COST OF ANTIBIOTICS USED FOR NOSOCOMIAL INFECTIONS IN A NEONATAL UNIT AT KALAFONG HOSPITAL

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

Johannesburg, May 2012
DECLARATION

I, Sentime Kitambala declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the branch of Pharmaceutical Affairs, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this, or any other university.

A SENTIME

18 day of MAY 2012
DEDICATION

To the sacred memory of the late William Ouvermans
To Benedicte Sentime Misamu
ABSTRACT

Introduction

Nosocomial infections which occur after 72 hours in hospitalised neonates cause morbidity and mortality particularly in very low birth weight neonates admitted to a neonatal intensive care unit (NICU). Prolonged hospitalisation and use of sophisticated, expensive antibiotics lead to spiraling costs. Prevention of nosocomial infections are of the essence to contain expenditure and prevent life-threatening complications in vulnerable neonates. A prospective, descriptive study was undertaken to determine the cost of antibiotics used in the neonatal unit at Kalafong Hospital for nosocomial infections.

Patients and Methods

Neonates with nosocomial infections admitted consecutively to the neonatal unit were studied prospectively by documenting the birth weight, site of infection, pathogen, outcome, admission to the NICU and antibiotics administered. The cost related to antibiotic use was determined for each antibiotic, for individual neonates (expressed as the mean and standard deviation) and for the group as a whole.

Results

Over a period of seven months (1/1/2011 – 31/7/2011) 682 neonates with a mean birth weight of 2375g ±668g were admitted to the neonatal unit for ≥72 hours of whom 53/682 (7.8%) developed a nosocomial infection and of the 53 who developed a nosocomial infection, eight demised (15.1%). Of the remaining 629 neonates who did not develop a nosocomial infection, 15/629 (2.4%) demised (p=0.7). Nosocomial infection occurred in 21/36 (58%) neonates <1000g vs 22/646 (3.4%) ≥1000g (p<0.01). Of 199/682 neonates admitted to the NICU, 42/199 (21.1%) developed a nosocomial infection vs 11/483 (2.3%)
not admitted to the NICU (p<0.01). Of 22 pathogens cultured from blood, coagulase negative *Staphylococcus aureus* was the most common (7/22). The total cost of second line antimicrobials (meropenem, vancomycin and fluconazole) for the study period of seven months was R27 032.00 of which an amount of R10 321.00 was spent on neonates weighing <1000g. The mean cost per neonate was R563.77±283 for meropenem (n=51), R70.23±32 for vancomycin (n=5) and R78.66±53 for fluconazole (n=6) of which drug wastage comprised at least 50% in each instance.

**Conclusions**

Extremely low birth weight (<1000g) and admission to the NICU place neonates at risk of nosocomial infection at Kalafong Hospital. Meropenem was the most commonly used second line antibiotic followed by vancomycin and fluconazole. Pharmaceutical curtailment of expenditure generated by nosocomial infections should be addressed by the manufacture of vials with a lower concentration of drug for neonates to minimise wastage.
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CHAPTER 1. LITERATURE REVIEW

1.1 Introduction

Neonatal deaths account for over one-third of the global burden of child mortality (Zaidi et al, 2005). The majority of neonatal deaths occur in developing countries where mortality rates are as high as 50 per 1000 live births (Hyder et al, 2003).

Neonatal infection, and nosocomial infection in particular, is the cause for many neonatal deaths, in spite of new advances in antibiotic therapy (Yalaz et al, 2006). A nosocomial infection – also referred to as a hospital-acquired infection - is defined by an infection acquired during hospitalisation, which was not present or incubating at the time of admission and may be incubating at the time of discharge only to manifest at a later stage (Clark et al, 2004).

Neonates, i.e. newborn infants up to 27 completed days of life, are at risk for nosocomial infection because of the hospital environment which is dramatically different from the sterile environment of the uterus. In addition, many of a newborn infant’s defense mechanisms are not fully developed such as phagocytic activity, immunoglobulin synthesis and T-lymphocyte function (Brady, 2005). Neonates admitted to neonatal units are exposed to invasive procedures and devices which compound the risk for the acquisition of a nosocomial infection (Mahfouz et al, 2010).

Nosocomial infection is associated with a prolonged length of hospital stay which results in an increased use of resources and spiraling costs without taking into account antibiotic or other therapeutic costs, as well as having a negative effect on quality of care and patient safety (Vincent, 2003).
morbidity in vulnerable patients in all levels of care and remains a major public health problem (WHO, 2002).

In developed countries with effective infection control measures the risk for the development of a nosocomial infection remains high. During 2002 in the USA approximately 1.7 million hospitalised patients had a nosocomial infection of whom 100 000 died (Borkow et al, 2010). In Switzerland approximately one of twenty and in Italy one of ten hospitalised patients contracted a nosocomial infection between 1996 and 2000 respectively (Lizioli et al, 2003; Pittet et al, 1999). In Germany the number of nosocomial infections for 2006 was between 400 000 and 600 000 and the attributable mortality between 10 000 and 15 000 patients (Gastmeier, 2008).

In developing countries the prevalence of nosocomial infections is not well established because of a lack of centralised guidelines, staff and resources (Hall, 1998). The risk of developing a nosocomial infection in a clinical setting in a developing country is higher than in a developed country and is the principal cause of morbidity and mortality among hospitalised neonates (Ahmed et al, 2002). Premature infants are particularly vulnerable with a nosocomial infection afflicting 30 - 60% and a mortality of 40 - 60% (Shama et al, 1993). The root cause may be poor infection control due to limited resources and staff shortages which impact negatively not only on patient care and hospital budgets but also on the economic well-being of countries (Ilan et al, 2005).

The magnitude of the problem, expressed as infection rates, may be stated as a percent of admissions, percent of live-born neonates or by the number of infections per 1000 patient days. Since up to one third of preterm neonates may have more than one nosocomial
infection episode, infection rates per patient day probably give a more accurate estimate of the magnitude of the problem, while rates per patient group gives an idea of the incidence rate (Clark et al, 2004).

Ongoing surveillance of hospital expenditure on nosocomial infection is important, to determine trending of cost due to the use of second and third line antimicrobials and sustainability (WHO, 2002). Ultimately nosocomial infection is preventable by means of an integrated and monitored programme emphasising effective hand-washing, appropriate use of antimicrobials and minimising invasive procedures. Good hand hygiene is the cornerstone in the prevention of nosocomial infections and is achieved by an appropriate hand-washing technique (duration of wash and chlorhexidine gluconate containing soap) (Boyce, 1999).

The impact of nosocomial infection is extensive and includes emotional stress, functional disability, increased length of hospital stay and increased monetary expenditure. It has become one of the leading causes of death worldwide in poor and rich population’s alike (Ponce-de-León, 1991). In resource-poor countries even the in-hospital transmission of HIV has evolved due to the unsafe administration of medications.

1.2 Nosocomial Infection in Neonates

1.2.1 Definition

Nosocomial infection means any infection (blood stream, lungs, central nervous system, skin or urinary tract) and is distinguished from nosocomial sepsis which relates to a blood stream infection. Nosocomial sepsis may on the other hand also be accompanied by pneumonia, meningitis or urinary tract infection. Confirmed nosocomial infection is defined
by a positive culture from a sterile site such as blood, urine and cerebrospinal fluid in the presence of clinical signs. A positive culture can however occur with no clinical signs, while clinical signs may be present with a negative culture.

Neonatal infections are described using the terms early-onset and late-onset infections. Early-onset infections are those presenting and confirmed within the first 72 hours of life and are related to maternal risk factors and birth canal acquisition, whereas late-onset infections occur after 72 hours of life, related to acquisition in the hospital environment. A neonatal nosocomial infection implies a late-onset infection in a hospitalised neonate (Clark et al, 2004; Harris et al, 2001).

For this study, a nosocomial infection is defined by an infection presenting after 72 hours of life, namely a late-onset infection. This infection is diagnosed in the presence of clinical symptoms and a positive culture from a sterile site (blood, urine, cerebrospinal fluid) or in the event of a negative blood culture, a raised C-reactive protein (CRP) value of ≥5mg/L and/or a neutrophil leucocytosis or leucopaenia.

1.2.2 Epidemiology

Over the past 30 years, improvements in neonatal care have increased the survival of critically ill neonates but these improvements have simultaneously generated associated morbidities one of which is nosocomial infection (Craft et al 2001; Zafar et al, 2001). In many neonatal care units it has become the major cause of morbidity and mortality and affects the cost of medical care by increasing resource consumption and the length of hospital stay (Gaynes et al, 1996; Mahieu et al, 2001). Studies from the USA report
nosocomial infection rates in neonatal units up to 25% (Stover et al, 2001; Sohn et al, 2001; Stoll et al, 2002).

In developing countries neonatal infections are estimated to cause 1.6 million deaths annually or 40% of all neonatal deaths (Zaidi et al, 2005; Vergnano et al, 2005). Neonatal infections, including nosocomial infections, as a cause of death in newborn infants ranged from 25% to 71% in recent hospital based studies in India and 16% to 55% in a survey in Kenyan first referral level hospitals (English et al, 2004). Rates of infection increase with decreasing gestational age and birth weight.

1.2.3 Pathogenesis
The most important risk factor for nosocomial infection in neonates is prolonged use of indwelling, intravascular catheters (Heeg, 2006). Indwelling intravascular lines are a common cause of nosocomial infections. Microbes enter extraluminally via the skin at the insertion site and through the catheter hub after colonization. Worldwide the majority of very low and extremely low birth weight neonates receive indwelling intravascular lines increasing the risk of line-related infections. The majority of bloodstream infections in these neonates are related to the intravascular lines and the most frequent pathogens are coagulase-negative staphylococci (Zingg et al, 2011). Other risk factors include associated illnesses which lead to the use of invasive procedures, exposure to antibiotics which select resistant bacterial strains, prolonged hospitalization, contaminated support equipment and enteral feeds and lipid-containing intravenous solutions used for parenteral hyperalimentation.
Gram-positive organisms may be introduced from the environment or the patient's skin. Gram-negative enteric bacteria are almost always derived from the patient's endogenous flora, which may have been altered by antecedent antibiotic therapy or populated by resistant organisms transferred from the hands of personnel or contaminated equipment. Therefore, situations that increase exposure of the newborn to these bacteria result in higher nosocomial infection rates.

Lack of knowledge and training about basic infection control processes, coupled with inadequate infrastructure, systems of care and resources contribute to these infections (Mahfouz et al, 2010). The rate of nosocomial sepsis increases with the degree of both prematurity and low birth weight. Neonates are susceptible to infection due to immaturity of immune function and impaired defense mechanisms.

Human breast milk has been shown to have a protective effect against infections. Neonates fed human breast milk are less likely to develop nosocomial infections compared to formula-fed neonates (Narayan et al, 1981). The anti-infective effect of human milk is dose dependent and neonates who receive human breast milk exclusively have fewer episodes of infection (Sohaner, 2001). Human breast milk is used exclusively in the neonatal unit at Kalafong Hospital. Adoptees and infants whose mothers are ill and/or are lactating ineffectively receive donor human breast milk from the on-site milk bank at the hospital.

Antibiotics are the most commonly prescribed medications in neonatal units especially during the first postnatal days, when most culture results are negative (Cotten et al, 2009). Virtually all extremely low birth weight neonates (<1000 g) receive empirical antibiotic
treatment during the first postnatal days despite a low incidence of culture-proven bacterial sepsis (Clark et al, 2006; Stoll et al, 2005). Antimicrobial agents perturb colonisation of the intestinal flora in extremely low birth weight infants and prolonged duration of the initial empirical antibiotic therapy may lead to increased rates of necrotising enterocolitis and death (Cotton et al, 2009).

Confirmed nosocomial infection occurs in around 30% of very low birth weight infants but antibiotic use (especially vancomycin) is more common. Suspected nosocomial infection therefore drives the use of broad-spectrum antibiotics and their overuse in turn predisposes neonates to serious infections such as candidaemia and gram-negative sepsis (Clark et al, 2004).

1.2.4 Clinical Presentation

Currently there seems to be no reliable tool for the early diagnosis of sepsis in neonates. Astute clinical observation of subtle clinical signs identifies individual infants who may have a nosocomial infection. The most common symptoms and signs include episodes of apnoea, temperature instability, feeding intolerance, abdominal distension, bradycardia, lethargy, hypotension, less vigorous sucking, respiratory distress, hypotonia, jaundice and vomiting (Fanaroff et al, 1998). An abnormal white cell count, unexplained metabolic acidosis, hyperglycaemia, an elevated CRP >5mg/dl or rising are the most common laboratory indicators (Fanaroff et al, 1998). The combination of clinical signs and laboratory values (elevated CRP, neutropenia, neutrophil leukocytosis, immature neutrophils) suggest the diagnosis of sepsis, but they have a poor positive predictive value. Adjunctive diagnostic tests include procalcitonin, cell surface markers CD11b and CD64, granulocyte colony-stimulating factor, interleukin 6, interleukin 8 and members of...
the interleukin 1 family and various leukocyte adhesion factors (Mishra et al, 2006). While
the sensitivity, specificity, as well as positive and negative predictive values are promising
for many of these tests alone and most compelling in combinations, the majority are not
available in clinical settings. Although culture methods may have improved in sensitivity
(not all bacterial and fungal organisms grow readily in clinical laboratory conditions)
additional molecular methods may be useful (Whitley, 2008; Palacios et al, 2008) but are
not widely available.

Despite the limitations of clinical signs and laboratory tests, they are used to diagnose
nosocomial infection and sepsis and are used to decide whom to treat and when to stop
treatment. The uncertainty generated by the absence of good predictors, laboratory tests
in particular, for nosocomial infection and sepsis is one of the causes for the overuse of
antibiotics in vulnerable neonates (Stoll et al, 2002).

1.2.5 Diagnosis of Nosocomial Sepsis

A positive blood culture remains the gold standard for the diagnosis of nosocomial sepsis.
However, two errors can be made in evaluating neonates with possible sepsis. These
include a type 1 error (false positive result due to a contaminant) and a type 2 error (false
negative result).

A type 1 error occurs when a positive culture is accepted as true when the neonate does
not truly have a bacteraemia. Type 1 errors lead to the overuse of antibiotics and can
subsequently increase the risks for more serious infections. The best way to avoid type 1
errors is to prevent contamination of blood samples for culture by coagulase negative
staphylococci.
A type 2 error occurs when a negative blood culture result is accepted as proof that the neonate is not infected when, in fact, the neonate has true bacteraemia that has not been detected by the blood culture. Consequently, type 2 errors can lead to under treatment of neonates with life-threatening sepsis.

Obtaining small volumes of blood in the presence of low-density bacteraemia or fungaemia runs an appreciable risk of not finding an organism with a blood culture (Schelonka et al, 1998). In neonatal and paediatric case control studies, as many as 60% culture results are falsely negative if only 0.5ml of blood is obtained in low-colony count sepsis (Kennaugh et al, 1984; Brown et al, 1995). Obtaining 1 ml of blood for culture improves culture yields in neonates, but this can represent a significant blood volume loss for very low birth weight neonates (Kennaugh et al, 1984; Brown et al 1995).

The use of ancillary tests such as the CRP and white cell count may increase the odds of correctly identifying those neonates who have sepsis, but have negative culture results due to problems with blood sampling. However, these ancillary tests may have a good negative predictive value (i.e. normal values are reassuring that blood-stream infection is not present) but a low positive predictive value. The latter implies that these tests may be positive in the absence of a blood-stream infection (Hengst, 2003).

Serial CRP measurements are more valuable than single measurements, and in neonates who are suspected of having sepsis, may be useful in conjunction with leucocyte counts to decide in making a decision to withhold or stop treatment after negative blood cultures, but
they should not be used in isolation to decide who should receive a full course of antibiotics (Benitz et al., 1998; Chan et al., 1997; Pourcyrous et al., 1993).

In very low birth weight infants, fungal and gram-negative pathogens are associated with a lower platelet count and more prolonged thrombocytopenia compared to gram-positive pathogens, therefore changes in platelet counts may be useful as a marker for these more serious infections (Guida et al., 2003).

Laboratory tests to diagnose infection are unreliable and no specific test has been shown to be useful to diagnose a blood-stream infection which needs a course of antibiotics. In most cases, the result reveals that many neonates are treated who do not have a nosocomial infection. This facilitates the growth of resistant organisms in a neonatal unit which in turn leads to an increased use of expensive antimicrobials and spiraling costs. Of the essence is therefore to put in place effective strategies to prevent nosocomial infections in vulnerable extremely low birth weight neonates.

1.2.6 Pathogens

Gram-positive and gram-negative bacteria are the most common causes of neonatal infections accounting for 55% and 31% of microbes respectively (Makhoul et al., 2002). Gram-negative rods are major pathogens of neonatal sepsis in developing countries as shown in a review of 11471 bloodstream samples in which 60% yielded gram-negative rods (Zaidi et al., 2005). Klebsiella pneumoniae is the major gram-negative pathogen and is responsible for 16% to 28% of blood-culture confirmed sepsis in different regions of the world (Duse, 2005). Africa and South Asia have high rate of Staphylococcus aureus infections, whereas Latin
America, South East Asia and the Middle East have high reported rates of coagulase-negative staphylococcal infections (Hyder, 2003). The spectrum of pathogens in South East Asia and Africa is different from that observed in neonates in developed regions where Group B streptococci, Escherichia coli and coagulase-negative staphylococci are the predominant pathogens (Sanghvi et al, 1996; Stoll et al, 2002).

Staphylococcus aureus remains a very important neonatal pathogen in developing countries accounting for 6% to 22% of bloodstream isolates in different regions. Gram-positive organisms, group D streptococci such as Enterococcus faecalis and Enterococcus faecium and haemolytic streptococci account for most invasive bacterial infections.

Candida species have become increasingly important as causative agents of nosocomial sepsis, occurring in 4% of very low birth weight infants (Benjamin et al, 2003) and are associated with significant morbidity such as chronic lung disease, periventricular leukomalacia, retinopathy of prematurity and adverse neurological outcomes (Friedman et al, 2000).

The virulence of organisms differs. Gram-negative rods such as K pneumoniae can cause a fulminant clinical course which may be rapidly fatal while fungal sepsis is more indolent than gram-negative sepsis, but more fulminant than infection due to coagulase-negative staphylococci. The latter’s virulence may be underestimated because positive cultures may represent skin contaminants rather than blood-stream infections (Clark et al, 2004).

1.2.7 Types of Neonatal Nosocomial Infections
Nosocomial infections in neonates can be classified according to the site of infection such as blood stream, urinary tract, respiratory tract, intestinal tract, meninges, bones and joints, skin and eyes.

1.2.8 Nosocomial Infection in Neonates related to Clinical Practice

Certain clinical practices are associated with an increased risk of acquiring a nosocomial infection. These include empirical antibiotic use (Villari et al, 2000), treatment with dexamethasone and H2 blocker therapy (Stoll et al, 1999), mechanical ventilation (Negata et al, 2002), central venous catheters (Trodie et al, 2003) prolonged exposure to total parenteral nutrition (Mahieu et al, 2001), delayed enteral feeds (Stoll et al, 1996) and exposure to broad-spectrum antibiotics, in particular third-generation cephalosporins (Saiman et al, 2001).

1.2.9 Cost of Neonatal Nosocomial Infection

Nosocomial infections in the USA increase the cost of hospitalisation for infants in all birth weight categories, amounting to $10 000 – $15 000 per occurrence and prolong the length of hospital stay from four to seven days (Payne et al, 2004). Cost of nosocomial infections in developing countries and South Africa in particular has not been studied. The cost of medical care and a lack of resources in South Africa deny the smallest neonates access to intensive care in state hospitals. No surveillance system is in place in South Africa to monitor the burden and cost of nosocomial infections in low birth weight neonates and in neonates admitted to neonatal units in general. Thus the possibility of a cost-saving strategy related to preventable nosocomial infections has not been entertained. Similarly, the use of expensive antibiotics such as the carbapenems, fluoroquinolones and glycopeptides in neonatal units is not monitored to identify trends and opportunities for cost containment.
CHAPTER 2. METHODOLOGY

2.1 Aim
To determine the cost of antibiotics used to treat nosocomial infections in the neonatal unit at Kalafong Hospital over a 7-months period.

2.2 Objectives
Specific objectives in the costing procedure were studied, namely the total cost, the average cost per neonate and per drug and the cost related to the wastage of drugs.

2.3 Justification
The results of this study will be of value for the neonatal unit on one hand and for the pharmacy on the other hand as well as the hospital in general. It is important to know the expenses related to these infections and strategise on how to minimise them. In addition, this study is also important as it contributes to measure one of the components of the incremental cost of nosocomial infections and hospital expenditures. This study will also be of tremendous importance for the clinicians as the cost is an important factor and determines the physicians' choices of medication in the treatment of patients with specific nosocomial infections. To date, no similar studies have been done in the neonatal unit at Kalafong Hospital and the country as a whole and the results will provide useful information regarding antibiotic expenditure.

2.4 Study design
A prospective, observational study was conducted.
2.5 Study site

The study was conducted in the neonatal unit at Kalafong Hospital. This is a level 2 hospital with a level 3 neonatal service and is a teaching hospital for under- and post graduate medical students of the University of Pretoria. The hospital serves the south and central areas of Tshwane and also provides selected services to the province of Mpumalanga.

The neonatal unit at Kalafong Hospital serves the on-site obstetric unit (6000 deliveries per year), Pretoria West Hospital and Laudium Obstetric Unit. Neonates born at home or in the ambulance on the way to the hospital are also admitted to the unit. Annually around 1200 neonates are admitted of whom 50% (±600 neonates) weigh <2500 g (low birth weight) and of this group a further 50% (±300 neonates) weigh <1500 g (very low birth weight). The neonatal unit is comprised of three subunits, namely the neonatal intensive care unit (NICU), neonatal high care unit (NHCU) and neonatal low care unit (NLCU). The unit has a capacity of 36 beds of which six are in the NICU, twenty in the NHCU and ten in the NLCU. Admission criteria for the NICU include neonates in need of respiratory support and/or intensive monitoring. Neonates with a birth weight <1000 g also qualify for admission to the NICU if these criteria are met. Respiratory support implies tracheal intubation and intermittent positive pressure ventilation and high frequency oscillation if indicated. Parenteral hyperalimentation is provided if indicated. Invasive monitoring is not offered and central venous lines are inserted if a specific indication is identified, such as the need for long term parenteral hyperalimentation. Admission criteria for the NHCU include low birth weight neonates not in need of respiratory support or only supplemental oxygen therapy and non-invasive respiratory support including continuous positive airway
pressure (CPAP). Term neonates in need of supplemental oxygen therapy or other forms of basic care such as nasogastric feeds, phototherapy and intravenous fluids are admitted to the NLCU. The bed occupancy in the subunits ranges between 90% and 100% at all times.

The antibiotic policy in the neonatal unit allows for the empiric administration of crystalline penicillin G and amikacin as first line antibiotics after birth to neonates with a presumed congenital infection due to perinatal risk factors for infection and/or clinical signs such as respiratory distress. Resolution of clinical symptoms and a normal complete blood count and CRP on day three of life allow for cessation of antibiotic therapy.

In the event of a presumed nosocomial infection, meropenem is administered as second line empiric therapy while results of investigations and blood cultures are awaited. Should the neonate deteriorate or cultured organisms are not sensitive to meropenem, vancomycin and/or fluconazole are administered.

Antibiotic therapy is de-escalated as soon as the causative organism is identified. The duration of therapy is as short as possible and determined by the clinical improvement and CRP. Meningitis is treated for 14 days or 21 days in the event of a gram-positive or a gram-negative infection respectively.

Central venous and arterial lines are not used routinely and are the exception. Neonates who cannot be fed enterally and will need long term parenteral hyperalimentation receive a central venous line. A case in point is an neonate born with gastroschisis.
General measures to limit nosocomial infections include strict hand hygiene and exclusive breast feeding. On entry into the unit, hand washing is done using a hibitane containing solution. An alcoholic hand spray solution is available at all times at neonates' bedsides for use before and after contact. Neonates receive trophic feeds consisting of human milk within 1-2 hours after birth. Donor human milk from an onsite human milk bank is administered to adoptees, orphans and neonates whose mothers have insufficient milk. Adoptees and orphans receive donor human milk for a minimum period of fourteen days and then receive a preconstituted, sterile milk formula.

2.6 Study population

Neonates admitted consecutively to the neonatal unit at Kalafong Hospital from 1 of January to 31 July 2011, and who remained in the unit for more than 72 hours were studied. The neonates who developed a nosocomial infection after 72 hours, were studied as a proportion of the total number of neonates admitted over the same period. Neonates who demised within 72 hours of admission were excluded from the study since the time period did not satisfy the required length of hospital stay of 72 hours.

2.7 Sample size

The sample size was determined by the number of neonates admitted over the period of 1 January 2011 to 31 of July 2011 and who remained in the neonatal unit for at least 72 hours.
2.8 Methods
2.8.1 Data Collection
Neonates who developed a nosocomial infection were allocated a number for the purpose of the study and to ensure confidentiality. Data were recorded prospectively and included demographics, clinical features and outcome of the neonates. Antibiotics prescribed by the attending doctor in the event of a nosocomial infection (i.e. second line antibiotics) were recorded by the chief investigator (SK) as well as the dose, frequency, duration and wastage. Costing of the antibiotics was performed using current prices obtained from the hospital pharmacy price list of January 2011 (Appendix 1). According to this list the price for meropenem was R143.00 for a 500 mg vial, the price for vancomycin R33.00 for a 500mg vial and for fluconazole R34.00 for a 200 mg vial. The costs of antibiotics were recorded prospectively throughout the period of study (from 1 January 2011 to 31 July 2011). A data collection form was designed where information on nosocomial infections were recorded including number and types of infections, occurrences date and pathogens, antibiotics prescribed, the dose, the duration of treatment as well as the amount of the unused medicines.

2.8.2 Nosocomial Infections
Nosocomial infections were diagnosed by the neonates' attending clinicians. At initiation of antibiotic therapy the clinician reported the name and age of the neonate to the principal investigator (SK) who then documented the antibiotic use prospectively on a data capture sheet (Appendix 2).

A nosocomial infection was provisionally diagnosed in the presence of clinical signs indicative of a possible bacteraemia which included feed intolerance such as vomiting.
abdominal distension, increased residual volumes, temperature instability, apnoea, hypotonia and hypotension. Blood investigations were then carried out to confirm the provisional clinical diagnosis and included a complete blood count, CRP, blood culture and a lumbar puncture if indicated. Empiric antibiotics were initiated in anticipation of the results and were discontinued after the blood culture results became available (minimum period of 72 hours). In the event of a negative blood culture but other abnormal biochemical markers, antibiotic therapy was continued until the CRP had decreased to <10mg/dl and clinical improvement was present. Antibiotic therapy was also continued in the presence of clinical signs suggestive of a nosocomial infection but not confirmed by a positive blood culture or abnormal biochemical markers. In which case the duration of antibiotic therapy was continued until the clinical signs had abated. These neonates were also documented as having a nosocomial infection. Neonates who developed a urinary tract infection were not included in the study since none had indwelling catheters which may have precipitated an infection and neonates are prone to urinary tract infections because of incomplete bladder emptying. The types of nosocomial infections, pathogens and antibiotics used were recorded prospectively on the data capture sheet.

2.8.3 Costing of Antibiotics

The actual cost of an antibiotic administered to a neonate was calculated by the product of the total number of doses multiplied by the unit price. The wastage was calculated by the product of the number of doses not used multiplied by the unit price. The total cost per neonate was determined by adding the cost of the administered (therapeutic) antibiotic to the cost of the wasted antibiotic. The total cost was determined for the group as a whole, for individual neonates and for individual second-line antibiotics.
Each vial or ampoule or container of antibiotic prescribed may have the exact number of doses necessary to complete the treatments regimen indicated, this amount of medicine is referred to as the therapeutic and the cost related to is the actual cost. In occasion, there is a remainder of unused doses that are in excess and should be discarded, this unused portion is wastage or lost and the cost related to is the cost of wastage.

2.9 Statistical Analysis

Data were captured in Excel in order to compute tables. The accuracy of the data was verified and validity checks were performed. Statistical analyses were performed using SAS, release 9.2 and Statistix version 9. Chi-squared and Fisher’s exact tests were used to compare categorical variables and Student’s t-test for continuous variables. P values <0.05 were considered to be significant.

2.9.1 Demographic Information

Race and gender of the neonates who developed a nosocomial infection were summarised by frequency count and percentage, and weight by the mean and standard deviation.

2.9.2 Clinical Data

The types of nosocomial infections and pathogens were summarised by frequency counts and percentages. The neonates’ ages at the time of infection were described as occurring after 72 hours and before day eight, day eight to day fifteen, day sixteen to day twenty-three and day 24 and thereafter and were summarized by frequency counts and percentages.
2.10 Ethical Considerations

Permission to conduct the study was obtained from the Ethics Committees of the Universities of Pretoria (Appendix 3) and the Witwatersrand (Appendix 4).
CHAPTER 3. RESULTS

3.1 Demographics

Over a period of seven months (1 January 2011 – 31 July 2011) 712 neonates were admitted to the neonatal unit at Kalafong Hospital. Thirty neonates died within 72 hours of life and were excluded from the study leaving a sample size of 682 neonates who comprised the study group. For easy reference, results have been presented according to birth categories of neonates, namely: birth weight ≤ 1000g; birth weight 1000g – 1499g; birth weight 1500g – 1999g; birth weight ≥ 2000g. Of these neonates, 53/682 (7.8%) developed a nosocomial infection. They were predominantly black (48/53) and the male: female ratio was 1:1.04 which reflected the demographic features of the study group as a whole.

3.2 Outcome

Of 53/682 neonates who developed a nosocomial infection, 8/53 (15.1%) died. The mortality of the neonates who did not develop a nosocomial infection was 2.4% (15/629) (p=0.7).

3.3 Age at Diagnosis of a Nosocomial Infection

A nosocomial infection occurred within the first week of life in 15/53 (28.3%) neonates, during the second week in 25/53 (47.2%) and after the second week in 13/53 (24.5%).

3.4 Culture-Positive Nosocomial Infection by Birth Weight

The prevalence of culture-positive nosocomial infections are shown in Table 1. Of the neonates with a birth weight <1000 g (mean 819 g ±118), 6/21 (28.6%) had a culture-
positive nosocomial infection. A nosocomial infection was diagnosed within the first 14 days of life in 12/21 (57.1%) and in 6/21 (28.6%) the clinical suspicion of nosocomial infection was not substantiated by special investigations.

Of the neonates with a birth weight 1000 g – 1499 g (mean 1159 g ±106) 2/14 (14.3%) had a culture-positive nosocomial infection. In 12/14 (71.4%) a nosocomial infection was diagnosed within the first 14 days of life and in 7/14 (50%) the clinical suspicion of nosocomial infection was not substantiated by special investigations.

Of the neonates with a birth weight <1500 g (mean 1893 g ± 382) 6/18 (33.3%) had a culture-positive nosocomial infection. In 16/18 (88.9%) a nosocomial infection was diagnosed within the first 14 days of life and in 6/18 (33.3%) the clinical suspicion of nosocomial infection was not substantiated by special investigations.
Table 1. Neonates with a blood culture-positive nosocomial infection by birth weight

<table>
<thead>
<tr>
<th>Birth weight (mean)</th>
<th>&lt;1000 g (n = 21)</th>
<th>1000 - 1499 g (n = 14)</th>
<th>≥1500 g (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>819 g ±118</td>
<td>1159 g ±106</td>
<td>1893 g ±382</td>
</tr>
<tr>
<td>Number of Positive blood culture</td>
<td>6/21 (28.6%)</td>
<td>2/14 (14.3%)</td>
<td>6/18 (33.3%)</td>
</tr>
<tr>
<td>Number of Nosocomial Infection not substantiated</td>
<td>6/21 (28.6%)</td>
<td>12/14 (71.4%)</td>
<td>6/18 (33.3%)</td>
</tr>
<tr>
<td>Number of Nosocomial infection within 14 days of life</td>
<td>12/21 (57.1%)</td>
<td>7/14 (50%)</td>
<td>16/18 (88.9%)</td>
</tr>
</tbody>
</table>

3.5 Nosocomial Infection by Weight Category

The study group (n = 682) was divided into four weight categories and the prevalence of nosocomial infection was determined for each weight category (Table 2).
Table 2. Prevalence of a nosocomial infection (NI) by birth weight

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>No of survivors (n = 682)</th>
<th>No of neonates with NI (n = 36)</th>
<th>No of survivors with NI (n = 71)</th>
<th>No of deaths with NI (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 g</td>
<td>27 (75%)</td>
<td>21 (58%)</td>
<td>18/27 (67%)</td>
<td>3/9 (33%)</td>
</tr>
<tr>
<td>1000 - 1499 g</td>
<td>67 (94%)</td>
<td>14 (20%)</td>
<td>1/67 (16%)</td>
<td>2/4 (50%)</td>
</tr>
<tr>
<td>1500 - 1999 g</td>
<td>151 (97%)</td>
<td>14 (9%)</td>
<td>14/151 (9%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>≥2000 g</td>
<td>413 (99%)</td>
<td>4 (0.01%)</td>
<td>4/413 (0.01%)</td>
<td></td>
</tr>
</tbody>
</table>

3.5.1 Birth Weight <1000 g

This group was comprised of 36 neonates of whom 21/36 (58%) developed a nosocomial infection. Twenty-seven of the neonates survived [27/36 (75%)]. Eighteen of the 27 survivors (67%) had a nosocomial infection versus 3/9 (33%) of the neonates who died. The mean weight for this category was 813 ±115.

3.5.2 Birth Weight 1000 g – 1499 g

In this group of 71 neonates, 14/71 (20%) developed a nosocomial infection. Sixty-seven of the neonates survived [67/71 (94%)]. Eleven of the 67 survivors (16%) developed a nosocomial infection versus 3/4 (75%) of the neonates who died. The mean weight for this category was 1267g ±146.
3.5.3 Birth weight 1500 g – 1999 g
In this group of 156 infants, 14/156 (9%) developed a nosocomial infection. One hundred and fifty-one survived [151/156 (97%)]. Fourteen of the 151 survivors (9%) developed a nosocomial infection versus 0/5 neonates who died. The mean weight for this category was 1752 g ±137.

3.5.4 Birth weight ≥2000 g
In this group of 419 infants, 14/156 (0.01%) developed a nosocomial infection vs 0/6 neonates who died. The mean weight for this category was 2930 g ±587.

3.6 Prevalence of Nosocomial Infection in Neonates Admitted to the NICU Versus Neonates not Admitted to the NICU
Of the study group of 682 neonates admitted in the neonatal unit, 199/682 (29%) neonates (mean birth weight 2047 g, ±92) were admitted to the NICU at any time during the study period and 42/199 (20%) developed a nosocomial infection. Of these 199 neonates, 184/199 (92%) survived and 37/184 (19%) developed a nosocomial infection (mean birth weight 1261 g, ±567). Fifteen neonates demised [15/199 (8%)] and 5/15 (33%) developed a nosocomial infection and succumbed to it (bacteraemia in four and necrotising enterocolitis in one) (mean birth weight 990 g, ±26). Of 682 admitted in the neonatal unit, 483 neonates were admitted in the NHCU and NLCU.

Of the 483 neonates (mean birth weight 2511 g ±809 g) not admitted to the NICU, 474/483 (98%) survived and 11/474 (2.3%) developed a nosocomial infection. Of the 9/474 (2%) who died, 0/9 had a nosocomial infection.
Table 3. Prevalence of nosocomial infection in neonates admitted to the NICU (n=199) versus neonates not admitted to the NICU (n=483)

<table>
<thead>
<tr>
<th></th>
<th>Admitted to NICU (n = 199)</th>
<th>Not admitted to NICU (n = 483)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>184 (93%)</td>
<td>474 (98%)</td>
<td></td>
</tr>
<tr>
<td>Number of nosocomial infection</td>
<td>42/199 (21.1%)</td>
<td>11/483 (2.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of survivors</td>
<td>37/184 (20.1%)</td>
<td>11/474 (2.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>5/15</td>
<td>0/9</td>
<td></td>
</tr>
<tr>
<td>Birth weight (mean, SD)</td>
<td>2047 g ±921</td>
<td>2511 g ±809</td>
<td></td>
</tr>
</tbody>
</table>

3.7 Microbial Pathogens

In 35/53 (66%) neonates treated for a nosocomial infection, no pathogens were isolated.

The pathogens isolated in the remaining 18/53 neonates are shown in Table 4.
Table 4. Pathogens associated with nosocomial infections and isolated from blood cultures

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus coagulase negative</td>
<td>7</td>
<td>68.2</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Group B Streptococcus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus – methicillin resistant (MRSA)*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Gram negative organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>2</td>
<td>22.7</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans*</td>
<td>1</td>
<td>9.1</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>22</td>
<td>100</td>
</tr>
</tbody>
</table>

*In combination with an MRSA.*

Coagulase negative Staphylococcus (CoNS) occurred most commonly (seven isolates) followed by Enterococcus faecium (four isolates), Enterococcus faecalis (two isolates) and Klebsiella oxytoca (two isolates). Pseudomonas aeruginosa, Group B Streptococcus, methicillin resistant Staphylococcus aureus (MRSA), Proteus mirabilis, Enterobacter cloacae and Candida parapsilosis were isolated as separate pathogens in six separate
neonates. The neonate with the MRSA was also infected with Candida albicans which was isolated on two occasions. This was the only neonate with a central line for the purpose of parenteral alimentation for gastroschisis.

3.8 Costing

3.8.1 Total Cost

The second line antibiotics used during the study period were meropenem, vancomycin and fluconazole. The costs relating to these drugs are shown in Table 5. The total cost attributed to the use of second line antibiotics for the duration of the study period amounted to R27 032.00.

Table 5. Total cost of antibiotics for nosocomial infections by birth weight category

<table>
<thead>
<tr>
<th></th>
<th>&lt;1000 g (n = 36)</th>
<th>1000 g-1499 g (n = 71)</th>
<th>1500 g-1999 g (n = 156)</th>
<th>≥2000 g (n = 419)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>R10 800 (n = 21)</td>
<td>R5 027 (n = 13)</td>
<td>R6 731 (n = 13)</td>
<td>R3 440 (n = 4)</td>
<td>R25 998</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>R248 (n = 2)</td>
<td>R105 (n = 1)</td>
<td>R63 (n = 1)</td>
<td>R29 (n = 1)</td>
<td>R445</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>R273 (n = 2)</td>
<td>R199 (n = 2)</td>
<td>R99 (n = 1)</td>
<td>R18 (n = 1)</td>
<td>R589</td>
</tr>
</tbody>
</table>

Meropenem was administered to 51/53 neonates and was the most commonly used second line antibiotic. Vancomycin was administered to 5/53 infants in combination with
meropenem and/or fluconazole. The latter antifungal drug was administered to 6/53 neonates.

3.8.2 Cost by Birth Weight Category
The cost was determined by birth weight category and antibiotic used.

3.8.2.1 Birth Weight <1000 g
In this group 21/36 (58%) neonates received second line antibiotics resulting in a total cost of R11 321.00.

3.8.2.2 Birth Weight 1000 g – 1499 g
Second line antibiotics were administered to 13/71 (18%) neonates with a total cost of R5 331.00.

3.8.2.3 Birth Weight ≥1500 g
Second line antibiotics were administered to 21/575 (3.7%) neonates with a total cost of R10 380.00.

3.8.3 Cost per Neonate
The mean cost by antibiotic per neonate is shown in Table 5. For meropenem the mean cost was R563.77 ±283.44. The cost of wasted drug amounted to R257.85 ±168.15 per neonate. The mean cost per neonate was R70.23 ±32.21 for vancomycin and R78.66 ±53.22 for fluconazole. The wastage was R5815 ±26.07 for vancomycin and R72.48 ±48.40 for fluconazole. The mean cost of antibiotic used for therapeutic purposes was
R305.92 ±281.19 for meropenem, R12.08 ±6.16 for vancomycin and R6.71 ±6.19 for fluconazole.

Table 6. Mean cost per neonate (therapeutic, wastage and total) for second line antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Therapeutic cost (mean, SD)</th>
<th>Wastage cost (mean, SD)</th>
<th>Total cost (mean, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>R305.92 ±281.19</td>
<td>R257.85 ±168.15</td>
<td>R563.77 ±283.44</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>R12.08 ±6.16</td>
<td>R58.15 ±26.07</td>
<td>R70.23 ±32.21</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>R6.19 ±6.75</td>
<td>R72.48 ±48.40</td>
<td>R78.66 ±53.23</td>
</tr>
</tbody>
</table>

3.8.4 Total Cost by Antibiotic

The cost of meropenem (administered to 51/53 neonates) amounted to R25 998.00 and the cost of vancomycin and fluconazole amounted to R445.00 and R589.00 respectively.
CHAPTER 4. DISCUSSION

To the best of our knowledge this is the first study to report the cost of antibiotics prescribed for nosocomial infections in a neonatal unit of a South African state hospital. Nosocomial infections in neonates admitted to neonatal units remain a serious problem because these infections are associated with an increased morbidity and mortality and a prolonged hospital stay, particularly in very low birth weight infants and those receiving intensive care.

The overall prevalence of nosocomial infections in the neonatal unit at Kalafong Hospital is 7.8% with 53 neonates developing a nosocomial infection of a total group of 682 admitted over a period of seven months during 2011. Of these 53 neonates with a nosocomial infection 24/53 (45.3%) were not substantiated by a positive culture or a raised CRP value and received antibiotic therapy because of clinical features suggestive of a nosocomial infection. In the birth weight category <1000 g, 6/21 (29%) neonates received antibiotic therapy for an unsubstantiated nosocomial infection, 12/14 (71%) neonates in the weight category 1000 g – 1499 g and 6/18 (33%) in neonates ≥1500 g. Neonates with a birth weight between 1000 g and 1499 g are at risk of being treated for a nosocomial infection unnecessarily. The number of neonates with substantiated nosocomial infection is rather 29/682 (4.3%) instead 53/682 (7.8%). This scenario illustrates the fact that overuse of antibiotics may occur because of insensitive laboratory tests and clinicians’ strategy to rather treat unnecessarily than to lose an infant to nosocomial infection.

As expected, the prevalence of nosocomial infection is highest in neonates <1000 g at 58% and decreases to 20% in neonates with a birth weight between 1000 g and 1499 g and 9% in neonates in the weight category 1500 g to 1999 g. Five neonates demised
because of a nosocomial infection during the study period and they weighed <1500 g at birth.

Twenty per cent (42/199) of neonates admitted to the NICU develop a nosocomial infection versus two per cent (11/483) not admitted to the NICU. Of the very low birth weight (<1500 g) neonates 30% develop a nosocomial infection versus 2% of the neonates with a birth weight >1500 g. The high prevalence of nosocomial infection in vulnerable groups namely neonates admitted to the NICU and neonates <1000 g suggest that preventative measures such as meticulous hand hygiene, human milk, limiting the use of invasive procedures and using antibiotics judiciously are inadequate or inconsistently applied. It may also be a reflection of the susceptibility of these neonates to infection due to immaturity of their defense mechanisms.

Nosocomial infection rates in neonates are of limited value because of the variation in methods of surveillance and different denominators used. However, a clear relation has been shown between low birth weight and nosocomial infection (Drews et al, 1995). The findings of this study support this relationship.

The predominant organisms in the neonates with positive blood cultures are gram positive (15/22) and of these coagulase negative staphylococci predominate (7/15). Two of these seven isolates are associated with a raised CRP, while the remaining 6/8 isolates may have been contaminants. This low yield than expected of coagulase negative staphylococci is to be expected since indwelling intravascular catheters are rarely used in the neonatal unit at Kalafong Hospital. Gram negative organisms comprise 5/22 isolates and two of these five isolates are of the genus Klebsiella. Both these neonates demise.
A predominant anatomical site of infection does not occur and the nosocomial infections are assumed to be blood stream related. Other common types of nosocomial infection such as bronchopneumonia and necrotising enterocolitis are rare in the study group.

During the study period two second line antibiotics (meropenem and vancomycin) and one antifungal agent (fluconazole) were used to treat nosocomial infections. Meropenem was administered in the majority of neonates (51/53) at a total cost of R27 032-00, equating to an average monthly expenditure of R3 500-00. The total cost for vancomycin and fluconazole amounted to R445-00 and R589-00 respectively – amounts which are negligible in the context of an intensive care unit. Since no costing data are available from neonatal units in South Africa to use as comparison with the antibiotic costs of the neonatal unit at Kalafong Hospital.

The cost of second-line antibiotics for nosocomial infections at R27 032-00 over a period of seven months is an affordable expenditure if compared with the total expenditure for the hospital. Most of this expenditure (R25 998-00) was for meropenem, which is to be expected, since it is the first choice for a nosocomial infection. As expected, neonates <1000 g have the highest antibiotic expenditure at R11 321-00 which halves for the next two categories.

Of concern in terms of expenditure on antibiotics for nosocomial infections in neonates studied is the wastage encountered. This amounts to at least 50% of drug dispensed and occurs because of high concentrations of drug in vials developed for adults. While health care workers remain the key players in the prevention of nosocomial infections to curb
expenditure, a large "hidden" expenditure has been identified by the results of this study, due to wastage of drugs.

As a general rule the cost of antibiotics can be reduced if the duration of therapy is shortened (Brady et al, 2010). The safety of a short duration of antibiotic therapy in neonates has not been studied by means of randomised controlled trials and the possibility of an adverse outcome remains a concern. It is recommended that preemptive therapy be discontinued in the absence of positive blood cultures (Rubin et al, 2002). However, blood cultures may be falsely negative and ancillary tests such as a CRP may be useful to guide the duration of antibiotic therapy but needs to be substantiated in premature neonates. Continuation of preemptive therapy in the absence of positive blood cultures in neonates is considered to be a safe practice in these high risk patients to prevent an adverse outcome even though expenditure may be increased.

Coagulase negative staphylococci are the most common microbial pathogens isolated (7/22). Of concern is that vancomycin - the antibiotic of choice - may induce microbial resistance which may escalate antibiotic therapy and increase expenditure. Vancomycin therapy in the context of the study was limited to neonates in whom coagulase negative staphylococci were isolated in two follow-up cultures and in whom ancillary tests such as a CRP were also indicative of a nosocomial infection. Overuse of vancomycin in neonates ≤1500 g is a common problem in neonatal units and NICUs in particular (Sinkowitz et al, 1997; Stoll et al, 2002). Stable neonates should not receive vancomycin as empiric therapy in anticipation of blood culture results since coagulase negative staphylococcal infections are rarely fulminant (Karlowicz et al, 2000).
Gram-negative organisms should not be treated with cephalosporins because overuse leads to the emergence of resistant organisms and fungal infections (de Man et al, 2000; Benjamin et al, 2000). Neonates with nosocomial infections in the neonatal unit at Kalafong Hospital are not treated with cephalosporins with the exception of neonatal meningitis. For the duration of the study no neonate received a cephalosporin.

The study has limitations. The duration of hospital stay was not determined as well as the patient days of exposure to second line antibiotics (days on treatment per 1000 patient-days) for nosocomial infections. In addition, specific case definitions such as incidence densities (infections/1000 neonates) are preferable for comparison of results with other units. The gestational ages of the neonates were not analysed. Women seek antenatal care late during pregnancy which leads to inaccuracies in determining the duration of pregnancy as determined using clinical methods.
CHAPTER 5. CONCLUSIONS AND RECOMMENDATIONS

The cost of antibiotics used for nosocomial infections in the neonatal unit at Kalafong Hospital has been determined and can be used as a benchmark to determine trends in expenditure. Very small volumes are used in low birth weight neonates which may prevent high monetary expenditure but mask the fact that the prevalence of nosocomial infections in vulnerable low birth weight neonates remains high. Pharmacists and clinicians should advocate for the development of neonate/child-friendly vials of expensive antibiotics such as meropenem, vancomycin and fluconazole used for nosocomial infections to limit unnecessary wastage and expenditure.

A system for the surveillance of nosocomial infections in neonatal units should be developed and adopted as the norm to facilitate ongoing surveillance in real time. In this way the incidence rates can be monitored over time periods to determine ongoing morbidity, mortality and costs. The information obtained should have an impact in a timely manner.

Judicious use of antibiotics should be the norm. This implies using antibiotics with a narrow spectrum and limiting the use of those which impact on the indigenous microbial flora of the gastrointestinal tract. Use of third-generation cephalosporins, meropenem and vancomycin should be minimised or restricted and used only for serious infections for which alternate antibiotics are not adequate or appropriate.

Reduction of neonatal mortality in developing countries should focus on nosocomial infections. Infection control programmes and antibiotic policies should be in place and audits done to evaluate compliance. Nosocomial infections require expensive healthcare
resources and these can be better employed in neonatal care by the prevention of these infections.
REFERENCES


Fanaroff, A.G., Korones, S.B. & Wright, L.L., et al. 1998. Incidence, presenting features, risks and factors and significance of late onset septicemia in very low birth weight infants: 


<table>
<thead>
<tr>
<th>Ref no</th>
<th>Description</th>
<th>Budget</th>
<th>Quantity</th>
<th>Price</th>
<th>Value</th>
</tr>
</thead>
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<td>A2282</td>
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<td>3073101297</td>
<td>1</td>
<td>R 33.10</td>
<td>R 33.10</td>
</tr>
<tr>
<td>0011</td>
<td>FLUCONAZOLE POWDER FOR ORAL SUSPENSION 50MG/5ML; Infam</td>
<td>3073101297</td>
<td>1</td>
<td>R 0.00</td>
<td>R 0.00</td>
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<td>3073101297</td>
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</tr>
<tr>
<td>X2410</td>
<td>MEROPENEM TRIHYDRATE ANHYDROUS INJECTION 500MG/VIAL</td>
<td>3073101297</td>
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<td>R 42.15</td>
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<tr>
<td>X2420</td>
<td>MEROPENEM TRIHYDRATE ANHYDROUS INJECTION 1G/VIAL</td>
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<td>1</td>
<td>R 59.23</td>
<td>R 59.23</td>
</tr>
<tr>
<td>X2800</td>
<td>VANCOMYCIN HYDROCHLORIDE INJECTION 500MG/VIAL</td>
<td>3073101297</td>
<td>1</td>
<td>R 42.15</td>
<td>R 42.15</td>
</tr>
<tr>
<td>X3100</td>
<td>VANCOMYCIN POWDER FOR INJECTION USP; 1000MG/VIAL</td>
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<td>1</td>
<td>R 59.23</td>
<td>R 59.23</td>
</tr>
</tbody>
</table>

Budget Total: R 576.76
Demand Total: R 576.76
Appendix 1: DATA COLLECTION SHEET

1. DEMOGRAPHIC INFORMATION

Patient Hospital Number: 
Age/DOB: 
Gender: [ ] M [ ] F 
Race: [ ] Black [ ] White [ ] Indian [ ] Coloured 
Gestational Age: 
Body mass index: 

2. Clinical Data

<table>
<thead>
<tr>
<th>Type of Nosocomial Infection</th>
<th>Pathogen</th>
<th>Date Diagnosed</th>
<th>Weight at time of Infection</th>
<th>Length of stay in the intensive care Unit</th>
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3. Antibiotics Prescribed

<table>
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<tr>
<th>Name of ITEMS/Description</th>
<th>Strength</th>
<th>Dose/24 hours</th>
<th>Frequency</th>
<th>Date Started + Time</th>
<th>Date Ended + Time</th>
<th>Total Duration of Treatment</th>
<th>Amount of Unused Medicine per Unit Dispensed</th>
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</table>
The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002557, Approved dd 22 May 2002 and Expires 13 Jan 2012.

**UNIVERSITEIT VAN PRETORIA**
**UNIVERSITY OF PRETORIA**
**YUNIBESITHI YA PRETORIA**

Faculty of Health Sciences Research Ethics Committee
Fakulteit Gesondheidswetenskappe Navorsingsetiekomitee

**DATE:** 20/07/2010

**PROTOCOL NO.** 119/2010

**PROTOCOL TITLE**
Cost of antibiotics used for nosocomial infections in a neonatal unit at Kalafong Hospital.

**INVESTIGATOR**
Principal Investigator: Pharmacist K Sentime

**SUPERVISOR**
Professor AG Gous

**STUDY DEGREE**
Masters (M. Pharm)

**MEETING DATE**
30/06/2010

The Protocol was approved on 30/06/2010 by a properly constituted meeting of the Ethics Committee subject to the following conditions:

1. The approval is valid for 2 years period, and
2. The approval is conditional on the receipt of 6 monthly written Progress Reports, and
3. The approval is conditional on the research being conducted as stipulated by the details of the documents submitted to and approved by the Committee. In the event that a need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

Members of the Research Ethics Committee:

Prof M J Bester
(female) BSc (Chemistry and Biochemistry), BSc (Hons)(Biochemistry), MSc(Biochemistry), PhD (Medical Biochemistry)

Prof R Delport
(female) BA Sci, B Commercia(Hons)(Intensive care Nursing), MSc (Physiology), PhD (Medicine), M Ed Computer Assisted Education

Prof VOL Karusseit
MBChB, MFGP(SA), MMed(Chg), FCS(SA) - Surgeon

Prof JA Ker
MBChB, MMed(Chg), MD - Vice-Dean (ex officio)

Dr NK Likiti
MBCHB - Representing Nursing Department of Health

Prof TS Marcus
(female) BSc(Phys), PhD (University of Leth, Poland) - Social scientist

Dr MP Mathabula
(female) Deputy CEO: Steve Biko Academic Hospital

Prof A Nienaber
(female) BA(Hons)(Wits), BSc, LLM(UFS), PhD, Dipl. Demometrics(UKUSA) - Legal advisor

Mrs MC Nzeku
(female) BSc(NUL), MSc(Biochem)(UCL, UK) - Community representative

Dr L M Nhle
MBChB(StSudafrica), FCPSA

Marie J Phatholi
(female) BSc(ETCSA), BSc(Oncology Nursing Science) - Nursing representative

Dr R Reynolds
(female) BPharm, FCPharm (CMSA) NRCPCH (Loc-Cert Mat. One (CMSA)

Dr T Rossouw
(female) M.B.Ch.B. (cum laude); M.Phil (Applied Ethics) (cum laude); MPH (Nutrition and Epidemiology (cum laude); D.Phil

Dr L Schoeman
(female) BPharm, BA(Hons)(Psych), PhD - Chairperson: Subcommitte for students' research

Mr Y Sikweyiya
MPH, SARETI Fellowship in Research Ethics; SARETI ERCTP; BSc(Health Promotion)
Postgraduate Dip (Health Promotion) - Community representative

MS: dd 2010/08/11: C:\Documents and Settings\kunlcushi\Local Settings\Temporary Internet Files\Content.REP\1\VOR1\119\119[1].DOC
UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mr Sentele Kitambala

CLEARANCE CERTIFICATE

PROJECT

M10842
Cost of Antibiotics used for Nosocomial Infections in a Neonatal Unit, at Kalafong Hospital

INVESTIGATORS

Mr Sentele Kitambala

DEPARTMENT

Department of Pharmacy & Pharmacology

DATE CONSIDERED

27/08/2010

DECISION OF THE COMMITTEE:

Approved unconditionally

DATE

15/12/2010

CHAIRPERSON

(Professor PE Cleaton-Jones)

GUIDELINES for written informed consent attached where applicable

cc: Supervisor: Prof AS Gous

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES