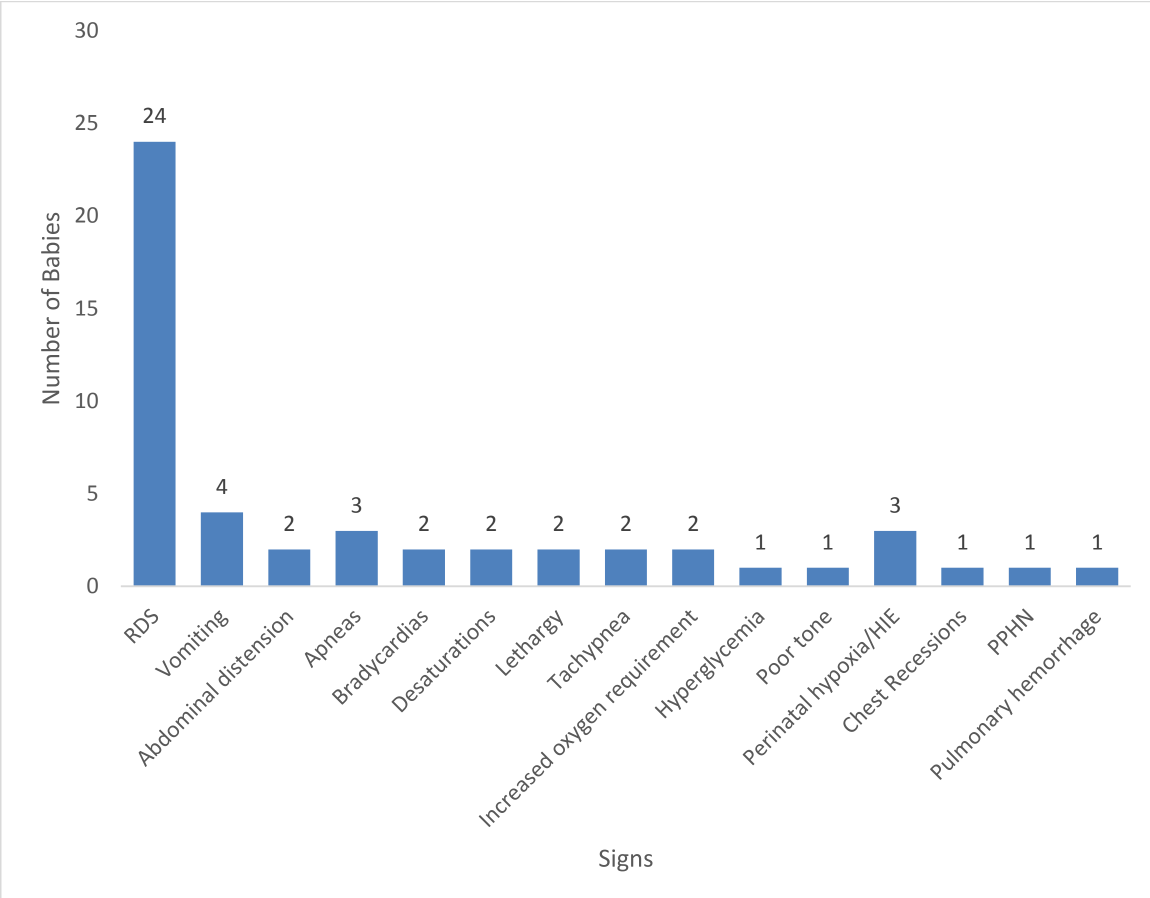
Antenatal risk factors	Number (%)
SPTL	18(64.3)
PPROM	6(21.4)
Maternal UTI**	1(3.6)
BBA*	2(7.1)
Chorioamnionitis	1(3.6)

*Born Before Arrival

**Urinary Tract Infection

The commonest clinical features for suspected EOS were RDS, and vomiting (Figure 5), though there many overlapping clinical features.

Figure 5: Signs of suspected EOS



16 (53.3%) out of the 30 babies with suspected EOS received Ampicillin - Gentamycin for >48 hours. (Table 11) Baby with confirmed E. coli EOS and the 2 babies with the contaminants isolated all received antibiotics for more than 72 hours.

Table 11: Duration of Antibiotics for suspected EOS

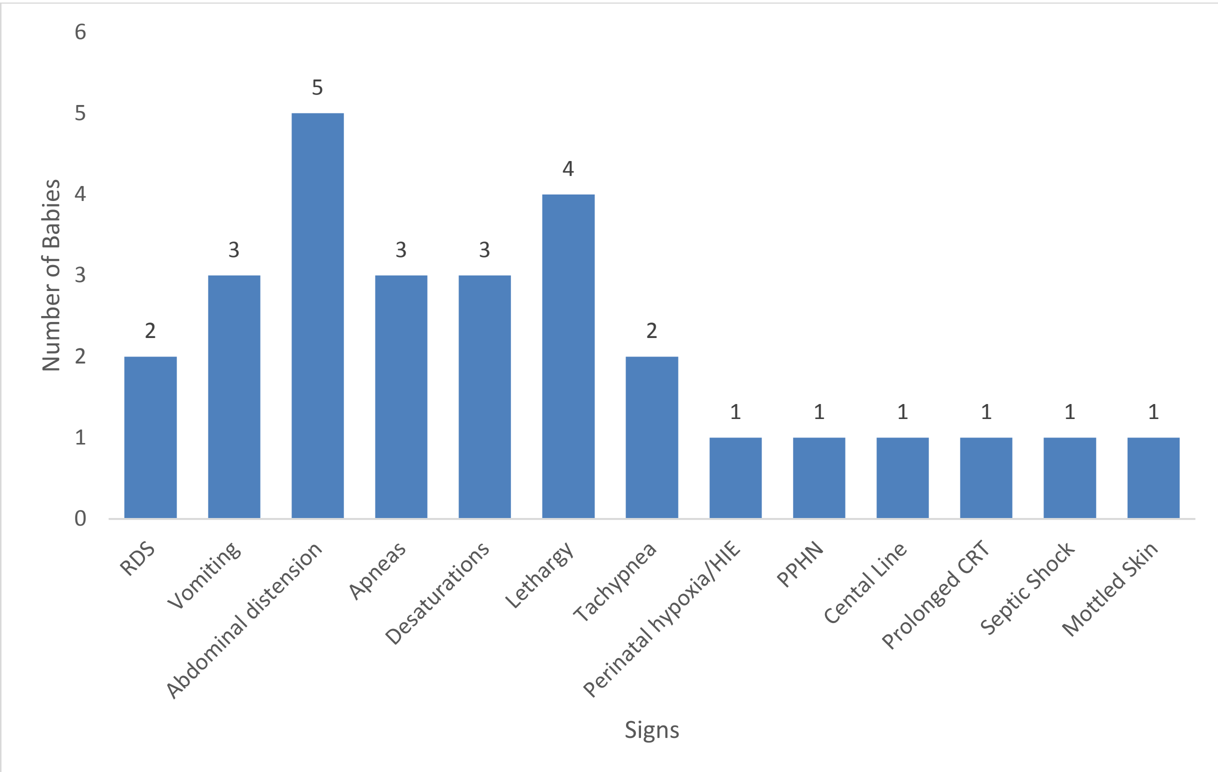
	Duration			
Antibiotics	≤ 48 hours	> 48 – 72 hours	>72 hours	Total
Ampicillin - Gentamycin	14	10	6	30

Suspected LOS:

10 babies received antibiotics for suspected LOS with 1 baby treated twice. ESBL K. pneumonia and M. morganii were the pathogens isolated from 2 different babies during the antibiotic usage audit for LOS. Bacillus species was the only contaminant identified from one baby.

Abdominal distension and lethargy were the commonest clinical features of suspected LOS. (Figure 6)

Figure 6: Signs of suspected LOS



There were 10 babies who received Meropenem in the antibiotic usage audit, though 1 of these babies received more than a single course of Meropenem making it a total of 11 courses. 7 (63.6%) of the 11 babies received antibiotics for > 48 hours. (Table 12) The babies with ESBL Klebsiella, Bacillus species and M. morganii sepsis all received antibiotics for more than 48 hours each.

Table 12: Duration of Antibiotics for suspected LOS

	Duration			
Antibiotics	≤ 48 hours	> 48 – 72 hours	>72 hours	Total
Meropenem	4	3	4	11

Sub study III: VON Quality audits

The VON day quality audits were surveys done to look at antibiotic use at the GSH neonatal unit. These were done over 2 days: the 9th of February and the 8th of November 2016. The 10 month interval was to allow for educational interventions like webinars and to judge its impact. The folders of all babies who were on antibiotics on the said days were identified. This included those who were already on antibiotics and those who had been initiated on antibiotics that same day. It was a point prevalence survey. No parent denied consent.

For the purposes of the VON data, GSH Neonatal unit is referred to as Centre 1052

VON Day Quality Audit February 2016 (Audit 1)

11 babies in total were found to be on antibiotics during the 1st audit with 6 of them in the level II NICU, and the remaining scattered between the main NICU and the special care ward. 54.5% of the infants on antibiotics were VLBW infants, with 72.7% of the total number falling in the 31 - 36 week gestation bracket. The VON audit among the other units in the VON network however showed infections spread almost evenly across the < 31, 31 – 36, and > 36 weeks gestation categories (34.5%, 31.3% & 34.2% respectively). (Table 11)

45.5% of the infants who received antibiotics were between 4 to 28 days old, with 54.5% on nasal Continuous Positive Airway Pressure (CPAP) and 9.1% requiring respiratory support via high flow nasal cannula. 36.4% were not on any form of respiratory support, as opposed to the figure of 42.3% from the overall VON database but had almost a quarter (24.8%) of the babies receiving mechanical ventilation. (Table 13)

Table 13: Infant Demographics

VON Day Quality Audit - Choosing Antibiotics Wisely
Infant Demographics
133 NICUs Audited 725 Infants on Antibiotics
February 2016

	Center 1052			All		
	Yes	Patients	%	Yes	Patients	%
Birth weight						
<1501g	6	11	54.5	290	725	40.0
1501 to 2500g	4	11	36.4	156	725	21.5
>2500g	1	11	9.1	279	725	38.5
Gestational age						
<31 weeks	3	11	27.3	250	725	34.5
31 to 36 weeks	8	11	72.7	227	725	31.3
>36 weeks	0	11	0.0	248	725	34.2
Chronological age						
1 to 3 days	4	11	36.4	261	725	36.0
4 to 28 days	5	11	45.5	282	725	38.9
>28 days	2	11	18.2	182	725	25.1
Current respiratory support						
Assisted ventilation via endotracheal tube (HFV or CMV)	0	11	0.0	180	725	24.8
Nasal ventilation or Nasal CPAP	6	11	54.5	140	725	19.3
High Flow Nasal Cannula	1	11	9.1	73	725	10.1
Oxygen only	0	11	0.0	25	725	3.4
No support	4	11	36.4	307	725	42.3

The commonest reasons for starting antibiotics at GSH were maternal risk factors and suspected or proven early onset sepsis or meningitis, a profile similar to the total VON figures. Other common reasons among all the other units in the VON network were suspected or proven late onset sepsis or meningitis, prophylaxis for fungal sepsis and suspected or proven necrotizing enterocolitis. (Table 14)

Table 14: Indications for Initiation of Antibiotics

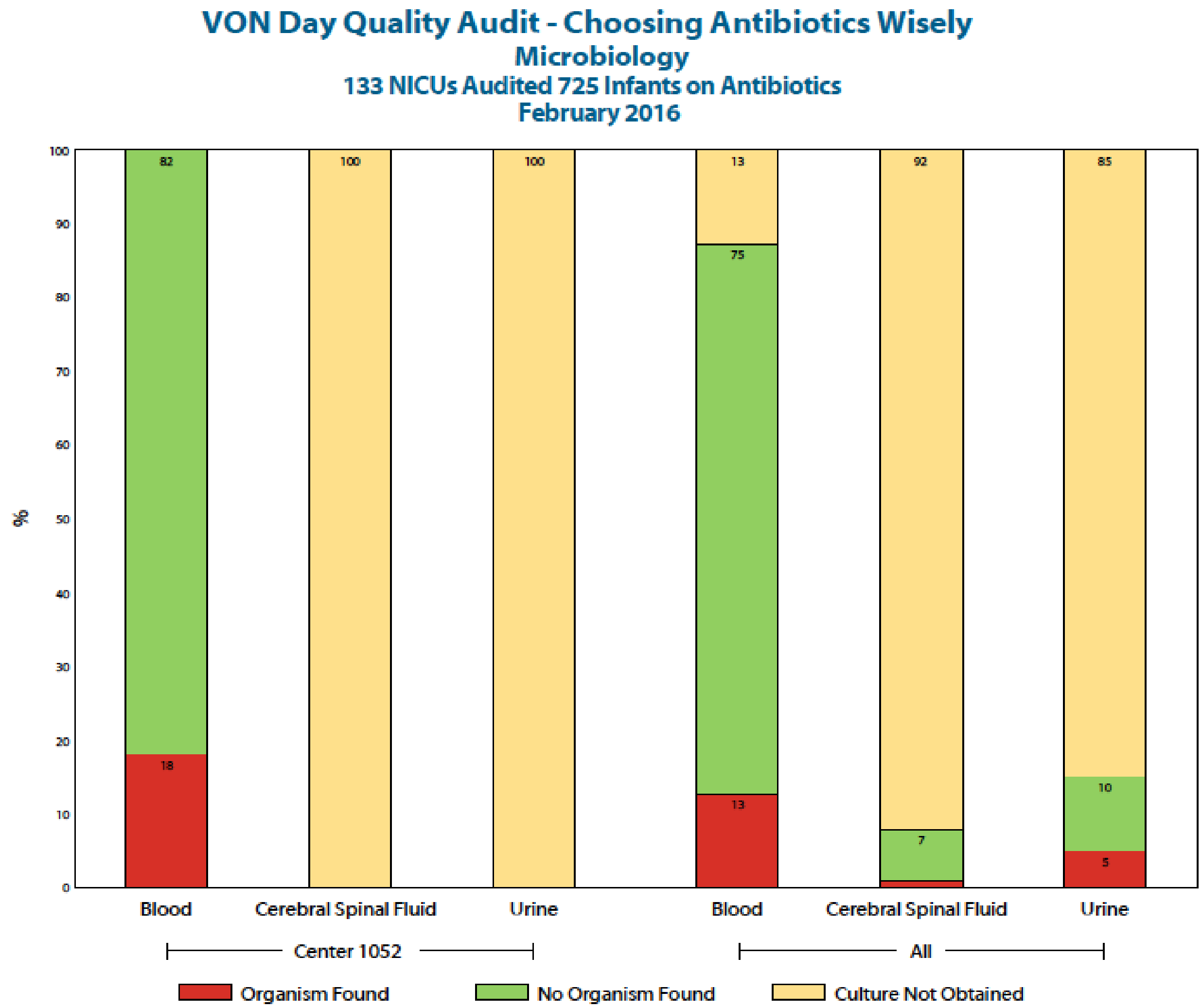
VON Day Quality Audit - Choosing Antibiotics Wisely
Indication(s) for Antibiotic Use
133 NICUs Audited 725 Infants on Antibiotics
February 2016

	Center 1052			All		
	Yes	Patients	%	Yes	Patients	%
What were the indications for starting the infant on antibiotic therapy?*						
Maternal risk factors	6	11	54.5	254	725	35.0
Suspected or proven early onset sepsis or meningitis	6	11	54.5	319	725	44.0
Suspected or proven late onset sepsis or meningitis	4	11	36.4	133	725	18.3
Suspected or proven ventilator associated pneumonia	0	11	0.0	22	725	3.0
Suspected or proven central venous line infection	0	11	0.0	27	725	3.7
Suspected or proven urinary tract infection	0	11	0.0	44	725	6.1
Suspected or proven necrotizing enterocolitis	0	11	0.0	51	725	7.0
Suspected or proven surgical site infection	0	11	0.0	18	725	2.5
Prophylaxis for urinary tract infection	0	11	0.0	29	725	4.0
Prophylaxis for surgery	0	11	0.0	30	725	4.1
Prophylaxis for fungal sepsis	0	11	0.0	55	725	7.6
Methicillin-resistant Staphylococcus aureus (MRSA) colonization	0	11	0.0	4	725	0.6
Other	0	11	0.0	114	725	15.7

At GSH, there was 18% positive blood cultures with no cultures obtained for urine and cerebrospinal fluid.

Positive cultures were 12%, 1% and 5% for Blood, CSF and Urine respectively among the other units in the VON network. (Figure 7)

Figure 7: Positive Bacterial cultures (Audit 1)



Commonest reasons for continued use of antibiotics for more than 48 hours at GSH were laboratory results concerning for risk of sepsis, and clinical signs concerning for risk of sepsis. In addition to these factors, VON also identified positive blood culture or culture from a normally sterile fluid, awaiting culture results, and central venous line or other device in place, as other common reasons for prolonged use of antibiotics among the other VON units. (Table 15)

Table 15: Reasons for > 48 hours of antibiotics

VON Day Quality Audit - Choosing Antibiotics Wisely
Reason for Continued Therapy
133 NICUs Audited 725 Infants on Antibiotics
February 2016

	Center 1052			All		
	Yes	Patients	%	Yes	Patients	%
Is there an order in the paper record or in the electronic medical record detailing when the antibiotics will be discontinued?	1	11	9.1	335	725	46.2
If the infant is on 48 hours of antibiotics, which of the following contributed to your decision to continue antibiotic therapy?*						
Positive blood culture or culture from other normally sterile fluid (including cerebral spinal fluid, blood, or urine)	0	3	0.0	97	412	23.5
Awaiting culture results	1	3	33.3	94	412	22.8
Laboratory results were concerning for risk of sepsis	3	3	100.0	172	412	41.7
Clinical signs concerning for risk of sepsis	2	3	66.7	171	412	41.5
Clinical signs concerning or diagnostic of necrotizing enterocolitis	0	3	0.0	38	412	9.2
Chest radiograph suggested possible pneumonia	0	3	0.0	40	412	9.7
Other site of infection (including wound infection)	0	3	0.0	43	412	10.4
Post-operative management	0	3	0.0	29	412	7.0
Central venous line or other device in place	0	3	0.0	62	412	15.0
Other	0	3	0.0	88	412	21.4

VON Day Quality Audit November 2016 (Audit 2)

After a series of educational interventions like webinars and the circulation of published articles in the area of antibiotic use in neonates, a 2nd audit was done 10 months after the 1st one at GSH. The 2nd audit was done on the 8th November 2016 at GSH.

There were a total of 6 babies found to be on antibiotics during the 2nd audit. 83.3% of the infants on antibiotics were < 1501g in weight, with 50% each in the <31 and 31 – 36 weeks gestation groups. There was an even distribution of numbers among the early and late onset sepsis categories, almost similar profile to that of all the VON units.

None of the infants on antibiotics at GSH for the 2nd audit were on any form of respiratory support, compared to 36.1% among the VON units. (Table 16)

Table 16: Infant Demographics

VON Day Quality Audit - Choosing Antibiotics Wisely
Infant Demographics
122 NICUs Audited 624 Infants on Antibiotics
November 2016

	Center 1052			All Centers		
	Cases	N	(%)	Cases	N	(%)
Birth weight						
<1501g	5	6	(83.3)	293	624	(47.0)
1501 to 2500g	1	6	(16.7)	124	624	(19.9)
>2500g	0	6	(0.0)	207	624	(33.2)
Gestational age						
<31 weeks	3	6	(50.0)	275	624	(44.1)
31 to 36 weeks	3	6	(50.0)	177	624	(28.4)
>36 weeks	0	6	(0.0)	172	624	(27.6)
Chronological age						
1 to 3 days	2	6	(33.3)	232	624	(37.2)
4 to 28 days	2	6	(33.3)	227	624	(36.4)
>28 days	2	6	(33.3)	165	624	(26.4)
Current respiratory support						
Assisted ventilation via endotracheal tube (HFV or CMV)	0	6	(0.0)	183	624	(29.3)
Nasal ventilation or Nasal CPAP	0	6	(0.0)	139	624	(22.3)
High Flow Nasal Cannula	0	6	(0.0)	54	624	(8.7)
Oxygen only	0	6	(0.0)	23	624	(3.7)
No support	6	6	(100.0)	225	624	(36.1)

Maternal risk factors, suspected or proven early onset sepsis or meningitis, and suspected or proven late onset sepsis or meningitis were the commonest indications for the initiation of antibiotics in the Unit. Suspected or proven necrotizing enterocolitis, prophylaxis for fungal sepsis and suspected or proven ventilator associated pneumonia were also additional common indications for starting antibiotic therapy among the other VON units. (Table 17) This profile is very similar to findings from the 1st VON audit done in February at GSH.

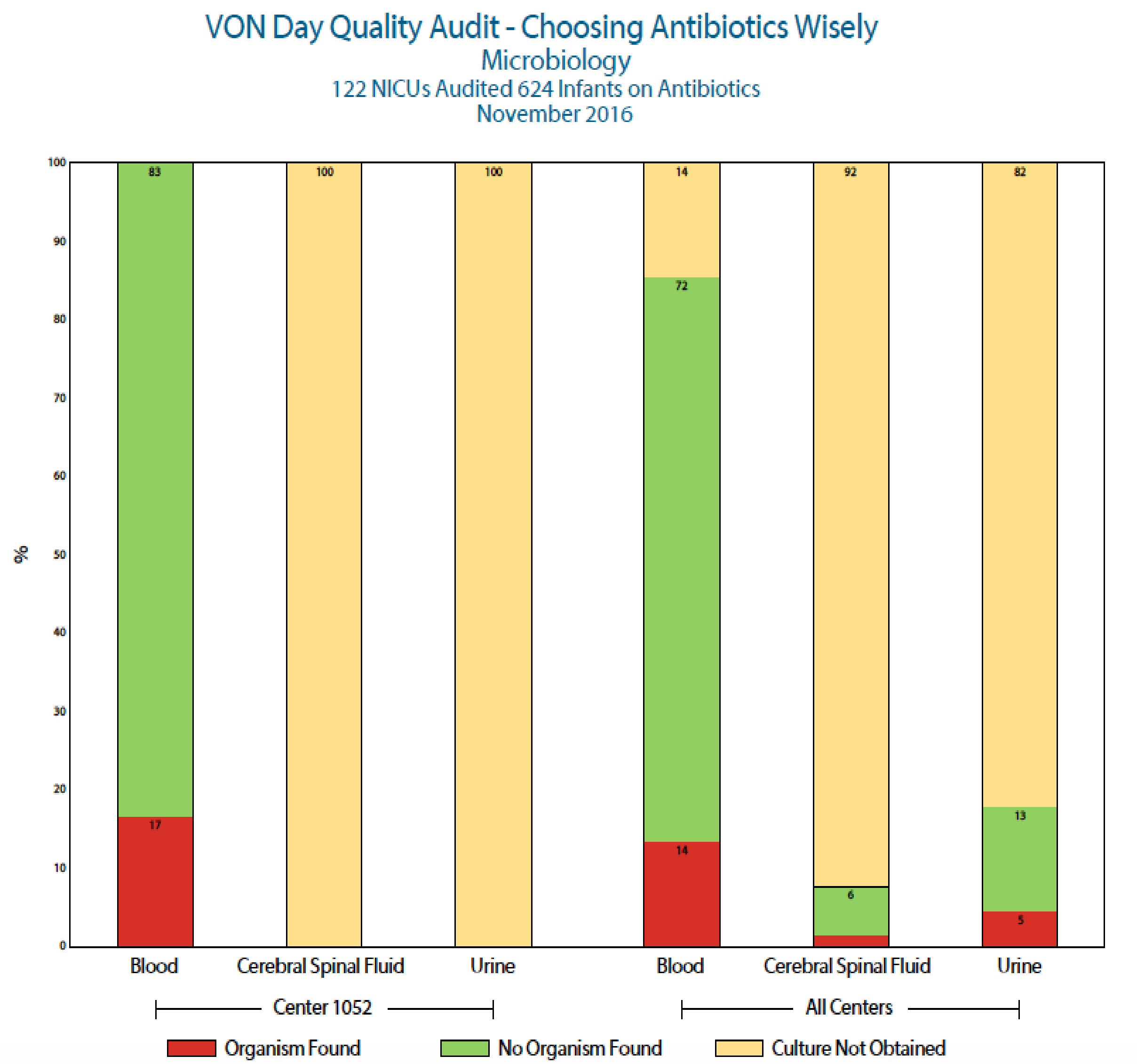
Table 17: Indications for Antibiotic Use

VON Day Quality Audit - Choosing Antibiotics Wisely
Indication(s) for Antibiotic Use
122 NICUs Audited 624 Infants on Antibiotics
November 2016

	Center 1052			All Centers		
	Cases	N	(%)	Cases	N	(%)
What were the indications for starting the infant on antibiotic therapy?*						
Maternal risk factors	2	6	(33.3)	198	624	(31.7)
Suspected or proven early onset sepsis or meningitis	2	6	(33.3)	269	624	(43.1)
Suspected or proven late onset sepsis or meningitis	3	6	(50.0)	131	624	(21.0)
Suspected or proven ventilator associated pneumonia	0	6	(0.0)	31	624	(5.0)
Suspected or proven central venous line infection	0	6	(0.0)	20	624	(3.2)
Suspected or proven urinary tract infection	0	6	(0.0)	23	624	(3.7)
Suspected or proven necrotizing enterocolitis	1	6	(16.7)	48	624	(7.7)
Suspected or proven surgical site infection	0	6	(0.0)	11	624	(1.8)
Prophylaxis for urinary tract infection	0	6	(0.0)	29	624	(4.6)
Prophylaxis for surgery	0	6	(0.0)	15	624	(2.4)
Prophylaxis for fungal sepsis	1	6	(16.7)	62	624	(9.9)
Methicillin-resistant Staphylococcus aureus (MRSA) colonization	0	6	(0.0)	2	624	(0.3)
Other	0	6	(0.0)	89	624	(14.3)

There was a 17% positive blood culture at GSH, with no urine or cerebrospinal fluid (CSF) cultures done. VON Data identified 14% positive blood cultures, 2% and 5% positive CSF and urine cultures respectively among the other units. (Figure 8)

Figure 8: Positive Bacterial cultures (Audit 2)



The major contributing factor to the continued use of antibiotics beyond 48 hours was laboratory results concerning for sepsis. In addition, clinical signs concerning for risk of sepsis, positive blood culture, or culture from other normally sterile fluid, and awaiting culture results were other common reasons found among the other VON units. (Table 18)

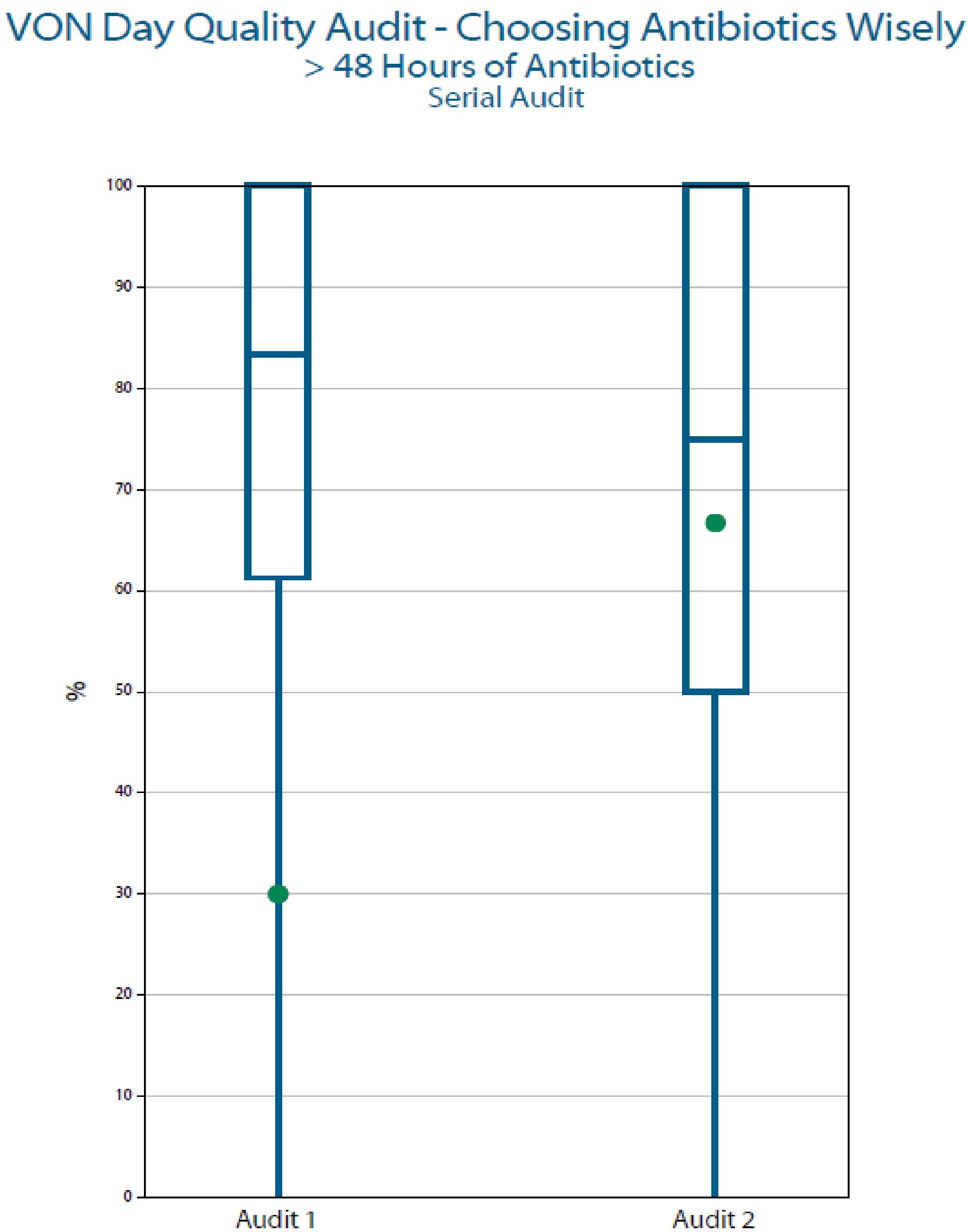
Table 18: Reasons for > 48 hours of antibiotics

VON Day Quality Audit - Choosing Antibiotics Wisely
Reason for Continued Therapy
122 NICUs Audited 624 Infants on Antibiotics
November 2016

	Center 1052			All Centers		
	Cases	N	(%)	Cases	N	(%)
Is there an order in the paper record or in the electronic medical record detailing when the antibiotics will be discontinued?	1	6	(16.7)	357	624	(57.2)
If the infant is on greater than 48 hours of antibiotics, which of the following contributed to your decision to continue antibiotic therapy?*						
Positive blood culture or culture from other normally sterile fluid (including cerebral spinal fluid, blood, or urine)	1	4	(25.0)	97	338	(28.7)
Awaiting culture results	1	4	(25.0)	53	338	(15.7)
Laboratory results were concerning for risk of sepsis	2	4	(50.0)	120	338	(35.5)
Clinical signs concerning for risk of sepsis	1	4	(25.0)	128	338	(37.9)
Clinical signs concerning or diagnostic of necrotizing enterocolitis	0	4	(0.0)	39	338	(11.5)
Chest radiograph suggested possible pneumonia	0	4	(0.0)	45	338	(13.3)
Other site of infection (including wound infection)	0	4	(0.0)	25	338	(7.4)
Post-operative management	0	4	(0.0)	17	338	(5.0)
Central venous line or other device in place	0	4	(0.0)	39	338	(11.5)
Other	0	4	(0.0)	79	338	(23.4)

Regarding infants who received antibiotics for more than 48 hours, a comparison of both audits showed GSH plotting below the lower quartile at 30% in the 1st audit, and at 67% between the median and the lower quartile in the 2nd audit. (Figure 9)

Figure 9: Infants who received antibiotics > 48 hours



CHAPTER 4: DISCUSSION AND CONCLUSION

The incidence of EOS among the VLBW infants at GSH according to the VON data was 1.0%, compared to a figure of 2.4% among the other VON networks. The < 24 and 24 – 26 week gestational age categories of infants contributed to the high rate of EOS among the other units in the VON networks (4.9% and 3.8% respectively). The much lower rate for GSH could be explained by the fact that as per the Unit's protocols, babies less than 26 weeks gestation are not initially offered invasive ventilation.

The GSH incidence rate however tends to be very similar to results found in other studies; one study found the incidence to be about 1.1% (9,16).

With respect to the incidence of LOS, which was 5.2% at GSH, as opposed to 12.1% among the other VON networks, it falls within the range of 0.61 – 14.2% identified by Dong and Speer (49). The much lower rate at GSH could possibly be explained by a couple of factors; a significant reduction in the use of central lines in the unit, a rise in the level of awareness about the habit of hand washing, and the use of dashboards in displaying positive cultures in the unit making the staff much more aware of their performance. The latter strategy is consistent with what Raban et al found at GSH that clinical indicators like dashboards is an effective antibiotic stewardship / infection control tool (47). Most of the data for the VON are from centres in highly developed countries which tend to manage much smaller babies and of extremely low gestational ages. LOS was much more common than EOS which is comparable to what was found in another South African neonatal unit (65).

A total of 874 blood cultures were done in the Unit for the year 2016 with all these babies receiving antibiotics, even though only 30 (3.4%) babies had true pathogens isolated. This brings to fore the issue of neonates with suspected sepsis especially EOS, being exposed to antibiotics in spite of the low culture yield and the concerns about the unnecessary exposure of neonates to antibiotics and the possible adverse side effects. This is rather disturbing since it has been established that inappropriate use of antibiotics in neonates can result in adverse effects like invasive candidiasis, Bronchopulmonary dysplasia, NEC and death (30–32).

Gestational age is a universally accepted determinant in neonatal sepsis, the more preterm the infant the higher the risk (66), which could be due to several factors including the low level of immune maturity and the numerous invasive procedures this group of infants are exposed to

(20). The VON results for GSH are in keeping with that of global figures since the rate of sepsis among the VLBW infants are higher than that of the bigger (> 1500g) infants. Even among the VLBW infants, the rates of EOS and LOS for both GSH and from the other VON centres which took part in the VON audits tend to decline with increasing gestational age.

Need for respiratory support was one of the features looked at under demographics, with more than half (54.5%) on nasal Continuous Positive Airway Pressure (CPAP) and almost 10% requiring support via high flow nasal cannula during the 1st audit in February, whereas there were no babies requiring respiratory support during the 2nd audit in November. The global VON audit data showed almost a quarter (24.8%) of the babies being mechanically ventilated in the 1st audit, with about half of the babies on antibiotics requiring mechanical ventilation or CPAP during the 2nd audit. This highlights what Stoll et al revealed that respiratory distress, especially among preterm infants is one of the leading signs of neonatal sepsis (21).

Maternal risk factors, suspected or proven early onset sepsis or meningitis, and suspected or proven late onset sepsis or meningitis were the commonest reasons for the initiation of antibiotics among the VLBW infant category according to the VON audits both at GSH and among the other units in the VON network. SPTL was the commonest maternal risk factor for EOS especially in preterm infants, followed by maternal UTI and PPROM. SPTL refers to the start of labour that occurs before the 37 weeks of gestation is completed. There are many identified causes of SPTL (67), though generally, 2 out of 5 preterm births are linked to an intrauterine infection and the connection between the two are very well established and accepted worldwide (68,69). These are similar to the risk factors identified globally, for example, maternal chorioamnionitis, PPROM, SPTL, apnea, respiratory distress and abdominal distension (70–72).

Signs of neonatal sepsis, especially EOS, are known to be broad and vague (73). The leading signs for EOS at GSH according to the Blood culture database were RDS, apneas and desaturations. (Figure 2) Lim et al found the commonest signs of neonatal sepsis, apneas, bradycardia and cyanosis to contribute almost 70% (74). Respiratory signs like apnea, tachypnea, and use of accessory muscles tend to be common in EOS (18) which would be consistent with the common clinical features found in this study.

Fever is not a common clinical feature of neonatal sepsis with the exception of when the mother has a febrile illness around the time of delivery (18), perhaps this could explain the obvious absence of fever as a common clinical feature.

The predominant clinical features picked up at GSH from the blood culture database for LOS were abdominal distension, desaturations, apneas and vomiting. (Figure 4) These common clinical features are not surprising since they are typical findings in Necrotizing enterocolitis (NEC), ischemic necrosis of the gut, which is a common condition among the preterm infants and could be an underlying cause of sepsis (75), and septic ileus, which has a similar presentation of abdominal distension.

Positive blood cultures at GSH were less than 20% during both VON quality audits. Yield from cultures, especially blood cultures have always been a confounding factor, especially in the VLBW infants, since one of the major factors influencing microorganism recovery is the amount of blood sample drawn from the infant (42). The current recommendation is to take at least 1ml of blood for culturing purposes in order to increase the chance of identifying the causative microorganism (41).

According to the Blood culture database, the profile of microorganisms isolated included Klebsiella spp, GBS, E. Coli, and CoNS, which is very similar to that of other tertiary centers globally, including a large referral centre in Zambia (70,72).

Maternal GBS was in the past recognized as a major cause of EOS until the inception of the IAP (69), though some studies have still found a high incidence of maternal GBS colonization / infection in Africa due to the very low practice of IAP in most regions (76). The practice of IAP in most countries could also explain the upward trend of the incidence of Gram negative pathogens causing EOS.

South Africa is one of the countries that does not screen for GBS routinely in pregnant mothers. Perhaps this could explain why GBS was the leading cause of EOS at GSH. (Figure 1) This is in keeping with the study by Stoll et al that GBS continues to be one of the leading causes of neonatal sepsis and meningitis thereby contributing to the high rates of neonatal morbidity and mortality (16). Nigeria found in a recent study that K. pneumonia and S. aureus were much more common causative organisms for neonatal sepsis than GBS (77). However, Grimwood et al and Khatoon et al also picked up a direct link between GBS colonization in pregnant women and good socioeconomic standing (78,79). McDonald et al identified a higher risk of SPTL as well as PROM in GBS positive mothers compared to GBS negative mothers (80).

All the LOS GBS were isolated from VLBW infants. Berardi et al found that preterm infants were the most at risk for GBS LOS, and that the practice of IAP tends to delay the presentation of signs of sepsis as well as reduce the severity of the disease (81).

All the GBS isolated during the Blood culture audit were sensitive to Ampicillin and Penicillin, which is very much in keeping with GSH's antibiotic protocol for EOS. This is also consistent with the findings in a previous South African study (82). Worldwide, Penicillin is used as the first line antibiotic for the treatment of GBS infections due to its well-known susceptibility to it, even though Kimura et al identified certain strains of GBS in Japan that had reduced susceptibility to Penicillin (83).

Apart from GBS, all other pathogens isolated for EOS during the blood culture audit were Gram negative organisms, which is not unusual compared to other studies. This is consistent with the study done by Motara et al which found all the causative organisms for EOS in another South African neonatal unit to be Gram negative (65). With the exception of K. pneumonia that was sensitive to Gentamycin, the remaining 3 Gram negative organisms isolated, which were ESBL Klebsiella, A. baumanii and S. marcesans were all resistant to Gentamycin. This is concerning that these organisms would not be covered by the usual first line antibiotics but this constitutes a small number, hence further surveillance should be done before changes to the antibiotic policy can be suggested.

The commonest pathogen causing LOS in the blood culture database was extended spectrum β lactamase (ESBL) K. pneumonia, which is consistent with what was found in a 2 period Iranian study (84). An Egyptian study also revealed K. pneumonia and other Gram negative organisms to be the commonest cause of LOS (85). Considering that all the ESBL K. pneumonia isolates were sensitive to Amikacin, Ciprofloxacin and the Carbapenems, perhaps Amikacin may be reconsidered for a second line as part of GSH's protocols for management of neonatal sepsis. This is especially vital since it could delay the emergence of Carbapenem resistant Klebsiella. Regarding the remaining Gram negative organisms for LOS, ESBL E. coli was found to be sensitive to Amikacin, though the 2 strains of A. baumanii and Serratia were found to be resistant. Coetzee et al also found the E. coli strains isolated in another South African neonatal unit to be sensitive to Amikacin (86). Stenotrophomonas is typically resistant to Amikacin and Meropenem which was evident in this study. The other strains of E. coli were not tested for sensitivity against Amikacin. Amikacin and Penicillin G were previously the antibiotics of choice for LOS at GSH, but had to be changed to Meropenem on account of increasing resistance to Amikacin especially among the ESBL Klebsiella species. The major concerns with Amikacin would be its nephrotoxic and ototoxic potential side effects as well as its limited CSF and gastrointestinal penetration, the latter being of concern especially in the management of NEC (87–89)**.**

ESBL have been responsible for the increasing rise of outbreaks in many NICUs worldwide on account of difficulty in finding the appropriate antibiotics due to its multi - drug resistant nature (84,90). The emergence of ESBL organisms makes the management of sepsis very frustrating for clinicians because of the numerous antibiotics they are resistant to. This definitely serves as a big challenge to antibiotic stewardship programs, especially in this era of limited availability and manufacturing of new antibiotics.

The Antibiotic usage database revealed E. coli to be the only pathogen isolated for EOS. This is not very surprising especially since Kari et al found GBS and E. coli to be 2 of the major pathogens causing EOS. The E. coli isolated here was sensitive to both Ampicillin and Gentamycin which baby received.

ESBL Klebsiella and M. morganii were the only pathogens isolated from 2 babies with LOS during the antibiotic usage audit. M. morganii is an Enterobacteriaceae that is typically associated with EOS and known to have a multi-drug resistant nature. Maternal chorioamnionitis is typically associated with it. The M. morganii isolated during the antibiotic usage audit was for an LOS which is not very typical (91–93).

CoNS remained the commonest contaminant according to the blood culture database at GSH both for EOS and LOS; even though some of them were managed as true pathogens since they had accompanying abnormal CRP values and unstable clinical states. Thylefors et al confirmed in a study that CoNS was the commonest blood culture contaminant (58 - 83%), even though the mortality associated with CoNS bacteraemia in the same study ranged from 4.9% to almost 30% (94). There is still a lot of controversy regarding the pathogenic capabilities of CoNS, especially since there is no ‘gold standard” for differentiating between CoNS that is a contaminant and one that is a true pathogen (95) This study considered all CoNS isolated for EOS as contaminants. Even though CoNS has been accepted as a significant cause for LOS especially in VLBW infants (96), only 3 of the CoNS isolated for LOS were considered as pathogens. Of these 3, 2 were associated with high CRPs 29 and 86, with accompanying clinical signs of periumbilical reddening, recurrent apneas and desaturations, and persistent vomiting. The 3rd baby with CoNS LOS was treated as a true sepsis on account of a sudden increase in the work of breathing and a sudden deterioration in the clinical status in spite of the CRP being 0. Not only does a high blood culture contaminant rate promote the unnecessary use of antibiotics, but it also confuses the clinician by creating more uncertainty about the approach to the management of the patient (95**).** Herwaldt et al did not find the use of clinical criteria to be reliable enough in terms of sensitivity and specificity in differentiating between a contaminant and a pathogen (97) The American Association of Microbiology sets the Blood culture contamination rate at 3%, and advocates for the use of dedicated Phlebotomy teams responsible for the taking of blood culture samples. At GSH, samples for blood cultures are taken by a wide range of Doctors: from Interns to Senior registrars, this could perhaps explain the current rate of contaminants (98).

There was only one positive fungal culture (C. albicans) in a VLBW infant for LOS as part of the blood culture audit. This could possibly be due to the low sensitivity of blood cultures for invasive candidiasis especially in preterm infants where it is usually difficult to obtain large volumes of blood for culturing (99). The policy of not routinely placing indwelling catheters could also help explain the low incidence of fungal infections at GSH. Swanson et al found gestational age, history of spontaneous delivery and exposure to antibiotics during the first week of life to be significant risk factors for the development of invasive candidal infections in preterm infants (100).

WHO recommends the use of Gentamycin and Ampicillin / Penicillin as first line drugs for the management of neonatal sepsis (101). Aminoglycosides (mainly Gentamycin) and Ampicillin were the most commonly used drugs at GSH as per the blood culture and antibiotic usage audits, which is very much in line with what most centers use. There have however been increasing reports of antimicrobial resistance to the commonly used antibiotics like Ampicillin and Gentamycin, and the third generation Cephalosporins, especially for Klebsiella spp, with a reported resistance of 96 – 99% and 94 – 97% for Ampicillin and Gentamycin, and the third generation Cephalosporins respectively (70). A South African study revealed antibiotic resistance levels of Gram negative organisms to Ampicillin and Gentamycin to be 94.6% and

86.7% respectively (82). On the other hand, an Iranian study reported Ampicillin and Gentamycin as the “good old” antibiotics that can be relied on as appropriate for the management of EOS (102). However, Gentamycin being an aminoglycoside has its use being limited by its potential adverse effects of nephrotoxicity and ototoxicity, and therefore the recommendation is for continuous monitoring of its levels regardless of the dose or duration (103,104). This monitoring of levels is however not being done routinely at GSH yet.

For both VON audits at GSH, no Methicillin Resistant Staphylococcus Aureus (MRSA), Vancomycin Resistant Enterococcus (VRE) or Gram negative bacilli resistant to 3rd generation Cephalosporins was isolated from blood cultures. However, the overall data among all the VON centers showed figures of 3.3%, 0.0% & 5.4% and 4.8%, 0.0% & 6.0% respectively for Audits 1 and 2. These audits show a small but significant rise in the incidence of MRSA and Gram negative bacilli resistant to 3rd generation Cephalosporins. This is consistent with some studies identifying MRSA in neonatal units, especially among preterm infants, to be on the rise (105,106).

Regarding the prolonged duration of antibiotics for more than 48 hours, even though GSH plotted below the lower quartile and the median in the VON 1st and 2nd audits respectively, compared to other units in the VON network, it still brings to fore the difficulties clinicians worldwide face where antibiotic stewardship in the NICU is concerned (20). The VON antibiotic quality audits highlighted some of the reasons for the continued use of antibiotics beyond 48 hours. These included pending laboratory results, the presence of a central venous line or any other device, an abnormal chest radiograph and clinical signs suggestive of sepsis. The antibiotic usage audit revealed that for suspected EOS, 16 out of 30 babies received antibiotics for more than 2 days, compared to 7 out of 11 suspected LOS cases, which is not in keeping with GSH’s protocol, that all antibiotics be discontinued by 48 hours if there is no bacterial growth. This could be due mainly to the fact that the CRP which is the most commonly used sepsis biomarker at GSH is not requested for early enough, sometimes just around the 48 - 72 hour mark, and hence the decision to stop or continue is dependent on how soon the CRP result is ready.

Perhaps an electronic hard stop may be considered for all negative cultures by 48 hours, which can only be undone with the input of the neonatologist treating the baby in agreement with the hospital’s Microbiologist and Pharmacist (25).

Reasons for the prolonged use of antibiotics can be varied ranging from the opinion of the attending neonatologist to persistent abnormal laboratory results concerning for sepsis. This is mainly due to a limited ability to distinguish between infectious and non-infectious conditions among neonates. Kiser et al identified 20.2% of neonates who received antibiotics based on mainly abnormal laboratory results (107). The Committee on Fetus and Newborn recommends relying on abnormal laboratory results if there is a history of maternal chorioamnionitis, especially in the presence of a sterile culture (108).

More and more clinicians are relying on acute phase proteins like CRP which has been found to have better sensitivity and specificity especially compared to the haematological indices like the total neutrophil count (109), for the management of neonatal sepsis. This explains why more than 80% of the babies with positive cultures at GSH had a CRP done; as this helps the clinicians make a more objective decision on whether or not to discontinue the antibiotics.

Limitations

1. There is a chance that some negative cultures were obtained because of small amounts of blood obtained for cultures
2. No urine and very few CSF cultures were done so difficult to comment on their contribution
3. 5 of the patient folders were lost to follow up and another 2 had missing data
4. As GSH is a tertiary unit, the results may not be translatable to other lower level neonatal units.

Recommendations

1. At least 1ml of blood to be taken for blood culture purposes
2. More Urine and CSF cultures to be done especially for LOS. This could help reduce the diagnoses of "suspected sepsis" since these cultures tend to have a high yield, and a missed diagnosis could have dire consequences
3. Amikacin may be reconsidered as a second line antibiotic as part of the GSH protocol for the management of neonatal sepsis in selected cases. Amikacin should only be started after renal function tests are done and found to be normal on account of its potential nephrotoxic and ototoxic adverse effects. It should be given till blood culture sensitivity results are available.

4. Appropriate monitoring of Aminoglycoside levels. This could be costly, since Gentamycin is a first line drug at GSH. However, this could also help reduce or even prevent adverse effects like renal dysfunctions in the long term.
5. In those infants who a CRP is required, this should be requested at 36 hours of antibiotics in order to be able to make the decision on whether or not to discontinue antibiotics latest by 48 hours
6. Monitoring of the sensitivity of the EOS organisms due to the 3 cases of resistance to the first line antibiotics
7. The adoption of very strict aseptic techniques including proper hand washing, for the sampling of blood for culture.
8. The need to remove central lines and catheters as soon as possible. This could contribute to lowering the incidence of LOS in the unit
9. The need for further studies to identify markers for distinguishing between contaminants and real pathogens in blood cultures

Conclusion

The rates of Early and Late Onset Sepsis at GSH are in keeping with global figures, though stricter antibiotic stewardship is recommended to limit the use and duration of antibiotics in the unit. Antibiotics currently in use at GSH are appropriate in most cases for the prevailing organisms although there are some resistant organisms.

REFERENCES

1. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric Use of Ampicillin and Cefotaxime, Compared With Ampicillin and Gentamicin, for Neonates at Risk for Sepsis Is Associated With an Increased Risk of Neonatal Death. Pediatrics. 2006 Jan 1;117(1):67–74.

2. Mahmood A, Karamat KA, Butt T. Neonatal sepsis: high antibiotic resistance of the bacterial pathogens in a neonatal intensive care unit in Karachi. JPMA J Pak Med Assoc. 2002 Aug;52(8):348–50.

3. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015 Feb;61(1):1–13.

4. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet Lond Engl. 2005 Mar 5;365(9462):891–900.

5. Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. J Infect. 2014 Jan;68 Suppl 1:S24-32.

6. Shane A, Stoll B. Recent Developments and Current Issues in the Epidemiology, Diagnosis, and Management of Bacterial and Fungal Neonatal Sepsis. Am J Perinatol. 2013 Jan 7;30(02):131–42.

7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801–10.

8. Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012 May;129(5):1006–15.

9. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J. 2011 Nov;30(11):937–41.

10. Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, et al. Early-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr. 1996 Jul;129(1):72–80.

11. Carstensen H, Christensen KK, Grennert L, Persson K, Polberger S. Early-onset neonatal group B streptococcal septicaemia in siblings. J Infect. 1988 Nov;17(3):201–4.

12. Schrag SJ, Cutland CL, Zell ER, Kuwanda L, Buchmann EJ, Velaphi SC, et al. Risk factors for neonatal sepsis and perinatal death among infants enrolled in the prevention of perinatal sepsis trial, Soweto, South Africa. Pediatr Infect Dis J. 2012 Aug;31(8):821–6.

13. Puopolo KM. Response to the American Academy of Pediatrics, Committee on the Fetus and Newborn statement, “management of neonates with suspected or proven early-onset bacterial sepsis.” Pediatrics. 2012 Oct;130(4):e1054-1055; author reply e1055-1057.

14. Bauserman MS, Laughon MM, Hornik CP, Smith PB, Benjamin DK, Clark RH, et al. Group B Streptococcus and Escherichia coli infections in the intensive care nursery in the era of intrapartum antibiotic prophylaxis. Pediatr Infect Dis J. 2013 Mar;32(3):208–12.

15. Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 2010 Nov 19;59(RR-10):1–36.

16. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011 May;127(5):817–26.

17. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics. 2005 Sep;116(3):595–602.

18. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-Onset Neonatal Sepsis. Clin Microbiol Rev. 2014 Jan;27(1):21–47.

19. Nightingale - Vermont Oxford Network [Internet]. [cited 2017 Jan 2]. Available from: https://nightingale.vtoxford.org/reports.aspx?c=5

20. Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and Late Infections in Newborns: Where Do We Stand? A Review. Pediatr Neonatol. 2016 Aug;57(4):265–73.

21. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002 Aug;110(2 Pt 1):285–91.

22. Berardi A, Cattelani C, Creti R, Berner R, Pietrangiolillo Z, Margarit I, et al. Group B streptococcal infections in the newborn infant and the potential value of maternal vaccination. Expert Rev Anti Infect Ther. 2015;13(11):1387–99.

23. Lukacs SL, Schrag SJ. Clinical Sepsis in Neonates and Young Infants, United States, 1988-2006. J Pediatr. 2012 Jun;160(6):960-965.e1.

24. Sivanandan S, Soraisham AS, Swarnam K. Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. Int J Pediatr. 2011;2011:712150.

25. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study [Internet]. [cited 2016 Sep 11]. Available from: http://www.sciencedirect.com/science/article/pii/S1473309916302055

26. Schulman J, Dimand RJ, Lee HC, Duenas GV, Bennett MV, Gould JB. Neonatal Intensive Care Unit Antibiotic Use. Pediatrics. 2015 Apr 1;peds.2014-3409.

27. Spitzer AR, Kirkby S, Kornhauser M. Practice variation in suspected neonatal sepsis: a costly problem in neonatal intensive care. J Perinatol Off J Calif Perinat Assoc. 2005 Apr;25(4):265–9.

28. Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR, et al. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J. 2005 Sep;24(9):766–73.

29. Antibiotic Resistance Threats in the United States, 2013 | Antibiotic/Antimicrobial Resistance | CDC [Internet]. [cited 2018 Jan 16]. Available from: https://www.cdc.gov/drugresistance/threat-report-2013/

30. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006 Aug;118(2):717–22.

31. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, et al. Prolonged Duration of Initial Empirical Antibiotic Treatment Is Associated With Increased Rates of Necrotizing Enterocolitis and Death for Extremely Low Birth Weight Infants. Pediatrics. 2009 Jan;123(1):58–66.

32. Novitsky A, Tuttle D, Locke RG, Saiman L, Mackley A, Paul DA. Prolonged early antibiotic use and bronchopulmonary dysplasia in very low birth weight infants. Am J Perinatol. 2015 Jan;32(1):43–8.

33. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr. 2011 Nov;159(5):720–5.

34. Patel SJ, Oshodi A, Prasad P, Delamora P, Larson E, Zaoutis T, et al. Antibiotic Use in Neonatal Intensive Care Units and Adherence with Centers for Disease Control and Prevention 12 Step Campaign to Prevent Antimicrobial Resistance. Pediatr Infect Dis J. 2009 Dec;28(12):1047–51.

35. Neonatal antibiotic treatment is a risk factor for early wheezing. - PubMed - NCBI [Internet]. [cited 2016 Aug 28]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18381533

36. Ting JY, Synnes A, Roberts A, Deshpandey A, Dow K, Yoon EW, et al. Association Between Antibiotic Use and Neonatal Mortality and Morbidities in Very Low-Birth-Weight Infants Without Culture-Proven Sepsis or Necrotizing Enterocolitis. JAMA Pediatr. 2016 Dec 1;170(12):1181–7.

37. Biomarkers of Neonatal Sepsis | Articles | Neoreviews [Internet]. [cited 2016 Sep 25]. Available from: http://neoreviews.aappublications.org/content/16/5/e297

38. Liu CL, Ai HW, Wang WP, Chen L, Hu HB, Ye T, et al. Comparison of 16S rRNA gene PCR and blood culture for diagnosis of neonatal sepsis. Arch Pediatr Organe Off Soc Francaise Pediatr. 2014 Feb;21(2):162–9.

39. Garcia-Prats JA, Cooper TR, Schneider VF, Stager CE, Hansen TN. Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics. 2000 Mar;105(3 Pt 1):523–7.

40. Serial Serum C-Reactive Protein Levels in the Diagnosis of Neonatal Infection | ELECTRONIC ARTICLE | Pediatrics [Internet]. [cited 2016 Oct 1]. Available from: http://pediatrics.aappublications.org/content/102/4/e41

41. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996 Aug;129(2):275–8.

42. Neal PR, Kleiman MB, Reynolds JK, Allen SD, Lemons JA, Yu PL. Volume of blood submitted for culture from neonates. J Clin Microbiol. 1986 Sep;24(3):353–6.

43. Knudson RP, Alden ER. Neonatal heelstick blood culture. Pediatrics. 1980 Mar;65(3):505–7.

44. Kalathia MB, Shingala PA, Parmar PN, Parikh YN, Kalathia IM. Study of Umbilical Cord Blood Culture in Diagnosis of Early-onset Sepsis Among Newborns with High-risk Factors. J Clin Neonatol. 2013 Oct;2(4):169–72.

45. Meena J, Charles MVP, Ali A, Ramakrishnan S, Gosh S, Seetha KS. Utility of cord blood culture in early onset neonatal sepsis. Australas Med J. 2015;8(8):263–7.

46. Bodonaik NC, Moonah S. Coagulase negative Staphylococci from blood cultures: contaminants or pathogens? West Indian Med J. 2006 Jun;55(3):174–82.

47. Raban MS, Bamford C, Joolay Y, Harrison MC. Impact of an educational intervention and clinical performance dashboard on neonatal bloodstream infections. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2015 Sep 21;105(7):564–6.

48. Diagnostic markers of infection in neonates -- Ng 89 (3): F229 -- ADC - Fetal and Neonatal Edition [Internet]. [cited 2016 Sep 25]. Available from: http://fn.bmj.com/content/89/3/F229.long

49. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015 May;100(3):F257-263.

50. Hornik CP, Benjamin DK, Becker KC, Benjamin DK, Li J, Clark RH, et al. Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr Infect Dis J. 2012 Aug;31(8):799–802.

51. da Silva O, Ohlsson A. How accurate are leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis? Paediatr Child Health. 1998 May;3(3):158–9.

52. Hofer N, Zacharias E, Müller W, Resch B. An Update on the Use of C-Reactive Protein in Early-Onset Neonatal Sepsis: Current Insights and New Tasks. ResearchGate. 2012 Apr 11;102(1):25–36.

53. Beltempo M, Viel-Thériault I, Thibeault R, Julien A-S, Piedboeuf B. C-reactive protein for late-onset sepsis diagnosis in very low birth weight infants. BMC Pediatr. 2018 30;18(1):16.

54. Lapillonne A, Basson E, Monneret G, Bienvenu J, Salle BL. Lack of specificity of procalcitonin for sepsis diagnosis in premature infants. The Lancet. 1998 Apr 18;351(9110):1211–2.

55. Mohsen AHA, Kamel BA. Predictive values for procalcitonin in the diagnosis of neonatal sepsis. Electron Physician. 2015 Aug;7(4):1190–5.

56. Adib M, Bakhshiani Z, Navaei F, Saheb Fosoul F, Fouladi S, Kazemzadeh H. Procalcitonin: a reliable marker for the diagnosis of neonatal sepsis. Iran J Basic Med Sci. 2012 Mar;15(2):777–82.

57. IDSA : Antimicrobial Stewardship [Internet]. [cited 2018 Sep 2]. Available from: https://www.idsociety.org/Stewardship_Policy/

58. Brett A, Bielicki J, Newland JG, Rodrigues F, Schaad UB, Sharland M. Neonatal and pediatric antimicrobial stewardship programs in Europe-defining the research agenda. Pediatr Infect Dis J. 2013 Dec;32(12):e456-465.

59. Weinstein RA. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. Emerg Infect Dis. 2001 Apr;7(2):188–92.

60. Newland JG, Hersh AL. Purpose and design of antimicrobial stewardship programs in pediatrics. Pediatr Infect Dis J. 2010 Sep;29(9):862–3.

61. Akpan MR, Ahmad R, Shebl NA, Ashiru-Oredope D. A Review of Quality Measures for Assessing the Impact of Antimicrobial Stewardship Programs in Hospitals. Antibiot Basel Switz. 2016 Jan 13;5(1).

62. Di Pentima MC, Chan S. Impact of antimicrobial stewardship program on vancomycin use in a pediatric teaching hospital. Pediatr Infect Dis J. 2010 Aug;29(8):707–11.

63. Principi N, Esposito S. Antimicrobial stewardship in paediatrics. BMC Infect Dis. 2016 Aug 18;16(1):424.

64. Mukhopadhyay S, Dukhovny D, Mao W, Eichenwald EC, Puopolo KM. 2010 perinatal GBS prevention guideline and resource utilization. Pediatrics. 2014 Feb;133(2):196–203.

65. Motara F, Ballot DE, Perovic O. Epidemiology of Neonatal Sepsis at Johannesburg Hospital. South Afr J Epidemiol Infect. 2005 Jan 1;20(3):90–3.

66. Mukhopadhyay S, Puopolo KM. Risk Assessment in Neonatal Early-Onset Sepsis. Semin Perinatol. 2012 Dec;36(6):408–15.

67. Kt SN, M RS, W E, Pangkahila E, P WA, Kawilarang S. Chorioamnionitis and Funisitis Increase the Risk of Preterm Labor and Early Onset Neonatal Sepsis. Biomed Pharmacol J. 2017 Jun 20;10(2):767–72.

68. Lamont RF. Infection in the prediction and antibiotics in the prevention of spontaneous preterm labour and preterm birth. BJOG Int J Obstet Gynaecol. 2003 Apr;110 Suppl 20:71–5.

69. Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 1996 May 31;45(RR-7):1–24.

70. Kabwe M, Tembo J, Chilukutu L, Chilufya M, Ngulube F, Lukwesa C, et al. Etiology, Antibiotic Resistance and Risk Factors for Neonatal Sepsis in a Large Referral Center in Zambia. Pediatr Infect Dis J. 2016 Jul;35(7):e191-198.

71. Gebremedhin D, Berhe H, Gebrekirstos K. Risk Factors for Neonatal Sepsis in Public Hospitals of Mekelle City, North Ethiopia, 2015: Unmatched Case Control Study. PloS One. 2016;11(5):e0154798.

72. G/Eyesus T, Moges F, Eshetie S, Yeshitela B, Abate E. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC Pediatr. 2017 Jun 6;17(1):137.

73. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am. 2004 Aug;51(4):939–59, viii–ix.

74. Lim WH, Lien R, Huang Y-C, Chiang M-C, Fu R-H, Chu S-M, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. Pediatr Neonatol. 2012 Aug;53(4):228–34.

75. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014 Jan 1;5(1):170–8.

76. Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, et al. Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017 Nov 6;65(suppl_2):S160–72.

77. Medugu N, Iregbu K, Iroh Tam P-Y, Obaro S. Aetiology of neonatal sepsis in Nigeria, and relevance of Group b streptococcus: A systematic review. PloS One. 2018;13(7):e0200350.

78. Grimwood K, Stone PR, Gosling IA, Green R, Darlow BA, Lennon DR, et al. Late antenatal carriage of group B Streptococcus by New Zealand women. Aust N Z J Obstet Gynaecol. 2002 May;42(2):182–6.

79. Khatoon F, Nigam A, Sharma NR, Srivastava R, Sangal R, Malik N. Prevalence and risk factors for group B streptococcal colonization in pregnant women in northern India. Int J Reprod Contracept Obstet Gynecol. 2016 Dec 7;5(12):4361–4.

80. McDonald H, Vigneswaran R, O'Loughlin JA. Group B streptococcal colonization and preterm labour. Aust N Z J Obstet Gynaecol. 1989 Aug;29(3 Pt 2):291–3.

81. Berardi A, Rossi C, Lugli L, Creti R, Bacchi Reggiani ML, Lanari M, et al. Group B streptococcus late-onset disease: 2003-2010. Pediatrics. 2013 Feb;131(2):e361-368.

82. Lebea MM, Davies V. Evaluation Of Culture-Proven Neonatal Sepsis At A Tertiary Care Hospital In South Africa. South Afr J Child Health. 2017 Dec 22;11(4):170–3.

83. Kimura K, Suzuki S, Wachino J, Kurokawa H, Yamane K, Shibata N, et al. First molecular characterization of group B streptococci with reduced penicillin susceptibility. Antimicrob Agents Chemother. 2008 Aug;52(8):2890–7.

84. Marzban A, Samaee H, Mosavinasab N. Changing trend of empirical antibiotic regimen: experience of two studies at different periods in a neonatal intensive care unit in Tehran, Iran. Acta Med Iran. 2010 Oct;48(5):312–5.

85. Mohsen L, Ramy N, Saied D, Akmal D, Salama N, Abdel Haleim MM, et al. Emerging antimicrobial resistance in early and late-onset neonatal sepsis. Antimicrob Resist Infect Control. 2017;6:63.

86. Coetzee M, Mbowane N, Witt T de. Neonatal sepsis: Highlighting the principles of diagnosis and management. South Afr J Child Health. 2017 Jul 5;11(2):99–103.

87. Palomino J, Pachón J. [Aminoglycosides]. Enferm Infecc Microbiol Clin. 2003 Feb;21(2):105–14; QUIZ 115, 120.

88. Germovsek E, Barker CI, Sharland M. What do I need to know about aminoglycoside antibiotics? Arch Dis Child Educ Pract Ed. 2017 Apr;102(2):89–93.

89. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev. 2010 Oct;23(4):858–83.

90. Folgori L, Bielicki J, Heath PT, Sharland M. Antimicrobial-resistant Gram-negative infections in neonates: burden of disease and challenges in treatment. Curr Opin Infect Dis. 2017 Jun;30(3):281–8.

91. Salen PN, Eppes S. Morganella morganii: a newly reported, rare cause of neonatal sepsis. Acad Emerg Med Off J Soc Acad Emerg Med. 1997 Jul;4(7):711–4.

92. Ranu SS, Valencia GB, Piecuch S. Fatal early onset infection in an extremely low birth weight infant due to Morganella morganii. J Perinatol Off J Calif Perinat Assoc. 1999 Nov;19(7):533–5.

93. Johnson JR, Feingold M. Case of chorioamnionitis in an immunocompetent woman caused by Morganella morganii. J Matern Fetal Med. 1998 Feb;7(1):13–4.

94. Thylefors JD, Harbarth S, Pittet D. Increasing bacteremia due to coagulase-negative staphylococci: fiction or reality? Infect Control Hosp Epidemiol. 1998 Aug;19(8):581–9.

95. Sidhu SK, Malhotra S, Devi P, Tuli AK. Significance of coagulase negative Staphylococcus from blood cultures: persisting problems and partial progress in resource constrained settings. Iran J Microbiol. 2016 Dec;8(6):366–71.

96. Isaacs D, Australasian Study Group For Neonatal Infections. A ten year, multicentre study of coagulase negative staphylococcal infections in Australasian neonatal units. Arch Dis Child Fetal Neonatal Ed. 2003 Mar;88(2):F89-93.

97. Herwaldt LA, Geiss M, Kao C, Pfaller MA. The positive predictive value of isolating coagulase-negative staphylococci from blood cultures. Clin Infect Dis Off Publ Infect Dis Soc Am. 1996 Jan;22(1):14–20.

98. Smith SM, Eng RHK, Lopez AB, Valena FD. Reducing Blood Culture Contamination: What Makes the Difference? Am J Infect Control. 2006 Jun 1;34(5):E78–9.

99. Berenguer J, Buck M, Witebsky F, Stock F, Pizzo PA, Walsh TJ. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis. Disseminated versus single-organ infection. Diagn Microbiol Infect Dis. 1993 Sep;17(2):103–9.

100. Swanson JR, Gurka MJ, Kaufman DA. Risk Factors for Invasive Fungal Infection in Premature Infants: Enhancing a Targeted Prevention Approach. J Pediatr Infect Dis Soc. 2014 Mar;3(1):49–56.

101. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO’s currently recommended antibiotics--systematic review and meta-analysis. Arch Dis Child. 2013 Feb;98(2):146–54.

102. Maayan-Metzger A, Barzilai A, Keller N, Kuint J. Are the “good old” antibiotics still appropriate for early-onset neonatal sepsis? A 10 year survey. Isr Med Assoc J IMAJ. 2009 Mar;11(3):138–42.

103. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity - a review of clinical studies published between 1975 and 1982. J Antimicrob Chemother. 1984 Jan;13 Suppl A:9–22.

104. Chattopadhyay B. Newborns and gentamicin—how much and how often? J Antimicrob Chemother. 2002 Jan 1;49(1):13–6.

105. Nelson MU, Gallagher PG. Methicillin-Resistant Staphylococcus aureus in the Neonatal Intensive Care Unit. Semin Perinatol. 2012 Dec;36(6):424–30.

106. Shirai Y, Arai H, Tamaki K, Konishi H, Kawase Y, Shimizu N, et al. Neonatal methicillin-resistant Staphylococcus aureus colonization and infection. J Neonatal-Perinat Med. 2017;10(4):439–44.

107. Kiser C, Nawab U, McKenna K, Aghai ZH. Role of guidelines on length of therapy in chorioamnionitis and neonatal sepsis. Pediatrics. 2014 Jun;133(6):992–8.

108. Polin RA, the COMMITTEE ON FETUS AND NEWBORN. Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis. PEDIATRICS. 2012 May 1;129(5):1006–15.

109. Da Silva O, Ohlsson A, Kenyon C. Accuracy of leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis: a critical review. Pediatr Infect Dis J. 1995 May;14(5):362–6.

APPENDICES

Appendix 1: Ethics approval letter

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

02 May 2017

HREC REF: 260/2017

Dr L Tooke
Neonatal Medicine
Room H46-60
Old Main Building

Dear Dr Tooke

PROJECT TITLE: ANTIBIOTIC USE IN A LEVEL III NICU IN SOUTH AFRICA-MPhil-candidate-Dr N Brobby)

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

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

Approval is granted for one year until the 30th April 2018.

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

We acknowledge that the student Dr N Brobby will be involved in this study.

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

Please quote the HREC REF in all your correspondence.

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 260/2017

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 260/2017

Appendix 2: Case Report Form (CRF)

ANTIBIOTIC USE IN A LEVEL III NICU IN SOUTH AFRICA

Q1. Study type All positive culture 2016 [0] One month audit [1]

Q2. Study ID:___________

Q3. Folder #: _________________

Q4. Birth Weight (g)____________

Q5. Organism (eg.*q4Normal_flora etc*)

a.	Normal skin flora	No [0] Yes [1]
b.	GBS	No [0] Yes [1]
c.	ESBL Klebsiella pneumoniae	No [0] Yes [1]
d.	Klebsiella pneumonia	No [0] Yes [1]
e.	CONS	No [0] Yes [1]
f.	E. coli	No [0] Yes [1]
g.	ESBL E. coli	No [0] Yes [1]
h.	Bacillus species	No [0] Yes [1]
i.	Serratia marcesans	No [0] Yes [1]
j.	Staphylococcus warneri	No [0] Yes [1]
k.	Stenotrophomonas maltophilia	No [0] Yes [1]
l.	Acinetobacter baumanii	No [0] Yes [1]
m.	Enterobacter cloacae complex	No [0] Yes [1]
n.	Candida albicans	No [0] Yes [1]
o.	Morganella morganii	No [0] Yes [1]

Q6. Sensitive to: (eg *q5aAmpicillin_sensitive* etc)

a.	Ampicillin	No [0] Yes [1]
b.	Penicillin	No [0] Yes [1]
c.	Ciprofloxacin	No [0] Yes [1]
d.	Trimethoprim Sulfamethoxazole (TS)	No [0] Yes [1]
e.	Amikacin	No [0] Yes [1]
f.	Ertapenem	No [0] Yes [1]
g.	Meropenem	No [0] Yes [1]
h.	Ampi-Amox	No [0] Yes [1]
i.	Amox-Clavu	No [0] Yes [1]
j.	Cefuroxime (IV/PO)	No [0] Yes [1]
k.	Cefotaxime/Ceftriaxone	No [0] Yes [1]
l.	Ceftazidime	No [0] Yes [1]
m.	Cefepime	No [0] Yes [1]
n.	Gentamycin	No [0] Yes [1]
o.	Piperacillin/ Tazobactam	No [0] Yes [1]
p.	Imipenem	No [0] Yes [1]

q. Cefoxitin No [0] Yes [1]
r. Colistin No [0] Yes [1]
s. Tigecycline No [0] Yes [1]
t. Clindamycin No [0] Yes [1]
u. Rifampicin No [0] Yes [1]
v. Erythromycin No [0] Yes [1]
w. Azithromycin No [0] Yes [1]
x. Cloxacillin No [0] Yes [1]
y. Tobramycin No [0] Yes [1]

Q7. Resistant to: (eg *q6aAmpicillin_Resistant* etc)

a. Ampicillin No [0] Yes [1]
b. Penicillin No [0] Yes [1]
c. Ciprofloxacin No [0] Yes [1]
d. Trimethoprim Sulfamethoxazole (TS) No [0] Yes [1]
e. Amikacin No [0] Yes [1]
f. Ertapenem No [0] Yes [1]
g. Meropenem No [0] Yes [1]
h. Ampi-Amox No [0] Yes [1]
i. Amox-Clavu No [0] Yes [1]
j. Cefuroxime (IV/PO) No [0] Yes [1]
k. Cefotaxime No [0] Yes [1]
l. Ceftriaxone No [0] Yes [1]
m. Ceftazidime No [0] Yes [1]
n. Cefepime No [0] Yes [1]
o. Gentamycin No [0] Yes [1]
p. Piperacillin/ Tazobactam No [0] Yes [1]
q. Imipenem No [0] Yes [1]
r. Cefoxitin No [0] Yes [1]
s. Colistin No [0] Yes [1]
t. Tigecycline No [0] Yes [1]
u. Clindamycin No [0] Yes [1]
v. Rifampicin No [0] Yes [1]
w. Erythromycin No [0] Yes [1]
x. Azithromycin No [0] Yes [1]
y. Cloxacillin No [0] Yes [1]
z. Tobramycin No [0] Yes [1]

Q8. Intermediate to: (eg *Q7aAmikacin_Intermediate* etc)

a. Amikancin (I) No [0] Yes [1]
b. Gentamycin (I) No [0] Yes [1]
c. Vancomycin (I) No [0] Yes [1]

Q9. CRP (mg/dL)__________
Q10. CSF Polymorphs_________
Q11. CSF Lymphocytes___________
Q12. CSF Erythrocytes_____________
Q13. WCC_________
Q14. Hb__________
Q15. Plt____________

Q16. Maternal Risk factors (eg. *MRS_q15aSPTL*)

a.	SPTL	No [0] Yes [1]
b.	PPROM	No [0] Yes [1]
c.	Maternal UTI	No [0] Yes [1]
d.	BBA	No [0] Yes [1]
e.	Chorioamnionitis	No [0] Yes [1]

Q17. Signs and symptoms (eg. *q16SS_RDS* etc)

a.	RDS	No [0] Yes [1]
b.	Feeding intolerance	No [0] Yes [1]
c.	Loose stools	No [0] Yes [1]
d.	Bloody Stools	No [0] Yes [1]
e.	Vomiting	No [0] Yes [1]
f.	Abdominal distension	No [0] Yes [1]
g.	Apneas	No [0] Yes [1]
h.	Bradycardias	No [0] Yes [1]
i.	Desaturations	No [0] Yes [1]
j.	Lethargy	No [0] Yes [1]
k.	Tachypnea	No [0] Yes [1]
l.	Grunting	No [0] Yes [1]
m.	Poor feeding	No [0] Yes [1]
n.	Increased WOB	No [0] Yes [1]
o.	Increased oxygen requirement	No [0] Yes [1]
p.	Temperature spikes	No [0] Yes [1]
q.	Hyperglycemia	No [0] Yes [1]
r.	Pallor	No [0] Yes [1]
s.	Poor tone	No [0] Yes [1]
t.	Periumbilical reddening	No [0] Yes [1]
u.	Progressive metabolic acidosis	No [0] Yes [1]
v.	Enteritis	No [0] Yes [1]
w.	Perinatal hypoxia/HIE	No [0] Yes [1]
x.	Hypotension	No [0] Yes [1]
y.	Respiratory distress	No [0] Yes [1]
z.	Chest recessions	No [0] Yes [1]
aa.	FMU-Bilateral PUJ	No [0] Yes [1]
bb.	Right hydronephrosis	No [0] Yes [1]
cc.	PPHN	No [0] Yes [1]
dd.	Central line	No [0] Yes [1]

ee. Prolonged CRT No [0] Yes [1]
ff. Septic Shock No [0] Yes [1]
gg. Mottled skin No [0] Yes [1]
hh. Pulmonary hemorrhage No [0] Yes [1]
ii. Tachycardia No [0] Yes [1]

Q18. a. Antimicrobials 1(eg. Q17aMeropenem)

Meropenem	[0]
Vancomycin	[1]
Ampicillin	[2]
Gentamycin	[3]
Ciprofloxacin	[4]
Cefotaxime	[5]
Cefoxitin	[6]
Cefepime	[7]
Cotrimoxazole	[8]
Fluconazole	[9]
Amphotericin B	[10]
None	[14]

b. Antimicrobials 1 Duration (*in hours*): ______
c. Number of episodes 1st episode [0] 2nd episode [1]

19. a. Antimicrobials 2

Meropenem	[0]
Vancomycin	[1]
Ampicillin	[2]
Gentamycin	[3]
Ciprofloxacin	[4]
Cefotaxime	[5]
Cefoxitin	[6]
Cefepime	[7]
Cotrimoxazole	[8]
Fluconazole	[9]
Amphotericin B	[10]
Never started	[11]
None	[14]

b. Antimicrobials 2 Duration (*in hours*): ______
c. Number of episodes 1st episode [0] 2nd episode [1]

20. a. Antimicrobials 3

Meropenem	[0]
Vancomycin	[1]
Ampicillin	[2]

Gentamycin	[3]
Ciprofloxacin	[4]
Cefotaxime	[5]
Cefoxitin	[6]
Cefepime	[7]
Cotrimoxazole	[8]
Fluconazole	[9]
Amphotericin B	[10]
None	[14]

b. Antimicrobials 3 Duration (*in hours*): ______
c. Number of episodes 1st episode [0] 2nd episode [1]

21. Infection type Late [0] Early [1]
22. Outcome Death [0] Discharge [1]

Appendix 3: VON list of Bacterial Pathogens

Bacterial Pathogens

Code	Description
101	Achromobacter species [including A. xylosoxidans (also known as Alcaligenes xylosoxidans) and others]
102	Acinetobacter species including multidrug-resistant Acinetobacter
103	Aeromonas species
104	Alcaligenes species [A. xylosoxidans and others]
201	Bacteroides species
202	Burkholderia species [B. capecia and others]
301	Campylobacter species [C. fetus, C. jejuni and others] including drug-resistant Campylobacter
302	Chryseobacterium species
303	Citrobacter species [C. diversus, C. freundii, C. koseri and others]
304	Clostridium species
501	Enterobacter species [E. aerogenes, E. cloacae, and others] including Carbapenem-resistant Enterobacter
502	Enterococcus species [E. faecalis (also known as Streptococcus faecalis), E. faecium, and others] including Vancomycin-resistant Enterococcus
503	Escherichia coli including Carbapenem-resistant Escherichia coli
601	Flavobacterium species
801	Haemophilus species [H. influenzae and others]
1101	Klebsiella species [K. oxytoca, K. pneumoniae and others] including Carbapenem-resistant Klebsiella and Cephalosporin-resistant Klebsiella
1201	Listeria monocytogenes
1301	Moraxella species [M. catarrhalis (also known as Branhamella catarrhalis) and others]
1302	Morganella morganii
1401	Neisseria species [N. meningitidis, N. gonorrhoeae and others] including drug- resistant N. gonorrhoeae
1601	Pantoea
1602	Pasteurella species
1603	Prevotella species
1604	Proteus species [P. mirabilis, P. vulgaris and others]

Code	Description
1605	Providencia species [P. rettgeri and others]
1606	Pseudomonas species [P. aeruginosa and others] including multidrug-resistant Pseudomonas aeruginosa
1801	Ralstonia species
1901	Salmonella species including drug-resistant Salmonella serotype Typhi
1902	Serratia species [S. liquefaciens, S. marcescens and others]
1903	Staphylococcus coagulase positive [aureus] including Methicillin-resistant Staphylococcus aureus and Vancomycin-resistant Staphylococcus aureus
1904	Stenotrophomonas maltophilia
1905	Group B Streptococcus or GBS [also known as Streptococcus agalactiae]
1906	Streptococcus anginosus [formerly Streptococcus milleri]
1907	Streptococcus pneumoniae
1908	Streptococcus pyogenes [Group A Streptococcus]