UTILISATION ANALYSIS OF ANTIBIOTICS FOR THE PAEDIATRIC INTENSIVE CARE UNIT.

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ABSTRACT

The study's aim was to conduct a retrospective and prospective survey to determine the sensitivity patterns and prevalence of bacterial isolates obtained from cultures in patients with documented infections in the Paediatric Intensive Care Unit (PICU). Also, a pharmacokinetic analysis of amikacin was done in order to determine an appropriate dosing schedule.

The most prevalent micro-organisms isolated from the retrospective survey (1995 and 1996) in the PICU was *Staphylococcus epidermidis*. *Escherichia coli* was the second most prevalent micro-organism in 1995 (also being most prevalent gram negative micro-organism for the 2 years), with *Staphylococcus aureus* occupying that position in 1996. The micro-organisms that demonstrated the greatest resistance in 1995 and 1996 were *Enterococcus faecium* and *Staphylococcus epidermidis*, respectively for the gram positives; and *Klebsiella pneumoniae* and *Enterobacter sp.*, respectively for the gram negatives.

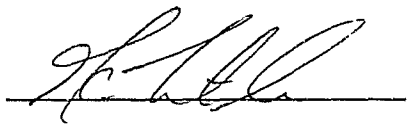
From the prospective survey, a total of 124 isolates were cultured (from 57 patients) of which 70.2% were considered nosocomial infections. Clinically significant nosocomial infections were the most prevalent infection group at 41.1%. Micro-organisms classified as clinically significant nosocomial infections were fairly resistant to commonly used antibiotics tested against them, except amikacin, imipenem and vancomycin.

The pharmacokinetic phase of the study found that the twice daily dosing regimen offered subtherapeutic peak serum concentrations, and high trough serum concentrations (which could predispose a patient to nephrotoxicity). The once daily dosing regimen resulted in peak concentrations that averaged 31.2 μg/ml and trough concentrations less than 5 μg/ml.

In conclusion, due to the evolving patterns in the development of resistance of micro-organisms to antibiotics it is important to implement a routine infection control surveillance in the PICU. In addition, the most appropriate means of reporting antibiotics sensitivities from the microbiology lab needs to be developed. This information should be evaluated on a regular basis in order to determine the most appropriate interventions and these interventions need to be monitored. In order to minimise the development of resistance the antibiotics need to be dosed appropriately and where necessary serum concentrations need to be obtained.

DECLARATION

I, Mopeli K. Ntabe declare that this dissertation is my own work. It is being submitted for the degree of Master of Pharmacy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



18 day of July, 1998.

To my family and Thenjiwe, for their love, support and encouragement.

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CHAPTER 1: INTRODUCTION

About 60 years ago, when a person walked into a hospital ward most of the cases one encountered were bacterial in nature, for example pneumonia, meningitis, bacteremia, typhoid fever, syphilis, etc. This was all in the pre-antimicrobial era. About 10 years ago in contrast, the predominant patient population had cases of cancer, heart disease or complications of diabetes or hypertension. All patients whose lives, had it been 50 years earlier, would have been in grave danger were spared as a result of the introduction and use of antimicrobial agents [Cohen,1992]. Medical practitioners suddenly had the ability to prevent, control transmission of or even cure infections. In fact in the 1980s, victories over infectious disease were declared to the point where significant cutbacks were made in antimicrobial development programs [Schentag, 1995].

Since the 1930s and 1940s, medical practitioners had literally remained ahead of most bacteria in the treatment of infections caused by resistant micro-organisms, since demands for more potent agents for resistant organisms had been met [Danziger, 1995]. Unfortunately today a very disturbing concept of "the prospect of therapeutic impotence" has been revisited [Kunin, 1993]. Patterns of discovery, prolific (and mostly inappropriate) use, and predictable decline in efficacy and purpose have been repeated following the introduction of new antimicrobials. This even prompted warnings by a prophetic few as far back as 40 years ago, who were none-the-less ignored. The opportunity to

prolong the effective life of much needed antimicrobials by using them appropriately was wasted by excessive use.

Although the development of new antimicrobial agents to combat resistant pathogens is actually a very feasible and desirable way to overcome such a problem, and had worked very well throughout the first part of the century [Danziger, 1995], "time is not exactly on our side", since it takes anywhere from 7 to 10 years for a drug to reach the market [Schentag, 1995], and pathogens now-a-days have become very adept at developing resistance. The increasing frequency of antimicrobial resistance is attributed to a combination of:

1. **Microbial characteristics** - these include the propensity to exchange genetic material, possess intrinsic resistance, survive varying environmental conditions, occupy particular ecological niches, easily colonise, and infect [Cohen,1992; Schentag, 1995].

2. **Human or environmental reservoirs in which resistant genes or organisms can persist** - the reservoirs are ecological niches (animate or inanimate) in which infectious organisms or genetic elements persist for the purpose of resistance development due to either exchange of genetic material, or continuous exposure to a particular pressure [Cohen,1992; Schentag, 1995].

3. **Selective patterns of antimicrobial use** - therefore there is a correlation between the frequency of antimicrobial use and frequency of antimicrobial resistance [Cohen,1992; Schentag, 1995].

4. **Societal and technologic changes that enhance the transmission and drug resistance of bacteria** - supportive care provided for medically compromised patients causes them to be focal points for the emergence and spread of resistant mutant organisms [Cohen,1992; Schentag, 1995].

The only feasible alternative left is for the medical community to become adaptive and develop strategies that prevent or limit the progress of pathogenic resistance [Schentag, 1995]. This is not possible without reliable information about the prevalence and the susceptibility of important human pathogens to antibiotics.

Since the growing antimicrobial resistance problem is an international problem, an informally constituted Antibiotic Study Group has been established in South Africa (as a result of recommendations by the World Health Organisation (WHO) Scientific Working Group on antimicrobial resistance) [Forder, 1995], to institute an Antibiotic Surveillance Programme to monitor the development of antibiotic resistance nationally. Included in the realm of some of the Study Group's objectives are:

1. to encourage a systematic approach to therapy based on rational choice of antibiotics for use in specific cases and discouraging indiscriminate use of antibiotics for prophylaxis and topical application.
2. encouraging the use of the serum assay services provided by medical school laboratories so as to improve standards of antibiotic treatment.

3. to publish on a regular basis tables of isolates and their resistance patterns [WHO Scientific Working Group, 1984].

Many of the studies that were based on the recommendations, concentrated mainly on adults [Till, Williams, Oliver, *et al*, 1991; Schentag, 1993; Thomas, Govil, Moses, *et al*, 1996], therefore there is a definite need to evaluate antimicrobial resistance problems in paediatrics, for in this patient population it is imperative for drugs used on them to be 100% effective due to combination of risk factors which compromise their state. However, assuming all the neonatal host risk factors were dealt with appropriately, we are still faced with an enormous problem, of the pathogens intrinsic ability to develop resistance.

There have been a number of antibiotic surveillance studies, however those that involved paediatrics mostly involved micro-organism prevalence in the paediatric wards [Hemming, James, Overall, *et al*, 1976; Sprunt, Leidy, Redman, 1978; Goldmann, 1981]. A dissertation by Funk [1992] was a little more specific when it: identified the prevalence of perinatally and nosocomially acquired bacteremia and fungaemia cultured from blood or cerebrospinal fluid isolates; identified the risk factors for infection, cause or common infections, and reported their outcomes; and analysed the susceptibility patterns of micro-organisms isolated with respect to antibiotics used and to changing antimicrobial policies. The results obtained were compared with reported studies. However when discussing the susceptibility patterns of the micro-organisms, their source or clinical significance was not taken into

consideration. Also pharmacokinetics were not included as possible reasons for resistance development.

This project concentrates on the efficacy of antimicrobial drugs in neonates and paediatrics against micro-organisms from various sources and varying clinical significance.

The 1995 antibiogram for the Paediatric Intensive Care Unit (PICU), showed that there were a number of bacterial species that had problematic tendencies in terms of prevalence and degree of antibiotic susceptibility. Micro-organisms that were found to be highly prevalent, in descending order were: *Staphylococcus epidermidis* (23.9%), *Escherichia coli* (10.2%), *Klebsiella sp.* (8.0%), *Streptococcus agalactiae* (7.4%), *Enterococcus faecalis* (6.3%) and *Pseudomonas aeruginosa* (5.1%). Those micro-organisms whose resistance were found to be an increasing threat to antibiotic use were: *Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumoniae, Klebsiella sp.* and *Pseudomonas aeruginosa.* The drug group highly affected by the pathogenic resistance was the cephalosporins. Besides the general antibiotic group results there were a number of startling individual results such as the growing resistance to piperacillin, amoxicillin/clavulanic acid, amikacin and the resistance of *Bacillus subtilis* to vancomycin.

From the 1995 antibiogram, a major decision made by the consultants in the PICU, was to discontinue the empiric use of cephalosporins, especially cefotaxime, for suspected nosocomial infections. Although the antibiogram

made an impact on the consultants, they were not thoroughly convinced with the results, for there were a number of factors not taken into consideration. For example, the antibiogram did not identify the sources of infection (i.e. whether the infections were community-acquired or nosocomially-acquired) or their clinical significance. As there is not a specific border (or value) designating antibiotic sensitivity and resistance, the sensitivity trend over a period of time can determine resistance development or regression. Since the 1995 antibiogram only offered information for one year, and to determine resistance patterns of antibiotics, their sensitivities have to observed over several years.

The prescribing practices of the registrars in the PICU, were consistent with conventional antibiotic dosing. However aminoglycosides and glycopeptides whose therapeutic efficacy is serum concentration dependent were exceptions. The dosing regimen adopted by the PICU was the twice daily dosing, as opposed to the recently accepted once daily dosing. This frequently resulted in high troughs (which were measured at unspecified times) which interfered with therapy, since the fear of nephrotoxicity in the paediatric population resulted in the discontinuation of amikacin. Measures conventionally employed to optimise pharmacological effect (i.e. obtaining high peak concentrations and low trough concentrations, initialising therapy with a loading dose and individualising the maintenance dose and dosing interval based on individualised pharmacokinetic parameters) were ignored. Therefore this study also included a pharmacokinetic analysis of amikacin.

1.1 RESEARCH OBJECTIVES

The aim was to conduct a prospective and retrospective survey of bacterial isolates obtained from cultures in paediatrics with infections. The goals of the study were:

1. to determine the sensitivity patterns and prevalence of clinically significant pathogenic micro-organisms in the PICU over time.
2. to identify the reasons for any possible problems once sensitivity/resistance trends are known
3. to develop appropriate interventions

CHAPTER 2: LITERATURE REVIEW

2.1 HISTORICAL BACKGROUND

Life has a funny way of repeating itself in almost all aspects of it. Like with clothes, where fashions may come and go, the return several decades down the line with a few improvements here and there but with the same general concept, bacterial diseases seem to follow this trend.

More than sixty years ago (a period termed the pre-antimicrobial era), the majority of cases encountered in a typical urban medical ward were pathogen-related in nature (for example pneumonia, meningitis, bacteremia, typhoid fever, syphilis, etc.) and these appeared in epidemic proportions and had few effective therapies to combat against them [Cohen, 1992]. Many of the patients, who were young presented with grim prognosis as mortality would arise as a result of the actual disease or its complications [Cohen, 1992]. In contrast between then and about 10 years ago, the prevalence of such pathogen-related cases declined, resulting in a relative rise in idiopathic cases such as cancer, heart disease, complications of diabetes or hypertension [Cohen, 1992]. Patients whose lives, had it been 60 years earlier, would have been in grave danger were saved as a result of the introduction and liberal use of antimicrobial agents [Danziger & Pendland, 1995]. The ability to prevent, control transmission or even treat infections had been achieved [Cohen, 1992]. In fact in the 1980s, victories over infectious disease were

declared to the point where significant cutbacks were made in antimicrobial development programs [Schentag, 1995].

Since the earlier half of this century, medical practitioners had literally remained ahead of most bacteria in the treatment of infections caused by resistant micro-organisms, since demands for more potent agents for resistant organisms had been met [Danziger, *et al.*, 1995]. Unfortunately today a very disturbing concept of "the prospect of therapeutic npotence" has revisited [Kunin, 1993] , because now micro-organisms that were at one time considered very easy to eradicate have become formidable opponents, making conditions that were at one time easy to treat now very difficult. Patterns of discovery, prolific (and mostly inappropriate) use, and predictable decline in efficacy and purpose has been repeated over and over following the introduction of new antimicrobials [Kunin, 1993]. This practice even prompted warnings by a prophetic few as far back as 40 years ago [Finland, Jones & Barnes, 1983], who were non-the-less ignored. The opportunity to prolong the effective life of much needed antimicrobials by using them appropriately was wasted by excessive unscrupulous use [Kunin, 1993].

2.2 IDENTIFIED REASONS FOR RESISTANCE DEVELOPMENT

Although the development of new antimicrobial agents to combat resistant micro-organisms is actually a very feasible and desirable way to overcome such a problem, and had worked very well throughout the first part of the century [Danziger, *et al.*, 1995], "time is not exactly on our side". It takes

anywhere from 7 to 10 years for a drug to reach the market [Schentag, 1995], and micro-organisms now-a-days have become very adept at developing resistance. Fortunately, investigations have been embarked on to explain why antimicrobial resistance occurs, with the results discerning important factors which if presented in assorted combinations, are able to determine the frequency of occurrence of drug-resistance in different ecosystems. The factors include:

1. microbial characteristics
2. human or environmental reservoirs in which resistant genes can persist
3. selective patterns of antimicrobial use
4. societal and technologic changes that enhance the transmission and drug resistance of bacteria [Cohen, 1992].

Microbial characteristics include the organisms ability to:

1. exchange genetic material (by either transformation, transduction or conjugation of plasmids)
2. possess intrinsic resistance (by chromosomal mutation or inductive expression of a latent chromosomal gene)
3. survive varying environmental conditions
4. occupy particular ecological niches or reservoirs (these are either imate or inanimate, in which an infectious organism or genetic element persists for the purpose of resistance development due to either exchange of genetic material, or continuous exposure to a particular pressure, and be transmitted)

5. ease to colonise, and infect [Cohen, 1992].

These are able to augment an organism's ability to emerge, persevere, or propagate [Cohen, 1992]. Therefore antibiotics are eventually rendered inactive by means of destruction or modification, prevention of access to the target site, or alteration of the antibiotic target site [Neu, 1992].

It is distinctly possible, to amplify the transmission and drug resistance of micro-organisms by societal and technological changes. Technological changes have facilitated improved infra-structure (thus improving on importation of resistant organisms) [Cohen, 1992; Kunin, 1993] and development of broad-spectrum antibiotics (which provide selective pressure to an increasing number of micro-organisms expediting resistance) [Cohen, 1992]. Societal changes such as changes in sexual activity and demographic changes (increased numbers of populations at risk of disease) also enhance development and transmission of antimicrobial-resistant organisms [Cohen, 1992]. Supportive care provided for medically compromised patients (appears to be an impact of the combination of societal and technological changes) can be focal points for the emergence and spread of resistant mutant organisms [Cohen, 1992; Schentag, 1995].

Reports have demonstrated a correlation between the frequency of antimicrobial use and the frequency of antimicrobial resistant bacteria [Neu, 1992; Kunin, 1993; Danzinger, *et al.*, 1995]. Long-term use and subtherapeutic dosing are associated with a greater risk of antimicrobial resistance development [Cohen, 1992].

2.3 NEONATAL/PAEDIATRIC RISK FACTORS FOR RESISTANCE DEVELOPMENT

Neonates and paediatrics require drugs to be 100% effective due to a combination of risk factors which compromise their state. The factors are:

1. birth weight or gestation
2. immunocompetence
3. presence of indwelling prosthesis
4. administration of Total Parenteral Nutrition (TPN) and lipids
5. exposure to antibiotics
6. colonisation of pathogenic bacteria [Hall, 1991].

An inverse relationship between birth weight or gestation and susceptibility to nosocomial infections has been established by many investigators, with low birth weight identified as the single factor most associated with increased infections [Goldmann, Durbin, & Freeman, 1981].

The inadequate bone marrow reserves of neutrophils and the decreased ability to regulate their release and regeneration, results in peripheral neutropenia as well as exhaustion of the neutrophil supply during sepsis [Hall, 1991]. The neutrophils from stressed neonates are also deficient in function where they lack adherence and chemotactic function, and intracellular

microbial killing, which render the neonate less able to localise and contain infection [Hall, 1991].

Indwelling prosthesis are associated with the initiation and persistence of invasive infections as they provide a safe niche for pathogens [Hall, 1991]. They offer them an opportunity to bypass the body's first barrier against infection, the skin, allowing invasion, adherence and colonisation into deeper tissues and the systemic circulation [Hall, 1991]. The persistence aspect is ensured by the provision of adherence which makes bacterial opsonization and ingestion more difficult [Hall, 1991].

Investigations have suggested that the duration of prior or current antibiotic therapy predisposes a patient to colonisation, nosocomial sepsis and development of increased resistance to pathogenic organisms [Hall, 1991].

Infants that require longer hospital stays along with intensive care are at risk of acquiring nosocomial infections [Goldmann, 1981]. The bacterial flora is radically different from what is normally expected, as a result predisposing the patient to infection [Hemming, Overall & Britt, 1976].

Associations between administrations of TPN and lipids and occurrence of infections have been observed and been attributed to presumably contaminated infusation fluids [Fleer, Senders, Visser, *et al.*, 1983]. Besides contamination being the only causative factor, another reason is they are

administered to the smallest, sickest neonates who are at risk of previously mentioned factors [Freeman, Goldmann, Smith, *et al.*, 1990].

Assuming all the neonatal host risk factors were dealt with appropriately, we are still faced with an enormous problem, of the pathogens' intrinsic ability to develop resistance.

2.4 IDENTIFIED RESISTANCE PATTERNS

As far back as 1959, a correlation had been detected between widespread use of chemotherapeutic and antibiotic agents and changes in the number and character of infections occurring in nurseries and maternity wards of hospitals [Finland, Jones & Barnes, 1959]. Since then, studies that have been conducted have involved:

1. proving a relationship between abnormal colonisation and infection [Sprunt, Leidy & Redman, 1978; Goldmann, 1981]
2. observing the prevalence of certain micro-organisms in nosocomial infections [Hemming, *et al.*, 1976; Thoburn, Fekety, & Cluff, *et al.*, 1968]
3. observing the sensitivity or resistance of micro-organisms notorious for causing epidemics or responsible for nosocomial infections [Neu, 1992].

4. and identifying the resistance mechanisms micro-organisms use against antibiotics [Cohen, 1992; Neu, 1992; Danziger, *et al.*, 1995, Dudley, 1995;].

These studies were not done in vain, for they have resulted in great progress in the fight against resistant micro-organisms. Aseptic techniques have been improved, optimal drug therapies have been devised, and new drug or drug combinations have been discovered as a result of the studies. Despite previous laborious victories, overall defeat seems imminent because antibiotic resistance is gaining [Kunin, 1993].

2.4.1 Measures undertaken to combat resistance

Two approaches which were developed to deal with the problem of antibiotic resistance were promoted by:

1. the International Congress of Chemotherapy (ICC) which advocated the informing of health professionals of the development of an array of new chemotherapeutic agents [Kunin, 1983].
2. the World Health Organisation (WHO) Scientific Working Group on Antimicrobial Resistance which advocated extensive world-wide surveillance of resistance, and development of methods which limited antibiotic use [Kunin, 1983; WHO memo, 1984].

It is not surprising the ICC approach was considered more desirable by the medical world [Kunin, 1983], even though the WHO group's proposed strategy was apparently more pragmatic.

An informally constituted Antibiotic Study Group has been established in South Africa (as a result of recommendations by the WHO Scientific Working Group) [Forder, 1995], to institute an Antibiotic Surveillance Programme to monitor the development of antibiotic resistance nationally. Included in the realm of some of the Study Group's objectives are to encourage a systematic approach to therapy based on rational choice of antibiotics for use in specific cases and discouraging indiscriminate use of antibiotics for prophylaxis and topical application; to encourage the use of the serum assay services provided by medical school laboratories so as to improve standards of antibiotic treatment; and to publish on a regular basis tables of isolates and their resistance patterns [WHO memo, 1984]. Since the beginning of the antimicrobial era and the subsequent emergence of resistant micro-organisms, scientists and the ever growing pharmaceutical industry have battled to devise more potent antibiotics to combat the growing resistant micro-organisms population. Because in the past such demands had always been met, the medical community expects that drugs will be discovered to treat resistant strains, and unfortunately these expectations have diminished the incentive for more rational antibiotic use [Danziger, *et al.*, 1995].

The only feasible alternative left is for the medical community to become adaptive and develop strategies that prevent or limit the progress of micro-organism resistance [Schentag, 1995]. This is not possible without co-operation in responsible prescribing by health care providers [Kunin, 1993] and reliable information about the prevalence and susceptibility of important human pathogens to antimicrobial agents [WHO memo, 1984]. Unfortunately

physicians wish to maintain their independent rights to prescribe drugs and bitterly resent attempts by others, no matter how expert, to infringe on their authority regardless of costs involved or eventual outcome [Kunin, 1983].

2.4.2 Resurgence achieved

According to Schentag [Schentag, 1993], the accelerated resistance development with β-lactam antibiotics (especially cephalosporins, specifically ceftazidime) is a common problem particularly if their use is increased to involve empiric therapies. Schentag *et al* restricted the use of ceftazidime for 3 months by frequently substituting it with a combination of tobramycin and piperacillin for empiric therapy of severe infections. After 3 months of the active intervention, ceftazidime sensitivities returned to baseline. Surprisingly there was no increased resistance to the tobramycin or piperacillin. In another investigation, an outbreak of *Klebsiella pneumoniae* infections resistant to ceftazidime were reported in a New York acute care hospital [Meyer, Urban, Eagan, *et al.*, 1993]. Although the outbreak evaded detection for about a year because most isolates appeared susceptible to some third generation cephalosporins, they were eventually identified during a routine infection control surveillance of multiresistant nosocomial infections. After restricting the use of ceftazidime and implementing barrier precautions for colonised and infected patients for 19 months, the frequency of ceftazidime-resistant *Klebsiella pneumoniae* declined.

These examples are proof that the WHO Scientific Working Group proposals do hold water, for with a lot of effort, imagination, and collective action, significant comebacks are possible.

CHAPTER 3: METHODS

The study was done in two parts.

3.1 PHASE 1 - THE RETROSPECTIVE STUDY

Phase 1 of the study consisted of a retrospective analysis of culture and sensitivity patterns of the Paediatric Intensive Care Unit (PICU) for the period of 1995 and 1996. The results were obtained from the South African Institute of Medical Research (SAIMR) and tabulated according to bacterial species and antibiotic susceptibilities. A total of 313 cultures were evaluated.

3.2 PHASE 2 - THE PROSPECTIVE STUDY

Phase 2 of the study consisted of a prospective analysis of positive culture results from the PICU from May to October 1997. Patients were considered eligible for the study if they were on antimicrobial therapy and a positive culture result was obtained. The patients were classified into 2 major groups, neonates and non-neonates. Neonates were infants less than 1 month of age and non-neonates were greater than 1 month. The neonates were divided according to weight: <1500 g; 1500 - 1999 g; 2000 - 2499 g; and ≥ 2500 g. Non-neonates were categorised by age: infants (those between 1 month and 1 year) and children (those older than 1 year). It was agreed that the cut off age for infants was to be 1 year because when looking at the history of the patients

admitted to the ward, those less than 1 year tended to be in and out of institutions and had a high probability of having a nosocomial infections, whereas those older than 1 year were more likely new admits to a hospital and more likely to have community acquired infections. Twenty nine neonates and 28 non-neonates were enrolled in the study. The age range was from 0 days to 13 years.

3.2.1 Surveillance procedures

On admission to the PICU the history pertaining to each patient was obtained along with the patients' demographic information such as weight, age, and sex.

The patients were evaluated on a daily basis for signs and symptoms of an infection and summary records were documented. This information was obtained from the patients' bed letter and routine laboratory results such as radiographic studies and culture reports.

All antibiotics that were prescribed for each patient were recorded, along with their doses, frequency, route of administration and length of treatment. The patients' charts were utilised to verify administration of their medication.

3.2.2 Classification of an infection

Infections were divided into:

1. Community acquired infections which are present on admission or acquired outside Johannesburg General Hospital (including previously attended health institutions) and clinically manifest themselves within 72 hours of admission to the hospital. Perinatally-acquired infections are also included into this group.
2. Nosocomial acquired infections which develop when a patient has resided in the unit for more than 72 hours (Hemming, *et al.*, 1976).

3.2.2.1 Clinical signifi ance or insignificance of an infection

The community and nosocomial infections were further divided into:

1. Clinically significant infections - once a positive culture result was obtained, a patient was considered to have a clinically significant infection if he received one or more courses of antibiotic treatment, had clinical signs and symptoms of an infection, and demonstrated abnormal diagnostic laboratory results.
2. Clinically insignificant infections - these were diagnosed if a patient was treated for not more than 3 days with an antibiotic, had no abnormal diagnostic laboratory results and the clinical symptoms resolved within 3 days.

3.2.3 Clinical signs and symptoms of an infection

Clinical diagnosis of infections was based on the following parameters:

1. Temperature irregularity - hypo- or hyperthermia
2. Change in behaviour - lethargy, irritability or change in tone
3. Skin - poor peripheral perfusion, cyanosis, mottling, pallor, petechiae, rashes, sclerema, jaundice
4. Feeding problems - feeding intolerance, vomiting, diarrhoea, abdominal distension with or without visible bowel loops
5. Cardiopulmonary - tachypnea, respiratory distress (grunting, flaring, retractions), apnoea, tachycardia, hypotension (tends to be a late sign)
6. Metabolic - hypo- or hyperglycaemia, metabolic acidosis

[Guerina, 1998].

The following laboratory results were used in the diagnosis of an infection:

1. positive culture results
2. abnormal full blood count (FBC)
    a. White blood cell counts taking into consideration leukocyte counts and neutrophil counts.
    b. Platelet counts
3. C-reactive protein - if greater than 15 after 24 hours
4. X-ray results consistent with a diagnosis of an infection

[Guerina, 1998].

3.2.3.1. Quality of sputum - Bartlett's Grading System

Sputum cultures were graded according to the Bartlett's Grading System to determine the significance or insignificance of the infection as seen in Table 3.1.

Table 3.1. Bartlett's Grading System

Cell type	Number of cells per low power field	Grade
Neutrophils	< 10	0
	10 - 25	+ 1
	> 25	+ 2
	Presence of mucus	+ 1
Epithelial cells	*10 - 25*	- 1
	> 25	- 2

If the final score was ≤ 0, no inflammation was considered present, therefore the specimen is considered saliva or contaminated by it (Johannesburg General Microbiology Lab).

3.2.4 Culture and sensitivity testing by the microbiology laboratory

Micro-organisms were identified by using standard laboratory methods, and their susceptibilities were assessed by using the Kirby-Bauer disk diffusion assay method (with National Committee for Clinical Laboratory Standards {NCCLS} adopted breakpoints).

The number of antibiotic sensitivities tested and reported to the ward for each isolate ranged from 2 to as many as 15. Only selected results were reported to the ward in order to offer the best alternatives for treating an infection. For the purpose of this study, all the antibiotics that were tested for each culture result were reported.

3.2.5 Sites of infection

The primary site of infection was classified according to the following criteria:

Sepsis

If a positive blood culture was obtained from peripheral vein sites rather than through indwelling vascular catheters and the patient had clinical signs and symptoms of an infection.

Pulmonary infections

If there was an appearance of an inflammatory infiltrate on a chest X-ray and a concurrent diagnosis of bacterial pneumonia (inflammation of the lungs with consolidation) had been made.

Wound/surface infections

If there was obvious inflammation or purulence (or both) and a bacterial pathogen was isolated from the wound or surface.

Cerebrospinal Fluid (CSF)

If a diagnosis was made in a patient with clinical features of meningitis and a pathogen was isolated from the cerebrospinal fluid (CSF).

Urinary tract infections

If a positive suprapubic needle aspirate urine culture, with or without pyuria or proteinuria was obtained.

Ear/eye infections

If a purulent discharge was obtained from the eye or ear and a bacterial pathogen was isolated from the eye or ear.

Abdominal infections

If a patient had clinical features of an abdominal infection supported by X-ray findings and the isolation of a pathogen from the peritoneal fluid if possible or the concurrent diagnosis of Necrotizing Enterocolitis (a type of acute intestinal necrosis).

3.2.6 Developing antibiograms

With the culture sensitivity results obtained from the Microbiology Lab, the percentage of isolate sensitivities to each antibiotic was calculated to represent its sensitivity. This is done as follows:

$$\text{Sensitivity} = \frac{\text{number of isolates sensitive to the antibiotic}}{\text{total number of isolates cultured}} \times 100$$

The higher the percentage value, the lower the resistance the micro-organism has (in other words the higher the susceptibility of the micro-organisms to the antibiotic).

3.3 PHARMACOKINETIC STUDY

Patients admitted into the PICU who received amikacin as part of their antibiotic treatment were included in the pharmacokinetic study which was done in two parts.

In the first part of this study, patients were administered their normal dosing regimen of 7.5 mg/kg intravenously over 30 minutes twice daily. Serum amikacin levels were obtained at steady state after the third dose. The peak concentrations were drawn 1 to 2 hours after the end of the infusion and the trough concentrations were drawn prior to the next dose.

In the second part of the study, the patients were administered a loading dose of 25 mg/kg intravenously over 30 minutes. Peak concentrations were drawn 2 hours after the end of the loading dose infusion and the trough concentration were drawn 10 hours after the end of the loading dose. Maintenance doses were calculated based on the patients individual pharmacokinetic parameters.

Serum amikacin concentrations were assayed by Fluorescence Polarisation Immunoassay technology (TDx® System, Abbott). The coefficient of variation was less than 5% for concentrations between 5 and 30 µg/ml, and the lowest measurable level that can be distinguished from zero with 95% confidence was 0.8 µg/ml.

The dosing regimen, patient weight and the drug serum concentrations (Cmax and Cmin) were used to calculate each individual patient's pharmacokinetic parameters. With the serum concentrations back extrapolated to the start of the infusion period to estimate the peak serum concentration, the apparent volume of distribution (Vd), elimination half-life ($t^1/_2$) and drug elimination rate (k_e) were calculated with the use of a linear one compartment model.

3.4 ANALYSIS OF DATA

3.4.1 Data analysis for Phase 1

The culture sensitivity results were tabulated into antibiograms by year. From there, the antibiograms from the 2 years were compared for any differences in micro-organism prevalence and progression of antibiotic resistance development (taking into consideration widely used antibiotic groups and individual antibiotics).

When comparing the annual sensitivities of an individual micro-organism, it was evaluated in the form of the Mean Percentage Sensitivity (MPS). This was obtained by calculating the mean of all the sensitivity percentages of antibiotics tested against the micro-organisms for the whole year.

When comparing the outcome of each individual antibiotic for the year its effectiveness is evaluated in the form of the Average Percentage Sensitivity (APS). This is obtained by calculating the mean of all the sensitivity percentages of isolates tested against the particular antibiotic for the year. For obtaining a sensitivity percentage representing the overall effectiveness of a drug group, the mean of all the APS of each individual member of a drug group would be calculated (mAPS).

3.4.2 Data analysis for Phase 2

The patient profiles were tabulated, the culture prevalence and sensitivity results were divided according to source (i.e. either nosocomial- acquired or community-acquired) and clinical significance (either clinically significant or clinically insignificant). Infection isolation sites and diagnoses were evaluated and antibiotic use was reviewed. The resistance patterns of the different classification of micro-organisms towards different antibiotic groups were identified and compared.

3.4.3 Statistical analysis

Statistical analysis of the data was performed by using the sample t test. A significance level of $p<0.15$ was used. The usually selected significance level of $p< 0.05$ was not used because the sample sizes were not ideally large enough to determine statistical significance with that confidence.

3.4.4 Data analysis for the pharmacokinetic study

The individual kinetic parameters of each patient were calculated by using the following formulae:

$$k_e = \frac{\ln [C_{max} / C_{min}]}{\Delta t}$$

$$t^1/_2 = \frac{0.693}{k_e}$$

$$Vd = \frac{k_o}{[C_{max} - C_{min}]\, k_e} \cdot \frac{(1 - e^{-k_e T})}{(1 - e^{-k_e \tau})}$$

From the individual kinetic parameters the projected parameters are calculated using the following formulae.

$$\tau = \frac{\ln [C_{max}/C_{min}]}{k_e} + T$$

$$k_o = [C_{max}]\,[Vd]\,[k_e]\,\frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e T})}$$

These projected parameters were compared to the standard dosing regimens in the PICU.

Abbreviations

Cmax - maximum serum concentration

Cmin - minimum serum concentration

Δ t - time between Cmax and Cmin

T - dose infusion time

k_e - elimination rate

t1/2 - half life

Vd - volume of distribution

τ - dose interval

k_o - dosing infusion rate

CHAPTER 4: RESULTS: Analysis of antibiogram - Phase 1

In the antibiogram for 1995 (Appendix 1) and 1996 (Appendix 2) for the PICU, a number of bacterial species demonstrated problematic tendencies in terms of prevalence and degree of antibiotic susceptibility. Organisms that were found to be highly prevalent are shown in Table 4.1 and Table 4.2.

Table 4.1 The top 10 most prevalent micro-organisms from 1995

Most prevalent organisms	Percentage (%)
staphylococcus epidermidis	23.9 (42)
escherichia coli	10.2 (18)
klebsiella sp.	8.0 (14)
streptococcus agalactiae	7.4 (13)
enterococcus faecalis	6.3 (11)
pseudomonas aeruginosa	5.1 (9)
streptococcus viridans	4.0 (7)
staphylococcus aureus	3.4 (6)
enterobacter cloacae	3.4 (6)
klebsiella pneumoniae	3.4 (6)

Table 4.2 The top 10 most prevalent micro-organisms from 1996

Most prevalent organisms	Percentage (%)
staphylococcus epidermidis	23.4 (32)
staphylococcus aureus	19.7 (27)
escherichia coli	10.2 (14)
enterococcus faecalis	8.0 (11)
klebsiella sp.	6.6 (9)
pseudomonas aeruginosa	6.6 (9)
klebsiella pneumoniae	3.6 (5)
enterobacter sp.	2.9 (4)
streptococcus pneumoniae	2.2 (3)
acinetobacter baumanii	2.2 (3)

For both years *Staphylococcus epidermidis* was the most prevalent micro-organism isolated (23.9% and 23.4% respectively), with *Escherichia coli* (10.2%) and *Klebsiella sp.* (8.0%) coming second and third respectively during 1995. For 1996 *Staphylococcus aureus* experienced a drastic increase from the previous year where it was the eighth most prevalent micro-organism (3.4%) to end up as the second most prevalent micro-organism (19.7%). *Escherichia coli* was the third most prevalent (10.2%) in 1996.

Table 4.3 Comparison of the top 10 most prevalent micro-organisms for the 2 years.

Most prevalent micro-organisms	1995 Percentage (%) (number of isolates = 176)	1996 Percentage (%) (number of isolates = 137)	Difference in annual frequency percentages (DAFP)
staphylococcus epidermidis	23.9 (42)	23.4 (32)	0.5
staphylococcus aureus	3.4 (6)	19.7 (27)	-16.3
escherichia coli	10.2 (18)	10.2 (14)	0.0
klebsiella sp.	8.0 (14)	6.6 (9)	1.4
enterococcus faecalis	6.3 (11)	8.0 (11)	-1.7
streptococcus agalactiae	7.4 (13)	1.5 (2)#	5.9
pseudomonas aeruginosa	5.1 (9)	6.6 (9)	-1.5
streptococcus viridans	4.0 (7)	1.5 (2)#	2.5
enterobacter cloacae	3.4 (6)	1.5 (2)#	1.9
klebsiella pneumoniae	3.4 (6)	3.6 (5)	-0.2
enterobacter sp.	1.7 (3)#	2.9 (4)	-1.2
streptococcus pneumoniae	1.1 (2)#	2.2 (3)	-1.1
acinetobacter baumanii	1.1 (2)#	2.2 (3)	-1.1

- not in the top 10 for that year.

The negative values illustrated in the difference in the annual frequency percentages (DAFP) column represents an increase in number of isolates obtained for a micro-organism from 1995 and a positive value represents a decrease from 1995. The majority of micro-organisms isolated from the two years occurred at approximately similar frequencies (with the DAFP less than or equal to ± 2) with the exception of *Streptococcus agalactiae* and

Streptococcus viridans which both decreased by more than 50% as seen in Table 4.3 (the differences of their annual frequency percentages were 5:9 and 2.5 respectively) .

Those organisms which have a mean percentage sensitivity (MPS) of less than 80% are shown in Table 4.4 and Table 4.5 for the years 1995 and 1996 respectively. The sensitivity values represents the average of all the sensitivities of the antibiotics each micro-organism was tested against. The organisms represented in the table are those that consisted of a minimum of 3 isolates per year.

Table 4.4 Micro-organisms that exhibited overall antibiotic sensitivity less than 80% in 1995.

GRAM POSITIVE		
bacillus cereus	5	56.5 ± 17.1
staphylococcus aureus	6	54.0 ± 18.5
staphylococcus epidermidis	42	44.5 ± 16.5
streptococcus viridans	7	56.4 ± 19.1
enterococcus faecalis	11	42.9 ± 25.7
enterococcus faecium	3	34.6 ± 23.7
GRAM NEGATIVE		
escherichia coli	18	78.7 ± 15.5
klebsiella pneumoniae	6	25.0 ± 21.3
klebsiella sp.	14	54.9 ± 16.2
pseudomonas aeruginosa	9	50.9 ± 20.2
strenotrophomonas maltophilia	3	50.0 ± 23.2

From Table 4.4, the micro-organisms that showed greatest resistance were the gram positives. *Klebsiella pneumoniae* had the greatest resistance for the gram negatives (25.0 ± 21.3%), while *enterococcus faecium* had the greatest resistance for the gram positive organisms (34.6 ± 23.7%).

Table 4.5 Micro-organisms that exhibited overall antibiotic sensitivity less than 80% in 1996

GRAM POSITIVE		
staphylococcus aureus	27	60.2 ± 15.1
staphylococcus epidermidis	32	49.9 ± 17.5
enterococcus faecalis	11	61.5 ± 22.7
GRAM NEGATIVE		
acinetobacter baumanii	3	61.1 ± 25.1
enterobacter sp.	4	38.9 ± 18.8
klebsiella pneumoniae	5	53.2 ± 16.4
pseudomonas aeruginosa	9	70.2 ± 10.9

In 1996 the number of micro-organisms with an MPS less than 80% was less than in 1995. The greatest resistance was found in the gram negative organisms. *Enterobacter sp.* had the greatest resistance for the gram negative organisms (38.9 ± 18.8%), while *Staphylococcus epidermidis* had the greatest resistance for the gram positive organisms (49.9 ± 17.5%).

Table 4.6 Comparison of susceptibility trends for 1995 and 1996

	1995		1996	
	# of isolates	MPS [%] ± SD	# of isolates	MPS [%] ± SD
GRAM POSITIVE				
bacillus cereus	5	56.5 ± 17.1		N/A
staphylococcus aureus	6	54.0 ± 18.5	27	60.2 ± 15.1
staphylococcus epidermidis	42	44.5 ± 16.5	32	49.9 ± 17.5
streptococcus viridans	7	56.4 ± 19.1	2	87.5 ± 17.7
enterococcus faecium	3	34.6 ± 23.7	1	66.7 ± 25.8
enterococcus faecalis	11	42.9 ± 25.7	11	61.5 ± 22.7
GRAM NEGATIVE				
acinetobacter baumanii	2	40.0 ± 21.6	3	61.1 ± 25.1
enterobacter sp.	3	82.2 ± 18.8	4	38.9 ± 18.8
escherichia coli	18	78.7 ± 15.5	14	85.1 ± 11.7
klebsiella pneumoniae	6	25.0 ± 21.3	5	53.2 ± 16.4
klebsiella sp.	14	54.9 ± 16.2	9	83.8 ± 13.1
pseudomonas aeruginosa	9	50.9 ± 20.2	9	70.2 ± 10.9
strenotrophomonas maltophilia	3	50.0 ± 23.2		N/A

N/A - those organisms that were not isolated, therefore not evaluated during the year.

When comparing the resistance patterns for 1995 and 1996 in Table 4.6, with the exception of *Enterobacter sp.*, every micro-organisms' average resistance experienced a decline. *Bacillus cereus* and *Strenotropomas maltophilia* were only isolated and tested during 1995 and not 1996.

Table 4.7 represents the bacterial resistance patterns to the most frequently used antibiotics in the PICU. In 1995, the drug group which presented with the greatest resistance towards it was the β-lactams. In 1995, the cephalosporins experienced the greatest resistance (49.3 ± 5.3%) followed by the penicillins (54.8 ± 14.7%). In 1996, although the β-lactams still remained the drug group which presented with the greatest bacterial resistance, it experienced a decline in resistance. Penicillins encountered the greatest resistance in 1996 (61.1 ± 7.8%), followed by cephalosporins (62.9 ± 5.5%).

Table 4.7 Percentage sensitivities of antibacterial agents used in the paediatric ICU at Johannesburg General.

	1995	1996
	mABS (%) ± SD	mABS (%) ± SD
Penicillins	54.8 ± 14.7	31.1 ± 7.8
Cephalosporins	49.3 ± 5.3	62.9 ± 5.5
Aminoglycosides	68.9 ± 3.5	72.3 ± 4.2
Erythromycin	61.4 ± 20.7	77.8 ± 17.1
Ciprofloxacin	99.3 ± 1.5	92.3 ± 13.9
Vancomycin	92.3 ± 13.9	100.0
Imipenem	93.6 ± 8.0	92.3 ± 13.9

All the antimicrobial agents tested, with the exception of ciprofloxacin and imipenem experienced a decline in resistance toward them over the 2 year period with the greatest improvement experienced by the cephalosporins (from 49.3 ± 5.3% to 62.9 ± 5.5%) .

Table 4.8 and Table 4.9 represent a comparison of antibiograms of penicillins and cephalosporins respectively for 1995 and 1996. The blank cells in the tables represent tests that were not evaluated. The micro-organism testing was not the same over the 2 years, for example *Enterococcus faecium* and *Streptococcus sp.* were not tested for oxacillin in 1996.

Various micro-organisms had an overall decrease in resistance when tested against penicillin. *Staphylococcus aureus* (sensitivity increased from 0% in 1995 to 18.5% in 1996); *Streptococcus pneumoniae* (sensitivity increased from 50% in 1995 to 66.7% in 1996); and *Streptococcus viridans* (sensitivity increased from 16.7% in 1995 to 100% in 1996) were amongst those that experienced the decrease, wheras *Enterococcus faecium* (sensitivity decreased from 50% in 1995 to 0% in 1996); *Enterococcus faecalis* (sensitivity decreased from 100% in 1995 to 90% in 1996) and *Staphylococcus epidermidis* (sensitivity decreased from 7.3% in 1995 to 0% in 1996) experienced an increased resistance to penicillin.

Staphylococcus epidermidis was the only micro-organism that had a decrease in resistance to oxacillin (from 22% to 40%).

Table 4.8 Comparison of percentage sensitivities of penicillins for 1995 and 1996

GRAM POSITIVE														
	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996
enterococcus faecium	50	0	0		100	100			0	100			37.5	66.7
enterococcus faecalis	100	90	0	0	100	90				100		100	66.7	76.0
enterococcus sp.	100		0		100								66.7	
grp C haemolytic strep	100		100		100								100.0	
staphylococcus aureus	0	18.5	33.3	33.3	0				40				18.3	25.9
staphylococcus epidermidis	7.3	0	22	40	7.3	0			33.3	33.3			17.5	18.3
streptococcus agalactiae	100	100	100	100	100	100							100.0	100.0
streptococcus sp.	100	100	100		100	100				100			100.0	100.0
streptococcus pneumoniae	50	66.7		100	100								75.0	83.4
streptococcus pyogenes		100												
streptococcus viridans	16.7	100	0		16.7	100				100			11.1	100.0
micrococcus sp.														
bacillus sp.	0		0		0								0.0	
bacillus cereus	20		20		20								20.0	
bacillus subtilis	0		0		0								0.0	
diphteroids														
propionebacterium sp.														

Table 4.8 continued.

GRAM NEGATIVE	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996
branhamella catarrhalis														
acinetobacter sp.					0		100		100				66.7	
acinetobacter baumanni					0	0	100	100	0	0		100	33.3	50.0
acinetobacter lwoffi						0		100				100		66.7
alkaligenes sp.					0	0	100	100	100			100	66.7	66.7
alkaligenes faecalis					0		100	0	50		100	0	62.5	0.0
enterobacter sp.					0	0	100	50	33.3	0	100	100	58.3	37.5
enterobacter aerogenes					0		100		0		100		50.0	
enterobacter cloacae					0	0	100	100	0	0	100	50	50.0	37.5
escherichia coli					5.6	20	45.5	46.2	80	100	100	100	57.8	66.6
haemophilus influenzae						100				100				100.0
klebsiella sp.					0	0	45.5	44.4	35.7	88.9	100	100	45.3	58.3
klebsiella oxytoca						0		0		50		100		37.5
klebsiella pneumoniae					0	0	0	40	0	20	100	80	25.0	35.0
proteus mirabilis					100	100	100	100	100	100	100	100	100.0	100.0
pseudomonas aeruginosa					0	50	88.9	66.7	12.5	50	80	88.9	45.4	63.9
pseudomonas sp.						0		100		0		100		50.0
citrobacter freudi														
salmonella sp.					0	0		100	0	0		100	0.0	50.0
uniden. gram -ve bacillus					0	0	100	100	0	0		100	33.3	50.0
veillonella						0		100		0		100		50.0
bacteroides fragilis														
prevotella melaninogen.														
stenotrophomonas mal.					0		100		50				50.0	
Overall % average resistance	49.5	63.9	31.3	54.7	30.3	40.0	84.3	65.2	35.3	55.4	97.8	87.1	54.8	61.1

Table 4.9 Comparison of percentage sensitivities of cephalosporins for 1995 and 1996

GRAM POSITIVE	Ceftazidime		Ceftriaxone		Cefotaxime		Cefepime		Ceftazidime + Clavulanate		Cefotaxime + Clavulanate		Cefepime + Clavulanate		Ceftriaxone + Clavulanate	
	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996
enterococcus faecium																
enterococcus faecalis	0														0	
enterococcus sp.	100														100.0	
grp C haemolytic strep	100														100.0	
staphylococcus aureus	66.7	37		37		37									66.7	37.0
staphylococcus epidermidis	59.6	48.3		40		38.5									59.6	42.3
streptococcus agalactiae	100	100													100.0	100.0
streptococcus sp.	100	100		100											100.0	100.0
streptococcus pneumoniae								100								100.0
streptococcus pyogenes																
streptococcus viridans	66.7	100		100											66.7	100.0
micrococcus sp.																
bacillus sp.	50														50.0	
bacillus cereus	25														25.0	
bacillus subtilis	0														0.0	
diphteroids																
propionebacterium sp.																

Table 4.9 continued

GRAM NEGATIVE	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996
branhamella catarrhalis																
acinetobacter sp.	0				100		100		100		100				80.0	
acinetobacter baumannl	0	0			0	0	0	0	100	100	0	0		100	20.0	33.3
acinetobacter lwoffi		0				100		100		100		100		100		83.3
alkaligenes sp.	0				0		0		0		0				0.0	
alkaligenes faecalis	0				0		0		33.3	0	0			0	6.7	0.0
enterobacter sp.	0	0		0	100	25	100	25	100	25	100	25		100	80.0	28.6
enterobacter aerogenes	0				100		100		100		100				80.0	
enterobacter cloacae	0	0		0	100	100	100	100	100	100	100	100		100	80.0	71.4
escherichia coli	88.2	85.7		83.3	87.5	100	88.2	100	88.2	84.6	86.7	100		100	87.8	93.4
haemophilus influenzae						100		100				100				100.0
klebsiella sp.	28.6	88.9		80	42.9	100	50	100	35.7	88.9	50	100		100	41.4	94.0
klebsiella oxytoca		50		100		50		50		50		50		100		64.3
klebsiella pneumoniae	0	20		100	0	20	0	40	0	40	0	40		50	0.0	44.3
proteus mirabilis	100	100		100	100	100	100	100	100	100	100	100		100	100.0	100.0
pseudomonas aeruginosa	0	50			0	50	22.2	50	100	55.6	22.2	50		75	28.9	55.1
pseudomonas sp.		0				0		0		100		0				20.0
citrobacter freudi		0		0		100		50		100		100		100		64.3
salmonella sp.					100						100				100.0	
unIden. gram -ve bacillus	0				0		0		0		0				0.0	
veillonella																
bacteroides fragilis																
prevotella melaninogen.																
stenotrophomonas mal.	0				0		0		50		0				10	
Overall % average resistance	35.4	45.9		61.7	48.7	58	47.2	68.9	64.8	72.6	50.6	68.9		85.4	49.3	65.9

Ampicillin experienced an increase in sensitivity from the following micro-organisms: *Streptococcus viridans* (from 16.7% to 100%); *Escherichia coli* (from 5.6% to 20%); and *Pseudomonas aeruginosa* (from 0% to 50%). *Enterococcus faecalis* (from 100% to 90%) and *Staphylococcus epidermidis* (from 7.3% to 0%) experienced an increase in resistance to ampicillin.

The only micro-organism that demonstrated a notable decrease in resistance towards piperacillin was *Klebsiella pneumoniae* (from 0% to 40%), otherwise *Alkaligenes faecalis* (from 100% to 0%), *Enterobacter sp.* (from 100% to 50%), *Klebsiella sp.* (from 45.5% to 44.4%) and *Pseudomonas aeruginosa* (from 88.9% to 66.7%) experienced an increase in resistance.

There were several micro-organisms that experienced a decrease in resistance to amoxicillin/clavulanic acid. From the gram positive organisms tested, *Enterococcus faecium* demonstrated an increase in sensitivity from 0% to 100% over the 2 years. From the gram negative organisms tested, *Escherichia coli* (from 80% to 100%), *Klebsiella sp.* (from 35.7% to 88.9%), *Klebsiella pneumoniae* (from 0% to 20%) and *Pseudomonas aeruginosa* (from 12.5% to 50%) experienced an increase in sensitivity to amoxicillin/clavulanic acid. *Enterobacter sp.* (from 33.3% to 0%) was the only micro-organism to experience an increase in resistance to amoxicillin/clavulanic acid.

The only micro-organism that expressed a decrease in resistance to piperacillin/tazobactam was *Pseudomonas aeruginosa* (from 80% to 88.9%) otherwise *Alkaligenes faecalis* (from 100% to 0%), *Enterobacter cloacae* (from

100% to 50%) and *Klebsiella pneumoniae* (from 100% to 80%) experienced an increase in resistance.

When comparing the change in sensitivity to cephalosporin in Table 4.9 the micro-organisms responsible for increasing resistance to penicillin are also responsible for development of resistance to the cephalosporins.

Micro-organisms that had a decrease in resistance to cefazolin were *Streptococcus viridans* (from 66.7% to 100%), *Klebsiella sp.* (from 28.6% to 88.9%), *Klebsiella pneumoniae* (from 0% to 20%) and *Pseudomonas aeruginosa* (from 0% to 50%). On-the-other-hand, *Staphylococcus aureus* (from 66.7% to 37.0%), *Staphylococcus epidermidis* (from 59.6% to 48.3%) and *Escherichia coli* (from 88.2% to 85.7%) had an increase in resistance.

Micro-organisms that had experienced an increase sensitivity to cefuroxime were *Escherichia coli* (from 87.5% to 100%), *Klebsiella sp.* (from 42.9% to 100%), *Klebsiella pneumoniae* (from 0% to 20%) and *Pseudomonas aeruginosa* (from 0% to 50%).

Micro-organisms that experienced a decrease in resistance to cefotaxime were *Escherichia coli* (from 88.2% to 100%), *Klebsiella sp.* (from 50% to 100%), *Klebsiella pneumoniae* (from 0% to 40%) and *Pseudomonas aeruginosa* (from 22.2% to 50%).

The micro-organisms that experienced a decrease in resistance to ceftazidime were *Klebsiella sp.* (from 35.7% to 88.9%) and *Klebsiella pneumoniae* (from 0% to 40%). *Alkaligenes faecalis* (from 33.3% to 0%), *Enterobacter sp.* (from 100% to 25%), *Escherichia coli* (from 88.2% to 84.6%) and *Pseudomonas aeruginosa* (from 100% to 55.6%) experienced an increase in resistance to ceftazidime.

Micro-organisms that demonstrated a decrease in resistance to ceftriaxone were *Escherichia coli* (from 86.7% to 100%), *Klebsiella sp.* (from 50% to 100%), *Klebsiella pneumoniae* (from 0% to 40%) and *Pseudomonas aeruginosa* (from 22.2% to 50%).

No comparison could be made for cephalexin and cefepime because they were only tested during 1996.

Micro-organisms isolated only during either year (for example *Enterococcus sp.* in 1995 and *Acinetobacter lwoffi* in 1996) could possibly affect the overall average resistance of an antimicrobial especially if there is a drastic difference in the number of isolates tested in the 2 years. Therefore those micro-organisms that were isolated and tested for both years gave a clearer resistance trend picture as illustrated in Table 4.10 and Table 4.11.

When comparing the selected average resistances of the antimicrobials to those of the cumulative antibiogram tested against all the isolates (or overall average resistance), the results are very comparable as demonstrated in

Table 4.10 Comparison of the penicillin antibiogram for micro-organisms that were isolated and tested for both years

	PEN		OXA		AMP		RIF		SUL		FUR		AVG	
GRAM POSITIVE	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996
enterococcus faecium	50	0	0		100	100			0	100			37.5	66.7
enterococcus faecalis	100	90	0	0	100	90				100		100	66.7	76.0
staphylococcus aureus	0	18.5	33.3	33.3	0				40				18.3	25.9
staphylococcus epidermidis	7.3	0	22	40	7.3	0			33.3	33.3			17.5	18.3
streptococcus agalactiae	100	100	100	100	100	100							100.0	100.0
streptococcus sp.	100	100	100		100	100				100			100.0	100.0
streptococcus pneumoniae	50	66.7		100	100								75.0	83.4
streptococcus viridans	16.7	100	0		16.7	100				100			11.1	100.0
GRAM NEGATIVE														
acinetobacter baumanni					0	0	100	100	0	0		100	33.3	50.0
alkaligenes faecalis					0		100	0	50		100	0	62.5	0.0
enterobacter sp.					0	0	100	50	33.3	0	100	100	58.3	37.5
enterobacter cloacae					0	0	100	100	0	0	100	50	50.0	37.5
escherichia coli					5.6	20	45.5	46.2	80	100	100	100	57.8	66.6
klebsiella sp.					0	0	45.5	44.4	35.7	88.9	100	100	45.3	58.3
klebsiella pneumoniae					0	0	0	40	0	20	100	80	25.0	35.0
proteus mirabilis					100	100	100	100	100	100	100	100	100.0	100.0
pseudomonas aeruginosa					0	50	88.9	66.7	12.5	50	80	88.9	45.1	63.9
Average	53.0	59.4	36.5	54.7	37.0	42.2	75.5	62.3	32.1	62.8	97.5	86.1	55.3	61.2

Table 4.11 Comparison of the cephalosporin antibiogram for micro-organisms that were isolated and tested for both years

GRAM POSITIVE	1995	1996	1995	1996	1995	1995	1995	1996	1995	1996	1995	1996
staphylococcus au eus	66.7	37		37							66.7	37
staphylococcus epidermidis	59.6	48.3		38.5							59.6	43.4
streptococcus agalactiae	100	100									100	100
streptococcus sp.	100	100									100	100
streptococcus viridans	66.7	100									66.7	100
GRAM NEGATIVE												
acinetobacter baumanni	0	0	0	0	0	0	100	100	0	0	20	20.0
alkaligenes faecalis	0		0		0		33.3	0	0		6.66	0
enterobacter sp.	0	0	100	25	100	25	100	25	100	25	80	20.0
enterobacter cloacae	0	0	100	100	100	100	100	100	100	100	80	80.0
escher ia coli	88.2	85.7	87.5	100	88.2	100	88.2	84.6	86.7	100	87.8	94.1
klebsiella sp.	28.6	88.9	42.9	100	50	100	35.7	88.9	50	100	41.4	95.6
klebsiella pneumoniae	0	20	0	20	0	40	0	40	0	40	0	32.0
proteus mirabilis	100	100	100	100	100	100	100	100	100	100	100	100
pseudomonas aeruginosa	0	50	0	50	22.2	50	100	55.6	22.2	50	28.9	51.1
Average	43.6	56.1	47.8	57.1	51.2	64.4	73.0	66.0	51.0	64.4	53.3	61.6

Table 4.12 (which is a combination of the average values at the bottom of Tables 4.8, Table 4.9, Table 4.10 and Table 4.11), with only one exception namely ceftazidime.

Table 4.12 Comparison of overall and selected average resistances of penicillins and cephalosporins over 1995 and 1996.

Penicillin	49.5	63.9	53.0	59.4
Oxacillin	31.3	54.7	36.5	54.7
Ampicillin	30.3	40.0	37.0	42.2
Piperacillin	84.3	65.2	75.5	62.3
Co-amoxiclav	35.3	55.4	32.1	62.8
Piptaz	97.8	87.1	97.5	86.1
Cefazolin	35.4	45.9	43.6	56.1
Cephalexin		61.7		
Cefuroxime	48.7	58.0	47.8	57.1
Cefotaxime	47.2	68.9	51.2	64.4
Ceftazidime	64.8	72.6	73.0	66.0
Ceftriaxone	50.6	68.9	51.0	64.4
Cefepime		85.4		

The overall average resistance to ceftazidime decreased from 1995 to 1996 (from 64.8% to 72.6%), while the selected average resistance over the 2 years indicated an increase in resistance (from 73.0% to 66.0%).

Even though the individual average values differed, the trend was in the same direction indicating the micro-organisms that were isolated and tested in either of the years did not greatly interfere with the antibiotic's overall resistance for the year. This was demonstrated in cases such as penicillin which experienced a decrease in the overall and selected average resistance toward

it, and piperacillin/tazobactam which demonstrated an increase in resistance in both the overall and selected average resistance towards it.

Table 4.13 and 4.14 represents a comparison of antibiograms of aminoglycosides and a combination of macrolides, fluoroquinolones, glycopeptides and carbapenem β-lactams respectively for 1995 and 1996. The blank cells in the tables represent tests that were not evaluated.

The following are a number of micro-organisms that had an overall decrease in resistance to amikacin: *Acinetobacter baumanni* (from 50% to 100%); *Klebsiella pneumoniae* (from 16.7% to 40%); *Klebsiella sp.* (from 71.4% to 100%) and *Pseudomonas aeruginosa* (from 77.8% to 88.9%).

There were several micro-organisms that experienced a decrease in resistance to gentamicin. From the gram positive micro-organisms tested, Enterococcus faecalis (from 50% to 83.3%) and Staphylococcus epidermidis (from 30% to 83.3%), to the gram negative micro-organisms tested, *Acinetobacter baumanni* (from 50% to 100%), *Klebsiella pneumoniae* (from 0% to 40%) and *Klebsiella sp.* (from 50% to 77.8%).

The following micro-organisms showed a decrease in resistance to Tobramycin: *Acinetobacter baumanni* (from 50% to 100%), *Alkaligenes faecalis* (from 33.3% to 100%), *Klebsiella pneumoniae* (from 0% to 40%), *Klebsiella sp.* (from 45.5% to 77.8%) and *Pseudomonas aeruginosa* (from 77.8% to 88.9%).

Table 4.13 Percentage sensitivities of aminoglycosides for 1995 and 1996

Organism	Gentamicin		Sensitivity		Tobramycin		Amikacin	
GRAM POSITIVE	1995	1996	1995	1996	1995	1996	1995	1996
enterococcus faecium			0				0	
enterococcus faecalis			50	83.3			50	83.3
enterococcus sp.			100				100	
grp C haemolytic strep			0				0	
staphylococcus aureus			33.3				33.3	
staphylococcus epidermidis			30	83.3			30	83.3
streptococcus agalactiae			36.4	0			36.4	0
streptococcus sp.			0				0	
streptococcus pneumoniae								
streptococcus pyogenes								
streptococcus viridans			100				100	
micrococcus sp.								
bacillus sp.			100				100	
bacillus cereus			100				100	
bacillus subtilis			0				0	
diphteroids								
propionebacterium sp.								
GRAM NEGATIVE								
acinetobacter baumanni	50	100	50	100	50	100	50	100
acinetobacter lwoffi		100				100		100
acinetobacter sp.	100		100		100		100	
alkaligenes faecalis	33.3	0	33.3		33.3	100	33.3	50
alkaligenes sp.	0		0		0		0	
branhamella catarrhalis								
enterobacter aerogenes	100		100		100		100	
enterobacter cloacae	100	100	100	100	100	100	100	100
enterobacter sp.	100	50	100	25	100	50	100	41.7
escherichia coli	100	93.3	81.3	71.4	80	75	87.7	79.9
haemophilus influenzae								
klebsiella oxytoca		50		50		50		50
klebsiella pneumoniae	16.7	40	0	40	0	40	5.6	40
klebsiella sp.	71.4	100	50	77.8	45.5	77.8	55.6	85.2
proteus mirabilis	100	100	100	100	100	100	100	100
pseudomonas aeruginosa	77.8	88.9	77.8	50	77.8	88.9	77.8	75.9
pseudomonas sp.		100		0		0		33.3
citrobacter freudi		100		100		100		100
salmonella sp.								
uniden. gram -ve bacillus	100		100		100		100	
veillonella								
bacteroides fragilis								
prevotella melaninogen.								
stenotrophomonas mal.	100		100		100		100	
Average	74.9	78.6	59.3	62.9	70.6	75.5		

Table 4.14 Percentage sensitivities of macrolides, fluoroquinolones, glycopeptides and carbapenem β-lactams for 1995 and 1996

Organisms	Erythromycin		Ciprofloxacin		Ofloxacin		Vancomycin		Imipenem		Ampicillin	
GRAM POSITIVE	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996	1995	1996
enterococcus faecium	0	100					100	100			50	100
enterococcus faecalis	60	16.7					100	100			80	58.4
enterococcus sp.	100						100				100	
grp C haemolytic strep	100						100				100	
staphylococcus aureus	33.3	37		100		66.7	100	100			66.7	75.9
staphylococcus epidermidis	51.2	46.9		0		0	100	100			75.6	36.7
streptococcus agalactiae	100	100					100	100			100	100
streptococcus sp.	100	100					100	100			100	100
streptococcus pneumoniae	100	100					100	100			100	100
streptococcus pyogenes		100										100
streptococcus viridans	83.3	100					100	100			91.7	100
micrococcus sp.												
bacillus sp.	50						100				75	
bacillus cereus	80						100				90	
bacillus subtilis	0						0				0	
diphteroids												
propionebacterium sp.												
GRAM NEGATIVE												
acinetobacter baumanni			100	100		100			100	100	100	100
acinetobacter lwoffi				100		100				100		100
acinetobacter sp.			100						100		100	
alkaligenes faecalis			100	100		100			66.7	0	83.4	66.7
alkaligenes sp.			100						100		100	
branhamella catarrhalis												
enterobacter aerogenes			100						100		100	
enterobacter cloacae			100						100	100	100	100
enterobacter sp.			100	100						100	100	100
escherichia coli			100	100		100			100	100	100	100
haemophilus influenzae												
klebsiella oxytoca										100		100
klebsiella pneumoniae			100	100		100			100	100	100	100
klebsiella sp.			100	100					100	100	100	100
proteus mirabilis			100	100		100			100	100	100	100
pseudomonas aeruginosa			88.9	100		100			100	100	94.5	100
pseudomonas sp.				100						100		100
citrobacter freudi				100		100				100		100
salmonella sp.			100								100	
uniden. gram -ve bacillus			100						100		100	
veillonella												
bacteroides fragilis												
prevotella melaninogen.												
stenotrophomonas mal.									50		75	
Average	66	77.8				86.7	92.3	100	93.6	92.3		

Like the previously mentioned antibiotics the following micro-organisms experienced an overall decrease in resistance to erythromycin over the 2 years: *Enterococcus faecium* (from 0% to 100%); *Staphylococcus aureus* (from 33.3 to 37%) and *Streptococcus viridans* (from 83.3 to 100%).

The reason micro-organisms experienced an overall increase in sensitivity to vancomycin from 92.3% in 1995 to 100% in 1996 was because in 1995 it was tested against *Bacillus subtilis* which was found to be completely resistant to it. Unfortunately it was never isolated again.

Imipenem and ciprofloxacin were the only antibiotics in this group not to experience an overall increase in sensitivity. *Pseudomonas aeruginosa* was the only micro-organism that had a decrease in resistance to ciprofloxacin (from 88.9% to 100%).

No comparison could be made for ofloxacin because it was only tested during 1996.

CHAPTER 5: RESULTS: Prospective study - Phase 2

5.1 PATIENT POPULATION

In the prospective study, out of a total of 165 patients admitted to the ward over a 6 month period (from May to October), only 57 patients were included into the study. Table 5.1 shows the profiles of patients admitted to the ward.

Table 5.1 Patients' profiles admitted to ward 276

	Neonates (birth - 1month)	Non-neonates (> 1month)	Total
Admissions	111	54	165
Male	65	35	100
Female	46	19	65
Inborn	63	0	63
New admissions	7	16	23
Transferred from another ward	12	21	33
Transferred from another hospital	29	17	46
Deaths in ward	18	10	28

The ratio of neonates to non-neonates is 2.1:1, whereas that of male patients to female patients is 1.5:1. The majority of the neonates admitted to the ward were inborns [56.8% (63/111)] followed by those transferred from other hospitals [26.1% (29/111)]. The majority of non-neonates admitted to the ward were transferred from another ward in Johannesburg General [38.8% (21/54)]. The death ratio of neonates to non-neonates was 1.8:1.

Neonates were categorised according to weight while the non-neonates were categorised by age as demonstrated in Table 5.2.

Low birth weight neonates (those that weighed less than 2500 g) made up 50.3% (83/165) of the total admissions to the ward. Those having birth weights of 1500 to 1999 g made up the largest single category of 21.2%

Table 5.2 A breakdown of patients' profiles admitted to ward 276

	NEONATES (birth - 1 month)				INFANTS (1 month - 1 year)	CHILDREN (1 - 5 years)	TOTAL
	<1499 g	1500 - 1999 g	2000 - 2500 g	>2500 g			
Admissions to ward 276	30	35	18	28	27	27	165
Male	16	23	10	16	16	19	100
Female	14	12	8	12	11	8	65
Inborn	21	19	10	13	0	0	54
New admission	0	3	2	2	5	11	22
Transferred from other ward	3	4	1	4	13	8	40
Transferred from another hospital	6	9	5	9	9	8	47
Deaths in ward	6	9	1	2	2	8	28
# of patients admitted to the study	9	12	3	5	16	12	57

(35/165), and had the largest death rate in the ward of 32.1% (9/28). The less than 1499 g category had the largest inborn admission of 38.9% (21/54). The largest group of patients admitted into the study was the infants category at 28.1% (16/57).

5.2 TOTAL INFECTIONS ISOLATED

In the six months of surveillance, a total of 124 isolates were cultured from 57 study patients (Table 5.3). Of the 124 isolates cultured, 70.2% (87/124) were classified as nosocomial infections, of which 58.6% (51/87) were considered clinically significant. The clinically significant nosocomial infections were also

Table 5.3 The breakdown of micro-organism infection by classification

GRAM POSITIVE					
staphylococcus aureus	7	4	1		12
staphyloc..ccus epidermidis	8	18	1	5	32
streptococcus agalactiae			2		2
streptococcus pneumoniae			1		1
streptococcus pyogenes	1		1		2
streptococcus sp.	1		3		4
streptococcus viridans			1		1
enterococcus faecalis	3	2	2		7
enterococcus faecium		1	1		2
micrococcus sp.			2		2
corynebacterium sp.			1	1	2
bacillus cereus		1			1
bacillus sp.		1			1
GRAM NEGATIVE					
acinetobacter baumanii			1		1
acinetobacter lwoffi	1				1
alkaligenes sp.			1		1
alkaligenes faecalis		1	1		2
enterobacter sp.	2	1			3
enterobacter cloacae	2	2			4
escherichia coli	8		3		11
haemophilus influenzae	2	1		1	4
klebsiella sp.	8	2	2		12
klebsiella pneumoniae			1		1
klebsiella oxytoca			1		1
proteus mirabilis	2		1	1	4
pseudomonas aeruginosa	5		1		6
campylobacter jejuni			1		1
bacteroides fragilis	1				1
stenotrophomonas maltophilia		1			1
burkholderia cepacia		1			1
Total	51	36	29	8	124

the most prevalent group at 41.1% (51/124). The most prevalent micro-organism isolated over the six month period was the *Staphylococcus epidermidis* (25.8%), which was well represented in the four different classification groups. *Staphylococcus epidermidis* was the most prevalent organism in the insignificant nosocomial infection group at 56.3% (18/32).

The most prevalent gram negative micro-organism isolated over the six month period was the *Klebsiella sp.* at 9.7% (12/124). It was most prevalent in the significant nosocomial infection group, however, it was not isolated in the clinically insignificant community infection class.

Clinically significant infections were more prevalent and presented with a wider variety of organisms than the clinically insignificant infections (Appendices 3 to 6). The significant community-acquired infections consisted of a larger amount of gram positive micro-organisms than gram negative ones (16 different micro-organsisms versus 13 different ones), while the significant nosocomially-acquired infections consisted of a larger amount of gram negative micro-organisms than gram positive ones (29 versus 22).

Table 5.4 Distribution of infections

	Neonates	Non-neonates	Total
Nosocomial	36	51	87
Community	22	15	38
Total	58	66	124

Table 5.5 Distribution of infections broken down by classification.

	Neonates	Non-neonates	Total
Significant nosocomial	22	29	51
Insignificant nosocomial	14	22	36
Significant community	19	10	29
Insignificant community	3	5	8

In Table 5.4 nosocomial infections are more prevalent in non-neonates with a frequency of 58.6% (51/87), while the community infections are more prevalent in the neonate population [57.8% (22/38)].

In Table 5.5 the significant and insignificant nosocomial infections occur more frequently in the non-neonatal group [56.9% (29/51) and 61.1% (22/36) respectively], while the significant community infections are more prevalent in the neonatal population [65.5% (19/29)]. The insignificant community infections was more prevalent in the non-neonatal group [62.5% (5/8)].

Table 5.6 Breakdown of types of infection by categories

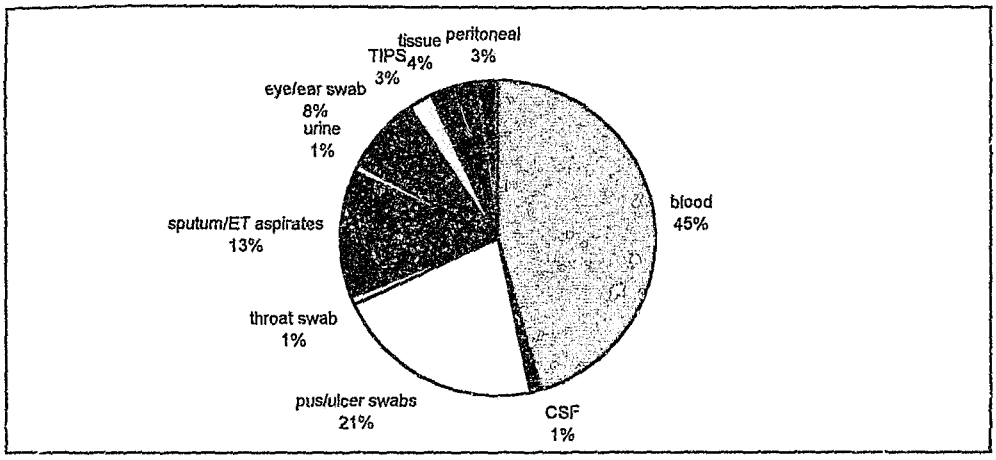
	NEONATES (0-1 month)			INFANTS - CHILDREN (1mth-12yrs)			
	1-7 days	8-14 days	15-21 days	22-30 days	1-5 yrs	6-12 yrs	
Significant nosocomial	3	10	3	6	20	9	51
Insignificant nosocomial	2	7	0	5	10	12	36
Significant community	4	10	1	4	6	4	29
Insignificant community	2	1	0	0	4	1	8
Total # of infections/grp	11	28	4	15	40	26	124

The infants group (those from 1 month to 1 year) exhibited the highest occurrence of nosocomial infections (regardless of significance) and overall infections in the study (Table 5.6).

5.3 SITES OF INFECTIONS

The frequency of organisms isolated at various infection sites are presented in Figure 5.1, with the three most prevalent sites of infection in order of frequency being blood (45%), pus (21%), and sputum/endotracheal (ET) aspirates (13%).

Figure 5.1 Frequency of organisms isolated from different infection sites



5.4 TYPES OF INFECTIONS DIAGNOSED

From the combination of observing the patients' clinical signs and symptoms, clinical laboratory results, and the attending physicians conclusions, diagnoses were made and their frequencies were charted in Figure 5.2. Septicaemia infections occurred most frequently, however the results represented in the pie chart reflect the occurrence of all infections. The breakdown of individual clinically significant micro-organism infections and their frequencies to the individual diagnoses are illustrated by Table 5.7.

The most commonly isolated organisms were *Escherichia coli* [13.7% (12/87)] and *Klebsiella sp.* [11.5% (10/87). They were fairly well distributed amongst the listed diagnoses (both were represented in 5 of the 8 different diagnoses groups). Septicaemia was the most prevalent diagnosis at 37.9% (33/87), with

Figure 5.2 Diagnosis frequency

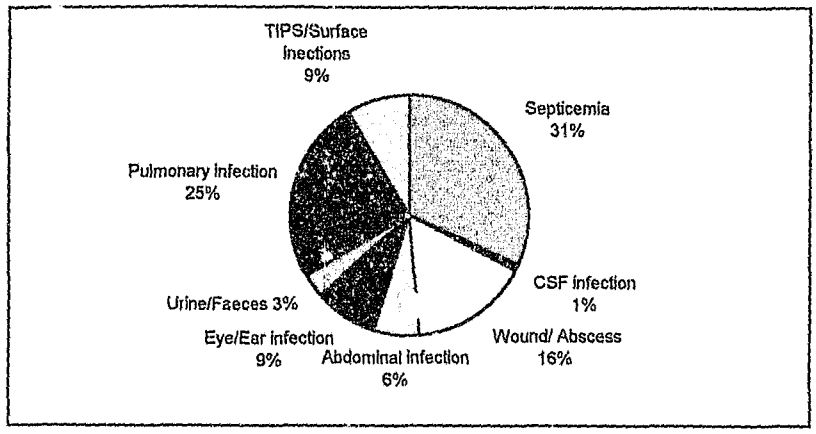


Table 5.7 Frequency of organisms in clinically significant infections associated with diagnosis

	Septicaemia	Wound/ Abscess	Eye/Ear infection	Pulmonary infection	Abdominal infection	CSF infection	TIPS/ Surface infection	Urine/ Faeces	Total
GRAM POSITIVE									
staph. aureus	3	2	1	2					8
staph. epidermidis	6		1		1				8
strep. agalactiae	2								2
strep. pneumoniae	1								1
strep. pyogenes	1			1					2
streptococcus . sp.	2		1	1					4
strep. viridans	1								1
enterococcus faecalis	1	2			2		1		6
enterococcus faecium	1								1
micrococcus sp.	2								2
corynebacterium sp.	1								1
GRAM NEGATIVE									
acinetobacter baumanii		1							1
acinetobacter lwoffi							1		1
alkaligenes sp.	1								1
alkaligenes faecalis	1								1
enterobacter sp.		1			1				2
enterobacter cloacae	1	1							2
escherichia coli	3	2	1	3	2				11
haemophilus influenzae				2					2
klebsiella sp.		5	1	2	1			1	10
klebsiella pneumoniae	1								1
klebsiella oxytoca	1								1
proteus mirabilis		1	2						3
pseud. aeruginosa	1	2	1	2					6
campylobacter jejuni	1								1
bacteroides fragilis	1								1
Total	32	17	8	13	7	0	2	1	80

Staphylococcus epidermidis being the most common organism [18.2% (6/33)] for this diagnosis.

5.5 FREQUENCY OF ANTIBIOTICS USED IN THE WARD

Table 5.8 Frequency of antibiotic groups used in patients included in study

	Neonates	Non-neonates	Total
Penicillins	119	33	152
Aminoglycosides	107	29	136
Cephalosporins	39	35	74
Glycopeptides	23	17	40
Nitroimidazole	6	11	17
Sulphas	2	6	8
Carbapenem β-lactams	3	4	7
Macrolides	0	4	4
Fluoroquinolones	1	2	3
Fucidin	2	0	2
Rifampicin	1	0	1
Total	303	141	444

As illustrated by Table 5.8, the largest group of antibiotics used in ward 276 were the penicillins [34.2% (152/444)] with the majority used in the neonatal population [78.3% (119/152)]. Aminoglycosides and cephalosporins were the second and third largest groups respectively. However according to an elaboration of Table 5.8 (Table 5.9), the most frequently prescribed antibiotic was amikacin [28.4% (124/444)].

The 1500 to 1999 g group had the highest antibiotic usage at 20.5% (91/444).

Table 5.9 The breakdown of individual antibiotics used in ward 276

Amikacin	26	29	26	26	10	9	126
Penicillin	24	26	24	24	2	4	104
Cefotaxime	11	13	6	6	10	7	53
Vancomycin	7	9	3	4	8	7	38
Tazocin	5	6	2	5	9	3	30
Flagyl	2	3	0	1	4	7	17
Gentamicin	0	0	0	0	5	5	10
Ampicillin			1	0	6	1	8
Imipenem		2	1	0	2	2	7
Cotrimoxazole		1		1	2	3	7
Ceftriaxone					2	5	7
Augmentin				1	2	4	7
Cefuroxime					3	3	6
Cefazolin				-1		4	5
Erythromycin					3	1	4
Ceftazidime		1		1		1	3
Ciprofloxacin		1			1	1	3
Cloxacillin				1	1		2
Fucidin	1			1			2
Teicoplanin						2	2
Amoxicillin					1		1
Rifampicin				1			1
Sulphadiazine						1	1
Total	76	91	63	73	71	70	444

5.6 SENSITIVITY TRENDS OF MICRO-ORGANISMS DEPENDING ON INFECTION TYPE

An important aspect not addressed in the first phase of the study was the source and the clinical significance of infections.

5.6.1. Resistance trends of significant nosocomial infections

5.6.1.1 Sensitivity patterns to penicillins

As seen in Table 5.10, penicillin was highly effective (100%) against the majority of the gram positive significant nosocomial infections, with the

Table 5.10 Percentage sensitivities of penicillins for significant nosocomial infections

	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Piperacillin + Tazobactam	Flucloxacillin
GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis	100 (3/3)	100 (3/3)				100 (2/2)	
enterococcus faecium							
staphylococcus aureus	0 (0/8)		25 (2/8)	25 (2/8)			
staphylococcus epidermidis	0 (0/9)		33.3 (3/9)	33.3 (3/9)			
streptococcus agalactiae							
streptococcus pneumoniae							
streptococcus pyogenes	100 (1/1)						
streptococcus sp.	100 (1/1)	100 (1/1)				100 (1/1)	
streptococcus viridans							
micrococcus sp.							
corynebacterium sp							
bacillus cereus							
GRAM NEGATIVE							
acinetobacter baumanii							
acinetobacter lwoffi					0 (0/1)		0 (0/1)
alkaligenes sp.							
alkaligenes faecalis							
enterobacter sp.		0 (0/2)			0 (0/2)	100 (2/2)	100 (2/2)
enterobacter cloacae		0 (0/2)			50 (1/2)	0 (0/2)	50 (1/2)
escherichia coli		0 (0/7)			0 (0/6)	66.7 (4/6)	100 (7/7)
haemophilus influenzae		100 (2/2)				100 (2/2)	
klebsiella sp.		0 (0/8)			25 (2/8)	25 (2/8)	62.5 (5/8)
klebsiella pneumoniae							
klebsiella oxytoca							
proteus mirabilis		0 (0/2)			100 (2/2)	100 (2/2)	100 (2/2)
pseudomonas aeruginosa					80 (4/5)		80 (4/5)
campylobacter jejuni							
bacteroides fragilis							
strenotrophomonas maltophilia							
burkholderia cepacia							
Mean ± SD	60 ± 27.4	37.5 ± 25.9	29.2 ± 3.0	29.2 ± 3.0	36.4 ± 20.7	74.0 ± 20.1	70.4 ± 18.5

exception of *Staphylococcus aureus* and *Staphylococcus epidermidis* both of which were completely resistant to penicillin (0%).

Gram positive micro-organisms and *Haemophilus influenzae* were most sensitive to. However, gram negative micro-organisms were completely resistant to it.

Staphylococcus species was fairly resistant to cloxacillin and oxacillin.

Proteus mirabilis (100%) and *Pseudomonas aeruginosa* (80%) were the only micro-organisms sensitive to piperacillin, whereas the rest of the micro-organisms that it was tested against it were resistant to it.

Amoxicillin/clavulanic acid only experienced resistance from *Enterobacter cloacae* (0%), *Klebsiella sp.* (25%) and *Escherichia coli* (66.7%).

Piperacillin/tazobactam was an improvement on piperacillin in that the only micro-organism that demonstrated complete resistance to it was *Acinetobacter iwoffi*. However *Enterobacter cloacae* and *Klebsiella sp.* had resistant patterns of 50% and 62.5% respectively.

5.6.1.2 Sensitivity patterns to cephalosporins

The first generation cephalosporins tested, cefazolin and cephalexin, had identical resistances from *Staphylococcus aureus* (28.6%) and *Staphylococcus epidermidis* (25%) as represented in Table 5.11. Their results from gram negative micro-organisms is not identical, but was very similar. *Enterobacter cloacae* was completely resistant (0%) to first generation cephalosporins, while *Escherichia coli* (33.3% and 50% respectively) and *Klebsiella sp.* (12.5% and 25% respectively) were highly resistant. The difference between the Enterobacter sp. results could possibly be due to the number of isolates tested between the two drugs (cefazolin was tested with 2 isolates of which 1 was

Table 5.11 Percentage sensitivities of cephalosporins for significant nosocomial infections.

	Cefazolin	Cephalexin	Cefuroxime	Ceftriaxone	Ceftazidime	Cefotaxime	Cefepime
GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis							
enterococcus faecium							
staphylococcus aureus	28.6 (2/7)	28.6 (2/7)	28.6 (2/7)				
staphylococcus epidermidis	25 (2/8)	25 (2/8)	25 (2/8)				
streptococcus agalactiae							
streptococcus pneumoniae							
streptococcus pyogenes							
streptococcus sp.	100 (1/1)	100 (1/1)					
streptococcus viridans							
micrococcus sp.							
corynebacterium sp.							
bacillus cereus							
GRAM NEGATIVE							
acinetobacter baumanii							
acinetobacter lwoffi					0 (0/1)		0 (0/1)
alkaligenes sp.							
alkaligenes faecalis							
enterobacter sp.	50 (1/2)	100 (1/1)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)	100 (2/2)
enterobacter cloacae	0 (0/2)	0 (0/1)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)
escherichia coli	33.3 (2/6)	50 (2/4)	57.1 (4/7)	57.1 (4/7)	57.1 (4/7)	57.1 (4/7)	100 (7/7)
haemophilus influenzae			100 (2/2)	100 (2/2)		100 (2/2)	
klebsiella sp.	12.5 (1/8)	25 (1/4)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	62.5 (5/8)
klebsiella pneumoniae							
klebsiella oxytoca							
proteus mirabilis	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)
pseudomonas aeruginosa					80 (4/5)		100 (5/5)
campylobacter jejuni							
bacteroides fragilis							
strenotrophomonas maltophilia							
burkholderia cepacia							
Mean ± SD	43.7 ± 18.9	53.6 ± 20.4	56.0 ± 14.7	65.8 ± 13.7	53.5 ± 15.9	65.8 ± 13.7	73.2 ± 19.3

sensitive, therefore the 50%, while cephalexin was tested with 1 isolate which happened to be sensitive, therefore 100%).

The second generation cephalosporin tested, cefuroxime, had identical resistances from *Staphylococcus aureus* (28.6%) and *Staphylococcus epidermidis* (25%) as the first generations. With regards to gram negative micro-organisms, the most worrisome micro-organism tested against cefuroxime was *Klebsiella sp.* (37.5%). *Enterobacter sp.* (50%), *Enterobacter*

cloacae (50%) and *Escherichia coli* (57.1%) also produced disconcerting resistance results.

The third generation cephalosporins, cefotaxime, ceftazidime and ceftriaxone, were only tested against gram negative micro-organisms, and their results were identical to those obtained with the cefuroxime. *Acinetobacter iwoffi* was also tested against ceftazidime and was completely resistant (0%) to it.

The fourth generation cephalosporin, cefepime, had the following micro-organisms demonstrate resistance against it: *Acinetobacter Iwoffi* (0%), *Enterobacter cloacae* (50%) and *Klebsiella sp.* (62.5%). *Enterobacter sp.*, *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa* were 100% sensitive to it.

5.6.1.3 Sensitivity patterns to aminoglycosides

The comparison of aminoglycoside results to significant nosocomial infections was exhibited in Table 5.12. Considering the prolific use of amikacin in ward 276, it was sensitive to most micro-organisms that it was tested against with the exception of *Enterobacter cloacae* (50%) and *Escherichia coli* (66.7%). Gentamicin produced the most perturbing results considering its sporadic use in the ward. All the gram negative micro-organisms tested against it were fairly resistant including *Proteus mirabilis* which was highly sensitive to amikacin and tobramycin. Tobramycin was marginally better than gentamicin, with

Acinetobacter lwoffi (100%), *Proteus mirabilis* (100%) and *Pseudomonas aeruginosa* (80%) being sensitive to it.

Table 5.12 Percentage sensitivities of aminoglycosides for significant nosocomial infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis		100 (1/1)	
enterococcus faecium			
staphylococcus aureus			
staphylococcus epidermidis			
streptococcus agalactiae			
streptococcus pneumoniae			
streptococcus pyogenes			
streptococcus sp.			
streptococcus viridans			
micrococcus sp.			
corynebacterium sp.			
bacillus cereus			
GRAM NEGATIVE			
acinetobacter baumanii			
acinetobacter lwoffi			100 (1/1)
alkaligenes sp.			
alkaligenes faecalis			
enterobacter sp.	100 (2/2)	50 (1/2)	50 (1/2)
enterobacter cloacae	50 (1/2)	50 (1/2)	50 (1/2)
escherichia coli	66.7 (4/6)	42.9 (3/7)	57.1 (4/7)
haemophilus influenzae			
klebsiella sp.	87.5 (7/8)	37.5 (3/8)	28.6 (2/7)
klebsiella pneumoniae			
klebsiella oxytoca			
proteus mirabilis	100 (2/2)	50 (1/2)	100 (2/2)
pseudomonas aeruginosa	80 (4/5)		80 (4/5)
campylobacter jejuni			
bacteroides fragilis			
strenotrophomonas maltophilia			
burkholderia cepacia			
Mean ± SD	80.7 ± 9.8	55.1 ± 11.3	66.5 ± 13.7

5.6.1.4 Sensitivity patterns to glycopeptides, fluoroquinolones and carbapenem β-lactams

The groups represented in Table 5.13 consist of drugs that were considered omnipotent to frequently occurring infections and considered the last line antibiotics.

Table 5.13 Percentage sensitivities of glycopeptides, fluoroquinolones and carbapenem β-lactams for significant nosocomial infections.

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis	100 (3/3)					
enterococcus faecium						
staphylococcus aureus	100 (8/8)	100 (4/4)				
staphylococcus epidermidis	100 (9/9)	80 (4/5)				
streptococcus agalactiae						
streptococcus pneumoniae						
streptococcus pyogenes						
streptococcus sp.	100 (1/1)					
streptococcus viridans						
micrococcus sp.						
corynebacterium sp.						
bacillus cereus						
GRAM NEGATIVE						
acinetobacter baumanii						
acinetobacter lwoffi			100 (1/1)	100 (1/1)	0 (0/1)	0 (0/1)
alkaligenes sp.						
alkaligenes faecalis						
enterobacter sp.			100 (1/1)		100 (2/2)	
enterobacter cloacae			100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)
escherichia coli					100 (7/7)	
haemophilus influenzae			100 (1/1)			
klebsiella sp.					100 (8/8)	
klebsiella pneumoniae						
klebsiella oxytoca						
proteus mirabilis					100 (2/2)	
pseudomonas aeruginosa			100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
campylobacter jejuni						
bacteroides fragilis						
strenotrophomonas maltophilia						
burkholderia cepacia						
Mean ± SD	100.0	90.0 ± 7.1	100.0	100.0	85.7 ± 18.9	66.7 ± 28.9

The micro-organisms that were tested against vancomycin were still highly susceptible to, however *Staphylococcus epidermidis* is only 80% sensitive to teicoplanin.

With the exception of the *Acinetobacter lwoffi* which exhibited complete resistance (0%), all the gram negative micro-organisms that were tested against the carbapenem β-lactams were highly sensitive to them.

The gram negative micro-organisms tested against ciprofloxacin were highly sensitive towards it.

5.6.2 Resistance trends of insignificant nosocomial infections

5.6.2.1 Sensitivity patterns to penicillins

Table 5.14 Percentage sensitivities of penicillins for insignificant nosocomial infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (rati
enterococcus faecalis	100 (2/2)	100 (2/2)				100 (2/2)	
enterococcus faecium	0 (0/1)	0 (0/1)				0 (0/1)	
staphylococcus aureus	0 (0/1)		66.7 (2/3)	66.7 (2/3)			
staphylococcus epidermidis	6.3 (1/16)		12.5 (2/16)	12.5 (2/16)			
streptococcus agalactiae							
streptococcus pneumoniae							
streptococcus pyogenes							
streptococcus sp.							
streptococcus viridans							
micrococcus sp.							
corynebacterium sp.							
bacillus cereus	0 (0/1)						
GRAM NEGATIVE							
acinetobacter baumanii							
acinetobacter lwoffi							
alkaligenes sp.							
alkaligenes faecalis					100 (1/1)		100 (1/1)
enterobacter sp.		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)
enterobacter cloacae		0 (0/2)			100 (2/2)	0 (0/2)	100 (2/2)
escherichia coli							
haemophilus influenzae		100 (1/1)				100 (1/1)	
klebsiella sp.		0 (0/2)			50 (1/2)	100 (2/2)	100 (2/2)
klebsiella pneumoniae							
klebsiella oxytoca							
proteus mirabilis							
pseudomonas aeruginosa							
campylobacter jejuni							
bacteroides fragilis							
strenotrophomonas maltophilia		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)
burkholderia cepacia					100 (1/1)		100 (1/1)
Mean ± SD	21.3 ± 22.1	28.6 ± 24.4	39.6 ± 19.2	39.6 ± 19.2	91.7 ± 10.2	42.9 ± 26.8	100.0

Enterococcus faecalis was the only micro-organism sensitive to penicillin. *Enterococcus faecium*, *Staphylococcus aureus* and *Bacillus cereus* were

completely resistant (0%) to it whereas *Staphylococcus epidermidis* was bordering on complete resistance.

Enterococcus faecalis and Haemophilus influenzae were both 100% sensitivity to ampicillin, however the rest of the micro-organisms tested against it, demonstrated complete resistance (0%) towards it.

Cloxacillin and oxacillin demonstrated identical results. *Staphylococcus aureus* was 66.7% sensitive and *Staphylococcus epidermidis* was 12.5% sensitive to them.

Gram negative micro-organisms that were tested with piperacillin were found to be completely sensitive to it (*Alkaligenes faecalis*, *Enterobacter sp.*, *Enterobacter cloacae*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*) with the exception being *Klebsiella sp.* where only 50% of the micro-organisms were sensitive.

Enterococcus faecalis, *Haemophilus influenzae* and *Klebsiella sp.* were highly sensitive to amoxicillin/clavulanic acid. Whereas, *Enterococcus faecium*, *Enterobacter sp.*, *Enterobacter cloacae and Stenotrophomonas maltophilia* were completely resistant to it

Piperacillin/tazobactam had the best overall results with all the micro-organisms that were tested against it having a 100% sensitivity.

5.6.2.2 Sensitivity patterns to cephalosporins

With the exception of a couple of micro-organisms that were tested for one and not the other, the first generation cephalosporins tested, cefazolin and cephalexin, had identical results. *Staphylococcus aureus* was the most sensitive micro-organism (66.7%). Amongst the gram negative micro-organisms tested, with the exception of *Klebsiella sp.* which had a resistance of 50%, *Enterobacter sp.* and *Enterobacter cloacae* were completely resistant to the first generation cephalosporins.

Table 5.15 Percentage sensitivities of cephalosporins for insignificant nosocomial infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis							
enterococcus faecium							
staphylococcus aureus	66.7 (2/3)	66.7 (2/3)	66.7 (2/3)				
staphylococcus epidermidis	12.5 (2/16)	12.5 (2/16)	12.5 (2/16)				
streptococcus agalactiae							
streptococcus pneumoniae							
streptococcus pyogenes							
streptococcus sp.							
streptococcus viridans							
micrococcus sp.							
corynebacterium sp.							
bacillus cereus	0 (0/1)						
GRAM NEGATIVE							
acinetobacter baumanii							
acinetobacter lwoffi							
alkaligenes sp.							
alkaligenes faecalis					100 (1/1)		100 (1/1)
enterobacter sp.	0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
enterobacter cloacae	0 (0/2)	0 (0/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)
escherichia coli							
haemophilus influenzae			100 (1/1)	100 (1/1)		100 (1/1)	
klebsiella sp.	50 (1/2)	50 (1/2)	50 (1/2)	100 (2/2)	50 (1/2)	100 (2/2)	100 (2/2)
klebsiella pneumoniae							
klebsiella oxytoca							
proteus mirabilis							
pseudomonas aeruginosa							
campylobacter jejuni							
bacteroides fragilis							
strenotrophomonas maltophilia	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)
burkholderia cepacia					100 (1/1)		100 (1/1)
Mean ± SD	18.5 ± 14.0	25.8 ± 15.4	61.3 ± 21.2	80.0 ± 22.4	91.7 ± 10.2	80.0 ± 22.4	100.0

The second generation cephalosporin tested, cefuroxime, experienced identical resistances from *Staphylococcus aureus* (66.7%) and *Staphylococcus epidermidis* (12.5%) as the first generation cephalosporins. As for the gram negative micro-organisms tested only *Klebsiella sp.* (50%) and *Strenophomonas maltophilia* (0%) were resistant to cefuroxime.

The majority of the gram negative micro-organisms that they were tested against the third generation cephalosporins, cefotaxime, ceftazidime and ceftriaxone, were highly sensitive to them. The exceptions being cefotaxime and ceftriaxone to *Stenotrophomonas maltophilia* (0%) and ceftazidime to *Klebsiella sp.* (50%).

All micro-organisms that were tested against the fourth generation cephalosporin, cefepime, were highly sensitive to it.

5.6.2.3 Sensitivity patterns to aminoglycosides

Enterobacter sp., *Enterobacter cloacae* and *Klebsiella sp.* were fully sensitive to amikacin. Whereas, *Alkaiigenes faecalis*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia* were fully resistant to it. Gentamicin and tobramycin had similar results to amikacin with the exception being Klebsiella sp. which was only 50% sensitive to them.

Table 5.16 Percentage sensitivities of aminoglycosides for insignificant nosocomial infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis			
enterococcus faecium			
staphylococcus aureus			
staphylococcus epidermidis			
streptococcus agalactiae			
streptococcus pneumoniae			
streptococcus pyogenes			
streptococcus sp.			
streptococcus viridans			
micrococcus sp.			
corynebacterium sp.			
bacillus cereus			
GRAM NEGATIVE			
acinetobacter baumanii			
acinetobacter lwoffi			
alkaligenes sp.			
alkaligenes faecalis	0 (0/1)		0 (0/1)
enterobacter sp.	100 (1/1)	100 (1/1)	100 (1/1)
enterobacter cloacae	100 (2/2)	100 (2/2)	100 (2/2)
escherichia coli			
haemophilus influenzae			
klebsiella sp.	100 (2/2)	50 (1/2)	50 (1/2)
klebsiella pneumoniae			
klebsiella oxytoca			
proteus mirabilis			
pseudomonas aeruginosa			
campylobacter jejuni			
bacteroides fragilis			
strenotrophomonas maltophilia	0 (0/1)	0 (0/1)	0 (0/1)
burkholderia cepacia	0 (0/1)		0 (0/1)
Mean ± SD	50.0 ± 27.4	62.5 ± 24.0	41.7 ± 24.6

5.6.2.4 Sensitivity patterns to glycopeptides, fluoroquinolones and carbapenem β-lactams

All the gram positive micro-organisms that they were tested against the glycopeptides, vancomycin and teicoplanin, were highly sensitive to them.

Table 5.17 Percentage sensitivities of glycopeptides, fluoroquinolones and carbapenem β-lactams for insignificant nosocomial infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis	100 (2/2)					
enterococcus faecium	100 (1/1)					
staphylococcus aureus	100 (3/3)	100 (3/3)				
staphylococcus epidermidis	100 (16/16)	100 (9/9)				
streptococcus agalactiae						
streptococcus pneumoniae						
streptococcus pyogenes						
streptococcus sp.						
streptococcus viridans						
micrococcus sp.						
corynebacterium sp.						
bacillus cereus	100 (1/1)					
GRAM NEGATIVE						
acinetobacter baumanii						
acinetobacter lwoffi						
alkaligenes sp.						
alkaligenes faecalis			0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)
enterobacter sp.					100 (1/1)	
enterobacter cloacae			100 (1/1)	100 (1/1)	100 (2/2)	100 (1/1)
escherichia coli						
haemophilus influenzae			100 (1/1)			
klebsiella sp.					100 (2/2)	
klebsiella pneumoniae						
klebsiella oxytoca						
proteus mirabilis						
pseudomonas aeruginosa						
campylobacter jejuni						
bacteroides fragilis						
strenotrophomonas maltophilia			0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)
burkholderia cepacia			0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)
Average	100.0	100.0	40.0 ± 27.4	25.0 ± 25.0	100.0	100.0

Alkaligenes faecalis, *Stenotrophomonas maltophilia* and *Burkholderia cepacia* were resistant to the fluoroquinolones, ciprofloxacin and ofloxacin. *Enterobacter cloacae* was sensitive to both, while *Haemophilus influenzae* was only sensitive to ciprofloxacin.

Gram negative micro-organisms that they were tested against the carbapenem ..tams, imipenem and meropenem, were found to be highly sensitive to them with the exception of *Burkholderia cepacia.*

5.6.3 Resistance trends of significant community infections

5.6.3.1 Sensitivity patterns to penicillins

Table 5.18 Percentage sensitivities of penicillins for significant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis	50 (1/2)	50 (1/2)				50 (1/2)	
enterococcus faecium	0 (0/1)	0 (0/1)				0 (0/1)	
staphylococcus aureus							
staphylococcus epidermidis	50 (1/2)		100 (2/2)	100 (2/2)			
streptococcus agalactiae	100 (2/2)	100 (2/2)				100 (2/2)	
streptococcus pneumoniae	100 (1/1)		100 (1/1)	100 (1/1)			
streptococcus pyogenes	100 (1/1)	100 (1/1)				100 (1/1)	
streptococcus sp.	100 (3/3)	100 (3/3)				100 (3/3)	
streptococcus viridans	100 (1/1)	100 (1/1)				100 (1/1)	
micrococcus sp.	100 (2/2)	100 (1/1)				100 (1/1)	
corynebacterium sp.							
bacillus cereus							
GRAM NEGATIVE							
acinetobacter baumanii					0 (0/1)		100 (1/1)
acinetobacter lwoffi							
alkaligenes sp.		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)
alkaligenes faecalis		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)
enterobacter sp.							
enterobacter cloacae							
escherichia coli	0 (0/4)				0 (0/4)	33.3 (1/3)	50 (2/4)
haemophilus influenzae							
klebsiella sp.		0 (0/2)			0 (0/2)	0 (0/2)	100 (2/2)
klebsiella pneumoniae		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)
klebsiella oxytoca		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)
proteus mirabilis		0 (0/1)			100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa					100 (1/1)		100 (1/1)
campylobacter jejuni		0 (0/1)					
bacteroides fragilis							
strenotrophomonas maltophilia							
burkholderia cepacia							
Mean ± SD	70.0 ± 21.1	39.3 ± 24.4	100.0	100.0	33.3 ± 25.0	48.8 ± 24.1	94.4 ± 8.4

With the exception of *Enterococcus faecalis* (50%), *Enterococcus faecium* (0%) and *Staphylococcus epidermidis* (50%) the majority of gram positive micro-organisms were highly sensitive to penicillin. *Escherichia coli* proved to be completely resistant to it.

With the exception of *Enterococcus faecalis* (50%) and *Enterococcus faecium* (0%) to all the gram positive micro-organisms that it was tested against ampicillin were highly sensitive to it. However all gram negative micro-organisms tested against ampicillin were completely resistant.

Staphylococcus epidermidis and *Streptococcus pyogenes* were highly sensitive to cloxacillin and oxacillin

Alkaligenes faecalis, *Proteus mirabilis* and *Pseudomonas aeruginosa* demonstrated complete sensitivity to piperacillin, while *Acinetobacter baumanii*, *Alkaligenes sp.*, *Escherichia coli*, *Klebsiella sp.*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* demonstrated complete resistance.

With the exception of *Enterococcus faecalis* (50%) and *Enterococcus faecium* (0%), the gram positive micro-organisms tested against amoxicillin/clavulanic acid were highly sensitive to it. As far as the gram negative micro-organisms were concerned, with the exception of *Proteus mirabilis* which was highly sensitive to amoxicillin/clavulanic acid, and *Escherichia coli* only having a sensitivity of 33.3%, *Alkaligenes sp.*, *Alkaligenes faecalis*, *Klebsiella sp.*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were completely resistant to it.

All the gram negative micro-organisms with the exception of *Escherichia coli* (50%) were highly sensitive to piperacillin/tazobactam.

5.6.3.2 *Sensitivity patterns to cephalosporins*

Gram positive micro-organisms that were tested as well as *Proteus mirabilis* were highly sensitive to the first generation cephalosporins, cefazolin and cephalexin. *Escherichia coli* had similar sensitivities to both of them.

Alkaligenes sp., *Alkaligenes faecalis*, *Klebsiella sp.*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were completely resistant to cefazolin.

Table 5.19 Percentage sensitivities of cephalosporins for significant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis							
enterococcus faecium							
staphylococcus aureus							
staphylococcus epidermidis	100 (2/2)	100 (2/2)	100 (2/2)				
streptococcus agalactiae	100 (2/2)	100 (2/2)					
streptococcus pneumoniae							
streptococcus pyogenes	100 (1/1)	100 (1/1)					
streptococcus sp.	100 (3/3)	100 (3/3)					
streptococcus viridans	100 (1/1)	100 (1/1)					
micrococcus sp.	100 (2/2)	100 (2/2)					
corynebacterium sp.							
bacillus cereus							
GRAM NEGATIVE							
acinetobacter baumanii					0 (0/1)		100 (1/1)
acinetobacter lwoffi							
alkaligenes sp.	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)
alkaligenes faecalis	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)
enterobacter sp.							
enterobacter cloacae							
escherichia coli	75 (3/4)	66.7 (2/3)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	100 (4/4)
haemophilus influenzae							
klebsiella sp.	0 (0/2)		0 (0/2)	0 (0/2)	0 (0/2)	0 (0/2)	100 (2/2)
klebsiella pneumoniae	0 (0/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)
klebsiella oxytoca	0 (0/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)
proteus mirabilis	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa					100 (1/1)		100 (1/1)
campylobacter jejuni				0 (0/1)		0 (0/1)	
bacteroides fragilis							
strenotrophomonas maltophilia							
burkholderia cepacia							
Mean ± SD	59.6 ± 24.8	95.8 ± 5.9	34.4 ± 24.1	21.9 ± 20.6	52.8 ± 25.4	21.9 ± 20.6	100.0

The second generation cephalosporin, cefuroxime, experienced identical resistance results as cefazolin although it was not tested against as many gram positive micro-organisms.

The majority of the gram negative micro-organisms that were tested with the exception of *Proteus mirabilis* were resistant to the third generation cephalosporins, cefotaxime, ceftazidime and ceftriaxone. *Alkaligenes sp.*, *Alkaligenes faecalis* and *Pseudomonas aeruginosa* were only sensitive to ceftazidime.

All the gram negative micro-organisms tested against the fourth generation cephalosporin, cefepime, were completely sensitive to it.

5.6.3.3 Sensitivity patterns to aminoglycosides

Amikacin experienced high levels of sensitivity from *Alkaligenes faecalis*, *Escherichia coli*, *Klebsiella oxytoca*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Those micro-organisms that were completely resistant to it were *Acinetobacter baumanii*, *Alkaligenes sp.*, *Klebsiella sp.* and *Klebsiella pneumoniae*. Similar results were obtained for gentamicin and tobramycin, with the exception *Klebsiella oxytoca* which was completely resistant and *Escherichia coli* that exhibited an increase in resistance (75%).

Table 5.20 Percentage sensitivities of aminoglycosides for significant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis			
enterococcus faecium		0 (0/1)	
staphylococcus aureus			
staphylococcus epidermidis			
streptococcus agalactiae			
streptococcus pneumoniae			
streptococcus pyogenes			
streptococcus sp.			
streptococcus viridans			
micrococcus sp.			
corynebacterium sp.			
bacillus cereus			
GRAM NEGATIVE			
acinetobacter baumanii	0 (0/1)		0 (0/1)
acinetobacter lwoff			
alkaligenes sp.	0 (0/1)	0 (0/1)	0 (0/1)
alkaligenes faecalis	100 (1/1)	100 (1/1)	100 (1/1)
enterobacter sp.			
enterobacter cloacae			
escherichia coli	100 (4/4)	75 (3/4)	75 (3/4)
haemophilus influenzae			
klebsiella sp.	0 (0/2)	0 (0/2)	0 (0/2)
klebsiella pneumoniae	0 (0/1)	0 (0/1)	0 (0/1)
klebsiella oxytoca	100 (1/1)	0 (0/1)	0 (0/1)
proteus mirabilis	100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa	100 (1/1)		100 (1/1)
campylobacter jejuni		100 (1/1)	
bacteroides fragilis			
strenotrophomonas maltophilia			
burkholderia cepacia			
Mean ± SD	55.6 ± 26.4	41.7 ± 25.0	41.7 ± 25.0

5.6.3.4 Sensitivity patterns to glycopeptides, fluoroquinolones and carbapenem β-lactams

Gram positive micro-organisms that were tested against vancomycin were found to be highly sensitive to it. Unlike the nosocomial infections teicoplanin was not tested.

Gram negative micro-organisms that were tested against the fluoroquinolonés were highly sensitive to them.

Table 5.21 Percentage sensitivities of glycopeptides, fluoroquinolones and carbapenem β-lactams for significant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis	100 (2/2)					
enterococcus faecium	100 (1/1)					
staphylococcus aureus						
staphylococcus epidermidis	100 (2/2)					
streptococcus agalactiae	100 (2/2)					
streptococcus pneumoniae	100 (1/1)					
streptococcus pyogenes	100 (1/1)					
streptococcus sp.	100 (3/3)					
streptococcus viridans	100 (1/1)					
micrococcus sp.	100 (2/2)					
corynebacterium sp.						
bacillus cereus						
GRAM NEGATIVE						
acinetobacter baumanii			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
acinetobacter lwoffi						
alkaligenes sp.			100 (1/1)	100 (1/1)	100 (1/1)	0 (0/1)
alkaligenes faecalis			100 (1/1)	100 (1/1)	100 (1/1)	0 (0/1)
enterobacter sp.						
enterobacter cloacae						
escherichia coli			100 (3/3)	100 (3/3)	100 (4/4)	100 (3/3)
haemophilus influenzae						
klebsiella sp.					100 (2/2)	
klebsiella pneumoniae			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
klebsiella oxytoca			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
proteus mirabilis					100 (1/1)	
pseudomonas aeruginosa			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
campylobacter jejuni			100 (1/1)	100 (1/1)	100 (1/1)	
bacteroides fragilis						
strenotrophomonas maltophilia						
burkholderia cepacia						
Mean ± SD	100.0		100.0	100.0	100.0	71.4 ± 24.4

Alkaligenes sp. and *Alkaligenes faecalis* were the only micro-organisms that demonstrated complete resistance against meropenem, while the micro-organisms that were tested against imipenem were highly sensitive to it.

5.6.4 Resistance trends of insignificant community infections

5.6.4.1 Sensitivity patterns to penicillins

Table 5.22 Percentage sensitivities of penicillins for insignificant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis							
enterococcus faecium							
staphylococcus aureus							
staphylococcus epidermidis	0 (0/5)		40 (2/5)	40 (2/5)			
streptococcus agalactiae							
streptococcus pneumoniae							
streptococcus pyogenes							
streptococcus sp.							
streptococcus viridans							
micrococcus sp.							
corynebacterium sp.							
bacillus cereus							
GRAM NEGATIVE							
acinetobacter baumanii							
acinetobacter lwoffi							
alkaligenes sp.							
alkaligenes faecalis							
enterobacter sp.							
enterobacter cloacae							
escherichia coli							
haemophilus influenzae		100 (1/1)				100 (1/1)	
klebsiella sp.							
klebsiella pneumoniae							
klebsiella oxytoca							
proteus mirabilis		100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa							
campylobacter jejuni							
bacteroides fragilis							
strenotrophomonas maltophilia							
burkholderia cepacia							
Mean ± SD	0	100.0	40.0	40.0	100.0	100.0	100.0

Staphylococcus epidermidis was resistant to the β-lactams, with cloxacillin and oxacillin only experiencing sensitivity levels of 40% and penicillin experiencing complete resistance (0%).

All the gram negative micro-organisms that were tested against ampicillin, amoxicillin/clavulanic acid, piperacillin and piperacillin/tazobactam were highly sensitive to them.

5.6.4.2 Sensitivity patterns to cephalosporins

Table 5.23 Percentage sensitivities of cephalosporins for insignificant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis							
enterococcus faecium							
etaphylococcus aureus							
staphylococcus epidermidis	40 (2/5)	40 (2/5)	25 (1/4)				
streptococcus agalactiae							
streptococcus pneumoniae							
streptococcus pyogenes							
streptococcus sp.							
streptococcus viridans							
micrococcus sp.							
corynebacterium sp.							
bacillus cereus							
GRAM NEGATIVE							
acinetobacter baumanii							
acinetobacter lwoffi							
alkaligenes sp.							
alkaligenes faecalis							
enterobacter sp.							
enterobacter cloacae							
escherichia coli							
haemophilus influenzae			100 (1/1)	100 (1/1)		100 (1/1)	
klebsiella sp.							
klebsiella pneumoniae							
klebsiella oxytoca							
proteus mirabilis	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa							
campylobacter jejuni							
bacteroides fragilis							
strenotrophomonas maltophilia							
burkholderia cepacia							
Mean ± SD	70.0 ± 21.2	70.0 ± 21.2	75.0 ± 21.7	100.0	100.0	100.0	100.0

The cefazolin, cephalexin and cefuroxime endured fair resistance from *Staphylococcus epidermidis* (40%, 40% and 25% respectively).

Both *Proteus mirabilis* and *Haemophilus influenzae* were highly sensitive to all the cephalosporins they were tested against.

5.6.4.3 Sensitivity patterns to aminoglycosides

Table 5.24 Percentage sensitivities of aminoglycosides for insignificant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis			
enterococcus faecium			
staphylococcus aureus			
staphylococcus epidermidis			
streptococcus agalactiae			
streptococcus pneumoniae			
streptococcus pyogenes			
streptococcus sp.			
streptococcus viridans			
micrococcus sp.			
corynebacterium sp.			
bacillus cereus			
GRAM NEGATIVE			
acinetobacter baumanii			
acinetobacter lwoffi			
alkaligenes sp.			
alkaligenes faecalis			
enterobacter sp.			
enterobacter cloacae			
escherichia coli			
haemophilus influenzae			
klebsiella sp.			
klebsiella pneumoniae			
klebsiella oxytoca			
proteus mirabilis	100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa			
campylobacter jejuni			
bacteroides fragilis			
strenotrophomonas maltophilia			
burkholderia cepacia			
Mean ± SD	100.0	100.0	100.0

Only *Proteus mirabilis* was tested, and was highly sensitive to all 3 aminoglycosides.

5.6.4.4 Sensitivity patterns to glycopeptides, fluoroquinolones and carbapenem β-lactam

Table 5.25 Percentage sensitivities of glycopeptides, fluoroquinolones and carbapenem β-lactams for insignificant community infections

GRAM POSITIVE	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)	sensitivity % (ratio)
enterococcus faecalis						
enterococcus faecium						
staphylococcus aureus						
staphylococcus epidermidis	100 (5/5)	100 (2/2)				
streptococcus agalactiae						
streptococcus pneumoniae						
streptococcus pyogenes						
streptococcus sp.						
streptococcus viridans						
micrococcus sp.						
corynebacterium sp.						
bacillus cereus						
GRAM NEGATIVE						
acinetobacter baumanii						
acinetobacter lwoffi						
alkaligenes sp.						
alkaligenes faecalis						
enterobacter sp.						
enterobacter cloacae						
escherichia coli						
haemophilus influenzae			100 (1/1)			
klebsiella sp.						
klebsiella pneumoniae						
klebsiella oxytoca						
proteus mirabilis					100 (1/1)	
pseudomonas aeruginosa						
campylobacter jejuni						
bacteroides fragilis						
strenotrophomonas maltophilia						
burkholderia cepacia						
Mean ± SD	100.0	100.0	100.0		100.0	

Only *Staphylococcus epidermidis* was evaluated with vancomycin and teicoplanin and was found to be highly sensitive to them.

Ofloxacin and meropenem were not tested. However *Haemophilus influenzae* was highly sensitive to ciprofloxacin, and *Proteus mirabilis* was highly sensitive to imipenem.

CHAPTER 6: RESULTS: Pharmacokinetic study

6.1 TWICE DAILY AMINOGLYCOSIDE DOSING

The results of the first part of the study are tabulated in Table 6.1.

Table 6.1 Phase 1 patient kinetic parameters

Patient 1	40	3 150	23 (7.3)	0.133	5.2	0.65	16.1	3.5
Patient 2	36	1 785	13 (7.3)	0.0864	8.0	0.87	18.9	7.0
Patient 3	31	1 350	10 (7.4)	0.0596	11.6	1.27	21.4	10.8
Patient 4	30	1 260	9 (7.1)	0.0596	11.6	1.22	21.4	10.8
Patient 5	37	2 800	20 (7.1)	0.118	5.9	0.733	15.5	4.0
Patient 6	42	3 190	24 (7.5)	0.160	4.3	0.637	14.4	2.3
Patient 7	30	1 140	9 (7.9)	0.117	5.9	0.462	27.5	7.2
Patient 8	40	2 790	20 (7.2)	0.109	6.4	1.06	12.2	3.9
Average	36	2 183	16 (7.3)	0.105	7.4	0.863	18.4	6.2

As demonstrated in Table 6.1, the patients included in this part of the study had an average gestational age of 36 weeks, and had an average weight of 2 183 g. Although the previous amikacin dosing protocol called for a dose of 7.5 mg/kg to be given twice a day, the average dose turned out to be 7.3 mg/kg given every 12 hours. From this dosing regimen, the average maximum serum concentration (Cmax) was subtherapeutic (less than the desired 35 µg/ml), whereas the average minimum serum concentration (Cmin) was greater than the desired concentration of < 5µg/ml.

From the calculated kinetic parameters, the estimated dosing regimen was calculated as seen in Table 6.2.

Table 6.2 Phase 1 patient estimated parameters

Patient 1	35	5	15.1	12	18.7
Patient 2	35	5	23.0	24	26.9
Patient 3	35	5	33.1	36	40.0
Patient 4	35	5	33.1	36	38.4
Patient 5	35	5	17.0	18	23.2
Patient 6	35	5	12.7	12	19.7
Patient 7	35	5	17.1	18	14.6
Patient 8	35	5	18.4	18	32.8
Average			21.2	21.8	26.8

Table 6.2 shows that both the dosing interval and the maintenance dose need to be increased in order to obtain the desired Cmax of 35 μg/ml and Cmin of < 5 μg/ml. On average, the dosing interval would have to be increased to at least 20 hours, while the maintenance dose would have to be increase to 27 mg/kg.

The above patients were further sub-divided according to their weight: greater than 2 000 g and less than 2 000 g.

Table 6.3 Kinetic parameters for patients > 2 000g

Patient 1	40	3 150	23 (7.3)	0.133	5.2	0.65	16.1	3.5
Patient 5	37	2 800	20 (7.1)	0.118	5.9	0.733	15.5	4.0
Patient 6	42	3 190	24(7.5)	0.160	4.3	0.637	14.4	2.3
Patient 8	40	2 790	20 (7.2)	0.109	6.4	1.06	12.2	3.9
Average	40	3 047	22 (7.2)	0.137	5.1	0.673	15.3	3.3

Table 6.4 Projected parameters for patients > 2 000g

Patient 1	35	5	15.1	12	18.7
Patient 5	35	5	17.0	18	23.2
Patient 6	35	5	12.7	12	19.7
Patient 8	35	5	18.4	18	32.8
Average			15.8	15	23.6

Table 6.5 Parameters for patients < 2 000g

Patient 2	36	1 785	13 (7.3)	0.0864	8.0	0.87	18.9	7.0
Patient 3	31	1 350	10 (7.4)	0.0596	11.6	1.27	21.4	10.8
Patient 4	30	1 260	9(7.1)	0.0596	11.6	1.22	21.4	10.8
Patient 7	30	1 140	9 (7.9)	0.117	5.9	0.462	27.5	7.2
Average	32	1 384	10.3 (7.4)	0.0807	9.3	0.956	22.3	9.0

Table 6.6 Projected parameters for patients < 2 000g

Patient 2	35	5	23.0	24	26.9
Patient 3	35	5	33.1	36	40.0
Patient 4	35	5	33.1	36	38.4
Patient 7	35	5	17.1	18	14.6
Average			26.6	28.5	30.0

The patients greater than 2 000g demonstrated on average generally higher elimination rates and a smaller volume of distribution than the infants less than 2 000 g. As a result their Cmaxs never reached therapeutic concentrations whereas their Cmins were less than 5 µg/ml. On evaluating the patients' estimated kinetic parameters in order to obtain a Cmax of 35 µg/ml and a Cmin of less than 5 µg/ml, the maintenance dose would have to be increased to 24 mg/kg and the dosing interval would have to be extended to 12 or 18 hours depending on the elimination rate of the patient

The group that was less than 2 000g had a much lower elimination rates and a higher volume of distribution than the infants greater than 2 000 g. As in the larger infants the Cmax was still subtherapeutic, however the Cmins were greater than 5 μg/ml. For therapeutic levels to be achieved the maintenance dose would have to be increased to 30 mg/kg, and the dosing interval would have to be adjusted according to the elimination rate of the patient.

6.2 ONCE DAILY AMINOGLYCOSIDE DOSING

Table 6.7 represents the results of the second part of the study.

Table 6.7 Phase 2 patient kinetic parameters

Patient 9	N/A	980	20 (20.4)	0.072	9.6	0.77	27.1	2.1
Patient 10	40	3 125	60 (19.2)	0.0713	9.7	0.60	37.4	7.0
Patient 11	N/A	4 300	100 (23.3)	0.118	5.9	0.89	25.9	2.1
Patient 12	32	1 325	26 (19.6)	0.0569	12.2	1.05	24.4	6.6
Patient 13	30	1 350	33 (24.4)	0.061	11.4	0.81	33.4	4.6
Patient 14	28	1 045	20 (19.1)	0.0551	12.6	0.89	24.9	4.4
Patient 15	40	2 570	60 (23.3)	0.0836	8.3	0.60	49.2	7.5
Patient 16	N/A	3 000	60 (20)	0.126	5.5	0.50	40.2	2.1
Patient 17	43	3 740	75(20)	0.104	6.7	0.75	29.3	2.4
Patient 18	N/A	6 000	120 (20)	0.155	4.5	0.61	31.8	2.1
Patient 19	30	1 120	16 (14.3)	0.0532	13.0	1.17	19.7	8.2
Average	34.7	2 596	54 (20.8)	0.0869	9.0	0.79	31.2	4.5

N/A - gestational age was not documented on patients records.

As demonstrated in Table 6.7 the patients included in this part of the study had an average gestational age of 34.7 weeks, and had an average weight of 2 596 g. Although the amikacin dosing protocol called for a loading dose of 25 mg/kg to be given followed by a daily dose of 20 mg/kg, the average initial

dose was 20.8 mg/kg. From this dose, the average maximum serum concentration (Cmax) was slightly subtherapeutic at 31.2 μg/ml (less than the desired 35 μg/ml), whereas the average minimum serum concentration (Cmin) was < 5μg/ml.

From the calculated kinetic parameters represented in Table 6.7, the maintenance doses were calculated as illustrated in Table 6.8.

Table 6.8 shows that on average the maintenance dose needs to be increased to 24 mg/kg to be administered over 24 hours for the desired Cmax and Cmin to be achieved. It is important to note that this increased maintanance dose is due to a few patients with large volumes of distribution affecting a small sample size, and therefore the recommendation to increase the maintanance dose should be considered with caution.

Table 6.8 Phase 2 patient estimated parameters

Patient 9	35	5	27.5	24	22.5
Patient 10	35	5	27.8	24	17.4
Patient 11	35	5	17.0	18	28.1
Patient 12	35	5	34.7	36	32.5
Patient 13	35	5	32.4	36	25.5
Patient 14	35	5	35.8	36	27.3
Patient 15	35	5	23.8	24	18.6
Patient 16	35	5	15.9	18	16.2
Patient 17	35	5	19.2	18	22.7
Patient 18	35	5	13.1	12	18.7
Patient 19	35	5	37.1	36	35.1
Average			25.8	25.6	24.1

The above patients were further sub-divided according to their weight: greater than 2 000 g and less than 2 000 g.

Table 6.9 Parameters for patients > 2 000g

Patient 10	40	3 125	60	0.0713	9.7	0.60	37.4	7.0
Patient 11	N/A	4 300	100	0.118	5.9	0.89	25.9	2.1
Patient 15	40	2 570	60	0.0836	8.3	0.60	49.2	7.5
Patient 16	N/A	3 000	60	0.126	5.5	0.50	40.2	2.1
Patient 17	43	3 740	75	0.104	6.7	0.75	29.3	2.4
Patient 18	N/A	6 000	120	0.155	4.5	0.61	31.8	2.1
Average	41	3 789	79.2	0.1097	6.8	0.66	35.6	3.9

N/A - gestational age was not documented on patients records.

Table 6.10 Projected parameters for patients > 2 000g

Patient 10	35	5	27.8	24	17.4
Patient 11	35	5	17.0	18	28.1
Patient 15	35	5	23.8	24	18.6
Patient 16	35	5	15.9	18	16.2
Patient 17	35	5	19.2	18	22.7
Patient 18	35	5	13.1	12	18.7
Average			19.5	19	20.3

Table 6.11 Parameters for patients < 2 000g

Patient 9	N/A	980	20	0.072	9.6	0.77	27.1	2.1
Patient 12	32	1 325	26	0.0569	12.2	1.05	24.4	6.6
Patient 13	30	1 350	33	0.061	11.4	0.81	33.4	4.6
Patient 14	28	1 045	20	0.0551	12.6	0.89	24.9	4.4
Patient 19	30	1 120	16	0.0532	13.0	1.17	19.7	8.2
Average		1 164	23.0	0.0596	11.8	0.938	25.9	5.2

N/A - gestational age was not documented on patients records.

Table 6.12 Projected parameters for patients < 2 000g

Patient 9	35	5	27.5	24	22.5
Patient 12	35	5	34.7	36	32.5
Patient 13	35	5	32.4	36	25.5
Patient 14	35	5	35.8	36	27.3
Patient 19	35	5	37.1	36	35.1
Average			33.5	33.6	28.6

The group of patients greater than 2 000g had similar kinetic parameters to those of Phase 1 with greater elimination rates and smaller volumes of distribution as compared to the group less than 2 000 g. However unlike in the first part of the study, their Cmaxs on average obtained therapeutic concentrations and their Cmins were still at a desirably low range. When examining their estimated kinetic parameters, in order for the serum concentrations to reach the desired levels of a Cmax of 35 μg/ml and a Cmin of 5 μg/ml, the average dosing regimen is about the same as that proposed in the study's protocol of 20 mg/kg. The dosing interval will need to be adjusted to the elimination rate of the individual patient, since it ranged from 12 to 24 hours, with the average being 19 hours.

Those patients weighing less than 2 000g had lower elimination rates and higher volumes of distributions. These results were similar to Phase 1. The serum concentrations that resulted were an improvement from the twice daily aminoglycoside dosing in that the Cmins were desirably low, with an average Cmax of 25.9 μg/ml. To achieve serum concentration levels of 35 μg/ml, the dose would have to be increased (from the protocol accepted dose of 20

mg/kg to about 28.6 mg/kg - or rounded up to 30 mg/kg), and the dosing interval would have to be increased to between 24 and 36 hours.

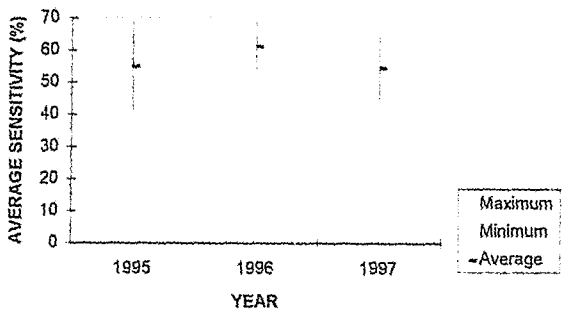
CHAPTER 7: ANALYSIS OF ANTIBIOTICS USED

The analysis section will deal with antibiotics that are used frequently in ward 276. It will discuss the performance of the antibiotics and offer suggestions as to when they should or should not be used.

7.1 PENICILLINS

As demonstrated by Figure 7.1 progress of the overall percentage sensitivity of penicillins has fluctuated over the 3 years ranging from 53.8 ± 15.0% in 1995 to 61.1 ± 7.8% in 1996 (p=0.0005). The following year the average sensitivity dropped to 53.6 ± 8.8%, which was also statistically significant from the previous year (p=0.0005).

Figure 7.1 The average percentage sensitivity of the penicillin group for 1995, 1996 and 1997.



7.1.1 Penicillin

Table 7.1 illustrates the individual responses of penicillin to the micro-organisms tested with it over the 3 years of the study. The sensitivity to penicillin increased significantly over the first 2 years, from 48.3 ± 22.4% to 63.9 ± 22.5% ($p = 0.0005$), but declined to 61.1 ± 24.9% during 1997.

Table 7.1 Comparison of penicillin sensitivity for 1995, 1996 and 1997.

Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE						
enterococcus faecium	3	33.3 (1/3)	1	0 (0/1)	11	0 (0/3)
enterococcus faecalis	11	100 (10/10)	11	90 (9/10)	3	90.9 (10/11)
enterococcus sp.	2	100 (2/2)				
grp C haemolytic strep.	1	100 (1/1)				
staphylococcus aureus	6	0 (0/6)	27	18.5 (5/27)	12	0 (0/11)
staphylococcus epidermidis	42	7.3 (3/41)	32	0 (0/32)	53	3.8 (2/53)
streptococcus agalactiae	13	100 (11/11)	2	100 (2/2)	2	100 (2/2)
streptococcus pneumoniae	2	50 (1/2)	3	66.7 (2/3)	1	100 (1/1)
streptococcus pyogenes			1	100 (1/1)	2	100 (2/2)
streptococcus sp.	1	100 (1/1)	2	100 (2/2)	4	100 (4/4)
streptococcus viridans	7	16.7 (1/6)	2	100 (2/2)	3	100 (3/3)
micrococcus sp.	1				2	100 (2/2)
bacillus sp.	2	0 (0/2)				
bacillus cereus	5	20 (1/5)			2	0 (0/2)
bacillus subtilis	1	0 (0/1)				
corynebacterium sp.					3	100 (1/1)
GRAM NEGATIVE						
escherichia coli	18		14		16	0 (0/4)
Mean ± SD		48.3 ± 22.4		63.9 ± 22.5		61.1 ± 24.9

The penicillin was almost exclusively tested against gram positive organisms with the exception of one incident in 1997 when *Escherichia coli* was tested with penicillin but found to be completely resistant. There were some species

of micro-organisms that were isolated and tested only in 1995 that may have contributed to the outcome of the average resistance, such as *Bacillus sp.* and *Bacillus subtilis* which were completely resistant to penicillin (0%). Other species such as *Enterococcus sp.* and *Group C haemolytic streptococcus* were found to be completely sensitive. However when observing the resistance patterns generated by micro-organisms common to all 3 years and tested with penicillin as in Table 7.2 problem areas can be recognised.

The micro-organisms that experienced an increase in their average sensitivity to penicillin were *Streptococcus pneumoniae* and *Streptococcus viridans*. *Streptococcus pneumoniae* over the 3 years was not a commonly isolated micro-organism therefore its is difficult to make an overall comparison between the years. In 1995 its sensitivity was 50% (1/2) from 2 isolates, which

Table 7.2 Comparison of penicillin sensitivity to micro-organisms commonly isolated during 1995, 1996 and 1997.

Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
enterococcus faecium	3	33.3 (1/3)	1	0 (0/1)	3	0 (0/3)
enterococcus faecalis	11	100 (10/10)	11	90 (9/10)	11	90.9 (10/11)
staphylococcus aureus	6	0 (0/6)	27	18.5 (5/27)	12	0 (0/11)
staphylococcus epidermidis	42	7.3 (3/41)	32	0 (0/32)	53	3.8 (2/53)
streptococcus agalactiae		100 (11/11)	2	100 (2/2)	2	100 (2/2)
streptococcus pneumoniae	2	50 (1/2)	3	66.7 (2/3)	1	100 (1/1)
streptococcus sp.	1	100 (1/1)	2	100 (2/2)	4	100 (4/4)
streptococcus viridans	7	16.7 (1/6)	2	100 (2/2)	3	100 (3/3)

increased to 66.7% (2/3) from 3 isolates in 1996, and further increased to 100% (1/1) from 1 isolate. *Streptococcus viridans* demonstrated a wider range

of sensitivities to penicillin from 16.7% (1/6 - 6 isolates out of 7) in 1995, to 100% during 1996 and 1997 from 2 and 3 isolates respectively.

Enterococcus faecalis, *Streptococcus agalactiae* and *Streptococcus sp.* maintained consistently high sensitivity averages over the 3 years.

Enterococcus faecium in 1995 had a 33.3% sensitivity to penicillin from 3 isolates. In 1996 and 1997 it was found to be completely resistant (0% sensitive). However, it was only tested against 1 (0/1) and 3 (0/3) isolates respectively.

Enterococcus faecalis over the period experienced a gradual decline in sensitivity from 100% (10/10 - from 10 out of 11 isolates) in 1995, to 90% (9/10 - from 10 out of 11 isolates) in 1996, to 90.9% (10/11 - from 11 out of 11 isolates) in 1997.

Streptococcus agalactiae and *Streptococcus sp.* remained fully sensitive to penicillin over the 3 years, even though some years the number of isolates were low (1 and 2 for *Streptococcus sp.* in 1995 and 1996 respectively, and 2 for *Streptococcus agalactiae* for both 1996 and 1997). In 1995 13 isolates were obtained with a 100% sensitivity which validated that *Streptococcus agalactiae* is still highly sensitive to penicillin.

Enterococcus faecium, *Staphylococcus aureus* and *Staphylococcus epidermidis* consistently demonstrated very high resistance patterns over the 3 year period.

Table 7.3 illustrates the sensitivity of the different classifications of micro-organisms acquired during the prospective phase of the study to penicillin.

Table 7.3 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against penicillin.

Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE								
enterococcus faecium			1	0 (0/1)	1	0 (0/1)		
enterococcus faecalis	3	100 (3/3)	2	100 (2/2)	2	50 (1/2)		
staphylococcus aureus	8	0 (0/8)	3	0 (0/1)				
staphylococcus epidermidis	9	0 (0/9)	16	6.3 (1/16)	2	50 (1/2)	5	0 (0/5)
streptococcus agalactiae					2	100 (2/2)		
streptococcus pneumoniae					1	100 (1/1)		
streptococcus pyogenes	1	100 (1/1)			1	100 (1/1)		
streptococcus sp.	1	100 (1/1)			3	100 (3/3)		
streptococcus viridans					1	100 (1/1)		
micrococcus sp.					2	100 (2/2)		
bacillus cereus			1	0 (0/1)				
GRAM NEGATIVE								
escherichia coli	7				4	0 (0/4)		

When taking the infection source and clinical significance into consideration, it is best to avoid using penicillin in nosocomial infections with the exception of *Enterococcus faecalis*, *Streptococcus sp.* and *Streptococcus pyogenes*. Due to the limited number of isolates obtained for the last three micro-organisms penicillin should still be used with caution in all nosocomial infections.

Penicillin was fairly effective against significant community infections. The only drawbacks penicillin experienced were from *Enterococcus faecium* (0% - 0/1), *Enterococcus faecalis* (50% - 1/2), *Staphylococcus epidermidis* (50% - 1/2) and *Escherichia coli* (0% - 0/4 {which probably should not have been tested}). Otherwise *Streptococcus agalactiae*, *Streptococcus sp.*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans* and *Micrococcus sp.* were 100% sensitive to it.

Staphylococcus epidermidis was the most frequently isolated micro-organism, of which about 60% of the isolates were classified as insignificant infections (Table 7.3). The majority of the *Staphylococcus epidermidis* isolates obtained were found to be resistant to penicillin.

7.1.2 Piperacillin/Tazobactam

Unlike penicillin, piperacillin/tazobactam has experienced a constant increase in micro-organism average resistance over the 3 years. As demonstrated in Table 7.4, the micro-organism sensitivity decreased from 97.8 ± 3.4% in 1995, to 87.1 ± 14.4 in 1996 (p=0.0005), to 83.5 ± 16.4% in 1997 (p=0.15). In 1995 it was not widely tested and those micro-organisms tested were completely sensitive with the exception of *Pseudomonas aeruginosa* which was marginally resistant (80%). In 1996 and 1997 the number of different micro-organisms tested increased and resulted in a wider range of percentage sensitivities which had their obvious effect on the averages.

Table 7.4 Comparison of piperacillin/tazobactam sensitivity for 1995, 1996 and 1997.

Organisms	# of isolates	% sensitivity (ratio)	# isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE						
enterococcus faecium	3		1		3	0 (0/1)
enterococcus faecalis	11		11	100 (1/1)	11	
GRAM NEGATIVE						
acinetobacter baumanni	2		3	100 (3/3)	1	100 (1/1)
acinetobacter lwoffi			1	100 (1/1)	1	0 (0/1)
alkaligenes faecalis	3	100 (2/2)	1	0 (0/1)	4	100 (4/4)
alkaligenes sp.	1				1	100 (1/1)
enterobacter aerogenes	1	100 (1/1)				
enterobacter cloacae	6	100 (5/5)	2	50 (1/2)	4	75 (3/4)
enterobacter gergoviae					1	100 (1/1)
enterobacter sp.	3	100 (2/2)	4	100 (4/4)	4	100 (4/4)
escherichia coli	18	100 (9/9)	14	100 (14/14)	16	87.5 (14/16)
klebsiella oxytoca			2	100 (2/2)	2	100 (2/2)
klebsiella pneumoniae	6	100 (1/1)	5	80 (4/5)	4	100 (4/4)
klebsiella sp.	14	100 (10/10)	9	100 (9/9)	15	80 (12/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	80 (4/5)	9	88.9 (8/9)	13	76.9 (10/13)
pseudomonas sp.			1	100 (1/1)		
stenotrophomonas mal.	3				1	100(1/1)
citrobacter freudi			2	100 (2/2)		
burkholderia cepacia					1	100 (1/1)
shawanella putrefaciens					1	100 (1/1)
Mean ± SD		97.8 ± 3.4		87.1 ± 14.4		83.5 ± 16.4

Table 7.5 Comparison of piperacillin/tazobactam sensitivity to micro-organisms commonly isolated during 1995, 1996 and 1997

GRAM POSITIVE	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
alkaligenes faecalis	3	100 (2/2)	1	0 (0/1)	4	100 (4/4)
enterobacter cloacae	6	100 (5/5)	2	50 (1/2)	4	75 (3/4)
enterobacter sp.	3	100 (2/2)	4	100 (4/4)	4	100 (4/4)
escherichia coli	18	100 (9/9)	14	100 (14/14)	16	87.5 (14/16)
klebsiella pneumoniae	6	100 (1/1)	5	80 (4/5)	4	100 (4/4)
klebsiella sp.	14	100 (10/10)	9	100 (9/9)	15	80 (12/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	80 (4/5)	9	88.9 (8/9)	13	76.9 (10/13)

Table 7.5 was created to examine the sensitivity of micro-organisms common to all 3 years that were tested against piperacillin/tazobactam in order to identify any problem areas.

Enterobacter sp. and *Proteus mirabilis* remained 100% sensitive to piperacillin/tazobactam over the 3 years. The validity of *Proteus mirabilis's* complete sensitivity to piperacillin/tazobactam could be questioned especially since the number of its isolates ranged from 1 for both 1995 and 1996 to 6 for 1997. *Enterobacter sp.* isolate frequency was less diverse, however the low frequency could still cause the same doubt.

Klebsiella pneumoniae, Alkaligenes faecalis and *Enterobacter cloacae* all experienced an increase in resistance during 1996, when fewer isolates were tested during that year, with a resurgence in sensitivity in 1997.

Micro-organisms that demonstrated progressive resistance tendencies towards piperacillin/tazobactam were *Escherichia coli, Klebsiella sp.* and *Pseudomonas aeruginosa.* The only micro-organism affected by a low annual tested isolate count was *Pseudomonas aeruginosa* in 1995 where only 5 out of 9 isolates were tested against piperacillin/tazobactam.

Table 7.6 evaluates the sensitivity patterns of piperacillin/tazobactam of different classes of micro-organism infections acquired during the prospective phase of the study.

Table 7.6 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against piperacillin/tazobactam.

	Nosocomial significant		Nosocomial insignificant		Community significant		Community insignificant	
GRAM NEGATIVE	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
acinetobacter baumanni					1	100 (1/1)		
acinetobacter lwoffi	1	0 (0/1)						
alkaligenes faecalis			1	100 (1/1)	1	100 (1/1)		
alkaligenes sp.					1	100 (1/1)		
enterobacter cloacae	2	50 (1/2)	2	100 (2/2)				
enterobacter sp.	2	100 (2/2)	1	100 (1/1)				
escherichia coli	7	100 (7/7)			4	50 (2/4)		
klebsiella oxytoca					1	100 (1/1)		
klebsiella pneumoniae					1	100 (1/1)		
klebsiella sp.	8	62.5 (5/8)	2	100 (2/2)	2	100 (2/2)		
proteus mirabilis	2	100 (2/2)			1	100 (1/1)	1	100 (1/1)
pseudomonas aeruginosa	5	80 (4/5)			1	100 (1/1)		
stenotrophomonas mal.			1	100 (1/1)				
burkholderia cepacia			1	100 (1/1)				

Significant nosocomial infections experienced the greatest resistance to piperacillin/tazobactam. Only *Escherichia coli*, *Enterobacter sp.* and *Proteus mirabilis* were completely (100%) sensitive, while *Acinetobacter lwoffi* (0% - 0/1), *Enterobacter cloacae* (50% - 1/2), *Klebsiella sp.* (62.5% - 5/8) and *Pseudomonas aeruginosa* (80% - 4/5) exhibited varying degrees of resistance. However *Acinetobacter lwoffi*, *Enterobacter cloacae*, *Enterobacter sp.* and *Proteus mirabilis* had a limited number of isolates therefore one can not conclusively declare resistance or sensitivity to piperacillin/tazobactam. The resistance of *Klebsiella sp.* and *Pseudomonas aeruginosa* infections to piperacillin/tazobactam is of concern as these organisms are fairly prevalent in ward 276.

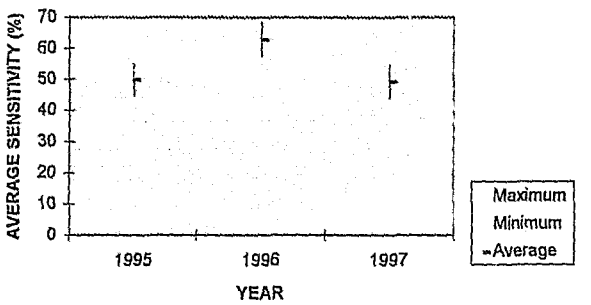
Escherichia coli was the only micro-organism isolated in the clinically significant community infection group that was resistant to piperacillin/tazobactam.

As far as the clinically insignificant infections were concerned, piperacillin/tazobactam was very effective with average sensitivities of 100% for both insignificant nosocomial and community infections.

6.2 CEPHALOSPORINS

The general sensitivity trend of the cephalosporins is similar to that of penicillins over the 3 years, however the difference between the average values is wider. The average sensitivity ranged from 49.2 ± 5.5% in 1997 to 62.9 ± 5.5% in 1996. The average sensitivity for 1995 was 49.9 ± 5.4%.

Figure 7.2 The average percentage sensitivity of cephalosporins for 1995, 1996, and 1997.



The increase and decrease in average sensitivities were statistically significant (p=0.0005).

7.2.1 Cefotaxime

Table 7.7 interprets the individual responses of cefotaxime to the micro-organisms tested against it over the 3 years of study. As the table demonstrates, the sensitivity fluctuated from 47.2 ± 23.9% in 1995, to 68.9 ± 20.0 in 1996 (p=0.0005), to 45.7 ± 20.8% in 1997 (p=0.0005).

Table 7.7 Comparison of cefotaxime sensitivity for 1995, 1996 and 1997.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE						
streptococcus pneumoniae	2		3	100 (1/1)	1	
GRAM NEGATIVE						
acinetobacter baumanni	2	0 (0/2)	3	0 (0/1)	1	
acinetobacter lwoffi			1	100 (1/1)	1	
acinetobacter sp.	1	100 (1/1)				
alkaligenes faecalis	3	0 (0/3)	1		4	0 (0/2)
alkaligenes sp.	1	0 (0/1)			1	0 (0/1)
enterobacter aerogenes	1	100 (1/1)				
enterobacter cloacae	6	100 (5/5)	2	100 (2/2)	4	75 (3/4)
enterobacter gergoviae					1	0 (0/1)
enterobacter sp.	3	100 (3/3)	4	25 (1/4)	4	75 (3/4)
escherichia coli	18	88.2 (15/17)	14	100 (14/14)	16	75 (12/16)
haemophilus influenzae			2	100 (1/1)	4	100 (4/4)
klebsiella oxytoca			2	50 (1/2)	2	50 (1/2)
klebsiella pneumoniae	6	0 (0/6)	5	40 (2/5)	4	25 (1/4)
klebsiella sp.	14	50 (7/14)	9	100 (9/9)	15	40 (6/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	22.2 (2/9)	9	50 (1/2)	13	
pseudomonas sp.			1	0 (0/1)		
campylobacter jejuni					1	0 (0/1)
stenotrophomonas mal.	3	0 (0/2)			1	0 (0/1)
salmonella sp.	2				1	100 (1/1)
citrobacter freudi			2	100 (2/2)		
uniden. gram -ve bacillus	1	0 (0/1)				
Mean ± SD		47.2 ± 23.9		68.9 ± 20.0		45.7 ± 20.8

Cefotaxime was almost exclusively tested against gram negative micro-organisms with the exception of an incident in 1996 when Streptococcus pneumoniae was tested against it and found to be 100% sensitive to it. Otherwise the number of different micro-organisms tested against cefotaxime over the 3 years was fairly consistent.

When examining the micro-organism sensitivity trends produced by those micro-organisms common to all 3 years and tested against cefotaxime in Table 7.8 possible problem areas could be recognised.

Table 7.8 Comparison of cefotaxime sensitivity to micro-organisms commonly isolated during 1995, 1996 and 1997.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
enterobacter cloacae	6	100 (5/5)	2	100 (2/2)	4	75 (3/4)
enterobacter sp.	3	100 (3/3)	4	25 (1/4)	4	75 (3/4)
escherichia coli	18	88.2 (15/17)	14	100 (14/14)	16	75 (12/16)
klebsiella pneumoniae	6	0 (0/6)	5	40 (2/5)	4	25 (1/4)
klebsiella sp.	14	50 (7/14)	9	100 (9/9)	15	40 (6/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)

Enterobacter cloacae over the period experienced a gradual decline in average sensitivity from 100% (5/5 - from 5 out of 6 isolates, and 2/2) in 1995 and 1996 respectively, to 75% (3/4) in 1997.

Proteus mirabilis maintained a 100% sensitivity to cefotaxime over the 3 year period. However, only one isolate was obtained each year.

Enterobacter sp. in 1995 was 100% (3/3) sensitive to cefotaxime and the following year the sensitivity fell to 25% (1/4). In 1997 the sensitivity recovered to 75% (3/4). Such erratic behaviour by micro-organisms could be explained by the limited number of isolates obtained.

Escherichia coli, *Klebsiella pneumoniae* and *Klebsiella sp.* all experienced fluctuating sensitivity results over the 3 year period. All 3 micro-organisms underwent an increase in sensitivity during 1996, which then decreased in 1997. *Escherichia coli* sensitivity values were relatively high, although the final 1997 sensitivity result had dropped to a point where its resistance could be troublesome (88.2 {15/17} in 1995, 100 % {14/14} in 1996 and, 75 {12/16} in 1997). *Klebsiella pneumoniae* and *Klebsiella sp.* were resistant to cefotaxime with the exception of *Klebsiella sp.* in 1996 where it was classified as 100% sensitive.

Table 7.9 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against cefotaxime.

Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
alkaligenes faecalis			1		1	0 (0/1)		
alkaligenes sp.					1	0 (0/1)		
enterobacter cloacae	2	50 (1/2)	2	100 (2/2)				
enterobacter sp.	2	50 (1/2)	1	100 (1/1)				
escherichia coli	7	57.1 (4/7)			4	75 (3/4)		
haemophilus influenzae	2	100 (2/2)	1	100 (1/1)			1	100 (1/1)
klebsiella oxytoca					1	0 (0/1)		
klebsiella pneumoniae					1	0 (0/1)		
klebsiella sp.	8	37.5 (3/8)	2	100 (2/2)	2	0 (0/2)		
proteus mirabilis	2	100 (2/2)			1	100 (1/1)	1	100 (1/1)
campylobacter jejuni					1	0 (0/1)		
stenotrophomonas mal.			1	0 (0/1)				

Table 7.9 evaluates the sensitivity patterns of the different classifications of micro-organisms acquired during the prospective phase of the study to cefotaxime.

Both nosocomial and community acquired significant infections were fairly resistant to cefotaxime. The only micro-organisms that had 100% sensitivity to cefotaxime were *Haemophilus influenzae* and *Proteus mirabilis*, otherwise the rest of the significant infections demonstrated high resistance tendencies (sensitivities ranging from 0% {mostly the significant community infections} to 75%). The *Escherichia coli* significant nosocomial isolates collected were found to be more resistant (57.1% {4/7}) than the community isolates (75% {3/4}). Klebsiella sp. nosocomial isolates were marginally more sensitive (37.5% {3/8}) than their community counterparts (0% {0/2}), even though the low isolate numbers for the community infections could not validate the reported complete resistance.

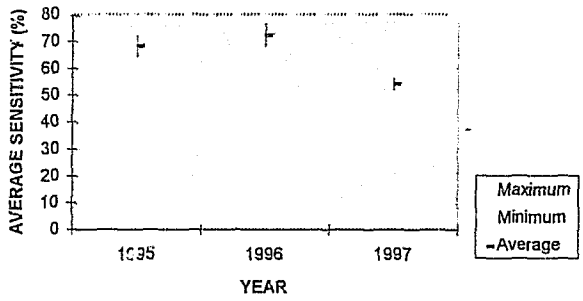
Cefotaxime experienced sensitivity from insignificant infections with almost all micro-organisms tested being completely sensitive (100%).

7.3 AMINOGLYCOSIDES

The overall percentage sensitivity to aminoglycosides over the 3 year period has demonstrated an increase in resistance as illustrated by Figure 7.3. Although the average sensitivity experienced a statistically significant increase

from 1995 to 1996 (from 68.3 ± 4.1% to 72.3 ± 4.2% respectively {p=0.0005}), it declined in 1997 (to 54.1 ± 2.2% {p=0.0005}).

Figure 7.3 The average percentage sensitivity of aminoglycosides for 1995, 1996 and 1997.



7.3.1 Amikacin

Table 7.10 exhibits the individual responses of amikacin to the micro-organisms tested against it over the 3 year period. The sensitivity to amikacin increased over the first 2 years, but significantly dropped from 78.6 ± 16.4% in 1996 to 58.5 ± 21.1% in 1997 (p=0.0005). Amikacin was exclusively tested against gram negative micro-organisms and the number of different micro-organisms tested against it were fairly consistent. In many cases only a limited number of isolates were obtained therefore conclusive sensitivity or resistance could not be determined. However problem areas were identified in Table 7.11.

Table 7.10 Comparison of amikacin for 1995, 1996 and 1997

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM NEGATIVE						
acinetobacter baumanni	2	50 (1/2)	3	100 (3/3)	1	0 (0/1)
acinetobacter lwoffi			1	100 (1/1)	1	
acinetobacter sp.	1	100 (1/1)				
alkaligenes faecalis	3	33.3 (1/3)	1	0 (0/1)	4	50 (1/2)
alkaligenes sp.	1	0 (0/1)			1	0 (0/3)
enterobacter aerogenes	1	100 (1/1)				
enterobacter cloacae	6	100 (5/5)	2	100 (2/2)	4	75 (3/4)
enterobacter gergoviae					1	100 (1/1)
enterobacter sp.	3	100 (3/3)	4	50 (2/4)	4	100 (4/4)
escherichia coli	18	100 (17/17)	14	93.3 (14/15)	16	84.6 (11/13)
klebsiella oxytoca			2	50 (1/2)	2	100 (2/2)
klebsiella pneumoniae	6	16.7 (1/6)	5	40 (2/5)	4	25 (1/4)
klebsiella sp.	14	71.4 (10/14)	9	100 (9/9)	15	73.3 (11/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	77.8 (7/9)	9	88.9 (8/9)	13	69.2 (9/13)
pseudomonas sp.			1	100 (1/1)		
stenotrophomonas mal.	3	100 (2/2)			1	0 (0/1)
citrobacter freudi			2	100 (2/2)		
uniden. gram -ve bacillus	1	100 (1/1)				
burkholderia cepacia					1	0 (0/1)
shawanella putrefaciens					1	100 (1/1)
Mean ± SD		74.9 ± 17.8		78.6 ± 16.4		58.5 ± 21.1

Table 7.11 Comparison of amikacin sensitivity to micro-organisms commonly isolated during 1995, 1996 and 1997.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
acinetobacter baumanni	2	50 (1/2)	3	100 (3/3)	1	0 (0/1)
alkaligenes faecalis	3	33.3 (1/3)	1	0 (0/1)	4	50 (1/2)
enterobacter cloacae	6	100 (5/5)	2	100 (2/2)	4	75 (3/4)
enterobacter sp.	3	100 (3/3)	4	50 (2/4)	4	100 (4/4)
escherichia coli	18	100 (17/17)	14	93.3 (14/15)	16	84.6 (11/13)
klebsiella pneumoniae	6	16.7 (1/6)	5	40 (2/5)	4	25 (1/4)
klebsiella sp.	14	71.4 (10/14)	9	100 (9/9)	15	73.3 (11/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	77.8 (7/9)	9	88.9 (8/9)	13	69.2 (9/13)

Acinetobacter baumanni and *Alkaligenes faecalis* were both affected by the limited number of isolates which most likely explains the wide sensitivity

variations (ranging from 0% {0/1} to 100% {3/3} and 0% {0/1} to 50% {1/2} respectively) over the time period.

Enterobacter sp. also demonstrated a fluctuation in sensitivity pattern which may also be explained by the limited number of isolates tested.

Proteus mirabilis maintained a 100% sensitivity to amikacin over the 3 year period.

Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella sp. and *Pseudomonas aeruginosa* were identified as problem micro-organisms where amikacin was concerned.

Enterobacter cloacae and *Escherichia coli* experienced gradual progressive increase in resistance over the 3 years. Even though the 1997 average sensitivity for *Escherichia coli* is not low enough to cause alarm, the rate of decline is worrisome.

Klebsiella pneumoniae, Klebsiella sp. and *Pseudomonas aeruginosa* demonstrated fluctuating sensitivity results over the 3 years. They all followed the same trend where in 1996 the sensitivity underwent a sensitivity resurgence before declining the following year. However, *Klebsiella pneumoniae* appears to be resistant to amikacin.

Table 7.12 evaluates the sensitivity pattern by different classes of micro-organism infections acquired during the prospective phase of the study to amikacin.

Table 7.12 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against amikacin.

GRAM NEGATIVE	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
acinetobacter baumanni					1	0 (0/1)		
alkaligenes faecalis			1	0 (0/1)	1	100 (1/1)		
alkaligenes sp.					1	0 (0/1)		
enterobacter cloacae	2	50 (1/2)	2	100 (2/2)				
enterobacter sp.	2	100 (2/2)	1	100 (1/1)				
escherichia coli	7	66.7 (4/6)			4	100 (4/4)		
klebsiella oxytoca					1	100 (1/1)		
klebsiella pneumoniae					1	0 (0/1)		
klebsiella sp.	8	87.5 (7/8)	2	100 (2/2)	2	0 (0/2)		
proteus mirabilis	2	100 (2/2)			1	100 (1/1)	1	100 (1/1)
pseudomonas aeruginosa	5	80 (4/5)			1	100 (1/1)		
stenotrophomonas mal.			1	0 (0/1)				
burkholderia cepacia			1	0 (0/1)				

As far as the significant nosocomial infections are concerned, the micro-organisms that seem fairly resistant to amikacin are *Enterobacter cloacae* and *Escherichia coli*. *Enterobacter cloacae's* resistance can not be conclusively determined due to the low isolate count that was obtained. Similarly, *Enterobacter sp.* and *Proteus mirabilis* were reported as being 100% sensitive, however only 2 isolates were tested. *Pseudomonas aeruginosa* and *Klebsiella sp.* nosocomial significant infections appeared to be fairly sensitive to it.

In the remaining infection groups, micro-organisms were reported as either completely sensitive or resistant to amikacin. However, once again due to the

limited number of isolates obtained the resistance patterns can not conclusively be determined.

7.3.2 Gentamicin

Table 7.13 Comparison of gentamicin sensitivity for 1995, 1996 and 1997

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE						
enterococcus faecium	3	0 (0/2)	1		3	0 (0/1)
enterococcus faecalis	11	50 (5/10)	11	83.3 (5/6)	11	100 (4/4)
enterococcus sp.	2	100 (2/2)				
grp C haemolytic strep.	1	0 (0/1)				
staphylococcus aureus	6	33.3 (2/6)	27		12	
staphylococcus epidermidis	42	30 (12/40)	32	83.3 (5/6)	53	
streptococcus agalactiae	13	36.4 (4/11)	2	0 (0/2)	2	
streptococcus sp.	1	0 (0/1)	2		4	
streptococcus viridans	7	100 (6/6)	2		3	
bacillus sp.	2	100 (2/2)				
bacillus cereus	5	100 (5/5)			2	
bacillus subtilis	1	0 (0/1)				
GRAM NEGATIVE						
acinetobacter baumanni	2	50 (1/2)	3	100 (1/1)	1	
acinetobacter sp.	1	100 (1/1)				
alkaligenes faecalis	3	33.3 (1/3)	1		4	100 (1/1)
alkaligenes sp.	1	0 (0/1)			1	0 (0/2)
enterobacter aerogenes	1	100 (1/1)				
enterobacter cloacae	6	100 (6/6)	2	100 (2/2)	4	75 (3/4)
enterobacter gergoviae					1	100 (1/1)
enterobacter sp.	3	100 (3/3)	4	25 (1/4)	4	50 (2/4)
escherichia coli	18	81.3 (13/16)	14	71.4 (10/14)	16	62.5 (10/16)
klebsiella oxytoca			2	50 (1/2)	2	50 (1/2)
klebsiella pneumoniae	6	0 (0/6)	5	40 (2/5)	4	0 (0/4)
klebsiella sp.	14	50 (7/14)	9	77.8 (7/9)	15	33.3 (5/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	83.3 (5/6)
pseudomonas aeruginosa	9	77.8 (7/9)	9	50 (1/2)	13	
pseudomonas sp.			1	0 (0/1)		
campylobacter jejuni					1	100 (1/1)
stenotrophomonas mal.	3	100 (2/2)			1	0 (0/
citrobacter freudi			2	100 (2/2)		
uniden. gram -ve bacillus	1	100 (1/1)				
Mean ± SD		59.3 ± 20.8		62.9 ± 18.0		

Like amikacin (Table 7.13), micro-organisms had an increase in sensitivity to gentamicin over the first 2 years, but experienced a statistically significant decline in sensitivity from 62.9 ± 18.0% in 1996 to 53.9 ± 20.6% in 1997 (p=0.05). However unlike amikacin, and for no apparent reason, the micro-organisms tested against gentamicin were not limited to the gram negative micro-organisms. The number of micro-organisms tested in 1995 was not consistent with the following 2 years, which may have affected gentamicin's average sensitivity for 1995.

Table 7.14 reported the sensitivity of micro-organisms common to all 3 years that were tested against gentamicin.

Table 7.14 Comparison of gentamicin sensitivity to micro-organisms commonly isolated during 1995, 1996 and 1997.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
enterococcus faecalis	11	50 (5/10)	11	83.3 (5/6)	11	100 (4/4)
enterobacter cloacae	6	100 (6/6)	2	100 (2/2)	4	75 (3/4)
enterobacter sp.	3	100 (3/3)	4	25 (1/4)	4	50 (2/4)
escherichia coli	18	81.3 (13/16)	14	71.4 (10/14)	16	62.5 (10/16)
klebsiella pneumoniae	6	0 (0/6)	5	40 (2/5)	4	0 (0/4)
klebsiella sp.	14	50 (7/14)	9	77.8 (7/9)	15	33.3 (5/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	83.3 (5/6)

Enterococcus faecalis experienced an increase in sensitivity every year to a point being completely sensitive (100%) in 1997. However, once again these results must be evaluated with caution as only 4 isolates were evaluated in 1997.

Escherichia coli, *Enterobacter cloacae* and *Proteus mirabilis* experienced a decrease in sensitivity over the 3 years. *Enterobacter cloacae* and *Proteus mirabilis* (which had low isolate counts) had 100% sensitivities for the first 2 years which decreased to 75% and 83.3% respectively in 1997. *Escherichia coli* experienced a constant rise in resistance over the 3 years.

Klebsiella pneumoniae and *Klebsiella sp.* followed the same trend with a slight increase in sensitivity in 1996. Both micro-organisms were fairly resistant to gentamicin.

Enterobacter sp. demonstrated a fluctuating trend starting as completely sensitive (100%) in 1995, and declined to 25% sensitivity in 1996 and was reported as only 50% sensitive in 1997.

Table 7.15 illustrates the sensitivity to gentamicin by the different classifications of micro-organisms acquired during the prospective phase of the study.

The majority of nosocomial and community acquired significant infections were fairly resistant to gentamicin. The micro-organisms that were 100% sensitive to gentamicin were *Enterococcus faecalis* (from the significant nosocomial group), *Alkaligenes faecalis*, *Proteus mirabilis* and *Campylobacter jejuni* (from the significant community group), otherwise the rest of the significant infections demonstrated resistance tendencies (sensitivities ranging from 0%

to 75%). *Escherichia coli* significant nosocomial isolates was found to be more resistant (42.9% {3/7}) than it's community counterpart (75% {3/4}). *Klebsiella sp.* nosocomial isolates were marginally more sensitive (37.5% {3/8}) than their community counterparts (0% {0/2}). However the low isolate numbers for the community infections could not conclusively determine complete resistance.

Table 7.15 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against gentamicin

Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE								
enterococcus faecium			2		1	0 (0/1)		
enterococcus faecalis	3	100 (1/1)	1		2			
GRAM NEGATIVE								
alkaligenes faecalis			1		1	100 (1/1)		
alkaligenes sp.					1	0 (0/1)		
enterobacter cloacae	2	50 (1/2)	2	100 (2/2)				
enterobacter sp.	2	50 (1/2)	1	100 (1/1)				
escherichia coli	7	42.9 (3/7)			4	75 (3/4)		
klebsiella oxytoca					1	0 (0/1)		
klebsiella pneumoniae					1	0 (0/1)		
klebsiella sp.	8	37.5 (3/8)	2	50 (1/2)	2	0 (0/2)		
proteus mirabilis	2	50 (1/2)			1	100 (1/1)	1	100 (1/1)
campylobacter jejuni					1	100 (1/1)		
stenotrophomonas mal.			1	0 (0/1)				

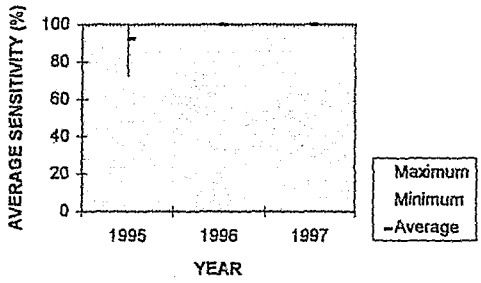
Both nosocomial and community acquired insignificant infections were fairly sensitive to gentamicin with the majority of the micro-organisms tested being completely sensitive (100%). The exceptions were *Klebsiella sp.* (50% {1/2}) and *Stenotrophomonas maltophilia* (0% {0/1}). However the number of isolates

for both groups were very low, therefore one could not decisively determine the resistance patterns.

7.4 GLYCOPEPTIDES

The general sensitivity trend of the glycopeptides was consistent over the 3 years ranging from 92.3 ± 13.9% to 100% as exhibited in Figure 7.4.

Figure 7.4 The average percentage sensitivity of glycopeptides for 1995, 1996 and 1997.



7.4.1 Vancomycin

Table 7.16 demonstrates the individual responses of vancomycin to the micro-organisms tested against it over the 3 years of the study.

Vancomycin was only tested against gram positive micro-organisms. The number of different micro-organisms tested against vancomycin fluctuated with 1996 having the lowest number.

A number of micro-organisms are still completely sensitive (100%) to vancomycin during the 3 year period (Table 6.17), although during 1995 *Bacillus subtilis* was found to be completely resistant (0% {0/1}) to it.

Table 7.16 Comparison of vancomycin sensitivity for 1995, 1996 and 1997.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE						
enterococcus faecium	3	100 (3/3)	1	100 (1/1)	3	100 (3/3)
enterococcus faecalis	11	100 (11/11)	11	100 (10/10)	11	100 (11/11)
enterococcus sp.	2	100 (2/2)				
grp C haemolytic strep.	1	100 (1/1)				
staphylococcus aureus	6	100 (6/6)	27	100 (27/27)	12	100 (12/12)
staphylococcus epidermidis	42	100 (41/41)	32	100 (32/32)	53	100 (53/53)
streptococcus agalactiae	13	100 (11/11)	2	100 (2/2)	2	100 (2/2)
streptococcus pneumoniae	2	100 (1/1)	3	100 (2/2)	1	100 (1/1)
streptococcus pyogenes			1		2	100 (1/1)
streptococcus sp.	1	100 (1/1)	2	100 (2/2)	4	100 (4/4)
streptococcus viridans	7	100 (6/6)	2	100 (2/2)	3	100 (3/3)
micrococcus sp.	1				2	100 (2/2)
bacillus sp.	2	100 (2/2)				
bacillus cereus	5	100 (5/5)			2	100 (2/2)
bacillus subtilis	1	0 (0/1)				
corynebacterium sp.					3	100 (1/1)
Mean ± SD		92.3 ± 13.9		100.0		100.0

Table 7.17 Comparison of micro-organisms commonly isolated during 1995, 1996 and 1997 sensitivity to vancomycin.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# iso. tested	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE						
enterococcus faecium	3	100 (3/3)	1	100 (1/1)	3	100 (3/3)
enterococcus faecalis	11	100 (11/11)	11	100 (10/10)	11	100 (11/11)
staphylococcus aureus	6	100 (6/6)	27	100 (27/27)	12	100 (12/12)
staphylococcus epidermidis	42	100 (41/41)	32	100 (32/32)	53	100 (53/53)
streptococcus agalactiae	13	100 (11/11)	2	100 (2/2)	2	100 (2/2)
streptococcus pneumoniae	2	100 (1/1)	3	100 (2/2)	1	100 (1/1)
streptococcus sp.	1	100 (1/1)	2	100 (2/2)	4	100 (4/4)
streptococcus viridans	7	100 (6/6)	2	100 (2/2)	3	100 (3/3)

Table 7.18 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against vancomycin

Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
GRAM POSITIVE								
enterococcus faecium			1	100 (1/1)	1	100 (1/1)		
enterococcus faecalis	3	100 (3/3)	2	100 (2/2)	2	100 (2/2)		
staphylococcus aureus	8	100 (8/8)	3	100 (3/3)				
staphylococcus epidermidis	9	100 (9/9)	16	100 (16/16)	2	100 (2/2)	5	100 (5/5)
streptococcus agalactiae					2	100 (2/2)		
streptococcus pneumoniae					1	100 (1/1)		
streptococcus pyogenes	1				1	100 (1/1)		
streptococcus sp.	1	100 (1/1)			3	100 (3/3)		
streptococcus viridans					1	100 (1/1)		
micrococcus sp.					2	100 (2/2)		
bacillus cereus			1	100 (1/1)				

As shown in Table 7.18, all the different classifications of micro-organisms tested for during the prospective phase of the study are completely sensitive (100%) to vancomycin.

7.5 CARBAPENEM β-LACTAMS

Figure 7.5 demonstrates that the overall percentage sensitivity to carbapenem β-lactams has been fairly consistent over the 3 years ranging from 92.3 ± 13.9% to 94.1 ± 12.2%.

7.5.1 Imipenem

Table 7.19 expresses the individual sensitivities to imipenem by the micro-organisms tested against it over the 3 years of the study.

Figure 7.5 The average percentage sensitivity of carbapenem β-lactams for 1995, 1996 and 1997.

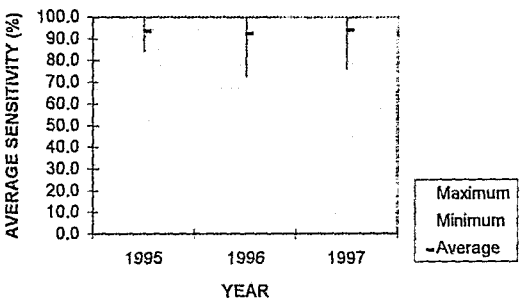


Table 7.19 Comparison of imipenem sensitivity for 1995, 1996 and 1997

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
acinetobacter baumanni	2	100 (2/2)	3	100 (3/3)	1	100 (1/1)
acinetobacter lwoffi			1	100 (1/1)	1	0 (0/1)
acinetobacter sp.	1	100 (1/1)				
alkaligenes faecalis	3	66.7 (2/3)	1	0 (0/1)	4	100 (4/4)
alkaligenes sp.	1	100 (1/1)			1	100 (1/1)
enterobacter aerogenes	1	100 (1/1)				
enterobacter cloacae	6	100 (4/4)	2	100 (2/2)	4	100 (4/4)
enterobacter gergoviae					1	100 (1/1)
enterobacter sp.	3		4	100 (4/4)	4	100 (4/4)
escherichia coli	18	100 (5/5)	14	100 (13/13)	16	100 (16/16)
klebsiella oxytoca			2	100 (2/2)	2	100 (2/2)
klebsiella pneumoniae	6	100 (6/6)	5	100 (5/5)	4	100 (4/4)
klebsiella sp.	14	100 (2/2)	9	100 (5/5)	15	100 (15/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	100 (9/9)	9	100 (9/9)	13	100 (13/13)
pseudomonas sp.			1	100 (1/1)		
campylobacter jejuni					1	100 (1/1)
stenotrophomonas mal.	3	50 (1/2)			1	100 (1/1)
citrobacter freudi			2	100 (2/2)		
uniden. gram -ve bacillus	1	100 (1/1)				
burkholderia cepacia					1	100 (1/1)
shawanella putrefaciens					1	100 (1/1)
Mean ± SD		93.6 ± 8.0		92.3 ± 13.9		94.1 ± 12.2

Imipenem was only tested against gram negative micro-organisms. The majority were completely sensitive (100%). *Alkaligenes faecalis* (for 1995 {66.7% [2/3]} and 1996 {0% [0/1]}), *Acinetobacter lwoffi* (for 1997 {0% [0/1]})

and *Stenotrophomonas maltophilia* (for 1995 {50% [1/2]}) were the only micro-organisms that demonstrated any resistance, but due to the low isolate count tested resistance can not conclusively be determined.

When observing the sensitivity trends produced by those micro-organisms common to all the 3 years and tested against imipenem (Table 7.20), with the exception of the previously mentioned *Alkaligenes faecalis*, all the micro-organisms are still completely sensitive to imipenem.

Table 7.20 Comparison of imipenem sensitivity to micro-organisms commonly isolated during 1995, 1996 and 1997.

	1995		1996		1997	
Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
acinetobacter baumanni	2	100 (2/2)	3	100 (3/3)	1	100 (1/1)
alkaligenes faecalis	3	66.7 (2/3)	1	0 (0/1)	4	100 (4/4)
enterobacter cloacae	6	100 (4/4)	2	100 (2/2)	4	100 (4/4)
escherichia coli	18	100 (5/5)	14	100 (13/13)	16	100 (16/16)
klebsiella pneumoniae	6	100 (6/6)	5	100 (5/5)	4	100 (4/4)
klebsiella sp.	14	100 (2/2)	9	100 (5/5)	15	100 (15/15)
proteus mirabilis	1	100 (1/1)	1	100 (1/1)	6	100 (6/6)
pseudomonas aeruginosa	9	100 (9/9)	9	100 (9/9)	13	100 (13/13)

On evaluating Table 7.21 all the micro-organisms regardless of source of infection are completely sensitive to imipenem, with the exception of *Acinetobacter lwoffi.* Due to the low isolate count collected and tested, *Acinetobacter lwoffi's* resistance can not conclusively be determined.

Table 7.21 Abbreviated antibiogram of micro-organisms from different sources and clinical significance tested against imipenem.

Organisms	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)	# of isolates	% sensitivity (ratio)
acinetobacter baumanni					1	100 (1/1)		
acinetobacter lwoffi	1	0 (0/1)						
alkaligenes faecalis			1	100 (1/1)	1	100 (1/1)		
alkaligenes sp.					1	100 (1/1)		
enterobacter cloacae	2	100 (2/2)	2	100 (2/2)				
enterobacter sp.	2	100 (2/2)	1	100 (1/1)				
escherichia coli	7	100 (7/7)			4	100 (4/4)		
klebsiella oxytoca					1	100 (1/1)		
klebsiella pneumoniae					1	100 (1/1)		
klebsiella sp.	8	100 (8/8)	2	100 (2/2)	2	100 (2/2)		
proteus mirabilis	2	100 (2/2)			1	100 (1/1)	1	100 (1/1)
pseudomonas aeruginosa	5	100 (5/5)			1	100 (1/1)		
campylobacter jejuni					1	100 (1/1)		
stenotrophomonas mal.			1	100 (1/1)				
burkholderia cepacia			1	100 (1/1)				

CHAPTER 8: DISCUSSION

The aim of the study was to conduct a prospective and retrospective survey of bacterial isolates obtained from cultures in paediatrics with infections. The objectives of the study were:

1. to determine the sensitivity patterns and prevalence of clinically significant and insignificant pathogenic micro-organisms in the PICU over time
2. to identify the reasons for any possible problems once resistance trends are known
3. to develop appropriate interventions.

The PICU of Johannesburg General admits between 30 and 40 patients a month and the average stay of a patient is 4 to 6 days. The majority of the patients admitted to the PICU ward were neonates which comprised 67.3% of the prospective study patient population of which 38.2% of them were inborns while 27.9% were admitted from other hospitals.

After constructing the antibiogram for 1996, and comparing it with that of 1995 the first issue that was addressed was the prevalence of some of the micro-organisms.

The prospective part of the study classified each infection by significance (i.e. either clinically significant or clinically insignificant) and by source (i.e. either

community-acquired or nosocomially-acquired). These are important factors as they are recognised as contributory to morbidity or mortality.

It was important to know the impact an infection exerted on a patient, since having cultured a micro-organism did not mean it automatically exerted its pathogenic effects on the host [Sprunt, *et al.*, 1978], especially in the neonatal patient group where diagnosing bacterial sepsis still remained a problematic exercise.

The perinatally-acquired and community-acquired infections were not differentiated in this study. This was done as a number of patients are born at home (or outside health care facilities) it would not be possible to accurately classify these infections. Therefore the infections were classified according to either community-acquired or nosocomially-acquired infections.

In addition, a further assumption was made as there is not a specific value which constitutes a definite border between sensitivity and resistance, for antimicrobials to antibiotics. An arbitrary value of 80% was selected to represent the lowest sensitivity value at which an antibiotic's use could be recommended to treat a micro-organism with a positive clinical outcome expected provided appropriate treatment was implemented. The trends in sensitivity patterns will also be discussed.

8.1 STAPHYLOCOCCAL INFECTIONS

The most prevalent micro-organism over the 3 year period was *Staphylococcus epidermidis*. It contributed to an average of 25.6% of the total number of micro-organisms cultured from the PICU for the 3 years. The isolate culture frequency ratio of neonates to non-neonates was 1.5:1. During the prospective phase of the study, 65.6% of the *Staphylococcus epidermidis* cultures were isolated from blood, resulting in the majority of septicaemic infections. Most of these infections were nosocomial in nature (78.1%) and 64.0% of the nosocomial cultures were clinically insignificant. The nosocomial infections that were clinically significant were as follows: septicaemia (54.5% {6/11}); abdominal infections and surface infections (9.1% {1/11}).

The above mentioned results were found to be consistent with a number of studies which recognised *Staphylococcus epidermidis* as the most frequently occurring micro-organism, yet depicted its overwhelming prevalence as possibly questionable due to its ambiguous characteristics [Hemming, *et al.*, 1976; Goldmann, 1978]. Originally *Staphylococcus epidermidis* was thought to be a skin contaminant of blood cultures since it is one of the most common skin organisms [Hall, 1991]. Contamination of blood cultures as a result of aseptic technique during venipuncture was a possible explanation. In addition, due to the insidious nature of *Staphylococcus epidermidis* it is difficult to make the diagnosis of an infection [Hall, 1991]. Nonetheless, there have been an increasing number of *Staphylococcus epidermidis* isolates reported in clinically

significant infections such as Necrotizing enterocolitis (NEC), also there have been increasing reports of resistance to vancomycin by *Staphylococcal species* [Hall, 1991], therefore occurrence of *Staphylococcus epidermidis* as a contaminant can not always be taken for granted. The need for intensive evaluation of a patient for clinical signs and symptoms of an infection regardless of how subtle they may appear to be is essential.

Staphylococcus epidermidis was also one of the most problematic gram positive micro-organisms with respect to the mean sensitivity to the antibiotics tested against it (reported mean sensitivities of 44.5 ± 16.5% in 1995, 49.9 ± 17.5% in 1996 and 43.8 ± 15.1% in 1997).

Over the 3 years of the study, the penicillins that were tested consistently against *Staphylococcus epidermidis* were penicillin and oxacillin. Sensitivity results to penicillin fluctuated between 0% and 7.3% over the period while those to oxacillin fluctuated between 22% and 40%. *Staphylococcus epidermidis* was also tested against ampicillin for 2 out of the 3 years and its sensitivity never exceeded 7.3%, whereas that to amoxicillin/clavulanic acid never exceeded 33.3%.

Over the 3 years, the only cephalosporin that was tested consistently against *Staphylococcus epidermidis* was cefazolin. Its sensitivity to cefazolin steadily declined from 59.6% to 26.9% over the time period. The increase in resistance for Staphylococcus infections is significant since cefazolin is considered the gold standard for surgical prophylaxis. Other cephalosporins tested against

Staphylococcus epidermidis were cephalexin and cefuroxime both of which experienced steady increases in resistance.

Another antibiotic that demonstrated progressive resistance to *Staphylococcus epidermidis* was erythromycin.

The glycopeptides (vancomycin) were the only drug *group Staphylococcus epidermidis* demonstrated complete sensitivity to.

A micro-organism that demonstrated multiple-antibiotic resistance was *Staphylococcus aureus*. However, *Staphylococcus aureus* is still sensitive to vancomycin.

According to several reports [Schwalbe, Stapleton & Gilligan, 1987; Hall, 1991], multiple antibiotic resistance is a common bacteriological feature among coagulase-positive (including *Staphylococcus aureus*) and coagulase-negative (including *Staphylococcus epidermidis*) Staphylococci micro-organisms. All strains that were recovered from patients with invasive infections were resistant to ampicillin, oxacillin, erythromycin and penicillin and most strains were resistant to gentamicin, methicillin and cephalosporins [Fleer, *et al*, 1983]. In Zimbabwe, antibiogram patterns showed similar multiple resistance of Staphylococci to penicillin, erythromycin and methicillin [Obi & Mazarura, 1996] to what was reported in this study. The frequency of Staphylococcus infections resistant to oxacillin was also apparently very high in ward 276 (reported sensitivities of 33.3% in 1995, 40% in 1996, and 28.3%

in 1997). As there is cross-resistance between methicillin and oxacillin one can assume that the majority of Staphylococcus infections will also be resistant to the penicillinase-resistant penicillins [Tosaka, Omoto, Kiyota, *et al*, 1991; Durmaz, Durmaz & Sahin, 1997]. Although the growing resistance to antibiotics can be correlated with increased use of particular antibiotics, even those antibiotics that are not widely used are still similarly affected [Lyytikainen, Vaara, Jarviluoma, 1996].

Due to the emergence of multiple resistant Staphylococcal infections, vancomycin has become the primary choice in treatment [Schwalbe, *et al*, 1987]. However, continued and increased use of vancomycin may promote the emergence of vancomycin-resistant Staphylococci, which to date has mostly been reported as coagulase-negative Staphylococci [Christensen & Gubbins, 1996]. In several cases, both vancomycin-resistant *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* have been isolated in adult patients, with more reports of vancomycin resistance associated with *Staphylococcus haemolyticus*. For example in one case, a 37 year old man with endstage renal disease and peritonitis associated with continuous ambulatory peritoneal dialysis had 8 strains of methicillin-resistant *Staphylococcus haemolyticus* isolated from his peritoneal fluid during his 3 month hospitalisation. The strain's vancomycin minimum inhibitory concentration {MIC} increased from 2 μg/ml to 8 μg/ml after the 3 months [Christensen, *et al*, 1996]. In another retrospective study of 63 isolates of coagulase-negative Staphylococci, 49% were found to be vancomycin-resistant (MIC ≥ 6.25 μg/ml), of which 62% were *Staphylococcus haemolyticus*

and only 13% were *Staphylococcus epidermidis* [Froggatt, Johnston, Galetto, *et al*, 1989].

There has also been a case report of vancomycin-resistance to *Staphylococcus aureus* in a 3 year-old. Vancomycin's MIC increased from <1 μg/ml to 1 μg/ml, following subtherapeutic vancomycin dosing [Jackson & Hicks, 1987].

With the sensitivity trends demonstrated by the Staphylococcal isolates from the PICU, it only seems a matter of time before vancomycin-resistant strains appear.

8.2 ENTEROCOCCAL INFECTIONS

Enterococcus faecalis, the third most prevalent gram positive micro-organism has also been a cause for concern. In 1995 there were reported mean sensitivities of 42.9 ± 25.7% and 61.5 ± 22.7% in 1996. However in 1997, it recovered to 97.0 ± 2.4%. *Enterococcus faecium* on the other-hand, was not as frequently isolated, but has exhibited a greater degree of multiple resistance (reported mean sensitivities of 34.6 ± 23.7% in 1995, 66.7 ± 25.8% in 1996, and 20.0 ± 22.4% in 1997).

Enterococcus faecalis over the 3 years was sensitive to penicillins (penicillin, ampicillin, and amoxicillin/clavulanic acid), gentamicin and vancomycin. It

exhibited complete resistance to oxacillin. *Enterococcus faecium* on-the-other-hand, demonstrated complete sensitivity to ampicillin and amoxicillin/clavulanic acid for the first 2 years. However during 1997 it was completely r stant to ampicillin and amoxicillin/clavulanic acid. Throughout the 3 years it was completely resistant to gentamicin, and completely sensitive to vancomycin.

Enterococci have emerged as important nosocomial pathogens with increasing antimicrobial resistance which are intrinsically resistant to β-lactams and aminoglycosides making vancomycin the mainstay of therapy [Noskin, 1997; Polk, 1997; Rybak, 1997]. Over the past 6 years, vancomycin-resistant Enterococci have disseminated throughout the United States and Europe [Noskin, 1997], and with their increasing prevalence they have become virtually untreatable [Gin & Zhanel, 1996]. Attention in research has focused on *Enterococcus faecium* since it is 2 to 4 times more resistant than *Enterococcus faecalis* [Rybak, 1997] and its vancomycin-resistance strain has been isolated more frequently than *Enterococcus faecalis* [Noskin, 1997]. Even though *Enterococcus faecium* has low virulence compared to *Enterococcus faecalis* and has often signified colonisation, it is still very capable of causing serious infections [Polk,1997]. Therefore, on average, Enterococcal infections exhibit relatively high virulence which result in high mortality rates.

Even though the Enterococci isolated during the study (especially *Enterococcus faecalis*) are still fairly susceptible to most antibiotics and there

have been no reports of vancomycin resistance, one still has to be vigilant where this micro-organism is concerned.

8.3 KLEBSIELLA INFECTIONS

Problematic gram negative micro-organisms were *Klebsiella pneumoniae* (with mean sensitivities of 25.0 ± 21.3% in 1995, 53.2 ± 16.4% in 1996 and 47.4 ± 20.4%) and *Klebsiella sp.* (with mean sensitivities of 54.9 ±16.2% in 1995, 83.8 ± 13.1% in 1996 and 52.2 ± 16.4% in 1997). *Klebsiella sp.* consisted of micro-organisms which could be identified as belonging to the Klebsiella species however their genus could not be determined.

The only antibiotics *Klebsiella pneumoniae* remained completely sensitive to over the 3 years were the fluoroquinolones (ciprofloxacin and ofloxacin) and the carbapenem β-lactams (imipenem and meropenem). Piperacillin/tazobactam experienced fluctuating sensitivities between 80% and 100%, whereas cefepime experienced resistance during the first year it was tested. In 1996, *Klebsiella pneumoniae* was 50% sensitive to it, and 75% sensitive the following year. Otherwise, *Klebsiella pneumoniaes'* sensitivities to other antibiotics tested against it ranged from 0% to 50%. *Klebsiella sp.* experienced the same trends as *Klebsiella pneumoniae* although the sensitivities to antibiotics tested against it were generally higher.

In the mid-1980s *Klebsiella pneumoniae* (and *Escherichia coli*) became resistant to third generation cephalosporins (cefotaxime, ceftriaxone and ceftazidime which are all considered β-lactamase-stable) as a result of new β-lactamases (TEM enzymes -3 to -15, and sulfohydrovariable {SHV} enzymes) and aminoglycosides as a result of aminoglycoside-modifying enzymes (which modify them by acetylation, adenylation or phosphorylation preventing them from binding with the micro-organisms' ribosomes) [Neu, 1992]. This explains the radical resistance demonstrated by this micro-organism against all the antibiotics tested against it over the 3 year period. Even though piperacillin/tazobactam has been used alone to combat this micro-organism in several studies [Meyer, et al, 1993; Rice, Eckstein & DeVente, 1996], synergy between two antibiotics that act by different mechanisms has been suggested as an alternate pharmacological route [Zemelman, Bello, Dominguez, *et al.*, 1993]. Combining separate antibiotics may limit the emergence of antimicrobial resistance [Lynch, 1993]. Therefore with the alarming increase in antibiotic resistance (especially by gram negative micro-organisms, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) combination therapy tends to provide a compelling argument in treating these resistant micro-organisms (i.e. combining any of the following: fluoroquinolones, carbapenems, fourth generation cephalosporins or piperacillin/tazobactam).

8.4 ESCHERICHIA COLI

The most prevalent gram negative micro-organism was *Escherichia coli.* Its average frequency per year was 9.8% of the total number of micro-organisms cultured from the PICU. For 2 out of the 3 years of the study, *Escherichia coli* was the second most prevalent micro-organism isolated in the ward, with *Staphylococcus aureus* being the second most frequently occurring micro-organism during 1996. Although it was isolated from various sites, 27.3% of the cultures were isolated from both pleural fluids and blood. The isolate culture frequency ratio of neonates to non-neonates was 0.8:1. All the micro-organisms isolated during the prospective phase of the study were clinically significant , of which 63.6% were of nosocomial origin.

These results were found to be consistent with a number of studies which found *Escherichia coli* to be one of the first and most prevalent gram negative micro-organisms infants are likely to encounter after birth especially in intensive care settings, yet with the ability to cause clinically significant infections [Hemming, *et al.*, 1976; Goldmann, 1978]. It has also been recognised as an important cause of community and nosocomial infections [Neu, 1992].

When taking the annual average sensitivities of *Escherichia coli* into consideration, it could not be considered a problem micro-organism in comparison with other micro-organisms (i.e. *Klebsiella pneumoniae*), however

its decrease in sensitivity was a cause for concern (with mean sensitivities of 78.7 ± 15.5% in 1995, 85.1 ± 11.7% in 1996 and 63.3 ± 16.6% in 1997). Even though the average sensitivity varied around 80%, it experienced a sudden drop during the last year of the study.

Escherichia coli demonstrated fluctuating patterns and varying rates of resistance progression to penicillins considered susceptible to gram negative micro-organisms. Ampicillin, piperacillin, amoxicillin/clavulanic acid and piperacillin/tazobactam were consistently tested against *Escherichia coli* for the 3 years. Sensitivity results to ampicillin never exceeded 20%, those to piperacillin varied between 6.7% and 46.2% and those to amoxicillin/clavulanic acid varied between 57.1% and 100%. Piperacillin/tazobactam experienced a gradual decline in *Escherichia coli* sensitivity from 100% for the first 2 years to 87.5% in the last year.

Over the 3 years, the cephalosporins tested consistently against *Escherichia coli* were cefazolin, cefuroxime, cefotaxime, ceftazidime and ceftriaxone. Cefazolin and ceftazidime experienced progressive declines in *Escherichia coli* sensitivity over the 3 years (from 88.2% to 41.7% and from 88.2% to 68.8%, respectively). Cefuroxime, cefotaxime and ceftriaxone experienced fluctuating sensitivity results above and below 80% over the 3 years (between 68.8% and 100%; 75% and 100%; and 75% and 100%, respectively).

Escherichia coli over the 3 years was tested against amikacin, gentamicin and tobramycin, all 3 experienced steady declines in sensitivity from 100% to 84.6%; 81.3% to 62.5%; and 81.8% to 60%, respectively.

Fourth generation cephalosporins (cefepime), fluoroquinolones (ciprofloxacin and ofloxacin) and carbapenem β-lactams (imipenem and meropenem) were the only drug groups that experienced complete sensitivity from *Escherichia coli*.

Escherichia coli has demonstrated resistance against penicillins (amoxicillin, ampicillin and piperacillin) and β-lactam β-lactamase inhibitor combinations (i.e. ampicillin/clavulanate and ampicillin/sulbactam) [Igari, Shitara, Shitara, *et al*, 1990; Neu, 1992]. This is of great concern as it appears that piperacillin/tazobactam might also experience similar resistance patterns already being experienced by amoxicillin/clavulanic acid.

8.5 PENICILLIN

Over the 3 years of the study, *Streptococcus agalactiae* isolated in the ward remained 100% sensitive to penicillin. In fact the only Streptococci that demonstrated any resistance to penicillin were *Streptococcus pneumoniae* (in 1995 and 1996), *Streptococcus viridans* (in 1995) and *Enterococcus faecium* (in 95, 1 6 and 1997). *Staphylococcus aureus* and *Staphylococcus epidermidis* consistently demonstrated very high resistance tendencies over

the 3 year period. As far as community acquired infections were concerned, all the Streptococci isolated were 100% sensitive to penicillin, even though conclusive sensitivity could not be determined due to the low isolate counts. The Enterococci and the Staphylococci significant community-acquired infections were the only micro-organisms that demonstrated resistance to penicillin.

When considering the prospective study's results, it is best to avoid using penicillin for those micro-organisms isolated as nosocomial infections. This is because Staphylococcal infections predominated in this class. *Enterococcus faecalis*, *Streptococcus pyogenes* and *Streptococcus sp.* remained completely sensitive to penicillin, however they were infrequently isolated as nosocomial infections.

In 1941, 40 000 units of penicillin administered a day for 4 days cured *Streptlococcus pneumoniae* pneumonia, while today 24 million units of penicillin a day does not guarantee survival from *Streptococcus pneumoniae* meningitis [Neu, 1992]. Penicillin has always been considered the drug of choice for treating infections caused by *Streptoococcus pneumoniae*, therefore when antibiotic resistance was first reported in 1957, it was believed not to pose a threat to the general population [Billeter, 1997]. For a long time penicillin was the drug of choice for community-acquired infections, and practitioners were erroneously inclined to dismiss the report of antibiotic resistance. Following the initial outbreaks of *Streptococcus pneumoniae* resistance in 1977 in South Africa, about 45% of them are now penicillin-

resistant and this is a world-wide phenomenon [Neu, 1992; Billeter, 1997]. Despite the unique Streptococcal susceptibility to penicillin demonstrated in the prospective phase of this study, and considering its overall current resistance patterns reported which continue to pose a challenge to physicians, these infections should not be taken for granted.

8.6 CEFOTAXIME AND CEFEPIME

In 1995 a major decision made by the consultants in the PICU, was to discontinue the empiric use of cephalosporins, especially cefotaxime. Cefotaxime, which was used empirically in the ward when a patient was suspected of having a nosocomial infection, had an average sensitivity of 47.2 ± 23.9% in 1995 [Appendix 1], having the second lowest average sensitivity of all cephalosporins. Although other micro-organisms such as *Acinetobacter sp.*, *Enterobacter sp.*, *Enterobacter aerogenes*, *Enterobacter cloacae* and *Proteus mirabilis* were still 100% sensitive to cefotaxime, it appeared as if the more prevalent micro-organisms in PICU such as *Pseudomonas aeruginosa* (22.2%), *Klebsiella sp.* (50%) and *Klebsiella pneumoniae* (0%) were resistant to it. Although *Escherichia coli* did not have sensitivity levels as low as the 3 previously mentioned micro-organisms its sensitivity to cefotaxime was of concern as it appeared to be developing resistance (88.2%). Despite not using cefotaxime empirically in the PICU for close to a period of 2 years, the incidence of resistance did not experience a recovery, due to the fact that it

was still widely utilised (the third most frequently used antibiotic in the PICU at 11.9%).

Over the 3 year period, *Enterobacter sp.*(100%, 25% and 75%, respectively), *Escherichia coli* (88.2%, 100% and 75%, respectively), *Klebsiella pneumoniae* (0%, 40% and 25%, respectively) and *Klebsiella sp.* (50%, 100% and 40%, respectively) all experienced fluctuating sensitivity results which indicated probable resistance development. *Pseudomonas aeruginosa* was tested with cefotaxime over the first 2 years and seemed to adopt the same trend (22.2% and 50%, respectively). Both nosocomial and community acquired significant infections tested were fairly resistant to cefotaxime, with the sensitivities ranging from 37.5% to 57.1%, and 0% to 75%, respectively [Appendix 4 and 6]. *Haemophilus influenzae* and *Proteus mirabilis* were the only micro-organisms isolated during the prospective phase of the study, that were 100% sensitive to cefotaxime. Notable micro-organisms (due to their prevalence) that demonstrated resistance to cefotaxime as clinically significant nosocomial and community acquired infections were *Escherichia coli* (57.1% and 75%, respectively) and *Klebsiella sp.* (37.5% and 0%, respectively).

Over the 2 years cefepime was tested, *Klebsiella pneumoniae* (50% and 75%, respectively) and *Pseudomonas aeruginosa* (75% and 81.8%, respectively) were the only micro-organisms that demonstrated consistent resistance. Otherwise, cefepime was the most effective cephalosporin available (85.4 ± 15.5% and 88.2 ± 12.8%, respectively). *Alkaligenes faecalis* (0% in 1996), *Acinetobacter lwoffi* (0% in 1997) and *Enterobacter cloacae* (75% in 1997)

were the other micro-organisms that demonstrated resistance to cefepime. Significant nosocomial infections produced the greatest resistance to cefepime with *Acinetobacter lwoffi*, *Klebsiella sp.* and *Enterobacter cloacae* (0%, 62.5% and 50%, respectively), otherwise the other infection groups were 100% sensitive to it.

Significant correlation have been identified between percentages of β-lactam resistance and usage of penicillinase-stable β-lactam agents, especially third generation cephalosporins [Lyytikainen, et al, 1996; Rice, *et al*, 1996]. A number of studies have also demonstrated, a decrease in the percentage of cephalosporin-resistance in association with a marked decrease in cephalosporin use [Modi, 1987; Schentag, 1993; Dudley, 1995; Rice, et al, 1996]. However contrary to expectations, despite the restriction to empiric use of cefotaxime for about 2 years the sensitivity did not change much (from 47.2% in 1995 to 45.7% in 1997, although it did rise to 68.9% in 1996).

8.7 PIPERACILLIN/TAZOBACTAM

Literature a few years ago introduced piperacillin/tazobactam as a broad spectrum β-lactam β-lactamase inhibitor with activity against gram positive micro-organisms, such as Staphylococci and Streptococci, as well as many gram negative aerobic and anaerobic micro-organisms [Daniel & Krop, 1996]. Nevertheless, in this study piperacillin/tazobactam has been tested and only used against gram negative micro-organisms.

Over the 3 years, the micro-organisms in the study that demonstrated isolated yet limited incidences of resistance towards piperacillin/tazobactam were *Escherichia coli* (87.5% in 1997), *Klebsiella pneumoniae* (80% in 1996), *Klebsiella sp.* (80% in 1997) and *Pseudomonas aeruginosa* (80% in 1995, 88.9% in 1996, and 76.9% in 1997). When comparing piperacillin/tazobactam to other antibiotics, it appears to be a fairly effective antibiotic. However, the reason the last 4 micro-organisms were mentioned was because they were the only micro-organisms not completely sensitive to piperacillin/tazobactam.

Significant nosocomial infections experienced the greatest resistance to piperacillin/tazobactam with *Klebsiella sp.* and *Enterobacter cloacae* (62.5% and 50% respectively). *Escherichia coli* during 1997 demonstrated an overall sensitivity of 87.5% which is fairly satisfactory. During the prospective phase of the study, *Escherichia coli* isolated was classified as clinically significant nosocomial and community acquired infections. The nosocomial-acquired *Escherichia coli* remained completely sensitive to piperacillin/tazobactam, while the community-acquired *Escherichia coli* was only 50% sensitive.

Beta-lactamase inhibitors (i.e. tazobactam) have been able to inhibit the β-lactamases (previously mentioned in the Klebsiella infection section) produced by *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella sp.*, however the antibiotics with which the β-lactamase inhibitors are combined (i.e. piperacillin) are not effective at eradicating these micro-organisms on their own [Neu,

1992]. In other words, tazobactam is able to bind irreversibly to the β-lactamase enzyme inactivating it, but the piperacillin is rendered ineffective either due to changes in penicillin-binding proteins or alterations in outer membrane permeability [Hart & Bailey, 1996]. When observing the sensitivity differences between piperacillin and piperacillin/tazobactam (49.1 ± 20.8% and 88.7 ± 12.7% respectively), tazobactam succeeds in greatly extending the activity of piperacillin. Therefore resistance to piperacillin/tazobactam is not an immediate problem.

Piperacillin/tazobactam is used as a substitute to the frequent use of third generation cephalosporins [Meyer, *et al*, 1993] for the sole reason that both the components of the antibiotic are low β-lactamase inducers compared to the cephalosporins which are considered high inducers [Neu, 1992]. Gram negative bacteria have chromosomal genes (*amp*C) which enables the production of β-lactamase (or cephalosporinase which has a high affinity for the cephalosporins [Neu, 1992]), and others have genes which regulate the production of the enzyme [Bennett & Chopra, 1993]. When the micro-organisms are exposed to antibiotics that are strong inducers such as cephalosporins, high levels of enzymes are produced coupled with a decreased outer membrane permeability resulting in a decrease in the amount of antibiotic allowed through in to the periplasmic space. This overwhelms the antibiotic and results in its destruction. When exposed to piperacillin/tazobactam, low levels of β-lactamase are produced and these antibiotics are less likely to be inactivated by β-lactamase. This could also

explain the difference in micro-organism sensitivities to cefotaxime and piperacillin/tazobactam.

8.8 AMIKACIN AND GENTAMICIN

In the PICU, amikacin is only prescribed to patients less than 1 year of age. Over the 3 year period, *Enterobacter cloacae* (100%, 100% and 75%, respectively), *Klebsiella pneumoniae* (16.7%, 40% and 25%, respectively), *Klebsiella sp.* (71.4%, 100% and 73.3%, respectively) and *Pseudomonas aeruginosa* (77.8%, 88.9% and 69.2%, respectively) were identified as problem micro-organisms where amikacin was concerned when observing their sensitivity trends. *Escherichia coli* over the first 2 years was 100% sensitive to amikacin, but during the third year the sensitivity dropped to 84.6%, which although still fairly sensitive was a cause for concern. As a significant nosocomial infection *Escherichia coli* was regarded as a problem micro-organism due to its prevalence, even though its sensitivity (66.7%) was higher than that of *Enterobacter cloacae* (50%) [Appendix 4].

Gentamicin is only used in patients older than 1 year of age in the PICU. *Enterobacter cloacae* (100%, 100%, and 75%, respectively), *Escherichia coli* (81.3%, 71.4%, and 62.5%, respectively), *Klebsiella pneumoniae* (0%, 40%, and 0%, respectively) and *Klebsiella sp.* (50%, 77.8% and 33.3%, respectively) experienced a constant rise or maintained resistance to gentamicin over the 3 years. *Escherichia coli* (42.9% sensitive) and *Klebsiella*

sp. (37.5% sensitive) as significant nosocomial infections proved problematic for gentamicin due to their relatively high frequency [Appendix 4].

Amikacin is modified either inefficiently or not at all by the majority of aminoglycoside-modifying enzymes, therefore remaining active against a number of aminoglycoside-resistant bacteria, and according to previous studies its exclusive use (also assumed appropriate dosing) may result in the general reduction of overall aminoglycoside resistance [Mayer, 1986; Starr, 1986].

Earlier studies recognised that the exclusive substitution of amikacin for other aminoglycosides does not necessarily result in an increase in amikacin resistance, and can cause a general resistance recovery of other aminoglycosides, such as gentamicin and tobramycin [Mayer, 1986; Starr, 1985]. Contrary to those results, in the PICU, all 3 aminoglycosides experienced declines in sensitivities to them, the difference being the rate of amikacin's decline being a lot slower than the other aminoglycosides. This probably was because in the PICU which houses both neonates (which are administered amikacin) and non-neonates (which are administered gentamicin) 2 separate aminoglycosides are given. These results are consistent with a study that determined cross-sensitivity between aminoglycosides when the MICs of amikacin and netilmicin were also increased when the Staphylococcal strains were exposed to gentamicin, tobramycin and isepamicin [Torres, Tajedor,Gonzalez, *et al*, 1996].

8.9 VANCOMYCIN

Over the last 20 years, vancomycin has become a first line agent in managing gram positive sepsis, especially that of nosocomial origin [Rotschafer, Hoang & Peterson, 1997]. Many believe that the continued, increased use of vancomycin may promote the emergence of vancomycin-resistant micro-organisms [Christensen, *et al*, 1996]. With the growing resistance reported to vancomycin for Staphylococcal and Enterococcal micro-organisms, given that current options in treating these micro-organisms are limited, this poses a real dilemma for future treatment [Christensen, *et al*, 1996; Noskin, 1997].

Vancomycin is still very effective to all the micro-organisms it was tested against in this study although 1 isolate of *Bacillus subtilis* in 1995 was found to be completely resistant to it. Although one is tempted to think this was just an isolated incident, one can not ignore the possibility of further reports as in the case of *Enterococcus faecium*.

8.10 IMIPENEM

Due to high prevalence of multi-resistant micro-organisms, imipenem has turned out to be an adequate alternative to other broad spectrum agents in the treatment of suspected nosocomial infections [Zemelman, *et al*, 1993]. Although resistance to carbapenem β-lactams rarely occurs, altered penicillin-

binding proteins or loss of an outer-membrane protein that provides a channel for the entry of imipenem are associated with its resistance [Sanders, 1985; Quinn, 1986]. Like the cephalosporins, imipenem is also a very effective β-lactamase inducer, and clinical isolates recently have been found that produce specialised imipenem-hydrolyzing β-lactamase [Neu, 1992].

Over the 3 year study period, the resistances to imipenem could not be conclusively determined because those micro-organisms that demonstrated any degree of resistance to it had low isolate counts. Therefore, with the exception of *Alkaligenes faecalis* and *Acinetobacter lwoffi*, all micro-organisms tested against imipenem in the PICU regardless of the source of the infection were still completely sensitive to it. However with its continued use it only seems a matter of time before resistance to imipenem proliferates.

8.11 PHARMACOKINETIC STUDY

Factors such as daily dose, frequency of administration or combination with other drugs have been addressed as possible reasons for the selection of amikacin resistance [Guilllermo, 1986]. When observing the results of the pharmacokinetic study, amikacin was not appropriately dosed with amikacin peak concentrations well below therapeutic levels. Therefore it would be interesting to see if correct dosing of amikacin resulting in therapeutic levels would result in a recovery in aminoglycoside sensitivity.

In the past, several studies demonstrated variable results in comparing once daily to multiple daily dosing [Zhanel & Craig, 1994]. Even though these studies have recently been extensively reviewed to a point where once daily dosing is considered as effective, if not more effective (and less nephrotoxic and ototoxic) than multiple daily dosing [Zhanel, *et al.*, 1994], unfortunately it has not been well studied in the paediatric population [Barclay, Begg, Hickling, 1994]. Nonetheless, current recommendations entail maximising aminoglycoside Cmax to MIC ratio (e.g. $\geq$ 8) along with employing individual pharmacokinetic parameters to increase therapeutic efficacy without increasing toxicity. Having the aminoglycoside concentrations fall below the MIC for a short period of time will not result in a therapeutic failure due to the drug's post-antibiotic effect (PAE)(which is a dose-dependent continued suppression of bacterial growth after the period of antibiotic exposure [Barclay, *et al*, 1994]). The PAE is determined in vitro after 1 to 2 hours of exposure to fixed antibiotic concentrations in a pharmacokinetic model simulating human pharmacokinetics [den Hollander, *et al.*, 1996]. This phenomenon encourages the use of longer dosage intervals, however a patient's rate of elimination will dictate the dosage interval [Zhanel, *et al.*, 1994]. Therefore the optimal aminoglycoside dosing regimen should be designed to maximise the area under the curve (AUC) by administering high doses, and giving the doses at intervals no greater than the duration of time that drug concentrations exceed the MIC plus the duration of the PAE [Zhanel, *et al*, 1994].

8.12 LIMITATIONS TO MICRO-ORGANISM SENSITIVITY ANALYSIS

In this study the culture sensitivity results were based on the Kirby-Bauer analysis method. There are limitations associated with this method of analysis since it offers an all or none type of response. Although resistance is synonymous with tolerance, the definition is perspective dependent. From a clinicians standpoint, resistance is thought of as categorical, "either sensitive or resistant" [Polk, 1997], which is how sensitivity or resistance is expressed from the Microbiology lab. From a microbiologist's stance, national standards for determining susceptibility (NCCLS-approved breakpoints) are of primary importance, and from a pharmacokineticist's viewpoint, serum concentrations versus time profiles with relation to MIC and minimum bactericidal concentration (MBC) are of primary importance. Unfortunately, there are varying levels of resistance which are not taken into consideration by the format in which culture sensitivity results are expressed. For example, a penicillin-resistant *Streptococcus pneumoniae*, could mean:

1. penicillin can not be used for treatment from a clinicians point of view
2. it is a different micro-organism compared with its historical counterpart since it has acquired new genetic information from a microbiologist point of view.
3. the MICs for this micro-organisms has simply increased in the serum concentration versus time curve (therefore the *Streptococcus pneumoniae* is still susceptible to penicillin but the dose of penicillin

would probably have to be increased) from the pharmacokineticist's point of view [Friedland & McCracken, 1994].

Therefore just to mention, the resistance or sensitivity of a micro-organism is not enough in instituting antibiotic therapy. One should rather make use of the MIC approach in order to make a more informed decision about the most effective antibiotic treatment and dose for a patient.

CHAPTER 9: CONCLUSIONS

Since infections in any ward are an important determinant of a patient's morbidity or mortality, the continued surveillance initiated by this study is essential as micro-organisms prevalence and sensitivity patterns are continuously changing over time. Therefore the results and analyses demonstrated by the study are needed to formulate antibiotic policies.

9.1 ANTIBIOTICS FOR GRAM POSITIVE MICRO- ORGANISMS

Due to the resistance to penicillin by nosocomial infections, penicillin should be reserved for community acquired infections.

With the emergence of gram positive micro-organisms which are resistant to multiple antibiotics including vancomycin, the future of antimicrobial therapy looks rather bleak since such infections are virtually untreatable. Over the last 20 years, vancomycin has been promoted from the last-line agent to the first-line in managing gram positive sepsis for many clinicians [Rotschafer, *et al*, 1997], and as a result a direct correlation (although circumstantial) between unrestricted use of vancomycin and vancomycin resistance has been identified. As a result, it is advisable to restrict the use of vancomycin to nosocomial infections where there is a strong suspicion that they are caused by methicillin-resistant Enterococcus or Staphylococcus, or in patients with a serious β-lactam allergy (in the case of non-neonates) in whom no other

alternative exists. Like the aminoglycosides, vancomycin is also a concentration-dependent bactericidal agent, therefore it is important to individualise the pharmacokinetic dosing parameters in order to avoid the emergence of subtherapeutic related resistance.

9.2 ANTIBIOTICS FOR GRAM NEGATIVE MICRO- ORGANISMS

Since most gram negative micro-organisms are susceptible to amikacin, its exclusive use (provided dosed appropriately) does not appear to exhibit an increase in its own resistance. In addition, amikacin has a favourable influence on the susceptibility to other aminoglycosides. Therefore, it can be used in both empiric and tailored regimens [Peetermans & Bobbaers, 1996]. As a result of this and also due to the decreased sensitivity to gentamicin it would be advisable to rather use amikacin. An important issue to remember in aminoglycoside dosing is to attain high peak concentrations, low trough concentrations, and calculate the maintenance dose and dosing interval based on the patient's individual pharmacokinetic parameters.

Imipenem appears to be an adequate alternative to other broad-spectrum agents in the treatment of infections due to nosocomial multi-resistant gram negative bacilli, however it should be used as a last-line agent. The reasons being, it is associated with a high risk of inducing convulsions in patients with previous neurological damage or renal failure [Principi, 1996]; and although it

is still a very effective antibiotic it would be predisposed to resistance development from frequent use; and it is a fairly costly drug.

Cefotaxime should be reserved for cases such as meningitis or clinically significant infections where micro-organisms have been identified as being sensitive to cefotaxime. The restriction initially imposed on the use of cefotaxime was probably not clearly defined since after the restriction it was the third most frequently administered antibiotic in the PICU. Therefore the reduction in cefotaxime administration was not enough to encourage a concomitant decline in cefotaxime-resistant micro-organisms.

Piperacillin/tazobactam is considered safe and effective as monotherapy for infections usually treated with a combination of antibiotics such as polymicrobial and nosocomial infections due to its wide spectrum of activity that includes gram positive micro-organisms, gram negative aerobic and anaerobic micro-organisms [Daniel, *et al.*, 1996]. At Johannesburg General Hospital, piperacillin/tazobactam's spectrum of activity was limited to gram negative micro-organisms, however with information of its efficacy extending to cover gram positive micro-organisms the issue of considering it a broad spectrum antibiotic ought to be addressed. It is primarily indicated for β-lactamase producing micro-organisms that are resistant to β-lactamase stable agents, and can be used as an empiric therapy in cases of serious infections. Also because its concentrations do not require monitoring, this may prove to be the more cost-effective choice [Hart, *et al.*, 1996]. It can be used as a

substitute for cephalosporins and aminoglycosides (if there is a concern about nephrotoxicity) [Hart, *et al.*, 1996].

9.3 RECOMMENDATIONS

1. Penicillin should only be used for suspected community acquired infections.

2. Cefotaxime's use should be restricted for cases such as meningitis or clinically significant infections where the micro-organisms have been identified as being sensitive to cefotaxime.

3. Piperacillin/tazobactam should be used as first-line therapy in all suspected nosocomial acquired gram negative infections. Piperacillin/tazobactam's activity against gram positive micro-organisms ought to be explored for possible use against them.

4. Vancomycin's use should be restricted to nosocomial infections suspected of being caused by methicillin-resistant Staphylococci (*Staphylococcus aureus* or *Staphylococcus epidermidis*) or Enterococci (*Enterococcus faecium* or *Enterococcus faecalis*); or in patients with a serious β-lactam allergy in whom no other alternative exists.

5. Amikacin should be used exclusively in the ward, replacing gentamicin (since its exclusive use has a favourable influence on the susceptibility of other aminoglycosides).

6. Aminoglycosides (amikacin) and glycopeptides (vancomycin) should have their concentration-dependent bactericidal activity and their PAE maximised by administering them at dosages based on patient's individual pharmacokinetic parameters. Amikacin should be administered as a loading dose of 25 mg/kg intravenously over 30 minutes. Peak concentrations should be drawn 2 hours after the end of the loading dose infusion and the trough concentrations are drawn 10 hours after the end of the loading dose. From there the maintenance dose is calculated based on the patient's individual pharmacokinetic parameters and administered at least 24 hours after the loading dose.

7. Imipenem's use should be reserved as a last line agent to prevent resistance development.

8. Culture and sensitivity results should be expressed as MICs instead of the current Kirby-Bauer method of analysis.

9. If *Klebsiella pneumoniae* or *Pseudomonas aeruginosa* are isolated or suspected of being the cause of a clinically significant nosocomial infection, administer two antibiotics which cover gram negative micro-organisms (i.e. piperacillin/tazobactam; ciprofloxacin; imipenem or cefepime).

10. Based on the antibiotic sensitivity profile, the following regimens are recommended for the PICU:

First line therapy:	combination of penicillin (only for suspected community infections) and amikacin.
Second line therapy:	amoxicillin/clavulanic acid or piperacillin/tazobactam (depending on suspicion of gram positive or negative infection) Either could be used as first line therapy in significant nosocomial infections or second line therapy in significant community infections.
Third line of therapy:	combination of vancomycin and imipenem or ciprofloxacin or cefepime.

APPENDIX 1: Antibiogram for 1995

Organisms	# of Isolates	Penicillin	Oxacillin	Ampicillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Amikacin	Gentamicin	Tobramycin	Netilmicin	Erythromyc.n	Clindamycin	Chloramphen	Sulfisoxazole
GRAM POSITIVE																				
staphylococcus aureus	6	0 (0/6)	33.3 (2/6)	0 (0/6)		40 (2/5)		66.7 (2/3)						33.3 (2/6)			33.3 (2/6)	33.3 (2/6)	100 (1/1)	
staphylococcus epidermidis	42	7.3 (3/41)	22 (9/41)	7.3 (3/41)		33.3 (10/30)		58.8 (10/17)						30 (12/40)			51.2 (21/41)	51.2 (21/41)	37.5 (6/16)	0 (0/1)
streptococcus agalactiae	13	100 (11/11)	100 (11/11)	100 (11/11)				100 (11/11)						36.4 (4/11)			100 (11/11)	90.9 (10/11)	100 (4/4)	
streptococcus pneumoniae	2	50 (1/2)										100 (1/					100 (2/2)	100 (2/2)	100 (2/2)	
streptococcus sp	1	100 (1/1)	100 (1/1)	100 (1/1)				100 (1/1)						0 (0/1)			100 (1/1)	100 (1/1)	100 (1/1)	
streptococcus viridans	7	16.7 (1/6)	0 (0/6)	16.7 (1/6)				66.7 (4/6)						100 (6/6)			83.3 (5/6)	83.3 (5/6)	100 (2/2)	
grp C haemolytic strep	1	100 (1/1)	100 (1/1)	100 (1/1)				100 (1/1)						0 (0/1)			100 (1/1)	100 (1/1)	100 (1/1)	
enterococcus faecium	3	33.3 (1/3)	0 (0/2)	50 (1/2)		0 (0/1)		0 (0/1)						0 (0/2)			0 (0/2)	0 (0/2)		0 (0/1)
enterococcus faecalis	11	100 (10/10)	0 (0/10)	100 (11/11)				25 (1/4)						50 (5/10)			60 (6/10)	10 (1/10)		0 (0/1)
enterococcus sp	2	100 (2/2)	0 (0/2)	100 (2/2)				100 (2/2)						100 (2/2)			100 (2/2)	100 (2/2)		
micrococcus sp	1																			
bacillus sp	2	0 (0/2)	0 (0/2)	0 (0/2)				50 (1/2)						100 (2/2)			50 (1/2)	0 (0/2)	100 (2/2)	
bacillus cereus	5	20 (1/5)	20 (1/5)	20 (1/5)				25 (1/4)						100 (5/5)			80 (4/5)	80 (4/5)	100 (1/1)	
bacillus subtilis	1	0 (0/1)	0 (0/1)	0 (0/1)				0 (0/1)						0 (0/1)			0 (0/1)	0 (0/1)	0 (0/1)	
diphtheroids	3																			
propionobacterium sp	1																			
GRAM NEGATIVE																				
branhamella catarrhalis	1																			
acinetobacter sp	1			0 (0/1)	100 (1/1)	100 (1/1)		0 (0/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)				
acinetobacter baumann	2			0 (0/2)	100 (2/2)	0 (0/2)		0 (0/2)	0 (0/2)	0 (0/2)	100 (2/2)	0 (0/2)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)				
alkaligenes sp	1			0 (0/1)	100 (1/1)	100 (1/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)				
alkaligenes faecalis	3			0 (0/3)	100 (3/3)	50 (1/2)	100 (2/2)	0 (0/3)	0 (0/2)	0 (0/3)	33.3 (1/3)	0 (0/2)	33.3 (1/3)	33.3 (1/3)	33.3 (1/3)	0 (0/1)				
enterobacter sp	3			0 (0/3)	100 (3/3)	33.3 (1/3)	100 (2/2)	0 (0/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (1/1)				
enterobacter aerogenes	1			0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)					
enterobacter cloacae	6			0 (0/6)	100 (5/5)	0 (0/5)	100 (5/5)	0 (0/6)	1L (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)				
escherichia coli	18			5.6 (1/18)	45.5 (5/11)	80 (12/15)	100 (9/9)	88.2 (15/17)	87 ^ 14/16)	88.2 (15/17)	88.2 (15/17)	88.2 (15/17)	88.7 (13/15)	100 (17/17)	81.3 (13/16)	81.8 (9/11)	100 (2/2)			0 (0/5)
klebsiella sp	14			0 (1/14)	45.5 (5/11)	35.7 (5/14)	100 (10/10)	28.6 (4/14)	42.9 (6/14)	50 (7/14)	35.7 (5/14)	50 (7/14)	50 (7/14)	71.4 (10/14)	50 (7/14)	45.5 (5/11)				0 (0/3)
klebsiella pneumoniae	6			0 (0/6)	0 (0/6)	0 (0/6)	100 (1/1)	0 (0/6)	0 (0/6)	0 (0/6)	0 (0/6)	0 (0/6)	16.7 (1/6)	0 (0/6)	0 (0/6)	0 (0/3)				
proteus mirabilis	1			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)				
pseudomonas aeruginosa	9			0 (0/9)	88.9 (8/9)	12.5 (1/8)	80 (4/5)	0 (0/9)	0 (0/9)	22.2 (2/9)	100 (9/9)	22.2 (2/9)	77.8 (7/9)	77.8 (7/9)	77.8 (7/9)	66.7 12/3)				
salmonella sp	2			0 (0/2)		0 (0/2)			100 (2/2)			100 (2/2)							0 (0/2)	
unidan. gram -ve bacillus	1			0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)				
veillonella	1																			
bacteroides fragilis	1																			
prevotella melaninogen.	1																			
stenotropomonas mal	3			0 (0/2)	100 (2/2)	50 (1/2)		0 (0/2)	0 (0/2)	0 (0/2)	50 (1/2)	0 (0/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (1/1)				
Average		48.3	31.3	25.9	84.3	35.3	97.8	35.0	46.7	47.2	64.9	53.7	74.9	59.3	70.6	61.7	66.0	57.6	76.1	0
SD		44.8	42.9	41.7	31.1	37.8	6.7	41.4	49.2	47.7	42.9	47.9	35.5	41.5	37.9	45.8	37.2	43.1	42.0	0

APPENDIX 1: Antibiogram for 1995

Organisms	Sulphamatho	Trimethoprim	Co-trimoxazole	Ciprofloxacin	Cinoxacin	Nalidixic acid	Vancomycin	Fusidic acid	Nitrofurantoin	Rifampicin	Imipenem	Average	SD
GRAM POSITIVE													
staphylococcus aureus	100 (5/5)	33 3 (2/6)					100 (5/6)	100 (6/6)		83 3 (5/6)		54	36 9
staphylococcus epidermidis	26 3 (10/38)	17 1 (7/41)				0 (0/1)	100 (41/41)	82 5 (33/40)	100 (1/1)	79 5 (31/39)		41 4	33 2
streptococcus agalactiae	54 6 (6/11)	81 8 (9/11)					100 (11/11)	9 1 (1/11)		100 (1/1)		82 5	30
streptococcus pneumoniae							100 (1/1)			100 (2/2)		85 4	18 9
streptococcus sp		0 (0/1)					100 (1/1)	0 (0/1)				72 7	48 7
streptococcus viridans	33 3 (2/6)	0 (0/8)					100 (6/6)	66 7 (4/6)		66 7 (2/3)		58 4	38 2
grp C haemolytic strep	100 (1/1)	100 (1/1)					100 (1/1)	0 (0/1)				83 3	38 9
enterococcus faecium	0 (0/2)	50 (1/2)					100 (3/3)	100 (2/2)	100 (1/1)			31	41 6
enterococcus faecalis	30 (3/10)	72 7 (8/11)				0 (0/1)	100 (11/11)	30 (3/10)	100 (1/1)			48 4	40 3
enterococcus sp	0 (0/2)	100 (2/2)					100 (2/2)	100 (2/2)				81 8	40 5
micrococcus sp													
bacillus sp	100 (2/8)	[illegible]					100 (2/2)	0 (0/2)				45 8	45
bacillus cereus	80 (4/5)	[illegible]					100 (5/5)	40 (2/5)		50 (1/2)		58 5	34 1
bacillus subtilis	0 (0/1)	[illegible]					0 (0/1)	0 (0/1)				8 3	28 9
diphteroids													
propionebacterium sp													
GRAM NEGATIVE													
branhamella catarrhalis													
acinetobacter sp		0 (0/1)		100 (1/1)							100 (1/1)	80	41 4
acinetobacter baumann		0 (0/2)		100 (2/2)							100 (2/2)	40	43 1
alkaligenes sp		0 (0/1)		100 (1/1)							100 (1/1)	28 7	45 8
alkaligenes faecalis		0 (0/3)		100 (3/3)							66 7 (2/3)	34 4	38 7
enterobacter sp		100 (3/3)		100 (3/3)								82 2	37 5
enterobacter aerogenes		100 (1/1)		100 (1/1)							100 (1/1)	80	41 4
enterobacter cloacae		100 (6/6)		100 (5/5)							100 (4/4)	80	41 4
escherichia coli		41 2 (7/17)		100 (17/17)	100 (4/4)	100 (2/2)			100 (6/6)		100 (5/5)	78 7	30 9
klebsiella sp		78 6 (11/14)		100 (14/14)					100 (3/3)		100 (2/2)	54 9	32 4
klebsiella pneumoniae		83 3 (5/6)		100 (6/6)							100 (5/5)	25	42 6
proteus mirabilis		100 (1/1)		100 (1/1)							100 (1/1)	100	0
pseudomonas aeruginosa		0 (0/9)		88 9 (8/9)							100 (9/9)	50 9	40 4
salmonella sp		100 (2/2)	100 (2/2)	100 (2/2)								62 5	51 8
uniden. gram -ve bacillus		0 (0/1)		100 (1/1)							100 (1/1)	48 7	51 6
veillonella													
bacteroides fragilis													
prevotella melaninogen													
stenotropomonas mal		0 (0/3)		100 (2/2)							50 (1/2)	50	48 3
Average	47 7	49 2	100	99 3	100	33 3	92 3	44 0	100	79 9	93 6		
SD	41 4	43 1		2 9		57 7	27 7	43 3	0	19 4	19 0		

APPENDIX 2: Antibiogram for 1996

Organisms	#Iso tested	Penicillin	Oxacillin	Ampicillin	Piperacillin	Co-amoxiclav	Piptaz	Cloxacillin	Cefazolin	Cephalexin	Cefotaxime	Ceftriaxone	Ceftazidime	Ceftriaxone	Cefepime	Amikacin	Gentamicin	Tobramycin	Erythromycin	Clindamycin	Chloramphenicol
GRAM POSITIVE																					
staphylococcus aureus	27	18.5 (5/27)	33.3 (8/24)					37 (10/27)	37 (10/27)	37 (10/27)		37 (10/27)							37 (10/27)	37 (10/27)	
staphylococcus epidermidis	32	0 (0/32)	40 (12/30)	0 (0/6)		33.3 (1/3)		38.5 (10/26)	48.3 (14/29)	40 (10/25)		38.5 (10/26)				83.3 (5/6)		48.9 (15/32)	48.9 (15/32)	100 (1/1)	
streptococcus agalactiae	2	100 (2/2)	100 (2/2)	100 (2/2)					100 (1/1)							0 (0/2)		100 (2/2)	100 (2/2)		
streptococcus pneumoniae	3	66.7 (2/3)	100 (2/2)								100 (1/1)			100 (2/2)				100 (3/3)	100 (3/3)	100 (3/3)	
streptococcus pyogenes	1	100 (1/1)																100 (1/1)			
streptococcus sp	2	100 (2/2)		100 (2/2)		100 (2/2)			100 (2/2)	100 (2/2)								100 (2/2)			
streptococcus viridans	2	100 (2/2)		100 (2/2)		100 (2/2)			100 (2/2)	100 (2/2)								100 (2/2)			
enterococcus faecium	1	0 (0/1)		100 (1/1)		100 (1/1)												100 (1/1)			
enterococcus faecalis	11	90 (9/10)	0 (0/5)	90 (9/10)		100 (5/5)	100 (1/1)										83.3 (5/6)	16.7 (1/6)	20 (1/5)		
GRAM NEGATIVE																					
r.sinetobacter baumann	3			0 (0/1)	100 (3/3)	0 (0/1)	100 (3/3)		0 (0/1)		0 (0/1)	0 (0/1)	100 (3/3)	0 (0/1)	100 (2/2)	100 (3/3)	100 (1/1)	100 (3/3)			
acinetobacter woffi	1			0 (0/1)	100 (1/1)		100 (1/1)		0 (0/1)		100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)		100 (1/1)			
alkalgenes faecalis	1				0 (0/1)		0 (0/1)						0 (0/1)		0 (0/1)	0 (0/1)		100 (1/1)			
enterobacter sp	4			0 (0/4)	50 (2/4)	0 (0/4)	100 (4/4)		0 (0/4)	0 (0/1)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	100 (2/2)	50 (2/4)	25 (1/4)	50 (1/2)			
enterobacter cloacae	2			0 (0/2)	100 (2/2)	0 (0/2)	50 (1/2)		0 (0/2)	0 (0/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)			
escherichia coli	14			20 (3/15)	46.2 (6/13)	100 (13/13)	100 (14/14)		85.7 (12/14)	83.3 (10/12)	100 (14/14)	100 (14/14)	84.6 (11/13)	100 (14/14)	100 (11/11)	93.3 (14/15)	71.4 (10/14)	75 (9/12)			
haemophilus influenza	2			100 (2/2)		100 (2/2)					100 (1/1)	100 (2/2)		100 (1/1)						100 (2/2)	
klebsiella sp	9			0 (0/9)	44.4 (4/9)	88.9 (8/9)	100 (9/9)		88.9 (8/9)	80 (4/5)	100 (9/9)	100 (9/9)	88.9 (8/9)	100 (9/9)	100 (5/5)	100 (9/9)	77.8 (7/9)	77.8 (7/9)			
klebsiella oxytoca	2			0 (0/2)	0 (0/2)	50 (1/2)	100 (2/2)		50 (1/2)	100 (1/1)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)	100 (2/2)	50 (1/2)	50 (1/2)	50 (1/2)			
klebsiella pneumoniae	5			0 (0/5)	40 (2/5)	20 (1/5)	80 (4/5)		20 (1/5)	100 (1/1)	40 (2/5)	20 (1/5)	40 (2/5)	40 (2/5)	50 (2/4)	40 (2/5)	40 (2/5)	40 (2/5)			
proteus mirabilis	1			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)		100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)			
pseudomonas aeruginosa	9			50 (1/2)	66.7 (6/9)	50 (1/2)	88.9 (8/9)		50 (1/2)		50 (1/2)	50 (1/2)	55.6 (5/9)	50 (1/2)	75 (6/8)	88.9 (8/9)	50 (1/2)	88.9 (8/9)			
pseudomonas sp	1			0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)		0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		100 (1/1)	0 (0/1)	0 (0/1)			
citrobacter freudi	2			0 (0/2)	100 (2/2)	0 (0/2)	100 (2/2)		0 (0/2)	0 (0/2)	100 (2/2)	50 (1/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)			
Average			63.9	54.7	40	65.2	55.4	87.1	37.8	45.6	61.7	66.9	58	72.8	88.9	85.4	78.6	62.9	75.5	77.5	60.6	100
SD			44.9	44.1	47.5	38.1	44.9	29.7	1.1	42.3	43.3	32.9	38.6	34.5	38.9	31	32.7	36	31.7	34.1	37.1	0

APPENDIX 2: Antibiogram for 1996

Organisms	Sulphametho	Trimethoprim	Co-trimoxazol	Ciprofloxacin	Ofloxacin	Nitrofurantoin	Vancomycin	Fusidic acid	Rifampicin	Imipenem	Meropenem	Tetracycline	Average	SD
GRAM POSITIVE														
staphylococcus aureus		81.5 (22/27)	91.7 (22/24)	100 (3/3)	66.7 (2/3)		100 (27/27)	100 (27/27)	88.9 (24/27)				60.2	30.2
staphylococcus epidermidis	100 (4/4)	37.5 (12/32)	80 (16/20)	0 (0/1)	0 (0/1)		100 (32/32)	88.5 (23/26)	96.9 (31/32)				49.9	35
streptococcus agalactiae	100 (2/2)	100 (2/2)					100 (2/2)		100 (2/2)				90.9	30.2
streptococcus pneumoniae			100 (2/2)				100 (2/2)		100 (3/3)				98.7	10.5
streptococcus pyogenes													100	0
streptococcus sp							100 (2/2)					100 (2/2)	100	0
streptococcus viridans							100 (2/2)					0 (0/2)	87.5	35.4
enterococcus faecium							100 (1/1)					0 (0/1)	66.7	51.6
enterococcus faecalis	0 (0/3)	100 (5/5)					100 (10/10)		100 (1/1)			0 (0/1)	81.5	45.3
GRAM NEGATIVE														
acinetobactur baumann		0 (0/1)		100 (3/3)	100 (2/2)					100 (3/3)	100 (2/2)		81.1	50.2
acinetobacter wolfi		0 (0/1)		100 (1/1)	100 (1/1)					100 (1/1)	100 (1/1)		81.3	40.3
alkaligenes faecalis				100 (1/1)	100 (1/1)					0 (0/1)	0 (0/1)		30	48.3
enterobacter sp		25 (1/4)		100 (2/2)		0 (0/2)				100 (4/4)			38.9	37.6
enterobacter cloacae		100 (2/2)								100 (2/2)			71.9	44.6
escherichia coli		42.9 (6/14)	100 (3/3)	100 (5/5)	100 (3/3)					100 (13/13)	100 (4/4)		85.1	23.3
haemophilus influenzae			100 (2/2)									100 (1/1)	100	0
klebsiella sp		77.8 (7/9)		100 (4/4)						100 (5/5)			83.8	26.1
klebsiella oxytoca		0 (0/2)								100 (2/2)			83.1	34
klebsiella pneumoniae		40 (2/5)		100 (5/5)	100 (4/4)					100 (5/5)	100 (4/4)		53.2	32.7
proteus mirabilis		100 (1/1)		100 (1/1)	100 (1/1)					100 (1/1)	100 (1/1)		100	0
pseudomonas aeruginosa		50 (1/2)		100 (8/8)	100 (8/8)					100 (9/9)	100 (8/8)		70.2	21.8
pseudomonas sp		0 (0/1)		100 (1/1)						100 (1/1)			40	50.7
citrobacter freudi		50 (1/2)		100 (1/1)	100 (1/1)					100 (2/2)	100 (1/1)		73.7	42.1
Average	80.7	50.3	90.3	82.3	86.7	0	100	94.3	97.2	92.3	87.5	40		
SD	37.7	38.9	17.3	27.7	32.2		0	8.1	4.8	27.7	35.4	54.8		

APPENDIX 3: Antibiogram for 1997

Organisms	# of Isolates	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cephalaxin	Cefotaxime	Ceturoxime	Ceftazidime	Ceftriaxone	Cefepime	Erythromycin	Clindamycin	Amikacin	Gentamicin	Tobramycin	Rifampicin
GRAM POSITIVE																					
staphylococcus aureus	12	0 (0/11)		33 3 (4/12)	33 3 (4/12)				36 4 (4/11)	36 4 (4/11)		36 4 (4/11)				33 3 (4/12)	25 (3/12)				75 (9/12)
staphylococcus epidermidis	53	3 8 (2/53)		28 3 (15/53)	28 3 (15/53)				26 9 (14/52)	26 9 (14/52)		25 5 (13/51)				35 8 (19/53)	35 6 (18/53)				81 1 (43/53)
streptococcus agalactiae	2	100 (2/2)	100 (2/2)				100 (2/2)		100 (2/2)	100 (2/2)						100 (2/2)					
streptococcus pneumoniae	1	100 (1/1)		100 (1/1)	100 (1/1)											100 (1/1)	100 (1/1)				100 (1/1)
streptococcus pyogenes	2	100 (2/2)	100 (1/1)				100 (1/1)		100 (1/1)	100 (1/1)						100 (2/2)					
streptococcus sp	4	100 (4/4)	100 (4/4)				100 (4/4)		100 (4/4)	100 (4/4)						100 (4/4)					
streptococcus viridans	3	100 (3/3)	100 (3/3)				100 (2/2)		100 (3/3)	100 (3/3)						100 (3/3)					
enterococcus faecalis	11	90 9 (10/11)	90 9 (10/11)				90 (9/10)									100 (1/1)			100 (4/4)		
enterococcus faecium	3	0 (0/3)	0 (0/3)			0 (0/1)	0 (0/3)	0 (0/1)											0 (0/1)		
micrococcus sp	2	100 (2/2)	100 (1/1)				100 (1/1)		100 (2/2)	100 (2/2)						100 (2/2)					
corynebacterium sp	3	100 (1/1)							0 (0/1)							100 (1/1)	100 (1/1)				
bacillus cereus	2	0 (0/2)							0 (0/2)							100 (2/2)					
GRAM NEGATIVE																					
acinetobacter baumanii	1					0 (0/1)		100 (1/1)					0 (0/1)		100 (1/1)			0 (0/1)		0 (0/1)	
acinetobacter lwoffi	1					0 (0/1)		0 (0/1)					0 (0/1)		0 (0/1)					100 (1/1)	
alkaligenes sp	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/2)	100 (3/3)	0 (0/2)	100 (3/3)			0 (0/3)	0 (0/2)	0 (0/3)	
alkaligenes faecalis	4		0 (0/2)			50 (2/4)	0 (0/2)	100 (4/4)	0 (0/2)		0 (0/2)	0 (0/1)	100 (2/2)	0 (0/1)	100 (2/2)			50 (1/2)	100 (1/1)	50 (1/2)	
enterobacter cloacae	4		0 (0/4)			75 (3/4)	0 (0/4)	75 (3/4)	0 (0/4)	0 (0/3)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)			75 (3/4)	75 (3/4)	75 (3/4)	
enterobacter gergoviae	1		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)	
enterobacter sp	4		0 (0/4)			25 (1/4)	50 (2/4)	100 (4/4)	25 (1/4)	33 3 (1/3)	75 (3/4)	50 (2/4)	50 (2/4)	75 (3/4)	100 (4/4)			100 (4/4)	50 (2/4)	50 (2/4)	
escherichia coli	16	0 (0/4)	0 (0/11)			8 7 (1/13)	57 1 (8/14)	87 5 (14/16)	40 (5/15)	41 7 (5/12)	75 (12/16)	68 8 (11/16)	68 8 (11/16)	75 (12/16)	100 (16/16)			84 5 (11/13)	62 5 (10/16)	60 (9/15)	
haemophilus influenzae	4		100 (4/4)				100 (4/4)				100 (4/4)	100 (4/4)		100 (4/4)							
klebsiella sp	15		0 (0/15)			26 7 (4/15)	46 7 (7/16)	80 (12/15)	20 (3/15)	42 9 (3/7)	40 (6/15)	35 7 (5/14)	33 3 (5/15)	40 (6/15)	80 (12/15)			73 3 (11/15)	73 3 (5/15)	26 6 (4/14)	
klebsiella pneumoniae	4		0 (0/4)			25 (1/4)	0 (0/3)	100 (4/4)	25 (1/4)	100 (1/1)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	75 (3/4)			25 (1/4)	0 (0/4)	0 (0/4)	
klebsiella oxytoca	2		0 (0/2)			50 (1/2)	50 (1/2)	100 (2/2)	50 (1/2)	100 (1/1)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)	100 (2/2)			100 (2/2)	50 (1/2)	50 (1/2)	
proteus mirabilis	6		50 (3/6)			100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)	100 (6/6)			100 (6/6)	83 3 (5/6)	100 (6/6)	
pseudomonas aeruginosa	13					76 9 (10/13)		76 9 (10/13)					76 9 (10/13)		61 8 (8/11)			69 2 (9/13)		84 6 (11/	
campylobacter jejuni	1		0 (0/1)								0 (0/1)			0 (0/1)					100 (1/1)		
bacteroides fragilis	1																				
stenotropomonas maltophilia	1		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)			0 (0/1)	0 (0/1)	0 (0/1)	
burkholderia cepacia	1					100 (1/1)		100 (1/1)					100 (1/1)		100 (1/1)			0 (0/1)		0 (0/1)	
salmonella sp	1		100 (1/1)								100 (1/1)			100 (1/1)							
shewanella putrefaciens	1					100 (1/1)		100 (1/1)					100 (1/1)		100 (1/1)			100 (1/1)		100 (1/1)	
Average			61 1	40 0	53 9	53 9	49 1	33 7	83 5	41 2	65 4	45 7	40 5	67 4	52 9	88 2	88 1	85 2	58 5	53 9	49 9	65 4
SD			49 7	48 5	40 0	40 0	41 5	39 1	32 7	42 2	40 1	41 5	35 4	38 7	41 6	25 5	26 5	40 4	42 1	41 1	40 7	13 0

APPENDIX 3: Antibiogram for 1997

Organisms	Chloramphen	Vancomycin	Fucidin	Ciprofloxacin	Ofloxacin	Cotrimoxazole	Trimethoprim	Imipenem	Meropenem	Teicoplanin	Tetracycline	Average	SD
GRAM POSITIVE													
staphylococcus aureus		100 (12/12)	100 (12/12)			66.3 (7/12)	50 (6/12)			100 (7/7)		51.2	31.2
staphylococcus epidermidis		100 (53/53)	75.5 (40/53)			26.4 (14/53)	24.5 (12/49)			93.8 (15/16)		43.6	30.2
streptococcus agalactiae		100 (2/2)									50 (1/2)	92.9	18.9
streptococcus pneumoniae	100 (1/1)	100 (1/1)				0 (0/1)						88.9	33.3
streptococcus pyogenes		100 (1/1)									0 (0/1)	85.7	37.8
streptococcus sp		100 (4/4)									75 (3/4)	98.4	9.4
streptococcus viridians		100 (3/3)									66.7 (2/3)	95.2	12.8
enterococcus faecalis		100 (11/11)									100 (1/1)	97	4.7
enterococcus faecium		100 (3/3)										20	44.7
micrococcus sp		100 (2/2)										100	0
corynebacterium sp		100 (1/1)				100 (1/1)						83.3	40.8
bacillus cereus		100 (2/2)				50 (1/2)	0 (0/2)					41.7	49.2
GRAM NEGATIVE													
acinetobacter baumanii				100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)			60	51.6
acinetobacter lwoffi				100 (1/10	100 (1/1)			0 (0/1)	0 (0/1)			33.3	50
alkaligenes sp				100 (1/1)	100 (1/1)		0 (0/1)	100 (1/1)	0 (0/1)			33.3	48.8
alkaligenes faecalis				25 (1/4)	25 (1/4)		0 (0/2)	100 (4/4)	75 (3/4)			43.1	42.7
enterobacter cloacae				100 (3/3)	100 (3/3)		75 (3/4)	100 (4/4)	100 (3/3)			64.5	35.7
enterobacter gergoviae				100 (1/1)	100 (1/1)		100 (1/1)	100 (1/1)	100 (1/1)			68.4	47.8
enterobacter sp				100 (1/1)			75 (3/4)	100 (4/4)				62.3	31.6
escherichia coli				100 (4/4)	100 (4/4)		38.5 (5/13)	100 (16/16)	100 (4/4)			83.3	33.2
haemophilus influenzae	100 (4/4)			100 (3/3)		50 (2/4)					100 (4/4)	94.4	15.7
klebsiella sp				100 (1/1)	100 (1/1)	0 (0/1)	64.3 (9/14)	100 (15/15)	100 (1/1)			52.2	32.7
klebsiella pneumoniae				100 (4/4)	100 (4/4)		50 (2/4)	100 (4/4)	100 (4/4)			47.4	40.7
klebsiella oxytoca				100 (2/2)	100 (2/2)		50 (1/2)	100 (2/2)	100 (2/2)			87.1	31.2
proteus mirabilis				100 (1/1)	100 (1/1)		50 (3/6)	100 (6/6)	100 (1/1)			93.9	15.8
pseudomonas aeruginosa				100 (13/13)	100 (13/13)			100 (13/13)	100 (12/12)			88.6	12.2
campylobacter jejuni	100 (1/1)			100 (1/1)	100 (1/1)			100 (1/1)				62.5	51.8
bacteroides fragilis													
strenotropomonas maltophilia				0 (0/1)	0 (0/1)		100 (1/1)	100 (1/1)	100 (1/1)			38.9	50.2
burkholderia cepacia				0 (0/1)	0 (0/1)			100 (1/1)	100 (1/1)			50	51.6
salmonella sp				100 (1/1)	100 (1/1)	100 (1/1)						100	0
shewanella putrefaciens				100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)			100	0
Average	100	100	87.5	85.5	83.8	48.1	48.4	94.1	95	96.9	65.3		
SD	0	0	17.3	34.7	36.4	38.9	33.6	24.3	35.1	4.4	37.4		

APPENDIX 4: Clinically significant nosocomial infection antibiogram

	# of isolates	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cephalexin	Cefotaxime	Cefuroxime	Ceftazidime	Ceftriaxone	Cefepime	Erythromycin	Clindamycin	Amikacin	Gentamicin	Tobramycin
GRAM POSITIVE																				
enterococcus faecalis	3	100 (3/3)	100 (3/3)				100 (2/2)												100 (1/1)	
enterococcus faecium																				
staphylococcus aureus	8	0 (0/8)		25 (2/8)	25 (2/8)				28.6 (2/7)	28.6 (2/7)		28.6 (2/7)				25 (2/8)	25 (2/8)			
staphylococcus epidermidis	9	0 (0/9)		33.3 (3/9)	33.3 (3/9)				25 (2/8)	25 (2/8)		25 (2/8)				55.6 (5/9)	55.6 (5/9)			
streptococcus agalactiae																				
streptococcus pneumoniae																				
streptococcus pyogenes	1	100 (1/1)														100 (1/1)				
streptococcus sp	1	100 (1/1)	100 (1/1)				100 (1/1)		100 (1/1)	100 (1/1)						100 (1/1)				
streptococcus viridians																				
micrococcus sp																				
corynebacterium sp																				
bacillus cereus																				
GRAM NEGATIVE																				
acinetobacter baumanii																				
acinetobacter lwoffi	1					0 (0/1)		0 (0/1)					0 (0/1)		0 (0/1)					100 (1/1)
alkaligenes sp																				
alkaligenes faecalis																				
enterobacter sp	2		0 (0/2)			0 (0/2)	100 (2/2)	100 (2/2)	50 (1/2)	100 (1/1)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)	100 (2/2)			100 (2/2)	50 (1/2)	50 (1/2)
enterobacter cloacae	2		0 (0/2)			50 (1/2)	0 (0/2)	50 (1/2)	0 (0/2)	0 (0/1)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)	50 (1/2)			50 (1/2)	50 (1/2)	50 (1/2)
escherichia coli	7		0 (0/7)			0 (0/6)	66.7 (4/6)	100 (7/7)	33.3 (2/6)	50 (2/4)	57.1 (4/7)	57.1 (4/7)	57.1 (4/7)	57.1 (4/7)	100 (7/7)			66.7 (4/6)	42.9 (3/7)	57.1 (4/7)
haemophilus influenzae	2		100 (2/2)				100 (2/2)				100 (2/2)	100 (2/2)		100 (2/2)						
klebsiella sp	8		0 (0/8)			25 (2/8)	25 (2/8)	62.5 (5/8)	12.5 (1/8)	25 (1/4)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	62.5 (5/8)			87.5 (7/8)	37.5 (3/8)	25 (2/7)
klebsiella pneumoniae																				
klebsiella oxytoca																				
proteus mirabilis	2		0 (0/2)			100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)			100 (2/2)	50 (1/2)	100 (2/2)
pseudomonas aeruginosa	5					80 (4/5)		80 (4/5)					80 (4/5)		100 (5/5)			80 (4/5)		80 (4/5)
campylobacter jejuni																				
bacteroides fragilis	1																			
stenotrophomonas maltophilia																				
burkholderia cepacia																				
Average			50.0	37.5	29.2	29.2	36.4	74	70.4	43.7	53.6	65.6	56.0	53.5	85.9	73.2	70.2	40.3	80.7	55.1	66.5
SD			54.6	51.6	5.9	5.9	41.3	40.2	36.9	37.7	40.7	27.3	29.3	31.7	27.3	38.5	36.7	21.6	19.6	22.6	27.4

APPENDIX 4: Clinically significant nosocomial infection antibiogram

	Rifampicin	Chloramphen	Vancomycin	Fucidin	Ciprofloxacin	Ofloxacin	Cotrimoxazole	Trimethoprim	Imipenem	Meropenem	Teicoplanin	Tetracycline	Average	SD
GRAM POSITIVE														
enterococcus faecalis			100 (3/3)										100.0	0
enterococcus faecium														
staphylococcus aureus	75 (6/8)		100 (8/8)	100 (8/8)			50 (4/8)	37.5 (3/8)			100 (4/4)		46.3	33.4
staphylococcus epidermidis	88.9 (8/9)		100 (9/9)	88.9 (8/9)			22.2 (2/9)	22.2 (2/9)			80 (4/5)		46.3	31.4
streptococcus agalactiae														
streptococcus pneumoniae														
streptococcus pyogenes													100.0	0
streptococcus sp			100 (1/1)									100 (1/1)	100.0	0
streptococcus viridians														
micrococcus sp														
corynebacterium sp														
bacillus cereus														
GRAM NEGATIVE														
acinetobacter baumanii														
achetobacter lwoffi					100 (1/1)	100 (1/1)			0 (0/1)	0 (0/1)			33.3	50
alkaligenes sp														
alkaligenes faecalis														
enterobacter sp					100 (1/1)			100 (2/2)	100 (2/2)				87.5	35.1
enterobacter cloacae					100 (2/2)	100 (2/2)		50 (1/2)	100 (2/2)	100 (2/2)			50.0	33.3
escherichia coli								42.8 (3/7)	100 (7/7)				55.5	29.7
haemophilus influenzae		100 (2/2)			100 (1/1)		50 (1/2)					100 (2/2)	84.4	16.7
klebsiella sp							0 (0/1)	62.5 (5/8)	100 (8/8)				39.9	27.6
klebsiella pneumoniae														
klebsiella oxytoca														
proteus mirabilis								0 (0/2)	100 (2/2)				84.4	35.2
pseudomonas aeruginosa					100 (5/5)	100 (5/5)			100 (5/5)	100 (5/5)			90	10.5
campylobacter jejuni														
bacteroides fragilis														
stenotropomonas maltophilia														
burkholderia cepacia														
Average	82.0	100.0	100.0	94.5	100.0	100.0	30.8	45.0	85.7	66.7	90.0	100.0		
SD	9.8	0	0	7.8	0	0	24.2	31.5	37.8	57.7	14.1	0		

APPENDIX 5: Clinicaly insignificant nosocomial infection antibiogram

	# of isolate	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cephalexin	Cefotaxime	Celuroxime	Ceftazidime	Ceftriaxone	Cefepime	Erythromycin	Clindamycin	Amikacin	Gentamicin	Tobramycin
GRAM POSITIVE																				
enterococcus faecalis	2	100 (2/2)	100 (2/2)				100 (2/2)													
enterococcus faecium	1	0 (0/1)	0 (0/1)				0 (0/1)													
staphylococcus aureus	3	0 (0/1)		66 7 (2/3)	66 7 (2/3)				66 7 (2/3)	66 7 (2/3)		66 7 (2/3)				66 7 (2/3)	50 (1/2)			
staphylococcus epidermidis	16	6.3 (1/16)		12 5 (2/16)	12 5 (2/16)				12 5 (2/16)	12 5 (2/16)		12 5 (2/16)				25 (4/16)	25 (4/16)			
streptococcus agalactiae																				
streptococcus pneumoniae																				
streptococcus pyogenes																				
streptococcus sp																				
streptococcus viridians																				
micrococcus sp																				
corynebacterium sp																				
bacillus cereus	1	0 (0/1)							0 (0/1)							100 (1/1)				
GRAM NEGATIVE																				
acinetobacter baumanii																				
acinetobacter lwoffi																				
alkaligenes sp																				
alkaligenes faecalis	1					100 (1/1)		100 (1/1)					100 (1/1)		100 (1/1)			0 (0/1)		0 (0/1)
enterobacter sp	1		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
enterobacter cloacae	2		0 (0/2)			100 (2/2)	0 (0/2)	100 (2/2)	0 (0/2)	0 (0/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)	100 (2/2)			100 (2/2)	100 (2/2)	100 (2/2)
escherichia coli																				
haemophilus influenzae	1		100 (1/				100 (1/1)				100 (1/1)	100 (1/1)		100 (1/1)						
klebsiella sp.	2		0 (0/2)			50 (1/2)	100 (2/2)	100 (2/2)	50 (1/2)	50 (1/2)	100 (2/2)	50 (1/2)	50 (1/2)	100 (2/2)	100 (2/2)			100 (2/2)	50 (1/2)	50 (1/2)
klebsiella pneumoniae																				
klebsiella oxytoca																				
proteus mirabilis																				
pseudomonas aeruginosa																				
campylobacter jejuni																				
bacteroides fragilis																				
stenotropomonas maltophilia	1		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)			0 (0/1)	0 (0/1)	0 (0/1)
burkholderia cepacia	1					100 (1/1)		100 (1/1)					100 (1/1)		100 (1/1)			0 (0/1)		0 (0/1)
Average		21.3	28.6	39.6	39.6	91.7	42.9	100	18.5	25.8	80.0	81.3	91.7	80.0	100.0	63.9	37.5	50.0	62.5	41.7
SD		44.1	48.8	38.3	38.3	20.4	53.5	0	28	30.7	44.7	42.4	20.4	44.7	0	37.6	17.7	54.8	47.8	49.2

APPENDIX 5: Clinically insignificant nosocomial infection antibiogram

	Rifampicin	Chloramphen	Vancomycin	Fucidin	Ciprofloxacin	Ofloxacin	Cotrimoxazole	Trimethoprim	Imipenem	Meropenem	Teicoplanin	Tetracycline	Average	SD
GRAM POSITIVE														
enterococcus faecalis			100 (2/2)										100	0
enterococcus faecium			100 (1/1)										25 0	50 0
staphylococcus aureus	66 7 (2/3)		100 (3/3)	100 (3/3)			66 7 (2/3)	66 7 (2/3)			100 (3/3)		67 4	24 9
staphylococcus epidermidis	87 5 (14/16)		100 (16/16)	62 5 (10/16)			18 8 (3/16)	12 5 (2/16)			100 (9/9)		35 7	35 4
streptococcus agalactiae														
streptococcus pneumoniae														
streptococcus pyogenes														
streptococcus sp														
streptococcus viridians														
micrococcus sp														
corynebacterium sp														
bacillus cereus			100 (1/1)				100 (1/1)	0 (0/1)					50 0	54 8
GRAM NEGATIVE														
acinetobacter baumanii														
acinetobacter lwoff														
alkaligenes sp														
alkaligenes faecalis					0 (0/1)	0 (0/1)			100 (1/1)	100 (1/1)			50 0	51 6
enterobact., sp.								100 (1/1)	100 (1 1)				75 0	44 7
enterobacter cloacae					100 (1/1)	100 (1/1)		100 (2/2)	100 (2/2)	100 (1/1)			78 9	41 9
escherichia coli														
haemophilus influenzae		100 (1/1)			100 (1/1)		0 (0/1)					100 (1/1)	88 9	33 3
klebsiella sp								50 (1/2)	100 (2/2)				65 5	31 0
klebsiella pneumoniae														
klebsiella oxytoca														
proteus mirabilis														
pseudomonas aeruginosa														
campylobacter jejuni														
bacteroides fragilis														
stenotropomonas maltophilia					0 (0/1)	0 (0/1)		100 (1/1)	100 (1/1)	100 (1/1)			38 9	50 2
burkholderia cepacia					0 (0/1)	0 (0/1)			100 (1/1)	100 (1/1)			60 0	51 8
Average	77 1	100 0	100 0	81 3	40 0	25 0	46 4	61 3	100 0	100 0	100 0	100 0		
SD	14 7		0	26 5	54 8	50 0	45 5	42 4	0	0	0			

APPENDIX 6: Clinically significant community infection antibiogram

	# of isolates	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cephalexin	Cefotaxime	Cefuroxime	Ceftazidime	Ceftriaxone	Cefepime	Erythromycin	Clindamycin	Amikacin	Gentamicin	Tobramycin
GRAM POSITIVE																				
enterococcus faecalis	2	50 (1/2)	50 (1/2)				50 (1/2)													
enterococcus faecium	1	0 (0/1)	0 (0/1)				0 (0/1)												0 (0/1)	
staphylococcus aureus																				
staphylococcus epidermidis	2	50 (1/2)		100 (2/2)	100 (2/2)				100 (2/2)	100 (2/2)		100 (2/2)				50 (1/2)	50 (1/2)			
streptococcus agalactiae	2	100 (2/2)	100 (2/2)				100 (2/2)		100 (2/2)	100 (2/2)						100 (2/2)				
streptococcus pneumoniae	1	100 (1/1)		100 (1/1)	100 (1/1)											100 (1/1)	100 (1/1)			
streptococcus pyogenes	1	100 (1/1)	100 (1/1)				100 (1/1)		100 (1/1)	100 (1/1)						100 (1/1)				
streptococcus sp	3	100 (3/3)	100 (3/3)				100 (3/3)		100 (3/3)	100 (3/3)						100 (3/3)				
streptococcus viridians	1	100 (1/1)	100 (1/1)				100 (1/1)		100 (1/1)	100 (1/1)						100 (1/1)				
micrococcus sp	2	100 (2/2)	100 (1/1)				100 (1/1)		100 (2/2)	100 (2/2)						100 (2/2)				
corynebacterium sp	1																			
bacillus cereus																				
GRAM NEGATIVE																				
acinetobacter baumanii	1					0 (0/1)		100 (1/1)					0 (0/1)		100 (1/1)			0 (0/1)		0 (0/1)
acinetobacter lwoffi																				
alkaligenes sp	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)			0 (0/1)	0 (0/1)	0 (0/1)
alkaligenes faecalis	1		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
enterobacter sp																				
enterobacter cloacae																				
escherichia coli	4	0 (0/4)				0 (0/4)	33.3 (1/3)	50 (2/4)	75 (3/4)	66.7 (2/3)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	100 (4/4)			100 (4/4)	75 (3/4)	75 (3/4)
haemophilus influenzae																				
klebsiella sp.	2		0 (0/2)			0 (0/2)	0 (0/2)	100 (2/2)	0 (0/2)		0 (0/2)	0 (0/2)	0 (0/2)	0 (0/2)	100 (2/2)			0 (0/2)	0 (0/2)	0 (0/2)
klebsiella pneumoniae	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)			0 (0/1)	0 (0/1)	0 (0/1)
klebsiella oxytoca	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)			100 (1/1)	0 (0/1)	0 (0/1)
proteus mirabilis	1		0 (0/1)			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa	1					100 (1/1)		100 (1/1)					100 (1/1)		100 (1/1)			100 (1/1)		100 (1/1)
campylobacter jejuni	1		0 (0/1)								0 (0/1)			0 (0/1)					100 (1/1)	
bacteroides fragilis																				
stenotropomonas maltophilia																				
burkholderia cepacia																				
Average		70.0	39.3	100.0	100.0	33.3	45.8	94.4	59.6	95.6	21.9	34.4	52.8	21.9	100.0	92.9	75.0	53.6	41.7	41.7
SD		42.2	48.7	0	0	50	48.2	16.7	49.5	11.8	41.1	48.1	50.7	41.1	0	18.9	35.4	52.7	50.0	50.0

APPENDIX 3: Clinically significant community infection antibiogram

	# of isolates	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cephalexin	Cefotaxime	Cefuroxime	Ceftazidime	Ceftriaxone	Cefepime	Erythromycin	Clindamycin	Amikacin	Gentamicin	Tobramycin
GRAM POSITIVE																				
enterococcus faecalis	2	50 (1/2)	50 (1/2)				50 (1/2)													
enterococcus faecium	1	0 (0/1)	0 (0/1)				0 (0/1)												0 (0/1)	
staphylococcus aureus																				
staphylococcus epidermidis	2	50 (1/2)		100 (2/2)	100 (2/2)				100 (2/2)	100 (2/2)		100 (2/2)				50 (1/2)	50 (1/2)			
streptococcus agalactiae	2	100 (2/2)	100 (2/2)				100 (2/2)		100 (2/2)	100 (2/2)						100 (2/2)				
streptococcus pneumoniae	1	100 (1/1)		100 (1/1)	100 (1/1)											100 (1/1)	100 (1/1)			
streptococcus pyogenes	1	100 (1/1)	100 (1/1)				100 (1/1)		100 (1/1)	100 (1/1)						100 (1/1)				
streptococcus sp	3	100 (3/3)	100 (3/3)				100 (3/3)		100 (3/3)	100 (3/3)						100 (3/3)				
streptococcus viridians	1	100 (1/1)	100 (1/1)				100 (1/1)		100 (1/1)	100 (1/1)						100 (1/1)				
micrococcus sp	2	100 (2/2)	100 (1/1)				100 (1/1)		100 (2/2)	100 (2/2)						100 (2/2)				
corynebacterium sp	1																			
bacillus cereus																				
GRAM NEGATIVE																				
acinetobacter baumanii	1					0 (0/1)		100 (1/1)					0 (0/1)		100 (1/1)			0 (0/1)		0 (0/1)
acinetobacter lwoffi																				
alkaligenes sp	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1,	0 (0/1)	100 (1/1)			0 (0/1)	0 (0/1)	0 (0/1)
alkaligenes faecalis	1		0 (0/1)			100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
enterobacter sp																				
enterobacter cloacae																				
escherichia coli	4	0 (0/4)				0 (0/4)	33 3 (1/3)	50 (2/4)	75 (3/4)	66 7 (2/3)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	100 (4/4)			100 (4/4)	75 (3/4)	75 (3/4)
haemophilus influenzae																				
klebsiella sp.	2		0 (0/2)			0 (0/2)	0 (0/2)	100 (2/2)	0 (0/2)		0 (0/2)	0 (0/2)	0 (0/2)	0 (0/2)	100 (2/2)			0 (0/2)	0 (0/2)	0 (0/2)
klebsiella pneumoniae	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (3/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)			0 (0/1)	0 (0/1)	0 (0/1)
klebsiella oxytoca	1		0 (0/1)			0 (0/1)	0 (0/1)	100 (1/1)	0 (0/1)		0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)			100 (1/1)	0 (0/1)	0 (0/1)
proteus mirabilis	1		0 (0/1)			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa	1					100 (1/1)		100 (1/1)					100 (1/1)		100 (1/1)			100 (1/1)		100 (1/1)
campylobacter jejuni	1		0 (0/1)								0 (0/1)			0 (0/1)					100 (1/1)	
bacteroides fragilis																				
stenotropomonas maltophilia																				
burkholderia cepacia																				
Average		70.0	39 3	100 0	100 0	33 3	48 8	94 4	59 6	95 8	21 9	34 4	52 8	21 9	100 0	92 9	75 0	55 6	41 7	41 7
SD		42 2	48 7	0	0	50	48 2	16 7	49 5	11 8	41 1	48 1	50 7	41 1	0	18 9	35 4	52 7	50 0	50 0

APPENDIX 6: Clinically significant community infection antibiogram

	Rifampicin	Chloramphenicol	Vancomycin	Fucidin	Ciprofloxacin	Ofloxacin	Cotrimoxazole	Trimethoprim	Imipenem	Meropenem	Teicoplanin	Tetracycline	Average	SD
GRAM POSITIVE														
enterococcus faecalis			100 (2/2)										62.5	25.0
enterococcus faecium			100 (1/1)										20.0	44.7
staphylococcus aureus														
staphylococcus epidermidis	50 (1/2)		100 (2/2)	100 (2/2)			0 (0/2)	0 (0/2)					69.2	38.4
streptococcus agalactiae			100 (2/2)									50 (1/2)	93.8	17.7
streptococcus pneumoniae	100 (1/1)	100 (1/1)	100 (1/1)				0 (0/1)						88.9	33.3
streptococcus pyogenes			100 (1/1)									0 (0/1)	87.5	35.4
streptococcus sp			100 (3/3)									66.7 (2/3)	95.8	11.8
streptococcus viridans			100 (1/1)									100 (1/1)	100.0	0
micrococcus sp			100 (2/2)										100.0	0
corynebacterium sp														
bacillus cereus														
GRAM NEGATIVE														
acinetobacter baumanii					100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)			50.0	51.6
acinetobacter lwoffi														
alkaligenes sp					100 (1/1)	100 (1/1)		0 (0/1)	100 (1/1)	0 (0/1)			33.3	48.6
alkaligenes faecalis					100 (1/1)	100 (1/1)		0 (0/1)	100 (1/1)	0 (0/1)			55.6	51.1
enterobacter sp.														
enterobacter cloacae														
escherichia coli					100 (3/3)	100 (3/3)		50 (2/4)	100 (4/4)	100 (3/3)			68.7	31.2
haemophilus influenzae														
klebsiella sp.								100 (2/2)	100 (2/2)				26.7	45.8
klebsiella pneumoniae					100 (1/1)	100 (1/1)		100 (1/1)	100 (1/1)	100 (1/1)			38.9	50.2
klebsiella oxytoca					100 (1/1)	100 (1/1)		0 (0/1)	100 (1/1)	100 (1/1)			38.9	50.2
proteus mirabilis								100 (1/1)	100 (1/1)				93.8	25.0
pseudomonas aeruginosa					100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)			100.0	0
campylobacter jejuni		100 (1/1)			100 (1/1)	100 (1/1)			100 (1/1)				62.5	51.8
bacteroides fragilis														
stenotrophomonas maltophilia														
burkholderia cepacia														
Average	75.0	100.0	100.0	100.0	100.0	100.0	0	43.8	100.0	71.4		54.2		
SD	35.4	0	0		0	0	0	49.6	0	48.8		41.7		

APPENDIX 7:C[illegible]ally insignificant community infection antibiogram

	# of isolates	Penicillin	Ampicillin	Cloxacillin	Oxacillin	Piperacillin	Co-amoxiclav	Piptaz	Cefazolin	Cephalexin	Cefotaxime	Cefuro[illegible]	Ceftazidime	Ceftriaxone	Cefepime	Erythromycin	Clindamyc[illegible]	Amikacin	Gentamicin	Tobramycin
GRAM POSITIVE																				
enterococcus faecalis																				
enterococcus faecium																				
staphylococcus aureus																				
staphylococcus epidermidis	5	0 (0/5)		40 (2/5)	40 (2/5)				40 (2/5)	40 (2/5)		25 (1/4)				40 (1/4)	40 (2/5)			
streptococcus agalactiae																				
streptococcus pneumoniae																				
streptococcus pyogenes																				
streptococcus sp																				
streptococcus viridians																				
micrococcus sp																				
corynebacterium sp	1																			
bacillus cereus																				
GRAM NEGATIVE																				
acinetobacter baumanii																				
acinetobacter lwoffi																				
alkaligenes sp																				
alkaligenes faecalis																				
enterobacter sp.																				
enterobacter cloacae																				
escherichia coli																				
haemophilus influenzae	1		100 (1/1)				100 (1/1)				100 (1/1)	100 (1/1)		100 (1/1)						
klebsiella sp.																				
klebsiella pneumoniae																				
klebsiella oxytoca																				
proteus mirabilis	1		100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)			100 (1/1)	100 (1/1)	100 (1/1)
pseudomonas aeruginosa																				
campylobacter jejuni																				
bacteroides fragilis																				
[illegible]notropomonas maltophilia																				
burkholderia cepacia																				
Average		0	100.0	40.0	40.0	100.1	100.0	100.0	70.0	70.0	100.0	75.0	100.0	100.0	100.0	40.0	40.0	100.0	100.0	100.0
SD			0				0		42.4	42.4	0	43.3		0						

APPENDIX ' , *cally insignificant community infection antibiogram*

	Rifampicin	Chloramphen	Vancomycin	Fucidin	Ciprofloxacin	Ofloxacin	Cotrimoxazole	Trimethoprim	Imipenem	Meropenem	Teicoplanin	Tetracycline	Average	SD
GRAM POSITIVE														
enterococcus faecalis														
enterococcus faecium														
staphylococcus aureus														
staphylococcus epidermidis	80 (4/5)		100 (5/5)	80 (4/5)			20 (1/5)	20 (1/5)			100 (2/2)		47.5	31.5
streptococcus agalactiae														
streptococcus pneumoniae														
streptococcus pyogenes														
streptococcus sp														
streptococcus viridans														
micrococcu - sp														
corynebacterium sp														
bacillus cereus														
GRAM NEGATIVE														
acinetobacter baumanii														
acinetobacter lwotfi														
alkaligenes sp														
alkaligenes faecalis														
enterobacter sp														
enterobacter cloacae														
escherichia coli														
haemophilus influenzae		100 (1/1)			100 (1/1)		100 (1/1)					100 (1/1)	100.0	31.3
klebsiella sp														
klebsiella pneumoniae														
klebsiella oxytoca														
proteus mirabilis								100 (1/1)	100 (1/1)				100.0	24.0
pseudomonas aeruginosa														
campylobacter jejuni														
bacteroides fragilis														
stenotropomonas maltophilia														
burkholderia cepacia														
Average	80.0	100.0	100.0	80.0	100.0		60.0	60.0	100.0		100.0	100.0		
SD							56.6	56.6						

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Ntabe

CLEARANCE CERTIFICATE PROTOCOL NUMBER M 970819

PROJECT	Utilization analysis of antibiotics for the paediatric Intensive Care Unit
INVESTIGATORS	Mr M Ntabe
DEPARTMENT	Pharmacy, Medical School
DATE CONSIDERED	970829

DECISION OF THE COMMITTEE

Approved unconditionally

DATE 970829

CHAIRMAN. .....(Professor P E Cleaton-Jones)

c c Supervisor: Ms M Avent
Dept of Pharmacy, Medical School

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DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 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 to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE.....SIGNATURE .....

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES