FACULTY OF HEALTH SCIENCES

# A UTILISATION ANALYSIS OF ANTIMICROBIAL DRUGS IN THE INTENSIVE CARE UNIT OF THE JOHANNESBURG HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Pharmacy.

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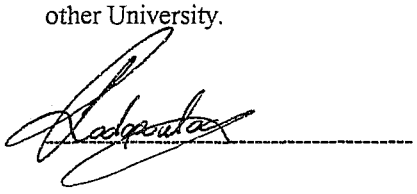
DECLARATION

I, George Rodopoulos, declare that this research report 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 in any other University.



4th day of May, 1998

*dedicated to Colleen- 'porcelina of the oceans blue'*

## ABSTRACT

A three month study to evaluate costs associated with the utilisation of antimicrobial drugs was undertaken in the Intensive Care Unit of the Johannesburg hospital. A total of 62 patients were entered in the study. Coagulase-negative *Staphylococcus* was found to be the most prominent bacterial pathogen (53%) followed by *Acinetobacter baumannii* (30.6%). *Candida albicans* was the most prominent yeast (53%). The study identified the use of catheters and mechanical ventilation as putative risk factors for the acquisition of infection in the ICU. The most frequently prescribed antimicrobial drug was gentamycin (21.7%). The acquisition cost of antimicrobial drugs was R 115 793.51 whilst the cost associated with the use of disposables for antimicrobial drug administration was R 15 075.67. Wastage costs were estimated to be R 3800. The total antimicrobial drug cost was therefore estimated to be R 134 669.18 ( i.e. R 2172.08 per patient). Five patients received inappropriate antimicrobial drug therapy. The cost of alternative treatment would have resulted in cost savings of not less than R 827.62. The information from this drug utilisation study helps to assess the current practice of antimicrobial use in the ICU setting and assists in developing future protocols which will optimise the allocation of available resources.

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## TABLE OF CONTENTS

## LIST OF FIGURES

## LIST OF TABLES

## INTRODUCTION

Intensive Care Units (ICU's) in hospitals offer medical assistance to the critically ill patient. This assistance often involves specialised care in respiratory, cardiac, trauma units and sometimes in units which offer care for multiple complications. No matter the nature of specialisation, all ICU's share an important clinical problem. Patients within these ICU's, are at a high risk of acquiring an opportunistic infection. When a patient is admitted into an ICU, the probability of that patient acquiring an infection is increased three-fold compared to a patient admitted to a general ward (Donowitz, 1982). The severity of the patient's underlying condition, duration of stay in hospital, the use of invasive procedures, contaminated life-support equipment, crowding and the prevalence of multiple resistant micro-organisms are just some of the predisposing factors for the prevalence of infections in the ICU (Chandrasekar, 1986).

Poly-antimicrobial drug therapy has almost become routine for the empirical treatment of life-threatening infections in these patients, even before the identification of the causative micro-organism(s) (Moellering, 1990). Although this approach may be beneficial, it has certain drawbacks. The most important of which is the emergence of secondary infection often caused by resistant bacteria and fungi.

One of the greatest concerns in an ICU is methicillin-resistant *Staphylococcus aureus*. The first outbreak of methicillin-resistant *Staphylococcus aureus* occurred in 1968 at Boston City Hospital (Barrett, 1968). As many as 93% of *Staphylococcus aureus* strains produce β-lactamase and are resistant to penicillin (Lyon, 1987). Methicillin-resistant

strains of *Staphylococcus aureus* are also characteristically resistant to many other antimicrobials including some tetracyclines, macrolides, lincosamides, chloramphenicol and some aminoglycosides. According to the EPIC study of 1992, 60% of staphylococcus strains were resistant to methicillin (Vincent et al., 1995).

The major concern is that by the turn of the next century all isolates of *Staphylococcus aureus* will be resistant to methicillin. This will leave no other option but to develop new anti-Staphylococcal drugs or to revert to much older drugs such as minocycline as the case was in 1994. In a study carried out at the King Faisal Specialist Hospital and Research Centre (Qadri et al., 1994), it was found that minocycline and vancomycin were able to inhibit all the isolates of methicillin-resistant *Staphylococcus aureus* tested, followed by ciprofloxacin (87%), clindamycin (54%) and chloramphenicol (51%). Fluoroquinolones had shown some promise originally, but between 1987 and 1989 there was a sharp rise in resistance from 3 to 60% at Temple University Hospital in Philadelphia (Wadsworth et al., 1992). It was recently shown that a combination of minocycline and rifampacin can be used orally to eradicate colonization by methicillin-resistant *Staphylococcus aureus* (Darouiche et al., 1991).

Intensive care units make use of a large variety of intravascular catheters such as peripheral venous and arterial catheters, central venous catheters and Swan-Ganz catheters. Central-venous catheters are responsible for almost 40% of catheter related blood-stream infections (Widmer, 1994). In the U.S., more than 5 million central venous catheters are inserted annually (Maki, 1991). In such cases, *Staphylococcus epidermidis*

is the most common blood-stream isolate followed by *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Jones, 1996).

Gram-negative micro-organisms which were thought to be well controlled are now re-emerging as pathogens of concern. Infections caused by Acinetobacter and Pseudomonas therefore remain a serious clinical problem within the critical-care setting. Multi-resistant strains of Acinetobacter have occurred since 1977 and there has been a noticeable increase in the number of outbreaks over the years, predominantly in intensive care units (Crowe, 1996). *Acinetobacter baumannii* is the most frequently reported species responsible for infections of the respiratory and urinary tract, as well as for meningitis and bacteremia in patients with severe underlying disease. In a retrospective study conducted in Hong-Kong, 80% of all Acinetobacter isolates were that of *Acinetobacter baumannii* (Siau et al., 1996). Evidence exists to show that they respond best when combination therapy is applied consisting of agents such as imipenem, ceftazidime, amikacin and the newer fluoroquinolones (Bergogne, 1995).

*Pseudomonas aeruginosa* was the third most frequently isolated nosocomial pathogen in the U.S. during the period 1986-1989 (Schaberg, 1991). The same frequency of isolation was reported in 1992 in Europe, during the large scale EPIC study involving 1417 intensive care units (Vincent et al., 1995). Due to this high degree of prevalence, *Pseudomonas aeruginosa* remains the most stubborn gram-negative pathogen in the ICU-setting and is the primary pathogen associated with the development of Ventilatory Assisted Pneumonia (VAP) (Spencer, 1994). As a result, the acquisition of a

pseudomonal infection is an important contributory factor for the high mortality rate within an ICU (Mosconi et al., 1991; Fagon et al., 1993).

Vancomycin tends to be one of the most effective drugs against gram-positive pathogens. However it is expensive, it requires intravenous administration and may cause severe adverse effects such as the red man syndrome (Sahai et al., 1990). Unfortunately the widespread use of vancomycin has led to the emergence of new resistant strains. Pallares et al. (1991) have found that a 161-fold increase in vancomycin usage occurred between 1991 to 1992 compared to vancomycin usage in 1977 (Pallares et al., 1991). Recent reports have indicated that pathogens such as *Staphylococcus haemolyticus*, have become less sensitive to vancomycin and certain strains have even shown resistance to another structurally similar glycopeptide, namely teicoplanin (Schwalbe, 1987; O'Hare, 1989).

Another clinical concern, is the increasing number of reports regarding resistance towards the third-generation cephalosporins, especially by gram-negative bacilli (Grassi, 1993). A new parenteral antimicrobial, cefepime, has been recently introduced to overcome the problem of emerging resistance. Cefepime is a fourth-generation cephalosporin with a broad spectrum of activity against both gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Thornsberry et al., 1993). Cefepime has also been found to be more active than ceftazidime against *Streptococcus pneumoniae* (Yee et al., 1993). It has also been demonstrated that cefepime administered at 1g twice daily, is comparable to ceftazidime which is administered at 1g three times daily in patients with pneumonia (McCabe et al.,

1996). Cefepime has also been shown to be more effective than ceftazidime in complicated and uncomplicated urinary tract infections. Holloway and Palmer (1996) demonstrated that a clinical response was achieved in 88% of cefepime patients with complicated urinary tract infection (UTI) compared with 79% of ceftazidime patients. For uncomplicated UTI, the clinical response rates were 100% and 87%, respectively (Holloway, 1996). Cefepime's wide range of activity against both gram-positive and gram-negative aerobic organisms, have made it a popular drug in the treatment of serious nosocomial infections.

In addition to the emergence of enhanced resistant bacterial pathogens, the incidence of yeast infections has also increased. *Candida albicans* was the fourth most commonly isolated pathogen from patients participating in the EPIC study (Vincent et al., 1995). The relatively high frequency of fungal/yeast recovery in ICU patients may be attributed to factors such as the empirical use of broad-spectrum antimicrobials drugs, catheter-related intervention, prolonged duration of stay in the ward and the state of the patient's immune system.

Treatment costs in ICUs are relatively high. In 1996, the cost per day per patient in a Canadian ICU was reported as being $ 1,508 ± 475 (1992 Canadian dollars) while the average cost per ICU stay was estimated at $ 7,520 ± 11,606 (Noseworthy et al., 1996). In the United States, costs per ICU-patient per ICU-stay range between $ 1,783 and $ 48,435 (Gyldmark, 1995). Technological and scientific advancement, the use of parenteral formulations and empirical poly-antimicrobial drug therapy are some of the

reasons for the major impact on costs within the critical care setting. Antimicrobial drugs alone, represent a significant portion of the total cost as regards the treatment and prevention of nosocomial infections; 6 to 21% of the pharmaceutical market and 3 to 25% of all prescriptions (Hillman, 1994). Furthermore, anti-infective drug therapy accounts for 30-50% of the total drugs bill in U.S. hospitals (Bootman, 1996). Generally intensive care units utilise a large number of antimicrobial drugs, and within these more than 80% of patients receive antimicrobials whether for the treatment or prophylaxis of infection (Gruneberg, 1994).

Antimicrobials are thus a good starting point for the investigation of an economic evaluation of patient care in ICU's. In the past, clinical studies of anti-infective drugs in ICU's focused mainly on therapeutic outcomes with little emphasis on cost effectiveness (Palladino, 1996). Those studies that attempted some form of economical evaluations simply examined the acquisition costs of the antimicrobial drugs. However, the determination of the true economic costs of such a programme is far more complicated and thus should also include 'hidden' costs associated with the use of these antimicrobial drugs such as the cost of disposables, wastage, and laboratory analyses.

This study attempts to monitor the utilisation of antimicrobial drugs in ICU's using pharmacoeconomic principles and provides recommendations, where possible, for cost effective measures to obtain better value for money. The main aim of the study was to analyse the costs associated with the use of antimicrobial drugs in the Intensive Care Unit of the Johannesburg hospital over a three-month period and in addition to identify the

prevalent micro-organisms in the ICU, the antimicrobial drug resistance and susceptibility patterns as well as putative risk factors associated with the acquisition of infection within the ICU.

This study therefore sets out to:

1. Calculate costs associated with the use of antimicrobials
2. To identify the prevalent micro-organisms in the ICU
3. To identify the antimicrobial resistance experienced in the study setting
4. To identify putative risk factors

## CHAPTER 2

## RESULTS - Patient characteristics

### 2.1 Patient demographics

The patient demographics for the 3-month study, 1 March - 31 May 1997, in ICU ward 576 of the Johannesburg hospital is shown in Table 2.1. Complete patient records consisting of age, gender, race, reason for admission, antimicrobial drug therapy, prevalent micro-organism, specimen types, invasive procedures, duration of stay in the ICU and outcome are summarised in Appendix A. The majority of the patients were Black (African) 37/62 (59.7%). The White and Indian population group comprised 23/62 (37.1%) and 2/62 (3.2%) of patients respectively. The majority of patients were female 37/62 (53.2%) with a mean age of 37 years (range 20-71).

**Table 2.1** Representation of patient demographics for the 3-month study

| | | |
|---|---|---|
| Total number of patients | 62 | |
| | Female | Male |
| Number of | 33 | 29 |
| Mean age of | 37 | 44 |
| | | |
| Total number of African patients | 37 | |
| | Female | Male |
| Number of | 24 | 13 |
| Mean age of | 34.8 | 41.2 |
| | | |
| Total number of White patients | 23 | |
| | Female | Male |
| Number of | 9 | 14 |
| Mean age of | 41.2 | 43.5 |
| | | |
| Total number of Indian patients | 2 | |
| | Female | Male |
| Number of | 1 | 1 |
| Mean age of | 23 | 65 |

2.2 Reasons for admission to the ICU.

Patients admitted to the ICU are shown in Table 2.2. Twenty four of the sixty two patients (38.7%) admitted to the ICU were post-operative patients transferred from surgical wards and comprised the largest group. A further sixteen patients (25.8%) were admitted with respiratory problems or complications thereof ( TB- 2 patients; COPD- 3 patients; Asthma- 3 patients; Pneumonia's- 8 patients). Six of the trauma patients (67%) were admitted as a result of motor vehicle accidents.

**Table 2.2** Reasons for admission to the ICU

| **Reason for admittance** | **Number of patients** |
|---|---|
| Post-operative complications | 24 |
| Renal failure | 3 |
| Cardiac complications | 1 |
| Airway complications i.e. | |
| - Asthma | 3 |
| - COPD | 3 |
| - Pneumonia | 8 |
| - TB | 2 |
| Haematological complications | 5 |
| Malaria | 2 |
| Trauma | |
| - Motor vehicle accidents | 6 |
| - Gun-shot or stab-wounds | 3 |
| Miscellaneous | 2 |

2.3 Duration of stay in the ICU.

Patient stay in the ward depended on the severity of the condition for admission (Table 2.3). The majority of patients remained in the ward for not longer than 10 days (64.5%). During the first ten days following admission mortality was high (40%) which was attributed to the severity of the patient's underlying pathology on admission to the ICU. Mortality rates declined for patients remaining in the ICU for up to 15 days- 3/11

(27.3%). Only two patients (3.2%) stayed in the ward for longer than 36 days and were transferred to general wards.

**Table 2.3** Duration of stay in the ICU

| Number of days in ward | Number of patients | Outcome: Transferred | Outcome: Died |
|---|---|---|---|
| 1-5 | 20 | 12 | 8 |
| 6-10 | 20 | 12 | 8 |
| 11-15 | 11 | 8 | 3 |
| 16-20 | 3 | 3 | 0 |
| 21-25 | 4 | 3 | 1 |
| 26-30 | 2 | 2 | 0 |
| 31-35 | 0 | 0 | 0 |
| 36 + | 2 | 2 | 0 |

2.4 Invasive procedures in the ICU-ward.

Invasive monitoring or procedures common in this ICU were urinary catheterisation (100%), and mechanical ventilation by means of endotracheal intubation (98.4%). In addition, central-venous catheters were inserted in 98.4% of patients. Table 2.4 is a representation of the most common types of invasive procedures patients were subjected to during the study.

**Table 2.4** Number of patients subjected to invasive procedures

| Invasive procedure/ therapy | Number of patients |
|---|---|
| Endotracheal tube | 61 |
| Intravenous central line | 61 |
| Arterial line | 59 |
| Urinary catheter | 62 |

All patients underwent invasive therapy during their stay in the ICU. The majority of patients (40%) underwent invasive therapy or monitoring for a period of 1-5 days.

Table 2.5 shows the duration and type of invasive procedure or monitoring, by patient number.

**Table 2.5** Number of patients with type and duration of invasive procedures

| Number of days | Number of patients on: ET-tube | IV-central | Art.-line | UR-catheter |
|---|---|---|---|---|
| 1-5 | 24 | 26 | 24 | 24 |
| 6-10 | 20 | 20 | 22 | 21 |
| 11-15 | 7 | 7 | 5 | 8 |
| 16-20 | 4 | 2 | 3 | 4 |
| 21-25 | 3 | 3 | 2 | 2 |
| 26-30 | 2 | 2 | 2 | 2 |
| 31-35 | 0 | 0 | 0 | 0 |
| 36-40 | 1 | 0 | 0 | 0 |
| 41-45 | 0 | 0 | 1 | 0 |
| 46-50 | 0 | 0 | 0 | 0 |
| 51+ | 0 | 1 | 0 | 1 |

Key: ET-tube = Endotracheal tube
IV-central = Central intravenous line
Art.-line = Arterial line
UR-catheter = Urinary catheter

## 2.5 Analysis of patient-microbiological data

A trend analysis of microbiological data, for the period 1 January 1994 to 31 May 1997, was undertaken for the ICU. The results shown in Table 2.6 suggest the increase in the prevalence of gram-positive infectious micro-organisms which are consistent with global trends (McGovan, 1991; Vincent et al., 1995).

It was observed that coagulase-negative *Staphylococcus* was the primary organism of concern and was isolated in up to 40% of patients. The other prevalent gram-positive organisms were *Staphylococcus aureus* and Streptococcus. Although the total number of

patient specimen isolates of the two latter micro-organisms has not been as high as that for Pseudomonas (Table 2.6), it has always been constant (Figure 2.1).

Gram-negative micro-organisms of concern were Acinetobacter and Pseudomonas. Acinetobacter has been the second most frequently isolated species of micro-organisms in the ICU, with *Acinetobacter baumannii* being the most common isolate of the species (Table 2.6).

**Table 2.6** Number of isolates of microbial species

| Species | Number of isolates |
|---|---|
| | |
| Coagulase negative *Staphylococcus* | 747 |
| *Acinetobacter* | 570 |
| *Pseudomonas* | 546 |
| *Enterobacter* | 452 |
| *Klebsiella* | 334 |
| *Enterococcus* | 327 |
| Coagulase positive *Staphylococcus* | 184 |
| *Streptococcus* | 87 |

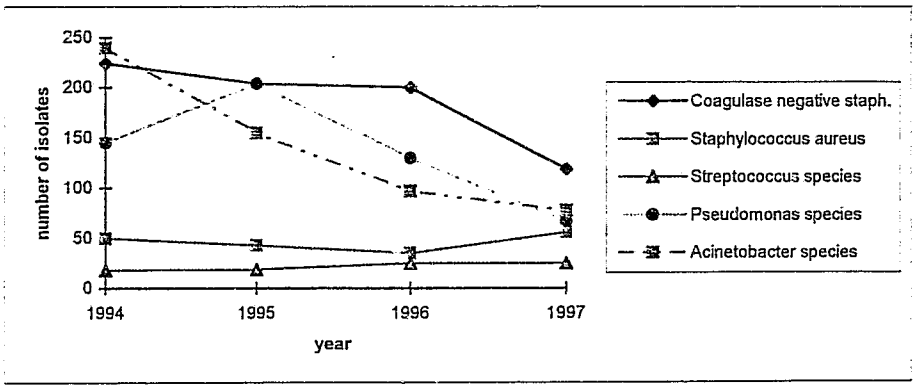


**Figure 2.1** Total number of isolates cultured for the ICU for the period 1994- May 1997

During the 3 month study (1 March - 31 May 1997) in the ICU, coagulase-negative *Staphylococcus* was the most frequently isolated micro-organism. Coagulase-negative

*Staphylococcus* was recovered from 33 of the 62 patients investigated (53%). This was followed by *Acinetobacter baumannii* (30.6%), *Staphylococcus aureus* (30.6%), *Enterococcus faecalis* (27.4%) and *Pseudomonas aeruginosa* (27.4%). There was a notable rise in the number of patients from whom *Acinetobacter baumannii* was recovered for the last month of the study. Table 2.7 shows the number of patients from whom various micro-organisms were recovered during the study.

More than 21% of all specimen types collected for bacterial culture tested positive for the presence of coagulase-negative *Staphylococcus*. This was followed by *Acinetobacter baumannii* (19.5%), *Staphylococcus aureus* (15.3%), *Pseudomonas aeruginosa* (11.1%) and *Enterococcus faecalis* (9.6%). Table 2.8 shows the number of specimen isolates that were cultured during the study.

**Table 2.7** Monthly analysis showing the number of patients from whom specified pathogens were recovered

| **Isolated pathogen** | **Number of patients isolated: March 1997** | **April 1997** | **May 1997** |
|---|---|---|---|
| *Acinetobacter baumannii* | 5 | 5 | 9 |
| *Acinetobacter lwoffii* | 2 | 1 | 0 |
| *Enterobacter cloacae* | 3 | 2 | 4 |
| *Enterococcus faecalis* | 7 | 5 | 5 |
| *Enterococcus faecium* | 1 | 1 | 1 |
| *Escherichia coli* | 2 | 2 | 2 |
| *Klebsiella* spp. | 3 | 2 | 3 |
| *Pseudomonas aeruginosa* | 5 | 5 | 7 |
| *Staphylococcus aureus* | 8 | 3 | 8 |
| Coagulase-negative *Staphylococcus* | 12 | 9 | 12 |
| *Streptococcus* spp. | 1 | 0 | 0 |

**Table 2.8** Monthly analysis listing the total number of specimen isolates cultured during the study period

| Isolated specimen | March 1997 | April 1997 | May 1997 |
|---|---|---|---|
| *Acinetobacter baumannii* | 12 | 14 | 20 |
| *Acinetobacter lwoffii* | 2 | 1 | 0 |
| *Enterobacter cloacae* | 4 | 2 | 8 |
| *Enterococcus faecalis* | 8 | 8 | 6 |
| *Enterococcus faecium* | 1 | 1 | 1 |
| *Escherichia coli* | 2 | 6 | 2 |
| *Klebsiella* spp. | 3 | 3 | 3 |
| *Pseudomonas aeruginosa* | 5 | 10 | 11 |
| *Staphylococcus aureus* | 15 | 10 | 10 |
| Coagulase-negative *Staphylococcus* | 21 | 15 | 29 |
| *Streptococcus* spp. | 1 | 0 | 0 |

## 2.6 Antimicrobial resistance and susceptibility patterns

After analysis of the microbiological data for the period of 1 January 1994 to 31 May 1997, the following results were obtained with regards to the antimicrobial resistance and susceptibility of the predominant micro-organisms in the ICU .

### 2.6.1 *Acinetobacter baumannii*

This organism proved to be a challenge to the ward not only because of its rising and persistent presence but also for effective antimicrobial drug treatment. *Acinetobacter baumannii* showed complete resistance to ampicillin (100%), cefazolin (100%), and high resistance to trimethoprim (99.4%), ceftriaxone (96.7%) and cefotaxime (96.3%). The organism was moderately resistant to ciprofloxacin (58.3%) and amikacin (55.7%) but was less resistant to tazobactam/piperacillin (34.5%) and markedly so to imipenem (1.7%).

Figure 2.2 is a representation of the antimicrobial drug resistance profile of *Acinetobacter baumannii* for the time period 1 January 1994 - 31 May 1997.

2.6.2 *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* showed a broad pattern of resistance with total resistance to ampicillin, cefazolin, cinoxacin, and high resistance to trimethoprim (99.1%). Moderate to low resistance was found against gentamycin (40%), tobramycin (32%) ciprofloxacin (28%) and to amikacin (26.5%). The introduction of cefepime showed promising activity against this organism with resistance being as low as 18.8% (Figure 2.3).

2.6.3 Coagulase negative *Staphylococcus*

Coagulase negative *Staphylococcus* was highly resistant to ampicillin (97.9%), penicillin (96.2%), erythromycin and clindamycin (87.3%). Moderate resistance was shown against chloramphenicol (58%) and fusidic acid (24.8%) whereas total susceptibility was shown to vancomycin (Figure 2.4).

2.6.4 *Staphylococcus aureus*

A very similar pattern of antimicrobial resistance was found to exist between *Staphylococcus aureus* and coagulase-negative *Staphylococcus*. Again there was high resistance to ampicillin (97.5%), and penicillin (95%) with moderate resistance to erythromycin and clindamycin (45%). The most valuable antimicrobials against this organism proved to be trimethoprim, chloramphenicol and vancomycin, the latter being the most useful as all strains tested were susceptible to it (Figure 2.5).

**Figure 2.2** *Acinetobacter baumannii* resistance profile for the period of January 1994 - May 1997 for the ICU

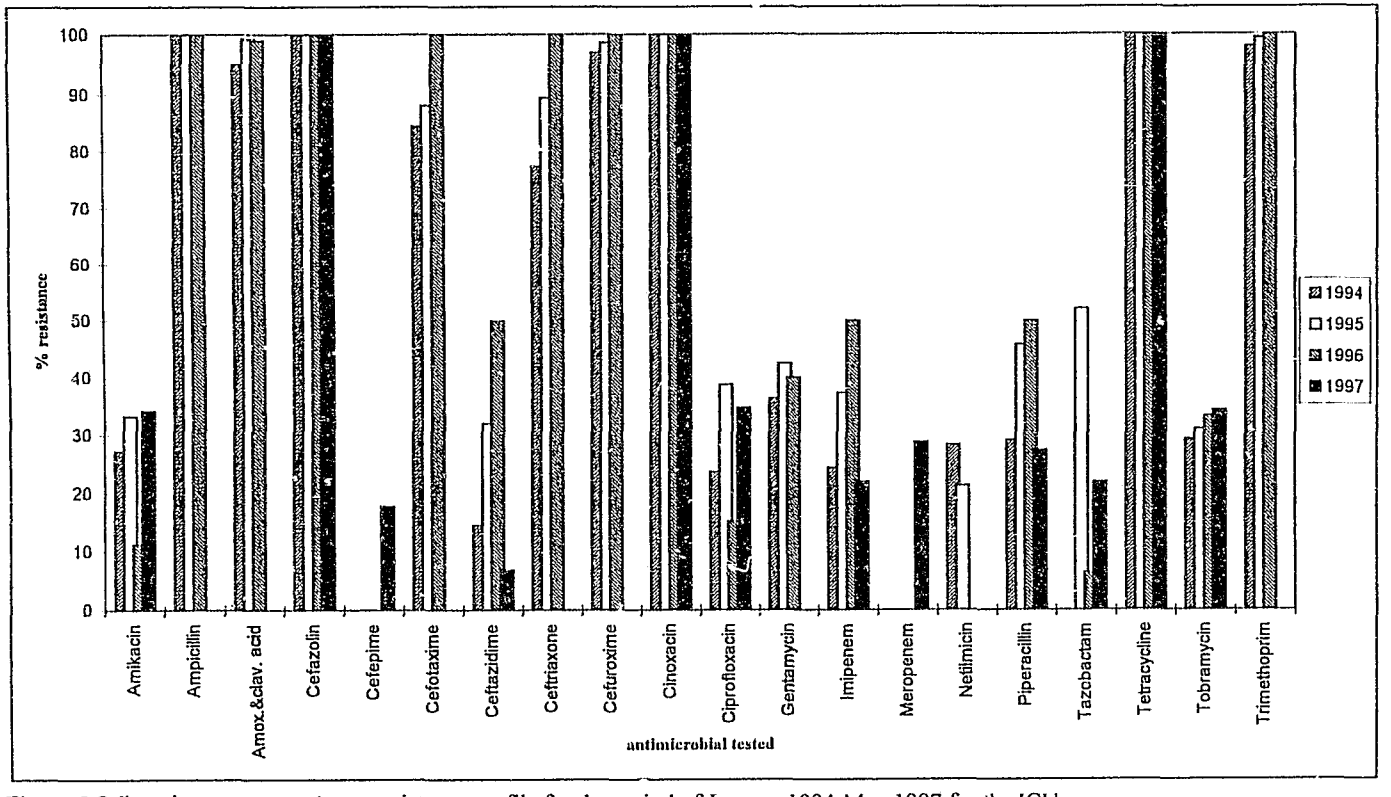


**Figure 2.3** *Pseudomonas aeruginosa* resistance profile for the period of January 1994-May 1997 for the ICU

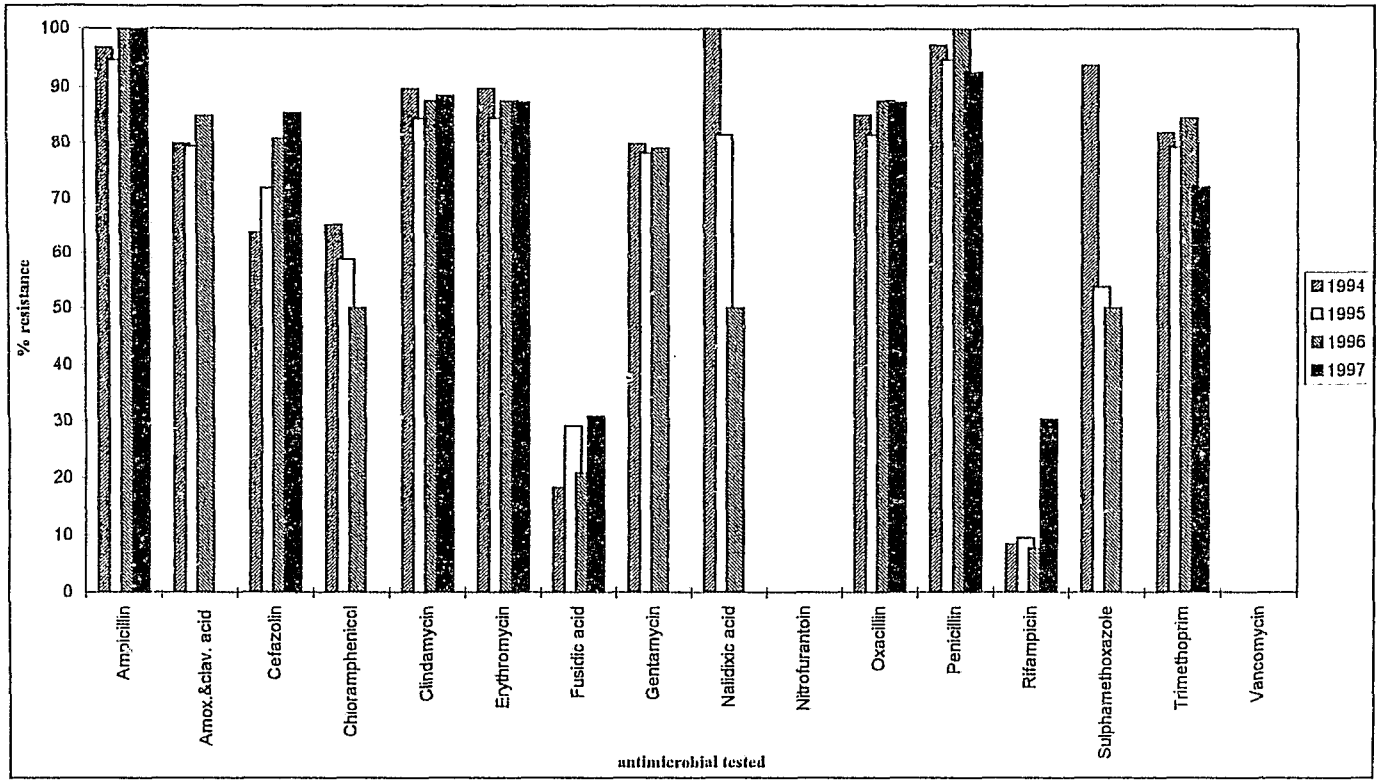


**Figure 2.4** Coagulase-negative *Staphylococcus* resistance profile for the period January1994-May 1997 for the ICU

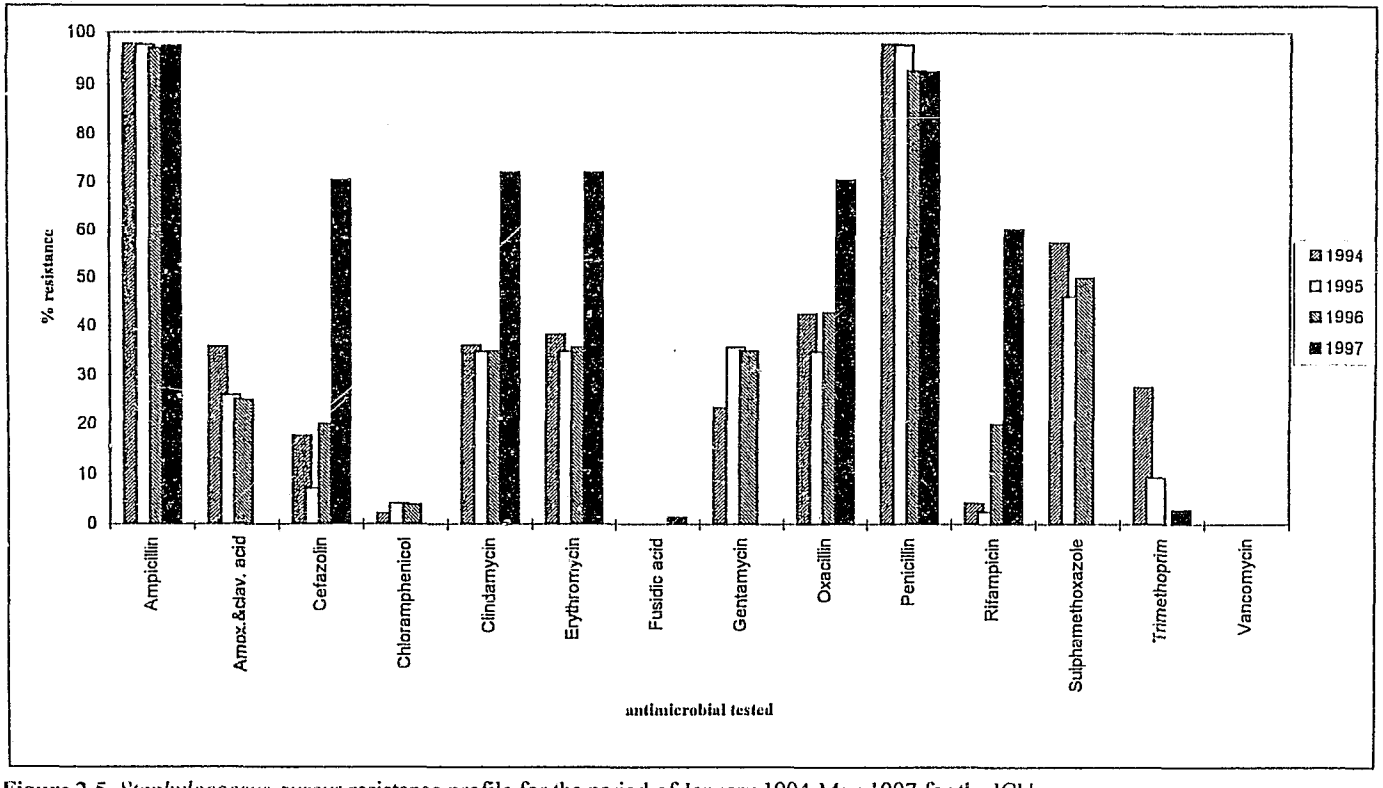


**Figure 2.5** *Staphylococcus aureus* resistance profile for the period of January 1994-May 1997 for the ICU

2.7 The appropriateness of antimicrobial drug therapy

All the patients investigated received one or more antimicrobial agents for the treatment of an infection or for prophylaxis. Analysis of the patient laboratory data revealed that only 5 out of 62 patients did not receive appropriate antimicrobial drug therapy. In three of these patients, *Staphylococcus epidermidis* was not treated with a recommended antimicrobial such as vancomycin (Sanford et al., 1997). In the other two patients, from whom *Acinetobacter baumannii* had been recovered, treatment with imipenem or piperacillin/tazobactam (Sanford et al., 1997) had not taken place. One of the latter two patients died. The patient's death was attributed to the severity of the patient's primary reason for admission: cerebral malaria. However, the majority of the patients were provided with appropriate antimicrobial drugs.

Table 2.9 is a summary of the five patients for whom inappropriate antimicrobial drug therapy was prescribed. The table also shows the recommended antimicrobial drug therapy that should have been implemented for each individual patient. The five patients are represented as patient numbers 12, 23, 46, 47 and 60 according to their order of admission into the ICU. The cost-implications of this inappropriate antimicrobial drug therapy is discussed and analysed in chapter 3.

**Table 2.9** Inappropriate versus appropriate antimicrobial drug prescribing in five ICU patients

| Patient | Prescribed antimicrobial drug therapy | Prevalent micro-organism(s) | Recommended antimicrobial drug therapy |
|---|---|---|---|
| 12 | Cefuroxime 750mg tds | Coag.neg.Staph.; *S.aureus* | Replace with Vancomycin 1g IVI |
| 23 | Ceftriaxone 1g bd | *A. baumannii* | Add Imipenem 500mg qid or Piperacillin/tazobactam tds |
| 46 | Cefuroxime 750mg tds | Coag.neg. Staph.; *S.aureus* | Replace with Vancomycin 1g IVI |
| 47 | Ciprofloxacin 100mg bd Piperacillin/tazobactam tds Gentamycin 240mg | Coag.neg.Staph.; *A. baumannii* | Replace with Vancomycin 1g IVI and Imipenem 500mg qid or Piperacillin/tazobactam tds |
| 60 | Amoxacillin & clav. acid Gentamycin 240mg Ciprofloxacin 100mg bd Cefepime 1g bd | *A. baumannii* | Replace with Imipenem 500mg qid or Piperacillin/tazobactam tds |

Refer to Appendix A for a complete individual patient summary of prevalent organisms and associated antimicrobial drug therapy.

## 2.8 Putative risk factors for the acquisition of infection within the ICU

A further objective of this study was to identify putative risk factors within the environment of an ICU for the acquisition of bacterial and fungal infection with the focus on invasive procedures such as catheterisation and mechanical ventilation. The study did not contain a large enough number of subjects to establish a clear relationship between any one risk factor and the acquisition of an infection. For this reason only putative risk factors for the acquisition of infection within the ICU could be identified.

### 2.8.1 The possible acquisition of infection resulting from the use of catheters

Gram-positive cocci are responsible for approximately 50% of all nosocomial infections (Sacho, 1990). This is mainly attributed to the emergence of methicillin resistant

*Staphylococcus aureus* and to the recent emergence of coagulase-negative *Staphylococcus* as a major nosocomial pathogen, especially in prosthetic device associated infections. The use of invasive therapy or monitoring is common practice in ICU's.

The ICU investigated was no exception, as almost all of the patients during the study were undergoing some kind of invasive therapy or monitoring. Of these patients 98.4% underwent central line catheterisation while 95.2% underwent arterial line catheterisation (Table 2.4).

Coagulase-negative *Staphylococcus* proved to be a prominent micro-organism in this particular ICU. Of the 62 patients investigated, 33 patients (53%) tested positive for the presence of coagulase-negative *Staphylococcus* through specimen culture. Over a three month period 67%, 56% and 42% of patients per month, respectively, had catheter tips infected with coagulase-negative *Staphylococcus* (Table 2.10).

**Table 2.10** Number of patients with coagulase negative *Staphylococcus* infection recovered from specimen type

| **Specimen type** | **March 1997** patients (12) | **April 1997** patients (9) | **May 1997** patients (12) |
|---|---|---|---|
| Blood culture | 3 (25%) | 2 (22%) | 2 (17%) |
| Swab material | 4 (33%) | 4 (44%) | 6 (50%) |
| Catheter tips | 8 (67%) | 5 (56%) | 5 (42%) |

In addition, over the same period, 25%, 22% and 17% of patients, respectively, had positive blood cultures for coagulase-negative *Staphylococcus*.

2.8.2 Endotracheal intubation as a possible risk factor for the development of pneumonia

The most common cause of nosocomial pneumonia are gram-negative bacilli, which account for more than 50% of cases. Although sputum is easily obtained and remains a popular specimen for the diagnosis of pneumonia, it should be borne in mind that these organisms are also commonly found in the upper respiratory tract without causing any infection.

*Acinetobacter baumannii* and *Pseudomonas aeruginosa* were prominent micro-organisms within this ICU. *Acinetobacter baumannii* was the second most commonly isolated organism after coagulase-negative *Staphylococcus*. *Acinetobacter baumannii* was recovered from 30.6% of patients while *Pseudomonas aeruginosa* was recovered from 27.4% of patients during the study. The micro-organisms were mainly recovered from patient sputum samples and from bronchoalveolar lavage and washings (Table 2.11).

**Table 2.11** Number of patients from whom *A. baumannii* and *P. aeruginosa* were recovered from various specimen types

| Specimen type | March 1997 | | April 1997 | | May 1997 | |
|---|---|---|---|---|---|---|
| | A. baum. | P. aerug | A. baum. | P. aerug | A. baum. | P. aerug |
| Sputum | 3 | 1 | 2 | 1 | 6 | 4 |
| Bronchoalveolar lavage | 1 | 1 | 5 | 1 | 1 | 0 |
| Swab | 1 | 2 | 0 | 0 | 3 | 0 |
| Catheter tip | 1 | 0 | 0 | 0 | 3 | 0 |
| Blood culture | 1 | 0 | 0 | 1 | 0 | 0 |
| Bronchial washing | 1 | 0 | 1 | 0 | 0 | 0 |

2.8.3 Yeast infection in the ICU

Although a yeast, *Candida* superseded all bacterial pathogens in the ICU ward with *Candida albicans* being the most frequently isolated member of the species. During the period January 1994 to May 1997, 269 patients were found to have *Candida albicans* cultured from one or more of their specimen sites (Table 2.12).

**Table 2.12** Number of patients and specimen sites/types from which *C. albicans* was cultured for the period January 1994- May 1997

| | 1994 | 1995 | 1996 | 1997 (Jan-May) |
|---|---|---|---|---|
| No. of patients | 81 | 84 | 53 | 51 |
| No. of specimens | 226 | 196 | 149 | 141 |

During the 3 month study the following results were obtained with regards to *Candida albicans* and its occurrence in the ICU ward (Table 2.13).

**Table 2.13** Number of patients and specimen sites or types from which *C. albicans* was cultured for the period March-May 1997

| | March 1997 | April 1997 | May 1997 | Total |
|---|---|---|---|---|
| No. of patients | 9 | 13 | 11 | 33 |
| No. of specimens | 18 | 38 | 31 | 87 |

A retrospective analysis of computerised data supplied by the SAIMR was used to identify the specimen types from which *Candida albicans* was most frequently isolated or cultured during the 3-month study. It was found that bronchoalveolar lavage (17.2%), rectal swabs (11.5%), bronchial washings (9.2%), urine (9.2%) and sputum (9.2%) were the specimen types from which *Candida albicans* was most frequently isolated or cultured.

## CHAPTER 3

## 3. Costs associated with antimicrobial usage during the 3-month study

### 3.1 Antimicrobial drug usage in the ICU during the 3 month study

All antimicrobials prescribed during the study were recorded on a daily basis. Figure 3.1 shows the total number of anti-infective dose units prescribed for the period 1 March 1997 to 31 May 1997. Gentamycin was the most frequently prescribed antimicrobial (21.7%).

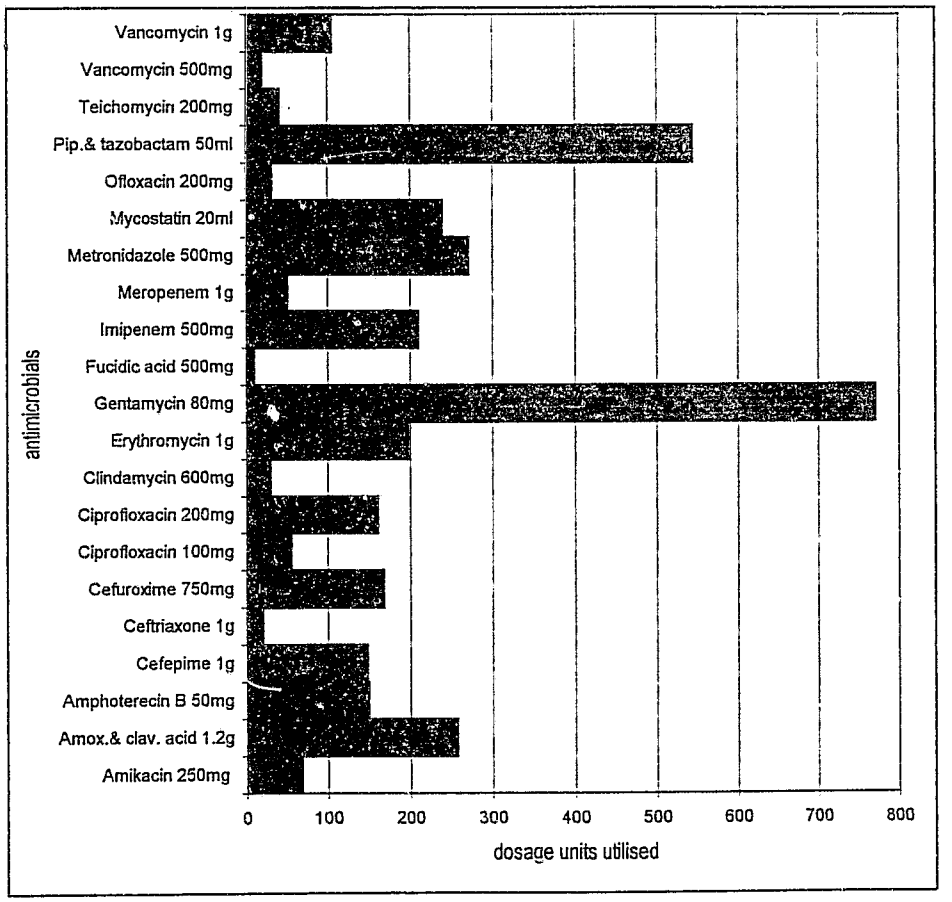


**Figure 3.1** Antimicrobial dosage units utilised during the 3-month study

This was followed by tazobactam/piperacillin (16.3%), amoxacillin/clavulanic acid (7.3%), imipenem (5.9%) and erythromycin (5.6%) The antiprotozoal, metronidazole (7.7%) and the antifungals nystatin (6.7%) and amphoterecin B (4.2%) were also prescribed.

3.2 Acquisition costs

The total acquisition cost for the antimicrobial drugs was estimated to be R 102 000.00. When metronidazole, nystatin and amphoterecin B were included, the total anti-infective acquisition cost was estimated to be R115 793.51 for the 3 month period. All antimicrobial drug acquisition prices and of disposables were obtained from the main dispensary of the Johannesburg Hospital and were quoted as per 1997 South-African rands. Table 3.1 shows the unit costs of the anti-infectives used in the ICU.

**Table 3.1** Anti-infectives used in the ICU and their acquisition costs

| **Antimicrobial / Anti-infective** | **Acquisition costs (Rands)** |
|---|---|
| Amikacin 2ml ampoule | 397.12 |
| Amphoterecin B 50mg | 11066.12 |
| Amoxacillin & clavulanic acid 1.2g vial | 3573.15 |
| Ciprofloxacin 100mg vial | 6275.75 |
| Ciprofloxacin 200mg vial | 10296.09 |
| Cefepime IV 1g vial | 4397.11 |
| Ceftriaxone 1g vial | 1475.80 |
| Cefuroxime 750mg vial | 1769.02 |
| Clindamycin 600mg ampoule | 545.20 |
| Erythromycin 1g vial | 8985.87 |
| Fucidic acid 500mg | 821.37 |
| Gentamycin 80mg ampoule | 971.70 |
| Imipenem 500mg vial | 21566.60 |
| Metronidazole 500mg | 902.01 |
| Mycostatin 20ml | 758.87 |
| Ofloxacin 200mg vial | 2861.12 |
| Tazobactam & piperacillin 50ml vial | 29831.20 |
| Teicoplanin 200mg vial | 2093.46 |
| Vancomycin 500mg vial | 772.20 |
| Vancomycin 1g vial | 6433.75 |
| | **R 115793.51** |

Figure 3.2 is a pie-chart presentation of the antimicrobial acquisition costs expressed as a percentage.

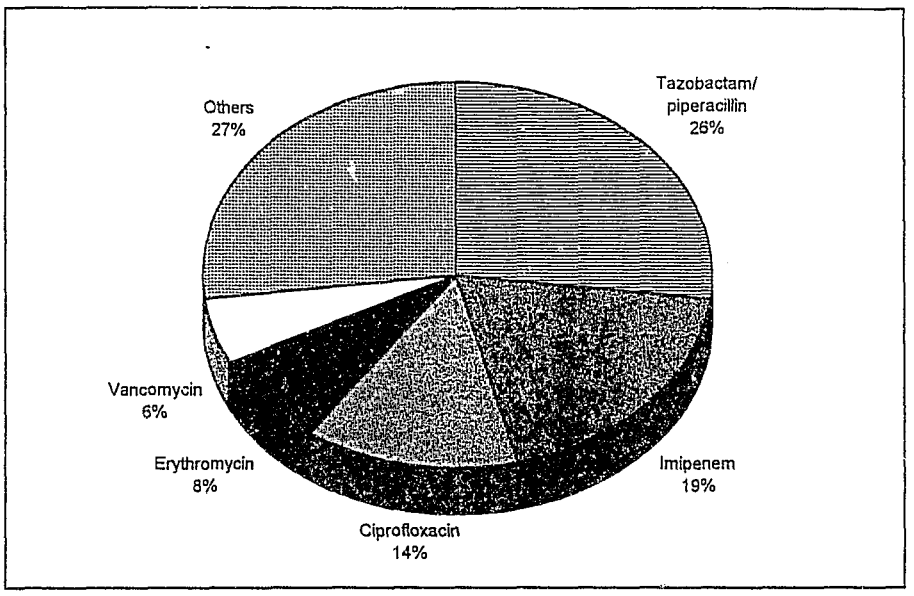


**Figure 3.2** Antimicrobial acquisition costs shown as a percentage for the 3 month study

3.3 Patient groups and the cost of antimicrobial drug therapy

Upon admission to the ICU, patients were classified according to one of the following groups: post-operative, trauma, respiratory, cardiac, renal, haematology or miscellaneous (Table 2.2). All patients investigated in the study received antimicrobials and the acquisition costs per group and per patient per group are shown in Table 3.2. Antimicrobial drug therapy for the patient group with respiratory problems was estimated at R 51 498.14 and accounted for 45% (Figure 3.3) of the total antimicrobial acquisition

cost. Antimicrobial drug therapy for the groups of post-operative and trauma patients accounted for 26% and 19% of the total antimicrobial acquisition cost, respectively.

**Table 3.2** Antimicrobial drug costs associated with the different patient groups in the ICU

| **Patient group** (n=62) | | **Antimicrobial drug cost per group (in Rands )** | **Average cost per patient per group (in Rands)** |
|---|---|---|---|
| Post-operative | 24 | 30011.74 | 1250.49 |
| Trauma | 9 | 22379.72 | 2486.64 |
| Respiratory | 16 | 51498.14 | 3218.63 |
| Cardiac | 1 | 2021.05 | 2021.05 |
| Renal | 3 | 3269.37 | 1089.79 |
| Haematology | 7 | 5964.24 | 852.03 |
| Miscellaneous | 2 | 699.68 | 349.84 |

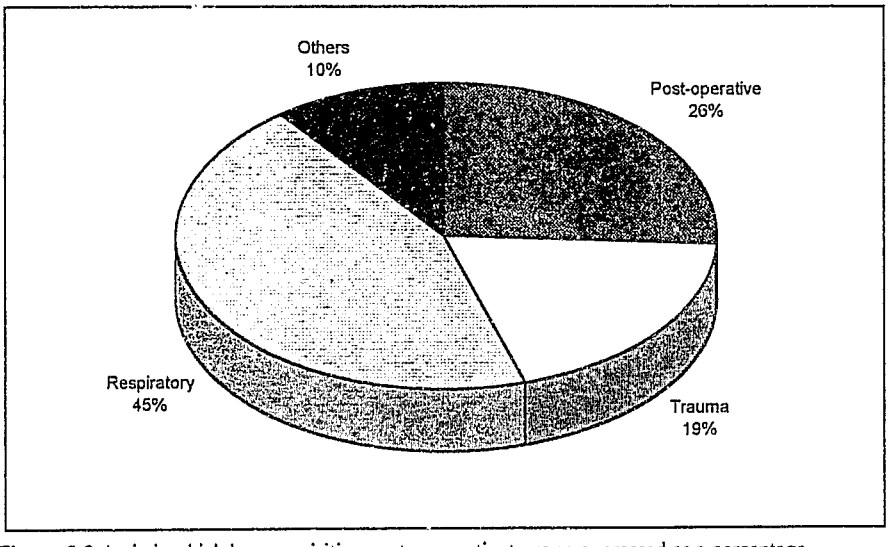


**Figure 3.3** Antimicrobial drug acquisition costs per patient group expressed as a percentage

3.4 Wastage costs

Of the 2154 units of anti-infectives prescribed during the 3 months of the study, 2043/2338 (87%) units were collected. Nursing staff were informed of the study and were requested to collect all 'used' antimicrobial vials in the collection units provided. These collection units were also clearly labelled and positioned at the working area where drug preparation took place. However, 13% of the prescribed antimicrobial drug units were not discarded appropriately, i.e. into the collection units provided. The above was a problem more frequently seen over weekends when the permanent or week day staff were temporarily replaced by the weekend staff. All the antimicrobial vials in these collection units were retrieved on a daily basis. The contents of these units were accurately measured, and the volumes collected were converted to a monetary figure which in turn was compared to the total acquisition cost of these antimicrobial drugs.

The study therefore defined the wastage cost as the cost associated with the volume of antimicrobial drugs that was discarded following preparation and consequently, patient administration.

The antimicrobial wastage according to the volume collected from the discarded containers/units is shown in Table 3.3. The monetary value due to wastage was estimated to be R 3800 and represents 3.3% of the total anti-infective acquisition cost. The antimicrobial which accounted for the greatest wastage was amphoterecin B representing 21% of the total wastage cost (Figure 3.4).

**Table 3.3** Antimicrobial/anti-infective units prescribed and % of those collected

| Antimicrobial / Anti-infective | Total units prescribed | Total units collected | % collected |
|---|---|---|---|
| Amphoterecin B 50mg | 169 | 137 | 81.0% |
| Amoxacillin & clavulanic acid 1.2g vial | 287 | 268 | 93.4% |
| Ciprofloxacin 100mg vial | 65 | 59 | 91.0% |
| Ciprofloxacin 200mg vial | 177 | 111 | 63.0% |
| Cefepime IV 1g vial | 167 | 155 | 93.2% |
| Ceftriaxone 1g vial | 20 | 11 | 55.0% |
| Cefuroxime 750mg vial | 187 | 157 | 84.0% |
| Erythromycin 1g vial | 207 | 147 | 71.0% |
| Imipenem 500mg vial | 220 | 204 | 92.8% |
| Meropenem 1g vial | 51 | 51 | 100% |
| Ofloxacin 200mg vial | 32 | 30 | 94.0% |
| Tazobactam & piperacillin 50ml vial | 560 | 532 | 95.0% |
| Teicoplanin 200mg vial | 41 | 41 | 100% |
| Vancomycin 500mg vial | 30 | 24 | 80.0% |
| Vancomycin 1g vial | 125 | 116 | 93.0% |

Tazobactam/piperacillin, erythromycin and vancomycin accounted for 19.3%, 10.2%, 10.2% of the collected wastage respectively (Figure 3.4).

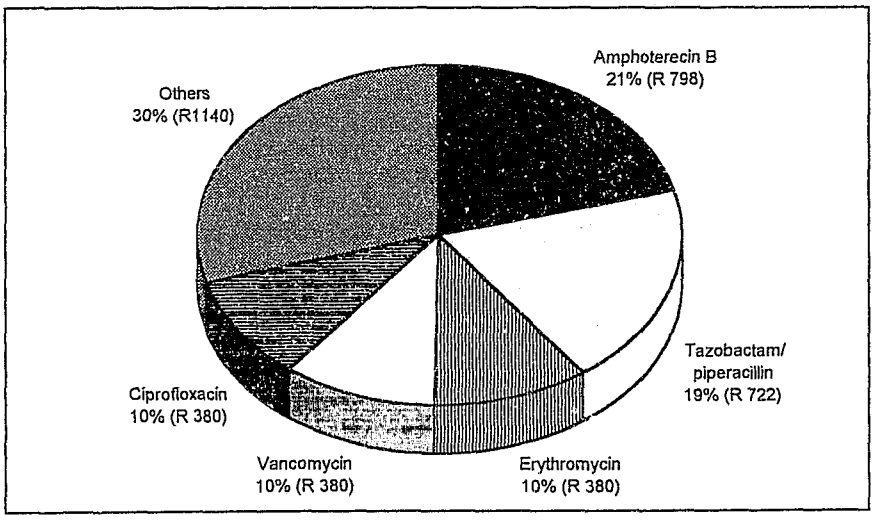


**Figure 3.4** Costs attributed to antimicrobial drug wastage in the ICU

A total of 149 dose units of amphoterecin B were prescribed in contrast to 543 units of tazobactam/piperacillin. However, amphoterecin wastage was greater. The reason being that patients were not always prescribed the full 50mg dose which corresponds to the constituted volume of an individual unit of amphoterecin B (see Appendix A). The remainder of the drug was then discarded, thus accounting for the considerable wastage of amphoterecin B.

3.5 Costs associated with the use of disposables for antimicrobial administration

Disposables such as syringes, needles, saline 'mini-bags', and IV droppers are some of the many accessories associated with the administration of antimicrobial drugs within an ICU. During the 3-month study a record was kept of the disposables used in conjunction with the antimicrobials administered. The following disposables were of major use within the ward: 50ml saline 'mini-bags', 15ml IV droppers, 5% dextrose 'mini-bags', 20ml syringes with needles, and alcohol swabs. The 15ml IV droppers were changed after 1 week of continuous use and were used in the administration of nearly all antimicrobials. Teicoplanin was the only antimicrobial that was not diluted i.e. using saline, and was administered intramuscularly. The analysis of the utilisation of disposables is shown in Table 3.4.

**Table 3.4** Presentation of the number of disposables used and their associated costs

| Disposables | Units recorded | Total cost (in Rands) | % of total disposable cost |
|---|---|---|---|
| 15 ml IV dropper | 121 | 506.99 | 3.36% |
| 50 ml saline 'mini-bag' | 1608 | 10371.60 | 68.80% |
| 5% dextrose 'mini-bag' | 400 | 2576.00 | 17.08% |
| 20 ml syringe with needle | 2008 | 1526.08 | 10.12% |
| Alcohol swabs | 2010 | 95.00 | 0.64% |
| Total Costs | | **R 15075.67** | |

For the 3 month study, it was found that the ICU used approximately 8155 units of disposables associated with the administration of antimicrobials at a total cost of R 15 075.67.

3.6 The cost-implications of inappropriate antimicrobial drug therapy in the ICU

Table 3.5 analyses the cost of antimicrobial drug therapy of the five patients in whom it was inappropriate and the costs associated if the appropriate antimicrobial drugs were to have been prescribed. The total cost of antimicrobial drug therapy for these five patients was R 5455.29. It was estimated that if appropriate antimicrobial drug therapy had been implemented the total cost for these five patients would have been either R 4600 or R 9700. The two values differ depending on the drug of choice for treating *Acinetobacter baumannii*. If imipenem were to have been the drug of choice, for the same duration of therapy, then the total cost for these five patients would have been R 4627.67 i.e. R 827.62 less than the prescribed antimicrobial drug therapy. If the combination of

piperacillin and tazobactam were to have been the drug of choice then the total cost for these five patients would have been R 9738.49 i.e. R 4283.20 more than the prescribed antimicrobial drug therapy. In this particular ICU, the combination of piperacillin and tazobactam was more frequently prescribed than imipenem i.e. 560 versus 220 dosage units prescribed (Table 3.3). However, *Acinetobacter baumannii* in this ICU was more susceptible to imipenem than to the combination of piperacillin and tazobactam i.e. 1.7% versus 34.5% (Figure 2.2). Therefore, imipenem should prove to be a more cost-effective drug in the long-run, for the treatment of serious gram-negative infections such as *Acinetobacter baumannii.*

It is important not to overlook the additional costs associated with the prescribing of inappropriate antimicrobial drugs. Inappropriate antimicrobial drug therapy may prolong a patient's stay in the ICU/hospital and further increase hospital costs (Spencer, 1994). In this study four surviving patients were not treated with the appropriate antimicrobial drugs thus they remained in the system for longer than necessary. It is therefore necessary that when a patient is admitted into the ICU, an effort should be made to identify possible infectious micro-organisms (through specimen culture) thus allowing for rapid and accurate antimicrobial drug therapy.

**Table 3.5** The difference in acquisition cost between the prescribed and the recommended antimicrobial drug therapies in five ICU patients

| Patient | Prescribed Antimicrobial therapy | Days in ICU | Cost of prescribed antimicrobial therapy (Rands) | Recommended antimicrobial drug therapy | Cost of recommended antimicrobial therapy (Rands) |
|---|---|---|---|---|---|
| 12 | Cefuroxime 750 tds<br>Mycostatin protocol | 1 | 28.38 | Replace with Vancomycin 1g IVI | 51.47 |
| 23 | Ceftriaxone 1g bd | 3 | 442.74 | Add Imipenem 500mg qid<br>or<br>Piperacillin./tazobactam tds | 1619.10<br><br>922.35 |
| 46 | Cefuroxime 750mg tds | 5 | 141.90 | Replace with Vancomycin 1g IVI | 257.35 |
| 47 | Ciprofloxacin 100mg bd<br>Piperacillin/tazobactam tds<br>Gentamycin 240mg | 7 | 2366.07 | Replace with Vancomycin 1g IVI with either<br>Imipenem 500mg qid<br>or<br>Piperacillin/tazobactam tds | <br><br>3105.13<br><br>1478.96 |
| 60 | Gentamycin 240mg<br>Amox./clav acid 1.2g tds<br>Ciprofloxacin 100mg bd<br>Cefepime 1g bd | 12 | 2476.20 | Replace with Imipenem 500mg qid<br>or<br>Piperacillin/tazobactam tds | 4705.44<br><br>1917.72 |
| **Total** | | | **R 5455.29** | | **R 9738.49** (if Imipenem is the drug of choice)<br>or<br>**R 4627.67** (if Piperacillin/tazobactam is the drug of choice). |

## CHAPTER 4

## DISCUSSION

### 4.1 The rise of gram-positive micro-organisms and the changing patterns of antimicrobial drug resistance

The rise of gram-positive infectious micro-organisms is a universal problem and South-Africa is no exception. In the past, gram-positive pathogens were effectively treated with just a small armament of drugs allowing for major anti-infective gram-negative drug development to take place. However, after the introduction of a new anti-infective drug the problem of over-usage, and in some cases, inappropriate selection for treating certain infections often followed. This mismanagement of anti-infective drug utilisation has allowed micro-organisms to develop enhanced resistance through various mechanisms therefore resulting in treatment failure and ultimately elevated costs for both the hospital and the patient.

Coagulase negative *Staphylococcus* was the most frequently isolated micro-organism in ICU ward 576, with over half of the study group investigated testing positive for its presence. Other gram-positive micro-organisms showing strong presence were *Staphylococcus aureus* and *Enterococcus faecalis*. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were the most commonly isolated gram-negative micro-organisms.

The notable increase in the recovery of *Acinetobacter baumannii* from patients during the last month of the study is of concern. Although these patients were isolated from other

patients in the ICU, it was also observed, on occasion, that not all ICU-personnel were taking the necessary precautions in preventing the possible cross-contamination of this organism to other patients in the ward. Acinetobacter is an opportunistic nosocomial pathogen which has become a difficult organism to eliminate. Therefore, it is essential that all ICU-personnel place emphasis on the importance of hand-washing before and after contact with the patient, including contact with the patient's records, and the wearing of disposable gowns and footwear. Due to the main objectives of the study adherence to hand-washing by ICU-personnel on a 24-hour basis was not monitored, hence, this practice or lack thereof was only noted occasionally.

Over the last 40 years staphylococci have acquired remarkable resistance mechanisms to nearly all newly introduced antimicrobials. Staphylococcal resistance to the penicillins is regarded today as a rule with resistance being as high as 70-90% (Jones, 1994). Vancomycin or teicoplanin remain the drugs of choice especially for serious staphylococcal infection. However clinical isolates of *Staphylococcus aureus* with reduced susceptibility to teicoplanin have been regularly reported from Europe and the US (Cormican, 1996) and although vancomycin resistance is uncommon it has been reported for isolates of *Staphylococcus haemolyticus* (Schwalbe, 1987).

In this study there were no reported cases of vancomycin resistance for the period of 1 January 1994 - 31 May 1997. Penicillin resistance of *Staphylococcus aureus* was high ranging from 92.7%-97.9%, whereas resistance for *Staphylococcus epidermidis* ranged from 92.7%-100%. Moreover, the combination of amoxacillin and clavulanic acid has

had significant activity against *Staphylococcus aureus* resulting in low levels of resistance i.e. 35.9% (1994), 25.92% (1995), and 25% (1996) (see Figure 2.5). There has been a notable increase in the resistance of *Staphylococcus epidermidis* against cefazolin with current resistance levels being 85.5%, compared to the 1994 resistance levels of 63.8% (Figure 2.4). Vancomycin was once again the antimicrobial for which *Staphylococcus epidermidis* had no resistance.

Regarding gram negative bacteria the National Nosocomial Infections Surveillance System (NNIS) noted in 1987 that *Pseudomonas aeruginosa* had a resistance of 10.3% for ceftazidime and in 1991 a slightly lower resistance of 9.1%. At some hospitals resistance against the third generation cephalosporin, cefotaxime was reported to be at 35% and for gentamycin, 12% (Schaberg, 1991). Stratton et al. (1991) noted that there was no resistance to imipenem in ICU patients, between 1987-1988. However, from 1990-1991, the resistance within the same ICU, against imipenem, was reported to be 40% (Stratton et al., 1991).The combination of tazobactam and piperacillin remains one of the more effective drugs against *Pseudomonas aeruginosa* with a reported susceptibility of 94% (Thornsberry, 1995).

In ICU ward 576 of the Johannesburg Hospital the resistance levels of *Pseudomonas aeruginosa* against this antimicrobial combination were 21.9% for the first 5 months of 1997. Since 1994 there has been a continuous rise of resistance against the cephalosporins such as ceftazidime, cefotaxime, and ceftriaxone (Figure 2.3). Cefuroxime and cefepime have had the most favourable results, with resistance in the

latter being as low as 17.8% since its introduction in the ICU. However, caution should be exercised in over-prescribing 'currently effective' antimicrobials, as the consequences of increasing resistance, can prove to be a serious clinical problem.

4.2 Putative risk factors for the acquisition of infection in the ICU

It is well established that the use of catheters is a major cause of blood-stream infections, and consequently of mortality in the ICU. Since more than 40% of primary bacteremias in ICU patients are associated with intravascular catheters (Haley 1981), the prevention of these infections is likely to have a major impact on the mortality and the economy of hospitals. Risk of catheter-related bacteremia is also related to the duration of catheterisation. It was found that the risk of infection increases exponentially after 3-5 days of catheterisation (Plit et al., 1988).

In this ICU, central venous catheters were inserted in 61 of the 62 patients (98.4%) during the three months investigated (Table 2.4). The central venous catheters were replaced after 7 days of continuous use, whilst arterial lines were replaced after approximately 7 days. Analysis of the patient laboratory data showed that over the three month period, 67% 56% and 42% of patients per month, respectively, had catheter tips infected with coagulase-negative *Staphylococcus* (Table 2.10). It was also found that over the same period, 25%, 22% and 17% of patients, respectively, had positive blood cultures for coagulase-negative *Staphylococcus*. The duration of stay of these patients was between 8 to 10 days. Since the study did not contain a large number of patients it

was difficult to establish a relationship between the use of catheters and the acquisition of infection. However the results obtained are consistent with other published data (Haley 1981; Plit et al., 1988).

The catheter tip is however, not the only site from which pathogens such as *S. epidermidis* may be cultured as this method of sampling does not take into account intraluminal colonisation. Hub colonisation, contaminated infusate, contaminated disinfectants and the hands of ICU personnel are further sources of contamination and of bacterial entry (Sitges-Sera, 1984; Widmer 1993). Although new microbiological methods are becoming available such as the use of ultrasound in detecting intraluminal colonisation (Raad, 1992), these techniques are expensive especially for hospitals in the public sector. If such methods of specimen sampling were to be introduced to this ICU it would identify the actual source of contamination.

Preventative measures appear to be more effective than curative or prophylactic treatment. One of the most effective preventative measures is disinfection of the sites for insertion of catheters with a chemical antiseptic, such as 70% alcohol, 10% povidone-iodine or 2-4% aqueous chlorhexidine (Maki, 1991). Alcohol solutions, particularly 60-70% n-propranolol or isopropanolol are generally more effective than antiseptic detergents and soaps. Isopropranolol is especially effective for the immediate reduction of the number of skin bacteria.

In this particular ICU chlorhexidine was the hand-disinfectant used by ICU-personnel. However it was noted that that not all ICU-personnel were taking the necessary precautions of disinfecting their hands before and after the examination of a patient. Poor compliance with infection control techniques or disregard for infection control guidelines such as hand-washing and the use of disinfectants can only increase the spread of infectious micro-organisms amongst patients within the ICU.

Pneumonia is the most frequent manifestation of infection in intensive care units with a reported incidence of between 7 and 44 episodes per 100 admissions (Craven, 1993). Furthermore, crude mortality rates from ventilatory assisted pneumonia (VAP), range from 20-70% with an attributable mortality accounting for one third of all deaths. More than 50% of patients in ICU's, especially those that are seriously immunocompromised, tend to acquire upper airway pathogen colonisation within 4-5 days after admission (Sacho, 1990). Craven et al. (1988) reported that mechanical ventilation was used in 49 of the 52 surgical-ICU patients and in 47 of the 52 medical-ICU patients with pneumonia. Furthermore, 50% of the mechanically ventilated surgical-ICU patients with pneumonia acquired their infection within 10 days of admission, whereas the mechanically ventilated medical-ICU patients acquired their infection within 8 days (Craven et al., 1988). Hence, mechanical ventilation by means of endotracheal intubation appears to be a predisposing factor for the acquisition of VAP in the ICU (Maki, 1989; Estes, 1995).

*Acinetobacter pneumonia* and *Pseudomonas aeruginosa* were gram-negative organisms of concern within this particular ICU ward. It was found that *Acinetobacter baumannii* was the second most frequently isolated micro-organism after coagulase-negative *Staphylococcus* (Table 2.8). Both *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were mainly recovered from patient sputum samples and from bronchoalveolar lavage and washings (Table 2.11). It was found that of the eight patients diagnosed with pneumonia, during the study, four could have acquired this infection while in the ICU. The latter had all been in the ward for longer than 10 days with no initial indication of any infection. All were intubated via endotracheal tube. In addition these patients presented with fever, and leukocytosis. One patient died after 24 days while the other 3 patients were successfully treated and transferred to other wards after an intubation period of approximately 15 days. *Acinetobacter baumannii* was identified as being the cause of the pneumonia in 3 of these patients. Pseudomonas was recovered from sputum samples of the patient that died. Ventilatory tubing in direct contact with the patient i.e. 'elephant tubing' and filters were replaced on a daily basis. Ventilatory tubing not in direct contact with the patient was replaced every alternate day.

A number of preventative measures have been established or proposed for the prevention of VAP (Spencer, 1994). These include changing the ventilator circuits every 2 days, the use of aseptic techniques during manipulation of the respiratory tract, ample disinfection, and the preservation of gastric acidity. Another approach to prevent VAP, although controversial, is the use of selective decontamination of the digestive tract: a procedure that involves the use of non-absorbable antimicrobial drugs. Whether the above

preventative measures are followed depends on the institution involved and factors such as adequate staff, finance and availability of disinfectant materials.

*Candida albicans* is a common inhabitant of the respiratory and gastrointestinal tracts and most patients do not develop any serious illness from it. However, any change to the host's defense mechanism resulting from the use of broad-spectrum antimicrobials or immunosuppressants, the presence of in-dwelling IV or urinary catheters, and prolonged duration of stay in the ICU ward increases the likelihood of proliferation of yeasts such as *Candida albicans* leading to systemic invasion and infection. Most patients with *Candida albicans* infection in the ICU have respiratory tract colonisation. Although endotracheal intubation prevents the aspiration of these micro-organisms from the oropharynx, it is often found that intubation by-passes the normal respiratory defense mechanism of a patient.

During the period January 1994 to May 1997, *Candida albicans* was the most frequently isolated micro-organism in the ICU ward. The yeast was isolated from one or more specimen type of 269 patients (Table 2.12). During the 3 month study 53% of patients had *Candida albicans* isolated from various specimen types. It was found that bronchoalveolar lavage (17.2%), bronchial washing (9.2%) and sputum ( 9.2%) were the specimen types from which *Candida albicans* was most frequently isolated.

Mechanical ventilation i.e. endotracheal intubation should be considered as a putative risk factor for the acquisition of yeast/fungal infections in the ICU.

The study therefore identified the use of catheters and mechanical ventilation as putative risk factors for the acquisition of bacterial, fungal or yeast infection in the ICU ward.

4.3 The cost of antimicrobial drug utilisation

The economic evaluation of antimicrobial drug usage is of major concern in health care provision and a number of factors should be investigated when such studies are undertaken. Acquisition costs alone do not reveal the true costs of drugs and their outcomes. In order to determine the true cost of antimicrobial utilisation, it is necessary to take into account factors such as the costs of preparation, administration, monitoring as well as associated outcomes.

This study focused mainly on two other factors in addition to the acquisition costs. These included the costs associated with the use of disposables (such as needles, syringes) and the cost of wastage associated with the use of antimicrobial drugs. At the time of the study it was not possible to obtain laboratory costs for antimicrobial resistance and susceptibility testing. If these costs had been included, the total cost associated with the use of antimicrobial drugs in the ICU would have been higher. The acquisition cost of the antimicrobial drugs for the three month study-period was estimated to be R 115 793.51. The cost associated with the use of disposables was estimated to be R 15 075.67 whilst the cost associated with the wastage of antimicrobial drugs was estimated to be R 3800. Therefore the total cost evaluated for the utilisation of antimicrobial drugs in the ICU for the three month period was R 134 669.18 (i.e. R 2172.08 per patient).

It was common practice within the ICU for physicians to refer to microbiological data before prescribing appropriate antimicrobial drugs. However, five patients were not prescribed appropriate antimicrobial drugs for reasons that could not be ascertained. Of

these five patients one patient died whilst the other four patients were transferred to other wards. The death of this one patient was attributed to the severity of his condition, which was, cerebral malaria. Due to the continuous admission of new patients to the ICU it was common practice for ICU-physicians to transfer patients that required no further critical care, to other wards. Therefore the other four patients were transferred to other wards shortly after they had been stabilised even though inappropriate antimicrobial drug therapy was prescribed. The study did not follow-up on the outcome of the patients after their transfer to the other wards, but it is well known that inappropriate drug therapy can prolong a patient's stay in the hospital thereby escalating costs for both the patient and or third party payer (Spencer, 1994). Savings of up to R 827.62 could have resulted if appropriate antimicrobial drugs had been prescribed to these patients (Table 3.5).

The study also highlighted two areas of current practice, which could also give rise to cost savings in the ICU. The first of these is the treatment of *Acinetobacter baumannii* infection. It was found that the combination of piperacillin and tazobactam was the drug most frequently prescribed for *Acinetobacter baumannii* infection (Table 3.3). However, according to the laboratory data, *Acinetobacter baumannii* was more susceptible to imipenem (Figure 2.2). Imipenem should be the drug of choice against *Acinetobacter baumannii* in this ward because it is more effective against this organism and likely to be more cost-effective. The second area is the need for improvement to compliance with infection control techniques (see Section 4.1). Such compliance can reduce unnecessary expenditure due to poor adherence to disinfection procedures.

In this study, it was found that the ICU was run in a cost-conscious manner. The majority of antimicrobial drugs prescribed were patient-specific and wastage of these drugs and of disposables was minimal. We estimated the average cost per ICU-patient to be R 2172.08. Antimicrobial drug costs reported in other pharmacoeconomic studies vary considerably and therefore make comparative analysis difficult. For example, Noseworthy et al. (1996) estimated the cost per patient in a Canadian ICU to be $ 1,508 ± 475 while in a recent study in the United States, costs per ICU-patient ranged between $ 1,783 and $ 48,435 (Gyldmark, 1995).

There are numerous factors responsible for differences in determining costs. The most important of these factors is the inclusion or exclusion of certain cost components such as the costs pertaining to laboratory, medical personnel, medication, building and capital costs. For example in this study laboratory costs were not included, whereas in other studies, such as that by Noseworthy et al. (1996), the laboratory cost component was included. Similarly, in this study other cost components included were the costs associated with the wastage of antimicrobial drugs which was not included in the study by Noseworthy et al. (1996). Therefore comparison of costs across studies can only be achieved when the components of the costs referred have been clearly identified.

Another factor regarding costs of drugs is the actual price that is paid. For example, the hospital has to pay an acquisition price when purchasing a drug. The hospital may then charge a mark-up price or a dispensing fee to the patient. To avoid misleading results across studies it is important that the sources of these costs be clearly identified i.e. whether these costs refer to the prices paid by the patient or by third party payers. For example in a survey of 71 hospitals in the United States the cost of one day's treatment

with gentamycin was $ 3.25 whereas the average daily charge to the patient was $ 15.12, a mark-up of 365% (Davey, 1991). Hence major cost bias would result if no distinction is made between the purchase price and the price charged to the patient. In this study the prices used were those paid by the hospital. The cost of one day's treatment with gentamycin in this study was R 3.69 which in current rand conversion is five times less than the acquisition cost in the U.S..

The nature of specialisation of an ICU and the patient-case or group-mix are additional factors that need to be considered when estimating drug costs. Therefore the cost-estimates of antimicrobial drugs may differ depending on the category of patients being treated. During this study, 62 patients were investigated. Of the 62 patients, 24 were classified as post-operative patients while 16 were classified as respiratory patients i.e. patients with respiratory complications such as asthma or pneumonia (Table 2.2). Even though the former group of patients was larger, the total antimicrobial acquisition cost for this group was R 21 486.40 less than that for the respiratory group of patients (Table 3.2). The average cost per respiratory-patient was R 3218.63 whilst that of a post-operative patient was R 1250.49. Therefore if this ICU was a dedicated respiratory ICU (and not a general ICU), the costs associated with the use of antimicrobial drugs would have been much higher.

In order to overcome these kinds of cost-associated problems it would be ideal for a standardised cost-concept model to be developed which will in the future allow for proper comparison of costs and lead to better understanding of cost-effective studies.

However due to differences in practice and cost structures in different countries such a model would be difficult to develop. However, within a country it may be possible to develop such a model. The aim of this study was not to develop such a cost-model but rather to analyse the utilisation of antimicrobial drugs within an ICU. We feel that the information contained within drug-utilisation studies is of vital importance as it helps us to assess the current ICU setting and it assists us in developing future protocols which will optimise the allocation and consumption of available resources.

## CHAPTER 5

## CONCLUSION

Over the last 40 years there has been a proliferation of specialised units with the aim of providing intensive care to seriously ill patients. Significantly, certain risks accompany the benefits of such specialised therapy. The most important being the aggregation of patients that are susceptible or highly likely to acquire an infection. Invasive procedures, impaired host-defense mechanisms, duration of stay and broad-spectrum antimicrobial drug therapy are some of the known risk factors likely to increase the risk of infection within an ICU. The use of broad-spectrum antimicrobial drugs is a significant risk factor that has contributed to the rise of antimicrobial drug resistance. The misuse of antimicrobial drugs has culminated in the world-wide trend of the increasing presence of gram-positive micro-organisms (McGovan, 1991; Vincent et al., 1995).

Accordingly, similar trends of increasing presence of gram-positive micro-organisms were identified in the ICU in this study. Coagulase-negative *Staphylococcus* was the major Gram positive organism of concern in the ICU for the period January 1994 - May 1997. During the 3-month study, 53% ( 33/62) of patients tested positive for the presence of coagulase-negative *Staphylococcus* through specimen culture. Other gram-positive micro-organisms of concern were *Staphylococcus aureus* and *Enterococcus faecalis*.

The study identified *Acinetobacter baumannii* and *Pseudomonas aeruginosa* as the predominant gram-negative micro-organisms within the ICU.

Furthermore the presence of yeasts was exceptionally high, *Candida albicans* being the most notable. Vancomycin and teicoplanin were the two drugs of choice for serious gram-positive infections, whereas imipenem, cefepime, tazobactam/piperacillin were the drugs of choice for serious gram-negative infections. Gentamycin was the most widely used drug during the 3 month study, accounting for 21.7% of the total antimicrobial dose units prescribed for this period. Over the last 4 years, *Pseudomonas aeruginosa* has shown a steady rise of resistance against the third generation cephalosporins (ceftriaxone and ceftazidime), but is reasonably susceptible to the fourth generation cephalosporin, cefepime, with resistance levels of 17.8%.

It was found that over the three month period 67%, 56% and 42% of patients per month, respectively, had catheter tips infected with coagulase-negative *Staphylococcus*. Both *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were mainly recovered from patient sputum samples and from bronchoalveolar lavage and washings. It was found that of the eight patients diagnosed with pneumonia, during the study, four could have acquired this infection while in the ICU. Furthermore, the presence of fungi/yeasts was exceptionally high, *Candida albicans* being the most notable. During the 3 month study 53% of patients had *Candida albicans* isolated from various specimen types. It was found that bronchoalveolar lavage (17.2%), bronchial washing (9.2%) and sputum ( 9.2%) were the specimen types from which *Candida albicans* was most frequently isolated. Mechanical ventilation and the use of catheters were regarded as putative risk factors for the acquisition of infectious micro-organisms in the ICU.

The study also focused on costs associated with the use of antimicrobials in the ICU. The three major costs were acquisition costs, cost of disposables, and cost of antimicrobial wastage. It was found that the total of these costs to the ICU were R 134 669.18 for 62 patients over a period of 3 months i.e. R 2172.08 per patient. This amount would have been greater if other costs such as laboratory costs for antimicrobial testing and the costs for treating antimicrobial drug failure as well as adverse drug events were included. Furthermore, due to the time-restraints of this research report it was not possible to place emphasis on other cost-components such as treatment of antimicrobial drug failure and costs of treating adverse drug events.

5.1 Recommendations

- In the investigated ICU antimicrobial drugs and associated disposables (i.e. syringes, needles, mini-bags etc.) were stored in areas, within the ICU, accessible to any person not under supervision. We therefore recommend that all forms of medication in the ICU be stored in a manner which would allow for controlled access, handling and distribution. The same would apply for disposables. Furthermore, the borrowing of medication between wards seemed to occur more often over weekends, when the main dispensary was closed, than over weekdays, making prompt and correct recording of the distribution of these medications necessary.
- *A. baumannii* in this ICU was more susceptible to imipenem than the combination of piperacillin and tazobactam. We therefore recommend that imipenem be the drug of choice for *A. baumannii*.

- Wastage of amphoterecin B was far greater than any other anti-infective drug prescribed in the ICU. Since multiple manipulation of these units may result in contamination we recommend that all antimicrobial drug unit doses be prepared aseptically 24-hours prior to patient administration. A study in the neonatal ICU of Baragwanath Hospital, Soweto, 1994, showed that a considerable amount of wastage occured in the ICU when doses were prepared by the nursing staff. A projected annual saving of R 58 000 was reported when such unit doses were prepared aseptically in a satellite pharmacy. (Gous, 1995). The involvement of a pharmacist can therefore significantly reduce the wastage of antimicrobial drugs. The risk of contamination can also be reduced.
- The ICU-pharmacist is a crucial member of the ICU health-care system. Montazeri and Cook documented a major educational role for a clinical pharmacist in a multidisciplinary ICU, and demonstrated a substantial reduction in drug costs as a result of pharmacist-initiated therapeutic consultations (Montazeri, 1994). Miyagawa and Rivera (Miyagawa, 1986) evaluated the effect of a clinical pharmacist in a 14-bed surgical ICU over a 13-week study period. The annual cost-saving was projected at $ 72 122. Furthermore, Katona and colleagues (Katona, 1989) demonstrated a projected annual net saving of $ 96 000 from placing a clinical pharmacist in a medical ICU. He/she will be able to assist the health care team with regards to the pharmaceutical care of patients, with the goal of improving an individual patient's quality of life through achievement of definite medication-related therapeutic outcomes. Furthermore, the ICU-pharmacist will be able to provide specialised drug-

related information to both physicians and nurses and will also be able to identify medicine related problems. Such problems may include the following:

- drug-interactions ( drug-drug, drug-disease, drug-food interactions)
- adverse drug reactions
- improper drug selection
- subtherapeutic dosage
- overdosage
- financial impact of therapy

The ICU-pharmacist can provide useful information about the antimicrobial drug prescribing behaviour of the ICU-physicians, via drug-utilisation reviews and from data based on prescriptions. Subsequently, such behaviour will prove his being a good medium of education. The analysis of antimicrobial drug information may initiate the development of antimicrobial prescription guidelines which will improve the efficiency of the utilisation of available resources. The result will be an improvement in the cost-effective management of the ICU.

## 5.2 Further areas of research

Areas of research not undertaken by this research report but which would be of further clinical benefit:

- Costs associated with the beneficial and/or adverse effects of antimicrobial drug usage.
- Costs associated with the laboratory testing of antimicrobial drugs with respect to resistance and susceptibility levels.

- A similar more detailed study of two or more ICU's within the same or separate hospital(s).
- Costs associated in a private sector ICU (third party payer).
- The implementation of a standardised cost-concept model.

## Patient Data - ICU 576 01/03/97-31/05/97

| Patient | Age | Sex | Race | Diagnosis | Antimicrobial therapy | Prevalent micro-organism | Specimen type | Tx appropriate? | ET-tube | IV central | Art. line | UR cath. | Per. drip | Days in ward | Transferre | Died | Cost of Ab tx (Rands) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 34 | m | b | Post-op | Ciproflox 300mg IVI 12 h<br>Mycostatin protocol | None | | Prophylactic | 6 | 6 | 6 | 6 | 0 | 6 | x | | 2094 12 |
| 2 | 25 | m | w | Trauma-MVA | Ciproflox 300mg IVI 12 h<br>Vancomycin 1g IV<br>Amphoterecin B 35 mg<br>Mycostatin protocol<br>Pip & tazobactam 1d<br>Gentamycin 240mg/d | Coag. neg *Staphylococcus* | Cath. TIP | Yes | 30 | 30 | 42 | 18 | 0 | 45 | x | | 6002 |
| 3 | 21 | f | w | Renal | Amox & clav acid 1 2g IV I<br>Gentamycin 240mg<br>Metronidazole 500mg 8h | None | | Prophylactic | 3 | 3 | 3 | 3 | 0 | 3 | x | | 152 02 |
| 4 | 62 | m | b | Post-op | Cefepime 2g bd<br>Amphoterecin B 40mg bd<br>Gentamycin 240mg<br>Mycostatin protocol<br>Metronidazole 500mg 8h | *C albicans* | Bronchial wash | Yes | 4 | 4 | 4 | 4 | 0 | 4 | | x | 998 4 |
| 5 | 66 | f | b | Post-op | Cefuroxime 750mg tds<br>Mycostatin protocol | *C albicans* | Swab | Prophylactic | 9 | 9 | 9 | 9 | 0 | 9 | x | | 255 42 |
| 6 | 32 | f | b | Post-op | Pip & tazobactam tds<br>Metronidazole 500mg 8h<br>Gentamycin 240mg<br>Mycostatin protocol | *P. aeruginosa* | Swab | Yes | 7 | 7 | 7 | 7 | 2 | 7 | x | | 1011 91 |
| 7 | 23 | f | I | Misc O/D | Cefepime 2g bd<br>Vancomycin 1g IV<br>Gentamycin 240mg<br>Mycostatin protocol | None | | Prohylactic | 3 | 3 | 3 | 3 | 0 | 3 | x | | 587 63 |
| 8 | 29 | f | b | Resp TB | Cefepime 2g bd<br>Vancomycin 1g IV<br>Ciproflox 300mg IVI 12 h<br>Gentamycin 240mg<br>Mycostatin protocol | *C albicans* | Bronch alve lav | Yes | 40 | 75 | 30 | 75 | 0 | 80 | x | | 11900 |
| 9 | 70 | m | w | Resp- COPD | Gentamycin 240mg<br>Cefuroxime 750mg tds<br>Vancomycin 1g IV<br>Mycostatin protocol | *P aeruginosa* | Sputum | Yes | 10 | 7 | 6 | 9 | 0 | 11 | | x | 809 67 |
| 10 | 25 | f | b | Post-op | Amox & clav acid 1 2g IV I<br>Gentamycin 240mg<br>Vancomycin 1g IV | *C albicans* | Sputum | Prophylactic | 3 | 3 | 3 | 3 | 0 | 3 | x | | 277 53 |
| 11 | 57 | m | w | Resp- pneum | Pip & tazobactam bd<br>Erythromycin 1g bd<br>Gentamycin 240mg<br>Mycostatin protocol | *A. baumannii* | Sputum; BAL | Yes | 5 | 5 | 5 | 5 | 0 | 5 | x | | 899 9 |
| 12 | 82 | m | b | Post-op | Cefuroxime 750mg tds<br>Mycostatin protocol | Coag. neg Staph; *S. aureus* | Swab, Sputum | No- add vanco | 1 | 1 | 1 | 1 | 0 | 1 | x | | 28 38 |
| 13 | 52 | f | b | Blood- SLE | Cefepime 2g bd<br>Clindamycin 4ml bd<br>Mycostatin protocol | | | | 5 | 5 | 5 | 5 | 0 | 5 | | x | 662 9 |
| 14 | 21 | m | w | Trauma- MVA | Amikacin 1d<br>Imipenem 500mg qid<br>Vancomycin 1g IV<br>Amphoterecin B 35 mg<br>Ciproflox 300mg IVI 12 h<br>Mycostatin protocol | *S. aureus*, Coag neg. Staph<br>*C albicans* | Swabs, TIP | Yes | 24 | 24 | 22 | 24 | 0 | 24 | x | | 8508 8 |
| 15 | 30 | m | b | Renal | Pip & tazobactam tds<br>Gentamycin 240mg<br>Amphoterecin B 35 mg | *C albicans*; | Urine, BAL | Yes | 10 | 10 | 10 | 10 | 0 | 10 | | x | 2289 8 |
| 16 | 20 | m | b | Blood | Gentamycin 240mg<br>Vancomycin 1g IV<br>Cefepime 2g bd | Coag. neg *Staphylococcus*<br>*C albicans* | TIP | Yes | 11 | 4 | 11 | 11 | 0 | 11 | | x | 2185 65 |

APPENDIX A

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ampholterecin B 35mg | | | | | | | | | | | | |
| 17 | 40 | f | b | Post-op | Metronidazole 500mg 8h<br>Amox & clav acid 1.2g IV 8h<br>Gentamycin 240mg<br>Mycostatin protocol | *P aeruginosa* | Blood culture | Yes | 5 | 5 | 5 | 5 | 0 | 5 | | x | 253 35 |
| 18 | 55 | f | w | Resp - pneum. | Pip & tazobactam tds<br>Gentamycin 240mg<br>Vancomycin 1g iV<br>Erythromycin qid<br>Metronidazole 500mg 8h<br>Mycostatin protocol | *P aeruginosa*<br>*C albicans* | BAL | Yes | 24 | 24 | 24 | 2 | 0 | 24 | | x | 6690 43 |
| 19 | 40 | f | b | Malaria | Ceftriaxone 1g bd<br>Mycostatin protocol | *C albicans* | BAL | Yes | 7 | 7 | 7 | 7 | 0 | 7 | x | | 1033 06 |
| 20 | 46 | f | b | Post-op | Cefuroxime 750mg tds<br>Gentamycin 240mg<br>Metronidazole 500mg 8h<br>Pip & tazobactam tds<br>Mycostatin protocol | *C albicans*, Enterobacter,<br>*E faecalis* | TIP | Yes | 14 | 14 | 14 | 14 | 0 | 14 | x | | 2821 14 |
| 21 | 51 | f | b | Resp - COPD | *Cefuroxime 750mg tds*<br>Gentamycin 240mg<br>Mycostatin protocol | *Coag neg Staphylococcus*<br>*S. viridans, P. aeruginosa* | Blood culture,<br>Sputum | Yes | 9 | 7 | 9 | 7 | 0 | 9 | x | | 288 63 |
| 22 | 20 | f | b | Post-op | Amox & clav acid 1.2g IV t<br>Metronidazole 500mg 8h<br>Gentamycin 240mg<br>Mycostatin protocol | *E faecalis* | Swab | Yes | 4 | 4 | 4 | 4 | 0 | 4 | x | | 202 66 |
| 23 | 37 | m | b | Malaria - cerebral | Ceftriaxone 1g bd<br>*Mycostatin protocol* | *C albicans, A baumannii* | TIP | No- add imipenem | 3 | 3 | 3 | 3 | 0 | 3 | | x | 442 74 |
| 24 | 46 | f | b | Resp - pneum | Pip & tazobactam tds<br>Cefuroxime 750mg tds<br>Gentamycin 240mg<br>Metronidazole 500mg 8h<br>Mycostatin protocol | *A baumannii*<br>*C albicans* | Sputum | Yes | 10 | 10 | 10 | 10 | 0 | 11 | x | | 2116 29 |
| 25 | 60 | f | b | Cardiac- HT | Amox & clav acid 1.2g IV t<br>Gentamycin 240mg<br>Metronidazole 500mg 8h<br>Cefepime 2g bd | *P aeruginosa, A baumannii* | BAL | Yes | 19 | 20 | 20 | 21 | 0 | 21 | x | | 2021 05 |
| 26 | 58 | f | w | Post-op | Amox & clav acid 1.2g IV t<br>Gentamycin 240mg<br>Pip & tazobactam tds<br>*Tarivid 400mg bd* | *A baumannii* | BAL | Yes | 14 | 6 | 9 | 27 | 0 | 27 | x | | 5002 6 |
| 27 | 55 | f | b | Post-op | Amox & clav acid 1.2g IV t<br>Gentamycin 240mg | None | | | 5 | 5 | 5 | 6 | 0 | 6 | x | | 246 24 |
| 28 | 65 | m | i | Post-op | Pip & tazobactam tds<br>Amikacin 500mg<br>Mycostatin protocol | *P aeruginosa* | BAL; *Sputum* | Yes | 9 | 9 | 9 | 9 | 0 | 9 | | x | 1490 85 |
| 29 | 34 | m | w | Post-op | Imipenem 500mg qid<br>Gentamycin 240mg<br>*Vancomycin 1g IV* | Coag neg *Staphylococcus* | TIP | Yes | 10 | 3 | 10 | 10 | 0 | 10 | x | | 2578 2 |
| 30 | 76 | m | w | Blood | Cefuroxime 750mg tds<br>Mycostatin protocol<br>Metronidazole 500mg 8h | *P. aeruginosa* | Swab | Yes | 7 | 7 | 7 | 7 | 0 | 7 | | x | *266 07* |
| 31 | 21 | f | b | Post-op | Amox & clav acid 1.2g IV t<br>Metronidazole 500mg 8h<br>Gentamycin 240mg | None | | Prophylactic | 2 | 2 | 2 | 2 | 0 | 2 | x | | 101 34 |
| 32 | 21 | f | b | Post-op | Pip & tazobactam tds<br>Metronidazole 500mg 8h<br>Gentamycin 240mg | None | | Prophylactic | 10 | 10 | 10 | 10 | 0 | 10 | | x | 1731 7 |
| 33 | 32 | f | b | Blood- Hep B | Pip & tazobactam bd<br>Gentamycin 240mg<br>Mycostatin protocol | None | | Prophylactic | 4 | 4 | 4 | 4 | 0 | 4 | | x | 440 92 |
| 34 | 26 | f | w | Resp - asthma | Amox & clav acid 1.2g IV t | None | | Prophylactic | 3 | 3 | 3 | 3 | 0 | 3 | x | | 298 8 |
| 35 | 44 | m | w | Renal | Pip & tazobactam tds<br>Amikacin 500mg | *P. aeruginosa* | Bronch. wash | Yes | 5 | 5 | 5 | 5 | 0 | 5 | | x | 827 25 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Mycostatin protocol | | | | | | | | | | | | | | |
| 36 | 26 | f | b | Misc - MC | Amox & clav acid 1.2g IV t | None | | | Prophylactic | 3 | 3 | 3 | 3 | 0 | 3 | x | | | 112 05 |
| | | | | | Mycostatin protocol | | | | | | | | | | | | | | |
| 37 | 36 | m | b | Resp - pneum | Erythromycin 1g qid | *P. aeruginosa* | BAL | | Yes | 10 | 11 | 11 | 11 | 0 | 11 | x | | | 3181 |
| | | | | | Gentamicin 240mg | *C. albicans* | | | | | | | | | | | | | |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| | | | | | Mycostatin protocol | | | | | | | | | | | | | | |
| 38 | 46 | f | w | Resp - pneum | Cefuroxime 750mg tds | *P. aeruginosa* | Sputum | | Yes | 11 | 10 | 11 | 10 | 0 | 11 | x | | | 3213 |
| | | | | | Erythromycin 1g qid | | | | | | | | | | | | | | |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| 39 | 44 | m | b | Post-op | Meropenem bd | Coag. neg *Staphylococcus* | TIP | | Yes | 0 | 11 | 0 | 11 | 0 | 11 | x | | | 2186 |
| | | | | | Amphoterecin B 35mg | | | | | | | | | | | | | | |
| | | | | | Vancomycin 1g IV | | | | | | | | | | | | | | |
| 40 | 38 | f | b | Post-op | Amox & clav acid 1.2g IV t | *C. albicans* | BAL | | Yes | 2 | 2 | 2 | 2 | 0 | 2 | x | | | 101 34 |
| | | | | | Metronidazole 500mg 8h | | | | | | | | | | | | | | |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| 41 | 34 | m | w | Resp - TB | Cefuroxime 750mg tds | *C. albicans* | Swab | | Prophylactic | 4 | 4 | 4 | 4 | 0 | 4 | x | | | 1157 81 |
| | | | | | Erythromycin 1g tds | | | | | | | | | | | | | | |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| 42 | 39 | f | b | Resp - pneum | Gentamycin 240mg | *C. albicans*; *P. aeruginosa* | *Sputum*; Swabs; | | Yes | 27 | 27 | 27 | 27 | 0 | 27 | x | | | 11213 92 |
| | | | | | Pip & tazobactam tds | Coag. neg *Staphylococcus* | TIP | | | | | | | | | | | | |
| | | | | | Erythromycin 1g qid | | | | | | | | | | | | | | |
| | | | | | Amphoterecin B 35mg | | | | | | | | | | | | | | |
| | | | | | Vancomycin 1g IV | | | | | | | | | | | | | | |
| | | | | | Ciprofloxacin 300mg IVI 12 h | | | | | | | | | | | | | | |
| | | | | | Meropenem 1g tds | | | | | | | | | | | | | | |
| | | | | | Tarivid 400mg bd | | | | | | | | | | | | | | |
| 43 | 20 | m | w | Blood- SLE | *Cefepime 1g bd* | *S. aureus* | Swab | | Yes | 5 | 5 | 5 | 5 | 0 | 5 | x | | | 932 9 |
| | | | | | Erythromycin 1g tds | | | | | | | | | | | | | | |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| 44 | 71 | m | w | Post-op | Amikacin 500mg | *P. aeruginosa* | Pus | | Yes | 11 | 0 | 0 | 11 | 0 | 11 | x | | | 1928 08 |
| | | | | | Metronidazole 500mg 8h | | | | | | | | | | | | | | |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| 45 | 31 | m | w | Post-op | Imipenem 500mg tds | Coag. neg *Staphylococcus* | TIP, Swab | | Yes | 8 | 8 | 8 | 8 | 0 | 8 | | | x | 2301 82 |
| | | | | | Amphoterecin B 45mg | | | | | | | | | | | | | | |
| | | | | | Vancomycin 1g IV | | | | | | | | | | | | | | |
| 46 | 29 | f | w | Trauma- MVA | Cefuroxime 750mg tds | *S. aureus*; Coag. neg Staph | Swab | | No- add vanco | 5 | 5 | 5 | 5 | 0 | 6 | x | | | 141 9 |
| 47 | 29 | m | b | Resp - asthma | Ciprofloxacin 100mg IVI 12 h | Coag. neg Staph, *A. baumannii* | TIP, Sputum | | No- add vanco | 7 | 7 | 7 | 7 | 0 | 7 | | | x | 2366 07 |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| 48 | 74 | m | b | Trauma- MVA | Pip & tazobactam tds | Coag. neg Staph, *P. aeruginos* | TIP, Sputum | | Yes | 15 | 11 | 12 | 15 | 0 | 15 | | | x | 3230 22 |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| | | | | | Vancomycin 1g IV | | | | | | | | | | | | | | |
| | | | | | Amikacin 500mg | | | | | | | | | | | | | | |
| | | | | | Ciprofloxacin 300mg IVI 12 h | | | | | | | | | | | | | | |
| 49 | 33 | f | b | Post-op | Amox & clav acid 1.2g IV t | *A. baumannii* | TIP | | Yes | 17 | 17 | 0 | 17 | 0 | 20 | x | | | 4048 31 |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| | | | | | Metronidazole 500mg 8h | | | | | | | | | | | | | | |
| | | | | | Cefepime 2g bd | | | | | | | | | | | | | | |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| 50 | 29 | m | w | Trauma- MVA | Amox & clav acid 1.2g IV t | Coag. neg Staphylococcus | TIP | | Yes | 7 | 4 | 7 | 7 | 0 | 9 | x | | | 1780 47 |
| | | | | | Gentamycin 240mg | | | | | | | | | | | | | | |
| | | | | | Cefepime 2g bd | | | | | | | | | | | | | | |
| | | | | | Vancomycin 1g IV | | | | | | | | | | | | | | |
| 51 | 31 | m | b | Trauma- stab | Vancomycin 1g IV | Coag. neg *Staphylococcus* | TIP | | Yes | 8 | 8 | 8 | 8 | 0 | 8 | x | | | 411 76 |
| 52 | 35 | f | b | Resp - pneum | Amox & clav. acid 1.2g IV t | *A. baumannii* | Sputum | | Yes | 18 | 11 | 6 | 18 | 0 | 18 | x | | | 4381 53 |
| | | | | | Gentamycin 240mg | *C. albicans* | | | | | | | | | | | | | |
| | | | | | Pip & tazobactam tds | | | | | | | | | | | | | | |
| | | | | | Erythromycin 1g qid | | | | | | | | | | | | | | |
| | | | | | Mycostatin protocol | | | | | | | | | | | | | | |
| | | | | | Amphoterecin B 30mg | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | 71 | f | w | Post-op | Cefepime 2g bd<br>Cefepime 2g bd<br>Amphoterecin B 40mg bd<br>Gentamycin 240mg<br>Mycostatin protocol<br>Metronidazole 500mg 8h | Coag neg *Staphylococcus* | Fluid | | 1 | 1 | 1 | 1 | 0 | 1 | | x | 239 97 |
| 54 | 23 | f | b | Post-op | Amox & clav acid 1 2g IV t<br>Mycostatin protocol | *C. albicans* | Sputum | Yes | 6 | 6 | 6 | 2 | 0 | 6 | x | | 263 24 |
| 55 | 46 | m | w | Resp - COPD | Pip & tazobactam tds<br>Gentamycin 240mg<br>Mycostatin protocol<br>Cefepime 2g bd | *P. aeruginosa, C. albicans* | Sputum | Yes | 23 | 23 | 18 | 17 | 0 | 23 | x | | 3443 314 |
| 56 | 29 | m | b | Trauma - gun | Amox & clav acid 1.2g IV t<br>Metronidazole 500mg 8h<br>Gentamycin 240mg<br>Vancomycin 1g IV | *S. aureus*; Coag neg Staph | Swab, TIP | Yes | 11 | 11 | 11 | 11 | 0 | 11 | x | | 1082 95 |
| 57 | 28 | m | b | Trauma - gun | Amox & clav acid 1 2g IV t<br>Gentamycin 240mg<br>Metronidazole 500mg 8h<br>Vancomycin 1g IV | Coag neg *Staphylococcus*<br>*C. albicans* | Blood culture<br>Urine | Yes | 16 | 10 | 17 | 8 | 0 | 17 | x | | 1673 65 |
| 58 | 60 | f | w | Resp - asthma | Amikacin 500mg<br>Pip & tazobactam tds | *P. aeruginosa* | Sputum | Yes | 10 | 10 | 10 | 10 | 0 | 10 | | x | 1407 52 |
| 59 | 32 | f | b | Post-op | Pip & tazobactam tds<br>Vancomycin 1g IV<br>Amphoterecin B<br>Imipenem 500mg tds<br>Gentamycin 240mg | Enterobacter | Specimen culture | Yes | 6 | 6 | 6 | 6 | 0 | 6 | | x | 2395 45 |
| 60 | 51 | m | w | Trauma - MVA | Gentamycin 240mg<br>Amox & clav acid 1 2g IV 8h<br>Ciproflox 100mg IVI 12h<br>Cefepime 1g bd | *A. baumannii* | Swabs, Sputum | No - add Imipenem | 12 | 12 | 4 | 12 | 0 | 12 | x | | 2476 2 |
| 61 | 25 | f | b | Post-op | Gentamycin 240mg<br>Metronidazole 500mg 8h<br>Pip & tazobactam tds | *E. faecalis* | Fluid | Yes | 3 | 3 | 3 | 3 | 0 | 3 | | x | 519 39 |
| 62 | 34 | f | w | Resp - pneum | Cefuroxime 750mg tds<br>Erythromycin 1g qid<br>Gentamycin 240mg | *P. aeruginosa* | Sputum | Yes | 5 | 5 | 5 | 5 | 0 | 6 | x | | 1234 26 |

Key

BAL- Broncho alveolar lavage
COPD- Chronic Obstructive Pulmonary Disease
MVA- Motor vehicle accident
O/D- Overdosage
Post op- Post operative
SLE- Systemic lupus erythematosus

References

Barrett FF, McGehee RF Jr., Finland M. Methicillin-resistant *Staphylococcus aureus* at Boston City Hospital: Bacteriologic and epidemiologic observations. New Engl J Med 1968; 279: 444-448.

Bergogne-Berezin E. The increasing significance of outbreaks of *Acinetobacter* spp.: the need for control and new agents. J Hosp Infect 1995; 30: 441-452.

Bootman JL, Milne RJ. Costs, innovation and efficiency in anti-infective therapy. Pharmacoeconomics 1996 (Suppl 1); 9: 31-39.

Chandrasekar PH, Kruse JA, Matthews MF. Nosocomial infection among patients in different types of intensive care units at a city hospital. Crit Care Med 1986; 14: 508-510.

Cormican MG, Jones RN. Emerging resistance to antimicrobial agents in gram-positive bacteria. Enterococci, Staphylococci, and non-pneumonal Streptococci. Drugs 1996; 51 (Suppl 1): 6-12.

Craven DE, Kunches LM, Lichtenberg DA, et al. Nosocomial infection and fatality in medical and surgical intensive care unit patients. Arch Intern Med 1988; 148:1161-1168.

Crowe M, Towner KJ, Humphreys H. Clinical and epidemiological features of an outbreak of *acinetobacter* infection in an intensive therapy unit. J Med Microbiol 1996; 44: 340-347.

Darouiche R, Wright C, Hammil R, et al. Eradication of colonization by methicillin-resistant *Staphylococcus aureus* by using oral minocycline-rifampin and topical mupirocin. Antimicrob Agents Chemother 1991; 35: 1612-1615.

Davey P, Malek M. Costs of hospital acquired infection. Pharm J 1991;246: 12-18.

Donowits LG, Wenzel RP, Hoyt JW. High risk of hospital acquired infection in the ICU patients. Crit Care Med 1982; 10: 355-357.

Estes RJ, Meduri GU. The pathogenesis of ventilator-associated pneumonia: 1. Mechanisms of bacterial translocation and airway inoculation. Int Care Med 1995; 21: 365-383.

Fagon JY, Chastre J, Hance AJ, et al. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94: 281-288.

Gous H, Venter JF, Gous AGS. A neonatal intensive care satellite pharmacy is justified. SAJP 1995;2: 40-41.

Grassi GG, Grassi C. Cefepime: overview of activity in vitro and in vivo. J Antimicrob Chemother 1993; 32 (Suppl B): 87-94.

Gruneberg RN, Wilson APR. Anti-infective treatment in intensive care: the role of the glycopeptides. Int Care Med 1994; 20: 17-22.

Gyldmark M. A review of cost-studies of intensive care units: problems with the cost-concept. Crit Care Med 1995; 23: 964-972.

Haley RW, Hooton TM, Culver DH, et al. Nosocomial infection in U.S. hospitals, 1975-1976. Estimated frequency by selected characteristics of patients. Am J Med 1981; 70:947-959.

Hillman A. Cost-effectiveness opportunities for new antibiotics. Pharmacoecomics 1994; (Suppl 5) 2: 40-43.

Holloway WJ, Palmer D. Clinical applications of new parenteral antibiotics in the treatment of severe bacterial infections. Am J Med 1996; 100 (Suppl 6A): 6A-67S.

Jones RN. Impact of changing pathogens and antimicrobial susceptibility patterns in the treatment of serious infections in hospitalized patients. Am J Med 1996; 100 (Suppl 6A): 3S-12S.

Katona BG, Ayd PF, Walters JK, et al. Effects of a pharmacist's and a nurse's interventions on drug therapy costs in medical intensive care unit. Am J Hosp Pharm 1989; 46:1179-1182.

Lyon BR, Skurray R. [ Untitled ]. Microbiol Rev 1987; 51: 88.

Maki DG. Risk factors for nosocomial infection in intensive care: 'device vs nature' and goals for the next decade. Arch Intern Med 1989; 149: 30-35.

Maki DG. Infection caused by intravascular devices: Pathogenesis, strategies for prevention. Royal Society of Medicine Services Limited, London, England 1991

McCabe R, Chirurgi V, Farkas SA, et al. A new therapeutic option for the treatment of pneumonia. Am J Med 1996; 100 (Suppl 6A): 6A-67S.

McGovan JE. Antibiotic resistance in hospital bacteria: current patterns, modes for appearance or spread, and economic impact. Rev Med Microbiol 1991; 2: 161-169.

Miyaga CE, Rivera JO. Effect of pharmacist interventions on drug therapy costs in a surgical intensive care unit. Am J Hosp Pharm 1986; 43:3008-3013.

Moellering RC. Principles of anti-infective therapy. In: Mandell GL, Douglas RG, Bennet GE, editors. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990: 206-218.

Montazeri M, Cook DJ. Impact of a clinical pharmacist in a multidisciplinary intensive care unit. Crit Care Med 1994; 22: 1044-1048.

Mosconi P, Langer M, Cigada M, et al. Epidemiology and risk factors of pneumonia in critically ill patients. Eur J Epidemiol 1991; 7: 320-327.

Noseworthy TW, Konopad E, Shustack A, et al. Cost accounting of adult intensive care methods and human capital inputs. Crit Care Med 1996; 24: 1168-1172.

O'Hare MD, Felmingham D, Gruneberg RN. The bacterial activity of vancomycin teicoplanin against methicillin-resistant strains of coagulase negative *Staphylococcus* spp. J Antimicrob Chemother 1989; 23: 800-802.

Palladino JA. Impact of health outcomes on clinical practice: focus on infectious disease. Infect Med 1996; (Suppl 13B): 43-49.

Pallares R, Dick R, Wenzel RP, et al. Trends in antimicrobial utilisation at a tertiary teaching hospital during a 15-year period (1978-1992). Infect Control Hosp Epidemiol 1991; 12: 525-534.

Plit ML, Lipman J, Fidelman J, et al. Catheter related infection. A plea for consensus with review and guidelines. Int Care Med 1988; 14:503-509.

Qadri SMH, Halim M, Ueno Y, et al. Susceptibility of methicillin-resistant *Staphylococcus aureus* to minocycline and other antimicrobials. Chemotherapy 1994; 40: 26-29.

Raad II, Sabbagh MF, Rand KH, et al. Quantitative tip culture methods and the diagnosis of central venous catheter related infections. Diagn Microbiol Infect Dis 1992; 15: 13-20.

Raad II, Rabih O, Darouiche MD. Catheter related septicemia risk reduction. Infect Med 1996; 13: 807-823.

Sacho H. Historical background of infection control- Introduction. In: Sacho H, editor. Perspectives on nosocomial infections. 1st ed. Department of Surgery, University of the Witwatersrand, 1990: 18-19.

Sahai J, Healy DP, Shelton MJ, et al. Comparison of vancomycin and teicoplanin induced histamine release and the "red man syndrome". Antimicrob Agents Chemother 1990; 34: 765-769.

Sanford JP. Recommended antimicrobial agents against selected organisms. In: Sanford JP, Gilbert DN, Moellering RC, Sande MA, editors. The Sanford guide to antimicrobial therapy. 27th ed. Vienna: Antimicrobial therapy Inc., 1997: 48-50.

Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med 1991; (Suppl 3B ) 91: 72-75.

Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase negative *Staphylococci*. N Engl J Med 1987; 316: 927-931.

Siau H, Yuen KY, Wong SS, et al. The epidemiology of *acinetobacter* infections in Hong-Kong. J Med Microbiol 1996; 44: 340-347.

Sitges-Serra A, Puig P, Linares J, et al. Hub colo...sation as the initial step in an outbreak of catheter related sepsis due to coagulase negative *Staphylococci* during parenteral nutrition. J Pa..nter Enteral Nutr 1984; 8:668-672.

Spencer RC. Epidemiology of infection in ICU's. Int Care Med 1994; 20: 2-6.

Thornsberry C, Brown SD, Yee YC et al. In vitro activity of cefepime and other antimicrobials: survey of European isolates. J Antimicrob Chemother 1993; 32 (Suppl B): 31-54.

Thornsberry C. Trends in antimicrobial resistance among today's bacterial pathogens. Pharmacotherapy 1995; 15: 3-8.

Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. JAMA 1995; 274: 639- 644.

Wadsworth SJ, Kim KH, Satishchandran V, et al. Development of new antibiotic resistance in methicillin susceptible *Staphylococcus aureus*. J Antimicrob Chemother 1992; 30: 821-826.

Widmer AF. IV-related infections. In: Wenzel RP, editor. Prevention and control of nosocomial infections. 2nd ed. Baltimore: Williams and Wilkins, 1993:556-579.

Widmer AF. Infection control and prevention strategies in the ICU. Int Care Med 1994; 20: 7-11.

Yee YC, Thornsberry C, Brown SD, et al. A comparative study of the in vitro activity of cefepime and other antimicrobial agents against penicillin-resistant *Streptococcus pneumoniae*. J Antimicrob Chemother 1993; 32 (Suppl B): 13-19.