NEONATAL SEPSIS AND ANTIBIOTIC SENSITIVITY PATTERNS AT A SOUTH AFRICAN TERTIARY NURSERY – EVOLUTION OVER A 15 YEAR PERIOD

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DECLARATION

I, Dr Nayestha Naidoo, 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 nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background

Neonatal infection is an important cause of morbidity and mortality in babies. The causative pathogens and their antibiotic susceptibility patterns should be monitored so that treatment regimens can be adjusted to maintain efficacy and avoid selection of resistant organisms.

Objectives

To compare the incidence of culture positive neonatal sepsis; and to describe the pathogens and antibiotic resistance profiles for significant organsims over a 15-year period in a tertiary nursery in Cape Town.

Methods

Retrospective blood culture data for 12 months were collected at three time points over a 15-year period. Blood cultures from 2004, 2013 and 2017 were analysed. All neonates with growth on blood cultures were included.

Results

During 2004 a total of 817 (43.3% of total admissions) blood cultures were taken, 171 (9.1% of total admissions) were culture positive. The most common invasive organisms were Klebsiella pneumoniae (31.8% of invasive organisms), S.aureus (26.1%) and enterococcus species (7.3%). There were 102 contaminants (12.5% of total cultures) of which 7.8% were due to Coagulase-negative Staphylococcus (CONS).

In 2013 a total of 1070 (46.8% of total admissions) blood cultures were taken, 124 (5.4% of total admissions) were culture positive. Common invasive organisms were Klebsiella pneumoniae (53.8% of invasive organisms), E. coli (12.8%) and S. aureus (10.3%). Forty-six blood cultures were deemed contaminated (4.3% of all cultures) and of these 2.1% were due to CONS.

In 2017, there were 581 blood cultures taken (26.5% of total admissions), 56 were culture positive (2.6% of total admissions). Commonly occuring invasive organisms

were Klebsiella pneumoniae (32.4% of invasive organisms), Group B streptococcus (16.2%) and Acinetobacter (13.5%). Twenty-nine blood cultures were considered contaminated (5.6% of cultures) of which 1.7% were CONS.

The gram-negative organisms showed an increasing resistance to penicillin, ampicillin and aminoglycosides but remained sensitive to carbapenems.

Conclusions

The initial reduction in positive blood cultures from 2004 to 2013 was primarily due to the reduction of contaminants, probably reflecting improved blood sampling techniques. The large reduction in Gram-negative organisms from 2013 to 2017 suggests improved infection control measures , but gram-negative organisms remained prominent in all three cohorts. Emergence of resistant organisms is concerning and in keeping with other nurseries worldwide. These data illustrate the need for antibiotic stewardship, infection control measures and ongoing surveillance.

ACKNOWLEDGEMENTS AND CONTRIBUTIONS

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ABBREVIATIONS

CONS - Coagulase Negative Staphylococcal

E. coli - Escherichia coli

S. aureus - Staphylococcus aureus

Klebsiella – Klebsiella pneumonia

GBS – Group B Streptococcus

ELBW – Extremely Low Birth Weight (1000g and less)

VLBW - Very Low Birth Weight (1500g and less)

EONS - Early Onset Neonatal Sepsis

LONS - Late Onset Neonatal Sepsis

GSH – Groote Schuur Hospital

NHLS – National Health Laboratory Services

NICU – Neonatal Intensive Care Unit

UCT – University Of Cape Town

VON – Vermont Oxford Network

WHO – World Health Organisation

AOR – Adjusted odds ratio

RR – Relative risk

CI – Confidence interval

CHAPTER ONE – LITERATURE REVIEW

INTRODUCTION

Neonates are vulnerable hosts for infection caused by pathogenic organisms such as bacteria, fungi or viruses. This may be because both term and preterm infants have innate immunity that is unable to respond adequately to infection. They exhibit both qualitative and quantitative defects in their complement system.(1) Preterm infants have much lower concentrations of immunoglobulins.(1) In addition, their immature skin forms a weak barrier against the environment. Admission to hospital can lead to multiple procedures being carried out which can place them at risk for acquiring infection. It is the sum of all these variables that lead them to succumb easily to infection.

According to the World Health Organisation (WHO), about 5 million neonates die annually.(2-4) Neonatal death is defined as a neonate dying within the first 28days of life.(4) Infection is one of the most important causes of neonatal death(4) and three quarters of all newborn deaths occurs in the first week of life.(5)

Neonatal sepsis is defined as a clinical syndrome in an infant 28 days of life or younger manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream.(6) A blood culture is considered the gold standard for diagnosis of sepsis. Once sepsis is diagnosed, it may be further categorised as early onset or late-onset infection.(1)

Early onset neonatal sepsis (EONS) is defined as a neonate who has clinical signs of infection within 72 hours of birth. Early onset infection is assumed to occur as a result of the infant acquiring the infection before or during delivery. Most early onset sepsis presents within the first 24 hours of life.(6) Clinical signs of infection poor feeding, lethargy, respiratory distress, apnea, cyanosis, temperature instability, vomiting, abdominal distension, diarrhoea, lethargy, convulsion, hypotonia, and irritability.(7) While evidence is lacking, the choice of antibiotics for suspected early neonatal sepsis may be guided by the spectrum of organisms

from microbiological surveillance cultures, for example the prevalence of Group B Streptococcus and Gram negative organisms.(8)

Late onset neonatal sepsis (LONS) is defined as a neonate who has clinical signs of infection after 72hours of life and is usually acquired in the nursery or out in the community.(1) Late-onset sepsis (LOS) acquired in hospital can be a complication of extreme prematurity.(9) Very late onset neonatal sepsis(VLONS) are infections occurring after 1month of life.(1) More resistant organisms are expected from hospital acquired late sepsis when compared to vertically transmitted, community acquired, early sepsis.(10) Studies have reported rates of hospital-acquired neonatal infections that are 3–20 times more common in resource- poor than in resource-rich countries.(11)

The organisms responsible for neonatal sepsis differ across countries and with the timing of onset of infection.(12) In addition to this, one organism may over time replace another as the leading cause of neonatal sepsis in a particular nursery or geographical region. This is further compounded by the fact that local drug resistance profiles change over time, thereby complicating treatment regimens.(13)

Overuse of broad spectrum antibiotics is what drives emergence of resistance but surveillance and antibiotic stewardship helps prevent inappropriate antibiotic use. In South Africa the surveillance programme as outlined by the department of health focuses on the ESKAPE pathogens (Enterococcus faecium/faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Escherichia coli species) and Candida within blood cultures only, as they are the leading causes of nosocomial infections throughout the world.(14)

Early and efficient diagnosis of neonatal sepsis remains nuanced as clinical manifestations of infection vary greatly. This necessitates the use of an empiric antibiotic therapy approach upon suspicion of sepsis.(13) A periodic survey of the causes of sepsis and their antibiotic sensitivity patterns is essential in the design of effective infection control programmes and in guiding empirical antibiotic therapy.(3, 15, 16)

The Groote Schuur Nursery is a tertiary unit that admits and manages babies of varying weights and maturity. The Groote Schuur Hospital (GSH) Neonatal Nursery,

with its 75-bed capacity, admits over 2000 neonates per year. Over 500 of these are Very Low Birth Weight (VLBW) infants - neonates weighing less than 1500g. The nursery offers Intensive Care facilities, with 8 beds for conventional and oscillatory ventilation, 12 beds with non-invasive ventilatory facilities.

The GSH Neonatal Unit policy for suspected sepsis is based on a consistent and disciplined approach to antibiotic usage to provide optimal broad spectrum cover while being cognisant about limiting the emergence of resistant organisms.(17)

Objectives

The objectives of this literature review were:

I) to describe the changing etiology of neonatal sepsis globally; and

ii) to describe the variation in antibiotic susceptibility patterns

METHODS

Search strategy

An electronic search of the relevant literature was undertaken on 5 February 2018 and again on 5 June 2019 using the PubMed, Ebscohost and Cochrane databases. Medical Subject Headings (MeSH) were used in these searches. Filters were applied to include studies in humans, studies in children and studies published after 2000. All article types were included. Results were screened based on relevance of title and review of the abstract. Only articles available in full text in English were included. Full texts were downloaded via the UCT library website. South African government protocols, WHO guidelines and textbooks about this topic were included in the search.

Inclusion criteria

- Human subjects
- Patients enrolled in the neonatal period ie. first 28days of life
- All patients with blood cultures taken
- Full free text in English

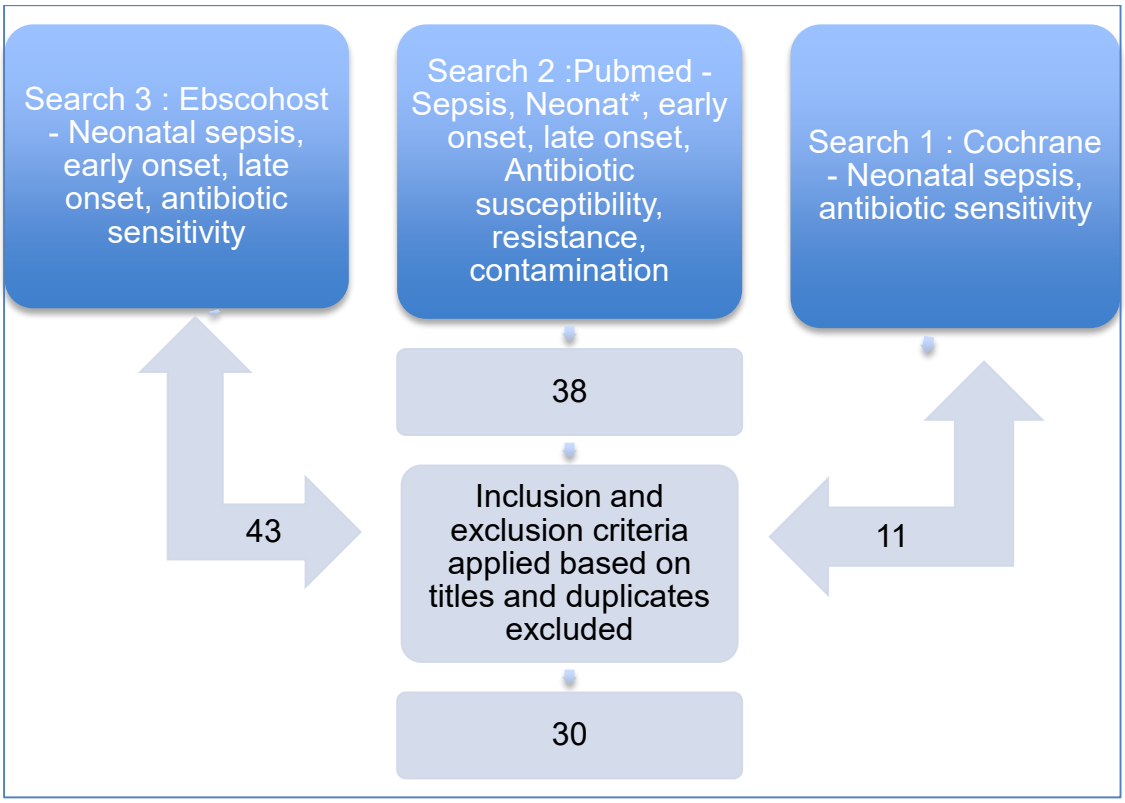
Exclusion criteria

- Samples other than blood cultures ie cerebrospinal fluid, pus swabs, ascitic or pleural taps
- Patients enrolled beyond the neonatal period
- Studies focusing on specific morbidity outcomes eg NEC , IVH etc
- Studies focusing on specific antibiotic usage or single bacterial isolates
- Studies before the year 2000
- Studies focusing on maternal factors
- Studies focusing on adjunctive diagnosis of sepsis ie. serum laboratory tests
- Studies not in English

RESULTS AND DISCUSSION

The yield of the search is shown in figure 1

Figure 1: The process and yield of the literature search.



Thirty full text articles fulfilled the criteria stipulated above and were included. The geographic origins of the papers is shown in table 1.1.

Table 1.1: Geographic origins of papers reviewed

Country	Number of papers
United States of America	4
Serbia	1
South Asia	2
India	4
China	2
Egypt	3
Pakistan	1
Bosnia	1
Brazil	1
Ghana	1
Australia	1
Nigeria	2
Vietnam	1
Turkey	1
South Africa	3
Tanzania	1
Iran	1

Risk factors for EONS

Risk factors for EONS have been published from facilities in the developing countries, Nigeria and China, which are capable of providing intensive neonatal care (ie ventilation and central lines) for their regions.(18, 19) Risk factors associated with EONS in these settings were : weight <1.5kg (Adjusted odds ratio (AOR) 3.3 (1.8-5.9)), lower socioeconomic class (AOR 3.08 (1.86-5.11)), gestational age < 32weeks (AOR 6.18 (2.6 - 15)), maternal infection (AOR 2.25 (1.05-4.78)), maternal GBS colonization, prolonged labour and prolonged rupture of membranes (AOR 5.7 (3.2-10.4)).(18, 19)

Micro-organism profile in EONS

Early onset neonatal sepsis was prominent in neonatal units in the following developing countries that were capable of providing either secondary or tertiary neonatal intensive care: Nigeria,(19) China,(18) India,(20) (21) and Pakistan.(22) There were no articles from developed countries to compare as they did not fulfill selection criteria. The Gram positive organisms, CONS and S. aureus were dominant in 3 studies from Nigeria, India and China,(18-20) whilst the gram negative organisms E. coli, Klebsiella and Acinetobacter were dominant in two studies from India and Pakistan.(21, 22) None of the articles reviewed specific medical sequelae related to pathogens identified for EONS. The high prevalence of EONS noted in these centres could possibly be attributed to perinatal events, vertical transmission from the maternal tract or early acquisition of pathogens from NICU or delivery rooms.(19, 21)

Risk factors for LONS

Three papers from developing and upper middle class countries; Tanzania, Brazil and Bosnia, highlighted risk factors associated with LONS.(23-25) These were prolonged rupture of membranes (p=0.0001), meconium stained liquor (p=0.0001), weight <1.5kg (Relative Risk (RR) 1.37 95% confidence interval (CI) 0.91-2.106), use of a central venous catheter (RR 3.44 95% CI 2.39-4.93), surgery (RR 2.03 95% CI 1.12-3.7), mechanical ventilation (RR4.36 95% CI 3.05-6.23), 5minute APGAR<3 (RR 2.45 95% CI 1.04-5.76) and gestational age < 28weeks.(23-25)

Micro-organism profile in LONS

Late onset neonatal sepsis was the prominent cause of neonatal sepsis in several papers from countries of variable financial status: Tanzania,(23) Vietnam,(26) Ghana,(27) Egypt,(28) Brasil,(24) South Africa,(13, 16) and Bosnia.(25) Ventilation could be offered in all these centres. The Gram-positive organisms; S. aureus, CONS and Enterococcus faecalis were dominant in Tanzania, Brasil, Bosnia, South Africa and Ghana.(13, 23-25, 27) The Gram negative organism; Klebsiella was dominant in another South African NICU(16) and fungi were responsible for LONS in a prospective cohort done in the largest neonatal unit in central Vietnam.(26) Gram negative organisms had a higher mortality rate as noted by Kayange et al

(p=0.0001).(23) None of the articles reviewed specific medical sequelae related to the organisms responsible for LONS.

Micro-organism profile in both early and late onset neonatal sepsis

The gram positive organism, Group B Streptococcus (GBS) is a significant cause of neonatal sepsis (EONS and LONS). Although it was first identified in the early 1960's, maternal prophylaxis against this pathogen has only been implemented since the 1990's. Currently there is a low prevalence of group B streptococci infection in Asia compared to a high incidence in high income countries such as the United States of America and England.(21, 29) S. aureus dominated in Sagamu, Nigeria and in a cross sectional study from Pune,India.(20, 23)

Coagulase negative staphylococcus (CONS) is another important gram positive organism implicated in both early and late neonatal sepsis.(30) There are no definitive guidelines on classification of CONS as true sepsis or contaminant.(31) Coagulase negative staphylococcus was noted to cause sepsis amongst premature infants a prospective study done in a NICU between 2003 and 2010 in Turkey (32) and in a study done in a South Africa in a tertiary NICU between 2009 and 2010.(15) A study done in Houston, Texas was done to distinguish true CONS infection from contamination and they proved within their NICU that invasive CONS infection occurred among infants with birth weight <2000 g ($p<0.001$) and gestational age <34 weeks ($p<0.001$).(33) However, CONS may not be as virulent as gram negative organisms or fungi and so clinical significance using isolation from more than one blood culture from different sites in the same neonate(33) may be helpful in each case specifically.(34, 35)

Gram negative organisms are also emerging as causing serious neonatal infections. E.coli, Klebsiella pneumoniae and Pseudomonas aeruginosa are such organisms found to cause both early and late sepsis.(13, 36) Gram negative organisms (Klebsiella pneumonia, E.Coli, Acintetobacter, Serratia) dominated in Egypt(10) (7) and South Africa.(16) No prophylaxis or screening exists for these organisms, therefore prompt identification and treatment is necessary.

Contamination

Contamination usually results from bacteria present in the environment or on the skin when sampling – it can increase NICU cost burden and falsely increase morbidity and mortality rates.(34) Clinicians need to make a decision on whether an isolate is a contaminant or not to determine appropriate treatment. Raban et al suggest that the rates of both neonatal sepsis and contaminated blood cultures can be decreased by using the following interventions : written policies prioritising hand washing; a 'bare-below-elbows' approach; a uniform blood culture technique; appropriate antibiotic use; and insertion and management of central lines according to a standardised protocol.(37) Video material was used to reinforce these techniques. By implementing the above, they reduced the level of neonatal sepsis ($p=0.002$) while also reducing contaminated blood cultures ($p<0.001$) within their unit.(34)

Change in organisms in a single unit over time

There were few papers that studied changing organisms in a particular unit over time. Two references briefly mention this – a Nigerian(19) and a South African(16) study. In Nigeria, a retrospective review was carried out on neonates receiving specialist care at a teaching hospital between Jan 2006 and December 2007 and a prospective review studied neonates between January to December 2008.(19) The authors found S. aureus to be commonest organism followed by Klebsiella pneumonia and E. coli. The data was compared with two earlier studies done in the last two decades. The commonest organism causing neonatal sepsis between 1987 – 1989 was S. aureus and Klebsiella was the most frequent organism between 1991- 1992.(19) Lebea at al(16) retrospectively described organisms in their South African neonatal unit (within an academic hospital) from January to December 2012. Gram negative organisms dominated the sepsis profile in the most recent study(2012) but gram positive (particularly CONS) dominated in their study done in 2002.(16) Both these studies confirm that organisms causing neonatal sepsis change over time and repeated surveillance is recommended within a specific institute.

Antibiotic susceptibility patterns

Two Cochrane meta-analyses have addressed the issue of empiric antibiotic regimens for neonatal sepsis. Both included randomised control trials done in the 1980's and early 1990's comparing monotherapy versus dual therapy antibiotic treatment.(8, 31) Mtitimila et al in 2004(8) reviewed antibiotic regimens for suspected early onset neonatal infections – including RCT from two developed countries; and Gordon et al in 2005(31) reviewed antibiotic regimens for suspected late onset neonatal infections – including RCTs from developed and developing countries. Both concluded that there is no evidence to suggest that any antibiotic regimen may be better than any other in the treatment of presumed neonatal sepsis and more studies are needed to resolve this.(8, 31)

Another Cochrane meta-analysis by Ungerer et al in 2004 (38) sought to seek answers about prophylactic versus selective antibiotics for asymptomatic term neonates born to mothers with risk factors for neonatal infection. The data they analysed came from two randomised control trials or quasi random methods of allocation – the trials were old, done in the 1970's, one from South Africa and the other from Belgium and ultimately inconclusive to guide clinical practice. In the same article they highlight that a delay in initiating antibiotic treatment when it is needed may increase neonatal morbidity and mortality (RR not estimable) although prophylactic use of antibiotics may result in antibiotic treatment of many infants who are not infected (favours selective antibiotic use RR 5.66 [2.44, 13.14]). (38) This further leads to complications of antibiotic therapy such as resistant infections and fungal infections.(38)

Resistant organisms are emerging within neonatal units.(10, 21, 39) Antibiotic resistance, mainly driven by antibiotic misuse and overuse, is a global phenomenon but worse in low-middle income countries.(40) All medical units (including neonatal) are becoming more aware of this growing superbug problem. A meta-analysis done which reviewed 109 studies involving countries from South Asia found alarmingly high rates of resistance (55-88%) to recommended first line antibiotics(ampicillin and gentamycin).(29) In a prospective study reviewing 25 years of data in a tertiary NICU in Australia, it was found to be a safe practice to stop antibiotics after 48-72 hours if cultures were negative, however it did not prevent the development of resistant Gram-negative organisms within their unit.(40) While awaiting the development of new

antibiotics, the development of multidrug resistant Gram negative bacteria is worrisome and highlights the need to preserve the antibiotics we have and use them appropriately.(41)

Evidence of changing antibiotic susceptibility profiles can be seen in a retrospective review done by Ogunlesi et al from Nigeria.(19) In this review, S. aureus was the commonest etiology in the first study (1987–1989) and they recommended a combination of cloxacillin and gentamicin in place of penicillin or ampicillin with gentamicin. Then Klebsiella was the commonest aetiology in the second study (1991–1992) and the second recommendation was a combination of cefotaxime and gentamicin for empirical treatment of neonatal sepsis. The recommendation from the first study was adopted and implemented, and subsequently so was the second recommendation. The authors recommended the same empiric antibiotic regimen after their retrospective review in 2006-2007 as their second review (1991-1992) but thereafter, the treatment should be tailored to the antibiotic sensitivity report obtained from the laboratory.(19)

CONCLUSION

As evident from the literature reviewed, the organisms responsible for neonatal sepsis differ across countries,(12) however there are few studies that document changing aetiology within a specific unit. Contaminated blood cultures may affect true sepsis profiles and has cost consequences to NICU's (34) globally and falsely encourages antibiotic overuse. Antibiotic sensitivity patterns also change continuously depending on pattern of organisms cultured. Resistant organisms are a growing clinical concern and periodically surveying the causes of sepsis and their antibiotic sensitivity patterns is pivotal in the design of effective infection control programmes and in guiding empirical antibiotic therapy.(3, 15, 16) These data illustrate the need for antibiotic stewardship, infection control measures and ongoing surveillance. More research is needed in this field.

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CHAPTER TWO – PUBLICATION READY MANUSCRIPT

ABSTRACT

Background: Neonatal infection is an important cause of morbidity and mortality in babies. The causative pathogens and their antibiotic susceptibility patterns should be monitored so that treatment regimens can be adjusted to maintain efficacy and avoid selection of resistant organisms.

Objectives: To compare the incidence of culture positive neonatal sepsis; and to describe the pathogens and antibiotic resistance profiles for significant organisms over a 15-year period in a tertiary nursery in Cape Town.

Methods: Retrospective blood culture data for 12 months were collected at three time points over a 15-year period. Blood cultures from 2004, 2013 and 2017 were analysed. All neonates with growth on blood cultures were included.

Results: During 2004 a total of 817 (43.3% of total admissions) blood cultures were taken, 171 (9.1% of total admissions) were culture positive. The most common invasive organisms were Klebsiella pneumoniae (31.8% of invasive organisms), S.aureus (26.1%) and enterococcus species (7.3%). There were 102 contaminants (12.5% of total cultures) of which 7.8% were due to Coagulase-negative Staphylococcus (CONS).

In 2013 a total of 1070 (46.8% of total admissions) blood cultures were taken, 124 (5.4% of total admissions) were culture positive. Common invasive organisms were Klebsiella pneumoniae (53.8% of invasive organisms), E. coli (12.8%) and S. aureus (10.3%). Forty-six blood cultures were deemed contaminated (4.3% of all cultures) and of these 2.1% were due to CONS.

In 2017, there were 581 blood cultures taken (26.5% of total admissions), 56 were culture positive (2.6% of total admissions). Commonly occurring invasive organisms were Klebsiella pneumoniae (32.4% of invasive organisms), Group B streptococcus

(16.2%) and Acinetobacter (13.5%). Twenty-nine blood cultures were considered contaminated (5.6% of cultures) of which 1.7% were CONS.

The gram-negative organisms showed an increasing resistance to penicillin, ampicillin and aminoglycosides but remained sensitive to carbapenems.

Conclusions: The initial reduction in positive blood cultures from 2004 to 2013 was primarily due to the reduction of contaminants, probably reflecting improved blood sampling techniques. The large reduction in Gram-negative organisms from 2013 to 2017 suggests improved infection control measures, but gram-negative organisms remained prominent in all three cohorts. Emergence of resistant organisms is concerning and in keeping with other nurseries worldwide. These data illustrate the need for antibiotic stewardship, infection control measures and ongoing surveillance.

Introduction

According to the World Health Organisation (WHO), an estimated 5 million neonates die annually with approximately 1.6 million deaths in developing countries due to neonatal sepsis[1-3]. Neonates are vulnerable to infection, partly due to an immature immune system that is unable to respond adequately to infection. They exhibit both qualitative and quantitative defects in their complement system and low concentrations of immunoglobulins[4]. Compounding this, their immature skin forms a weak barrier against the environment and admission to hospital may involve invasive procedures which can place them at risk for acquiring infection.

Neonatal sepsis is defined as a clinical syndrome in an infant aged 28 days or younger, manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream[5]. It may be further categorised as early-onset sepsis (EOS), occurring within the first 72 hours, or late-onset (LOS) sepsis, occurring after 72 hours[4]. EOS is infection acquired before or during delivery with 85% presenting within the first 24 hours[5]. LOS is associated with Hospital-acquired Infections (HAIs) or community acquired sepsis. More resistant organisms are expected from hospital-acquired late sepsis when compared to vertically transmitted or community acquired sepsis [6]. It has been documented in previous studies that hospital-acquired

neonatal infections are 3–20 times higher in resource-poor than resource-rich countries[7].

Gram positive organisms such as Group B Streptococcus (GBS) are a major cause of neonatal sepsis (EOS and LOS), first identified in the early 1960's. The neonatal infection rate of GBS through vertical transmission ranges from 1-2/1000 live births and maternal prophylaxis against this pathogen has been implemented in some countries around the world since the 1990's. [8]. Coagulase negative staphylococcal (CONS) can be implicated in both early and late neonatal sepsis – there are no definitive guidelines on classification of CONS as a pathogen or a contaminant but it may be considered a contaminant in the absence of central lines or other instrumentation [9] [10]. Gram negative organisms are also emerging as a cause of serious neonatal infections. E.coli, Klebsiella pneumoniae and Pseudomonas Aeruginosa are such organisms found to cause both early and late sepsis.[11, 12] No prophylaxis or screening exists for these organisms, therefore prompt identification and treatment is necessary.

Overuse of broad-spectrum antibiotics is what drives emergence of resistance. Surveillance and antibiotic stewardship help prevent inappropriate antibiotic use. In South Africa the surveillance programme as outlined by the department of health focuses on the ESKAPE pathogens (Enterococcus faecium/faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Escherichia coli species) and Candida within blood cultures only, as they are the leading causes of nosocomial infections throughout the world[13].

The Groote Schuur Hospital (GSH) Neonatal Unit, with its 75-bed capacity, admits more than 2000 neonates per year with over 500 of these being classified as Very Low Birth Weight infants (infants below 1500g). The nursery is a tertiary referral centre for the Metro West geographical service area of the Western Cape, South Africa. The GSH Neonatal Unit policy for suspected sepsis is based on a consistent approach to antibiotic usage to provide optimal cover while being mindful about limiting the emergence of resistant micro-organisms[14]. Empiric antibiotic usage is determined by local epidemiological and susceptibility data. Periodically surveying the causes of sepsis and their antibiotic sensitivity patterns is pivotal in the design of effective infection control programmes and in guiding empirical antibiotic therapy [2,

[15, 16]. We therefore sought to describe the changes in cultured organisms and their antibiotic sensitivities, over an extended period in our nursery.

Objectives

The objectives of this study were:

1. To compare the incidence of culture positive neonatal sepsis over a 15-year period in our tertiary neonatal unit
2. To compare the pathogens and antibiotic resistance profiles over the same period.

Methods

Blood culture and sensitivity data were retrospectively collected from the National Health Laboratory Service (NHLS) and ward databases. For interval surveillance purposes, three time periods were included for comparison: 2004, 2013 and 2017. These periods were chosen because the first complete database was established in 2004; 2013 reflects a quality improvement project undertaken to determine changing sensitivities and 2017 was the most current year of a complete set of data. Due to the nature of the database, only blood cultures that were flagged positive were included – those flagged positive from cerebrospinal fluid, pleural or ascitic fluid, pus swabs and other tissue cultures were not evaluated.

A blood culture is considered the gold standard for sepsis diagnosis. At the GSH neonatal unit, absolute indicators for blood culture and empiric antibiotic treatment include maternal invasive bacterial infection requiring antibiotics (suspected or confirmed), confirmed or suspected infection in twin, respiratory distress starting more than 4 hours after birth, mechanical ventilation in a term baby, seizures and signs of shock. Relative indications include prelabour ROM, GBS in previous baby, maternal fever greater than 38 degrees, apnoea, altered behaviour/tone, but empiric antibiotics would only be initiated if more than one of the above were present[14].

Positive blood cultures were further scrutinised to determine whether they were likely contaminants or likely invasive organisms. With regards to invasive organisms, it is important to note that the GSH maternity department does not routinely do GBS

screening. Organisms that were considered to be contaminants were: Coagulase Negative Staphylococcus (CONS) and less common organisms including Corynebacterium, Morganella, Bacillus cereus, Staphylococcal epidermidis and Streptococcus (viridans, sanguinis, mitis, bovis, salivarus). These were considered contaminants because central lines are not routinely inserted for infants being managed at GSH nursery and this approach did not differ during the 15-year time period.

Data were analysed with Stata software version 12 (Statacorp, College Station, Tex., USA). Proportions were compared using the chi-squared or Fisher-exact test depending on expected frequencies. Statistical significance was set at $p<0.05$. Ethical approval for the study was obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee.

Results

The frequencies of positive blood cultures and organisms cultured for the three time periods are shown in Table 1. The number of admissions increased from 2004 to 2013 and was similar thereafter. The total number of blood cultures taken per number of admissions decreased from 43.3 % in 2004 to 26.5 % in 2017 - a progressive and highly significant reduction ($p<0.001$). The proportion of positive blood cultures also decreased progressively and significantly from 9.1% to 2.6%. The decrease in positive cultures was reflected both in the contaminants (12.5% to 5.6%) and the invasive organisms (3.7% to 1.7%). The most frequent contaminants were CONS and these species also showed a sustained reduction.

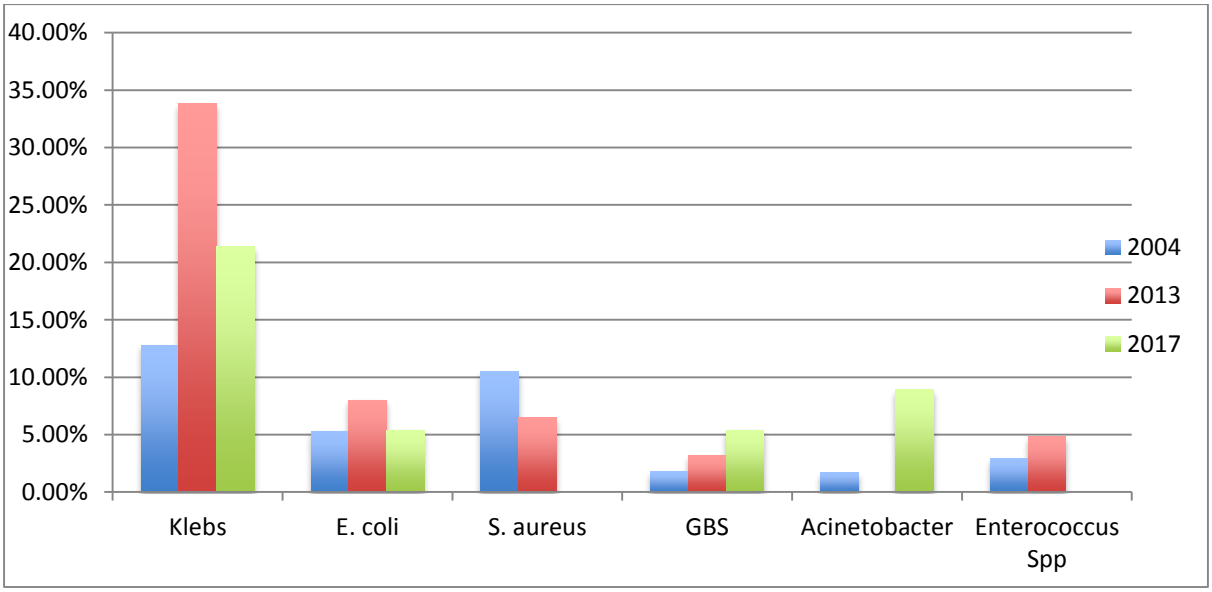
Table 1: Frequencies of positive cultures and organisms cultured

	2004	2013	2017	p-value
Admissions	1887	2285	2190	-
Blood cultures taken n (% of admissions)	817 (43.3)	1070 (46.8) *	581(26.5) †	< 0.001
Positive cultures n (% of admissions)	171 (9.1)	124 (5.4) *	56 (2.6) †	< 0.001
Culture positivity rate (% of cultures taken)	21%	12%*	10%	< 0.001
Invasive organisms n (% of admissions)	69 (3.7)	78 (3.4)	37 (1.7) †	< 0.001
Contaminants n (% of cultures)	102 (12.5)	46 (4.3) *	29 (5.6)	< 0.001
CONS n (% of cultures)	64 (7.8)	22 (2.1) *	10 (1.7)	< 0.001
Acinetobacter n (% of invasive organisms)	2 (2.9)	0	5 (13.5) †	0.002
Enterobacter species n (% of invasive organisms)	4 (5.8)	2 (2.6)	1 (2.7)	0.549
Enterococcus species n (% of invasive organisms)	5 (7.3)	6 (7.7)	0	0.228
E. Coli n (% of invasive organisms)	9 (13)	10 (12.8)	4 (10.8)	0.681
GBS n (% of invasive organisms)	3 (4.3)	4 (5.1)	6 (16.2)	0.056
H. Influenzae n (% of invasive organisms)	2 (2.9)	0	0	0.185
Klebsiella n (% of invasive organisms)	22 (31.8)	42 (53.8) *	12 (32.4) †	0.012
Pseudomonas n (% of invasive organisms)	2 (2.9)	1 (1.3)	2 (5.4)	0.443
Staph aureus n (% of invasive organisms)	18 (26.1)	8 (10.3) *	0 †	0.001
Serratia n (% of invasive organisms)	3 (4.3)	3 (3.8)	1 (2.7)	0.914
Listeria n (% of invasive organisms)	0	1 (1.3)	2 (5.4)	0.106
Sternotrophomonas n (% of invasive organisms)	0	1 (1.3)	1 (2.7)	0.431
Candida sp n (% of invasive organisms)	0	3 (3.8)	3 (8.1)	0.077

* $p < 0.05$ compared to 2004; † $p < 0.05$ compared to 2013

There were 13 different invasive organisms identified in the three cohorts. The most common was Klebsiella pneumonia. The frequencies of the six most common organisms are shown in Figure 1. There was a significant increase in Klebsiella pneumonia from 2004 to 2013; and a subsequent decrease from 2013 to 2017 ($p<0.05$), although in 2017 the frequency was the same as 2004. Only S. aureus had a significant reduction at each time point ($p<0.05$). Over the three cohorts, methicillin-resistant staphylococcus aureus (MRSA) was only cultured once in 2013. Of note, previously almost non-existent Acinetobacter baumannii emerged as a significant organism in 2017 ($p<0.05$). In 2017, all cultured Acinetobacter showed resistance to carbapenems (whereas they were sensitive in 2004). The frequencies of GBS progressively increased, but the differences were not significant.

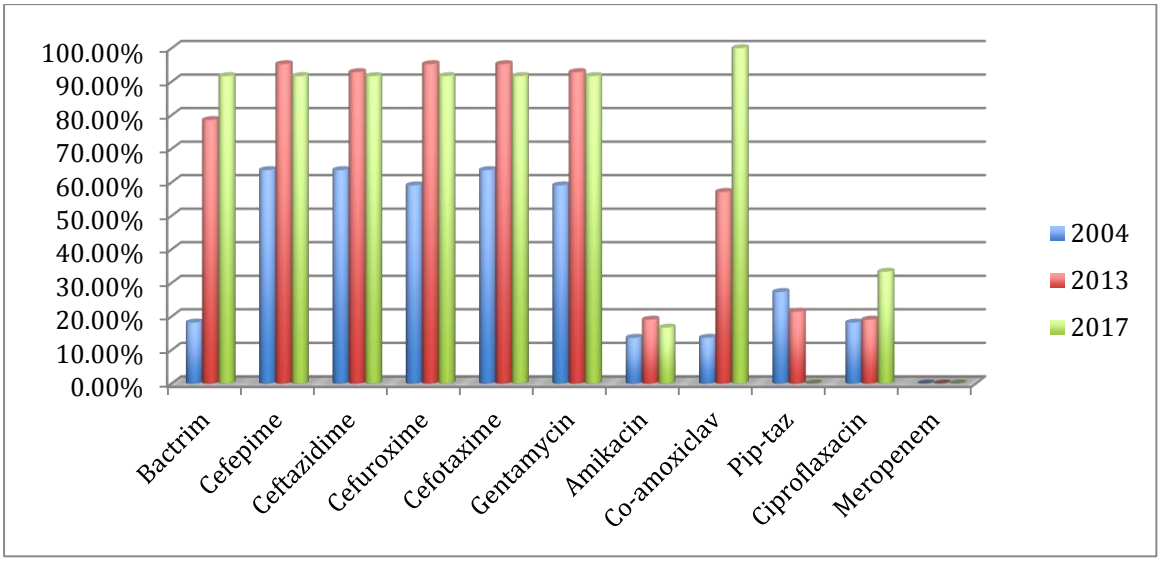
Figure 1: Most common invasive organsisms as a percentage of all invasive organisms



The antibiotic sensitivities of invasive organisms were variable. The Klebsiella pneumonia group was the largest group and hence the most useful to consider as a benchmark. The variation in antibiotic sensitivity for this group is shown in Figure 2. Comparatively, the Klebsiella pneumonia organisms cultured in later cohorts of 2013 and 2017, showed an overall resistance to Bactrim, Cephalosporins, Gentamycin and Co-amoxiclav – ESBL species dominated with more than 90% resistance to Cefepime, Ceftazidime and Cefotaxime during these two time periods. Most

organisims remained sensitive to Amikacin, Piptazobactam and Ciprofloxacin. All organisms remained sensitive to Meropenem.

Figure 2: Frequencies of antibiotic resistance for Klebsiella Pneumonia



Discussion

This study shows a progressive decrease in number of blood cultures taken and organisms cultured during the 15-year period; but also, emergence of resistant organisms. The reduction in blood cultures taken may reflect application of more stringent indications for culture. The clinical signs for neonatal sepsis are often nonspecific and in the GSH Neonatal Unit neonates who meet suspected sepsis criteria are screened.

Antibiotic resistance, mainly driven by antibiotic misuse and overuse, is a global phenomenon and across the world and all medical units (including neonatal) are becoming wary of this multi resistant organism problem. While awaiting the development of new antibiotics, we must be careful against multidrug resistant Gram negative bacteria, highlighting the need to preserve what we have and use it appropriately[17].

In our first cohort (2004), the total number of positive blood cultures were slightly more than that documented by F. Motara et al (171 vs 140)[12]. Although they are a

South African neonatal unit (not tertiary), their invasive organisms cultured was far greater in number than any of our cohorts but this is likely because they considered CONS as an invasive organism (132 invasive organisms vs 69 for GSH)[12] . Our total number of positive blood cultures was lower (and decreased in our latter cohorts) as compared to a tertiary neonatal unit in South Africa as documented in E. Ballot et al[15] (171-124-56 vs 246). We suspect the reason for our much lower positive yield was due to our focussed screening protocols and because we considered CONS a contaminant in our unit.

The reduction in blood cultures taken may alternatively reflect improved infection control measures and a decreased frequency of HAIs. The infection control measures that were introduced included written policies prioritising and reinforcing hand washing and a 'bare-below-elbows approach', establishing a uniform blood culture technique, antibiotic stewardship and insertion and management of central lines according to a standardised protocol [18].

Although the frequency of both invasive organisms and contaminants were reduced during the 15-year period, the greatest reduction in positive cultures was seen in the number of contaminants. The decrease in invasive organisms may be due to improved infection control measures since the number of infants admitted from other hospitals increased during this time so it is less likely due to the demographic of the admitted infants.

CONS cultured far less in our unit over our three cohorts than what was seen by Lebea et al. (23.7%) in their tertiary neonatal unit review[16]. Particularly in our later cohorts (2013 and 2017), the reduction in contamination rates during the study was probably due to more stringent blood-taking protocols and blood culture bundles that were implemented to ensure all cultures taken were done in sterile manner. By continually auditing how staff take samples and ensuring that we screen only those neonates with suspected sepsis, we hope this will aid in further decreasing contamination in our unit in the future. By continuing to implement the above measures and by continuing to educate our staff as demonstrated by Raban et al within our unit, we have continued to demonstrate our earlier findings in decreasing contamination [18].

Unlike the low GBS rates documented by Lebea et al (1.3%) [16] and F. Motara et al

(1.5%)[12], GBS remains of concern in our unit. The trend towards increased frequency of GBS infection stresses the need for maternal screening and intrapartum prophylaxis. We agree with Koenig et al that despite being in an era of screening, GBS continues to be an important cause of sepsis, and thus remains a significant public health issue. Measures that augment its diagnosis and prevention are important to prevent neonatal morbidity and mortality.[8]

Early and efficient diagnosis of neonatal sepsis remains nuanced as clinical manifestations vary greatly. This necessitates the use of an empiric antibiotic therapy approach based upon the suspicion of sepsis [12]. While evidence is lacking, the choice of antibiotics for suspected neonatal sepsis may be guided by the spectrum of organisms from surveillance of cultures, for example the prevalence of Group B Streptococcus and Gram negative organisms [19].

It is important to monitor changing organisms within a neonatal unit with emerging new pathogens. The emergence of resistant organisms is of concern in any unit worldwide. MRSA is known to be an important pathogen in the NICU setting. In our study however, the nursery is relatively spared but it is a well documented threat we must continue to monitor[20]. Acinetobacter baumanii showed a statistically significant emergence in 2017 ($p<0.05$) compared to 2013 and 2004 cohorts. Acinetobacter was also completely resistant to carbapenems in 2017 as compared to 2004. This resistance pattern has been shown in other institutes [16, 21]. It is prudent to continue monitoring for highly resistant organisms to effectively manage the vulnerable population we manage. The organisms responsible for neonatal sepsis differ across nurseries[22]. Surveillance is critical because one organism may over time replace another as the leading cause of neonatal sepsis in a particular nursery or geographical region. This is further compounded by the fact that local drug resistance profiles change over time, thereby complicating treatment regimens [12].

At GSH Neonatal Unit, penicillin or ampicillin (if penicillin is out of stock) and gentamycin are our first line empirical antibiotics of choice for suspected sepsis and have been so over all three time periods. For suspected LOS in 2004 we empirically used penicillin/ampicillin and amikacin. Data from the 2013 cohort resulted in a change following the emergence of resistant organisms to the two antibiotics particularly the aminoglycosides. All infants that develop suspected nosocomial

sepsis are now commenced on a carbapenem (meropenem) to which all organisms remain fully sensitive. Once the organism is identified and the sensitivity pattern is known, antibiotics are downscaled appropriately. At GSH Neonatal unit, probiotics were not used during the 15 year period under review.

Limitations and Strengths

The study has limitations. It is retrospective from a single unit and the data was limited to what was available on the NHLS database. There was no review of files to obtain demographic and further clinical details, however the number of admissions has remained relatively stable over the time periods studied. Due to the nature of the data set, no comment could be made about previous unit protocols nor could we comment on the timing of infection control measures implemented. The strengths of the study are that it refers to complete blood culture data over three separate time intervals and is based in a unit with uniform, protocol-based management principles.

Conclusion

This study provides insight into the evolving pathogens and guides the appropriate antibiotics for empiric therapy in our nursery. The initial reduction in positive blood cultures from 2004 to 2013 was primarily due to the reduction of contaminants, probably reflecting improved blood sampling techniques and unit protocols. The large reduction in Gram-negative organisms from 2013 to 2017 indicates improved infection control measures, but gram-negative organisms remained prominent in all three cohorts. Emergence of resistant organisms is concerning and in keeping with other nurseries worldwide. These data illustrate the need for antibiotic stewardship, infection control measures and ongoing surveillance.

Conflict of interest / Funding sources

None.

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APPENDIX A : INSTRUCTIONS TO AUTHORS (SAMJ)

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

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

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

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

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

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

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion

section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections:

Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that <u>may</u> appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.

- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide
  consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).

- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

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

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

Rather:

Each row of data must have its own proper row.

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

Rather:

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

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

Rather:

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

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

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

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

APPENDIX B : ETHICS APPROVAL

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 March 2017

HREC REF: 164/2017

Prof Michael Harrison
Neonatology
H-Floor, OMB

Dear Prof Harrison

PROJECT TITLE: A SURVEY OF NEONATAL SEPSIS AND ANTIBIOTIC SENSITIVITY PATTERNS AT GROOTE SCHUUR NURSERY, COMPARING 2004 WITH 2013 (MMed-candidate Dr N Naidoo)

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

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 30 March 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)

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.

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

The HREC acknowledge that the student, Dr Nayestha Naidoo will also be involved in this study.

Yours sincerely

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

HREC 164/2017

APPENDIX C : STUDY DEVIATION

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30·03·2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	4/3/2019

Comments to PI from the HREC
Thank you for the deviation document

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	18/12/18		
HREC REF Number	164/2017	Current Ethics Approval was granted until	30/03/2018
Protocol title	A SURVEY OF NEONATAL SEPSIS AND ANTIBIOTIC SENSITIVITY PATTERNS AT GROOTE SCHUUR NURSERY, COMPARING 2004 WITH 2013 (MMed-candidate Dr N Naidoo)		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes No X		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof M Harrison /Student Nayestha Naidoo		
Department / Office Internal Mail Address			

HUMAN RESEARCH ETHICS COMMITTEE
FHS016
04 MAR 2019
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature		Date	

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	27/02/2019
HREC REF Number	164/2017
Project Title	Neonatal sepsis and antibiotic sensitivity patterns at a south african tertiary nursery – evolution over a 15year period
Protocol number (if applicable)	
Principal Investigator	Prof M.C Harrison / Student – Dr Nayestha Naidoo
Department / Office Internal Mail Address	m.harrison@uct.ac.za

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
Ethics has expired as the study took longer than anticipated to gather information required

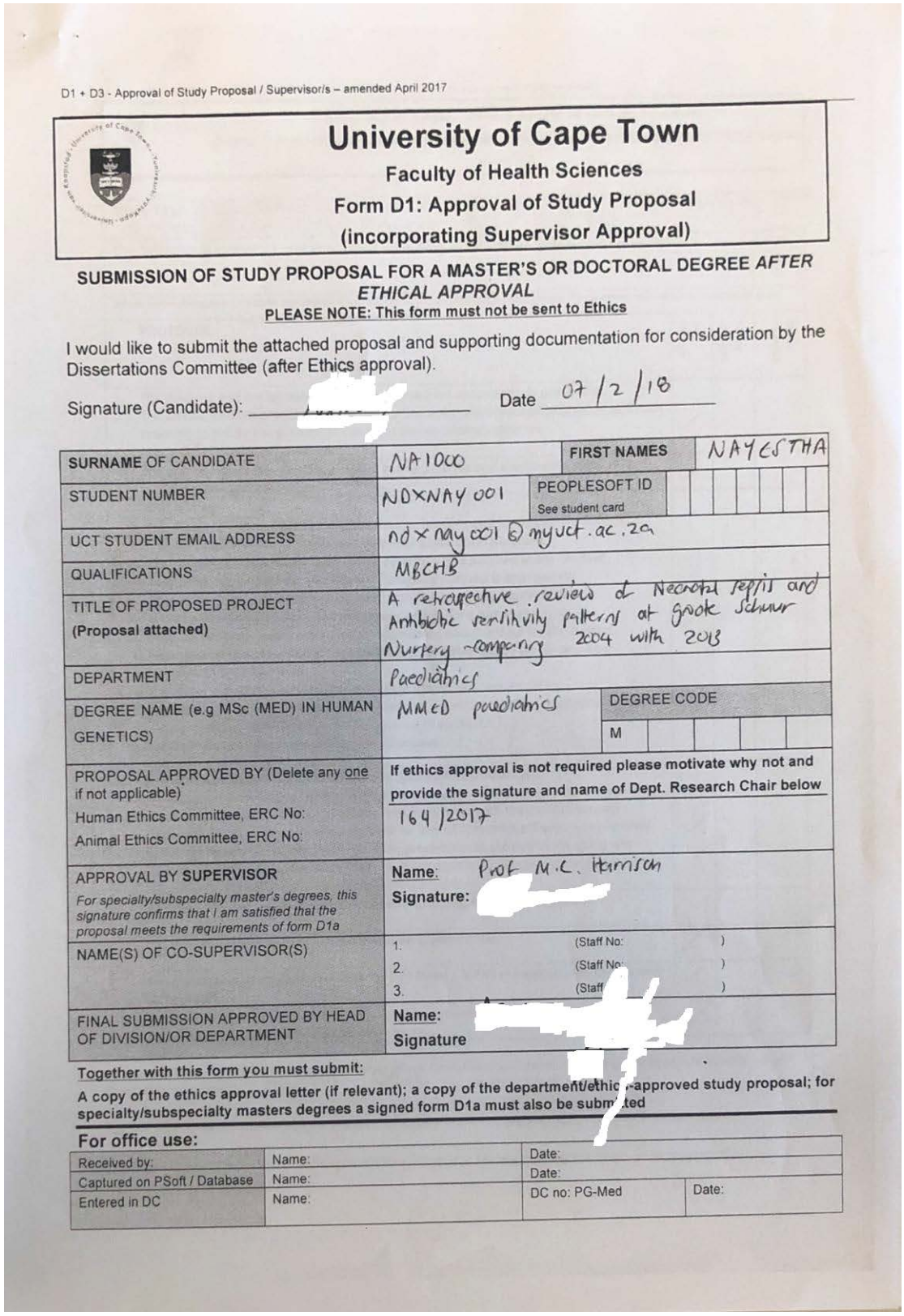
3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.
Information is now completed and write up is underway. Timeline to submission is within the next few weeks.

4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.			
Signature of PI		Date	**4/03/2019**

APPENDIX D : DEPARTMENT RESEARCH APPROVAL



D1 + D3 - Approval of Study Proposal / Supervisor/s – amended April 2017

University of Cape Town

Faculty of Health Sciences

Form D1: Approval of Study Proposal

(incorporating Supervisor Approval)

SUBMISSION OF STUDY PROPOSAL FOR A MASTER'S OR DOCTORAL DEGREE *AFTER ETHICAL APPROVAL*

PLEASE NOTE: This form must not be sent to Ethics

I would like to submit the attached proposal and supporting documentation for consideration by the Dissertations Committee (after Ethics approval).

Signature (Candidate): _____ Date 07/2/18

SURNAME OF CANDIDATE	NA1000	**FIRST NAMES**	NAYCSTHA
STUDENT NUMBER	NDXNAY001	PEOPLESOFT ID See student card	
UCT STUDENT EMAIL ADDRESS	ndxnay001@myuct.ac.za		
QUALIFICATIONS	MBCHB		
TITLE OF PROPOSED PROJECT **(Proposal attached)**	A retrospective review of Neonatal sepsis and Antibiotic sensitivity patterns at Groote Schuur Nursery comparing 2004 with 2013		
DEPARTMENT	Paediatrics		
DEGREE NAME (e.g MSc (MED) IN HUMAN GENETICS)	MMED paediatrics	DEGREE CODE M	
PROPOSAL APPROVED BY (Delete any one if not applicable) Human Ethics Committee, ERC No: Animal Ethics Committee, ERC No:	**If ethics approval is not required please motivate why not and provide the signature and name of Dept. Research Chair below** 164/2017		
APPROVAL BY **SUPERVISOR** *For specialty/subspecialty master's degrees, this signature confirms that I am satisfied that the proposal meets the requirements of form D1a*	**Name:** Prof M.C. Harrison **Signature:**		
NAME(S) OF CO-SUPERVISOR(S)	1. (Staff No:) 2. (Staff No:) 3. (Staff)		
FINAL SUBMISSION APPROVED BY HEAD OF DIVISION/OR DEPARTMENT	**Name:** **Signature**		

Together with this form you must submit:

A copy of the ethics approval letter (if relevant); a copy of the department/ethics-approved study proposal; for specialty/subspecialty masters degrees a signed form D1a must also be submitted

For office use:

Received by:	Name:	Date:	
Captured on PSoft / Database	Name:	Date:	
Entered in DC	Name:	DC no: PG-Med	Date: