FACTORS INFLUENCING ANTIBIOTIC USE IN THE PAEDIATRIC INTENSIVE CARE UNIT AT UNIVERSITAS HOSPITAL FROM 1998 TO 2007

by

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B. Pharm.

A dissertation submitted in fulfilment of the requirements for the Magister in Medical Sciences degree

M.Med.Sc. (Pharmacology)

in the

Faculty of Health Sciences at the
University of the Free State
Bloemfontein

February 2013

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SUPERVISOR STATEMENT

I, Professor A. Walubo, the supervisor of this dissertation entitled: Factors influencing antibiotic use in the Paediatric Intensive Care Unit at Universitas Hospital from 1998 to 2007, hereby certify that the work in this project was done by Riana van Wyk at the Department of Pharmacology, University of the Free State.

I hereby approve submission of this dissertation and also affirm that it has not been submitted previously to this or any other institution or the assessors, either as a whole or partially, for admission to a degree or any other qualification.

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Signature Date

STUDENT STATEMENT

I, Riana van Wyk, certify that this dissertation hereby submitted by me for the M.Med.Sc. Pharmacology degree at the University of the Free State is my independent effort and had not previously been submitted for a degree at another university or faculty. I furthermore waive copyright of the dissertation in favour of the University of the Free State.

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ACKNOWLEDGEMENTS

Thank you to my supervisor, Prof. A. Walubo for his advice, knowledge, guidance and time.

Thank you to the Records Department (Universitas Hospital), Dr. L.J. Solomon, the Matron and staff of the Paediatric Intensive Care Unit (Universitas Hospital), as well as the Toxicology laboratory (University of the Free State), for their assistance with and contributions to the study.

Thank you to my family and friends for their support.

Thank you to God Who gave me strength and perseverance.

LIST OF FIGURES

LIST OF ACRONYMS/ABBREVIATIONS

BBB	:	Blood brain barrier
CNS	:	Central nervous system
C/S	:	Culture and sensitivity
CSF	:	Cerebrospinal fluid
CV	:	Coefficient of variation
CVS	:	Cardiovascular system
DNA	:	Deoxyribonucleic acid
ESBL	:	Extended-spectrum beta-lactamases
GIT	:	Gastro-intestinal tract
GUT	:	Genito-urinary tract
HIV	:	Human immunodeficiency virus
ICU	:	Intensive Care Unit
kg	:	Kilogram
LOS	:	Length of stay
MRSA	:	Methicillin-resistant *Staphylococcus aureus*
PABA	:	Para-amino benzoic acid
PBPs	:	Penicillin-binding proteins
PICU	:	Paediatric Intensive Care Unit
PRP	:	Penicillin-resistant pneumococci
Pts	:	Patients
SD	:	Standard deviation
UTI	:	Urinary tract infection
VISA	:	Vancomycin-intermediate-resistant *Staphylococcus aureus*
VRE	:	Vancomycin-resistant enterococci

ABSTRACT

Many antibiotics have been developed and are available on the market. An increase in the use of antibiotics in hospitals was observed and antibiotics are among the medicines most commonly prescribed to paediatric patients. Resistance to antibiotics is increasing and is a major problem not only in the Paediatric Intensive Care Unit at Universitas Hospital in Bloemfontein, but in South Africa in general. The continued value and effectiveness of antibiotics depend on careful use to avoid bacterial resistance from developing. Thus, guidelines for rational antibiotic use and prevention of resistance should be developed and implemented. This requires an understanding of the factors influencing antibiotic use in a particular setting, in this case the Paediatric Intensive Care Unit at Universitas Hospital. Therefore, the aim of this study is to describe the factors that influence the use of antibiotics in the Paediatric Intensive Care Unit from 1998 to 2007.

This research consisted of a retrospective study of the records of patients admitted to the Paediatric Intensive Care Unit from 1998 to 2007. Using a datasheet, the following information was captured and evaluated: patients' demography, indication for admission, co-morbid conditions, antibiotic and other drug therapy, culture and sensitivity and other relevant parameters.

Of the 1 221 patients admitted during the study period, information could only be retrieved for 967 patients, and of these 685 patients (385 males and 299 females) met the study criteria. The Paediatric Intensive Care Unit performance, measured as Intensive Care Unit utilisation, was optimal at 63%, implying that no patient needing intensive care was denied. The most common conditions on admission were respiratory (23.4%), gastro-intestinal (22%) and cardiovascular (19%) related problems. Pneumonia (8.9%) was the most common infective condition. The most common infective complications while in the Paediatric Intensive Care Unit were pneumonia (35.6%), septicaemia (11.1%) and urinary tract infection (8.8%). Broad-spectrum antibiotics were prescribed the most widely. The top ten antibiotics included cefotaxime

(18.2%), amikacin (14.7%), vancomycin (9.8%), cefuroxime (8.1%) imipenem (7.5%), metronidazole (7.2%), penicillin G (6.5%), cloxacillin (4.1%), co-trimoxazole (2.7%) and gentamicin (2.4%).

The top ten bacteria genera cultured were *Staphylococcus* (29.3%), *Klebsiella* (11.9%), *Acinetobacter* (11.7%), *Pseudomonas* (11.2%), *Escherichia* (8.5%), *Enterococcus* (5.9%), *Streptococcus* (4.1%), *Enterobacter* (4.1%), *Stenotrophomonas* (3.4%) and *Haemophilus* (2%). There was high resistance of the *Staphylococcus* genus to penicillins and penicillin-allergy substitutes (>80%, with methicillin-resistance of 85%), but no resistance to vancomycin was observed. The *Klebsiella* and *Pseudomonas* genera exhibited considerable resistance to most aminoglycosides (40–78%) and cephalosporins (70–100%), but *Klebsiella* remained sensitive to imipenem (1.9%), while *Pseudomonas* was moderately sensitive to amikacin (22.9%). The nosocomial bacteria genera *Acinetobacter* and *Stenotrophomonas* were resistant (>70%) to almost all antibiotics excluding tobramycin (25.8%) for *Acinetobacter* and co-trimoxazole (10.5%) for *Stenotrophomonas*.

Lastly, the persistently challenging factors that influenced antibiotic use in the Paediatric Intensive Care Unit from 1998 to 2007 were common bacteria cultured from specific specimens, bacterial innate resistance, interaction of bacterial and host factors (multiple and severe infections), disease pattern, new antibiotics, overuse of antibiotics, length of stay, personal preferences and treatment guidelines. In conclusion, it was illustrated that bacterial resistance to antibiotics is increasing, and that antibiotic use in the Paediatric Intensive Care Unit at Universitas Hospital was greatly influenced by the efforts to contain antibiotic resistance.

PUBLICATIONS AND CONFERENCE/CONGRESS PRESENTATIONS

1. Van Wyk R and Walubo A. The pattern of antibiotic use in patients admitted to the Paediatric Intensive Care Unit (PICU) of Universitas Academic Hospital. Proceedings of the 46th Annual congress of the South African Society for Basic and Clinical Pharmacology (SASBCP) in association with the Department of Family Medicine (UP), and Toxicology Society of South Africa (TOXSA), 29 September – 2 October 2012, University of Pretoria, Pretoria, South Africa.

2. Van Wyk R and Walubo A. Characteristics of patients on admission to the Paediatric Intensive Care Unit (PICU) of Universitas Academic Hospital from 1998 to 2007. Proceedings of the 46th Annual congress of the South African Society for Basic and Clinical Pharmacology (SASBCP) in association with the Department of Family Medicine (UP), and Toxicology Society of South Africa (TOXSA), 29 September – 2 October 2012, University of Pretoria, Pretoria, South Africa.

3. Van Wyk R and Walubo A. Antimicrobial Resistance in South Africa: “Craving for a Magic Bullet”. EHRLICH II – 2nd World Conference on Magic Bullets. Celebrating the 100th Anniversary of the Nobel Prize Award to Paul Ehrlich, 3 - 5 October 2008, Nürnberg, Germany.

CHAPTER 1

GENERAL INTRODUCTION

Many antibiotics have been developed over the past 60 years or more, to such an extent that some infections that were incurable then are now easily treatable, leading to improved survival of patients (Chambers *et al*., 1998b). However, the use of antibiotics has expanded mainly in the past 30 years, during which an increased use of antibiotics in hospitals was observed (Stein, 2005). Surveys at hospitals found that approximately one third of patients receive at least one anti-infective drug during hospitalisation, and antibiotics were among the most widely prescribed medicines in paediatric patients (Stein, 2005; Bowlware & Stull, 2004).

The activity of antibiotics is due to their selectivity for targets that are unique to bacteria (Chambers *et al*., 1998b). However, the continued value of antibiotics is dependent on careful use so as to avoid the emergence of resistant bacteria by acquired resistance. Acquired resistance is the resistance of bacteria to an antibiotic to which it was initially sensitive. It commonly occurs after exposure of the bacteria to the antibiotic, but it may also occur through other mechanisms.

Antibiotic resistance remains a major problem in all settings where antibiotics are regularly used, specifically in Intensive Care Units (ICUs). Antibiotic resistance contributes to reduced effectiveness of antibiotics and increased health costs and therefore policies for proper use of antibiotics are warranted in ICUs (Van Houten *et al*., 1998). Rational prescribing practices ought to be emphasised whereby antibiotics should be used after accurate diagnosis, in appropriate doses and treatment periods.

Although the availability of many broad-spectrum antibiotics and their aggressive marketing may contribute to the wide spread use of antibiotics, the most compelling use of broad-spectrum antibiotics in the ICUs is for severely ill patients that need empirical aggressive therapy, and the more resistant nosocomial bacteria against which prophylaxis is required. Such practices, though warranted, predispose to further risk of

developing resistance. Therefore, it was recommended that; knowledge from periodic antibiotic utilisation reports, longitudinal surveillances of antibiotic use, sensitivity and antibiotic prescribing patterns, are critical for optimisation of antibiotic use in ICU, in particular the development and re-evaluation of the ICU antibiotic policy (Shankar *et al*., 2005; Van Houten *et al*., 1998).

In the face of continuing development of resistance, considerable effort should be made to protect and maintain the effectiveness of antibiotics (Chambers *et al*., 1998b). Efforts should also be made to identify and understand factors relating to the bacteria, patient and antibiotic that influence the use of antibiotics so that the effectiveness of antibiotics can be preserved and new policies can be put into place. The Paediatric Intensive Care Unit (PICU) at Universitas Hospital in Bloemfontein also experienced such antibiotic resistance problems that it was briefly shut down for disinfection in 2007. Therefore, the aim of this study is to describe the factors that have influenced the use of antibiotics in the PICU over the past ten years, 1998 to 2007, with a hope that this will contribute to the development of improved strategies to prevent antibiotic resistance in the ICU.

The factors influencing the choice of an appropriate antibiotic can be divided into patient (host) factors, bacterial factors, medicine (antibiotic) factors and environmental (institutional) factors (Figure 1.1). As indicated earlier, a thorough understanding of these factors is a prerequisite for the selection or identification of factors that influence antibiotic use in a particular institution. Therefore, for the literature review section, the factors that can influence antibiotic use are reviewed as follows in four parts: antibiotic factors, bacterial factors, host factors and environmental factors.

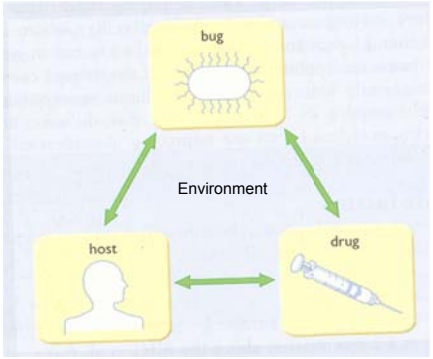


Figure 1.1: Factors influencing the antibiotic choice (Page *et al*., 2006)

CHAPTER 2

FACTORS THAT INFLUENCE ANTIBIOTIC USE
PART I: ANTIBIOTIC FACTORS

2.0 Introduction

Antibiotic-related factors that can influence the choice of antibiotic include the antibiotic's bacterial spectrum of action, pharmacokinetics, pharmacodynamics, adverse effects, pharmaceutical characteristics (formulation), adequate dosage and duration of therapy, cost of therapy and availability (Brenner & Stevens, 2006; Page *et al*., 2006; Gibbon, 2005; Stein, 2005; Townsend & Ridgway, 2005; Ritter *et al.*, 1999; Lampiris & Maddix, 1998; Chambers & Sande, 1996). Appreciation of these factors requires a thorough understanding of the pharmacology of antibiotics and some clinical aspects of antibiotic use.

2.1 Pharmacology of some antibiotics

2.1.1 Introduction

Antibiotics are substances produced by some micro-organisms (bacteria, fungi, actinomycetes) that can suppress the growth of other micro-organisms and/or may eventually kill them (Chambers & Sande, 1996). However, common usage often extends the term "antibiotics" to include the synthetic antibacterial agents (e.g. sulphonamides, quinolones), which are not produced by microbes (Chambers & Sande, 1996). Here, the term "antibiotics" will be used to include all of the antibacterial agents.

2.1.2 Mechanism of action

The activity of antibiotics is due to their selectivity for targets that are unique to bacteria (Chambers *et al*., 1998b). Therefore, antibiotics can easily be classified according to their mechanism of action or their site of action, as indicated in Figure 2.1.

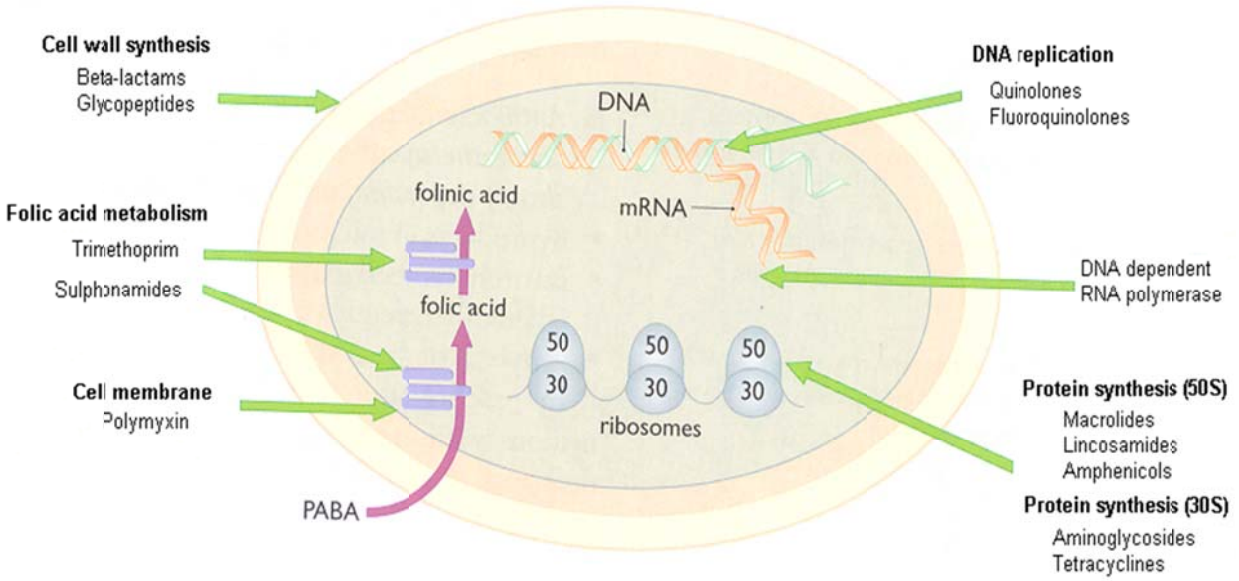


Figure 2.1: Sites of antibiotic action in bacteria (Page *et al*., 2006)

2.1.2.1 *Inhibitors of bacterial cell wall synthesis*

Some antibiotics inhibit bacterial cell wall synthesis and cause destruction of the bacteria. These include beta-lactam antibiotics, such as penicillins, cephalosporins and carbapenems as well as the glycopeptide antibiotics (Chambers & Sande, 1996). The beta-lactam antibiotics inhibit bacterial cell wall synthesis by binding to the penicillin-binding proteins (PBPs), leading to the inhibition of cross-linking of the peptidoglycan (Brenner & Stevens, 2006), while glycopeptides (vancomycin) inhibit the polymerisation of the peptidoglycan.

2.1.2.2 *Inhibitors of bacterial protein synthesis*

Antibiotics such as the macrolides, amphenicols and the lincosamides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit, while others such as the aminoglycosides and tetracyclines bind to the 30S bacterial ribosomal subunit (Chambers & Sande, 1996).

2.1.2.3 *Inhibitors of bacterial nucleic acid synthesis*

The quinolones and fluoroquinolones inhibit nucleic acid synthesis by inhibiting the deoxyribonucleic acid (DNA)-gyrase enzyme (Chambers & Sande, 1996). Metronidazole, on the other hand, inhibits nucleic acid synthesis by binding to intracellular macromolecules (Rossiter, 2012).

2.1.2.4 *Anti-metabolites*

Antibiotics such as the sulphonamides and trimethoprim inhibit bacterial growth by blocking specific metabolic steps that are essential to the bacteria (Chambers & Sande, 1996). They prevent folic acid synthesis by competitive inhibition with para-amino benzoic acid (PABA) for the dihydropteroate synthase enzyme, the first step of folic acid synthesis; thus inhibiting the action of dihydropteroate synthase and the synthesis of dihydrofolate which lead to the inability to form nucleic acid bases (Chambers & Jawetz, 1998). Trimethoprim inhibits the dihydrofolate reductase enzyme in the second step of bacterial folic acid synthesis (formation of tetrahydrofolate).

2.1.3 Spectrum of antibiotic activity and common indications

Antibiotics have either a narrow- or broad-spectrum of activity. Antibiotics that affect both Gram-positive and Gram-negative bacteria are regarded as broad-spectrum antibiotics, while those which act on either bacteria, are regarded as narrow-spectrum antibiotics. Examples of narrow-spectrum antibiotics include some penicillins (penicillin

G and cloxacillin), vancomycin and erythromycin which act mainly against Gram-positive bacteria, while broad-spectrum antibiotics include aminoglycosides and fluoroquinolones which act against both Gram-positive and Gram-negative bacteria.

2.1.3.1 *Penicillins*

Because of the different classes with different spectra, penicillins are still widely used for many infections caused by Gram-positive bacteria. Penicillin G is still the drug of choice for bacteria such as *Streptococcus*, *Actinomyces*, *Corynebacterium diphtheria*, *Treponema pallidum* and leptospira (Rossiter, 2012), while ampicillin and amoxicillin are still used for *Haemophilus* and *Enterococcus*. Co-amoxiclav is effective against most community-acquired beta-lactamase-producing bacteria, *S*. *aureus*, *H*. *influenzae*, *E*. *coli*, *Salmonella*, *Shigella*, *Klebsiella*, *Bacteroides* and anaerobes (Rossiter, 2012). Piperacillin is active against *Pseudomonas aeruginosa* and some resistant Gram-negative bacteria (in combination with aminoglycoside), and the combination of piperacillin/tazobactam has similar indications as co-amoxiclav in addition to *Pseudomonas*, Gram-negative bacilli and anaerobe. Cloxacillin is active against *S*. *aureus*.

2.1.3.2 *Cephalosporins*

The spectrum of activity of cephalosporins depends on the group whereby the first-generation cephalosporins are more active against Gram-positive bacteria, while the spectrum widens to Gram-negative from the second-generation to the fourth-generation.

The second-generation cephalosporins, cefuroxime and cefoxitin are effective against beta-lactamase producing *H*. *influenzae*, *E*. *coli*, *B*. *fragilis*, *Klebsiella* and indole-positive *Proteus*, while the third-generation cephalosporins, cefotaxime and ceftriaxone, have good activity against most Gram-positive and Gram-negative bacteria, except *P*. *aeruginosa* (Rossiter, 2012). Cefepime (fourth-generation cephalosporin) has a broad-spectrum of activity and is effective against *P*. *aeruginosa*. Because cefotaxime can

cross the blood brain barrier (BBB), it is the most preferred cephalosporin for bacterial meningitis.

2.1.3.3 *Carbapenems*

Carbapenems have a very broad-spectrum of activity, including Gram-positive and Gram-negative aerobic and anaerobic bacteria as well as cephalosporin-resistant bacteria e.g. *Enterobacter*, *Serratia*, *Citrobacter*, *Acinetobacter*, *Proteus*, *Providencia* and *Morganella* and serious polymicrobial and nosocomial infections e.g. *Pseudomonas* and *Acinetobacter* (Török *et al*., 2009).

2.1.3.4 *Aminoglycosides*

Aminoglycosides are active against many Gram-negative bacilli, including *Pseudomonas* and mycobacteria, but also *Enterococcus* and *Staphylococcus*, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Rossiter, 2012). Currently, amikacin is the most effective aminoglycoside, with limited development of resistance (Rossiter, 2012). Tobramycin is thought to be more active than gentamicin against *Pseudomonas* and *Acinetobacter*. It can also be used for the long-term management of chronic pulmonary colonisation by *P*. *aeruginosa* in cystic fibrosis patients six years and older (Rossiter, 2012).

2.1.3.5 *Glycopeptides*

Vancomycin is generally reserved for the treatment of infections due to staphylococci (*S*. *aureus*, *S*. *epidermidis* and MRSA) and penicillin-resistant enterococci, as well as an alternative antibiotic for the prophylaxis and treatment of endocarditis in penicillin-allergic patients (Rossiter, 2012; Mermel *et al*., 2001).

2.1.3.6 *Sulphonamides*

Co-trimoxazole was extensively used as a broad-spectrum antibiotic, but therapeutic effectiveness has considerably decreased, due to the emergence of widespread resistance, especially among Enterobacteriaceae and pneumococci (Rossiter, 2012). It is not recommended for use outside of human immune deficiency virus (HIV) infection, because of a high risk of toxicity, unless there are no other alternatives. In HIV-infected patients, co-trimoxazole is the drug of choice for treating *Pneumocystis jirovecii* pneumonia, toxoplasmosis and *Isospora belli*, and it is also used as prophylaxis against these infections as well as other bacterial infections (Rossiter, 2012). It is also used for some multi-drug-resistant bacteria, e.g. *Acinetobacter*, *B*. *cepacia* and *Stenotrophomonas* (Török *et al*., 2009).

2.1.3.7 *Fluoroquinolones*

Ciprofloxacin has a potent Gram-negative activity, particularly against Enterobacteriaceae, *Pseudomonas*, *Haemophilus* and *Legionella* (Rossiter, 2012).

2.1.3.8 *Macrolides*

Erythromycin is a useful alternative in penicillin-allergic patients for streptococcal infections, although resistance has become more common (Rossiter, 2012). In addition, it is also effective against *Bordetella pertussis*, pneumonia due to *Legionella*, mycoplasma and *Chlamydia*, *Corynebacterium diphtheria* and some anaerobes (especially oral organisms). The Gram-negative spectrum is limited to *Campylobacter*, *Moraxella catarrhalis* and *H*. *ducreyi* (Rossiter, 2012). It can also be used for the treatment of community-acquired pneumonia and atypical pneumonia. Administered orally, it stimulates the gastro-intestinal motility (Török *et al*., 2009). However, due to better kinetic profiles, particularly the longer half-life and lack of enzyme inhibition by the newer macrolides, azithromycin and clarithromycin, these macrolides are now preferred over erythromycin.

2.1.3.9 *Metronidazole*

Although essentially an anti-parasitic agent, metronidazole, in combination with an appropriate antibiotic, offers effective synergy against anaerobic bacteria, *C*. *difficile* and *H*. *pylori* (Török *et al*., 2009).

2.1.4 Pharmacokinetics

2.1.4.1 *Absorption*

In the clinic, the route used for antibiotic administration will not only determine the choice of antibiotic, but also the time of onset of action, cost of treatment and patient compliance. The intravenous route for antibiotic administration is preferred in critically ill patients, in order to achieve effective concentrations in the shortest time, leading to quick onset of action (Lampiris & Maddix, 1998). It is also preferred in severe infections such as bacterial meningitis and endocarditis, and in patients with conditions that will impair oral absorption (e.g. severe nausea and vomiting, gastrectomy, etc.) (Lampiris & Maddix, 1998). Furthermore, due to the lack of oral formulations, as well as poor enteral absorption of the solutions, some antibiotics such as vancomycin, aminoglycosides, carbapenems and antipseudomonal penicillins, have to be administered intravenously. On the other hand, some antibiotics such as the tetracyclines, co-trimoxazole, quinolones, chloramphenicol, metronidazole and clindamycin have similar pharmacokinetic properties when administered orally or parenterally (Lampiris & Maddix, 1998).

2.1.4.2 *Distribution*

Distribution is the transport of a drug in body fluids via the bloodstream to various tissues of the body. This involves drug molecules having to cross biological barriers or cell membranes to reach the site of action or elimination. Biological barriers of clinical importance include the BBB and placental barrier, while barriers for absorption and

elimination include the wall of the intestine and capillaries, the renal filtration system and the liver, to mention but a few (Katzung, 1998). Most antibiotics are well distributed to most body tissues and fluids, except for the cerebrospinal fluid (CSF) (Lampiris & Maddix, 1998). Unfortunately, due to differences in physical-chemical characteristics, some antibiotics cross biological barriers better than others do.

Penicillins, most cephalosporins, aminoglycosides, vancomycin, erythromycin, clindamycin and tetracycline have poor distribution across the BBB, except during meningeal inflammation when the BBB functioning is disrupted by disease (Gibbon, 2005). On the other hand, the third-generation cephalosporins, carbapenems, metronidazole, co-trimoxazole and chloramphenicol penetrate the BBB, hence these antibiotics can be used for the treatment of meningitis (Rossiter, 2012).

2.1.4.3 *Metabolism and excretion*

The liver is the main organ responsible for the elimination of drugs by metabolism, while the kidney is the main organ for the excretion of drugs and their metabolites (Correia, 1998; Benet *et al*., 1996). The route of elimination is one of the major determinants of the choice of antibiotic, because the efficiency of drug elimination depends on the performance of the eliminating organ, i.e., the liver or kidney. For example, impairment of renal or hepatic function may results in decreased antibiotic elimination (Lampiris & Maddix, 1998) and antibiotics that are eliminated by the kidneys are more effective for urinary tract infections (Brenner & Stevens, 2006). Most antibiotics and their metabolites are eliminated primarily by the kidneys (Chambers & Sande, 1996).

Antibiotics that exhibit hydrophilic, ionic and low protein-binding characteristics are mainly excreted unchanged by the kidney. Examples include the penicillins, cephalosporins, carbapenems, aminoglycosides, vancomycin and sulphonamides (Rossiter, 2012; Gibbon, 2005). Antibiotics that exhibit lipophilic, less ionic and moderate to high protein-binding, are mainly eliminated by metabolism in the liver. Examples include some cephalosporins (e.g. cefotaxime), chloramphenicol,

tetracycline, erythromycin and clindamycin (Rossiter, 2012). However, many antibiotics exhibit equivocal elimination by the liver and kidney (Rossiter, 2012; Gibbon, 2005).

2.1.5 Adverse effects

Adverse effects can influence the choice of antibiotic, because they can limit the use of an antibiotic in a patient, e.g., in the case of a drug allergy, if administered may injure the patient or aggravate the condition. The most common adverse effects of the most commonly used antibiotics are allergy/hypersensitivity, ototoxicity, nephrotoxicity, seizures and kernicterus.

Allergy: Antibiotics commonly implicated in antibiotic allergy are the penicillins, cephalosporins and co-trimoxazole. Nevertheless, all antibiotics can cause hypersensitivity allergic reactions. The sulphonamide in co-trimoxazole is associated with severe dermatological and systemic hypersensitivity reactions, which can also lead to kernicterus (Rossiter, 2012).

Ototoxicity and nephrotoxicity: Antibiotics associated with ototoxicity and nephrotoxicity include aminoglycosides and vancomycin. Co-trimoxazole is associated with nephrotoxicity due to crystaluria.

Seizures: Carbapenems, especially imipenem, some of the cephalosporins and penicillins, are associated with seizures, although rare (Rossiter, 2012).

Some of the other adverse effects of specific antibiotics are well known and are used to guide the precautionary use of these antibiotics. The use of an antibiotic in a patient may be hampered by the patient's intolerance to the antibiotic and this may be due to patient or antibiotics factors. Therefore, some antibiotics may not be allowed to be used in some patients, i.e., they are contra-indicated, while for some, their use in such patients may be allowed upon meeting some conditions, i.e., precautionary use or relative contra-indication. For example, the use of fluoroquinolones in children is limited

by their association with damage to growing cartilage of weight-bearing joints; chloramphenicol use in children is limited due to its preponderance to cause idiopathic bone marrow suppression and grey baby syndrome; the use of tetracyclines in children is limited by their preponderance to deposition in bones and teeth discolouration; erythromycin may cause diarrhoea due to direct stimulation of the gut motility; aminoglycosides are associated with neuromuscular junction blocking; therefore they are contra-indicated in myasthenia gravis; and sulphonamides can cause haemolytic anaemia in patients with glucose-6-phosphate-dehydrogenase deficiency (Rossiter, 2012).

2.1.6 Drug interaction

Drug interaction is one of the major determinants of choice of antibiotic, because it can cause adverse effects. Antibiotic interactions may be between co-administered antibiotics or between antibiotics and other drugs.

Interaction of antibiotics with other antibiotics

Examples of antibiotic interactions include the co-administration of aminoglycosides with other antibiotics that cause ototoxicity and nephrotoxicity (vancomycin, cephalosporins and sulphonamides) that can aggravate this adverse effect; and the co-administration of aminoglycosides with other antibiotics that cause neuromuscular junction blockade (vancomycin and clindamycin)that can aggravate this adverse effect (Gibbon, 2005).

Interaction of antibiotics with other drugs

Examples of interactions include non-steroidal anti-inflammatory drugs and anticoagulants that may increase the risk of bleeding when it is used in conjunction with cephalosporins; carbapenems that decrease the plasma concentration of valproic acid, leading to breakthrough convulsions; if carbapenems are used in conjunction with theophylline, there is an increased risk of convulsions; the co-administration of aminoglycosides or vancomycin with other drugs (furosemide and amphotericin B) that cause ototoxicity and nephrotoxicity can aggravate this adverse effect; and the co-

administration of aminoglycosides or vancomycin with other drugs that cause neuromuscular junction blockade (succinylcholine) can aggravate this adverse effect (Gibbon, 2005; Turner, 2001). Some antibiotics such as erythromycin, ciprofloxacin and chloramphenicol, as well as drugs such as cimetidine, are potent inhibitors of hepatic microsomal enzymes. Therefore, concomitant use any of these drugs with drugs eliminated by hepatic metabolism, e.g. theophylline, warfarin and midazolam, may lead to toxicity of these drugs (Gibbon, 2005; Turner, 2001).

2.2 Some clinical aspects of antibiotic use

The principle of antibiotic prescribing requires a clinician to use antibiotics singly or in combination and for an adequate period of time in order to ensure effective elimination of the offending bacteria. This requires thorough knowledge of antibiotic combinations that are most effective for particular diseases and at an affordable cost.

2.2.1 Antibiotic combinations

Antibiotic combinations are usually used to provide broad-spectrum empirical treatment for severe infections (e.g. sepsis), to treat polymicrobial infections (e.g. intra-abdominal abscess), to decrease the emergence of resistant strains, to decrease dose-related toxicity by using reduced doses of each component in the combination, to decrease the duration of therapy (Lampiris & Maddix, 1998), to enhance antibiotic activity in the treatment of a specific infection (synergism), to provide appropriate therapy for multi-drug resistant bacteria, for serious infections in the immune-compromised, for nosocomial infections and where the range of potential bacteria is wide (Török *et al*., 2009; Gibbon, 2005; McLellan & Gray, 2001; Chambers & Sande, 1996). Disadvantages of combination antibiotics include increased cost, the development of resistance and toxicity in the patient.

Initial combinations should include antibiotics from different classes and usually consist of a broad-spectrum beta-lactam, combined with a glycopeptide and/or an

aminoglycoside. These drugs cover a large variety of bacteria and can be empirically used for Gram-negative bacterial infections, including *Pseudomonas* (Taccone *et al*., 2010). Gram-negative coverage typically involves a beta-lactam, fluoroquinolone or aminoglycoside. The combination of beta-lactams and aminoglycosides/vancomycin is an example of synergism where the beta-lactams act on the cell wall to enable the aminoglycoside/vancomycin to gain entry to the bacteria with bactericidal activity. The combination of cephalosporins and penicillin also give a synergistic antibacterial action (Turner, 2001). The combination of vancomycin and imipenem is an example of broad-spectrum effectivity.

2.2.2 Pharmacodynamics

The pharmacodynamics of antibiotics include bactericidal versus bacteriostatic activity, antibiotic synergism, antibiotic antagonism and post-antibiotic effect.

Bacteriostatic and bactericidal antibiotics are equivalent in treating most infections in immune-competent patients, but bactericidal antibiotics should be used in situations where the patient's defences are impaired (Lampiris & Maddix, 1998).

Bactericidal antibiotics can also be divided into antibiotics that exhibit concentration-dependent killing (e.g. aminoglycosides and fluoroquinolones) and antibiotics that exhibit time-dependent killing (e.g. beta-lactam antibiotics and vancomycin) (Lampiris & Maddix, 1998). With concentration-dependent killing, the aminoglycosides and fluoroquinolones kill the bacteria when the antibiotic's concentration is well above the minimum inhibitory concentration (Lampiris & Maddix, 1998). The rate and extent of killing increases with increasing antibiotic concentration, thus maximising the peak serum concentrations will result in increased efficacy and decreased resistance (Lampiris & Maddix, 1998). This effect also allows for a once daily dosing of, for example, gentamicin (Török *et al*., 2009).

On the other hand, beta-lactams, macrolides and vancomycin exhibit time-dependent killing and here the bactericidal action continues as long as the concentration is above the minimum inhibitory concentration. Increasing the concentration does not lead to increased killing (Török *et al*., 2009; Lampiris & Maddix, 1998).

Some antibiotics exhibit post-antibiotic effect, i.e., the time during which bacterial growth is inhibited after antibiotic concentrations falls below the minimum inhibitory concentration (Török *et al*., 2009). Aminoglycosides and fluoroquinolones are examples of antibiotics that exhibit a post-antibiotic effect. As such, high aminoglycoside doses administered once daily result in enhanced bactericidal activity and extended post-antibiotic effect (Lampiris & Maddix, 1998). Several factors influence the presence and duration of a post-antibiotic effect and these include the type of bacteria, type of antibiotic, concentration of antibiotic, duration of antibiotic exposure and antibiotic combinations (Török *et al*., 2009). The mechanism is unclear, but it may be due to a delay in the bacteria re-entering a log-growth period (Török *et al*., 2009).

2.2.3 Dosage and duration of therapy

Adequate antibiotic dosage and duration of therapy are necessary for maximising treatment benefit with minimum adverse effects and risk of development of resistance. Factors that influence dosage and duration of therapy include the weight and age of the patient, site and severity of the infection, type of bacteria, host factors, concurrent drugs used, pharmacokinetics and pharmacodynamics of the antibiotic (Gibbon, 2005; Ritter *et al*., 1999; Lampiris & Maddix, 1998). The best is to follow the recommended dosage guidelines which reflect evidence-based practice (McLellan & Gray, 2001). The dosing may be guided by plasma levels by doing therapeutic drug monitoring for some antibiotics like aminoglycosides (Ritter *et al*., 1999).

2.2.4 Antibiotic availability and cost

Regarding the availability of antibiotics in the public health sector, the availability of specific antibiotics on the national Essential Drug List and the provincial code list differs, depending on whether health institution is primary, secondary or tertiary.

Whereas cost should not override the needs of the patient, broad-spectrum and newer antibiotics tend to be more expensive than older and narrow-spectrum antibiotics (McLellan & Gray, 2001). Furthermore, using antibiotic-combination therapy will be more expensive than single-antibiotic therapy and if more than one course of antibiotic therapy is prescribed in one patient, the cost will also be higher. The true cost of antibiotic therapy includes the acquisition costs, the cost of the antibiotic, preparation, administration and consumables costs, monitoring costs (laboratory tests), costs of unwanted medicine effects and complications (Page *et al*., 2006; Cooke, 1998).

2.2.5 New antibiotics

When new antibiotics are available, their superiority (e.g. better activity, wider spectrum of activity, safer adverse effects profile, better pharmacokinetics and easier administration and dosage regimes) leads to increased use (overuse?) of these antibiotics with consequent emergence of resistant bacteria.

2.2.6 Personal preferences

Personal preferences of the attending physicians can also contribute to the choice of a specific antibiotic prescribed at a specific time.

CHAPTER 3

FACTORS THAT INFLUENCE ANTIBIOTIC USE PART II: BACTERIAL FACTORS

3.0 Introduction

The diagnosis of an infection is made on the basis of history and clinical examination, supported by appropriate investigations (e.g. cultures and sensitivity), because among other reasons, the selection of antibiotics depends on the disease- and resistance pattern, the site of infection and the severity of the infection (Page *et al*., 2006; Gibbon, 2005; Ritter *et al*., 1999). Appreciation of these factors requires a thorough understanding of the pathophysiology of antibiotic resistance and, the epidemiology and pathogenesis of some bacteria.

3.1 Antibiotic resistance

3.1.1 Introduction

Antibiotic resistance is the ability of bacteria to withstand the effects of an antibiotic. Antibiotic resistance can be primary or acquired. Whilst primary resistance is due to inheritance, acquired resistance is the resistance of a bacteria to an antibiotic to which it was initially sensitive. The latter commonly occurs after exposure of the bacteria to the antibiotic, but it may also occur through other mechanisms. Antibiotic use leads to selective killing of the susceptible bacteria leading to preferential survival of naturally resistant clones (Heath & Breathnach, 2002). Also, after antibiotic exposure, previously susceptible bacteria may acquire resistance by genetic transfer of resistance genes between bacteria or other mechanisms such as mutation (Ritter *et al*., 1999). This is in agreement with the reports that the incidence of resistance is related to the prescription

and use of specific antibiotics and the widespread use of broad-spectrum antibiotics in hospitals are likely to promote this (Ritter *et al*., 1999). Studies have shown an association between prior use of antibiotics and the development of resistance (Van Houten *et al*., 1998).

3.1.2 Mechanisms of antibiotic resistance

The mechanism of antibiotic resistance may be related to the specific mechanism of antibiotic action in the bacteria or non-specific whereby it affects unrelated antibiotics (Finch, 2005). The different mechanisms of antibiotic resistance include enzymatic inactivation, modification of the site of action, development of alternative metabolic pathways and reduced antibiotic accumulation due to efflux pumps or reduced permeability of the antibiotic (Figure 3.1). However, some bacteria, particularly the nosocomial bacteria, may express many of these mechanisms simultaneously, though at different degrees (Pong & Bradley, 2004). It was observed that resistance occurs more rapidly with bacteriostatic antibiotics (e.g. tetracyclines, macrolides and sulphonamides) than with bactericidal antibiotics (e.g. beta-lactams and aminoglycosides), most probably because the bactericidal antibiotic kills the bacteria immediately (Stratton, 2003).

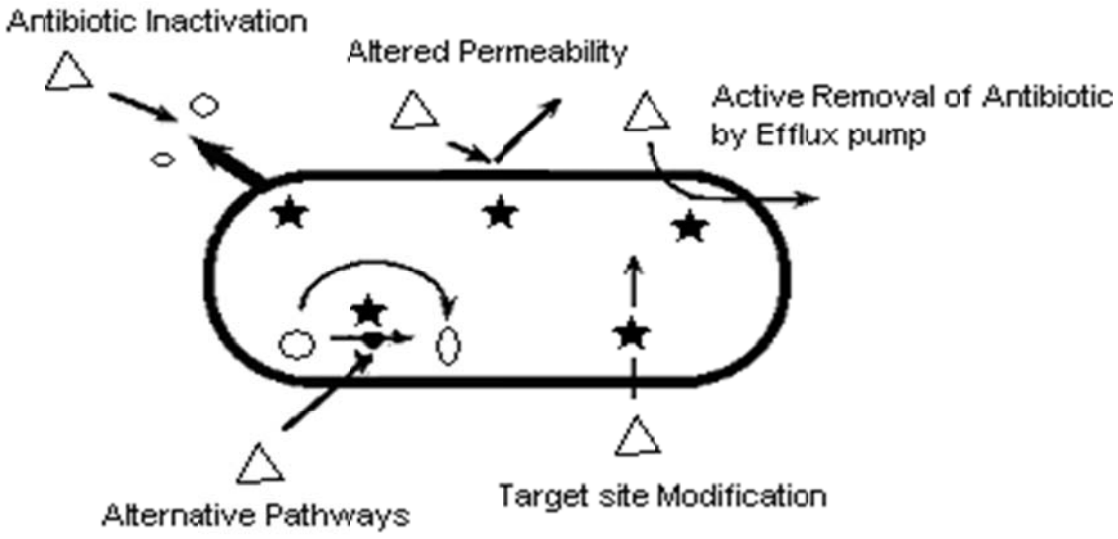


Figure 3.1: The different mechanisms of antibiotic resistance (adapted from Levy, 1998)

3.1.2.1 *Enzymatic inactivation*

Some bacteria produce enzymes that inactivate antibiotics, for example, beta-lactamases (e.g. penicillinase) inactivate penicillins and cephalosporins by hydrolysing the beta-lactam ring (Figure 3.2A & 3.2B; Pong & Bradley, 2004; Heath & Breathnach, 2002; Chambers *et al*., 1998b). Also other antibiotics that are inactivated include the acetylation of chloramphenicol (Figure 3.2C), adenylation, acetylation and/or phosphorylation of aminoglycosides (Figure 3.2D) and hydrolysation of macrolides by esterases (Pong & Bradley, 2004; McLellan & Gray, 2001; Ritter *et al*., 1999; Chambers, 1998). Bacteria that can form beta-lactamases and modifying-enzymes include *Enterobacter*, *Citrobacter*, *Serratia*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella*, *Staphylococcus*, *Haemophilus* and *Moraxella* (Patel & Crank, 2005).

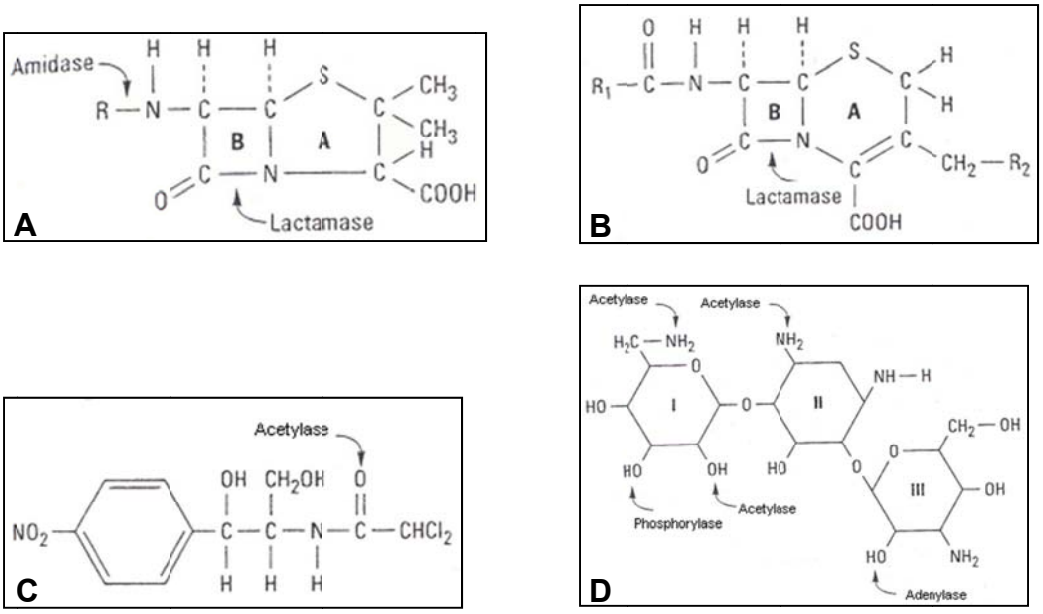


Figure 3.2: Site (beta-lactam ring) of enzymatic attack and inactivation of penicillins (**A**) and cephalosporins (**B**; Chambers *et al*., 1998b), site of enzymatic acetylation of chloramphenicol (**C**) and inactivation of aminoglycosides (**D**; Chambers *et al*., 1998a)

3.1.2.2 *Modification of the site of action*

Modification of the bacterial target can take the form of an enzyme with reduced affinity for an inhibitor or an altered organelle with reduced drug-binding properties (Ritter *et al*., 1999). Examples of this mode of resistance include:

- alteration of the PBPs, the binding site of beta-lactam antibiotics, by the methicillin-resistant *Staphylococcus aureus* (MRSA) (Pong & Bradley, 2004; Chambers *et al*., 1998b) and by *Neisseria*, *Haemophilus influenzae*, *Proteus mirabilis* and *Pseudomonas aeruginosa* (Patel & Crank, 2005; Chambers & Jawetz, 1998);
- alteration of the peptidoglycan binding site of vancomycin;
- alteration of the 50S and 30S ribosomal binding sites of macrolides, aminoglycosides, tetracyclines and lincosamides;
- alteration in the binding site of DNA-gyrase of fluoroquinolones (Pong & Bradley, 2004; Heath & Breathnach, 2002); and
- alteration of DNA-gyrase by *Escherichia coli* (Patel & Crank, 2005; Chambers & Jawetz, 1998).

3.1.2.3 *Development of alternative metabolic pathways*

An example of this mechanism is sulphonamide-resistant bacteria that develop an alternative pathway for the synthesis of folic acid and nucleic acids and thus do not require PABA (Heath & Breathnach, 2002). The alternative pathway may also be by overproduction of PABA by the sulphonamide-resistant bacteria, to such an extent that PABA out-competes the sulphonamide for the dihydropteroate synthase enzyme, leading to the continued production of folic acid (Chambers & Jawetz, 1998).

3.1.2.4 *Reduced antibiotic accumulation*

Reduced antibiotic accumulation either can be by efflux pumps or reduced membrane permeability.

- **Efflux pumps:** Resistant bacteria actively remove the antibiotic from the bacteria by efflux pumps. Efflux pumps for beta-lactam antibiotics, fluoroquinolones, macrolides and tetracyclines have been demonstrated in some resistant bacteria (e.g. *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Escherichia coli*, *Klebsiella*, *Neisseria*, *Proteus*, *Pseudomonas*, *Salmonella* and *Serratia*) (Finch, 2005; Patel & Crank, 2005; Pong & Bradley, 2004; McLellan & Gray, 2001; Chambers *et al*., 1998b).
- **Reduced permeability:** Some resistant bacteria restrict entry of the antibiotic into the bacteria by altering cell wall permeability. Examples include decreased accumulation of tetracyclines, penicillins, cephalosporins and sulphonamides (Heath & Breathnach, 2002; Ritter *et al*., 1999). *Pseudomonas aeruginosa* may display resistance based on a deficiency of a specific porin protein in the cell wall, with decreased concentration of the antibiotic, e.g. imipenem-resistance (Pong & Bradley, 2004). Other bacteria that can change the porins include *Enterobacter* and *Serratia* (Patel & Crank, 2005).

3.1.3 Testing for antibiotic resistance

Antibiotic resistance is normally confirmed by undertaking culture and sensitivity (C/S) tests. The common antibiotic resistant bacteria include MRSA, vancomycin-intermediate-resistant *Staphylococcus aureus* (VISA), vancomycin-resistant enterococci (VRE), penicillin-resistant pneumococci (PRP), Gram-negative bacteria, extended-spectrum beta-lactamases (ESBL) in Gram-negative bacteria, multiple antibiotic-resistant nosocomial Gram-negative bacteria (*Acinetobacter*, *Pseudomonas*) and multi-antibiotic-resistant enteric pathogens (*Salmonella*, *Campylobacter*) (McLellan & Gray, 2001).

3.1.4 Driving factors for increased antibiotic resistance

Inappropriate use of antibiotics: There is overwhelming evidence that inappropriate use of antibiotics, especially the broad-spectrum antibiotics, is one of the major contributing factors for the development of antibiotic resistance (Livermore, 2005; Mohr *et al*., 2005; Niederman, 2005; Allegranzi *et al*., 2002). Inappropriate use here means either the administration of an incorrect dose and/or for inadequate duration and for a wrong or unproven indication. The inappropriate use of antibiotics leads to unnecessary exposure of the bacteria to antibiotics, thereby increasing the risk of acquired resistance (Allen, 2005; Mohr *et al*., 2005). This is confirmed by the reports that bacterial resistance is most prevalent in settings where antibiotic use is particularly heavy, for example, in the ICU (Livermore, 2005).

However, antibiotic exposure may also occur in justifiable circumstances such as the increased use of a specific antibiotic due to high prevalence of a susceptible infection, and the use of antibiotics for prophylaxis as well as for empirical treatment.
The best example of resistance due to antibiotic overuse is penicillin resistant *S. aureus* and subsequently MRSA. Soon after penicillin had been introduced in the 1950s, strains of penicillin-resistant *S. aureus* appeared, due to the production of beta-lactamase enzymes. The resistant bacteria spread so quickly that by the mid-1950s they were the dominant population with less than 10% penicillin-sensitive strains (McDonald, 2006; Clark *et al*., 2003; Heath & Breathnach, 2002). The subsequent use of methicillin, a beta-lactamase-resistant penicillin, was also associated with the rapid emergence of MRSA, with the first report in the early 1960s, after which it became endemic in many hospitals during the 1980s (McDonald, 2006; Clark *et al*., 2003; Allegranzi *et al*., 2002; Heath & Breathnach, 2002). Overall, the use of penicillin was responsible for the development of MRSA.

Patient debility: Patient debility predisposes to the development of antibiotic resistance because severely ill patients have suppressed immune systems, which are important for the action of antibiotics, particularly the bacteriostatic antibiotics. In such

instances, the antibiotic becomes ineffective, resulting in inappropriate exposure to the bacteria. In addition, severely ill patients receive multiple antibiotics, which may predispose to multi-antibiotic resistance. Furthermore, the duration of hospitalisation also contributes to the risk of developing and spreading of resistance, and this is augmented by the fact that patients in ICU are crowded in a relatively confined area (Essack, 2006; Allen, 2005; Rice, 2003). The presence of invasive medical devices like catheters, nasogastric tubes and mechanical ventilation, surgery and wounds also favours the emergence and spread of resistant bacteria (Essack, 2006; Shankar *et al*., 2005).

Modification of normal flora: Normal flora in the gut is also affected by antibiotics, as such, their exposure to antibiotics, particularly the broad-spectrum antibiotics, may lead to development of antibiotic resistance (Gould, 1999). However, this is relevant when the normal flora becomes pathogenic, particularly in debilitated patients with impaired defences.

Mutations: Spontaneous mutations in the bacteria may lead to resistant mutants, which are therefore unaffected by the antibiotic which selectively kill only susceptible strains (Livermore, 2005; Gould, 1999). Thereafter the resistant clone grows, leading to an overt antibiotic resistant infection. Here, the antibiotic has led to the growth of a clone which normally would not have grown in the presence of the susceptible strains.

Non-compliance: Non-compliance by the patient with the prescribed treatment can contribute to therapy failure and antibiotic resistance development, because of the incorrect use of the antibiotic. Non-compliance include not filling the prescription, not starting therapy, delaying therapy, omitting doses, missing doses, not taking doses at the right time, incorrect administration and early cessation of therapy (Niederman, 2005).

Non-adherence to treatment guidelines: Antibiotic guidelines are intended to ensure that the right treatment is given to the right patient, but if they are not followed, it can

lead to inappropriate antibiotic use and a decrease in effectiveness (Allen, 2005; Niederman, 2005). Guidelines discourage bad usage, including over-long or unnecessary prophylaxis or treatment, or the use of antibiotics likely to be inactive against the pathogens (Livermore, 2005).

Other factors: Previous antibiotic use in a specific patient, previous hospitalisation of the patient and transfer from another unit or hospital to a specific unit, e.g. ICU, also predispose the patient to the development and transfer of antibiotic resistance (Essack, 2006).

3.1.5 Impact of antibiotic resistance

Antibiotic resistance is costly in both human and financial terms (Shlaes *et al*., 1997). Human terms refer to increased mortality and morbidity, while financial terms refer to health-care costs. In general, resistant infections and nosocomial infections increase health-care costs due to an increased length of hospital stay and the use of expensive drugs, compared to susceptible infections and also increased morbidity and mortality (Shankar *et al*., 2005; Shlaes *et al*., 1997).

Resistance to common antibiotics has led to the introduction of new antibiotics, which are normally more expensive, thereby increasing the cost of treatment. In addition, resistance to antibiotics leads to major changes in the management of infections, which includes infection control measures, all of which complicate the management of the disease and health-care costs (Finch, 2005; Rice, 2003).

Morbidity and mortality are increased in ICU patients with infections resistant to first-line empirical antibiotics (Livermore, 2005; Shlaes *et al*., 1997). The presence of antibiotic resistant bacteria has been associated with increased rates of re-operation, surgical site infection and abscess formation in intra-abdominal infection (Livermore, 2005). The outcomes are worse and the costs higher (Livermore, 2005).

3.2 The epidemiology and pathogenesis of selected bacteria

3.2.1 Empirical and prophylactic antibiotic use

Empirical therapy is used during severe infection to prevent deterioration of the condition by inducing quick killing of the infecting bacteria while waiting for C/S test results. On the other hand, because some bacteria, particularly nosocomial bacteria, are difficult to eradicate, prevention in the form of antibiotic prophylaxis is more often preferred. Antibiotic prophylaxis is commonly indicated to prevent wound infection after surgical procedures and in patients at risk (immune-compromised) because of a disease, organ transplant or chemotherapy (Chambers & Sande, 1996). Therefore, the empiric use of antibiotics as well as antibiotic prophylaxis requires thorough knowledge of the epidemiology of bacteria for accurate prediction of the most likely causative bacteria. Such epidemiology knowledge should include information on the pathogenesis and antibiotic sensitivity of the bacteria. In general, broad-spectrum bactericidal antibiotics are the most commonly used for empirical therapy, while more specific antibiotics are used for prophylaxis.

3.2.2 Disease pattern

The disease pattern or types of diseases that are treated in a specific unit is one of the major determinants of antibiotic use at a certain time. The seasons can influence the disease pattern and antibiotic use and there is usually an increase in use of some antibiotics during the winter months.

3.2.3 Pathogenesis of the bacteria

The specific bacteria responsible for the infection or the likely infecting bacteria are important because of the different characteristics of Gram-negative and Gram-positive bacteria, which will influence the choice of antibiotic. Some bacteria have a preponderance for specific tissues/organs such as lungs leading to pneumonia, blood

leading to septicaemia, skeletal bone leading to bone infection (osteomyelitis), urinary tract leading to urinary tract infection, etc. Even then, bacteria can be intracellular or extracellular, which poses a challenge to antibiotic selection with regard to tissue and cellular penetration.

3.2.3.1 *Gram-positive bacteria*

***Staphylococcus*:** Staphylococci (especially *S. aureus*) are part of normal flora on the skin and anterior nares of 10–40% of people (Török *et al*., 2009). *S. aureus* can cause a wide variety of infections, including skin and soft-tissue infections, pneumonia, bone and joint infections, bacteraemia, endocarditis and meningitis (Török *et al*., 2009). MRSA may present as asymptomatic carriage in anterior nares, axilla, perineum and umbilicus in infants, but can cause nosocomial wound infection, bacteraemia or ventilator-associated pneumonia. Risk factors for MRSA include indwelling catheters, surgical wounds, severe underlying disease and ICU stay (Török *et al*., 2009). Coagulase-negative staphylococci, e.g. *S. epidermidis*, infections are often associated with the presence of prosthetic material such as intravascular catheters, cardiac valves and joint implants and can cause nosocomial bacteraemia (most commonly), endocarditis, intravascular catheter-related infections, CSF shunt infections, peritoneal dialysis catheter-associated peritonitis, urinary tract infection (UTI), bacteraemia in immune-compromised patients and vascular graft infections (Török *et al*., 2009).

***Streptococcus*:** *S. pneumoniae* colonises the nasopharynx in 20-40% of healthy children and can cause otitis media, sinusitis, meningitis, pneumonia, endocarditis, septic arthritis, osteomyelitis and peritonitis; while the viridans streptococci are also commensals of the upper respiratory tract, female genital tract and gastro-intestinal tract, with large numbers present in the mouth, causing endocarditis, bacteraemia, meningitis and pneumonia (Török *et al*., 2009). Group A *Streptococcus* (*Streptococcus pyogenes*) are upper respiratory tract commensals in up to 10% of children and most commonly cause pharyngitis (Török *et al*., 2009).

***Enterococcus*:** Enterococci are environmental bacteria that are found in soil, water, and food, and are part of the normal gut flora (Török *et al*., 2009). In the hospital setting, enterococci are readily transmissible between patients, and risk factors for nosocomial infections include gastro-intestinal colonisation, severe underlying disease, prolonged hospitalisation, prior surgery, renal failure, neutropenia, urinary or vascular catheters and ICU admission (Török *et al*., 2009). It can cause UTI (most common), bacteraemia, endocarditis, intra-abdominal and pelvic infections, skin, wound-, and soft-tissue infections, meningitis and respiratory infections (rare) (Török *et al*., 2009).

3.2.3.2 *Gram-negative bacteria*

***Klebsiella*:** *Klebsiella* are usually non-infective colonizers of the human gut and infections are rare in the immune-competent patient (Török *et al*., 2009). They tend to cause nosocomial and opportunistic infections, including UTI, pneumonia, bronchitis, surgical wound infections and bacteraemia (Török *et al*., 2009).

***Pseudomonas*:** *Pseudomonas* are non-fermenting Gram-negative bacillus and are found almost anywhere in the environment. They can also colonise moist sites, e.g. the perineum, ear and axilla (Török *et al*., 2009). They usually colonise hospital sink traps, taps and drains, as well as ventilator tubing. They are also highly successful opportunistic nosocomial bacteria, largely due to their resistance to many antibiotics, their ability to adapt to physical conditions and minimal nutritional requirements (Török *et al*., 2009). Nosocomial infections include pneumonia (characteristically 'late'/more than 72 hours ventilator-associated pneumonia), UTI, surgical wound infections and blood sepsis, and mechanically ventilated patients are at particular risk (Török *et al*., 2009). Other infections include endocarditis, eye infections, bone and joint infections, post-operative neurosurgical infections and ear infections (Török *et al*., 2009). *Pseudomonas* are difficult to eradicate from the lungs, due to the fact that they tend to form micro-abscesses and cause necrosis of alveolar walls, and this is commonly incriminated for relapses in cases of ventilator-associated pneumonia (Török *et al*., 2009).

***Escherichia*:** *E. coli* strains range from commensal bacteria to highly pathogenic variants which can infect the gut and urinary tract, as well as other sites, causing nosocomial UTI, enteric infections, bacteraemia, post-operative wound sepsis, pneumonia and infections associated with invasive devices such as intravenous lines and endotracheal tubes (Török *et al*., 2009).

Enterobacter: *Enterobacter* are common gut flora which rarely cause infection in the normal host. *E. aerogenes* and *E. cloacae* commonly cause nosocomial infections such as wound sepsis, pneumonia and UTI (Török *et al*., 2009). Risk factors for infection include indwelling lines, recent invasive procedure, diabetes mellitus and neutropenia (Török *et al*., 2009).

***Acinetobacter*:** *Acinetobacter* is becoming increasingly important as a cause of nosocomial infections, and is often multi-resistant to antibiotics. Increasing antibiotic-selective pressure and the ability to survive in the hospital environment (including on curtains and in dust) have contributed to the success as an opportunistic bacteria (Török *et al*., 2009). Nosocomial spread in the ICU is common and may occur via equipment (particularly ventilators), gloves, surfaces, keyboards, contaminated solutions and healthcare workers. Risk factors for infection include intensive care, ventilation, urinary catheter, intravenous lines, increased length of stay, treatment with broad-spectrum antibiotics, total parenteral nutrition, surgery and wounds (Török *et al*., 2009). *Acinetobacter* is able to infect almost every organ system, including respiratory tract (most common site, particular ventilator-associated pneumonia), urinary tract, intracranial (post-neurosurgery) tissue, soft tissue and wounds, eye, endocardium and bone (Török *et al*., 2009).

***Stenotrophomonas*:** *Stenotrophomonas maltophilia* is an aerobic, non-fermenting Gram-negative opportunistic bacillus with an amazing ability to survive in a wide range of environments. It is increasingly seen as a cause of nosocomial infection and is frequently multi-drug resistant. It is notable for its high intrinsic resistance, including to carbapenems, beta-lactams and fluoroquinolones (Török *et al*., 2009). It has been

isolated from multiple sources in the hospital, including water, nebulisers, dialysis machines, intravenous fluids, thermometers, etc., and transmission of nosocomial infections have been associated with water or contaminated disinfectant solutions (Török *et al*., 2009). Studies have shown that most outbreaks result from antibiotic-selective pressure (especially the extensive use of imipenem) and exposure to multiple environmental strains, rather than cross-infection (Török *et al*., 2009). Risk factors for infections include intensive care, increased length of stay, treatment with broad-spectrum antibiotics, malignancy (especially if immune-suppressed), urinary catheters, intravenous lines, intubation, total parenteral nutrition and neutropenia (Török *et al*., 2009). *Stenotrophomonas maltophilia* can cause a variety of infections, ranging from superficial to deep tissue or disseminated disease, and common sites include the respiratory tract (most common, particularly ventilator-associated pneumonia), skin and soft tissue, intra-abdominal, urinary tract, eye and implants (Török *et al*., 2009).

3.3 Antibiotic resistance in South Africa

Antibiotic resistance is a problem in South Africa as well; owing to the widespread use of antibiotics. Several studies have shown that resistance is of concern to hospitals, due to nosocomial infections, but community-acquired infections have also exhibited a change in the resistance pattern.

3.3.1 Gram-positive bacteria

MRSA: The incidence of MRSA in South Africa is alarming. Klugman, (1998) reported MRSA in up to 50% of the nosocomial isolates, while in a four-year (2001–2004) survey at seven South African academic hospitals, an average incidence of 46.4% (23–83%) was reported (Sein *et al*., 2005). Recently, in a six-month survey in 12 private laboratories, the incidence of MRSA was 36% (29–46%) (Brink *et al*., 2007). Whilst vancomycin-resistant MRSA strains were reported in other countries, this has not been

observed in South Africa (Brink *et al*., 2007; McDonald, 2006; Clark *et al*., 2003; Klugman, 1998).

Streptococcus pneumonia: The incidence of antibiotic resistant pneumococci in South Africa has risen tremendously. The first report of fully resistant and multiple-drug-resistant pneumococci in South Africa was in 1978 (Klugman, 1998). By 1997, PRP was 45% having risen from 31.3% in 1996 (Klugman, 1998). However, in another report, the incidence of PRP in community-acquired lower-respiratory tract infections in South Africa rose from 29.4% in 1996 to 35.8% in 1997 (Felmingham *et al*., 2000). In general, the increase in antibiotic resistance and therefore PRP was partly attributed to HIV (Klugman, 1998). Most alarming is that by 2001, the incidence of PRP among respiratory pathogens in South Africa was 76% and was reported as the highest in the world (Liebowitz *et al*., 2003). In one academic hospital, the incidence of PRP increased from 14% in 2001 to 37% in 2004 (Sein *et al*., 2005).

Vancomycin-resistant *Enterococcus* (VRE): The first strains of VRE and teicoplanin-resistant *Enterococcus* in South Africa were described in 1996, but it was suggested that these strains were likely to have been imported (Klugman, 1998). In general, the incidence of VRE in South Africa is not known.

3.3.2 Gram-negative bacteria

Haemophilus influenzae: In South Africa, a low incidence of beta-lactamase-producing *H. influenzae* (±10%) was reported (Klugman, 1998). However, high resistance to ampicillin was reported at one academic hospital, rising from 33% in 2001 to 40% in 2003 (Sein *et al*., 2005).

Klebsiella pneumonia: Antibiotic-resistant *K. pneumoniae* is already high, with an average incidence of 45.6% (18–70%) gentamicin-resistance from 2001 to 2004, while ciprofloxacin-resistance over the same period was 11.3% (0–34%) (Sein *et al*., 2005). This was associated with a high prevalence of ESBL producing *K. pneumoniae* of

36.7% (18–62%). In a recent study in the private practice, average resistance of *K. pneumoniae* to ciprofloxacin was 31% (0–49%) and to ampicillin was 98% (88–100%) (Brink *et al*., 2007).

Others: Antibiotic resistance for *Pseudomonas aeruginosa* is also high, but most disturbing is the high resistance to newer antibiotics such as meropenem (42%), imipenem (45%), cefepime (53%) and ciprofloxacin/levofloxacin (46%) (Brink *et al*., 2007). Resistant *Escherichia coli* have also been reported with 12–26% to ciprofloxacin, 11% to cefuroxime and 6% to cefepime (Brink *et al*., 2007).

Overall, all the South African studies have confirmed an increasing problem of bacterial resistance to the major antibiotics.

CHAPTER 4

FACTORS THAT INFLUENCE ANTIBIOTIC USE
PART III: PATIENT FACTORS

4.0 Introduction

The host is the major point of interest by bacterial invasion and for whom antibiotics are used to eradicate the invader. Specifically, the interaction of the host with the bacteria determines the pathogenesis and site of infection, while interaction of the host with the antibiotic determines the distribution of the antibiotic (pharmacokinetics) to the site of infection and subsequent action on the bacteria (pharmacodynamics). Therefore, a thorough knowledge of the patient factors that influence bacterial invasion (pathogenesis) and pharmacokinetics/pharmacodynamics of antibiotics are a prerequisite for selection of appropriate antibiotics for specific conditions. Such factors include, to mention but a few, age, weight, genetics, organ function, underlying diseases, host defence mechanism/immune status and critically illness (Page *et al*., 2006; Gibbon, 2005; Ritter *et al*., 1999; Lampiris & Maddix, 1998; Chambers & Sande, 1996).

4.1 Age

Children, in general, respond to some drugs differently from adults due to differences in the pharmacokinetics and pharmacodynamics of some drugs, and sometimes the underlying mechanism is not clear, for example, the half-life of amikacin is 3 to 8 hours in neonates/infants, compared to 2 to 3 hours in adults (Howard & McCracken, 1975). Idiosyncratic reactions in children include Reye's syndrome with aspirin, the grey baby syndrome with chloramphenicol, hyperactivity with phenobarbitone, as well as sedation by methylphenidate.

4.2 Weight

Although, accurate dose calculation in children is achieved by use of body surface area, body weight is still widely used for dosing of most drugs, because it is easier to obtain the weight than the body surface area. This has created difficulty in standardising dose because of wide variations in body weight with age. As a result, most institutions have developed guidelines for weight-based dosing of drugs (equivalent to body surface area) for some antibiotics, and these need to be consulted to ensure appropriate antibiotic dosing.

4.3 Genetic factors

Some genetic factors that affect drugs can be identified early in children, and examples include abnormal glucuronidation of bilirubin metabolism, which implies defective glucuronidation of drugs, porphyria and glucose-6-phosphate dehydrogenase deficiency. Glucose-6-phosphate dehydrogenase deficiency is associated with drug-induced haemolysis by sulphonamides, chloramphenicol and fluoroquinolones, while several drugs that include erythromycin, chloramphenicol and sulphonamides are contra-indicated in patients with porphyria (Rossiter, 2012; Chambers & Sande, 1996).

4.4 Hepatic- and/or renal function

The liver and kidneys are the most important organs responsible for drug (or antibiotic) metabolism and excretion; therefore, impairment of liver and/or renal function can reduce metabolism and excretion of antibiotics, which can lead to toxicity (Chambers & Sande, 1996).

Patients with severe hepatic disease would require some lowering of doses for those antibiotics metabolised by the liver, but it is better to avoid these drugs under such circumstances. Furthermore, because the liver is responsible for protein synthesis, chronic impairment of liver function is associated with reduced albumin concentrations.

This leads to increased free fraction of acidic drugs and risk of toxicity (Mehrotra *et al*., 2004).

In patients with renal impairment, the half-life of some antibiotics such as ampicillin, piperacillin, cefuroxime, vancomycin, ciprofloxacin, aminoglycosides and sulfamethoxazole is prolonged (Rossiter, 2012). Therefore, these antibiotics should be used with caution in patients with renal impairment.

4.5 Underlying diseases and the immune status

Underlying diseases can suppress the patient's immune system, alter the pharmacokinetics of the antibiotic and the patient can be at a higher risk for certain adverse effects of certain antibiotics. Diseases like diabetes mellitus, tuberculosis and HIV, as well as drugs like cancer chemotherapy and corticosteroids, can suppress the immune system of a patient. A suppressed immune system can lead to repeated bacterial, fungal and viral infections and also opportunistic infections, e.g. tuberculosis, *Pneumocystis jirovecii* pneumonia, candidiasis, cryptococcosis, cytomegalovirus infections, Herpes simplex infections, Varicella zoster infections, toxoplasmosis, pneumococcal bacteraemia and salmonella bacteraemia, especially in the HIV-positive patient (Klugman, 1998). These infections complicate the condition with the need for more antibiotics. For instance, in patients with HIV, co-trimoxazole is used for prophylaxis and treatment of *Pneumocystis jirovecii* pneumonia.

4.6 The critically ill patient

Critically ill patients often present with several conditions which may affect the distribution and/or elimination of antibiotics. In general, the hydrophilic and moderately lipophilic antibiotics are more at risk for pharmacokinetic changes in the critically ill patient (Pea *et al*., 2005).

Causes for an increase in the extracellular fluid (i.e., increased volume of distribution with antibiotic dilution) in the critically ill patient include pleural effusion, ascites,

mediastinitis, fluid therapy, oedema, sepsis, trauma, post-surgical drainages and hyopalbuminaemia (Pea *et al*., 2005). Critically ill patients exhibit fluid instability and wide variations in fluid volumes due to administration of different fluids as well as disease induced accumulation of fluids in particular body compartments. Overzealous administration can increase the body fluid volume, leading to increased volume of distribution for some drugs, particularly the hydrophilic antibiotics such as the aminoglycosides (Roberts & Lipman, 2009). This can lead to lower peak concentrations, which is a disadvantage for concentration-dependent antibiotics (Mehrotra *et al*., 2004). A critically ill patient also exhibit a significant larger volume of distribution for some antibiotics, such as amikacin, due to micro-capillary leaks and interstitial tissue oedema associated with sepsis (Marik, 1993). It was suggested that larger loading doses may be appropriate in patients who have sepsis (Marik, 1993). The inflammatory response associated with sepsis also results in large fluid shifts and third space losses (and lower albumin) initially with a high cardiac output. In turn these changes result in increased creatinine clearance and increased renal drug clearance; therefore, unless these effects are offset by ensuing renal and/or hepatic impairment, with subsequent drug accumulation, antibiotic levels may be too low for optimal efficacy (Pinder *et al*., 2002).

Causes for enhanced renal clearance include burns, leukaemia, the hyperdynamic condition occurring in the early phase of sepsis (leading to increased cardiac output and renal blood flow) and hypoalbuminaemia, while causes for reduced renal clearance include renal impairment (due to underlying conditions e.g. trauma, multiple organ failure, burns, cardiogenic/hypovolaemic shock or nephrotoxic drugs) and dialysis (Pea *et al*., 2005).

4.7 Invasive devices

Although invasive devices have been mentioned under the bacteria factors (part II), they are also mentioned here to emphasise that they increase the risk of developing infections.

Ventilator-associated pneumonia is common in the ICU, affecting 8–20% of ICU patients and up to 27% of mechanically ventilated patients, with a mortality rate ranging from 20–50%, reaching more than 70% when it is caused by multi-resistant and invasive bacteria (Rea-Neto *et al*., 2008). The risk factors include the duration of mechanical ventilation, chronic pulmonary disease, sepsis, acute respiratory distress syndrome, neurological disease, trauma, malnutrition, immunosuppression, prior use of antibiotics, red cell transfusions, supine position, nasogastric tube (aspiration and gastro-intestinal reflux through tube), absent cough reflex, inadequate hygiene of healthcare staff (e.g. hand washing, glove change), intervention (e.g. suctioning or handling of the ventilator circuit) and tracheostomies (Rea-Neto *et al*., 2008).

Tracheostomies provide direct access for bacteria to enter the lower-respiratory tract through the formation of a biofilm. Ventilator-associated pneumonia is thought to increase the mortality of the underlying disease by about 30% and is also associated with considerable morbidity, including prolonged ICU length of stay, prolonged mechanical ventilation, and increased costs of hospitalisation (Rea-Neto *et al*., 2008).

Staphylococci (e.g. coagulase-negative staphylococci, *S*. *epidermidis*, *S. aureus*), aerobic Gram-negative bacilli and *Candida albicans* most commonly cause catheter-related septicaemia (Mermel *et al*., 2001). The incidence of central venous catheter-related infections ranges from 3–60% and risk factors include age, birth weight, underlying diseases (e.g. cancer, HIV, prematurity, short bowel syndrome), patient factors (e.g. neutropenia), drugs used, type of device and nature of the infusate (e.g. lipid emulsions), the type of catheter, the unit/ward, the location of the site of insertion, aseptic techniques used and the duration of catheter placement (Mermel *et al*., 2001).

Most nosocomial UTIs are associated with catheterisation and most hospitalised patients are catheterised, although UTIs in the ICU account for a smaller proportion of bacteraemias (Hooton *et al*., 2010). The incidence of bacteriuria associated with catheters is 3–8% per day and the most important risk factor is the duration of catheterisation (Hooton *et al*., 2010). Other risk factors include systemic antibiotic

therapy, females, microbial colonisation of the drainage bag, catheter insertion outside the theatre, poor catheter care, underlying diseases with immune suppression (e.g. diabetes mellitus), diarrhoea, renal insufficiency (also elevated serum creatinine at the time of catheterisation), catheterisation late in hospital course and debilitation (Hooton *et al*., 2010).

4.8 Local factors at the site of infection

Local factors at the site of infection that influence antibiotic choice include pus, hemoglobin, the pH, anaerobic conditions and foreign bodies. Pus at the site of infection binds aminoglycosides and vancomycin, resulting in the decrease of effectiveness, while large accumulation of haemoglobin in infected hematomas can bind penicillin and tetracyclines with a decrease in effectiveness (Chambers & Sande, 1996).

The pH in abscess cavities and confined infected sites like the pleural space, CSF and urine is usually low, resulting in marked loss of antibiotic activity e.g. aminoglycosides, erythromycin and clindamycin. The anaerobic conditions found in abscess cavities may impair the activity of aminoglycosides due to reduced vascular supply and subsequent impaired penetration (Chambers & Sande, 1996).

The presence of a foreign body in the infected site reduces the likelihood of successful antibiotic therapy. The prosthetic cardiac valves, joints, vascular prosthesis and shunts are perceived as foreign by phagocytes and in an attempt to destroy it, degranulation occurs resulting in the depletion of intracellular bactericidal substances. Thus, these phagocytes are relatively inefficient in killing bacteria. Bacteria may also attach to the foreign body and are then relatively resistant to antibiotics (Chambers & Sande, 1996).

4.9 Patient compliance

Patient compliance is important for effective antibiotic therapy, as it ensures good medicine storage, appropriate drug administration at the correct dose and dosing

frequency for the right duration of therapy. Factors that affect patient compliance include antibiotic factors (e.g. multiple daily dosing, difficult combination regimes, adverse effects and complicated dose instructions or administration), patient factors (e.g. forgetfulness, mental impairment, physical handicap and beliefs) and prescribing doctor factors (e.g. poor communication, autocracy and condemning). However, in the ICU setting, problems with compliance are obviated by the fact that medicines are administered by the healthcare workers.

CHAPTER 5

FACTORS THAT INFLUENCE ANTIBIOTIC USE
PART IV: ENVIRONMENTAL FACTORS

5.0 Introduction

Environmental factors involve the institutional setup, including managers and healthcare workers. In the ICU setting this means operations that ensure availability of functional equipment, consumables, medicines (including antibiotics), healthcare workers and optimum capacity for acceptance of patients which include number of beds. In this section the methods for evaluation of the performance of an ICU are reviewed. Knowledge of ICU performance is a prerequisite for determining whether the ICU is adequate and well utilised for the number of patients in the hospital. Such information is essential for planning an antibiotic-use strategy. Furthermore, ICU performance gives a clear understanding of the admission characteristics with regard to number of patients in ICU and in the waiting line, as well as length of stay (LOS), and from these, the average capacity utilisation of the ICU is obtained. This information is obtained by use of mathematical models based on the Queuing Theory.

5.1 The Queuing Theory

Although there might be no visible queue in the ICU, there is a booking process by which patients are referred to the ICU, and are admitted based on a 'first in-first out' basis, although at times some emergencies make the severely ill to jump the queue. Therefore, the referring physicians need to be sure of the waiting time for admission to ICU to ensure that critical treatment of patients is maintained while waiting and that such waiting time is reasonable. If the referring clinician is aware of a long delay in the admission of patients to the ICU, he/she will be compelled to start patients on antibiotics

or any medicine that a patient needs urgently before admission. As such, several analytical models used to evaluate service systems, in this case ICU services, have been developed. If used carefully, such models help in balancing the capacity of the ICU to provide a service within the expected time. These models are based on the Queuing Theory, the formal study of waiting lines (Render, 2003)

5.2 Procedure for the Queuing Theory

The Queuing Theory uses the Poisson probability distribution to describe arrivals to the service facility and the exponential probability distribution to describe service times. Based on these data distributions and specific equations, the Queuing Theory can be used to determine:

- the percentage of time that a service facility is idle;
- the probability of a specific number of patients in the service system;
- the average number of patients in the system;
- the average time each patients spends in the system (waiting plus service time);
- the average number of patients in the waiting line;
- the average time each patient spends in the waiting line; and
- the percentage of time, or probability, that an arriving patient must wait for service.

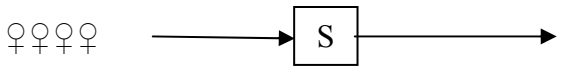
Basic Queuing Theory uses a Poisson distribution to estimate the pattern in which patients arrive for service. The Poisson is a discrete probability distribution that expresses the probability of a number of events occurring in a fixed period of time if these events occur with a known average rate and independently of the time since the last event. The Poisson is considered a more appropriate estimate of random arrival patterns than the standard normal probability distribution. Unlike the normal distribution, which is symmetrical, the Poisson has a long tail (on the right) and it is not symmetrical. Unlike the normal, which gives equal probabilities to values on either side of a mean, the Poisson recognises that random arrival rates cluster about the mean, cannot be less than zero, and have a low probability of being much higher than the mean.

5.3 Types of queues

There are different types of queues or line models depending on the type of service. In the hospital environment, the most common models are Single-Server, Single-Line and Multiple-Server, Single-Line Models.

5.3.1 Single-Server, Single-Line Model

This is the simplest version. There is one server and one line.



To use the model requires estimating:

λ = the expected number of arrivals per time period (mean rate of arrival)

μ = the expected number of services possible per time period (mean service rate)

However, in order to use the queuing simulation formula, the distribution of arrivals must exhibit a 'Poisson distribution', and the service times must exhibit an 'exponential probability distribution'.

Poisson distribution: To use the queuing simulation formula, the mean rate of arrival (λ) must first be shown to exhibit a Poisson distribution. This is illustrated by the use of the Poisson distribution formula:

$$P(x) = \frac{\lambda^x e^{-\lambda}}{x!}$$

where *x!* is the proposed (assumed) number of patient arrivals in the time period, and *e* is the natural log and is a constant 2.71828. Therefore, suppose one knows that the arrival rate in an ICU is 45 patients per hour or 45/60 = 0.75 per minute, then, one would like to know the probability of having 0, 1, or 2 patients arrive at the same minute. The 0, 1, or 2 patients per minute are the proposed (assumed) number of patient arrivals (*x!*). Then the probabilities of say, 0, 1, and 2 patients arrivals during a one-minute period can be calculated as follows:

$$P(0) = \frac{0.75^0 e^{-.75}}{0!} = e^{-.75} = 0.4724$$

$$P(1) = \frac{0.75^1 e^{-.75}}{1!} = 0.75e^{-.75} = 0.3543$$

$$P(2) = \frac{0.75^2 e^{-.75}}{2!} = \frac{(0.75)^2 e^{-.75}}{2} = \frac{(0.5625)(0.4724)}{2} = 0.1329$$

This can be plotted as Poisson probability (*P*) versus the assumed number of patients as indicated in the plot below (Figure 5.1).

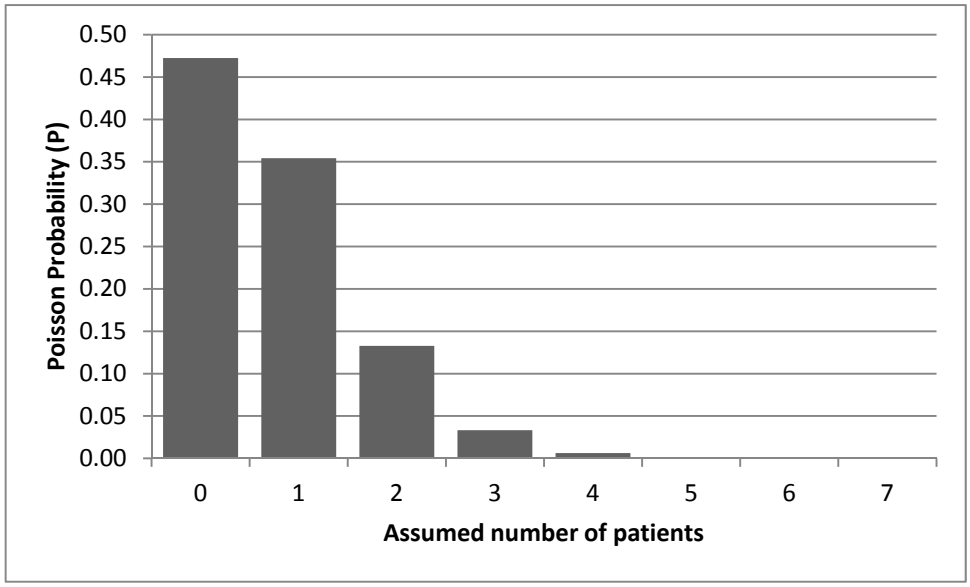
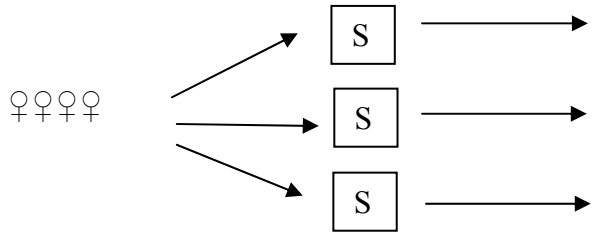


Figure 5.1: Illustration of Poisson distribution

Distribution of service times: To use the queuing simulation formula, the service times must exhibit an 'exponential probability distribution'. The simple assumption made here is that service times follow an exponential probability distribution. It describes the time between events in a Poisson process, i.e., a process in which events occur continuously and independently at a constant average rate. With this assumption, then the probability that the service time will be less than or equal to a time of length *t* is: *P* (service time $\leq t$) = $1\text{-}e^{-\mu t}$. The details to illustrate this aspect graphically could not be attained here.

5.3.2 Multiple-Server, Single-Line Model

Multiple-server systems have more than one server available to the waiting line. When a patient gets to the head of the line, the patient is served by the next available server. In these models: m = the number of beds, λ = the mean arrival rate and μ = the mean service rate.



Then the following parameters can be derived from the respective formulas:

1. The probability that no patients are in the ICU is:

$$P_o = \frac{1}{\sum_{n=0}^{m-1} \frac{(\lambda/\mu)^n}{n!} + \frac{(\lambda/\mu)^m}{m!}\left(\frac{m\mu}{m\mu-\lambda}\right)}$$

2. The average number of patients (L_q) in the waiting line is:

$$L_q = \frac{(\lambda/\mu)^m \lambda\mu}{(m-1)!(m\mu-\lambda)^2} P_o$$

3. The average number of patients in the system (L), both waiting and being served:

$$L = L_q + (\lambda/\mu)$$

4. The average time a patient spends in the system (W), same as length of stay (LOS):

$$W = 1/\mu = L/\lambda$$

5. The average time a patient spends in the queue waiting for service (W_q):

$$W_q = L_q/\lambda$$

6. The average ICU utilisation rate (ρ: proportion of patients served per bed):

$$(\rho) = (\lambda/m\mu)$$

CHAPTER 6

STUDY PROTOCOL

6.1 Aim and Objectives

6.1.1 Summary of observations from the review

- There are many antibiotics available on the market.
- Antibiotics are among the medicines most commonly prescribed to paediatric patients.
- Bacterial resistance to antibiotics is increasing and is a major problem not only in the Paediatric Intensive Care Unit at Universitas Hospital in Bloemfontein, but in South Africa in general.
- Antibiotic resistance contributes to reduced effectiveness of antibiotics and increased health costs and therefore policies for proper use of antibiotics are warranted in ICUs (Van Houten *et al*., 1998).
- Before such policies can be implemented, detailed knowledge of antibiotic prescribing patterns is important (Van Houten *et al*., 1998).
- Knowledge of antibiotic prescribing patterns and culture and sensitivity tests are critical for optimisation of antibiotic use in ICU, in particular the development and re-evaluation of the ICU antibiotic policy (Shankar *et al*., 2005; Van Houten *et al*., 1998).
- There is a need to prevent resistance by developing and implementing guidelines for antibiotic use.
- The development of antibiotic use guidelines requires an understanding of the factors that influence antibiotic use in a particular setting.

6.1.2 Aim of the study

The aim of this study is to describe the factors that influence the use of antibiotics in the Paediatric Intensive Care Unit at Universitas Hospital from 1998 to 2007.

6.1.3 Specific objectives of the study

1. To describe the admission characteristics. This involves determining:
    - the patient demography in the PICU;
    - the prevalence of different problems/diseases on admission and during stay in the PICU;
    - the outcome and length of stay and
    - the evaluation of the PICU performance.

2. To describe the antibiotic use in the PICU. This involves:
    - identifying and describing the prevalence of the different antibiotics used in the PICU and
    - describing the antibiotic prescribing practice on admission and during stay in the PICU.

3. To describe the antibiotic resistance prevalence and pattern in the PICU.
   This involves:
    - identifying and describing the prevalence of the different bacteria cultured in patients in the PICU and
    - describing the prevalence and pattern of resistance of the common bacteria to common antibiotics used in the PICU.

4. To evaluate the factors that influence antibiotic use in the PICU.
   This involves:
    - comparing and contrasting (associating) the different parameters of the results with parameters on antibiotic use.

6.1.4 Expected Outcome

- Knowledge of the major factors that influence the use of antibiotics in the PICU at Universitas Hospital from 1998 to 2007.
- That this information will contribute to the development of improved strategies to prevent antibiotic resistance in the PICU.

6.2 Methods

6.2.1 General

This is a ten year analytical retrospective study to describe the factors relating to the patient, the antibiotic and the bacteria, influencing antibiotic use in the PICU at Universitas Hospital in Bloemfontein from January 1998 to December 2007. The study was approved by the appointed Evaluation Committee and ethical approval of the study was obtained from the Ethics Committee of the Faculty of Health Sciences, University of the Free State (ETOVS Nr 130/08). Permission by the Head of Clinical Services of Universitas Hospital as well as the Head of the Department of Paediatric and Child Health were obtained to conduct the study at Universitas Hospital and to access patients' records and files (Appendix A1 & A2 page 154-5). The attending physician at the PICU and the matron in charge were also informed regarding the study. Special arrangements were made with the Records Department to obtain the necessary information from the patient's files and records. Special arrangements were also made with the Department of Pharmacology Toxicology laboratory for the use of the hospital computer system for additional patient information regarding laboratory tests.

6.2.2 Procedures

Patients admitted during the period of January 1998 to December 2007 were identified from the admission list of the PICU. The hospital numbers for these patients were used

to access the patient records in the hospital's Records Department. Patients who met the study criteria were then selected for further evaluation.

The selection/inclusion criteria of the study:

- Patients who were admitted to the PICU at Universitas Hospital from January 1998 to December 2007 and were treated with systemic antibiotics.

The exclusion criteria of the study:

- Patients who were admitted to the PICU at Universitas Hospital from January 1998 to December 2007 and were not treated with systemic antibiotics.

Data collection

A review of records of patients admitted to the PICU at Universitas Hospital who were treated with systemic antibiotics was done. A datasheet (Appendix A3 page 156) was completed for each patient and an alternative form of identification was used to protect the patient identity (year-month-subject number: e.g. 19980101). The data captured included information on admission, the patient, the bacteria cultured and the antibiotics used. Regarding admission, the date of admission and discharge, the referral source, and the outcome were recorded. For patient information, age, gender, weight, invasive devices, underlying diseases, drug allergies and concurrent medicine use were sought. Information about the infecting bacteria was recorded together with general problems or clinical diagnosis. It included primary (problems on admission) and secondary diagnosis (complications), surgical procedures performed during the stay in the PICU as well as culture and sensitivity results. The antibiotic information included antibiotics initiated before admission to the PICU, antibiotic use during the first three days of admission, as well as antibiotics used after three days of admission (including where antibiotic therapy was stopped and changed after three days of therapy).

The availability of the information recorded on the datasheet was proven by undertaking a pilot study of ten patient files, i.e. five files from 1998 and five from 2008. As a result, information on the cost of medicines was not available and therefore this question was excluded from the final datasheet. Of note, the earlier records were no longer available;

therefore, the 1997 records could not be used to fulfill the biostatistical principle of sampling outside the study period.

6.2.3 Data analysis

Data was summarized in an Excel® spreadsheet and was analyzed using GraphPad InStat® statistical software of the Department of Pharmacology. Results were summarised using descriptive statistics, and where applicable, non-parametrical statistical methods (Mann Whitney U-test) were used for comparison of data with the level of significance at $p < 0.05$.

6.2.4 Evaluation of the PICU performance

The probability of having no patient in the PICU (P_0), the average number of patients in the system (L) and in the waiting line (Lq), the average length of stay (W) as well as the overall PICU utilisation (ρ) were calculated using standard formulas for a multiple server, single-line model (Render, 2003).

$$P_o = \frac{1}{\sum_{n=0}^{m-1} \frac{(\lambda/\mu)^n}{n!} + \frac{(\lambda/\mu)^m}{m!}\left(\frac{m\mu}{m\mu-\lambda}\right)}$$

$L = (\lambda/\mu)$, $Lq = L - (\lambda/\mu)$, $W = (L/\lambda)$, $\rho = (\lambda/m\mu)$, m = number of beds (service channels), μ = service rate (patients/day)

However, the arrival rates and length of stay in the PICU were tested for Poisson distribution and exponential probability distribution respectively, before using them in the calculation of the PICU utilisation by the Queuing (waiting line) Theory (Render, 2003).

Poisson distribution was illustrated by plotting Poisson probability versus the estimated arrival rates (x) derived from the equation: $P(x) = \frac{\lambda^x e^{-\lambda}}{x!}$

where λ = actual arrival rate in the study sample.

CHAPTER 7

RESULTS PART I:
ADMISSION CHARACTERISTICS

This chapter consists of three sections, namely PICU and patient demography, admission characteristics and complications while in the PICU, and an evaluation of the PICU performance. The PICU is introduced with regard to location, number and pattern of admissions, followed by a detailed description of patient demography (age, gender, weight, etc.). The pattern of problems on admission, and subsequent complications while in the PICU are illustrated, after which results of the PICU performance are presented.

7.1 Admissions

The PICU is a five-bed ICU located on the tenth floor of Universitas Hospital, Bloemfontein, the only tertiary-care hospital in the Free State Province. The PICU admits acutely ill or severe cases for acute management in a favourable environment with regard to availability of equipment, medicines and expert medical teams.

From the PICU admission list, 1 305 patients were admitted over the ten-year study period (Figure 7.1A). However, because the number of patients admitted for 2002 and 2005 was too small, it was excluded from further analysis, leading to a total of 1 221 patients admitted for the eight years (Figure 7.1B & Table B1 page 158). Of these 1 221 patients, information could only be retrieved for 967 patients, and of these, 685 patients met the study criteria (received systemic antibiotics) (Figure 7.1C & Table B1 page 158).

On average, 85.6 ± 12.8 patients of the 685 (study sample) were admitted per year, with a monthly average of 7.2 ± 1.1 patients per month (Figure 7.1D & Table B2 page 158), leading to a coefficient of variation (CV%; SD/mean x 100) of approximately 15%. There was no seasonal variation in admissions.

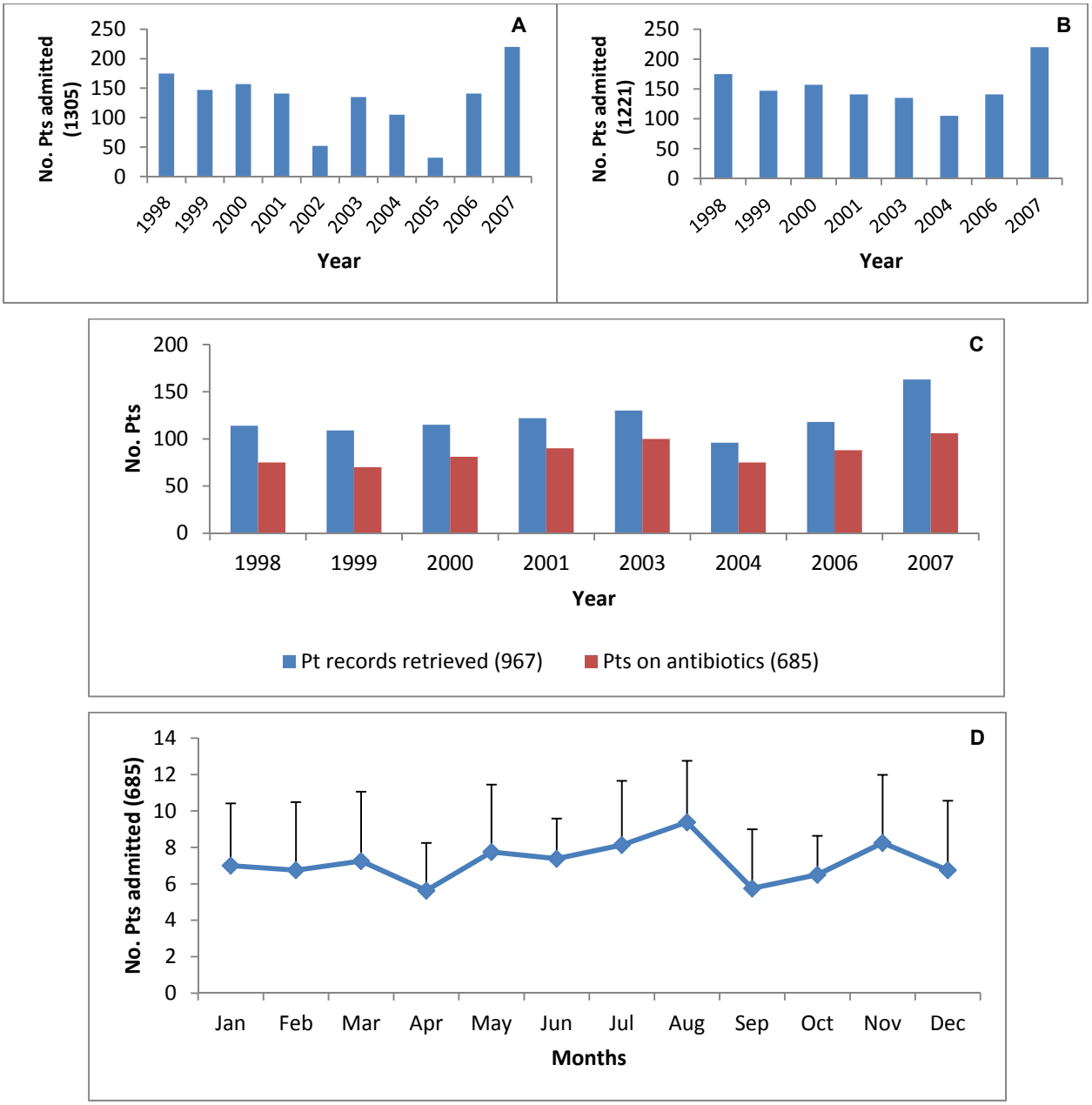


Figure 7.1: The total annual admissions over the ten-year study period (1305) (**A**), the total admissions excluding 2002 & 2005 (**B**), the number of patient records retrieved versus the number of patients meeting the study criteria per year (**C**) and the average number of patients (mean ± SD) admitted per month for the study sample (**D**)

7.2 Patient demography

7.2.1 Age

The 685 patients were divided into three age groups; children (1 to 15 years), infants (1 to 11 months) and neonates (1 to 29 days). The majority (49.2% [337/685]) of patients were children, followed by infants (41% [281/685]) (Table B3 page 159). The number in the children group was uniform from year to year with a median of 41 (32–53) per year (Figure 7.2). There was a steady increase in admission of infants from 1999 onwards with a median of 36 (19–47) per year. Admissions for the neonates remained stable over the years with a median of 9 (3–10) per year. Of note, in 2004 there was a drop in admissions for children and infants groups, most probably due to changes in the admission policy of the hospital, whereby Pelonomi Hospital became the main admission secondary hospital to Universitas Hospital in Bloemfontein.

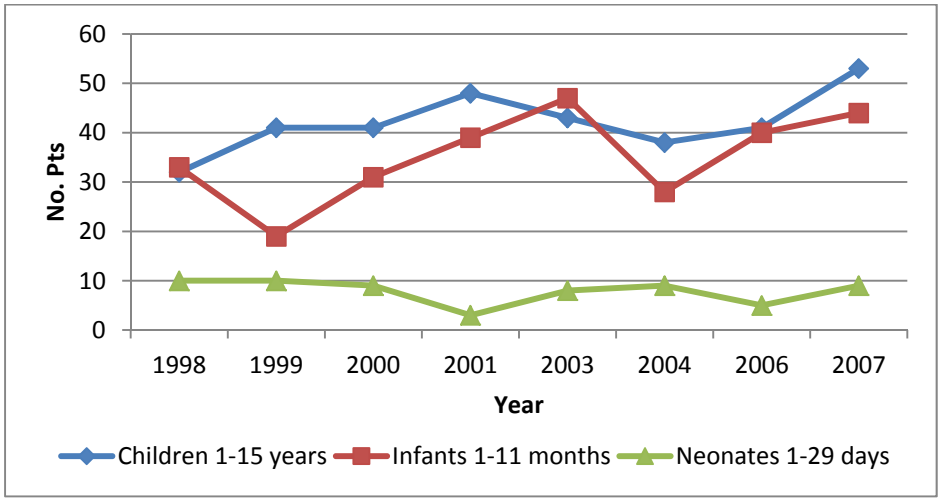


Figure 7.2: The number of patients admitted per age group per year

7.2.2 Gender

In general, more males were admitted from year to year (Figure 7.3). Male admissions accounted for 56.2% (385/685) of patients and females 43.7% (299/685) (Table B4 page 159).

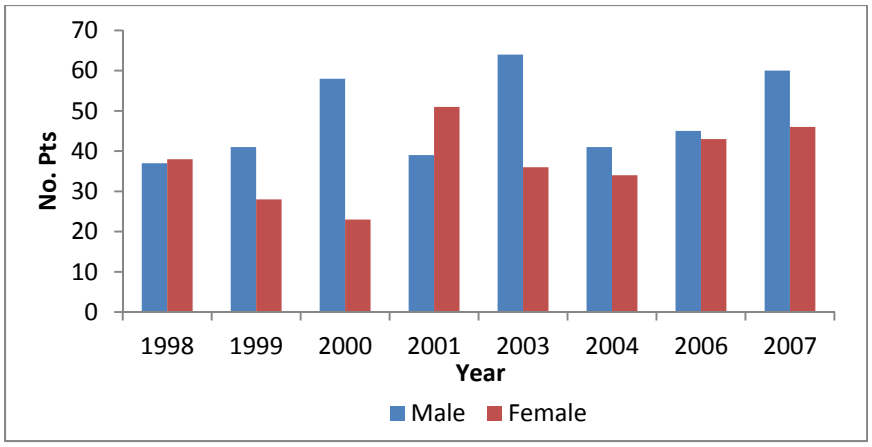
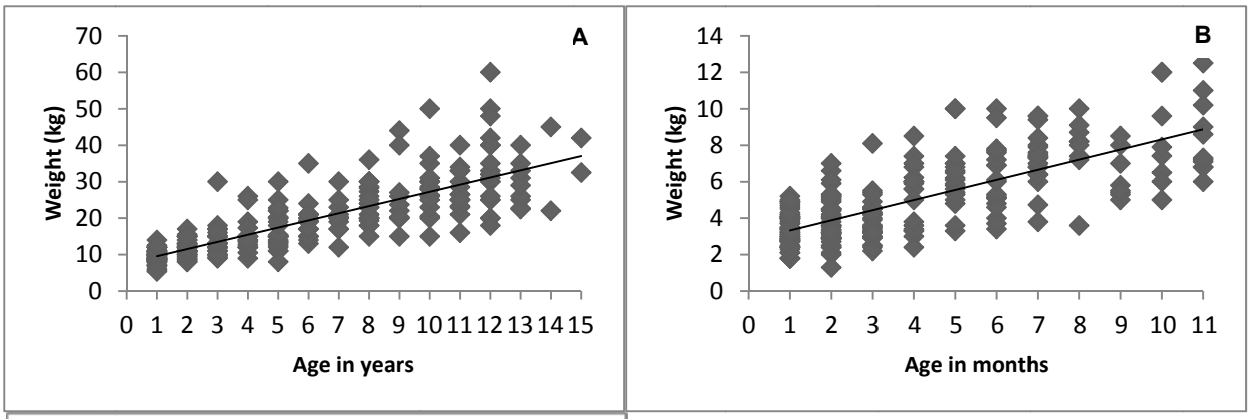


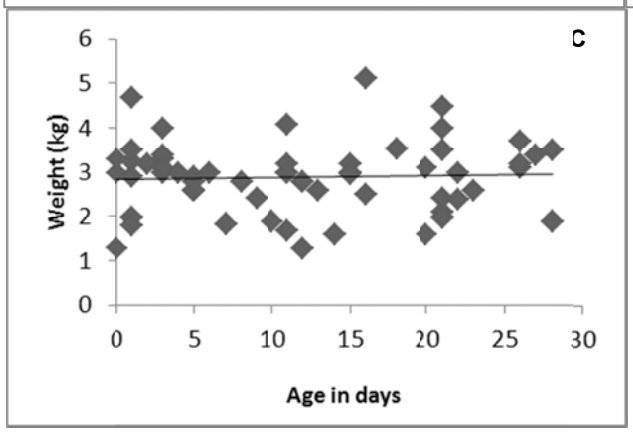
Figure 7.3: The annual gender profiles of the patients on admission to the PICU

7.2.3 Weight

Figure 7.4 shows the trend of patient weights by age for each age group. The average weight for the children group increased from 9.5 ± 2 kilograms (kg) at 1 year to 33.9 ± 11 kg at 12 years of age (Figure 7.4A). The average weight for the infants increased from 3.4 ± 0.9 kg at 1 month to 8.4 ± 2 kg at 11 months (Figure 7.4B). There was wide variation in the weights for neonates with a median of 3 (3.1–5.1) kg, with no trend detected (Figure 7.4C). The weight for the infant group was between the 2 and 25 percentile on the female growth chart.

Figure 7.5 shows the distribution of patient weight in each age group. In the children group, most patients (107) had a weight of 11–15 kg, followed by 6–10 kg (65 patients) (Figure 7.5A & Table B5i page 160). In the infants group, most patients (62) had a weight of 2.5–3.4 kg, followed by 3.5–4.4 kg (48 patients) and 4.5–5.4 kg (45 patients) (Figure 7.5B & Table B5ii page 160). In the neonates group, most patients (33) had a weight of 2.5–3.4 kg (Figure 7.5C & Table B5iii page 160).





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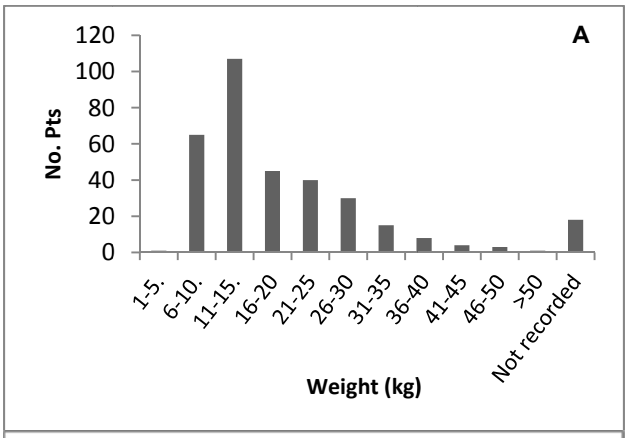

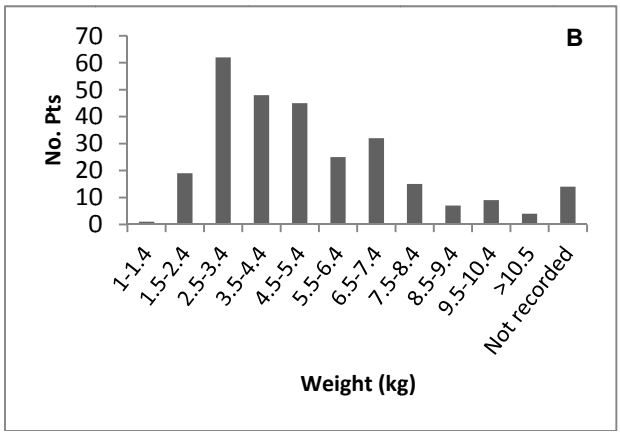

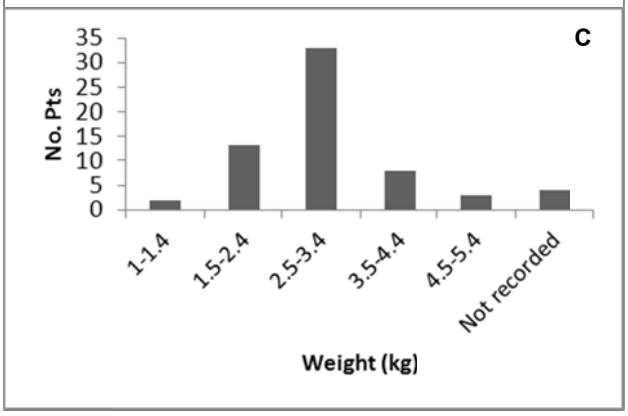

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7.3 Problems/diagnoses on admission and during stay in the PICU

7.3.1 Problems/diagnoses on admission

'Diagnoses' refer to cases where a distinct disease entity was identified, while 'problems' refer to non-disease conditions or entities such as stridor, acidosis, etc. For the purpose of this thesis, the term 'problems' was used to indicate either (diagnosis or problem). Problems on admission may or may not be the indications (reasons) for admission, and may be more than one. Overall, there were 1 735 problems on admission and most patients (69.5% [476/685]) had more than one problem on admission, implying that these patients had non-infectious underlying disorders (Figure 7.6 & Table B6 page 161).

When grouped systemically, the top ten problem groups (infectious and non-infectious) on admission accounted for 91.7% (1 591/1 735) and were: respiratory (23.4% [406/1 735]), gastro-intestinal (22% [381/1 735]), cardiovascular (19% [330/1 735]), genito-urinary (6.2% [107/1 735]), malignancies (6.1% [105/1 735]), central nervous system (5.3% [92/1 735]), haematological (4.4% [77/1 735]), HIV (2.3% [40/1 735]), endocrine (1.7% [30/1 735]) and musculo-skeletal (1.3% [23/1 735]) (Figure 7.7 & Table B7 page 161). The top three groups, i.e., respiratory, gastro-intestinal and cardiovascular problems accounted for 64.4% (1 117/1 735) of the total problems.

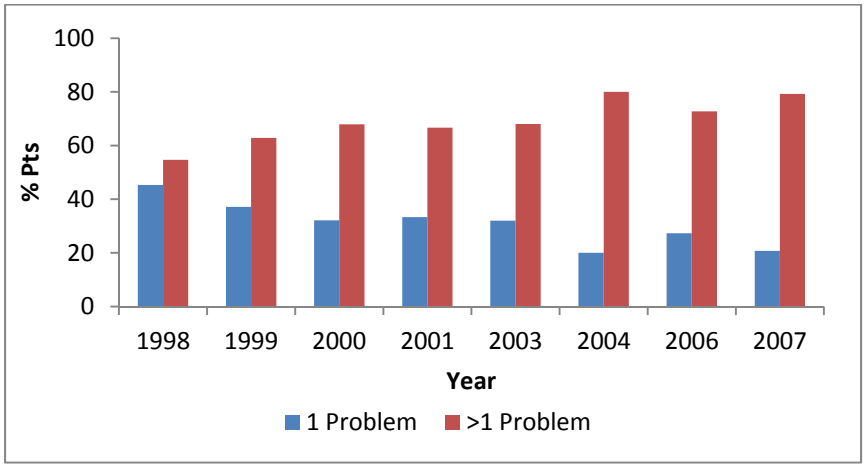


Figure 7.6: The annual proportion (%) of patients admitted with one or more problem

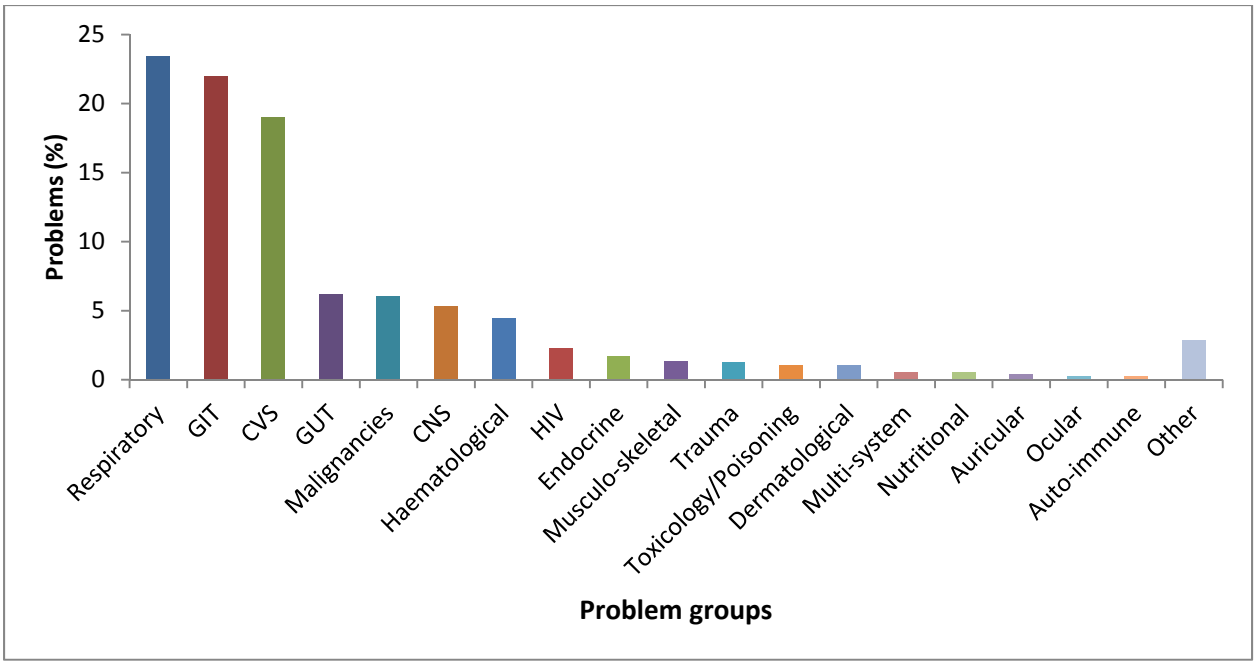


Figure 7.7: The proportion (%) of problem groups on admission

For reporting on the 'specific problems' under each of the top ten problem groups, only the 'specific problems' that occurred more than ten times (>10) were reported. Consequently, the specific problems for each problem group were as follows:

- **Respiratory**: pneumonia (8.9% [155/1 735]), tuberculosis (1% [17/1 735]), croup (0.6% [11/1 735]), respiratory obstruction (1.3% [22/1 735]), stridor (1% [18/1 735]), tracheostomy (0.8% [14/1 735]) and pleural effusion (0.7% [12/1 735]).
- **Gastro-intestinal**: bowel problems (9.4% [163/1 735]), including bowel obstruction (1.2% [21/1 735]), bowel intussusception (1.2% [20/1 735]), colostomy (1% [18/1 735]) and bowel resection (0.8% [13/1 735]), liver and bile problems (4.2% [73/1 735]), oesophageal problems (1.7% [30/1 735]), stomach problems (0.9% [16/1 735]) and pancreas problems (0.7% [12/1 735]). Congenital gastro-intestinal defects included hernias (diaphragm, inguinal and umbilical) (2.1% [23/1 735]), biliary atresia (1.1% [19/1 735]), anus imperforatum (0.7% [12/1 735] and Hirschsprung's disease (0.6% [11/1 735]).
- **Cardiovascular**: congenital heart and artery defects (8.9% [155/1 735]), including ductus arteriosus (1.8% [32/1 735]), ventricular septal defect (1.4%

[25/1 735]) and atrial septal defect (0.9% [15/1 735]), heart failure (2.5% [43/1 735]), pulmonary hypertension (1.8% [31/1 735]), pericardial effusion (0.9% [15/1 735]) and shock (0.9% [15/1 735]). Eighty-five (85) patients had congenital heart problems on admission, and 11 were diagnosed with congenital heart lesions while in the PICU.

- **Genito-urinary**: kidney problems (5% [87/1 735]), including renal failure (1.5% [26/1 735]) and urinary tract infections (1.2% [20/1 735]).
- **Malignancies**: nephroblastoma (1% [18/1 735]), brain tumours (0.9% [16/1 735]) and leukaemia (0.9% [15/1 735]).
- **Central nervous system**: convulsions / epilepsy (1% [17/1 735]), hydrocephalus (0.9% [15/1 735]), meningitis (0.8% [14/1 735]) and neural tube defects (0.8% [13/1 735])
- **Haematological**: septicaemia (2.9% [50/1 735])
- **Endocrine**: diabetes mellitus and diabetic complications (1.2% [20/1 735]) in ten patients
- **Trauma**: motor vehicle accidents (1.3% [22/1 735])
- **Auto-immune diseases** 0.3% (5 patients), of which two patients had myasthenia gravis
- Not specified sepsis 2.2% (38)

Again, there were no seasonal variations in the specific problems on admission. Of note, congenital defects accounted for 19.7% (341) of the problems on admission, and of these, 15.3% were due to cardiovascular (8.9% [155]) and gastro-intestinal (6.4% [111]) congenital defects. There were also ten patients with multi-system congenital problems.

7.3.1.1 *Referring source*

The referring source is a major factor with regard to the types of clinical problems on admission to the PICU. Infections differ depending on where the patients are referred from, i.e., patients from hospital wards are most likely to have nosocomial infections,

while patients admitted via casualty are most likely to have community-acquired infections. In this study, an average of 64.5% (442/685) of the patients were admitted via the hospital wards (including theatre), while 32.6% (223) were admitted via casualty, including patients referred from other hospitals (Figure 7.8 & Table B8 page 162). As observed earlier, there was no seasonal variation in admissions from both ward and casualty.

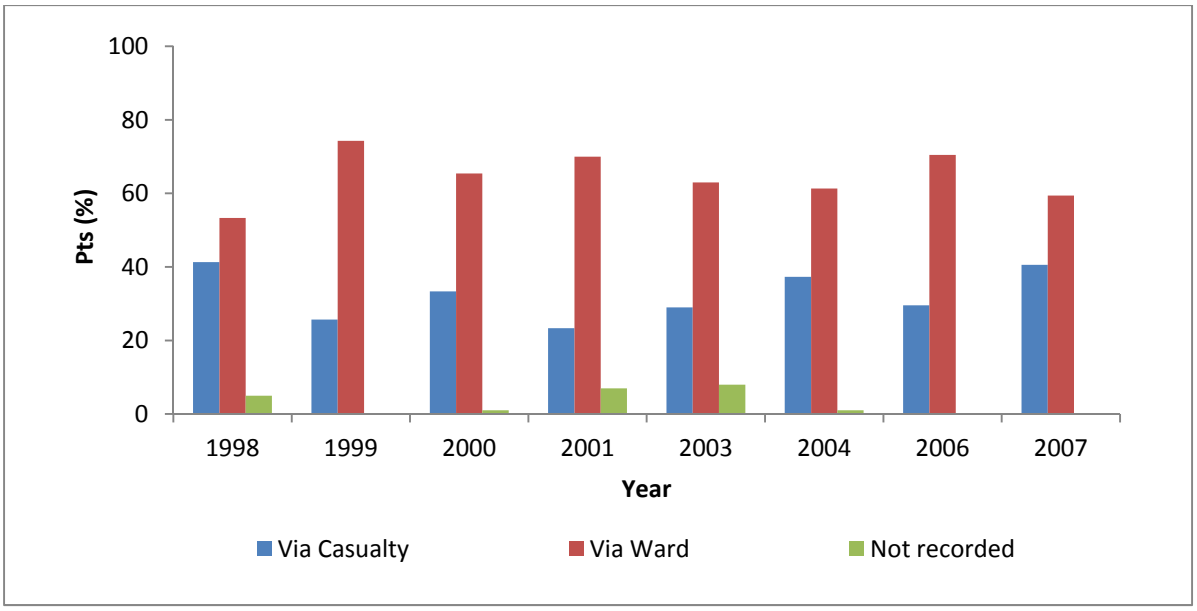


Figure 7.8: The annual proportion (%) of patients admitted via casualty and wards/theatre

7.3.1.2 *Post-operative care*

Post-operative surgery was a major factor in the clinical problems on admission, whereby 41.8% (286/685) of the patients admitted were for post-operative care after major surgery. In these patients, 345 surgical procedures were done, of which the most common were surgery for gastro-intestinal problems (172), excision of malignancies (58) and surgery for respiratory problems (37).

7.3.2 Problems/diagnoses during stay in the PICU

7.3.2.1 *Medical complications*

Medical complications include infective and non-infective complications. Examples of non-infective complications are anaemia and pneumothorax. During their stay in the PICU, 507 patients (74% [507/685]) developed complications, of which 61% (309/507) patients had infections. Overall, there were 1 875 medical complications, of which 500 (26.7%) were infective complications, and these included fungal infections. When the medical complications were grouped by systems, the top ten accounted for 93.2% (1 747/1 875) of the complications and they were: respiratory (28.5% [534/1 875]), genito-urinary (17% [318/1 875]), haematological (16% [300/1 875]), cardiovascular (8.3% [156/1 875]), gastro-intestinal (7.7% [145/1 875]), central nervous system (4.2% [78/1 875]), dermatological (3.8% [71/1 875]), endocrine (3.8% [71/1 875]), temperature abnormalities (2.7% [51/1 875]) and toxicology/poisoning (1.2% [23/1 875]). The top three groups, i.e., respiratory, genito-urinary and haematological problems accounted for 61.4% (1 152/1 875) of the total medical complications.

Regarding the infective complications (500), the most common (>5% each) infections accounted for 61.4% (307/500), namely pneumonia (35.6% [178/500]), septicaemia (11.4% [57/500]), urinary tract infections (8.8% [44/500]) and wound sepsis (5.6% [28/500]). The fungal infections accounted for 15.4% (77/500) of infective complications.

7.3.2.2 *Surgical procedures*

Surgical procedures here refer to operations for problems that developed in patients while in the PICU. A total of 157 patients underwent 207 surgical procedures while in the PICU. The top three surgical groups were: gastro-intestinal (32.9% [68/207]), respiratory (29.5% [61/207]) and cardiovascular (18.8% [39/207]) procedures, and accounted for 81.2% (168/207) of all the surgical procedures done.

7.3.2.3 *Invasive devices*

Overall, 99% (679) of the study sample had invasive devices while in the PICU (Table B9i page 162). Intravenous lines were the most common (99.9% [678/679]), followed by endotracheal tubes (49.9% [339/679]) and urinary catheters (31.8% [216/679]) (Figure 7.9 & Table B9ii page 162).

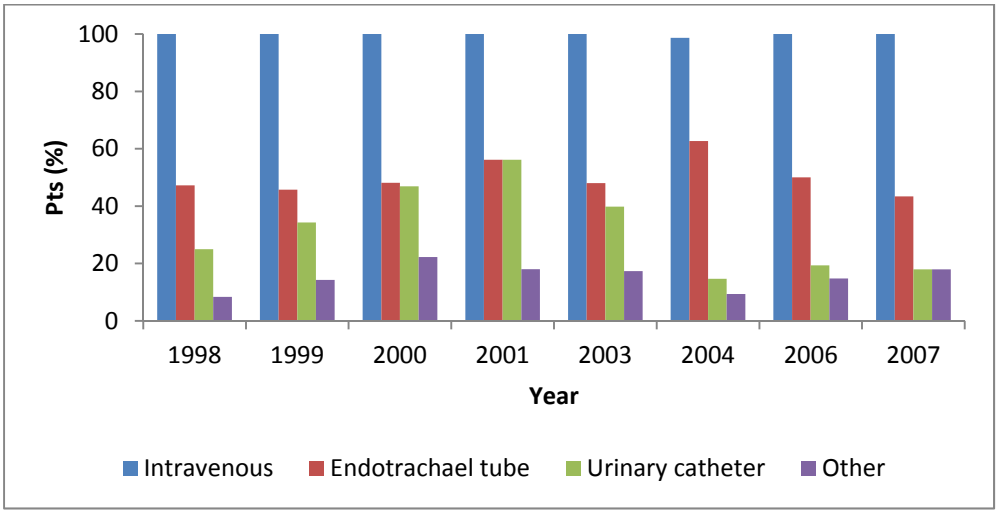


Figure 7.9: The annual proportion (%) of patients with different invasive devices

7.3.2.4 *Antibiotic allergies*

Ten patients (1.5%) were allergic to antibiotics (Table B10 page 163). Six patients were known to be allergic to a specific antibiotic, but four patients were identified while on antibiotic therapy in the PICU. These patients presented with allergic rashes while on the antibiotics and the therapy was subsequently stopped. These patients included one on penicillin, two on vancomycin and one on cefotaxime. The most common allergies were penicillin (four) and co-trimoxazole (three). The two patients that were diagnosed to be allergic to penicillin accounted for 0.95% of all the patients that were on penicillin therapy in the PICU.

7.4 Outcome and length of stay in the PICU

7.4.1 Outcome

Overall, 40 patients died during stay in the PICU and 642 patients were discharged to paediatric wards or home. This gives an average mortality rate of 5.8% (Figure 7.10 & Table B11 page 163). Six of the 40 patients were one month old.

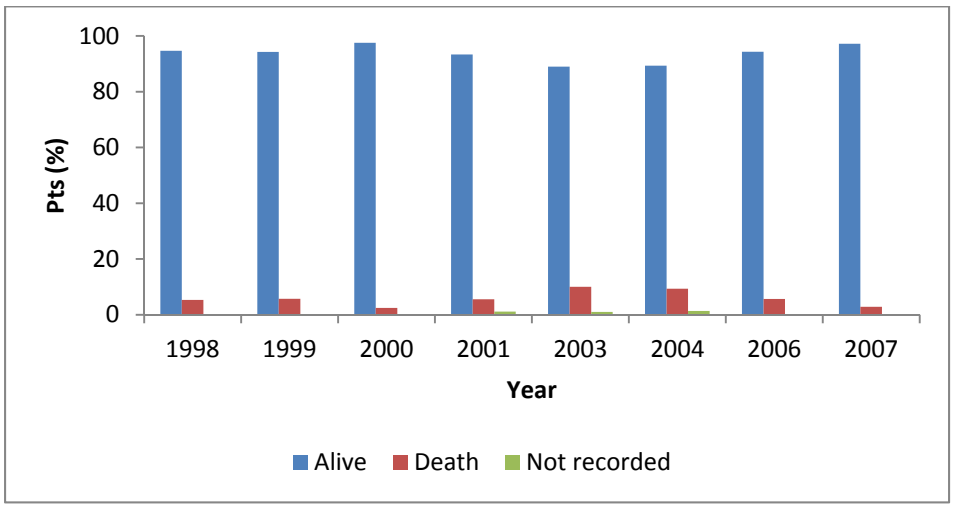


Figure 7.10: The annual proportion (%) of outcomes for patients treated in the PICU

7.4.2 Length of stay (LOS) in the PICU

The LOS in the PICU ranged between 1 day and 65 days, with an average of 7.5 (7.48) days and a median of 5 days (SD 6.77) for 679 patients. Twenty-six percent (26% [178/685]) of the patients stayed in the PICU for 1 to 3 days, 51% (348/685) of the patients stayed for 4 to 9 days and 22.3% (153/685) stayed 10 days and longer (Figure 7.11 & Table B12 page 164). In general, most patients (73.1% [501/685]) stayed longer than 3 days in the PICU. Of the 178 patients who stayed for 1 to 3 days in the PICU, 97 (54.5%) patients were children (aged 1-15 years) and 67 (37.6%) patients were infants (aged 1-11 months). Of the 348 patients who stayed for 4 to 9 days in the PICU, 186 (53.5%) patients were children and 131 (37.6%) patients were infants (Figure 7.12 & Table B13 page 164).

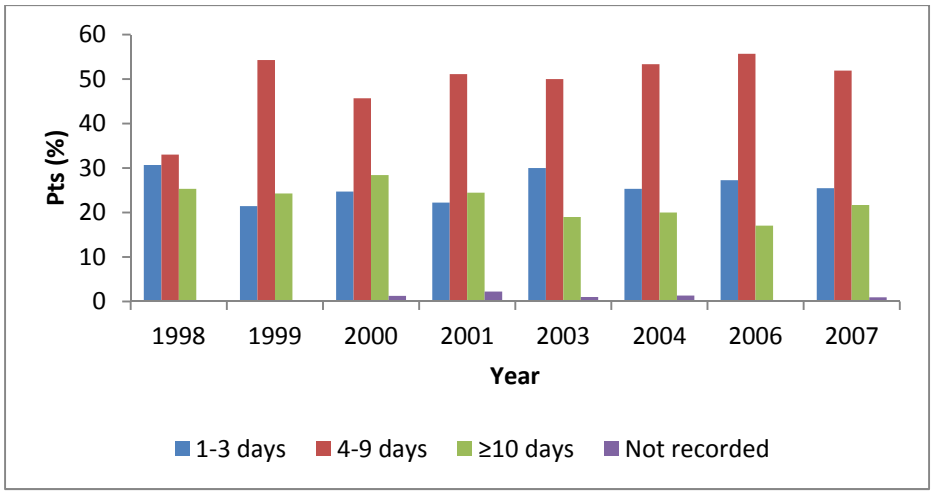


Figure 7.11: The annual proportion (%) of patients for each length of stay in the PICU

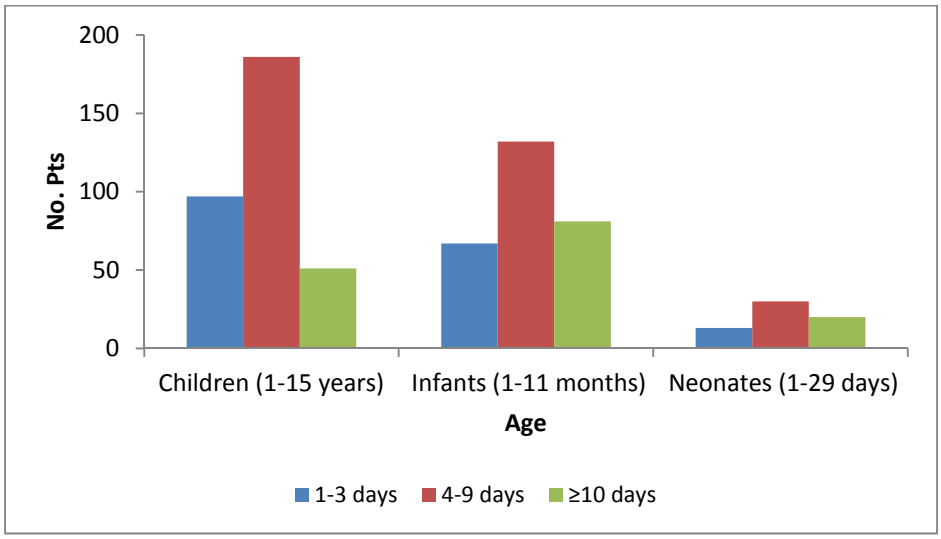


Figure 7.12: The number of patients for each length of stay per age group

7.5 Evaluation of the PICU performance

Evaluation of the PICU performance involved analysis of admission rates, length of stay (LOS) in the PICU and rate of PICU utilisation using the Queuing Theory.

Firstly, because the PICU had a single system through which the booking was made, and it had 5 beds, it was best described as a Multiple-Server, Single-Line Model (Figure 7.13).

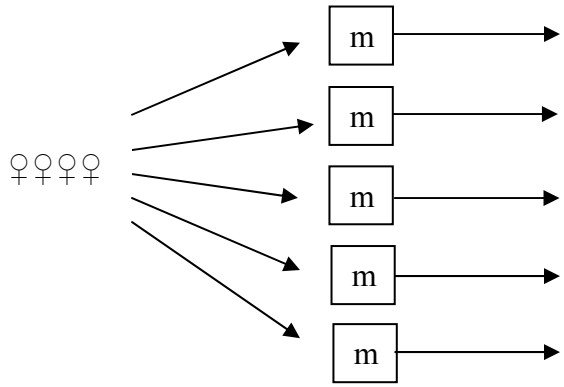


Figure 7.13: An illustration of a Phase/Multiple Server System

Since arrival at the PICU was random, and most of the time was on a first come, first served basis, the data were subjected to queuing theory in order to determine:

- the probability that no patients are in the PICU;
- the average number of patients (L_q) in the waiting line;
- the average number of patients in the system (L), both waiting and being served;
- the average time a patient spends in the system (W or LOS);
- the average time a patient spends in the queue waiting for service (W_q) and
- the average PICU utilisation rate (ρ: bed utilisation).

However, as indicated earlier, in order to apply the Queuing Theory, the distribution of arrivals must be shown to exhibit a 'Poisson distribution', and the service times (LOS) must be shown to exhibit an 'exponential probability distribution'. Figure 7.14A illustrates the Poisson distribution of arrivals for the total study period, while Figure 7.14B illustrates the exponential probability distribution of service times (LOS) for the same period. The detailed calculations were done using the Excel® program data analysis tool (not shown).

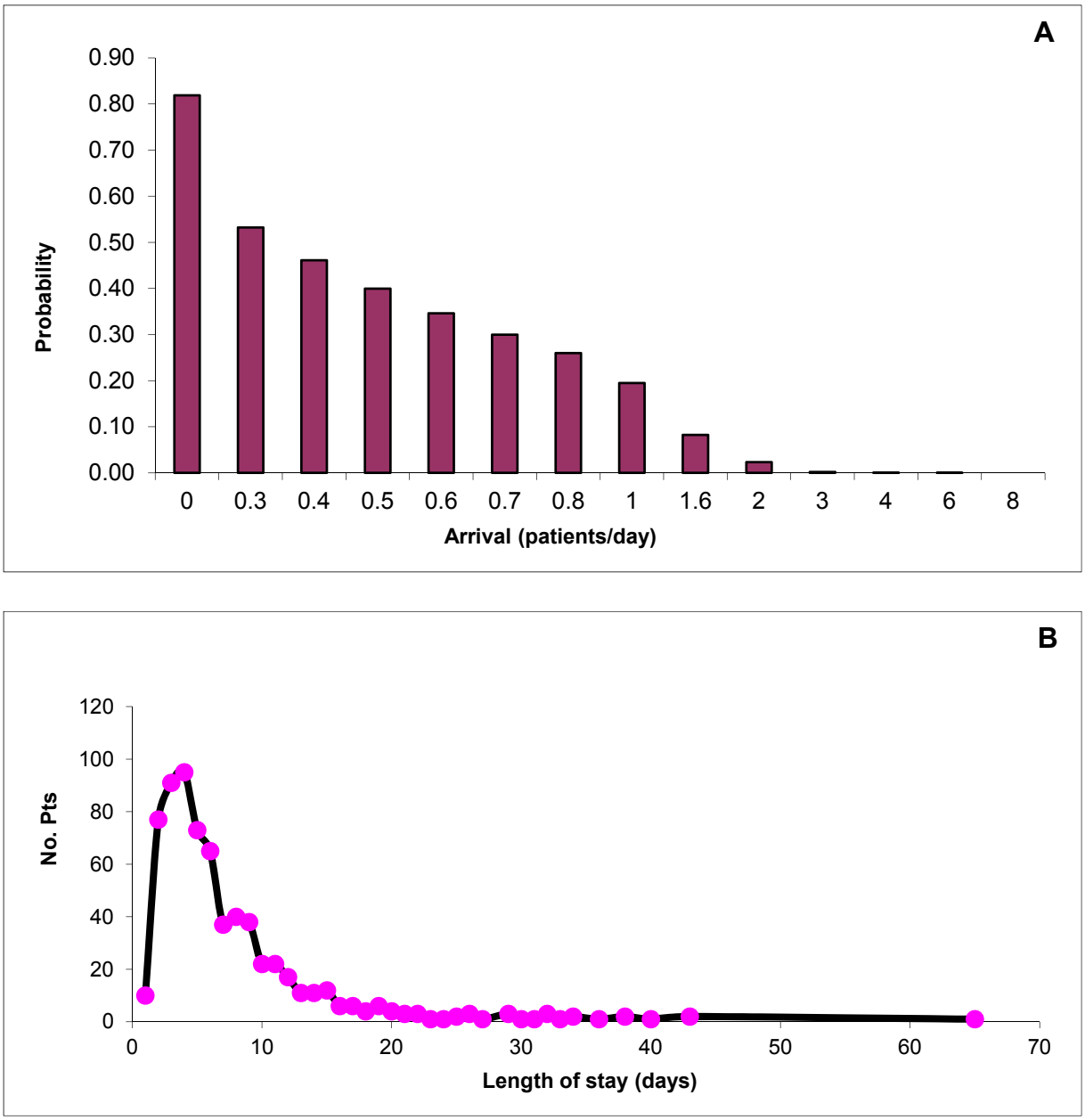


Figure 7.14: An illustration of Poisson distribution for the arrival rate for admissions (**A**) and exponential probability distribution for length of stay in the PICU (**B**)

7.5.1 Application of the Queuing Theory

Since the distribution of arrivals exhibited a 'Poisson distribution', and the service times (LOS) exhibited an 'exponential probability distribution', the queuing theory formulas were applied to derive the appropriate parameters mentioned earlier as follows (Appendix B1 page 165):

7. The probability that no patients are in the PICU is:

$$P_o = \frac{1}{\sum_{n=0}^{m-1} \frac{(\lambda/\mu)^n}{n!} + \frac{(\lambda/\mu)^m}{m!}\left(\frac{m\mu}{m\mu-\lambda}\right)}$$ = 0.000795 ≈ **0.0**

Therefore, the probability of having no patient in the PICU is zero.

8. The average number of patients (L_q) in the waiting line is:

$$L_q = \frac{(\lambda/\mu)^m \lambda\mu}{(m-1)!(m\mu-\lambda)^2} P_o$$ = **0.0**

There were no patients in the waiting line or queue waiting for service.

9. the average number of patients in the system (L), both waiting and being served:

$L = L_q + (\lambda/\mu)$ = 3.1642 = **4 patients**

10. The average time a patient spends in the system (W or LOS):

$W = 1/\mu = L/\lambda$ = 7.462687 = **7.5 days**

11. The average time a patient spends in the queue waiting for service (W_q):

$W_q = L_q/\lambda$ = **0.0**

There were no patients in the waiting line or queue waiting for service.

12. The average PICU utilisation rate (ρ: bed utilisation):

$(\rho) = (\lambda/m\mu)$ = 0.632836 = **63%**

This implies that on average only 63% of the bed capacity is used.

7.6 Summary

a) Regarding general admission and patient demography:

- 685 patients received antibiotics, which was 70.8% of the retrieved records (967) and 56.1% of the admitted patients (1 221).
- An average of 85.6 ± 12.8 patients (of the 685) was admitted every year.
- The majority of admissions were children between 1–15 years of age (49.2%), followed by infants (41%), with more males (56.2%) admitted than females (43.7%).

b) Regarding problems on admission:

- The 685 patients had 1 735 problems on admission, and these were either infective or non-infective.
- The top three problem groups accounted for 64.4% and were respiratory (23.4%), gastro-intestinal (22%) and cardiovascular (19%).
- For respiratory problems, pneumonia accounted for 38.2% (155/406).
- Most patients (64.5%) were referred from the hospital wards and theatre, whereby theatre referrals accounted for 41.8%.

c) Regarding problems during stay in the PICU:

- Medical complications:
    - 507 patients (74%) developed complications, and of these, 61% (309/507) had infections.
    - There was 1 875 medical complications of which 26.7% were due to infections.
    - The top three medical complication groups accounted for 61.4% and they were respiratory (28.5%), genito-urinary (17%) and haematological (16%).
    - The top three infective complications accounted for 55.8% of the total infective complications and were pneumonia (35.6%), septicaemia (11.1%) and UTI (8.8%).

- Surgical procedures and invasive devices:
    - 157 patients underwent 207 surgical procedures while in the PICU.
    - The top three surgical groups accounted for 81.2%: gastro-intestinal (32.9%), respiratory (29.5%) and cardiovascular (18.8%).
    - Almost all patients (99%) had invasive devices while in the PICU, whereby the intravenous lines were the most common (99.9%), followed by endotracheal tubes (49.9%) and urinary catheters (31.8%).

d) Regarding outcome and length of stay in the PICU:

- 5.8% of patients died while in the PICU.
- The average length of stay was 7.5 days and 51% of the patients stayed for 4 to 9 days, while 26% of the patients stayed for 1 to 3 days.

e) Regarding the PICU performance:

- The PICU operated in such a way that there were no patients waiting to be admitted, i.e., no patients in waiting lines.
- At any particular time, four patients were being served in the PICU.
- The average length of stay was 7.5 days.
- The PICU utilisation or bed occupancy was 63%.

CHAPTER 8

RESULTS Part II
ANTIBIOTIC USE IN THE PICU PATIENTS

This section describes the pattern of antibiotic use with regard to number, type (chemical group or spectrum of activity), regimen (combination), time of admission and during the stay in the PICU, as well as specific indication or underlying problems, age and other relevant factors that can influence antibiotic prescribing. This is reported, starting with an overview on all the antibiotics prescribed in the PICU. Thereafter, antibiotics initiated before admission and continued in the PICU, followed by antibiotics used within the first three days, antibiotics used after three days, antibiotic combinations, as well as the relationship between antibiotic use and clinical problems/diagnosis, age, and concurrent medicines are reported.

8.1 An overview of the antibiotics prescribed

As it were, 685 patients (study sample) received antibiotic therapy in the PICU, which implies that 70.8% (685/967) of patients admitted to the PICU received antibiotics. In the same perspective, on average, 85.6 ± 12.8 patients received antibiotics per year, leading to a monthly average of 7.2 ± 1.1 patients per month. Figure 8.1 shows the proportion of patients on antibiotics at different times in the PICU, i.e., prescribed before admission and continued, within the first three days and after three days in the PICU. Approximately 29% ± 5.8% of patients were on antibiotics before admission, 79.9% ± 3.3% were prescribed (including modification of antibiotic regimens) in the first three days, and 23.2% ± 4.6% required adjustment on antibiotic therapy after three days (Table C1 page 166).

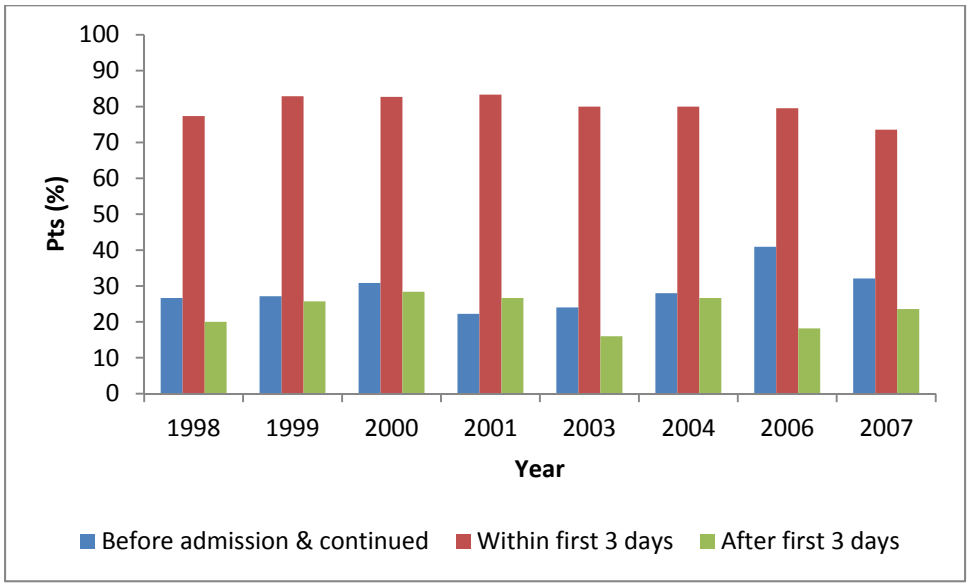


Figure 8.1: The proportion (%) of patients on antibiotics at different times in the PICU

A total of 38 different antibiotics were prescribed in the PICU over the study period, with an annual median of 25 (20–28) antibiotics per year (Figure 8.2 & Table C2 page 167). However, of the 1 571 antibiotic prescriptions over the study period, the top ten antibiotics accounted for 81.2% (1 276/1 571) and these were: cefotaxime (18.2% [286/1 571]), amikacin (14.7% [231/1 571]), vancomycin (9.8% [154/1 571]), cefuroxime (8.1% [127/1 571]), imipenem (7.5% [118/1 571]), metronidazole (7.2% [113/1 571]), penicillin G (6.5% [102/1 571]), cloxacillin (4.1% [64/1 571]), co-trimoxazole (2.7% [43/1 571]) and gentamicin (2.4% [38/1 571]).

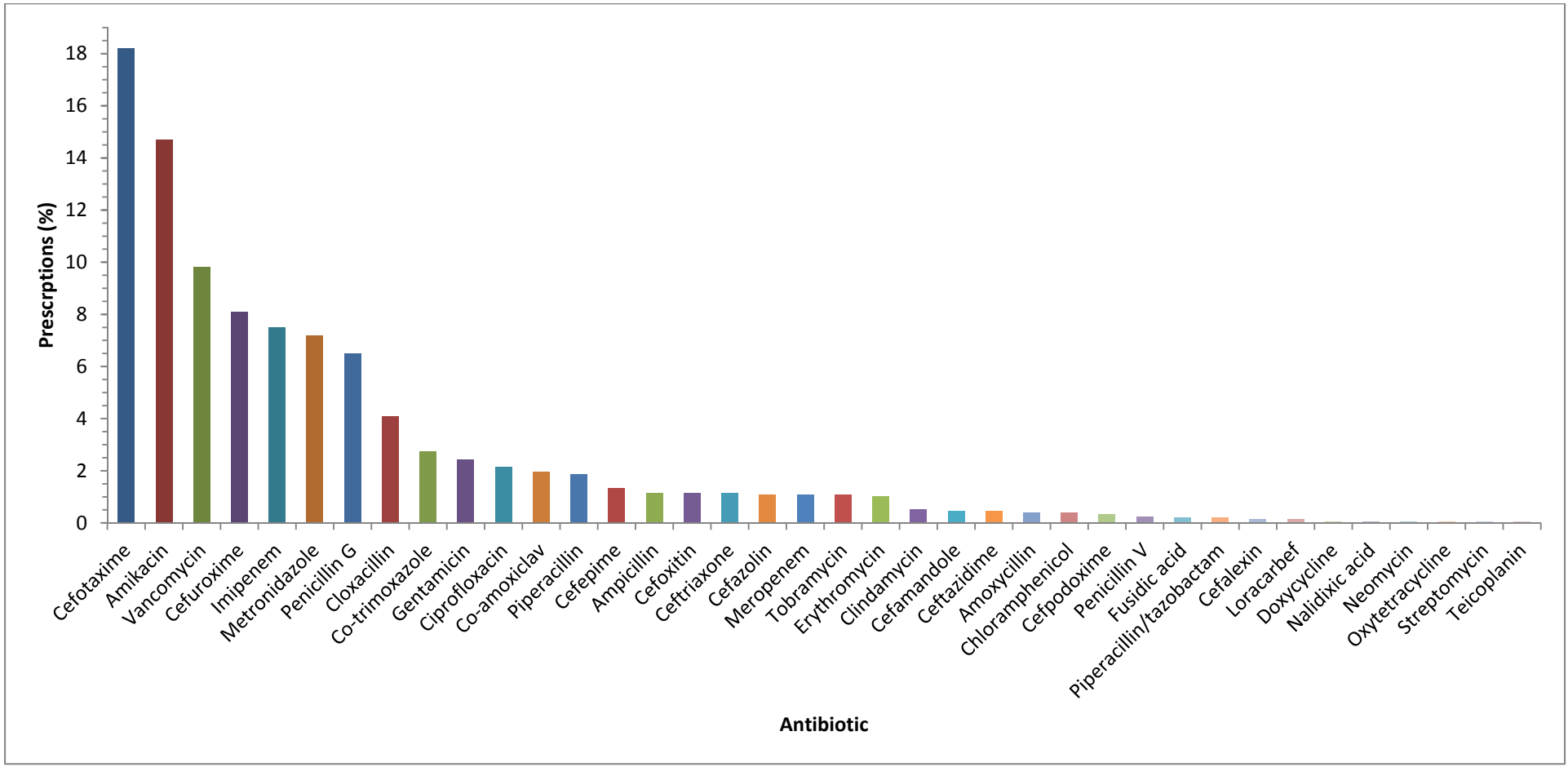


Figure 8.2: The proportion (%) of individual antibiotic prescriptions for the 38 antibiotics used in the PICU from 1998–2007

Even then, most of the antibiotics commonly used in the PICU exhibited wide differences in their use as either single or combination regimens. For example:

- cefotaxime was prescribed 151 times as a single agent, versus 135 times as part of a combination regimen;
- amikacin was prescribed 10 times as a single agent, versus 221 times as part of a combination regimen;
- penicillin G was prescribed eight times as a single agent, versus 94 times as part of a combination regimen;
- cefuroxime was prescribed 70 times as a single agent, versus 57 times as part of a combination regimen;
- vancomycin was prescribed five times as a single agent, versus 149 times as part of a combination regimen and
- imipenem was prescribed 13 times as a single agent, versus 105 times as part of a combination regimen.

There was no remarkable seasonal (annual) variation in the use of the top ten antibiotics (Figure 8.3). However, the pattern of amikacin and penicillin G use was in unison because they are used as a combination. Also, there was a progressive increase in the use of co-trimoxazole from 2000 (four prescriptions) to 2007 (10 prescriptions), most probably due to the treatment of opportunistic infections (*Pneumocystis jiroveci*) and some nosocomial infections (*Stenotrophomonas*). There was also progressively increased use of the new-comer meropenem, especially from 2004 (three prescriptions) to 2007 (nine prescriptions).

Sixty-six percent (66%) of the top ten antibiotics were broad-spectrum and bactericidal, while 34% were narrow-spectrum and bactericidal (vancomycin, metronidazole, penicillin G and cloxacillin). This preference for bactericidal antibiotics was also exhibited even after classifying prescriptions per antibiotic group used in the PICU where 98% (1 539/1 571) of prescriptions were for bactericidal antibiotics versus 2% (32/1 571) for the bacteriostatic antibiotics (Table C3 page 168). The top five bactericidal antibiotic groups were: cephalosporins (32.5% [510/1 571]),

aminoglycosides (18.3% [288/1 571]), penicillins (16.4% [257/1 571]), glycopeptides (9.9% [155/1 571]) and carbapenems (8.6% [135/1 571]), while the bacteriostatic antibiotics were mainly erythromycin (macrolides) (1% [16/1 571]), clindamycin (lincosamides) (0.5% [8/1 571]) and chloramphenicol (amphenicols) (0.4% [6/1 571]) (Figure 8.4A & 8.4B).

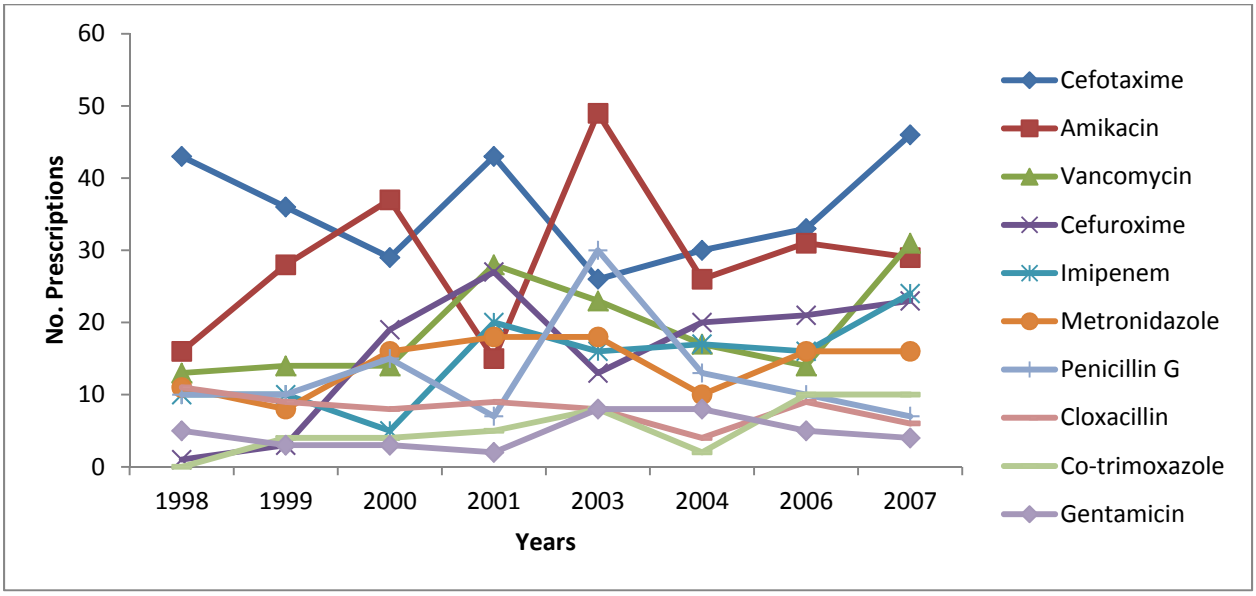


Figure 8.3: The annual number of prescriptions for the top ten antibiotics used in the PICU

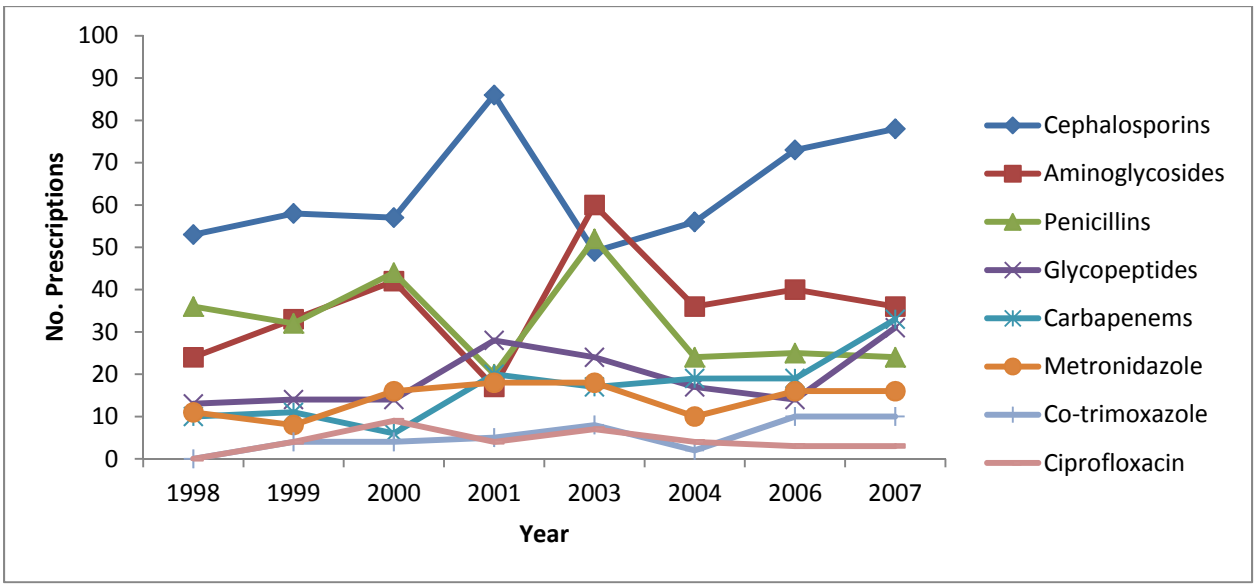


Figure 8.4A: The annual number of prescriptions for bactericidal antibiotics used in the PICU

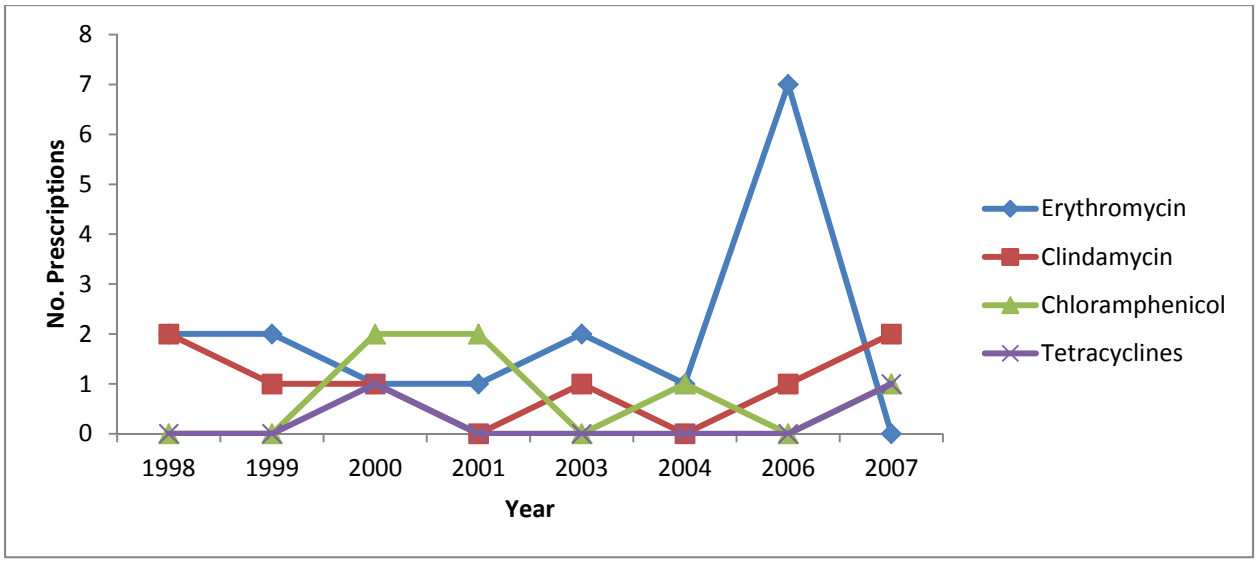


Figure 8.4B: The annual number of prescriptions for bacteriostatic antibiotics used in the PICU

8.2 Antibiotics initiated before admission and continued in the PICU

Initially 35% (240/685) of patients were admitted to the PICU while on antibiotics initiated from the referral source, but antibiotics were stopped in 41 of these patients (Table C4 page 168). Effectively, 29.1% (199/685) of patients continued with antibiotics initiated before admission.

For the afore mentioned 199 patients, a total of 31 different antibiotics were prescribed, with an annual median of 13 (9–17) antibiotics per year (Figure 8.5 & Table C5 page 169). Of the 292 antibiotic prescriptions over the study period for this phase, the top nine antibiotics accounted for 81.8% (239/292) and they were: cefotaxime (24.3% [71/292]), amikacin (13.7% [40/292]), cefuroxime (8.2% [24/292]), imipenem (8.2% [24/292]), vancomycin (7.5% [22/292]), penicillin G (6.2% [18/292]), cloxacillin (4.8% [14/292]), metronidazole (4.5% [13/292]) and co-trimoxazole (4.5% [13/292]) (Figure 8.6).

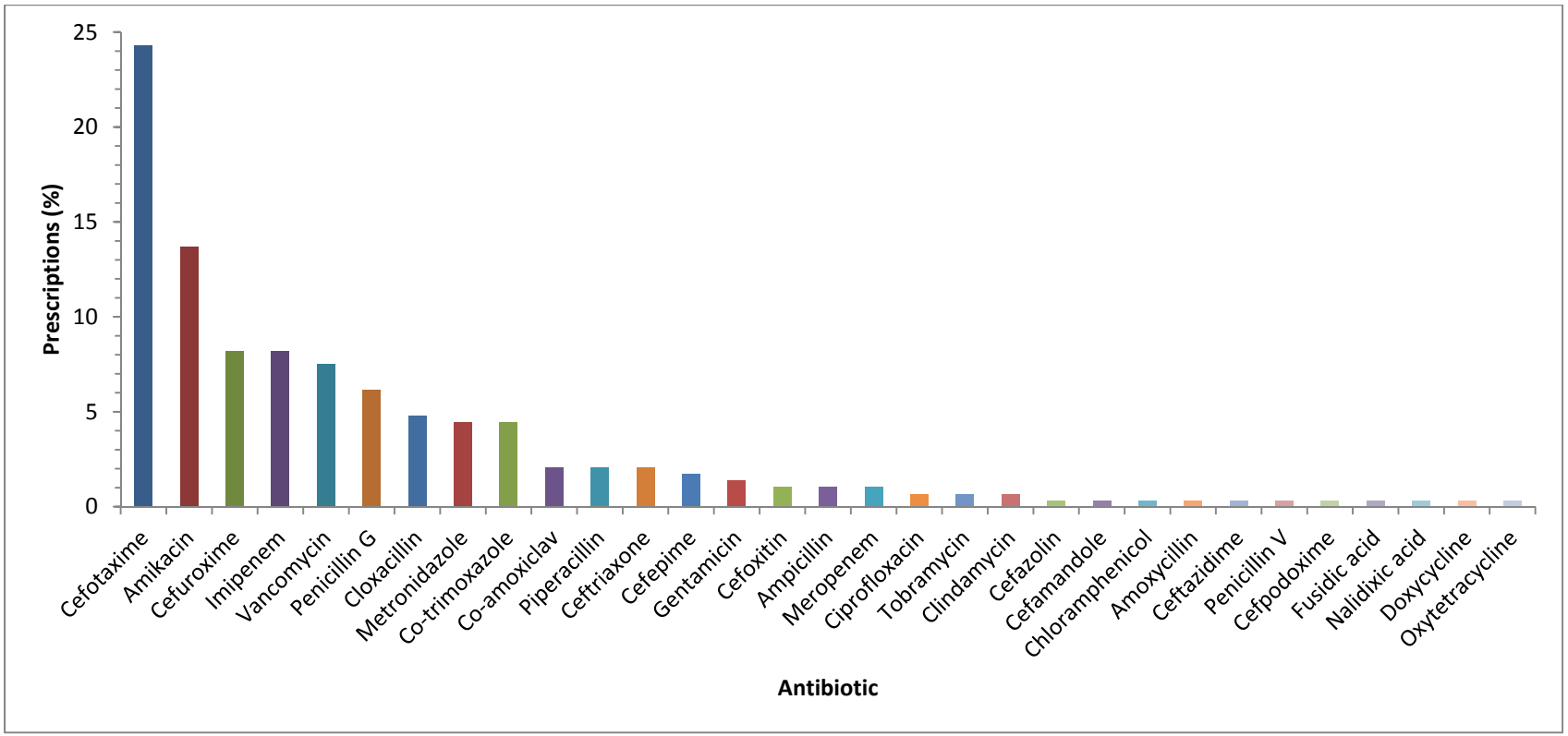


Figure 8.5: The proportion (%) of individual antibiotic prescriptions for the 31 antibiotics initiated before admission and continued in the PICU

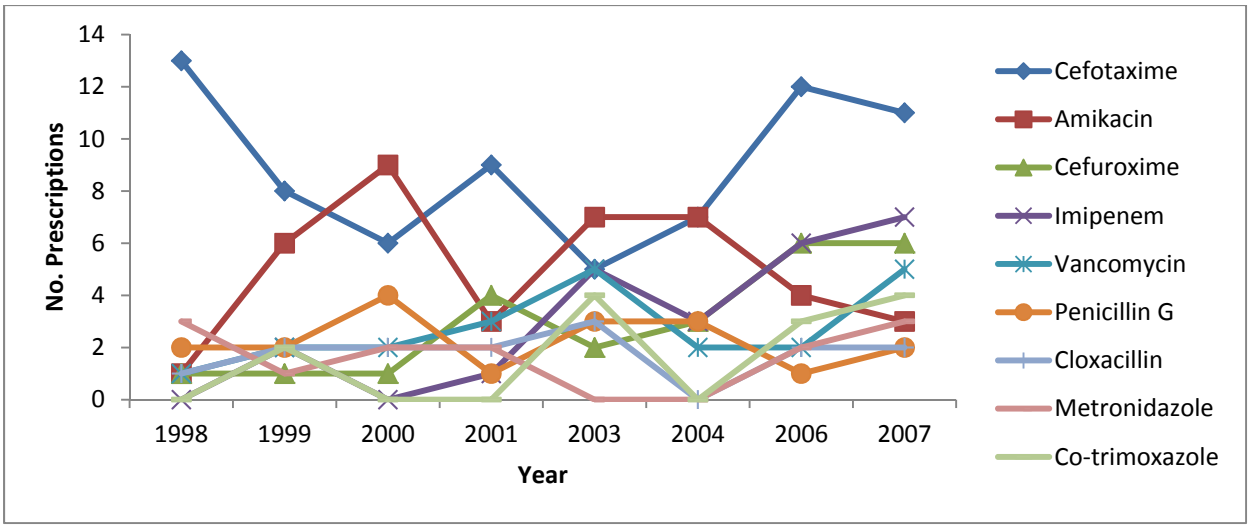


Figure 8.6: The annual number of prescriptions for the top nine antibiotics initiated before admission and continued in the PICU

Characteristically the top four antibiotics (cefotaxime, amikacin, cefuroxime and imipenem) are broad-spectrum bactericidal antibiotics, while the other four (vancomycin, penicillin G, metronidazole and cloxacillin) are narrow-spectrum bactericidal antibiotics used for more specific infections. There was no remarkable seasonal variation in antibiotic use. Overall, 98.3% (287/292) of antibiotics prescribed in the 199 patients were bactericidal, while 1.7% (5/292) were bacteriostatic (Figure 8.7 & Table C6 page 170). Of the bactericidal antibiotic groups, cephalosporins accounted for 38.7% (113/292), penicillins 16.8% (49/292), aminoglycosides 15.8% (46/292), carbapenems 9.3% (27/292) and glycopeptides 4.5% (13/292). Cephalosporins' use increased in 2004 to 2007, while carbapenems' use increased from 2001 to 2007.

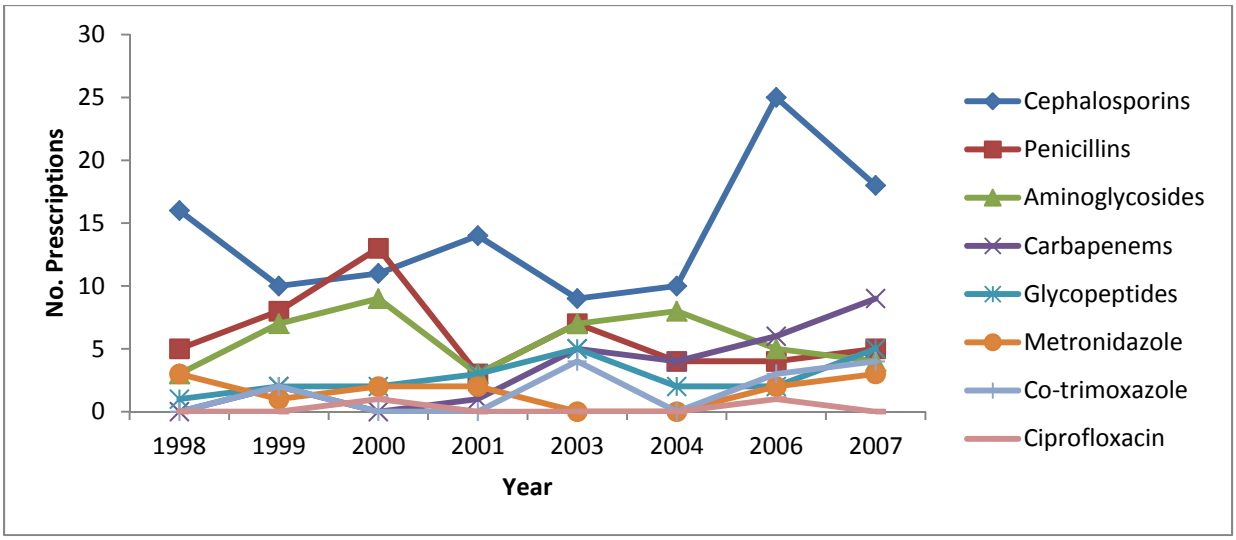


Figure 8.7: The annual number of prescriptions for bactericidal antibiotics initiated before admission and continued in the PICU

8.3 Antibiotics initiated/modified within the first three days in the PICU

In the first three days, 79.9% ± 3.3% (546/685) of patients were started on antibiotics or had their antibiotic regimen modified (Table C1 page 166). However, because 17 patients (2.5%) did not receive any antibiotics within the first three days, this implies that, overall, 97.5% (668/685) of patients were on antibiotics within the first three days of admission (including patients that were continued on the antibiotics initiated before admission).

A total of 33 different antibiotics were prescribed within the first three days of PICU stay over the study period, with an annual median of 21 (17–22) antibiotics per year (Figure 8.8 & Table C7 page 171). Of the 957 antibiotic prescriptions over the study period for this phase, the top ten antibiotics accounted for 83.2% (796/957) and they were: cefotaxime (20.2% [193/957]), amikacin (15.7% [150/957]), cefuroxime (9.5% [91/957]), metronidazole (9.2% [88/957]), penicillin G (8.5% [81/957]), vancomycin (6.8% [65/957]), cloxacillin (4.3% [41/957]), imipenem (4.1% [39/957]), co-amoxiclav (2.5% [24/957]) and gentamicin (2.5% [24/957]) (Figure 8.9).

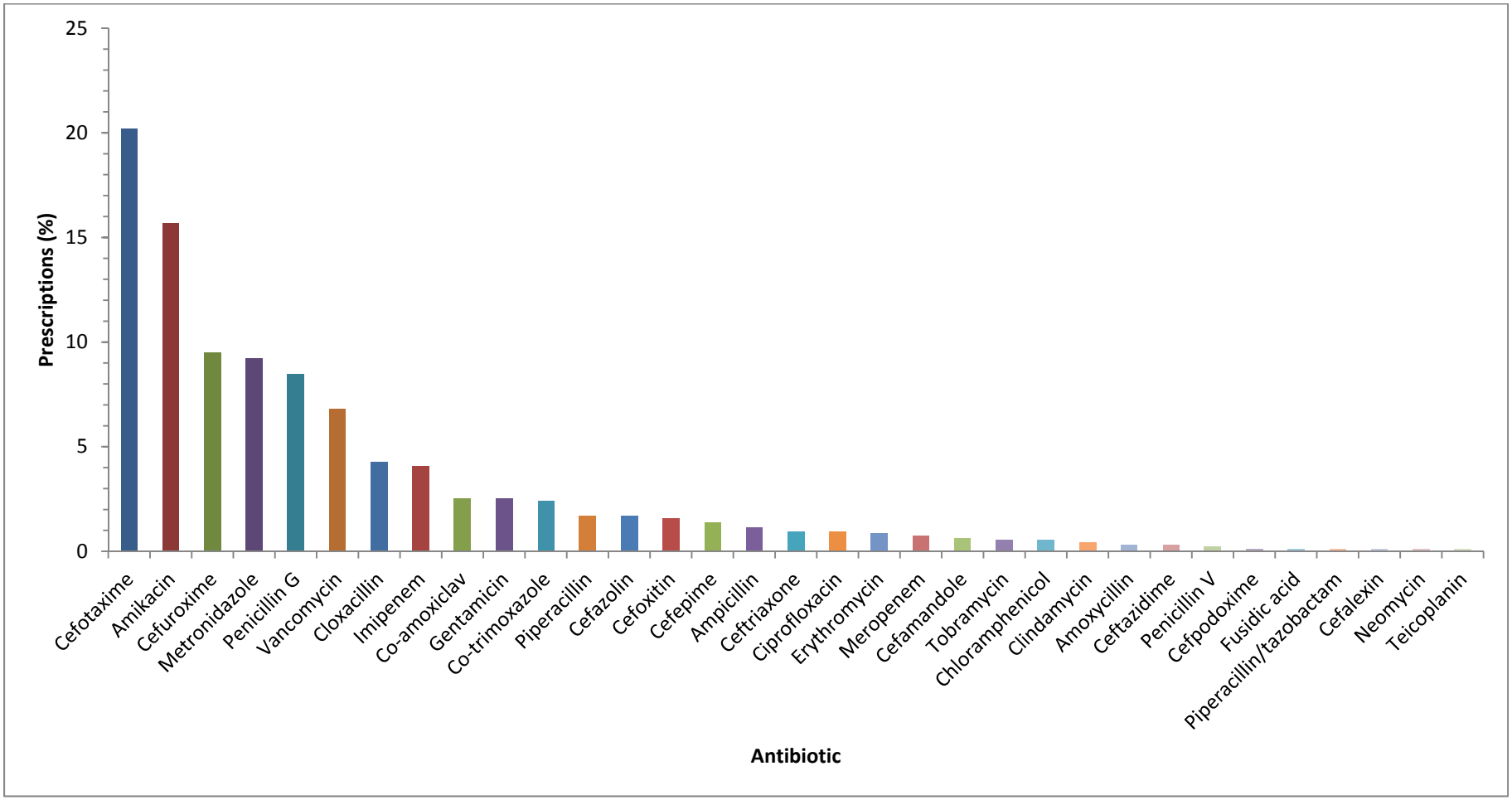


Figure 8.8: The proportion (%) of individual antibiotic prescriptions for the 33 antibiotics used within the first three days in the PICU

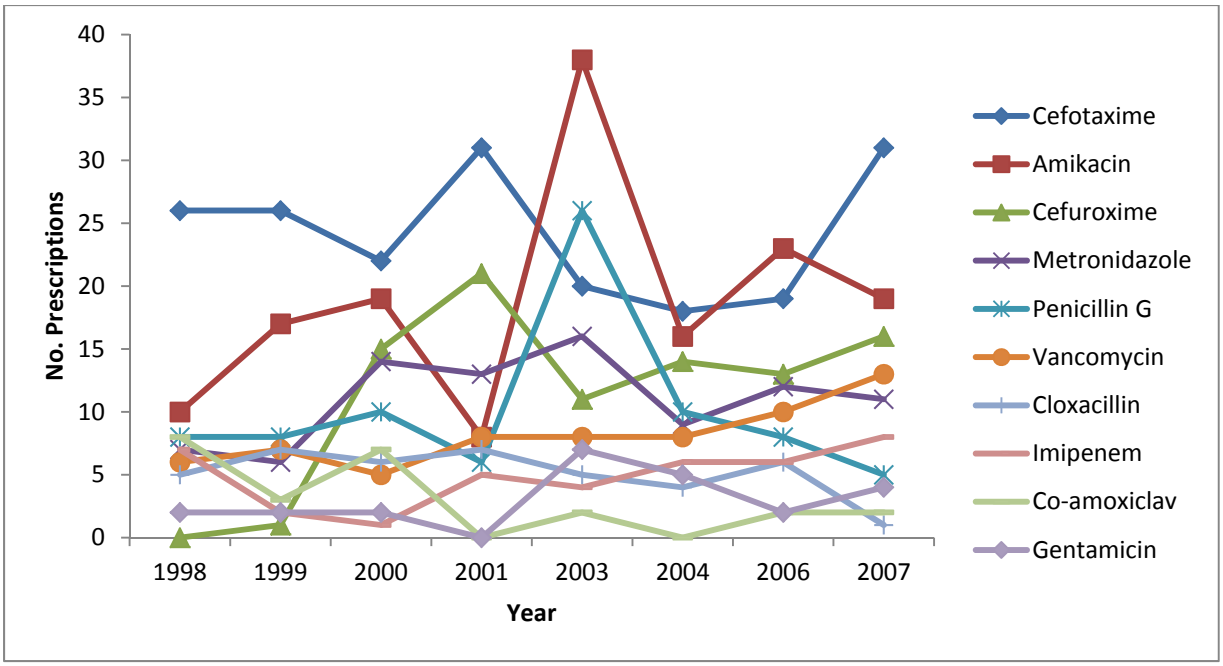


Figure 8.9: The annual number of prescriptions for the top ten antibiotics used within the first three days in the PICU

Interestingly, the pattern of antibiotic selection observed earlier was broken, whereas the top three were broad-spectrum and bactericidal antibiotics (cefotaxime, amikacin and cefuroxime), the next four were narrow-spectrum and bactericidal antibiotics (metronidazole, penicillin G, vancomycin and cloxacillin), followed by broad-spectrum and bactericidal antibiotics (imipenem and gentamicin). Of note, the top ten antibiotics were similar to those initiated before admission, except for co-trimoxazole that was replaced by gentamicin. Meropenem, cefepime and cefuroxime showed an increased use over the study period.

Overall, 98.2% (940/957) of antibiotics prescribed were bactericidal antibiotics, while 1.8% (17/957) was bacteriostatic antibiotics (Figure 8.10 & Table C8 page 172). Of the bactericidal antibiotics, cephalosporins accounted for 36.4% (348/957), aminoglycosides 18.8% (180/957), penicillins 18.7% (179/957), metronidazole 9.2% (88/957) and glycopeptides 6.9% (66/957).

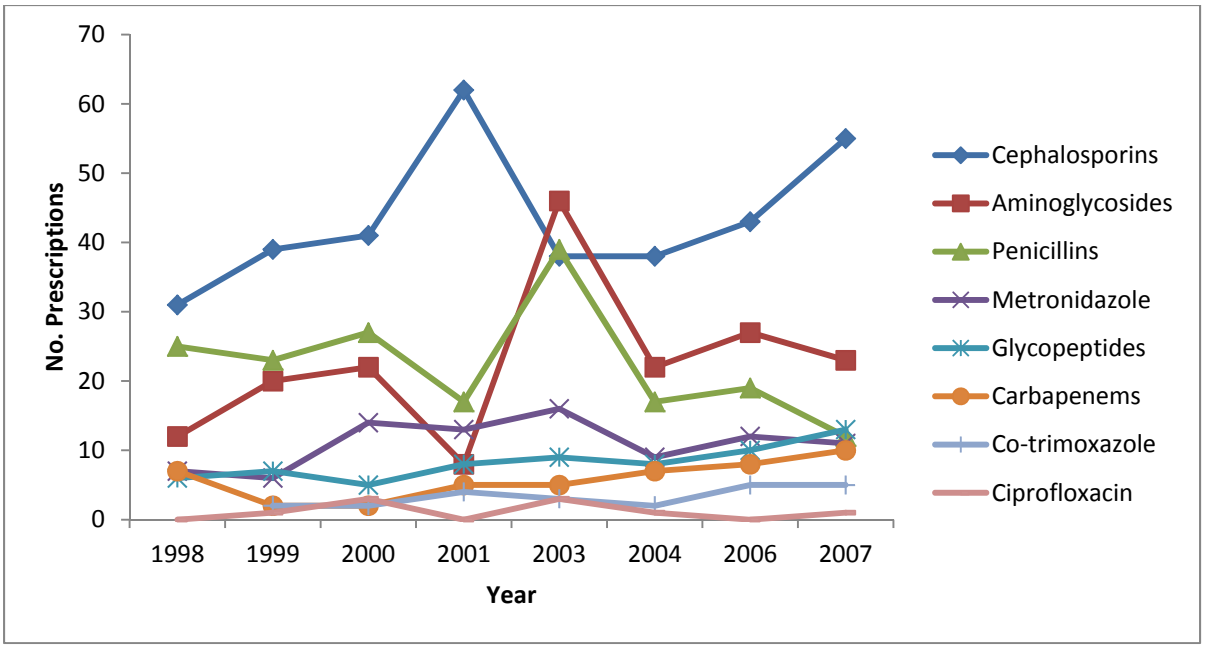


Figure 8.10: The annual number of prescriptions for bactericidal antibiotics used within the first three days in the PICU

8.4 Antibiotics initiated/modified after three days in the PICU

Overall, 23.2% ± 4.6% (157/685) patients were started on antibiotics or their antibiotic regimen was modified after three days in the PICU (Table C1 page 166). This includes 17 patients (2.5%) who did not receive antibiotics within the first three days.

A total of 29 different antibiotics were prescribed after three days of stay in the PICU over the study period, with an annual median of 15 (12–16) antibiotics per year (Figure 8.11 & Table C9 page 173). Of the 322 antibiotic prescriptions over the study period for this phase, the top ten antibiotics accounted for 81.1% (261/322) and they were: vancomycin (20.8% [67/322]), imipenem (17.1% [55/322]), amikacin (12.7% [41/322]), ciprofloxacin (7.1% [23/322]), cefotaxime (6.8% [22/322]), cefuroxime (3.7% [12/322]), metronidazole (3.7% [12/322]), gentamicin (3.1% [10/322]), tobramycin (3.1% [10/322]) and cloxacillin (2.8% [9/322]) (Figure 8.12).

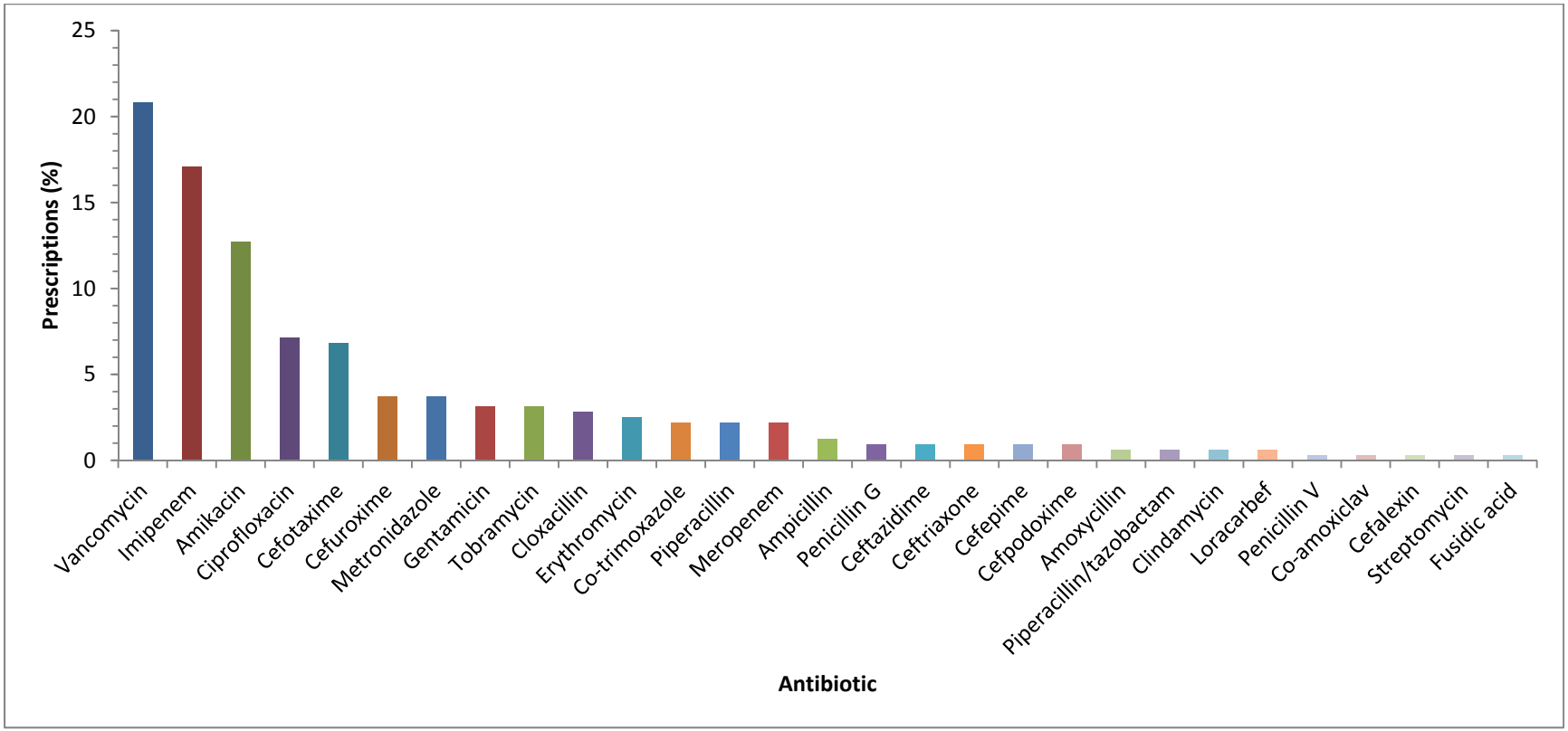


Figure 8.11: The proportion (%) of individual antibiotic prescriptions for the 29 antibiotics used after three days in the PICU

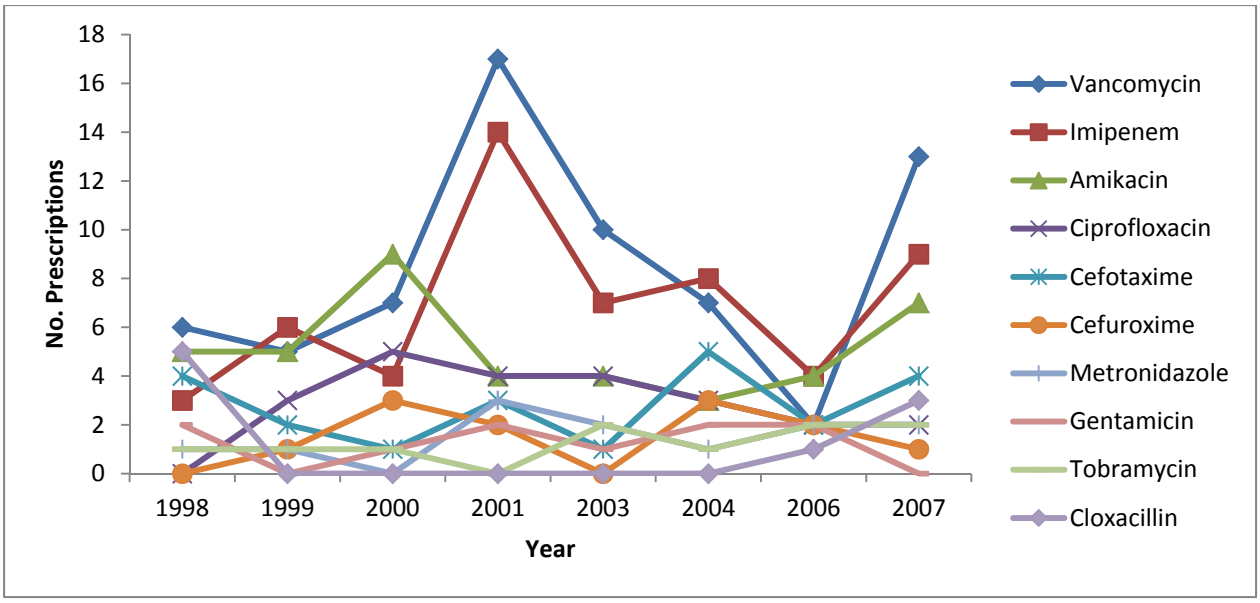


Figure 8.12: The annual number of prescriptions for the top ten antibiotics used after three days in the PICU

Surprisingly, vancomycin, a narrow-spectrum bactericidal antibiotic, was the top antibiotic, followed by the broad-spectrum antibiotics, imipenem, amikacin, ciprofloxacin, cefotaxime and cefuroxime. The other narrow-spectrum bactericidal antibiotics in the top ten were metronidazole and cloxacillin. Of note, three aminoglycosides were among the top ten antibiotics (amikacin, gentamicin and tobramycin). Specifically, the new-comers were tobramycin and ciprofloxacin.

Again, the bactericidal antibiotics were prescribed more (96.9% [312/322]) than the bacteriostatic antibiotics (3.1% [10/322]) (Figure 8.13 & Table C10 page 174). Of the bactericidal antibiotics, glycopeptides accounted for 20.8% (67/322), carbapenems 19.3% (62/322), aminoglycosides 19.3% (62/322), cephalosporins 15.2% (49/322), penicillins 9% (29/322) and ciprofloxacin 7.1% (23/322). The pattern of antibiotic use for vancomycin and imipenem were in unison most probably because this combination is preferred after three days of stay in the PICU.

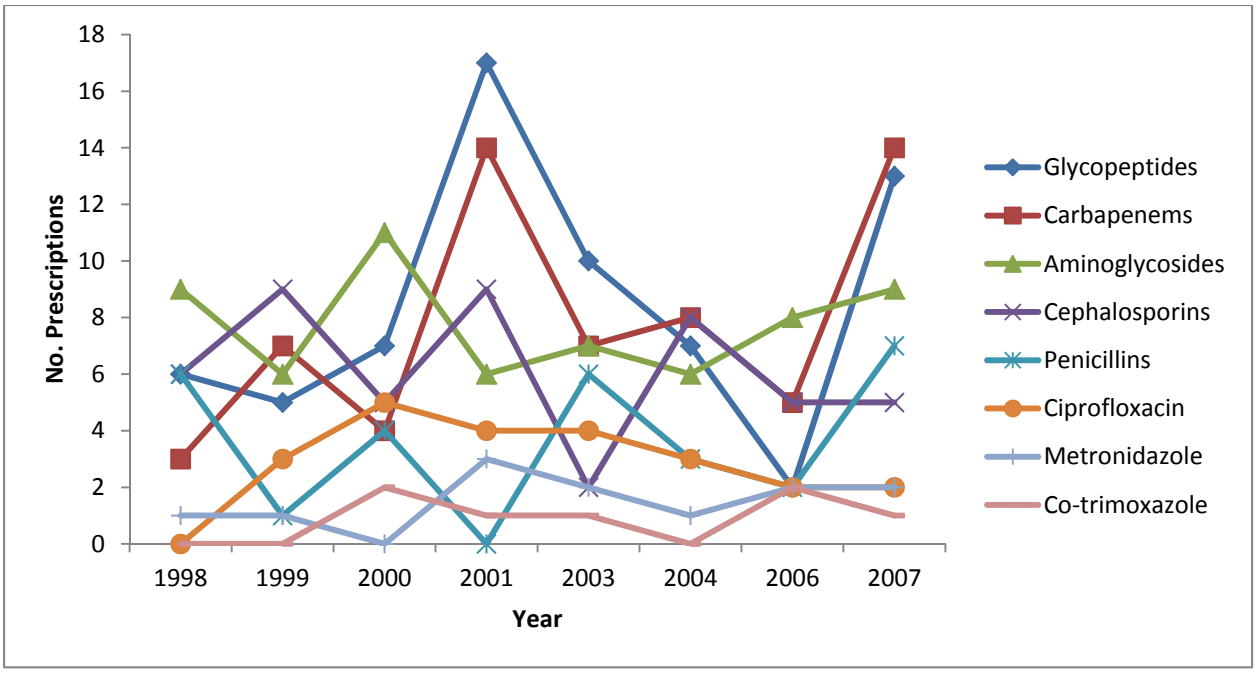


Figure 8.13: The annual number of prescriptions for bactericidal antibiotics used after three days in the PICU

8.5 Antibiotic combinations prescribed

Overall, 63.1% ± 6.6% (434/685) of patients in the PICU were treated with antibiotic combinations (Figure 8.14 & Table C11 page 174).

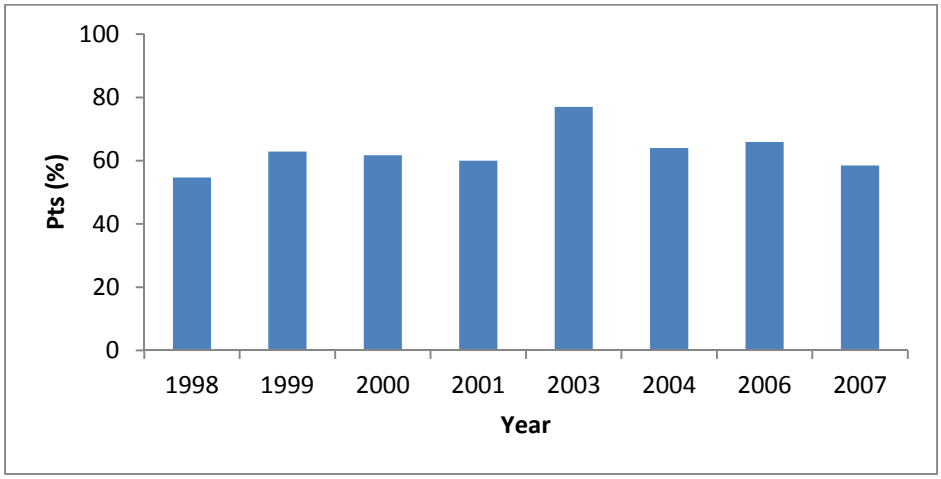


Figure 8.14: The annual proportion (%) of patients treated with antibiotic combinations

8.5.1 Two-combination antibiotic regimen

Within the first three days, 300 prescriptions for a two-combination antibiotic regimen were issued. Figure 8.15 shows the distribution of the different two-combination antibiotic regimens used within the first three days. The top eight regimens accounted for 65% (195/300) of these prescriptions and they were: penicillin G and amikacin (14% [42/300]), imipenem and vancomycin (14% [42/300]), cefotaxime and amikacin (8.3% [25/300]), cefuroxime and amikacin (8.3% [25/300]), cefotaxime and metronidazole (7% [21/300]), cefotaxime and cloxacillin (5% [15/300]), piperacillin and amikacin (4.7% [14/300]), and cefotaxime and vancomycin (3.7% [11/300]) (Figure 8.15 & Table C12 page 175). Beta-lactams and aminoglycosides (44.3% [133/300]), and glycopeptides (22.3% [67/300]) and metronidazole (11.7% [35/300]) were the preferred combinations. After the first three days, 98 prescriptions for a two-combination antibiotic regimen were issued, of which the top antibiotic combination was imipenem and vancomycin (35.7% [35/98]), with the rest scoring below 5% each (Table C13 page 175). Beta-lactams and glycopeptides (45.9% [45/98]) or aminoglycosides (23.5% [23/98]) were the preferred combinations.

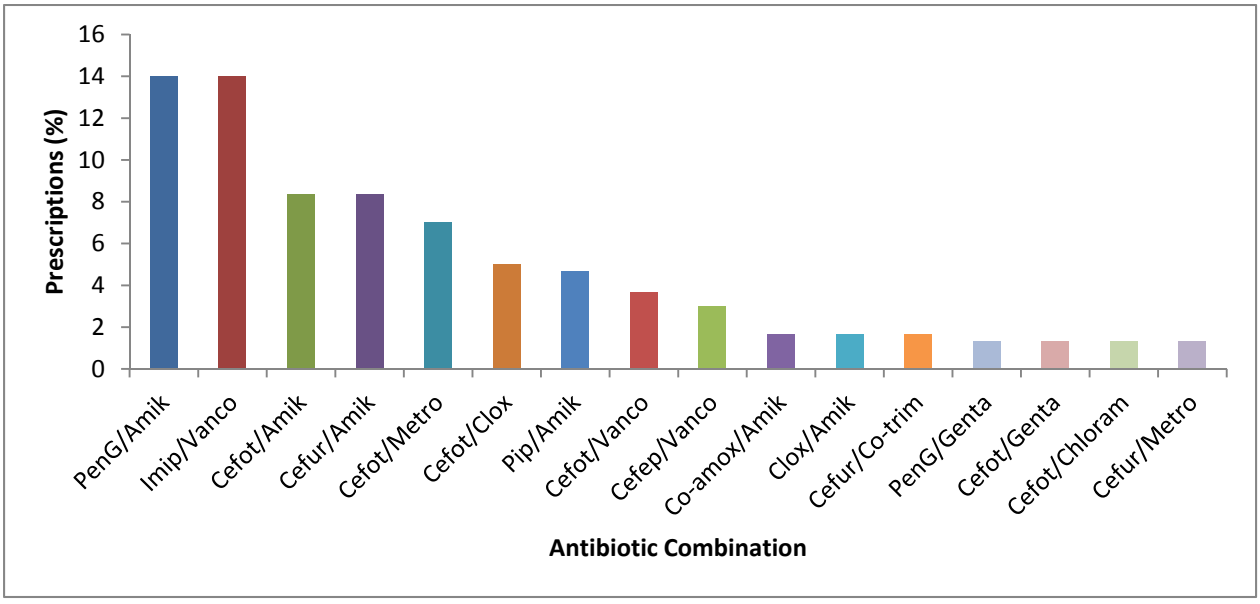


Figure 8.15: The proportion (%) of the common two-combination antibiotic regimens used within the first three days in the PICU

(Key: PenG = Penicillin G; Amik = Amikacin; Imip = Imipenem; Vanco = Vancomycin; Cefot = Cefotaxime; Cefur = Cefuroxime; Metro = Metronidazole; Clox = Cloxacillin; Pip = Piperacillin; Cefep = Cefepime; Co-amox = Co-amoxiclav; Co-trim = Co-trimoxazole; Genta = Gentamicin; Chloram = Chloramphenicol)

8.5.2 Three-combination antibiotic regimen

Within the first three days, 97 prescriptions for a three-combination antibiotic regimen were issued. Figure 8.16 shows the distribution of the different three-combination antibiotic regimens used within the first three days. The top five regimens were penicillin G, amikacin and metronidazole (18.6% [18/97]), penicillin G, gentamicin and metronidazole (9.3% [9/97]), cefuroxime, amikacin and metronidazole (7.2% [7/97]), cefotaxime, amikacin and metronidazole (6.2% [6/97]), and cefotaxime, amikacin and co-trimoxazole (5.2% [5/97]) (Figure 8.16 & Table C14 page 176). Beta-lactams, aminoglycosides and metronidazole was the preferred three-combination antibiotic group (53.6% [52/97]). After the first three days, the top antibiotic combinations were cefotaxime, amikacin and metronidazole (17.4% [4/23]) and imipenem, vancomycin and co-trimoxazole (13% [3/23]) (Table C15 page 176).

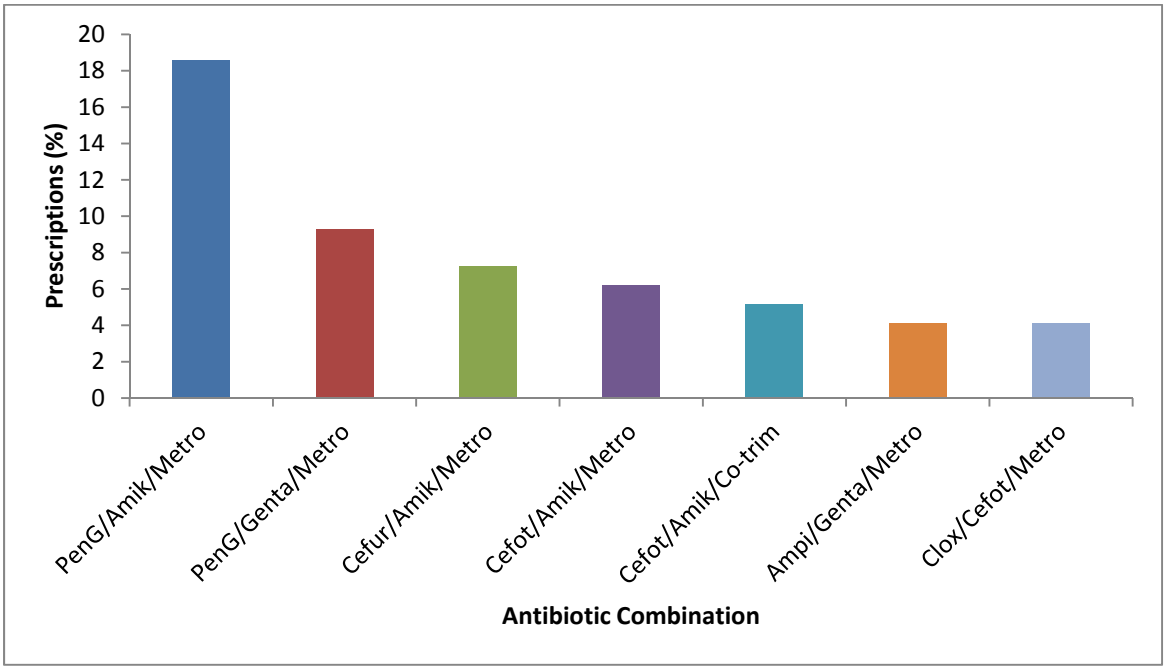


Figure 8.16: The proportion (%) of the common three-combination antibiotic regimens used within the first three days in the PICU

(Key: PenG = Penicillin G; Amik = Amikacin; Metro = Metronidazole; Genta = Gentamicin; Cefur = Cefuroxime; Cefot = Cefotaxime; Co-trim = Co-trimoxazole; Ampi = Ampicillin; Clox = Cloxacillin)

8.6 Antibiotic use by clinical diagnosis/problem

Tentative clinical diagnosis is a common concept in the PICU during which a diagnosis is made according to clinical presentation and antibiotics are prescribed according to the most prevalent bacteria in the setting. Therefore, it is a major determinant of antibiotics used.

Over the study period there were a total of 1 735 problems (or clinical diagnosis) in patients admitted to the PICU. Of these, the most challenging problems were pneumonia, septicaemia and UTI. There were 155 cases of pneumonia on admission and 178 new cases during PICU stay. Regarding septicaemia, 50 cases were recorded on admission and 57 new cases during PICU stay, while for UTI there were 17 cases on admission and 44 new cases during PICU stay.

8.6.1 Pneumonia

Figure 8.17 shows the antibiotics prescribed for pneumonia on admission (Figure 8.17A & Table C16i page 177), after three days (Figure 8.17B & Table C16ii page 178), and for the new cases (Figure 8.17C & Table C16iii page 179). In general, broad-spectrum bactericidal antibiotics were used whereby, for the first three days, amikacin and beta-lactam antibiotics (cefotaxime, cufuroxime and penicillin G) were preferred, while amikacin, vancomycin and imipenem, plus ciprofloxacin or metronidazole were preferred after three days and for the new cases in the PICU.

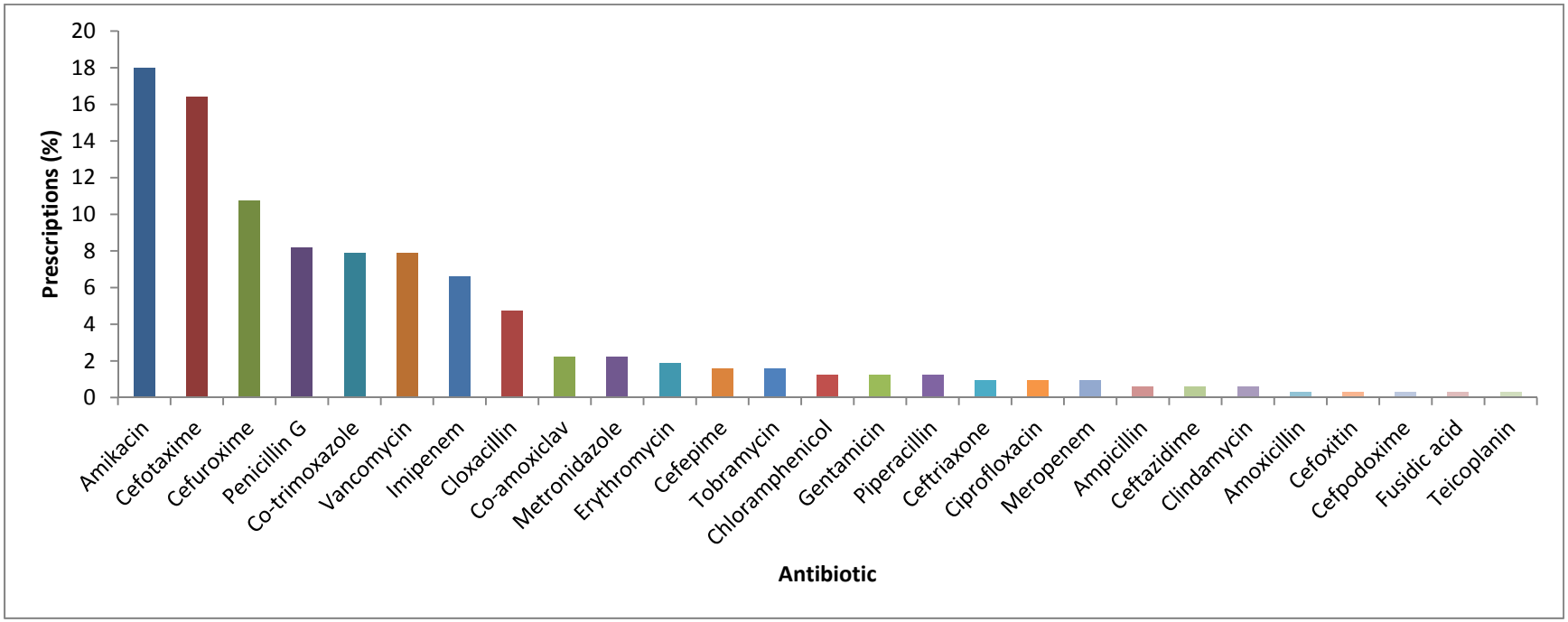


Figure 8.17A: The proportion (%) of individual antibiotic prescriptions for the antibiotics used for pneumonia on admission and within the first three days in the PICU

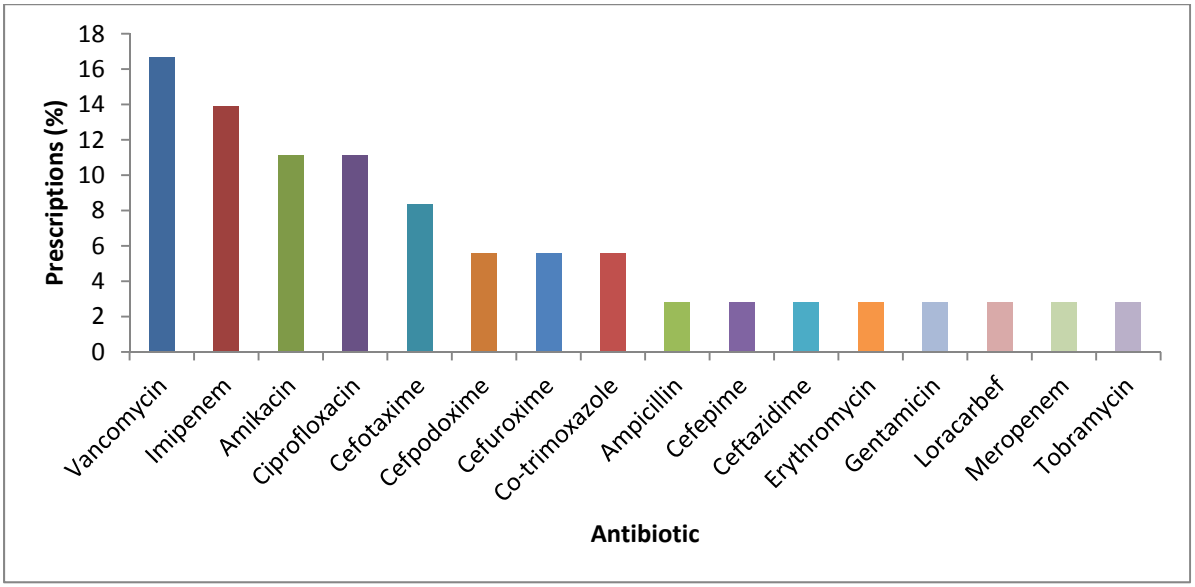


Figure 8.17B: The proportion (%) of individual antibiotic prescriptions for the antibiotics used after three days for the same pneumonia on admission in the PICU

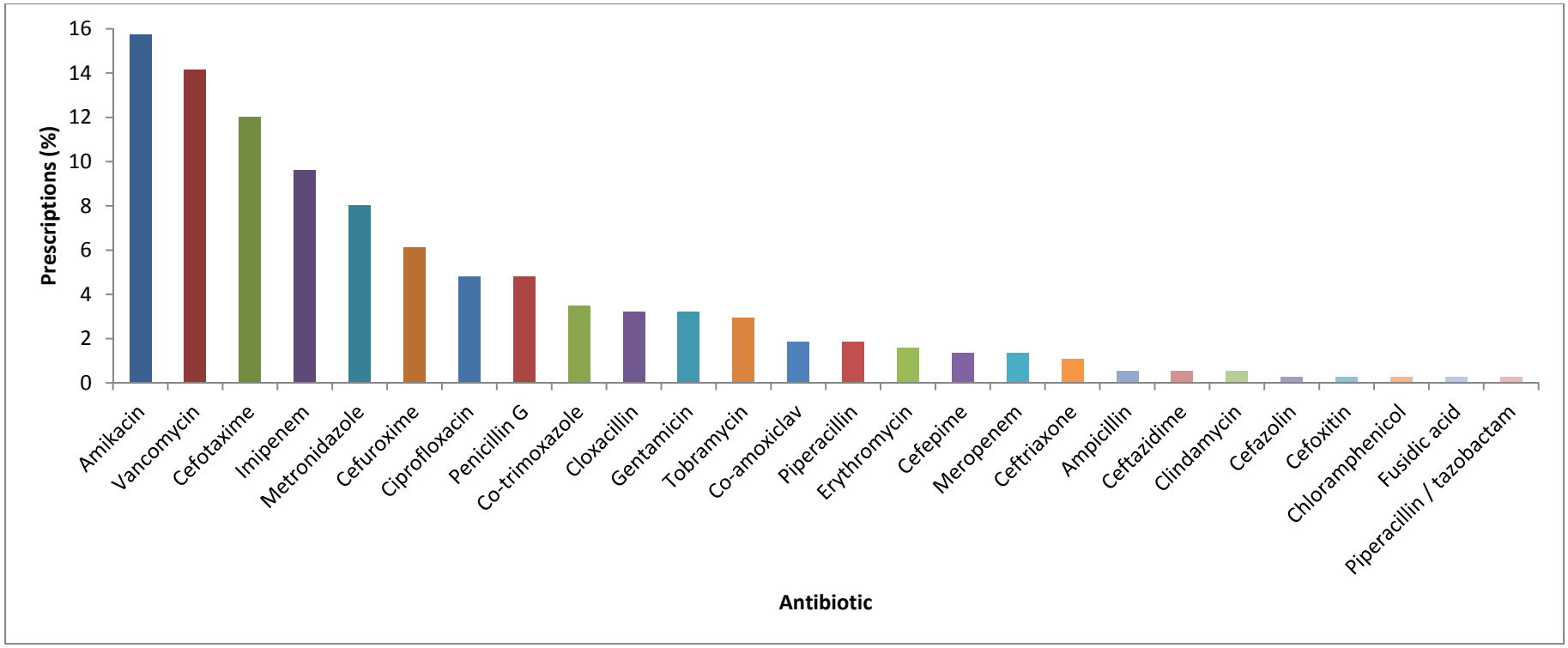


Figure 8.17C: The proportion (%) of individual antibiotic prescriptions for the antibiotics used for new cases of pneumonia in the PICU

8.6.2 Septicaemia

Figure 8.18 shows the antibiotics prescribed for septicaemia on admission (Figure 8.18A & Table C17i page 180), and for the new cases (Figure 8.18B & Table C17ii page 181). Here both broad- and narrow-spectrum antibiotics were used, whereby, on admission, vancomycin, penicillin G and metronidazole were the narrow-spectrum antibiotics, while amikacin, cefotaxime and imipenem were the broad-spectrum antibiotics. For the new cases of septicaemia, the same antibiotics were used, except for the order where vancomycin was on top, while penicillin G was replaced by ciprofloxacin.

8.6.3 Urinary tract infection

Figure 8.19 shows the antibiotics prescribed for UTI on admission (Figure 8.19A & Table C18i page 181), and for the new cases (Figure 8.19B & Table C18ii page 182). Both broad- and narrow-spectrum antibiotics were used, whereby, on admission, vancomycin was the narrow-spectrum antibiotic, while amikacin, cefotaxime, cefuroxime and imipenem were the broad-spectrum antibiotics. For the new cases of UTI, the same antibiotics were used, except for the order where amikacin was on top, while cefuroxime was replaced by ciprofloxacin.

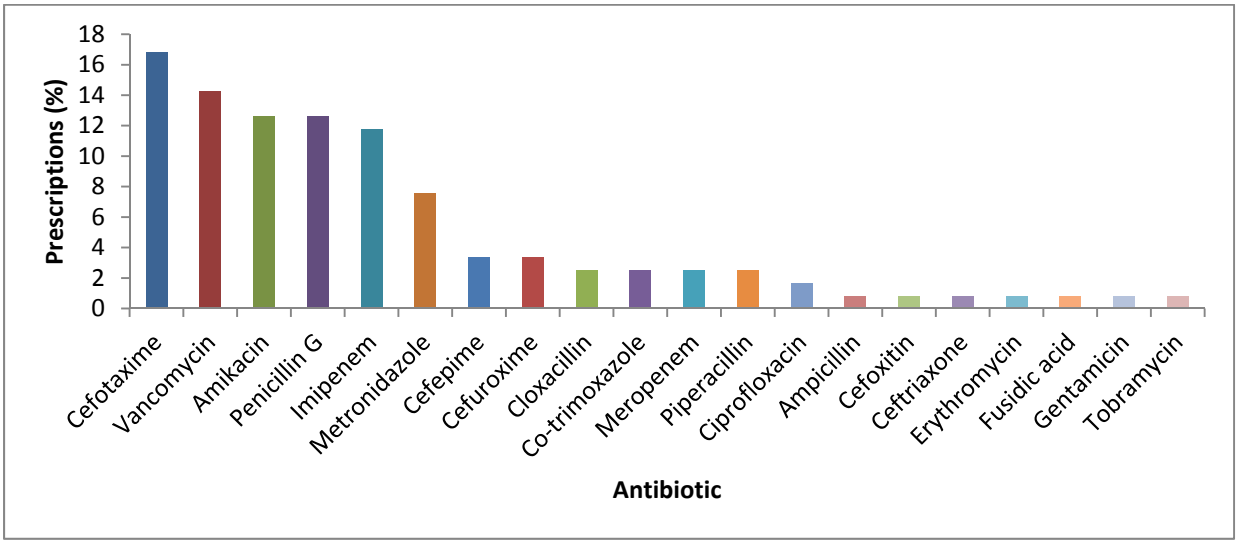


Figure 8.18A: The proportion (%) of individual antibiotic prescriptions for the antibiotics used for septicaemia on admission and within the first three days in the PICU

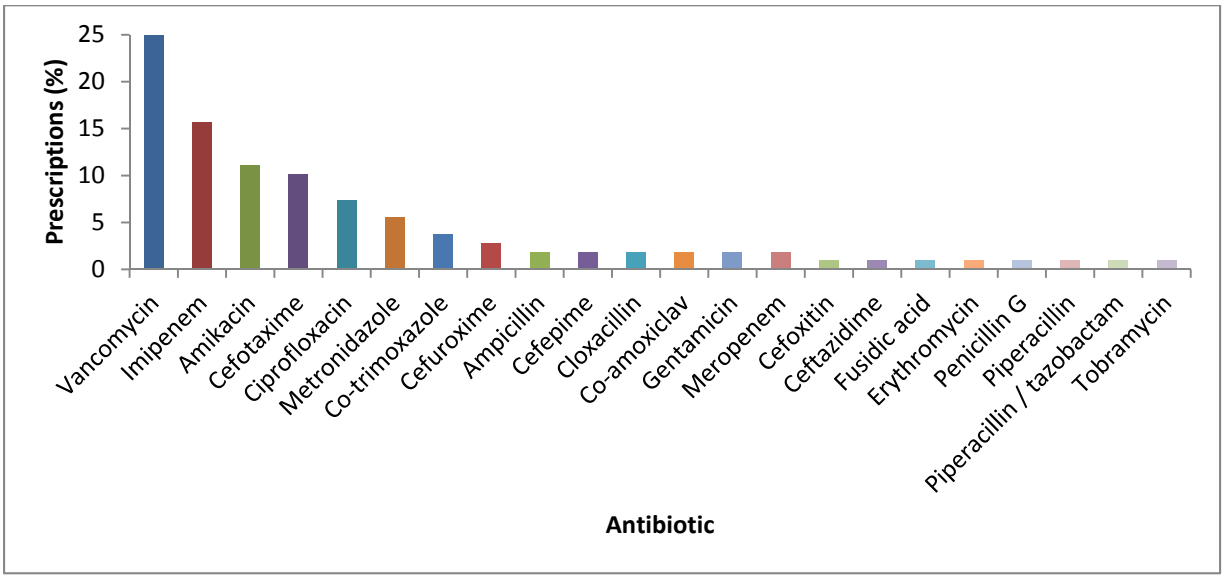


Figure 8.18B: The proportion (%) of individual antibiotic prescriptions for the antibiotics used for new cases of septicaemia in the PICU

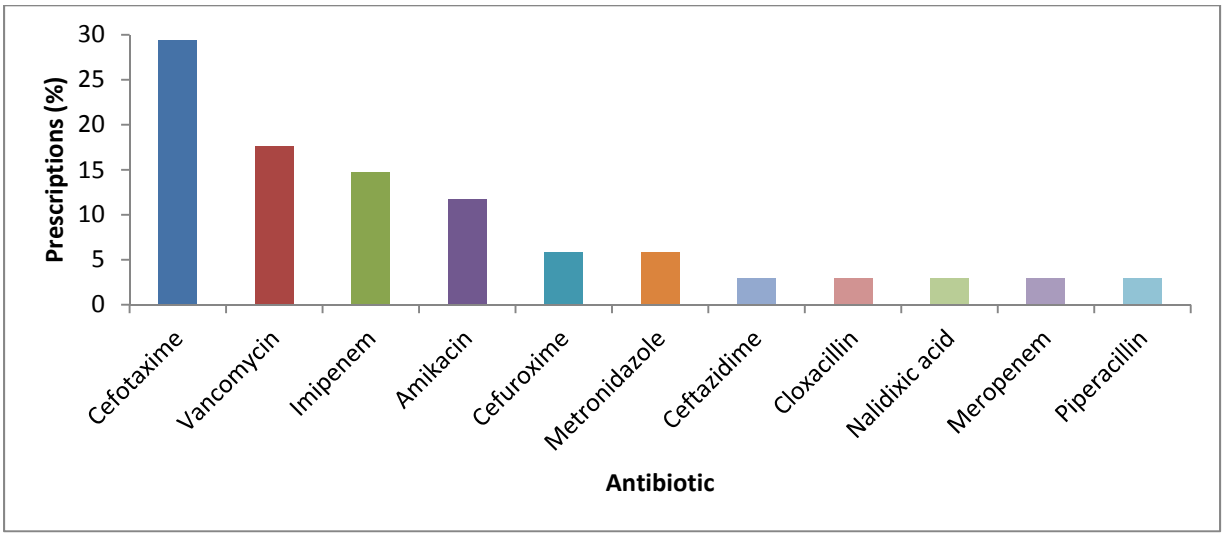


Figure 8.19A: The proportion (%) of individual antibiotic prescriptions for the antibiotics used for UTI on admission and within the first three days in the PICU

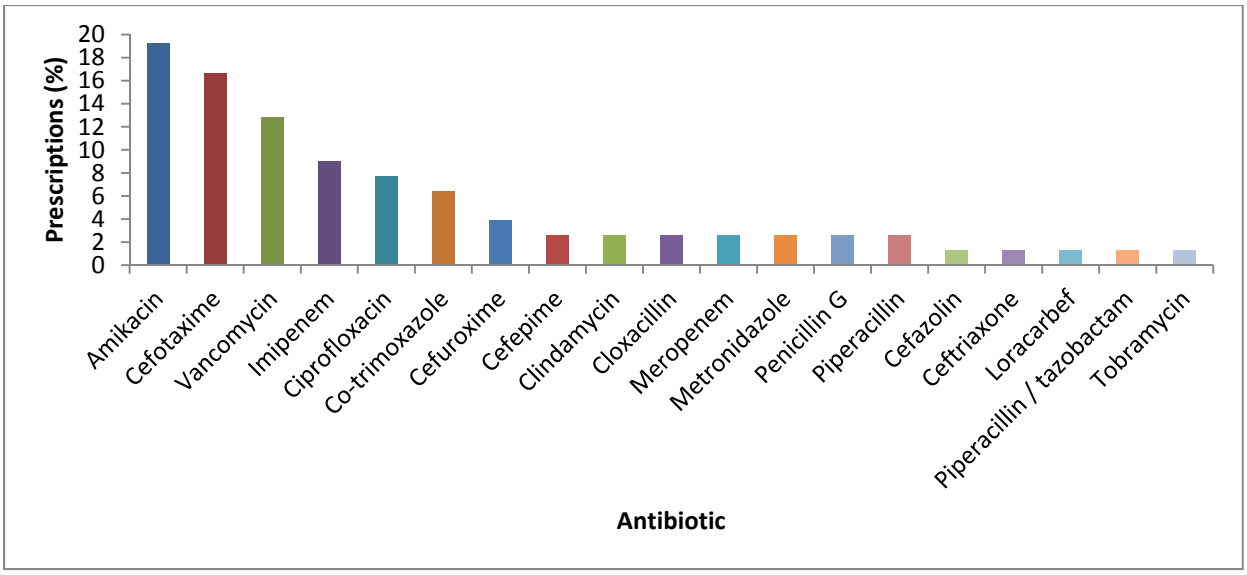


Figure 8.19B: The proportion (%) of individual antibiotic prescriptions for the antibiotics used for new cases of UTI in the PICU

8.6.4 Post-operative care

This refers to antibiotics prescribed in patients after surgery, i.e., for prophylaxis and/or treatment of infections. Therefore, these patients may include those with pneumonia, septicaemia and UTI. Figure 8.20 (Table C19 page 183) shows the antibiotics prescribed for patients post-operatively. Both broad- and narrow-spectrum antibiotics were used, whereby; metronidazole and penicillin G were the narrow-spectrum antibiotics, while amikacin, cefotaxime and cefuroxime were the broad-spectrum antibiotics.

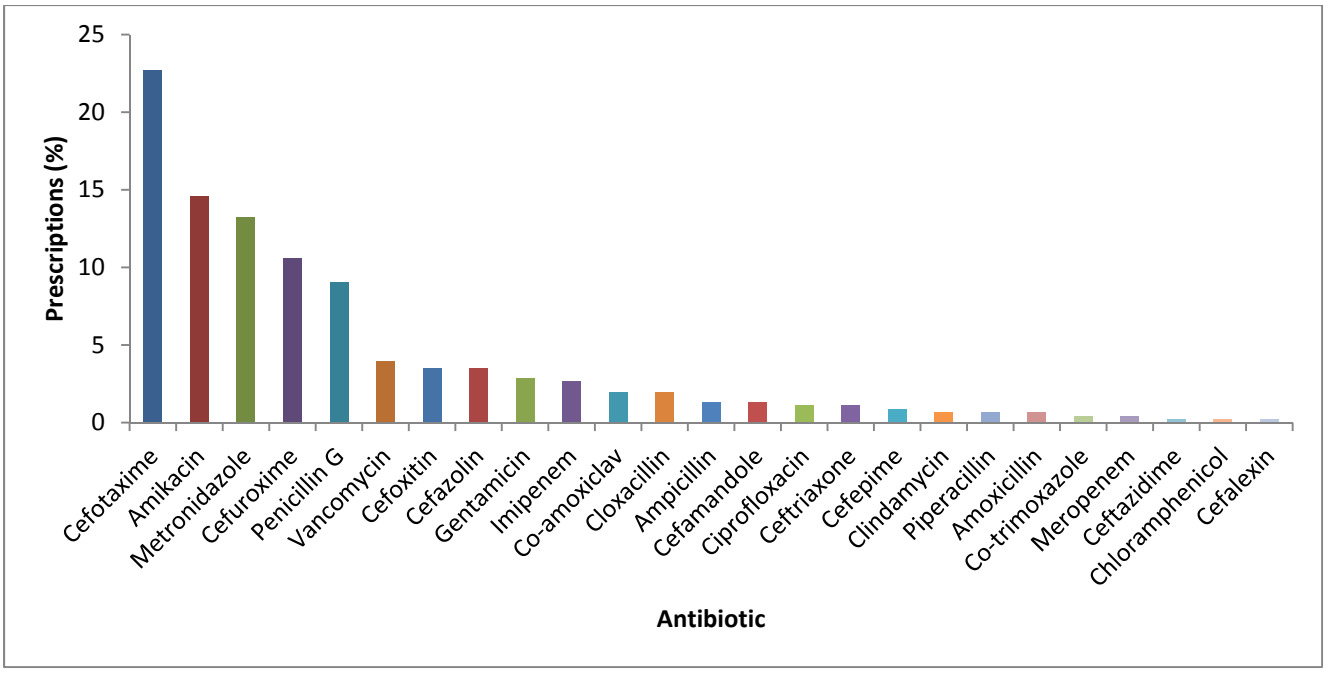


Figure 8.20: The proportion (%) of individual antibiotic prescriptions for the antibiotics used in post-operative patients on admission in the PICU

8.7 Antibiotics prescribed for different ages

As stated earlier, there were three patient age groups, i.e., the children, infants and neonates groups. Figure 8.21 shows the antibiotics prescribed for the children group (Figure 8.21A & Table C20i page 184), the infants group (Figure 8.21B & Table C20ii page 185) and the neonates group (Figure 8.21C & Table C20iii page 186). In all ages, similar antibiotics were used, except for the order.

Broad- and narrow-spectrum antibiotics were used, whereby; vancomycin, metronidazole and penicillin G were the narrow-spectrum antibiotics, while amikacin, cefotaxime, cefuroxime and imipenem were the broad-spectrum antibiotics. The top two antibiotics, cefotaxime and amikacin, were the same in all age groups. However, it appears they were used as a combination in the infants and neonates groups.

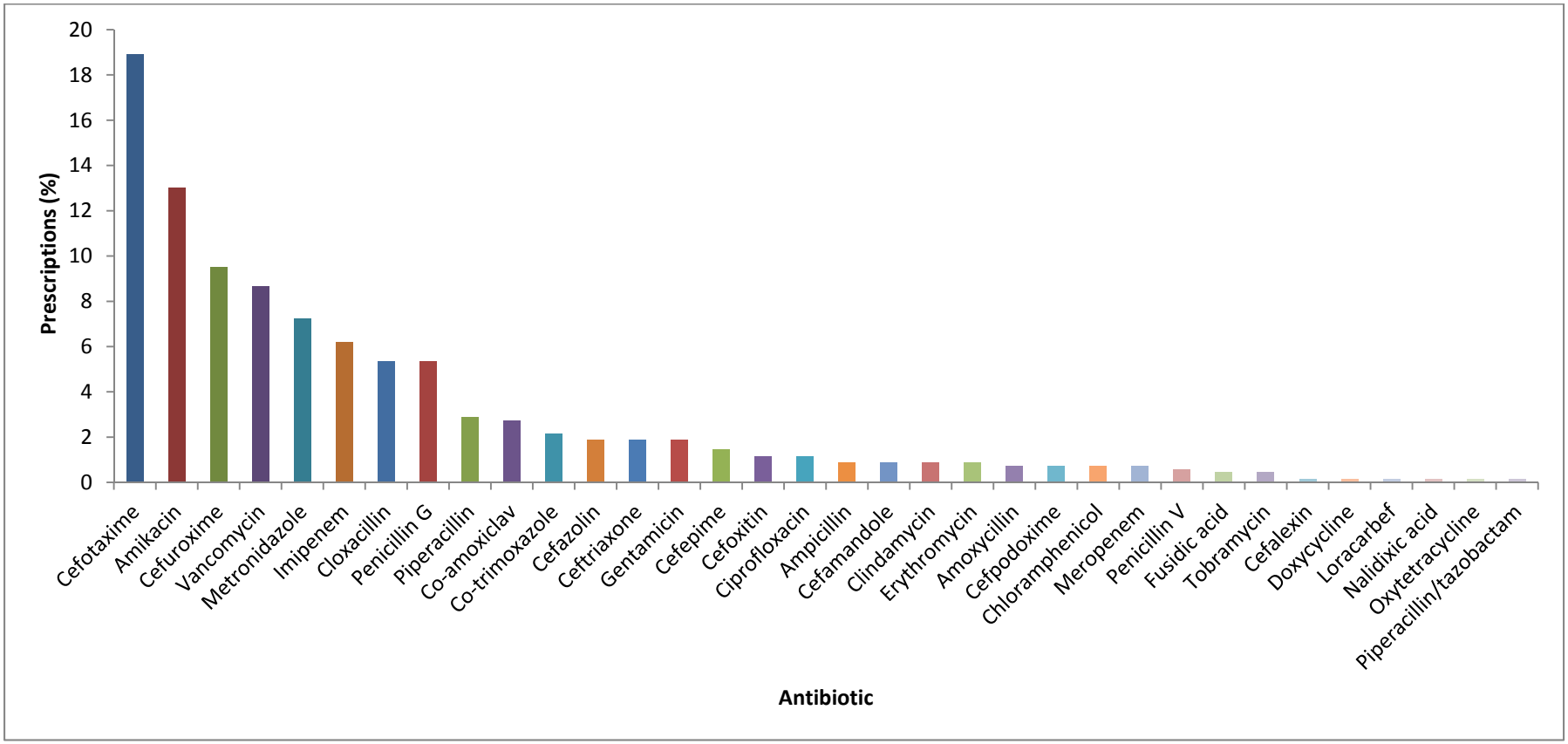


Figure 8.21A: The proportion (%) of individual antibiotic prescriptions for the antibiotics used in the children group in the PICU

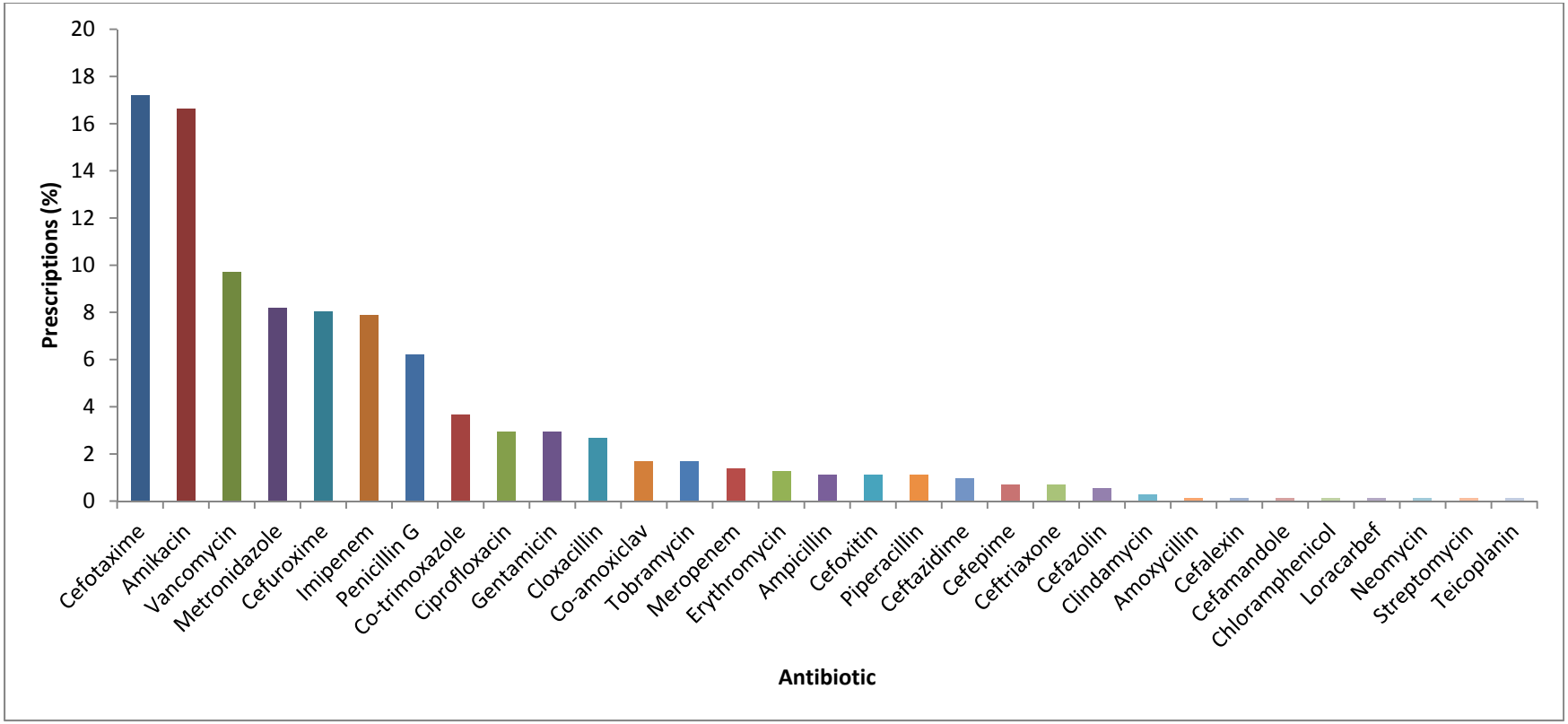


Figure 8.21B: The proportion (%) of individual antibiotic prescriptions for the antibiotics used in the infants group in the PICU

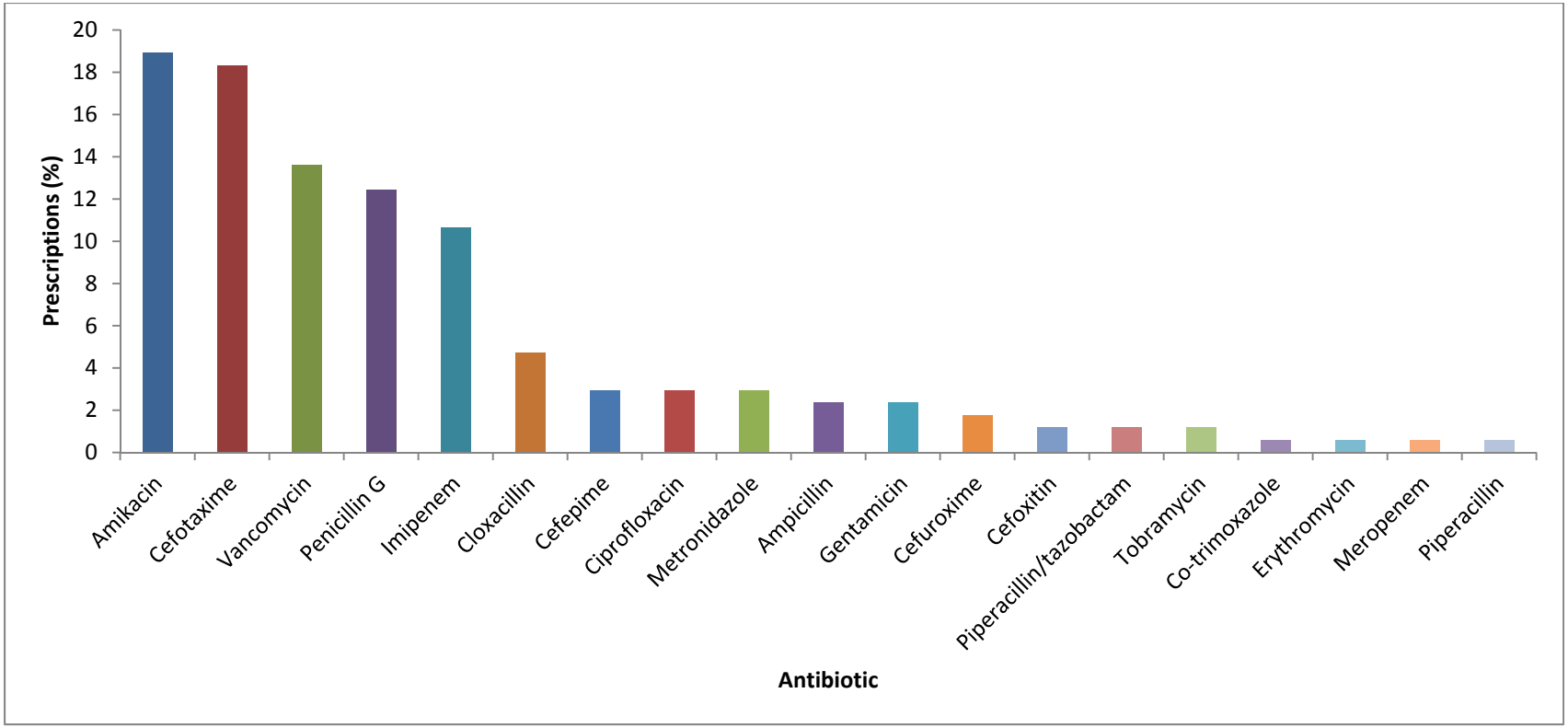


Figure 8.21C: The proportion (%) of individual antibiotic prescriptions for the antibiotics used in the neonates group in the PICU

8.8 Route of administration

The intravenous route was used for administration of 93.9% (1 475/1 571) of the antibiotics prescribed in the PICU, at an annual rate of 93.8% (Figure 8.22 & Table C21 page 187). Oral route was used in 6% (94/1 571) of the prescriptions, at an annual rate of 6.1%. The top ten antibiotics prescribed orally included co-trimoxazole, co-amoxiclav, cefuroxime, erythromycin, cefpodoxime, amoxycillin, metronidazole, cloxacillin, penicillin V and gentamicin.

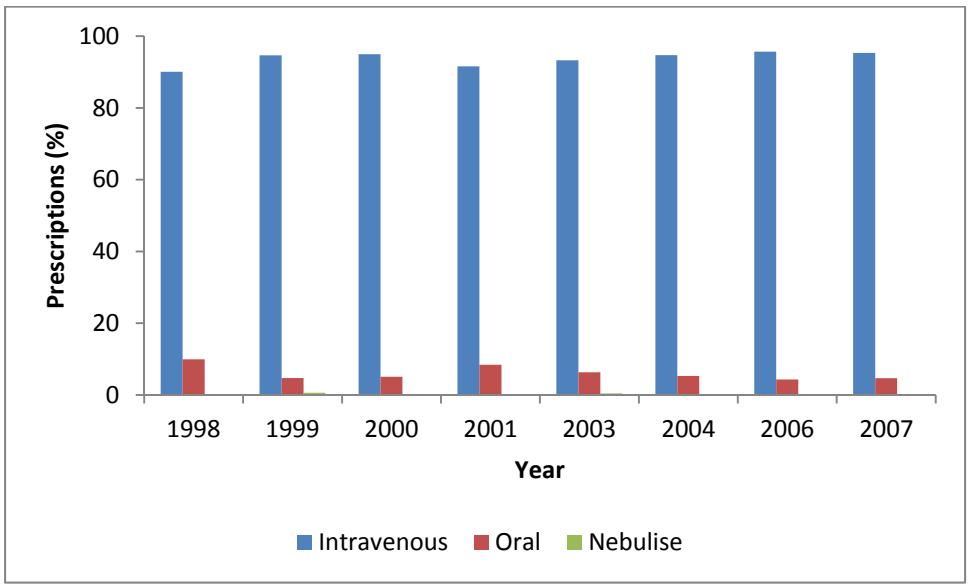


Figure 8.22: The annual proportion (%) of the different routes used for administration of antibiotics in the PICU

8.9 Antibiotic cost

The real cost of treatment could not be evaluated due to lack of information on actual doses administered versus that prescribed, variable treatment regimens (administration frequency and length of treatment) due to disease, age, weight etc., lack of costs for accessories such as administration intravenous-sets and lack of antibiotic prices for each year, to mention but a few. Therefore, prices for 2012 were used to indicate the most likely cost implications of antibiotic use in the PICU.

Figure 8.23 shows the 2012-cost-per-unit-price (e.g. per vial) for the most commonly used antibiotics selected from each of the top ten antibiotics used within the first three days (Figure 8.9 page 73), after three days (Figure 8.12 page 76) and total antibiotics (Figure 8.3 page 66).

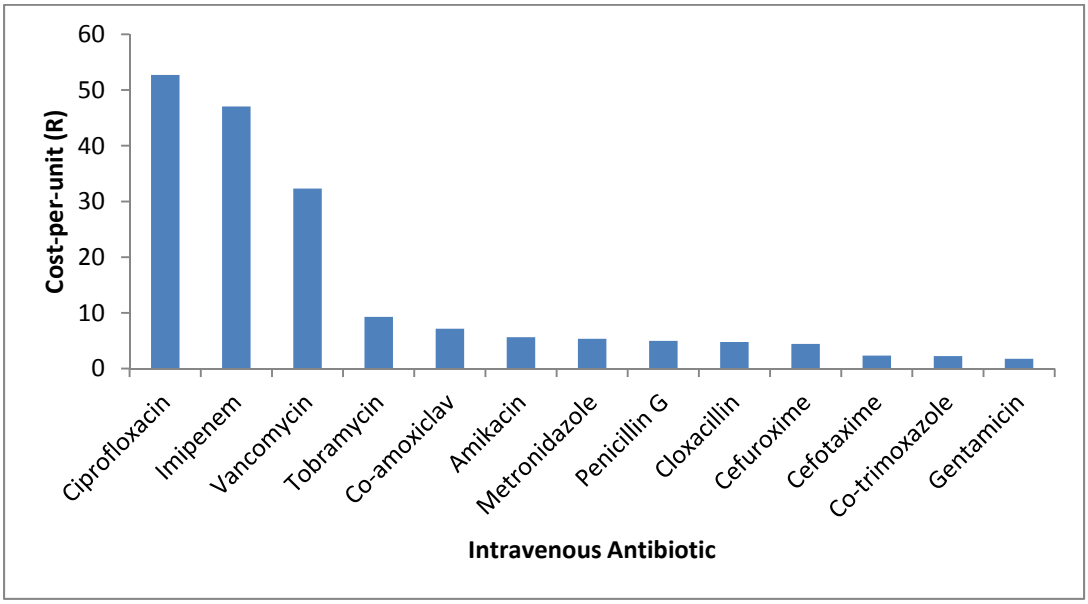


Figure 8.23: The 2012-cost-per-unit-price of the most commonly used intravenous antibiotics in the PICU

Whereas cost of antibiotics was not a limiting factor in the selection of antibiotics, it is important for budgetary purposes. Fortunately, the most commonly prescribed antibiotics (cefotaxime, cefuroxime, amikacin, penicillin G and gentamicin) were the cheapest, making antibiotic use in the PICU presumably more cost effective. On the other hand, the antibiotics that are reserved for more severe infections (vancomycin, imipenem, ciprofloxacin and tobramycin) were the most expensive. Of note, some of these antibiotics were newer compared to the cheaper ones.

8.10 Summary

a) Overview:

- Overall, a total of 38 different antibiotics were prescribed in the PICU over the study period.
- Of the 1 571 antibiotic prescriptions, the top ten antibiotics accounted for 81.2% and these were: cefotaxime (18.2%), amikacin (14.7%), vancomycin (9.8%), cefuroxime (8.1%), imipenem (7.5%), metronidazole (7.2%), penicillin G (6.5%), cloxacillin (4.1%), co-trimoxazole (2.7%) and gentamicin (2.4%).
- Bactericidal antibiotics were preferred, where 66% of the top ten antibiotics were broad-spectrum and bactericidal, while 34% were narrow-spectrum and bactericidal (vancomycin, metronidazole, penicillin G and cloxacillin).

b) Regarding antibiotics initiated before admission and continued in the PICU:

- Effectively, 29.1% (199/685) of patients continued with antibiotics initiated before admission.
- A total of 31 different antibiotics that were initiated before admission were continued in the PICU (292 prescriptions) of which the top nine antibiotics accounted for 81.8% and they were: cefotaxime (24.3%), amikacin (13.7%), cefuroxime (8.2%), imipenem (8.2%), vancomycin (7.5%), penicillin G (6.2%), cloxacillin (4.8%), metronidazole (4.5%) and co-trimoxazole (4.5%).
- The top four antibiotics initiated before admission and continued in the PICU were cefotaxime, amikacin, cefuroxime and imipenem.

c) Regarding antibiotics initiated within the first three days in the PICU:

- 79.9% ± 3.3% (546/685) patients were started on antibiotics or had their antibiotic regimen modified within the first three days.
- A total of 33 different antibiotics were used in 957 prescriptions of which the top ten antibiotics accounted for 83.2% and they were: cefotaxime (20.2%), amikacin (15.7%), cefuroxime (9.5%), metronidazole (9.2%), penicillin G (8.5%),

vancomycin (6.8%), cloxacillin (4.3%), imipenem (4.1%), co-amoxiclav (2.5%) and gentamicin (2.5%).

- The top ten antibiotics were similar to those initiated before admission, except for co-trimoxazole that was replaced by gentamicin.
- The top four antibiotics used within the first three days were cefotaxime, amikacin, cefuroxime and metronidazole.

d) Regarding antibiotics initiated after three days in the PICU:

- 23.2% ± 4.6% (157/685) patients were started on antibiotics or their antibiotic regimen was modified after three days in the PICU.
- A total of 29 antibiotics were used in 322 prescriptions of which the top ten antibiotics accounted for 81.1% and they were: vancomycin (20.8%), imipenem (17.1%), amikacin (12.7%), ciprofloxacin (7.1%), cefotaxime (6.8%), cefuroxime (3.7%), metronidazole (3.7%), gentamicin (3.1%), tobramycin (3.1%) and cloxacillin (2.8%).
- Tobramycin and ciprofloxacin were the new-comers in the top ten antibiotics used.
- Antibiotic therapy was more specific most probably because it is guided by culture and sensitivity results. However, the change to other/newer antibiotics implies emergence of more resistant bacteria.
- The top four antibiotics used after the first three days were vancomycin, imipenem, amikacin and ciprofloxacin.

e) Regarding antibiotic combinations:

- Most of the patients (63.4%) in the PICU were treated with antibiotic combinations.
- Within the first three days:
    - 300 prescriptions for a two-combination antibiotic regimen were issued. The top eight regimens accounted for 65% of these prescriptions and they were: penicillin G and amikacin (14%), imipenem and vancomycin (14%), cefotaxime and amikacin (8.3%), cefuroxime and amikacin (8.3%),

cefotaxime and metronidazole (7%), cefotaxime and cloxacillin (5%), piperacillin and amikacin (4.7%), and cefotaxime and vancomycin (3.7%).

- The three-combination antibiotic regimens were composed by the addition of metronidazole to the two-combination antibiotic regimen.

- After the first three days:
  - 98 prescriptions for a two-combination antibiotic regimen were issued, of which the top antibiotic combination was imipenem and vancomycin (35.7%), with the rest scoring below 5% each.
  - The three-combination antibiotic regimens were composed by addition of metronidazole or co-trimoxazole to the two-combination antibiotic regimen.

f) Regarding antibiotic use by clinical diagnosis/problem:

- The most common diagnoses were pneumonia, septicaemia and UTI.
- For pneumonia, amikacin and beta-lactam antibiotics (cefotaxime, cufuroxime and penicillin G) were preferred within the first three days, while amikacin, vancomycin and imipenem, plus ciprofloxacin or metronidazole was preferred after three days and for the new cases in the PICU.
- For septicaemia, the most common antibiotics were a combination of narrow- (vancomycin, penicillin G and metronidazole) and broad-spectrum (amikacin, cefotaxime and imipenem) antibiotics.

g) Regarding antibiotics prescribed for different ages:

- There was no difference in antibiotics used in children, infants and neonates.
- The top four antibiotics for children were cefotaxime, amikacin, cefuroxime and vancomycin.
- The top four antibiotics for infants were cefotaxime, amikacin, vancomycin and metronidazole.
- The top four antibiotics for the neonates were amikacin, cefotaxime, vancomycin and penicillin G.
- However, it appears they cefotaxime and amikacin were used as a combination in the infants and neonates groups.

CHAPTER 9

RESULTS Part III
THE PREVALENCE AND PATTERN OF ANTIBIOTIC RESISTANCE IN THE PICU

In this section the characteristics of the specimens for C/S tests, the different bacteria cultured, as well as the respective prevalence and pattern of bacterial antibiotic resistance are described. These factors are important in the selection and prescribing of antibiotics.

9.1 Culture and sensitivity

Of the 685 patients in the study sample, C/S was requested in 451 (65.8%) patients, and from these, 1 637 specimens were produced (Figure 9.1 & Table D1 page 188). This indicates that 35% of patients received empirical antibiotic therapy. Of the 1 637 specimens, bacteria were detected (grown) in 452 (27.7%) specimens and these were effectively from 238 (52.8%) patients (Table D2 page 188). This indicates that 52.8% of patients suspected of bacterial infections were confirmed on bacterial culture.

During C/S, 78.8% (356/452) of specimens yielded one bacterial species (but not necessarily the same) each, while 17.9% (81/452) yielded two species each, 3.1% (14/452) yielded three species each and 0.2% (1/452) yielded four species. Therefore, a total of 564 bacterial species were cultured (i.e., 356 + 162 + 42 + 4), and antibiotic sensitivity results were obtained for 530 (94%) bacteria species.

Although, not much related to the number of bacteria grown per specimen, of the 238 patients, 131 (55%) patients had one bacterial species grown on culture (but not necessarily the same), while 107 (45%) patients had more than one bacterial species grown.

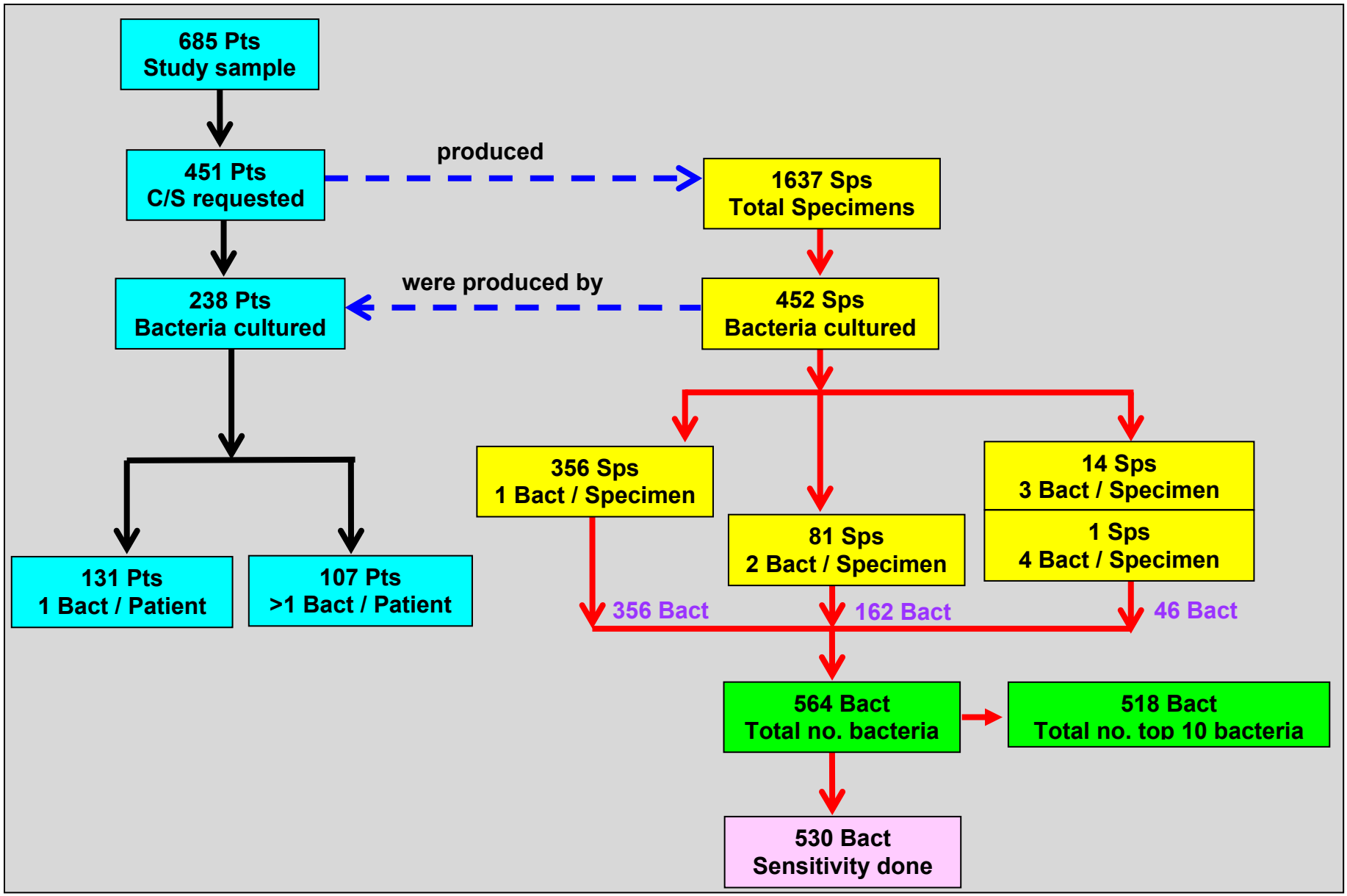


Figure 9.1: An illustration of the number of patients and specimens for which culture and/or sensitivity tests was done

Key: Bact = Bacteria, Pts = Patients, Sps = Specimens

9.2 Bacteria

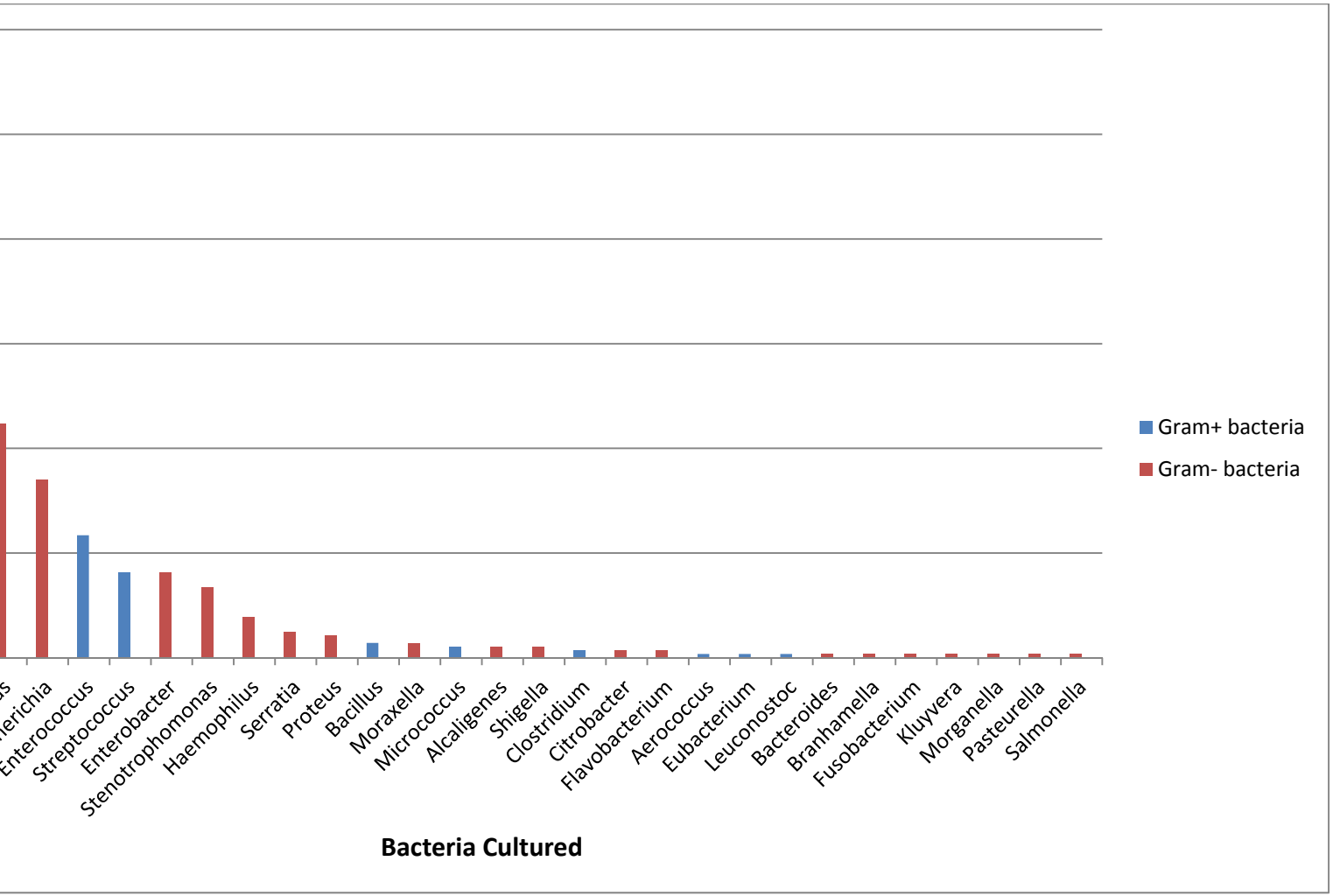
Overall, 30 different bacteria genera were grown, leading to a total of 564 bacteria species that were either Gram-positive or Gram-negative (Figure 9.2 & Table D3 page 189). The top ten bacteria genera cultured accounted for 91.8% (518/564), viz; *Staphylococcus* (29.3% [165/564]), *Klebsiella* (11.8% [67/564]), *Acinetobacter* (11.7% [66/564]), *Pseudomonas* (11.2% [63/564]), *Escherichia* (8.5% [48/564]), *Enterococcus* (5.9% [33/564]), *Streptococcus* (4.1% [23/564]), *Enterobacter* (4.1% [23/564]), *Stenotrophomonas* (3.4% [19/564]) and *Haemophilus* (2% [11/564]). Figure 9.3 is a flow diagram illustrating how the total and annual prevalence of the top ten common bacteria genera were determined.

9.2.1 Gram-positive bacteria

The Gram-positive bacteria genera accounted for 41.3% (233/564) of the cultures, and the most common Gram-positive bacteria genera comprised of *Staphylococcus* (29.3% [165/564]), *Enterococcus* (5.9% [33/564]) and *Streptococcus* (4.1% [23/564]) (Figure 9.2 & Table D3 page 189).

In Figure 9.4, the prevalence of *Staphylococcus* genus progressively increased from 1998 (nine per year) to 2001 (30 per year), dropped to ten per year in 2004, but increased again to a peak in 2007 (34 per year). Although the changes in the number of *Enterococcus* and *Streptococcus* genera grown were lower than for staphylococci, a similar pattern was observed with an increase that peaked in 2007.

The implications of these observations would better be appreciated if correlated with information on antibiotic sensitivity.



proportion (%) of positive cultures for each of the 30 bacteria genera in the PICU from 1998–2007

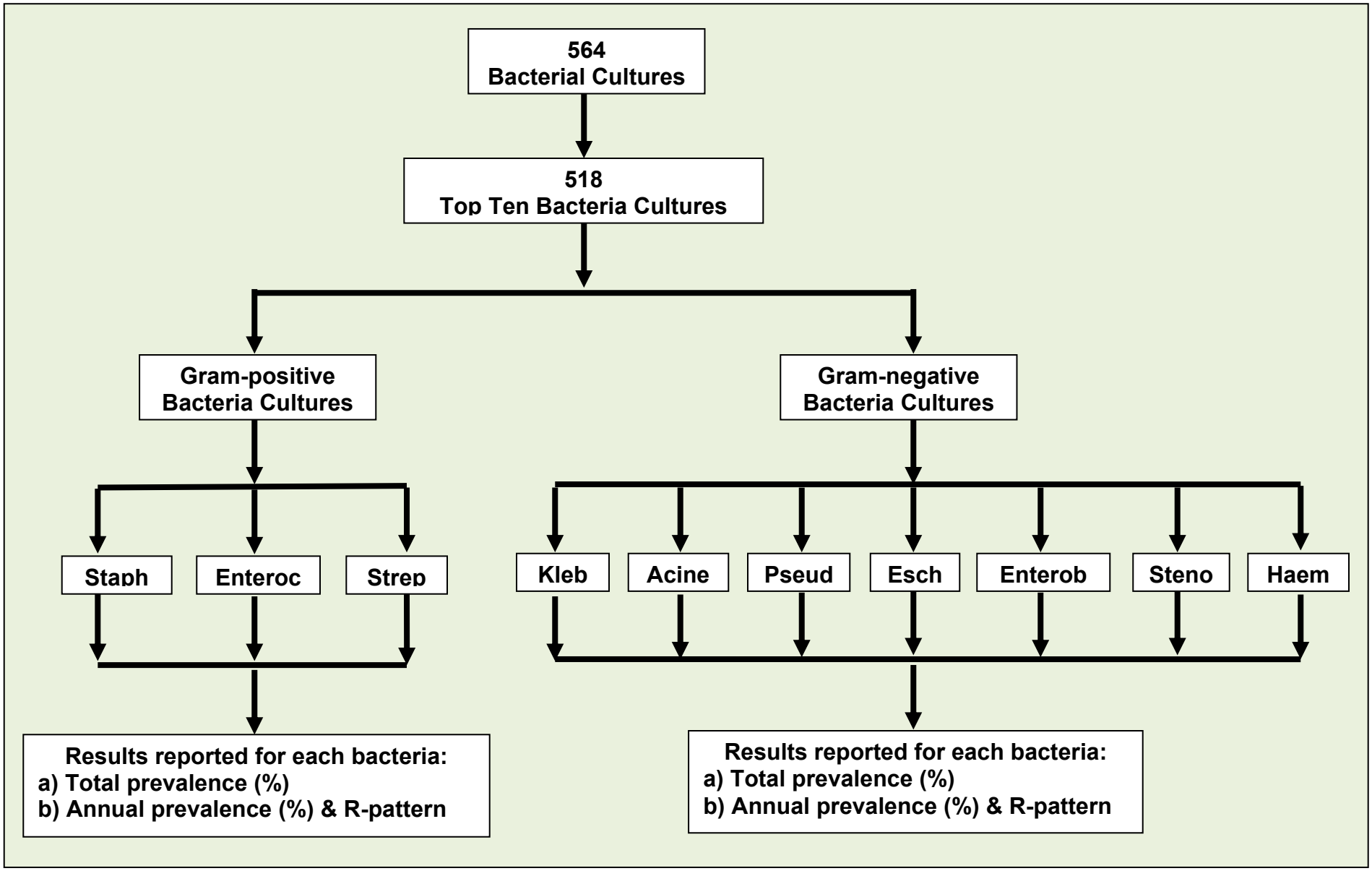


Figure 9.3: A flow diagram illustrating the selection of bacteria genera for the determination of the total and annual prevalence as well as the antibiotic resistance pattern

Key: Staph = *Staphylococcus*, Enteroc = *Enterococcus*, Strep = *Streptococcus*, Kleb = *Klebsiella*, Acine = *Acinetobacter*, Pseud = *Pseudomonas*, Esch = *Escherichia*, Enterob = *Enterobacter*, Steno = *Stenotrophomonas*, Haem = *Haemophilus*, R = Resistance

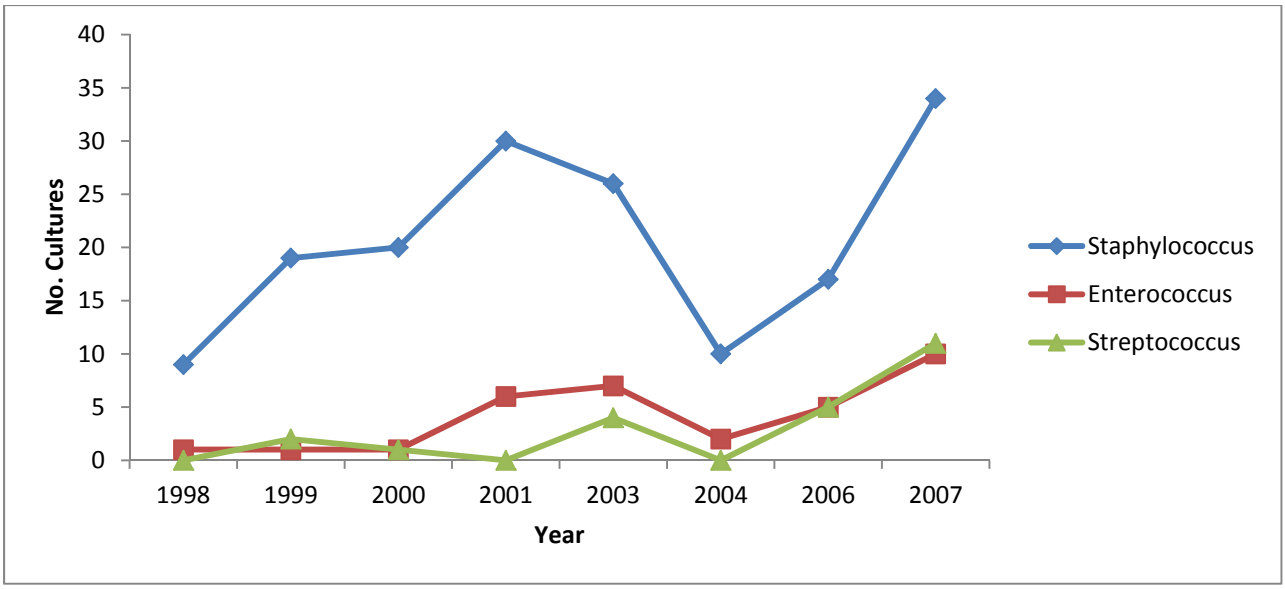


Figure 9.4: The annual number of positive cultures for the common Gram-positive bacteria genera

9.2.2 Gram-negative bacteria

The majority (58.7% [331/564]) of bacteria genera were Gram-negative, with the most common being *Klebsiella* (11.8% [67/564]), *Acinetobacter* (11.7% [66/564]), *Pseudomonas* (11.2% [63/564]), *Escherichia* (8.5% [48/564]), *Enterobacter* (4.1% [23/564]), *Stenotrophomonas* (3.4% [19/564]) and *Haemophilus* (2% [11/564]) (Figure 9.2 page 103 & Table D3 page 189).

In Figure 9.5, the prevalence of *Klebsiella* genus increased from seven per year in 2000 to 11 per year in 2001 and ten per year in 2003, and despite the drop in 2004 (four per year) and 2006 (five per year), it peaked to 25 per year in 2007. This observation coincides with the year (2007) of *Klebsiella* outbreak that led to temporarily closure (evacuation) of the PICU for disinfection. The prevalence of *Acinetobacter* and *Stenotrophomonas* genera exhibited a similar pattern, whereby they both increased reaching a peak in 2003 (*Acinetobacter* 23 per year and *Stenotrophomonas* eight per year) and 2007 (*Acinetobacter* 16 per year and *Stenotrophomonas* eight per year). Of note, these two bacteria are nosocomial bacteria commonly grown from tracheal aspirates and are very resistant to antibiotics. The *Pseudomonas* genus exhibited wide

variations reaching peaks in 1999 (11 per year), 2003 (ten per year) and 2006 (15 per year). The increased prevalence in 2007 needs to be interpreted with care, because more specimens (340) were collected in 2007 than in other years (<90 per year) (Table D2 page 188).

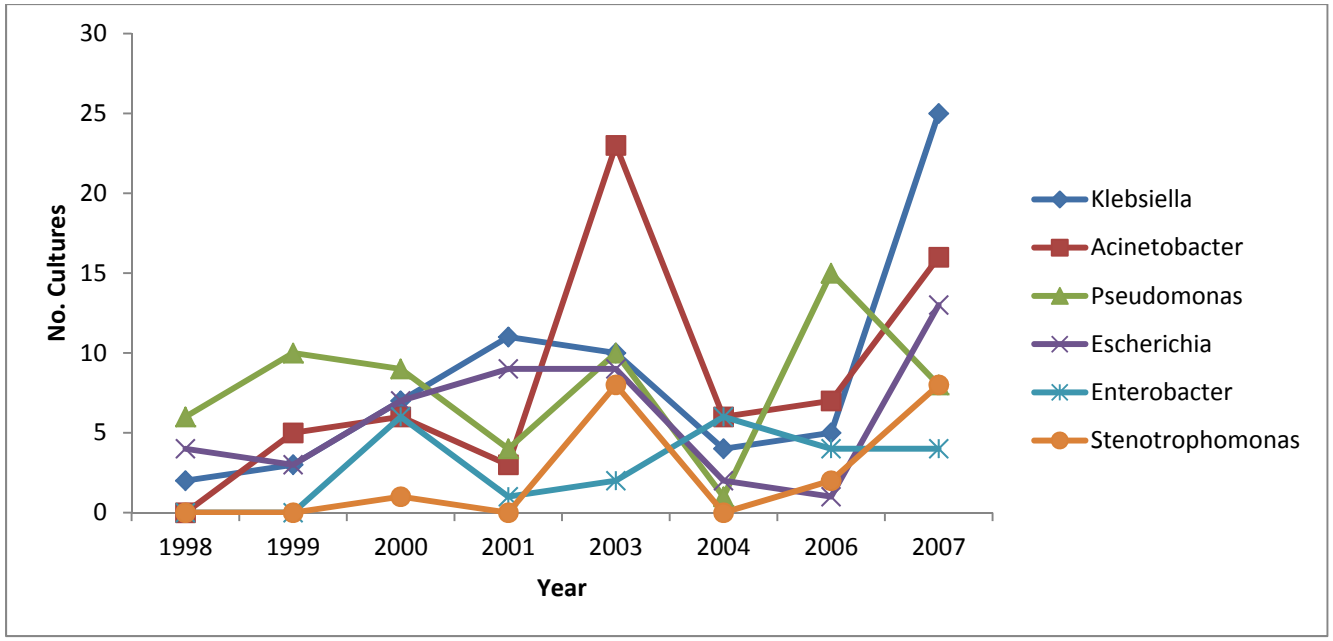


Figure 9.5: The annual number of positive cultures for the common Gram-negative bacteria genera

9.2.3 Specimens

From a total of 1 637 specimens collected, bacteria were cultured from 452 specimens (Figure 9.1 page 101). Regarding these specimens, five types of specimens accounted for the majority of specimens, i.e., 91.1% (412/452). They comprised of tracheal aspirates 192 (42.5%), blood 112 (24.8%), urine 54 (12%), pus 35 (7.7%) and catheter point 19 (4.2%) (Figure 9.6 & Table D4 page 190).

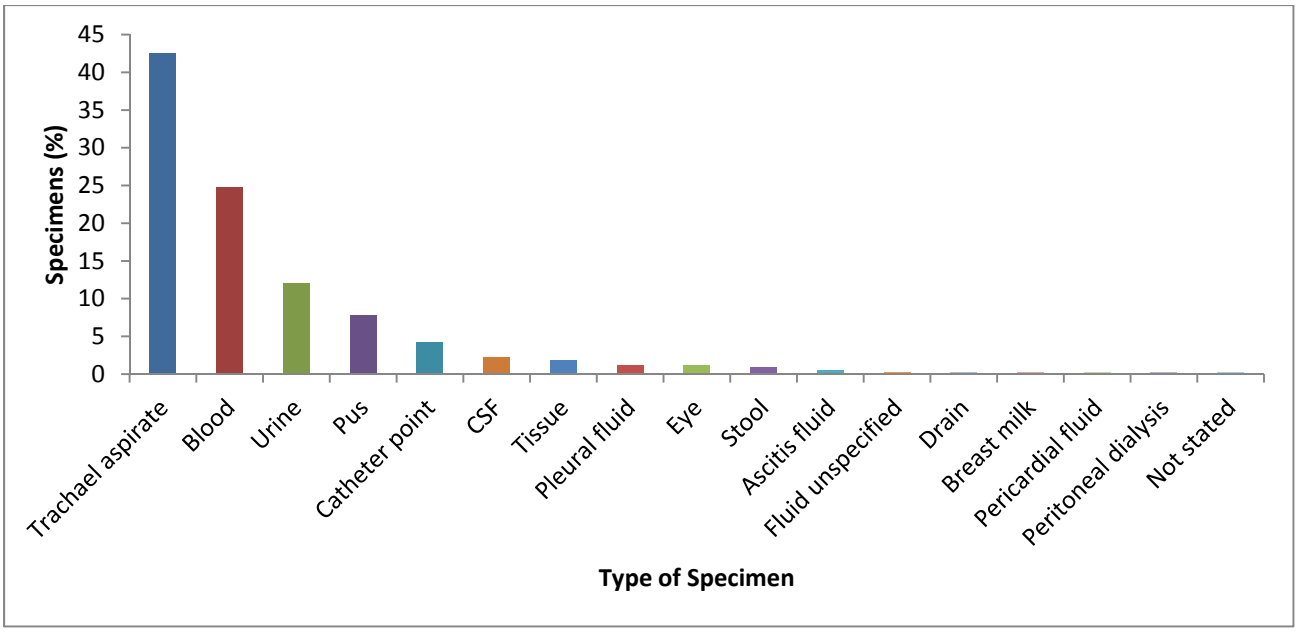


Figure 9.6: The proportion (%) of the different types of specimens with positive bacteria cultures

9.2.3.1 *Specimens and bacterial growth*

The pattern of bacterial growth in the top five types of specimens (tracheal aspirate, blood, urine, pus and catheter point) was evaluated for the common Gram-positive- and Gram-negative bacteria cited earlier.

Of the 165 *Staphylococcus* genus cultures, 70 (42.4%) were cultured from blood specimens, while 39 (23.6%) were cultured from tracheal aspirate specimens (Figure 9.7 & Table D5 page 191). Of the 23 *Streptococcus* genus cultures, 10 (43.5%) were cultured from blood specimens and 4 (17.4%) from tracheal aspirates, while *Enterococcus* genus was mostly cultured from urine specimens (15/33 cultures [45.5%]).

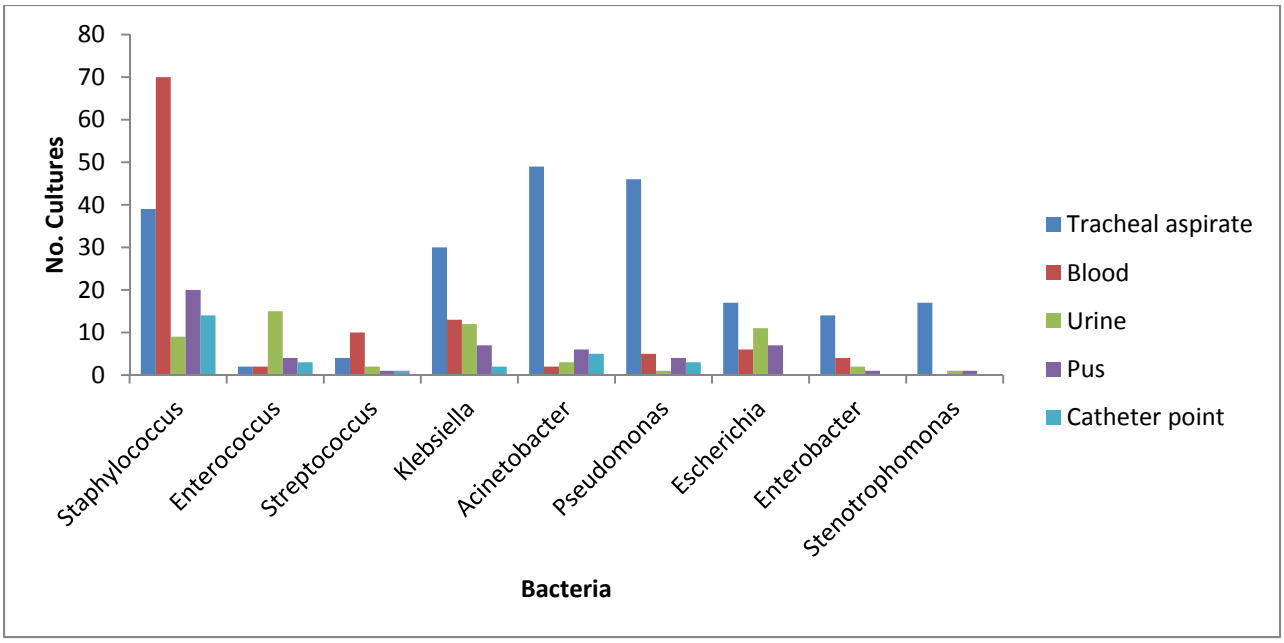


Figure 9.7: The number of positive cultures for the different bacteria genera (top nine) in the different specimens (top five)

Of the 67 *Klebsiella* genus cultures, 30 (44.8%) were cultured from tracheal aspirates, while 13 (19.4%) were cultured from blood and 12 (17.9%) from urine specimens (Figure 9.7 & Table D5 page 191). Most of the cultures for *Pseudomonas*, *Enterobacter*, *Acinetobacter* and *Stenotrophomonas* genera were cultured from tracheal aspirates: *Pseudomonas* 46/63 (73%), *Enterobacter* 14/23 (60.9%), *Acinetobacter* 49/66 (74.2%) and *Stenotrophomonas* 17/19 (89.5%). Of the 48 *Escherichia* genus cultures, 17 (35.4%) were cultured from tracheal aspirates, while 11 (22.9%) were cultured from urine specimens.

Overall, Gram-negative bacteria genera (*Acinetobacter*, *Pseudomonas*, *Klebsiella*, *Stenotrophomonas*, *Escherichia* and *Enterobacter*) were mainly cultured from tracheal aspirates (90.1% [173/192]), while Gram-positive bacteria genera (*Staphylococcus*, *Streptococcus* and *Enterococcus*) were mainly cultured from blood specimens (73.2% [82/112]). These observations may be linked to clinical diagnosis whereby more pneumonia would be associated with Gram-negative bacteria, septicaemia with Gram-positive bacteria, and UTI with *Enterococcus* and *Escherichia* genera.

9.3 The prevalence and pattern of antibiotic resistance

The prevalence of antibiotic resistance was evaluated for the common Gram-positive and Gram-negative bacteria genera. For Gram-positive, they were: *Staphylococcus*, *Enterococcus* and *Streptococcus*, for Gram-negative: *Klebsiella*, *Acinetobacter, Pseudomonas*, *Escherichia*, *Enterobacter, Stenotrophomonas* and *Haemophilus* (Figure 9.2 page 103).

Figure 9.8 is a flow diagram illustrating how the total and annual prevalence of antibiotic bacterial resistance for each of the top ten common bacteria genera were determined. First, the total number of cultures tested for each antibiotic was plotted on a graph for each bacteria genus (Figures 9.9A [i–iii] & 9.9B [i–vii]). Thereafter, only those antibiotics for which there were adequate numbers of cultures tested per antibiotic (≥9) were selected for evaluation of the prevalence of antibiotic resistance.

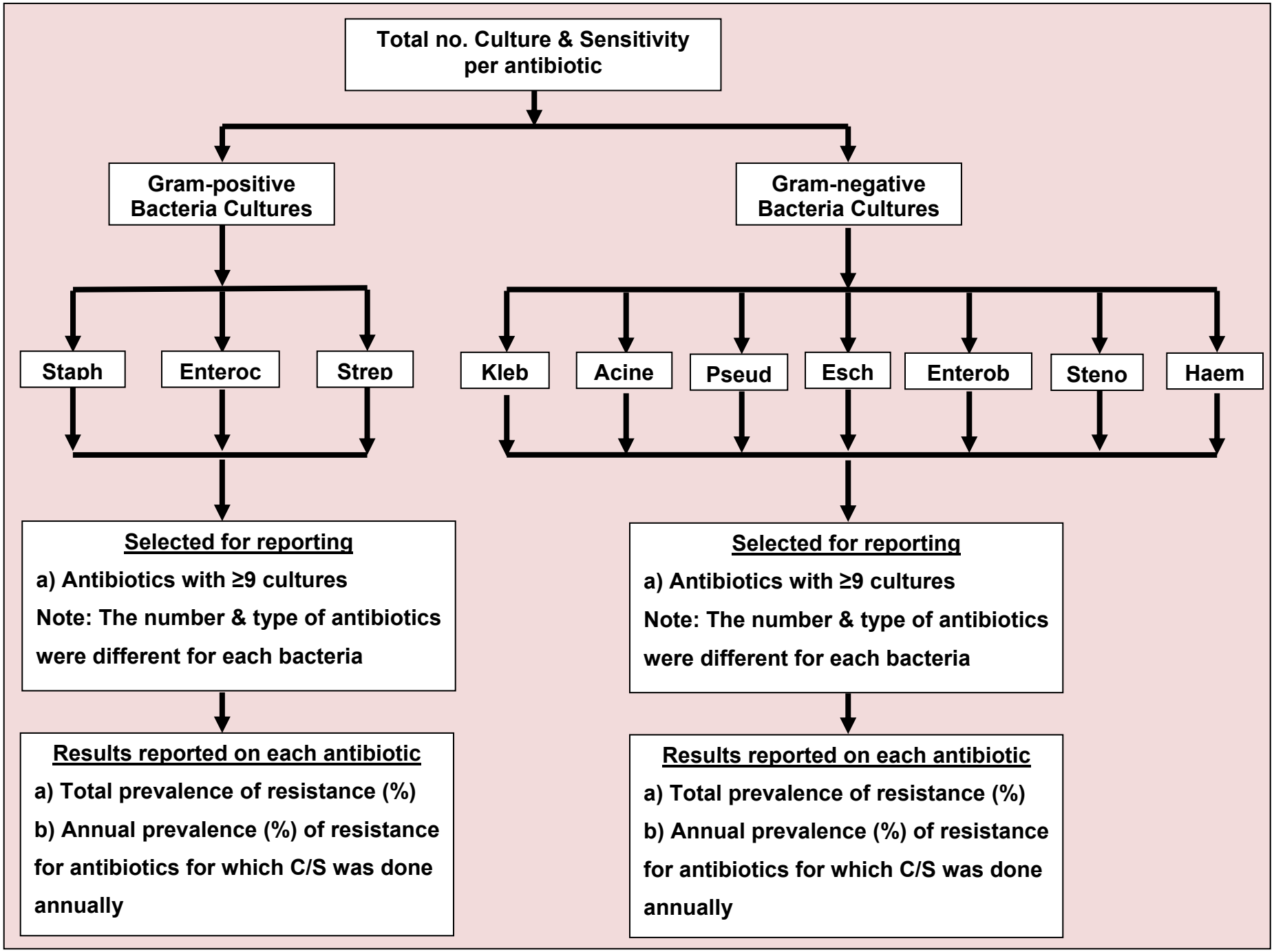


Figure 9.8: A flow diagram for the selection of antibiotics used for the evaluation of bacterial antibiotic resistance

Key: Staph = *Staphylococcus*, Enteroc = *Enterococcus*, Strep = *Streptococcus*, Kleb = *Klebsiella*, Acine = *Acinetobacter*, Pseud = *Pseudomonas*, Esch = *Escherichia*, Enterob = *Enterobacter*, Steno = *Stenotrophomonas*, Haem = *Haemophilus*

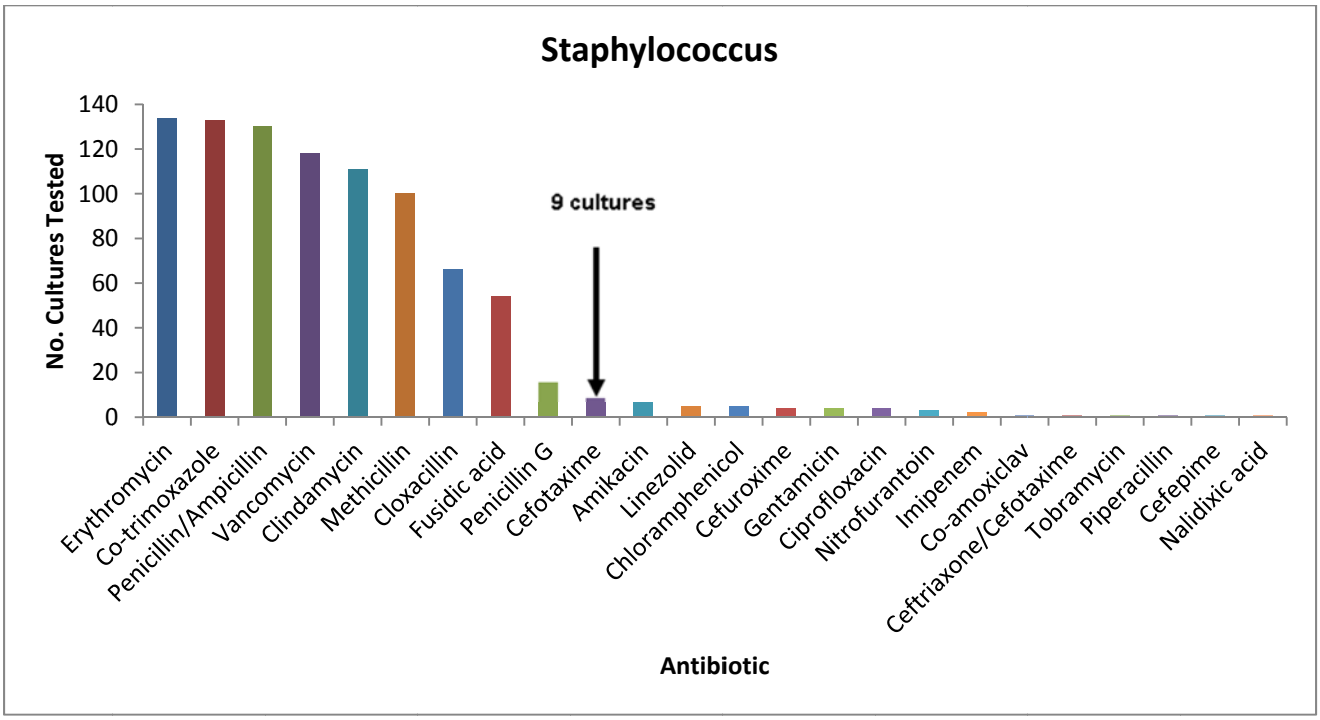


Figure 9.9Ai: The number of *Staphylococcus* genus cultures tested for antibiotic sensitivity

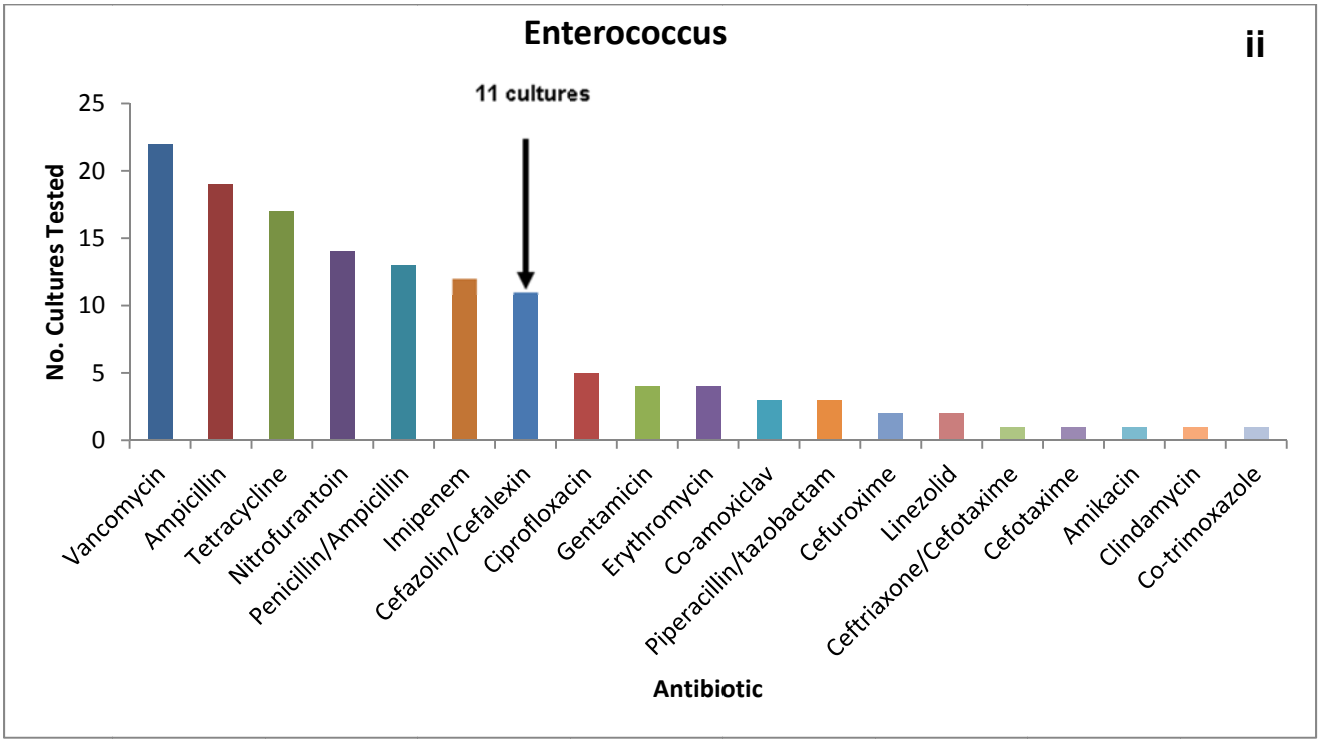


Figure 9.9Aii: The number of *Enterococcus* genus cultures tested for antibiotic sensitivity

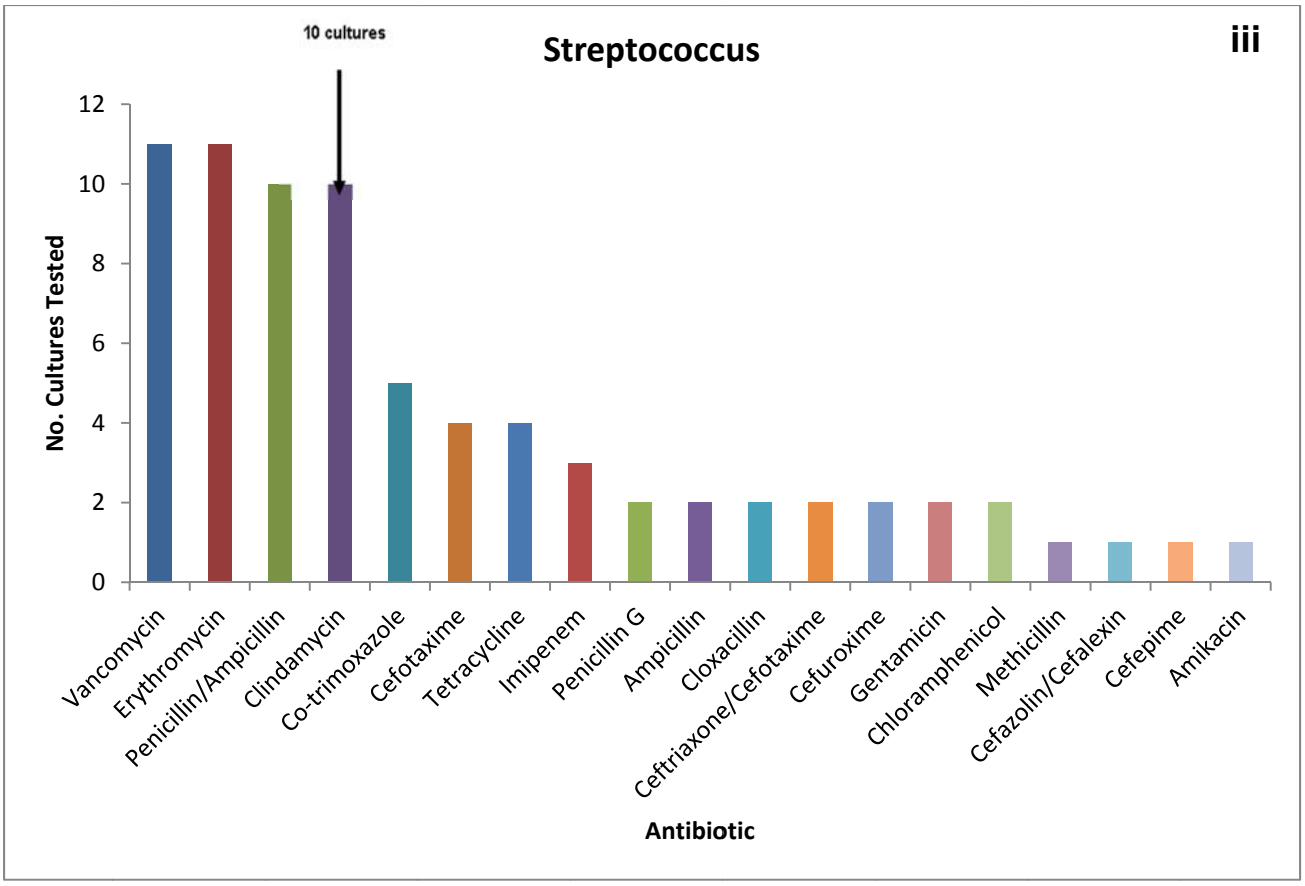


Figure 9.9Aiii: The number of *Streptococcus* genus cultures tested for antibiotic sensitivity

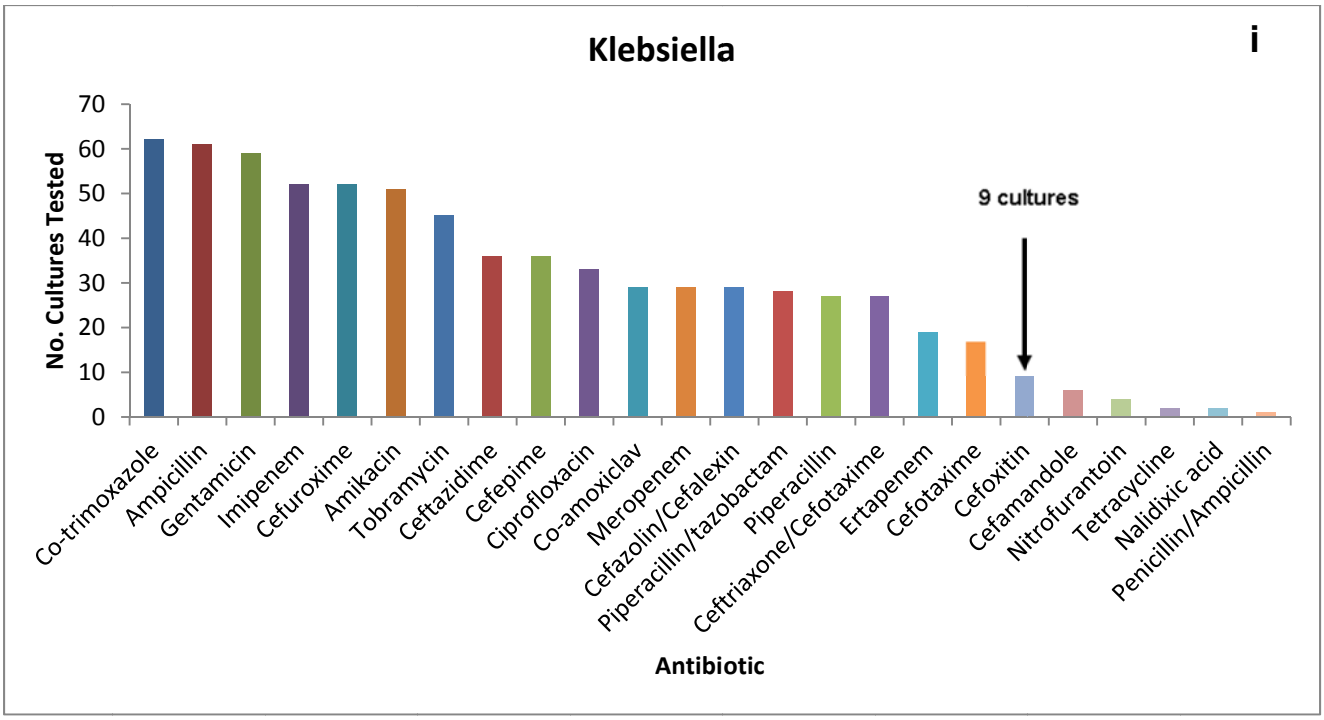


Figure 9.9Bi: The number of *Klebsiella* genus cultures tested for antibiotic sensitivity

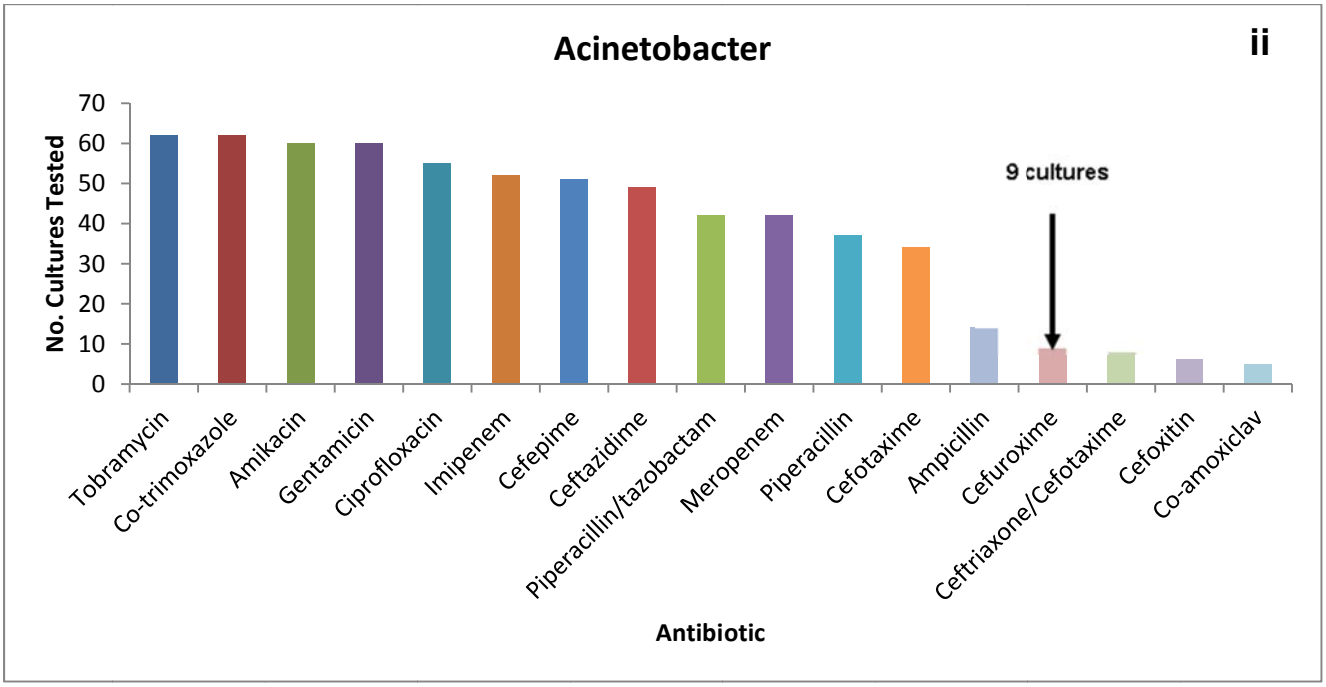


Figure 9.9Bii: The number of *Acinetobacter* genus cultures tested for antibiotic sensitivity

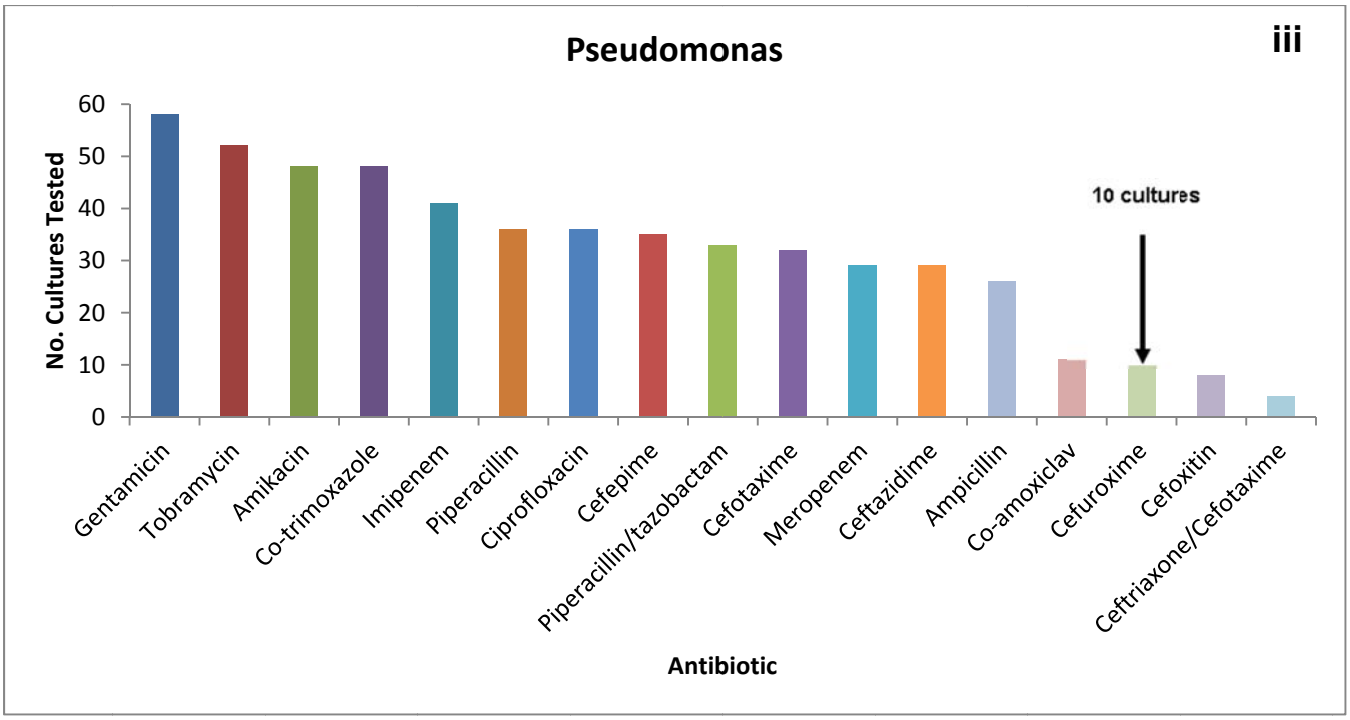


Figure 9.9Biii: The number of *Pseudomonas* genus cultures tested for antibiotic sensitivity

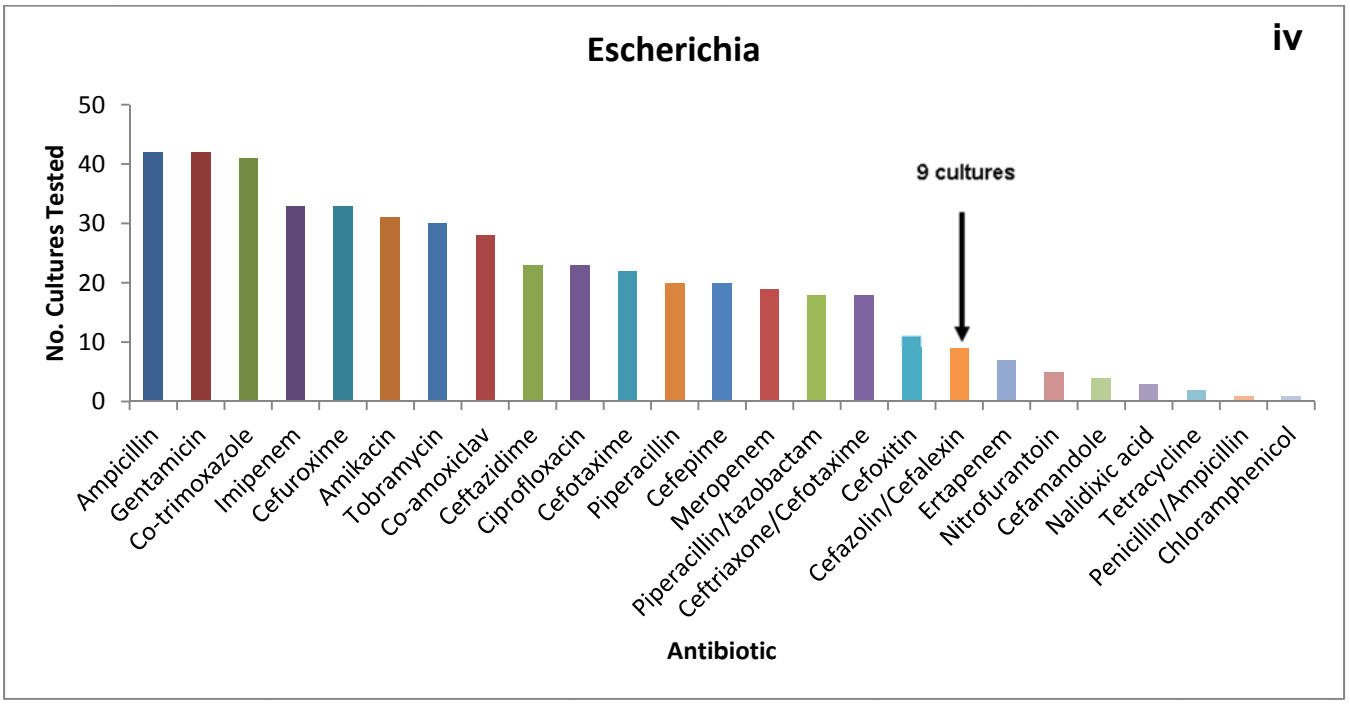


Figure 9.9Biv: The number of *Escherichia* genus cultures tested for antibiotic sensitivity

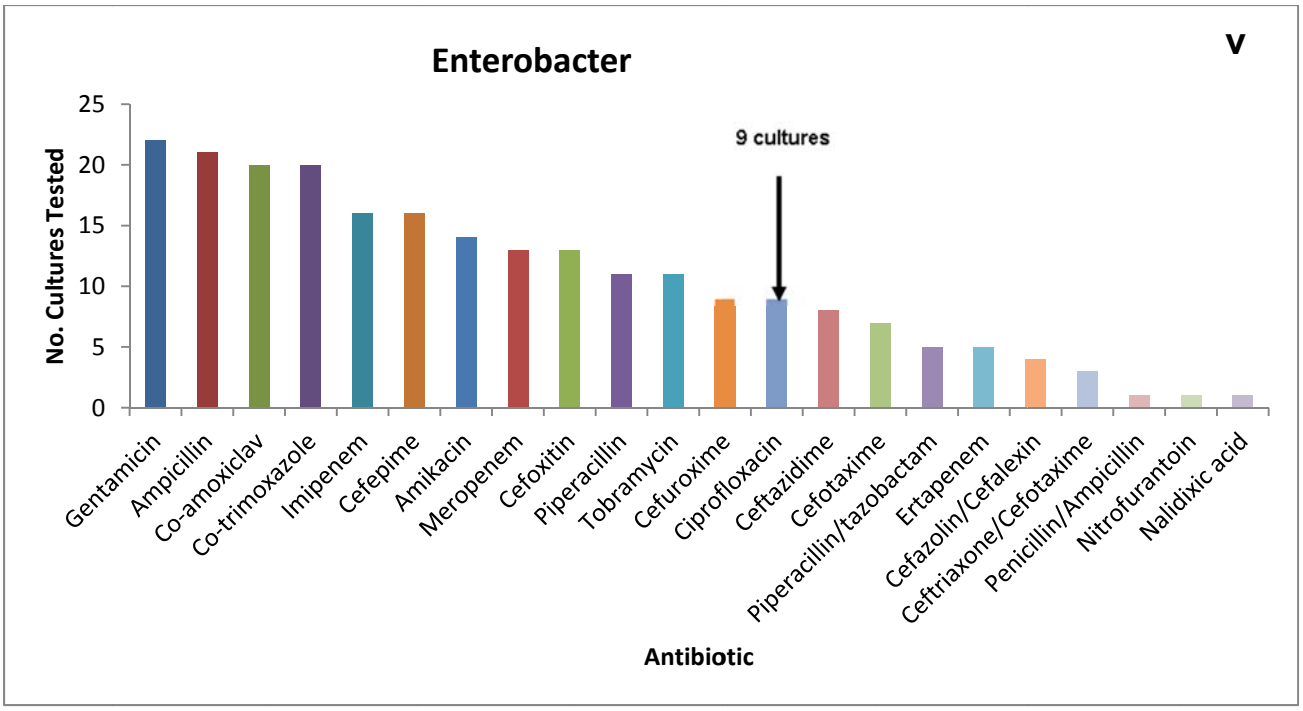


Figure 9.9Bv: The number of *Enterobacter* genus cultures tested for antibiotic sensitivity

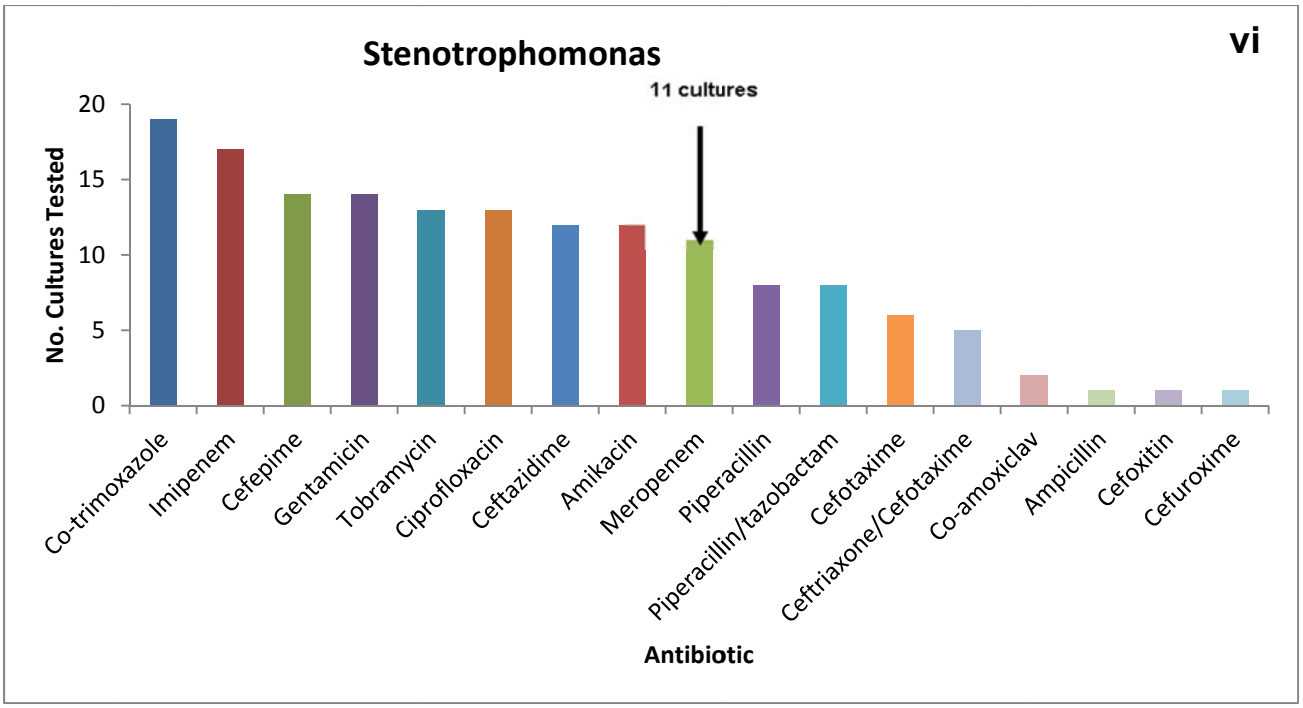


Figure 9.9Bvi: The number of *Stenotrophomonas* genus cultures tested for antibiotic sensitivity

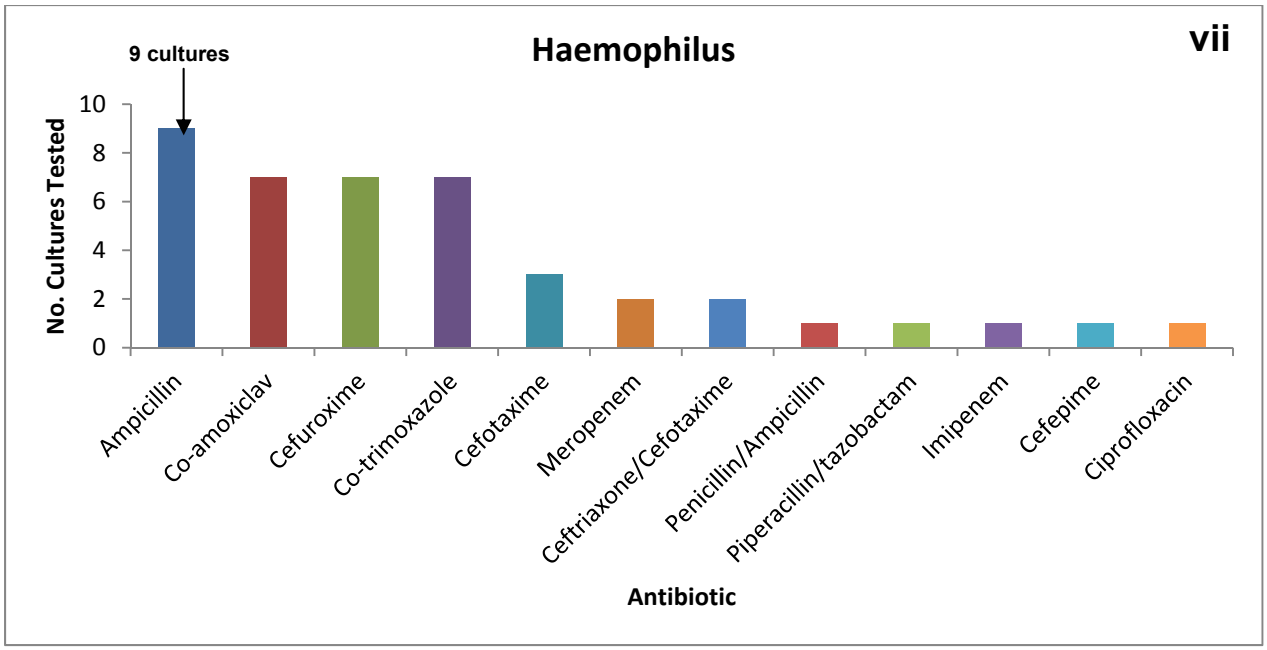


Figure 9.9Bvii: The number of *Haemophilus* genus cultures tested for antibiotic sensitivity

9.3.1 Gram-positive bacteria

***Staphylococcus*:** As indicated earlier, Figure 9.9Ai (page 111) shows the plot for the total number of cultures tested for *Staphylococcus* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: erythromycin, co-trimoxazole, penicillin/ampicillin, vancomycin, clindamycin, methicillin, cloxacillin, fusidic acid, penicillin G and cefotaxime (Figure 9.9Ai). These antibiotics were also identified as beta-lactams (penicillin/ampicillin, methicillin, cloxacillin, penicillin G and cefotaxime) and antibiotic substitutes for penicillin allergy (erythromycin, co-trimoxazole, vancomycin, clindamycin and fusidic acid) (Figure 9.10).

The total prevalence of resistance for *Staphylococcus* genus from 1998–2007 was 98.5% to penicillin/ampicillin, 85% to methicillin, 83% (55/66) to cloxacillin, 100% to penicillin G, 66.7% to cefotaxime, 76.9% to erythromycin, 66.9% to co-trimoxazole, 48.7% to clindamycin and 33.3% to fusidic acid (Figure 9.10 & Table D6 page 192).

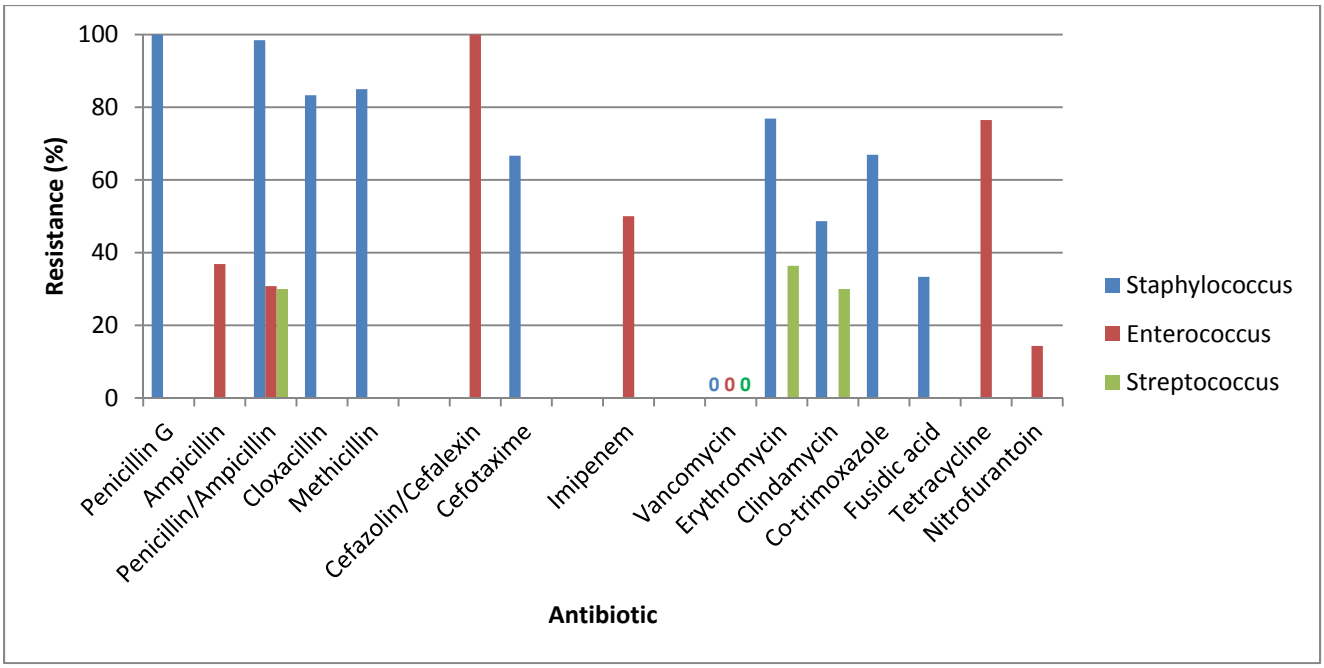


Figure 9.10: The proportion (%) of resistant cultures of *Staphylococcus, Enterococcus* and *Streptococcus* genera to some antibiotics

Regarding cloxacillin resistance, 38% (21/55) was due to *S. aureus*, which exhibited 70% (21/30) resistance.

The annual prevalence of resistance for *Staphylococcus* genus from 1998–2007 ranged from 92.3–100% to penicillin/ampicillin, 63.2–100% to methicillin, 57.9–86.7% to erythromycin and 40–82.4% to co-trimoxazole (Figure 9.11). However, no resistance was reported to vancomycin over all the years.

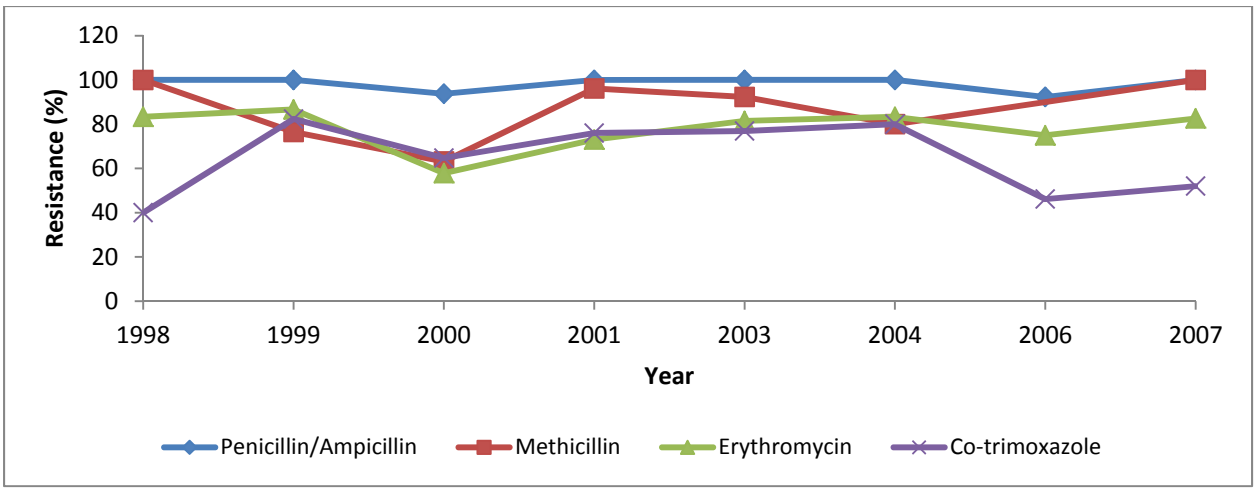


Figure 9.11: The annual prevalence (%) of resistance for *Staphylococcus* genus to selected beta-lactams and co-trimoxazole from 1998–2007

***Enterococcus*:** Figure 9.9Aii (page 111) shows the plot for the total number of cultures tested for *Enterococcus* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: vancomycin, ampicillin, tetracycline, nitrofurantoin, penicillin/ampicillin, imipenem and cefazolin/cefalexin (Figure 9.9Aii).

The total prevalence of resistance for *Enterococcus* genus from 1998–2007 was 36.8% to ampicillin, 76.5% to tetracycline, 14.3% to nitrofurantoin, 30.8% to penicillin/ampicillin, 50% to imipenem and 100% to cefazolin/cefalexin (Figure 9.10 page 117 & Table D7 page 193). The *Enterococcus* genus exhibited high resistance to tetracycline and cefazolin/cefalexin, but no resistance to vancomycin.

The annual prevalence of resistance for *Enterococcus* genus from 1998–2007 was 100% to cefazolin/cefalexin, and ranged from 66.7–100% to tetracycline. The C/S results for the other antibiotics were too few for evaluation in this respect.

Streptococcus: Figure 9.9Aiii (page 112) shows the plot for the total number of cultures tested for *Streptococcus* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: vancomycin, erythromycin, penicillin/ampicillin and clindamycin (Figure 9.9Aiii).

The total prevalence of resistance for *Streptococcus* genus from 1999–2007 was 36.4% to erythromycin, 30% to penicillin/ampicillin and 30% to clindamycin (Figure 9.10 page 117 & Table D8 page 194). The *Streptococcus* genus exhibited low resistance to all the antibiotics tested with no resistance to vancomycin.

The annual prevalence of resistance for *Streptococcus* genus from 1999–2007 ranged from 33.3–50% to erythromycin. The C/S results for the other antibiotics were too few for evaluation in this respect.

9.3.2 Gram-negative bacteria

***Klebsiella*:** As indicated earlier, Figure 9.9Bi (page 113) shows the plot for the total number of cultures tested for *Klebsiella* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: co-trimoxazole, ampicillin, gentamicin, imipenem, cefuroxime, amikacin, tobramycin, ceftazidime, cefepime, ciprofloxacin, co-amoxiclav, meropenem, cefazolin/cefalexin, piperacillin/tazobactam, piperacillin, ceftriaxone/cefotaxime, ertapenem, cefotaxime and cefoxitin (Figure 9.9Bi).

The total prevalence of resistance for *Klebsiella* genus from 1999–2007 was 71% to co-trimoxazole, 100% to ampicillin, 69.5% to gentamicin, 1.9% to imipenem, 73.1% to cefuroxime, 15.7% to amikacin, 77.8% to tobramycin, 94.4% to ceftazidime, 61.1% to cefepime, 15.2% to ciprofloxacin, 34.5% to co-amoxiclav, 86.2% to cefazolin/cefalexin, 21.4% to piperacillin/tazobactam, 88.9% to piperacillin, 96.3% to ceftriaxone/cefotaxime, 70.6% to cefotaxime and 22.2% to cefoxitin (Figure 9.12 & Table D9 page 195). No resistance was reported to meropenem and ertapenem.

The annual prevalence of resistance for *Klebsiella* genus from 1999–2007 ranged from 45.5–100% to co-trimoxazole, 55.6–100% to gentamicin, 42.8–100% to cefuroxime, 0–62.5% to amikacin, 50–100% to tobramycin, 75–100% to ceftazidime and 80–100% to piperacillin (Figure 9.13A & 9.13B). The annual prevalence of resistance to ampicillin was 100% for all the years.

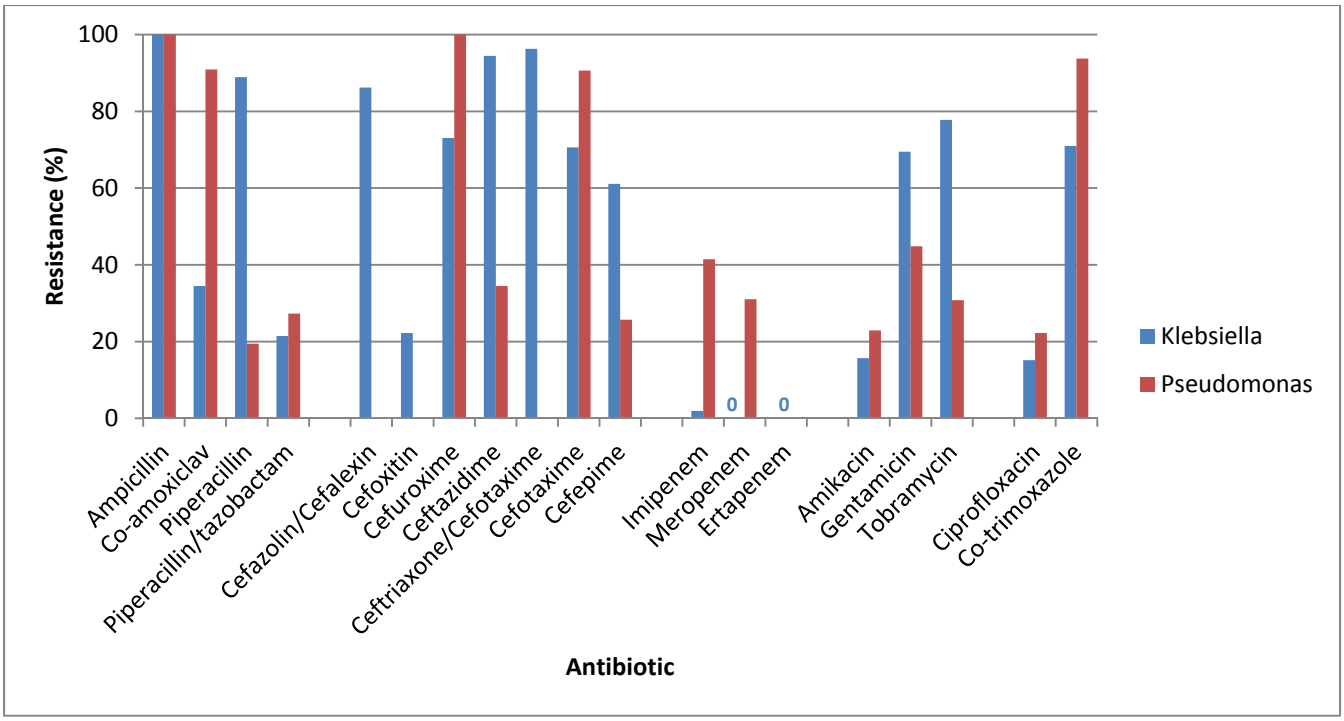


Figure 9.12: The proportion (%) of resistant cultures of *Klebsiella* and *Pseudomonas* genera to some antibiotics

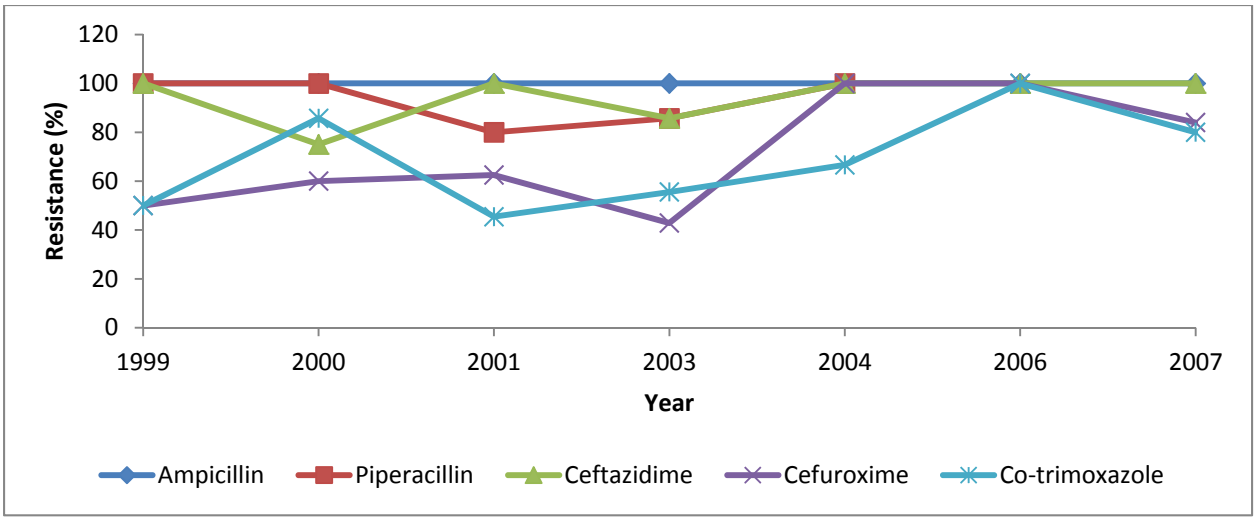


Figure 9.13A: The annual prevalence (%) of resistance for *Klebsiella* genus to selected beta-lactams and co-trimoxazole from 1999–2007

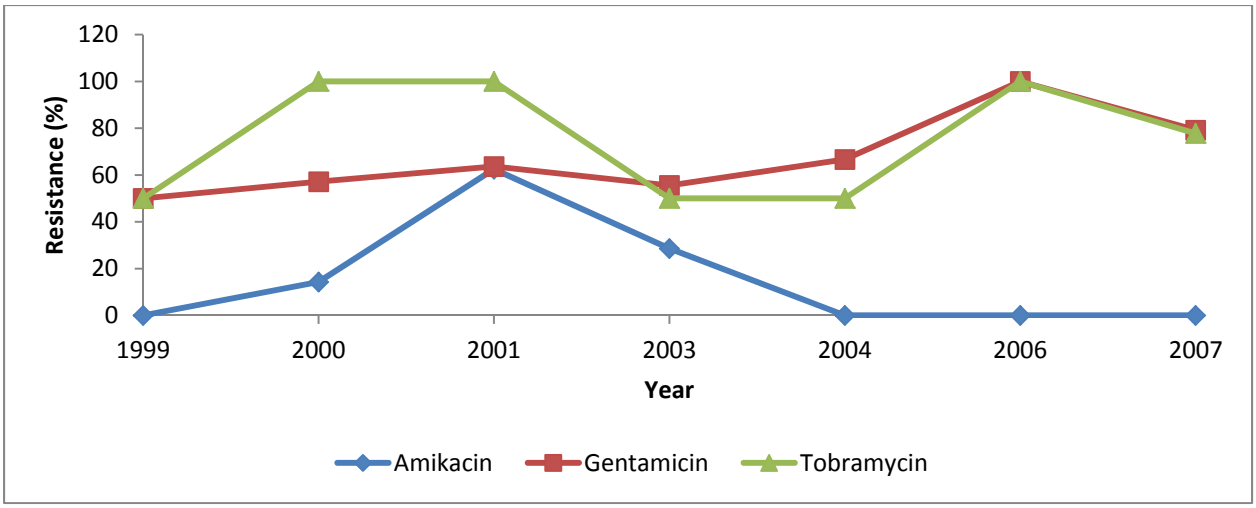


Figure 9.13B: The annual prevalence (%) of resistance for *Klebsiella* genus to aminoglycosides from 1999–2007

***Pseudomonas*:** Figure 9.9Biii (page 114) shows the plot for the total number of cultures tested for *Pseudomonas* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: gentamicin, tobramycin, amikacin, co-trimoxazole, imipenem, piperacillin, ciprofloxacin, cefepime, piperacillin/tazobactam, cefotaxime, meropenem, ceftazidime, ampicillin, co-amoxiclav and cefuroxime (Figure 9.9Biii).

The total prevalence of resistance for *Pseudomonas* genus from 1998–2007 was 44.8% to gentamicin, 30.8% to tobramycin, 22.9% to amikacin, 93.8% to co-trimoxazole, 41.5% to imipenem, 19.4% to piperacillin, 22.2% to ciprofloxacin, 25.7% to cefepime, 27.3% to piperacillin/tazobactam, 90.6% to cefotaxime, 31% to meropenem, 34.5% to ceftazidime, 100% to ampicillin, 90.9% to co-amoxiclav and 100% to cefuroxime (Figure 9.12 page 120 & Table D10 page 196).

The annual prevalence of resistance for *Pseudomonas* genus from 1998–2007 (excluding 2004 with only one culture) ranged from 28.6–60% to imipenem, 11.1–50% to ciprofloxacin and 77.8–100% to cefotaxime (Figure 9.14A & 9.14B). No trend could be seen with the aminoglycosides due to few cultures in some years (Figure 9.14C).

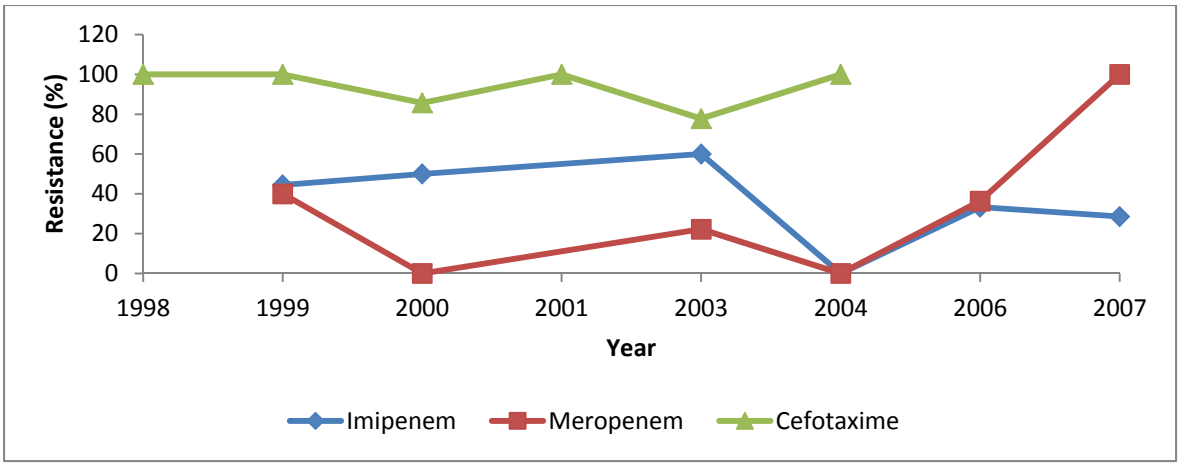


Figure 9.14A: The annual prevalence (%) of resistance for *Pseudomonas* genus to selected beta-lactams from 1998–2007

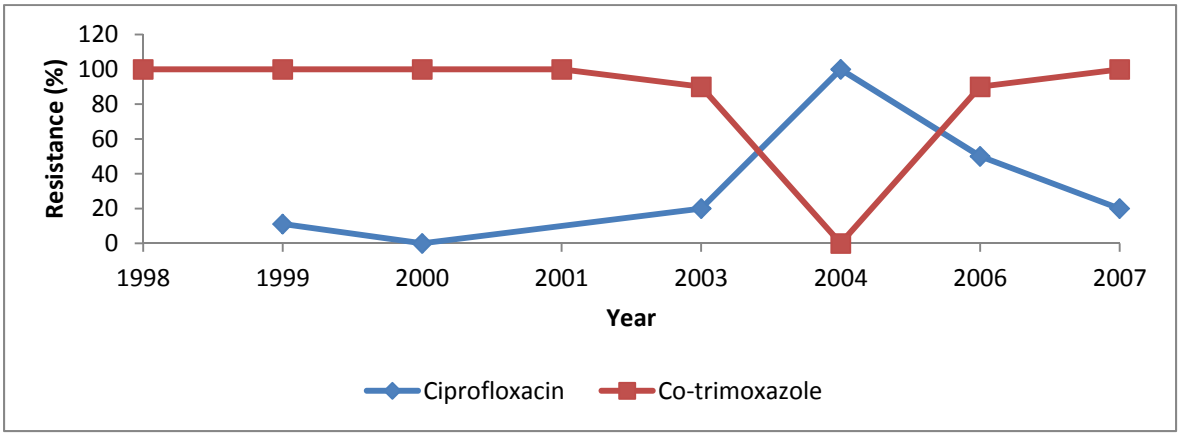


Figure 9.14B: The annual prevalence (%) of resistance for *Pseudomonas* genus to ciprofloxacin and co-trimoxazole from 1998–2007

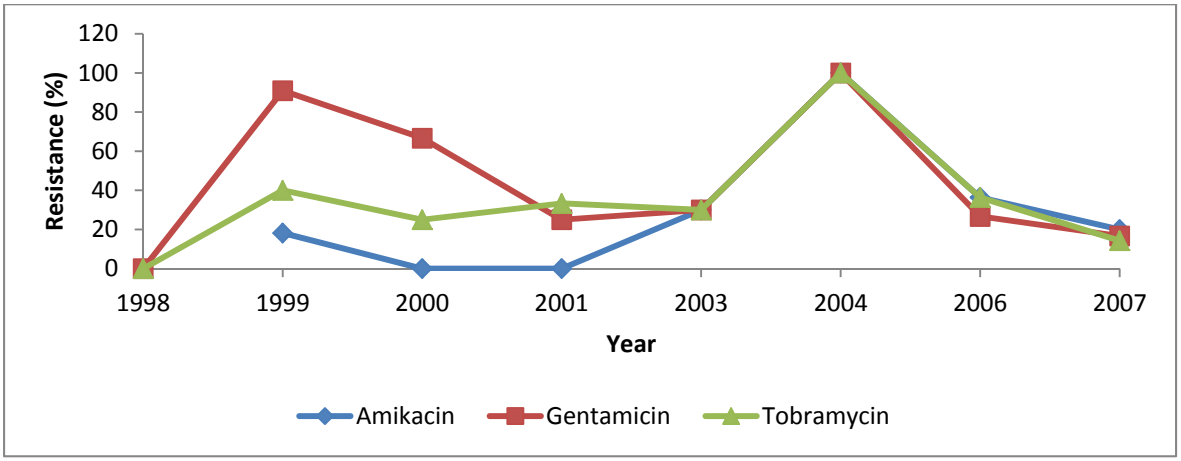


Figure 9.14C: The annual prevalence (%) of resistance for *Pseudomonas* genus to aminoglycosides from 1998–2007

***Escherichia*:** Figure 9.9Biv (page 114) shows the plot for the total number of cultures tested for *Escherichia* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: ampicillin, gentamicin, co-trimoxazole, imipenem, cefuroxime, amikacin, tobramycin, co-amoxiclav, ceftazidime, ciprofloxacin, cefotaxime, piperacillin, cefepime, meropenem, piperacillin/tazobactam, ceftriaxone/cefotaxime, cefoxitin and cefazolin/cefalexin (Figure 9.9Biv).

The total prevalence of resistance for *Escherichia* genus from 1998–2007 was 92.9% to ampicillin, 45.2% to gentamicin, 90.2% to co-trimoxazole, 48.5% to cefuroxime, 25.8% to amikacin, 63.3% to tobramycin, 21.4% to co-amoxiclav, 73.9% to ceftazidime, 4.4% to ciprofloxacin, 45.5% to cefotaxime, 95% to piperacillin, 30% to cefepime, 5.6% to piperacillin/tazobactam, 61.1% to ceftriaxone/cefotaxime, 9.1% to cefoxitin and 77.8% to cefazolin/cefalexin (Figure 9.15 & Table D11 page 197). No resistance were reported to imipenem and meropenem.

The annual prevalence of resistance for *Escherichia* genus from 1998–2007 (excluding 2006 with one culture) ranged from 86–100% to ampicillin, 81.8–100% to co-trimoxazole and 44.4–100% to ceftazidime (Figure 9.16A). No trend could be seen with the aminoglycosides due to a few cultures in some years (Figure 9.16B).

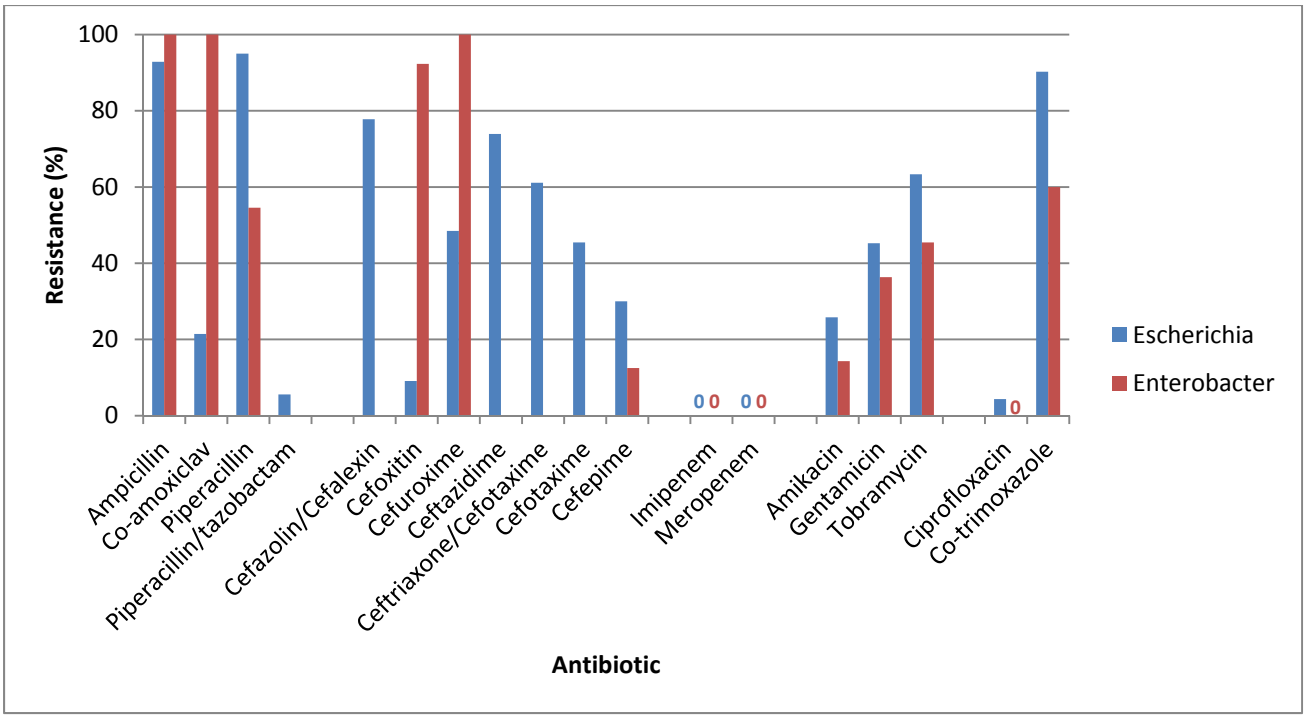


Figure 9.15: The proportion (%) of resistant cultures of *Escherichia* and *Enterobacter* genera to some antibiotics

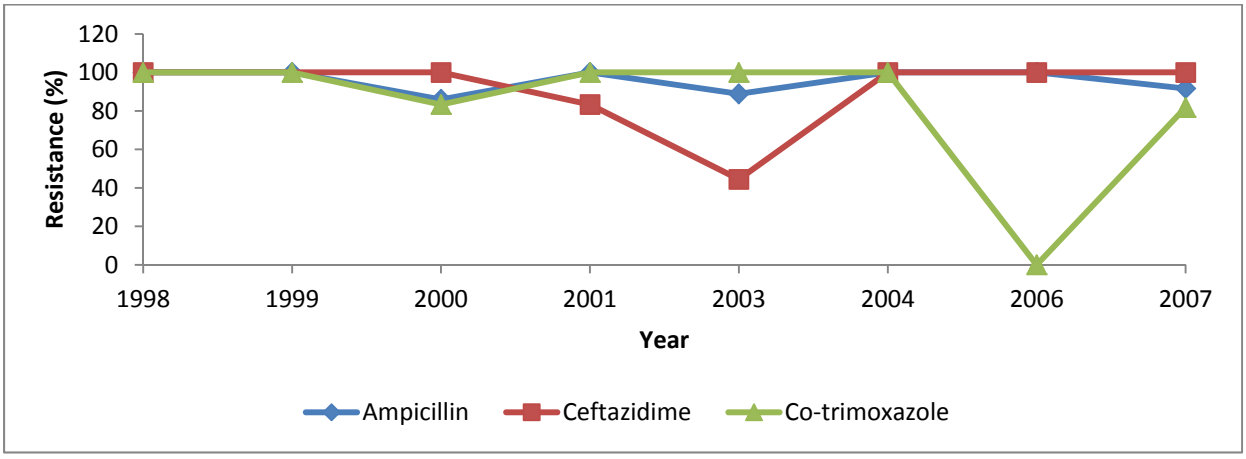


Figure 9.16A: The annual prevalence (%) of resistance for *Escherichia* genus to selected beta-lactams and co-trimoxazole from 1998–2007

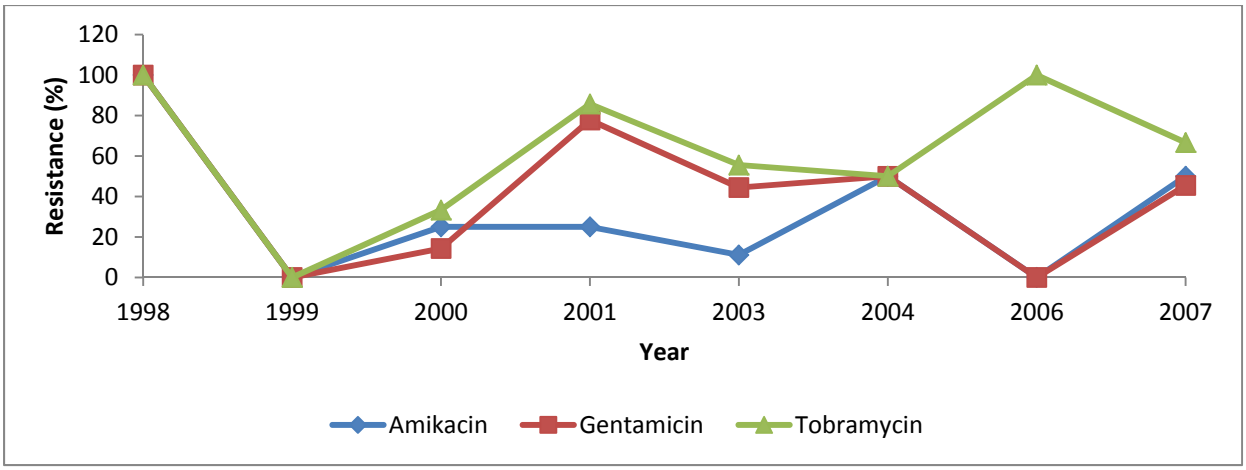


Figure 9.16B: The annual prevalence (%) of resistance for *Escherichia* genus to aminoglycosides from 1998–2007

***Enterobacter*:** Figure 9.9Bv (page 115) shows the plot for the total number of cultures tested for *Enterobacter* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: gentamicin, ampicillin, co-amoxiclav, co-trimoxazole, imipenem, cefepime, amikacin, meropenem, cefoxitin, piperacillin, tobramycin, cefuroxime and ciprofloxacin (Figure 9.9Bv).

The total prevalence of resistance for *Enterobacter* genus from 2000–2007 was 36.4% to gentamicin, 100% to ampicillin, 100% to co-amoxiclav, 60% to co-trimoxazole, 12.5% to cefepime, 14.3% to amikacin, 92.3% to cefoxitin, 54.6% to piperacillin, 45.5% to tobramycin, and 100% to cefuroxime (Figure 9.15 page 124 & Table D12 page 198). No resistance was reported to imipenem, meropenem and ciprofloxacin.

The annual prevalence of resistance for *Enterobacter* genus from 2000–2007 was 100% for all the years to ampicillin, as well as co-amoxiclav.

***Haemophilus*:** Figure 9.9Bvii (page 116) shows the plot for the total number of cultures tested for *Haemophilus* genus sensitivity versus each of the respective antibiotics. Only ampicillin had a total of nine cultures. Of note, ampicillin is also used as an indicator of beta-lactamase mediated resistance to other penicillins. Unfortunately, the nine

cultures were not adequate for further evaluation of prevalence, i.e., four cultures in 2007 and the rest one or two in different years.

***Acinetobacter*:** Figure 9.9Bii (page 113) shows the plot for the total number of cultures tested for *Acinetobacter* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: tobramycin, co-trimoxazole, amikacin, gentamicin, ciprofloxacin, imipenem, cefepime, ceftazidime, piperacillin/tazobactam, meropenem, piperacillin, cefotaxime, ampicillin and cefuroxime (Figure 9.9Bii).

The total prevalence of resistance for *Acinetobacter* genus from 1999–2007 was 25.8% to tobramycin, 82.3% to co-trimoxazole, 81.7% to amikacin, 73.3% to gentamicin, 80% to ciprofloxacin, 65.4% to imipenem, 74.5% to cefepime, 79.6% to ceftazidime, 81% to piperacillin/tazobactam, 71.4% to meropenem, 83.8% to piperacillin, 85.3% to cefotaxime, 100% to ampicillin, and 100% to cefuroxime (Figure 9.17 & Table D13 page 199).

The annual prevalence of resistance for *Acinetobacter* genus from 1999–2007 (excluding 2004 due to few cultures) ranged from 6.3–100% to tobramycin, 50–100% to co-trimoxazole, 50–100% to amikacin, 50–100% to gentamicin, 60–100% to ciprofloxacin, 25–100% to imipenem, 50–100% to cefepime, 68.2–100% to ceftazidime, 0–100% to meropenem and 50–100% to piperacillin (Figure 9.18A, 9.18B & 9.18C). Although the *Acinetobacter* genus showed high resistance to the aminoglycosides, the annual prevalence of resistance generally depicted peaks and troughs with no trend.

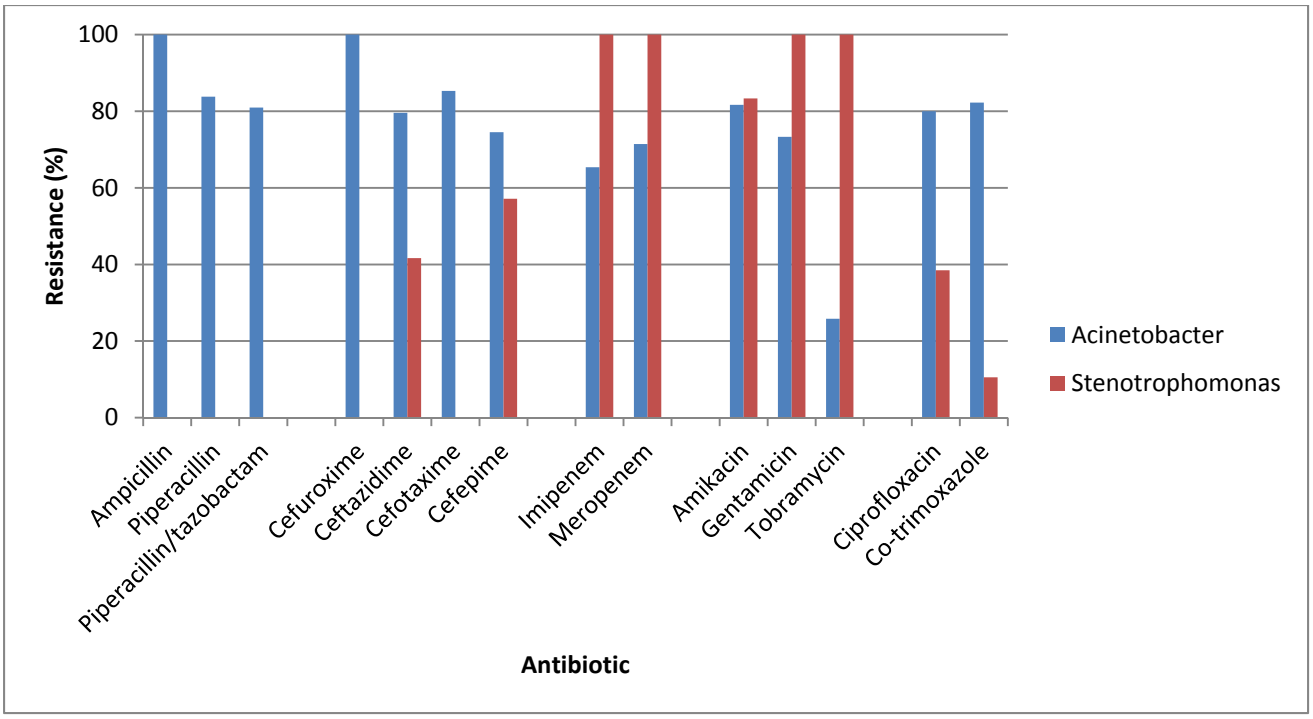


Figure 9.17: The proportion (%) of resistant cultures of *Acinetobacter* and *Stenotrophomonas* genera to some antibiotics

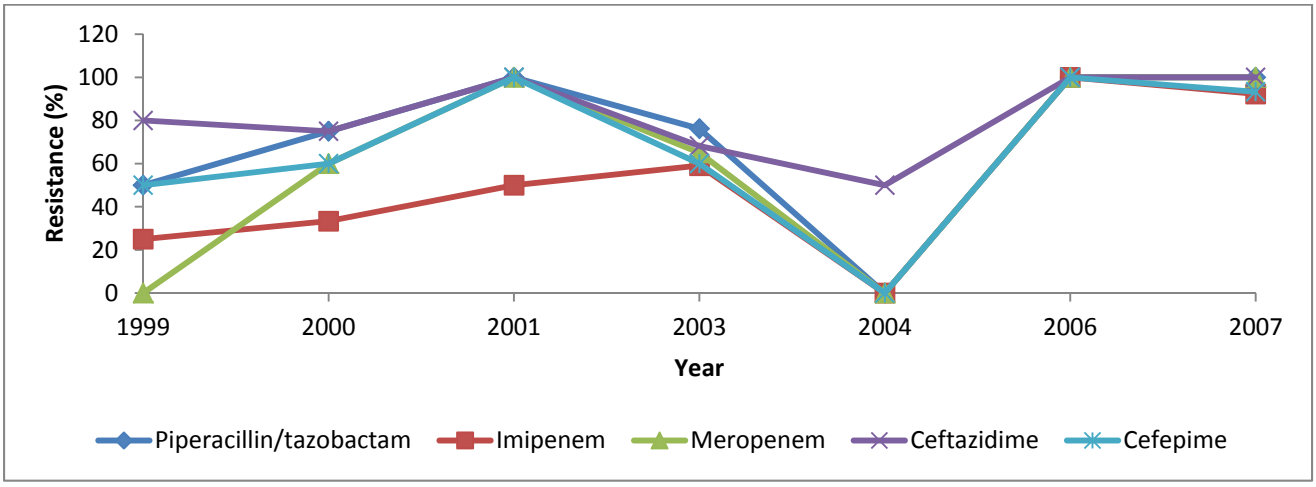


Figure 9.18A: The annual prevalence (%) of resistance for *Acinetobacter* genus to selected beta-lactams from 1999–2007

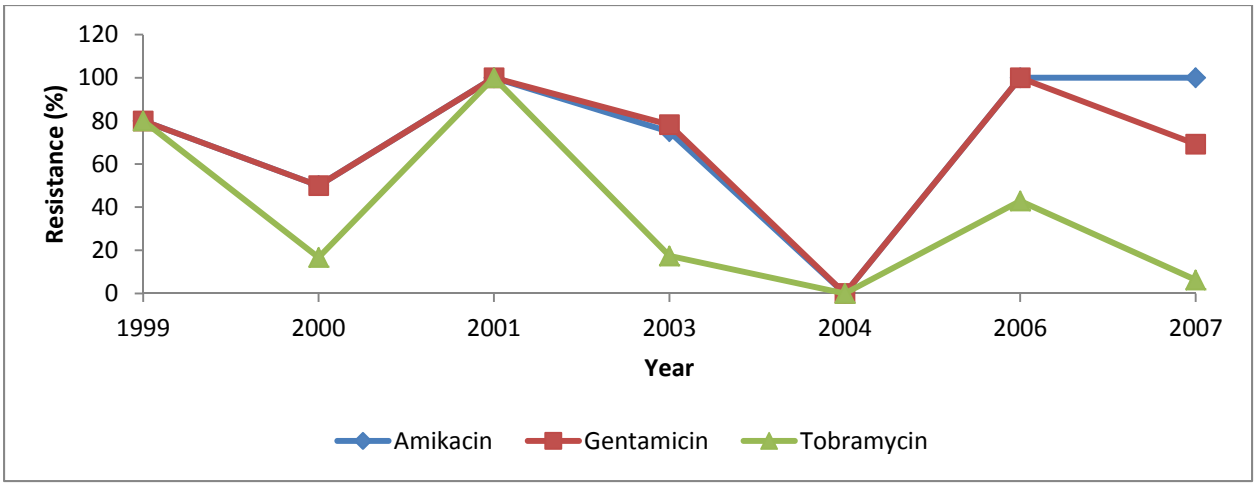


Figure 9.18B: The annual prevalence (%) of resistance for *Acinetobacter* genus to aminoglycosides from 1999–2007

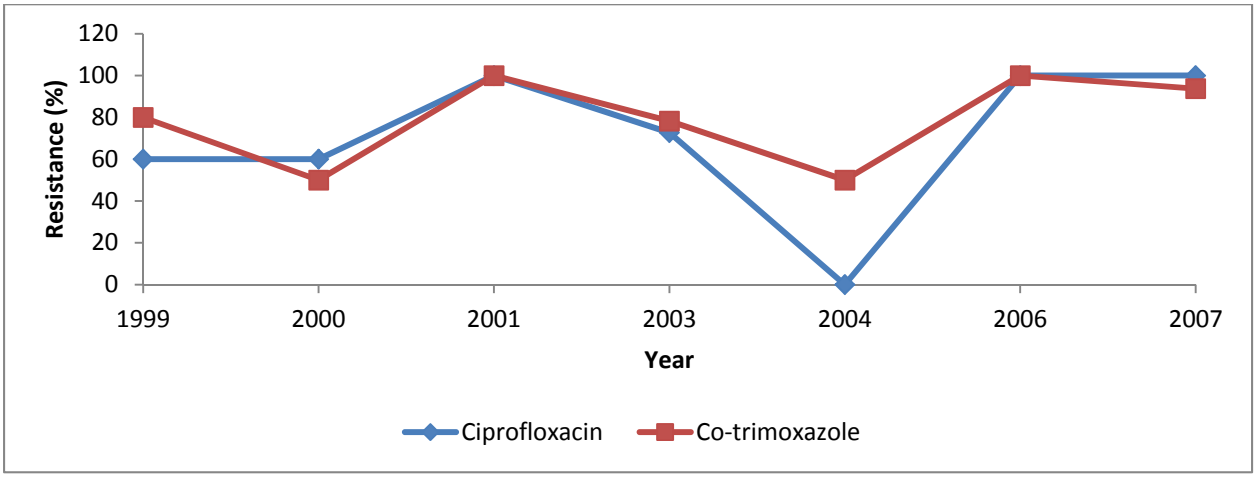


Figure 9.18C: The annual prevalence (%) of resistance for *Acinetobacter* genus to ciprofloxacin and co-trimoxazole from 1999–2007

***Stenotrophomonas*:** Figure 9.9Bvi (page 115) shows the plot for the total number of cultures tested for *Stenotrophomonas* genus sensitivity versus each of the respective antibiotics. The following antibiotics were selected for further evaluation for resistance because each had a total of nine or more cultures: co-trimoxazole, imipenem, cefepime, gentamicin, tobramycin, ciprofloxacin, ceftazidime, amikacin and meropenem (Figure 9.9Bvi).

The total prevalence of resistance for *Stenotrophomonas* genus from 2000–2007 was 10.5% to co-trimoxazole, 100% to imipenem, 57.1% to cefepime, 100% to gentamicin, 100% to tobramycin, 38.5% to ciprofloxacin, 41.7% to ceftazidime, 83.3% to amikacin and 100% to meropenem (Figure 9.17 page 127 & Table D14 page 200).

The annual prevalence of resistance for *Stenotrophomonas* genus from 2000–2007 ranged from 0–50% to co-trimoxazole, 0–75% to ciprofloxacin and 50–100% to amikacin (Figure 9.19). The annual prevalence of resistance to imipenem, gentamicin, tobramycin and meropenem was 100% for each year.

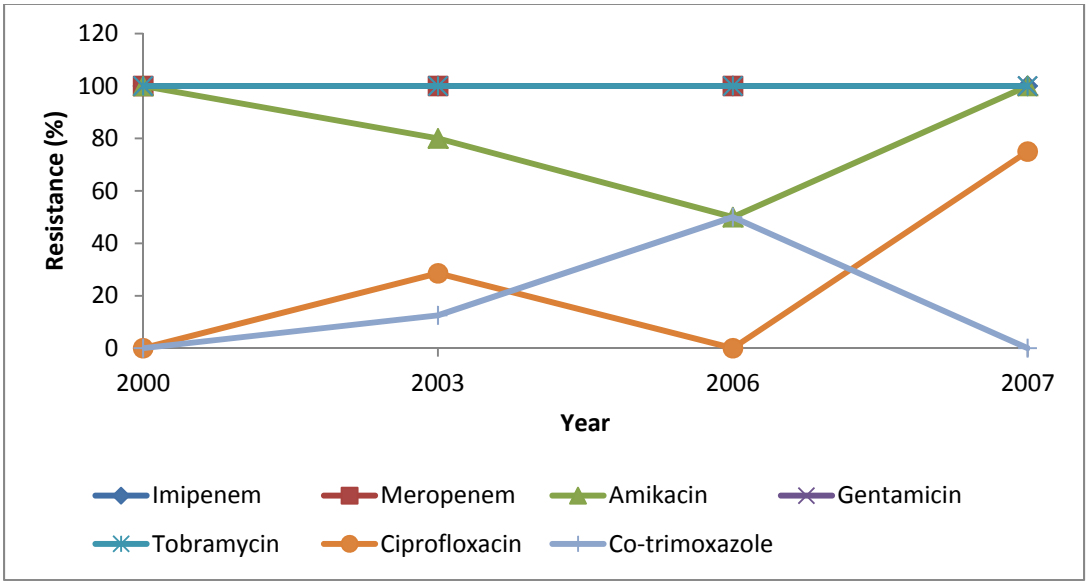


Figure 9.19: The annual prevalence (%) of resistance for *Stenotrophomonas* genus to selected beta-lactams, aminoglycosides, ciprofloxacin and co-trimoxazole from 2000–2007

9.4 Summary

Regarding culture and sensitivity:

- C/S was ordered for 65.8% (451) of patients in whom antibiotics were used (685), implying that empirical therapy was used in 35% of patients.
- From a total of 1 637 specimens collected, bacteria were cultured from 452 specimens. Of these, the top five types of specimens accounted for 91.1% (412/452), with tracheal aspirates accounting for 42.5%, and blood 24.8%.
- Gram-positive bacteria genera (*Staphylococcus* and *Streptococcus*) were mainly cultured from blood, while Gram-negative bacteria genera (*Acinetobacter*, *Pseudomonas*, *Klebsiella*, *Stenotrophomonas*, *Escherichia* and *Enterobacter*) were mainly cultured from tracheal aspirates.
- Of the 451 patients, bacteria were cultured in 238 patients (452 specimens) and these yielded 564 bacteria.
- Of the 564 bacteria, the top ten genera accounted for 518 (91.8%), and these were:
    - Gram-positive: *Staphylococcus* (29.3%), *Enterococcus* (5.9%) and *Streptococcus* (4.1%);
    - Gram-negative: *Klebsiella* (11.8%), *Acinetobacter* (11.7%), *Pseudomonas* (11.2%), *Escherichia* (8.5%), *Enterobacter* (4.1%), *Stenotrophomonas* (3.4%) and *Haemophilus* (2%).

Regarding the prevalence and pattern of antibiotic resistance:

- Only the top ten bacteria listed above, were used for further analysis.
- Gram-positive bacteria:
    - The *Staphylococcus* genus exhibited high resistance to penicillins and substitutes for penicillin allergy. Annual resistance ranged from 92–100% over the ten year period.
    - The *Enterococcus* genus exhibited high resistance to ampicillin, cefazolin/cefalexin, imipenem and tetracycline.

- Gram-negative bacteria:
    - The *Klebsiella* genus exhibited high resistance to cephalosporins (60–100%), tobramycin (77.8%), gentamicin (69.5%) and co-trimoxazole (71%). The annual resistance pattern over the ten years was high for the afore-mentioned antibiotics (>60%).
    - The *Pseudomonas* genus exhibited high resistance to carbapenems (imipenem 41.5% and meropenem 31%), cephalosporins (cefuroxime 100% and cefotaxime 90.6%), aminoglycosides (tobramycin 30.8% and gentamicin 44.8%) and co-trimoxazole 93.8%. The annual resistance pattern for cefotaxime ranged from 77.8–100%.
    - The *Escherichia* genus exhibited high resistance to cephalosporins, aminoglycosides (tobramycin 63.3% and gentamicin 45.2%), and co-trimoxazole 90.2%.
    - The *Enterobacter* genus resistance was similar to that of the *Escherichia* genus.
    - The *Acinetobacter* and *Stenotrophomonas* genera were highly resistant to almost all antibiotics, excluding tobramycin (25.8%) for *Acinetobacter* and co-trimoxazole (10.5%) for *Stenotrophomonas*.

CHAPTER 10

EVALUATION FOR FACTORS INFLUENCING ANTIBIOTIC USE IN THE PICU

Factors influencing antibiotic use in the PICU were evaluated by associating the different parameters of the results with parameters on antibiotic use. They include factors that have been accomplished or achieved and those that still pose challenges.

10.1 Accomplished factors

These include:

- **Fundamental factors**, such as age, critically ill patients and environment, which formed the basis for the formation of the PICU facility.
- **Challenging, but controlled factors**, such as some of the antibiotic (selection and dosing) and host factors (patient condition and compliance).

Accomplished factors could best be described as the successes of the PICU. These specific factors influencing antibiotic use (relating to the environment, host and antibiotic), were successfully taken into account or controlled, while still ensuring appropriate antibiotic use. Specifically, in this case:

- Cost was not a limiting factor in the selection of antibiotics, which enabled the selection of antibiotics based on patient disease requirements.
- No significantly adverse drug reactions were reported, implying proper selection and use of antibiotics.
- No antibiotic was eliminated from use due to resistance, which implies appropriate management of antibiotic use.
- The combination antibiotics were selected well with regard to synergy and pharmacokinetics.

- The performance or usage of the facility was optimum for there were no waiting lines, and the average length of stay of seven days was reasonable.

10.2 Persistently challenging factors

The persistently challenging factors include some bacterial- antibiotic- and environmental factors.

10.2.1 Bacterial factors

10.2.1.1 *Clinical diagnosis*

- Clinical diagnosis leads to requesting C/S on a specific type of specimen. The type of bacteria cultured in a specific specimen will influence antibiotic selection, particularly in empirical use.

  i) Pneumonia and broad-spectrum antibiotics: From the results, the highest numbers of specimens (42.5%) were tracheal aspirates, which indicated pneumonia (Figure 10.1A).

  - Also, more Gram-negative bacteria genera were cultured from tracheal aspirates (*Acinetobacter*, *Pseudomonas*, *Escherichia*, *Enterobacter*, *Stenotrophomonas* and *Klebsiella*), indicating that they were the most common cause of the pneumonia (Figure 10.1B).
  - On the other hand, broad-spectrum antibiotics (cefotaxime, amikacin, cefuroxime, imipenem, amikacin and ciprofloxacin) were the antibiotics used most in the PICU (Figure 10.1C & 10.1D).
  - Therefore, Gram-negative induced pneumonia was associated with a high use of broad-spectrum antibiotics, and in view of the fact that only 34.7% (238/685) of the patients had a positive bacteria culture, suffices it to conclude that the selection and use of these antibiotics were largely based empirically on the type of specimen.

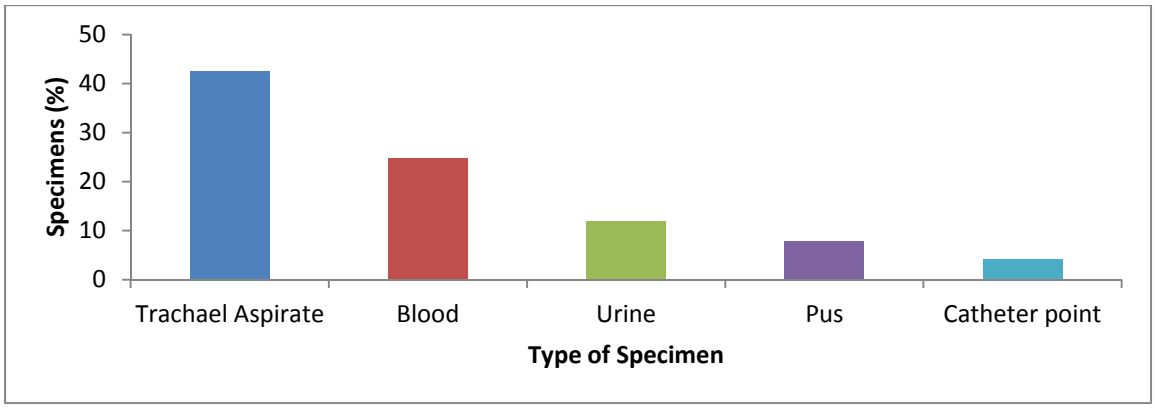


Figure 10.1A: The proportion (%) of the top five types of specimens with positive bacteria cultures

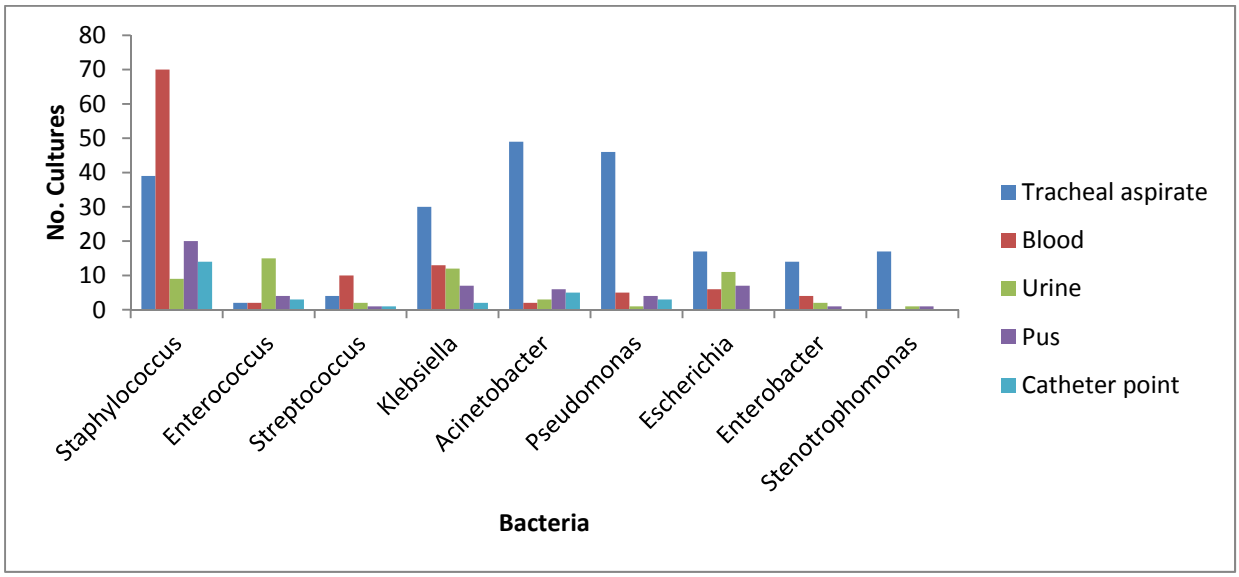


Figure 10.1B: The number of positive cultures for the different bacteria genera (top nine) in the different specimens (top five)

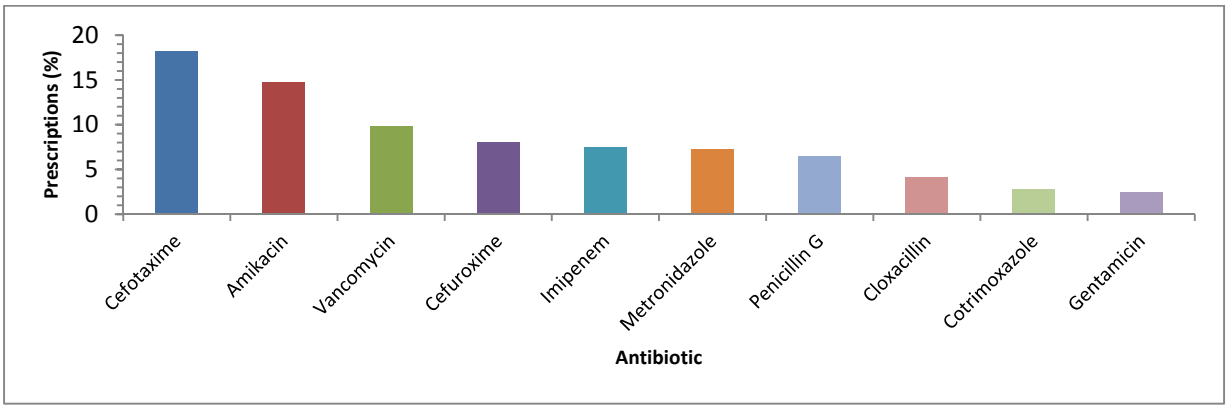


Figure 10.1C: The proportion (%) of individual antibiotic prescriptions for the top ten antibiotics prescribed in the PICU from 1998–2007

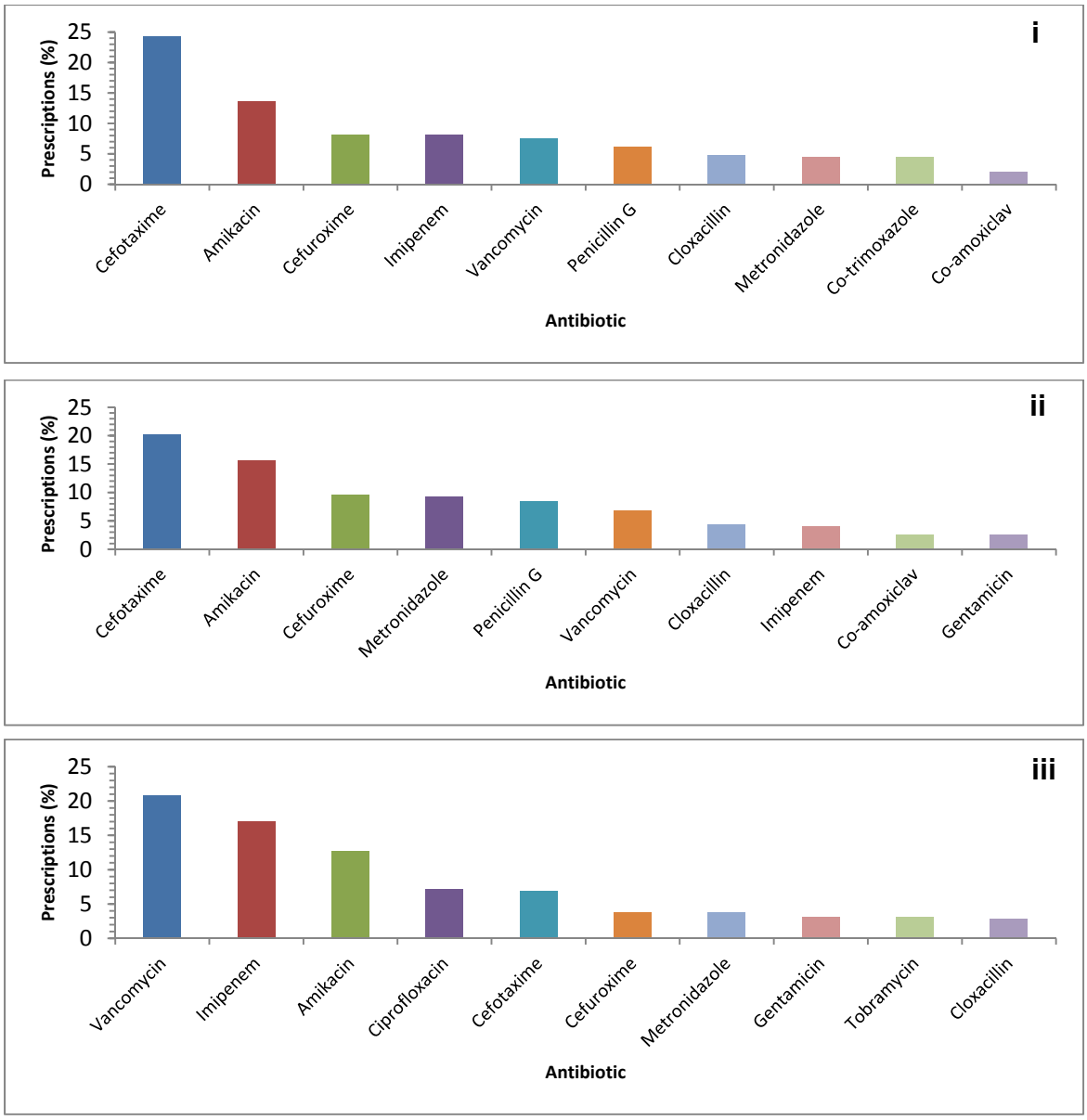


Figure 10.1D: The proportion (%) of individual antibiotic prescriptions for the top ten antibiotics used in the PICU: before admission & continued (**i**), within the first three days (**ii**), and after three days of admission (**iii**)

ii) Septicaemia and vancomycin: Blood specimens were the second highest (24.8%), which indicated septicaemia (Figure 10.1A).

- More Gram-positive bacteria genera were cultured from blood specimens (*Staphylococcus* and *Streptococcus*), indicating that they were the most common cause of septicaemia (Figure 10.1B).

- On the other hand, vancomycin was the antibiotic of choice for *Staphylococcus* and *Streptococcus*, because no resistance to vancomycin by these bacteria was reported (Figure 10.1E).
- Vancomycin was also one of the antibiotics used most in the PICU (especially after three days) (Figure 10.1D), while the *Staphylococcus* genus was the most cultured bacteria (Figure 10.1F).
- Therefore, Gram-positive septicaemia led to a high use of vancomycin.
- Also, Gram-positive induced septicaemia was associated with a high use of vancomycin, and in view of the fact that only 35% (238/685) of the patients had a positive bacteria culture, suffices it to conclude that the selection and use of vancomycin was largely based empirically on the type of specimen.

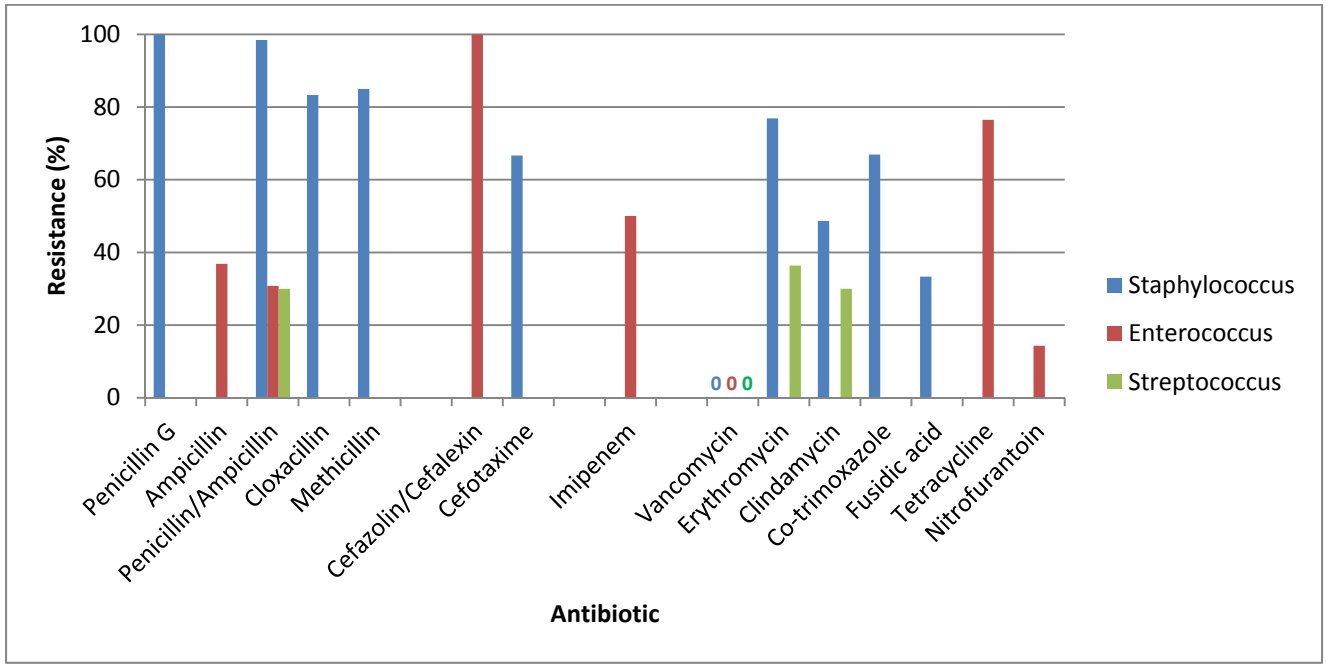


Figure 10.1E: The proportion (%) of resistant cultures of *Staphylococcus, Enterococcus* and *Streptococcus* genera to some antibiotics

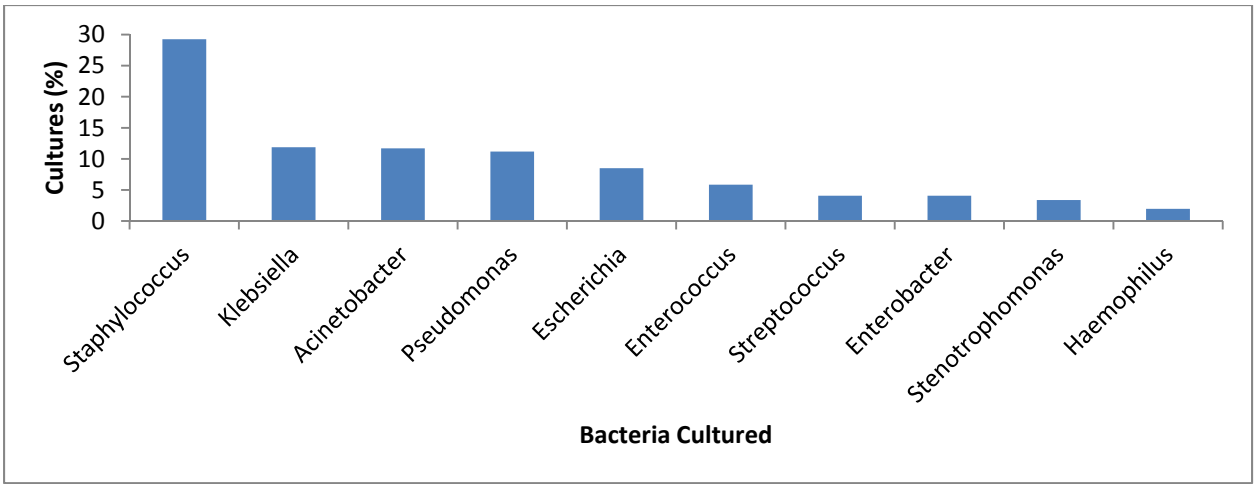


Figure 10.1F: The proportion (%) of positive cultures for the top ten bacteria genera in the PICU from 1998–2007

10.2.1.2 *Innate resistance*

- The role of innate resistance in antibiotic selection was more obvious in the use of narrow-spectrum antibiotics such as cloxacillin, vancomycin and piperacillin, which were indicated for treatment of *S. aureus*, *S. epidermidis* and *Pseudomonas* infections, respectively.
- For the other bacteria, innate resistance was demonstrated by the nosocomial bacteria genera (*Stenotrophomonas* and *Acinetobacter*). These bacteria exhibited resistance to almost all the broad-spectrum antibiotics, excluding co-trimoxazole for *Stenotrophomonas*, and tobramycin for *Acinetobacter* (Figure 9.17 page 127).

10.2.1.3 *Interaction of bacterial and host factors*

- In view of the fact that
    - o broad-spectrum antibiotics (cefotaxime, amikacin, cefuroxime, imipenem, amikacin and ciprofloxacin) were the antibiotics used most in the PICU (Figure 10.1C & 10.1D),

- the majority of the patients (63.1% ± 6.6%) used combination antibiotics of two or three empirically selected antibiotic regimens (Figure 8.14 to 8.16 page 81-3), and
- the observation that metronidazole was the third agent for the top three-combination antibiotic regimens (Figure 8.16 page 83),

- suffices it to conclude that multiple infections, difficult infections and severely ill patients lead to using broad-spectrum combination antibiotics.

10.2.1.4 *Disease pattern*

- The influence of the disease pattern on antibiotic use would be best illustrated when there are seasonal outbreaks of particular infections, but this was not the case in this research.
- However, although co-trimoxazole was the preferred antibiotic for *Stenotrophomonas*, the progressive increase in the use of this antibiotic from 1998 to 2007 was most probably due to its use for HIV-associated opportunistic infections (Figure 10.2).

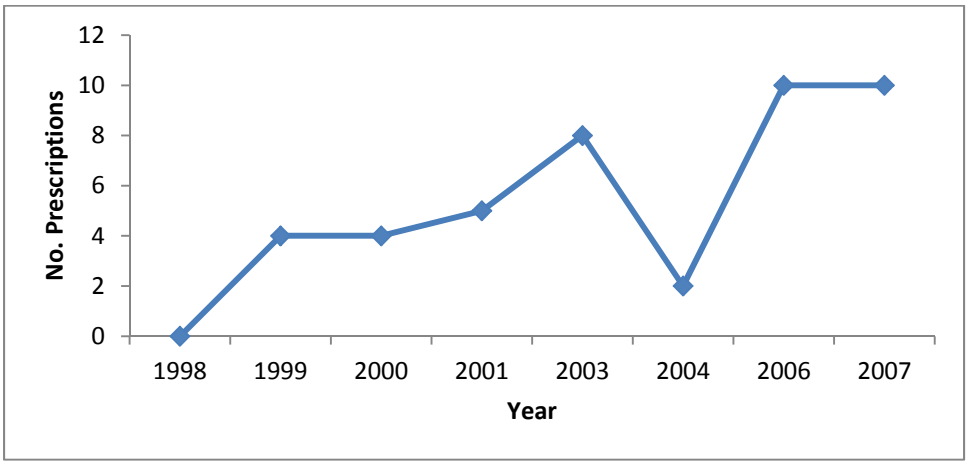


Figure 10.2: The annual number of co-trimoxazole prescriptions in the PICU

10.2.2 Antibiotic factors

10.2.2.1 *New antibiotics*

- There was a progressively increased use of meropenem, most probably because it was a new and effective antibiotic and safer than imipenem (Figure 10.3). Meropenem is less likely to cause convulsions.

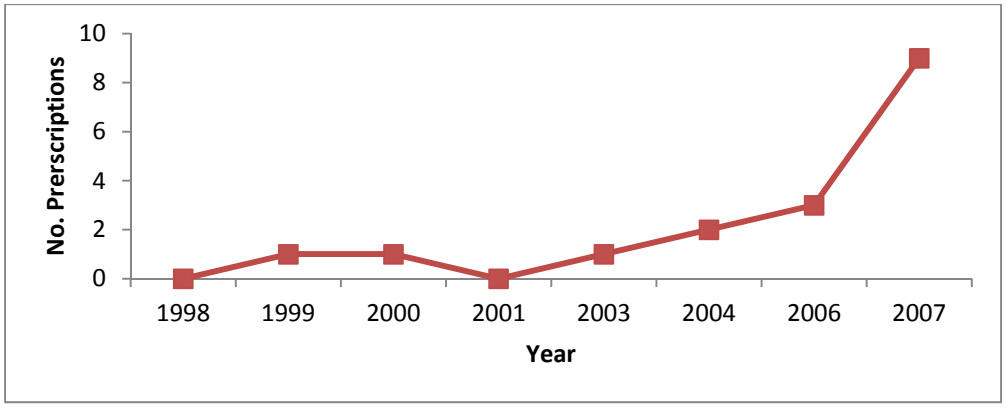


Figure 10.3: The annual number of meropenem prescriptions in the PICU

10.2.2.2 *Overuse of antibiotics*

- High resistance by *Klebsiella* and *Pseudomonas* genera to cephalosporins (cefotaxime and cefuroxime), penicillin and older aminoglycosides (tobramycin and gentamicin) was observed (Figure 10.4 & 10.5).
- Yet, these antibiotics, especially the cephalosporins, were the antibiotics used most (Figure 10.1C & 10.1D).
- Therefore it can be concluded that increased and/or prolonged use of these antibiotics led to the development of resistance, which is probably why other antibiotics replace cephalosporins after three days (Figure 10.1Diii).

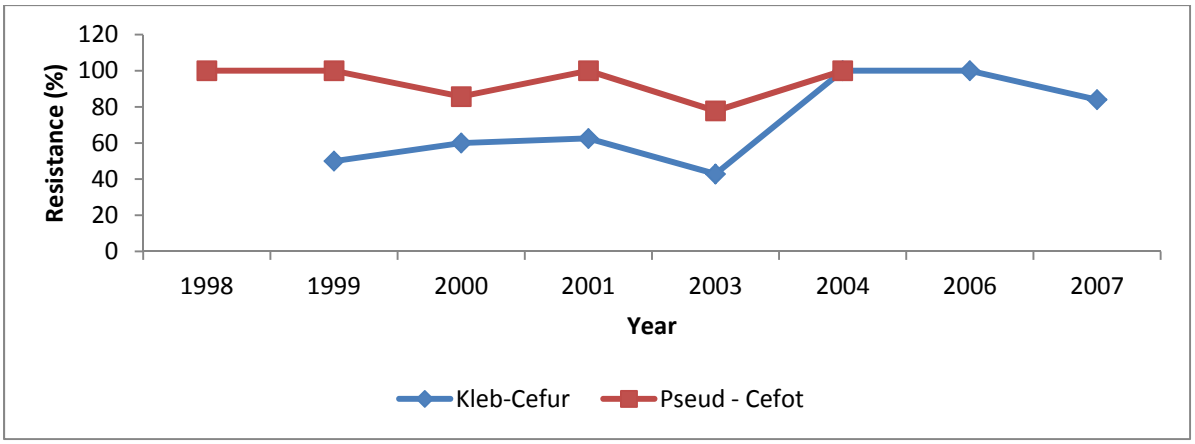


Figure 10.4: The annual prevalence (%) of resistance for *Klebsiella* genus to cefuroxime; and *Pseudomonas* genus to cefotaxime

Key: Kleb = *Klebsiella*, Cefur = Cefuroxime, Pseud = *Pseudomonas*, Cefot = Cefotaxime

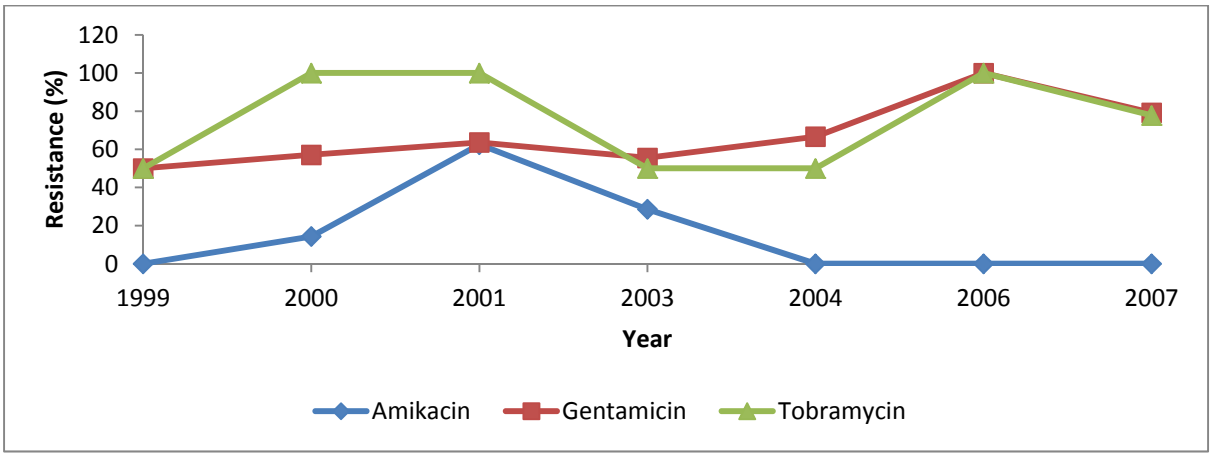


Figure 10.5: The annual prevalence (%) of resistance for *Klebsiella* genus to aminoglycosides from 1999–2007

10.2.2.3 *Personal preferences*

- Despite the consistent high resistance of all Gram-negative bacteria genera to cephalosporins, there was still a persistent empirical use of cephalosporins (cefotaxime and cefuroxime). This can suggest that the physicians' preference were most probably playing a role in the choice of antibiotic.

10.2.3 Environmental factors

10.2.3.1 *Length of stay*

- Length of stay influenced antibiotic use, because resistant bacteria are acquired during a lengthy stay. These nosocomial bacteria are often resistant to many antibiotics and therefore the sensitivity test results will dictate the choice of antibiotic prescribed. For example, no resistance to vancomycin was reported for the common Gram-positive bacteria genera and this antibiotic was the top prescribed antibiotic after three days in the PICU (Figure 10.1Diii & 10.1E). In the same perspective, low resistance to ciprofloxacin was reported for some of the Gram-negative bacteria genera (*Enterobacter*, *Escherichia*, *Klebsiella* and *Pseudomonas*) and therefore this antibiotic was also introduced as part of the top four antibiotics used after three days in the PICU (Figure 10.1Diii).

10.2.3.2 *Treatment guidelines*

- The PICU guideline for the management of septic shock recommends empirical use of cephalosporins (cefuroxime) as first-line antibiotic.

Extract from the guideline

"Initial Antibiotics:
Commence IMMEDIATELY after cultures taken from all possible body fluids.
First line: **Cefuroxime** (Zinacef ®) 25 – 50mg/kg/dose 6 – 8 hourly + **amikacin** (non-neonates up to 10 years: 25mg/kg/dose daily on day 1 then 18 mg/kg/dose as daily dose. Above 10 years old 20mg/kg/dose daily on day 1 then15mg/kg/dose daily. Maximum 360mg/day)
Cefotaxime (Claforan ®) is reserved for meningitis. 50mg/kg/dose 6 hourly. Neonates: week 1: 12 hourly, weeks 2-3: 8 hourly, thereafter 6 hourly.
Change antibiotics according to culture reports or if no response after 48 hours.**"**

- However, it was observed earlier that the most common cause of septicaemia was the *Staphylococcus* genus.
- Although the *Staphylococcus* genus exhibited a 66.7% resistance to cefotaxime, and 100% to cefuroxime, the samples tested were very few, implying that there was no proof of sensitivity of *Staphylococcus* to these antibiotics.

- Therefore, the empirical use of these antibiotics rather than proven sensitivity was responsible for their being among the top prescribed antibiotics on admission and within the first three days.
- Thereafter, they were surpassed by vancomycin and imipenem, confirming that the empirical cephalosporin regimen was not as effective in all patients.
- This shows that the guideline for septic shock led to (influenced) continued prescribing of ineffective antibiotics thereby delaying the use of more effective antibiotics.
- Therefore, these guidelines, and probably those for meningococcal meningitis need, to be reviewed with the intention to determine the roles of these cephalosporins in the empirical therapy for these conditions.
- Whilst the empirical use of cephalosporins could have been based on their broad-spectrum and bactericidal action, and favourable safety profile, these seem to have been surpassed by the increasing antibiotic-resistant bacteria.

In conclusion, the need to prevent the development of antibiotic resistance was the major driving factor that influenced the selection and use of antibiotics in the PICU.

CHAPTER 11

DISCUSSION

In this thesis, the common factors that influenced antibiotic use in the PICU at Universitas Hospital were successfully identified, implying that the aim of this study was achieved. This is the first detailed retrospective study of PICU undertaken over a prolonged period – detailed, because it covered information on the antibiotic, patient, bacteria and environment; and prolonged, because it covered a ten-year period. Studying such information over a prolonged period provides more accurate and reliable data, which can, for instance, be used to determine changes in an antibiotic strategy.

It was found that the bid to combat antibiotic resistance was the major driver for all factors that influenced antibiotic use in the PICU. The common bacteria cultured from specific specimens, innate resistance and disease pattern influenced antibiotic selection for empirical therapy, while the overuse of antibiotics, length of stay, personal preferences and treatment guidelines also influenced antibiotic selection under other circumstances.

However, as is the case in most retrospective studies, the study was hampered by the unavailability and incompleteness of some records. This limited the number of admissions in 2002 and 2005. Also, although cost was not a limiting factor, this retrospective study could not detect the antibiotic stock-control; therefore, its impact on the availability of antibiotics could not be assessed. Furthermore, even though the study was not designed to detect the application of antibiotic guidelines/policies, this would be difficult because, despite specific diagnoses such as pneumonia, etc., broad-spectrum antibiotics were used empirically.

The sample size was regarded as representative of the total admissions, as it covered 56.1% (685/1 221) of the total admissions at 58% ± 11% of the annual admissions. A

similar sample size (56.6%) was used in a one year prospective study of the neonatal ICU at University Children's Hospital, Zurich, Switzerland (Fisher *et al*., 2000).

This study highlighted an alarming increase in antibiotic resistance, whereby each of the most common bacteria genera exhibited considerable resistance to most of the antibiotics available. The most common bacteria genera cultured were *Staphylococcus* (29.3%), *Klebsiella* (11.9%), *Acinetobacter* (11.7%), *Pseudomonas* (11.2%), *Escherichia* (8.5%), *Enterococcus* (5.9%), *Streptococcus* (4.1%), *Enterobacter* (4.1%), *Stenotrophomonas* (3.4%) and *Haemophilus* (2%).

The *Staphylococcus* genus exhibited high resistance to all penicillins and penicillin-allergy substitutes. Specifically, the methicillin resistance of 85% is one of the highest ever reported (see page 116). However, there was no resistance to vancomycin and, all 118 cultures tested were negative.

The *Klebsiella* genus exhibited high resistance to gentamicin (69.5%) and tobramycin (77.8%), as well as to cefuroxime (73.1%) and cefotaxime (70.6%), while it remained sensitive to imipenem (1.9%), amikacin (15.7%) and ciprofloxacin (15.2%). This pattern of resistance is similar to that reported by others where no resistance was observed for *K. pneumoniae* to carbapenems, but 45.6% resistance to gentamicin and 31% to ciprofloxacin were observed (Brink *et al*., 2007; Sein *et al*., 2005).

The *Pseudomonas* genus exhibited 100% resistance to cefuroxime and 90.6% to cefotaxime, with moderate resistance to gentamicin (44.8%), imipenem (41.5%) and tobramycin (30.8%), with amikacin and ciprofloxacin resistance at 22.9% and 22.2%, respectively. This is similar to previously reported high *Pseudomonas* resistance to newer antibiotics, such as meropenem 42%, imipenem 45%, cefepime 53% and ciprofloxacin/levofloxacin 46% (Brink *et al*., 2007).

The nosocomial bacteria genera *Acinetobacter* and *Stenotrophomonas* were resistant (>70%) to almost all antibiotics, excluding tobramycin (25.8%) for *Acinetobacter* and co-trimoxazole (10.5%) for *Stenotrophomonas*.

Regarding infective complications while in the PICU, the top three infective complications accounted for 55.8% of the total infective complications, namely pneumonia (35.6%), septicaemia (11.1%) and UTI (8.8%). These conditions are similar to the prevalence of nosocomial infections in PICU reported by Richards *et al*. (1999), i.e., 28% septicaemia, 21% pneumonia and 15% UTI.

In conclusion, it was illustrated that bacterial resistance to antibiotics is increasing, and that antibiotic use in the PICU at Universitas Hospital in Bloemfontein was greatly influenced by its effort to contain antibiotic resistance.

CHAPTER 12

CONCLUSION AND RECOMMENDATIONS

In conclusion, this study has established that:

- The majority of patients admitted to the PICU were children and infants.
- 70.8% of the patients admitted to the PICU were treated with systemic antibiotics (excludes topical).
- Most patients came from the hospital wards and theatre.
- The most common conditions on admission were respiratory, gastro-intestinal and cardiovascular-related problems, and pneumonia was the most common infective condition.
- The most common infective complications while in the PICU were pneumonia, septicaemia and UTI.
- Broad-spectrum antibiotics were the most widely used antibiotics in the PICU.
- The most common (top ten) antibiotics prescribed were cefotaxime, amikacin, vancomycin, cefuroxime, imipenem, metronidazole, penicillin G, cloxacillin, co-trimoxazole and gentamicin.
- The most common (top ten) bacteria genera cultured were *Staphylococcus*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Escherichia*, *Enterococcus*, *Streptococcus*, *Enterobacter*, *Stenotrophomonas* and *Haemophilus.*
- There was high resistance of *Staphylococcus* genus to penicillins and penicillin-allergy substitutes, but no resistance to vancomycin was observed.
- *Klebsiella* and *Pseudomonas* genera exhibited considerable resistance to aminoglycosides and cephalosporins, but *Klebsiella* remained sensitive to imipenem, while *Pseudomonas* was moderately sensitive to ciprofloxacin and amikacin.
- The nosocomial bacteria genera *Acinetobacter* and *Stenotrophomonas* were highly resistant to almost all antibiotics, excluding tobramycin for *Acinetobacter* and co-trimoxazole for *Stenotrophomonas*.

- The PICU's performance, measured as ICU utilisation, was optimal at 63%, implying that no patient needing ICU care was denied.
- The persistently challenging factors that influenced antibiotic use in the PICU were:
    - Bacterial factors: common bacteria cultured from specific specimens, clinical diagnosis, bacterial innate resistance, interaction with host factors (multiple and severe infections), and disease pattern.
    - Antibiotic factors: new antibiotics, overuse of antibiotics and personal preferences.
    - Environmental factors: length of stay and treatment guidelines.

RECOMMENDATIONS

- Because the study collected data over a prolonged period (ten years), the information obtained on the prevalence and pattern of bacteria, antibiotics and host factors is regarded as accurate and reliable; hence it should be used for further planning in the PICU, including developing a better antibiotic strategy.
- PICU should develop an antibiotic strategy addressing the persistent challenging factors identified in this study.
- In view of the high use of cephalosporins versus increased resistance by the relevant bacteria, the guidelines for septic shock and meningococcal meningitis should be reviewed.
- Continuous antibiotic surveillance in the PICU is necessary.

FURTHER STUDIES

- In view of the high resistance to penicillin G and cephalosporins, their effectiveness; therefore, their respective roles in the combination regimens with aminoglycosides need to be established.
- Studies to elucidate the mechanisms of resistance of the different bacteria to the different antibiotics are necessary.

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Appendix A: Methods
Appendix A1

26 February 2008

The CEO of Universitas Hospital
Universitas Academic Hospital
BLOEMFONTEIN

Dear Dr.

RE: Request to access patient files from the records department and Paediatric Intensive Care Unit

Study title: Factors influencing antibiotic use in the Paediatric Intensive Care Unit at Universitas hospital from 1998 to 2007

I am currently working at the Department of Pharmacology at the University of the Free State. Here, I am requesting to undertake the above mentioned retrospective study using records of patients that were admitted to Paediatric Intensive Care Unit at Universitas Hospital from 1998 to 2007. The aim of the study is to determine the major factors that influenced the use of antibiotics in the Paediatric Intensive Care Unit at Universitas Hospital over the past ten years, 1998 to 2007, with a hope that this will contribute to the development of improved strategies to prevent antibiotic resistance in the unit.

I would appreciate it if I could obtain written consent from you for the purpose of access to these patient files. All files would be handled with strict confidentiality. I have attached the summary and protocol of the proposal for your attention. The study duration is two years and communication of results to any forum (congress / meeting) will be after your approval.

Please note, the study will only be done after approval by the Ethics Committee.

Thank you for your time and consideration.

Regards

Ms R. van Wyk

Senior Pharmacist: Department of Pharmacology, University of the Free State
Tel: 051 401 3090 / 3284
email: vanwykr.md@ufs.ac.za

Appendix A2

26 February 2008

Prof. A. Venter
Head: Department of Paediatrics and Child Health
University of the Free State
BLOEMFONTEIN

Dear Prof. Venter

RE: Study: Factors influencing antibiotic use in the Paediatric Intensive Care Unit at Universitas hospital from 1998 to 2007

I am currently working at the Department of Pharmacology at the University of the Free State. Here, I am informing you that I plan to undertake my M.Med.Sc. (Pharmacology) with the above mentioned title, using records of patients that were admitted to Paediatric Intensive Care Unit at Universitas Hospital from 1998 to 2007. The aim of the study is to determine the major factors that influenced the use of antibiotics in the Paediatric Intensive Care Unit at Universitas Hospital over the past ten years, 1998 to 2007, with a hope that this will contribute to the development of improved strategies to prevent antibiotic resistance in the unit.

I have attached the summary of the proposal for your attention. Please note, the study will only be done after approval by the Ethics Committee and permission of the CEO of Universitas hospital to access the patient files. I have also informed Dr. L.J. Solomon and Dr. S.S. Matela about the planned study.

Thank you for your time and consideration.

Regards

Ms R. van Wyk

Senior Pharmacist: Department of Pharmacology, University of the Free State
Tel: 051 401 3090 / 3284
Fax: 051 444 1523
email: vanwykr.md@ufs.ac.za

Appendix A3

DATASHEET FOR PATIENTS ON ANTIBIOTICS, PAEDIATRIC INTENSIVE CARE UNIT PATIENTS, UNIVERSITAS HOSPITAL

Subject Study Nr: _____ Hospital Registration Nr: _____

Date of admission in hospital				
Date of admission in PICU				
Referred from				
Date of discharge from PICU				
Discharge destination	Ward		Home	
Mortality	Discharged		Death	
Date of discharge from hospital				

1. Section A: Bacterial Factors

a) Diagnosis	Primary	
	Secondary	
	Type of infection	

b) Problem list: _____

_____

_____

c) Surgical procedures during stay in PICU:

Date	Procedure

d) Microbiology

Date	Sample type / origin	Bacteria cultured	Sensitivity test results

2. Section B: Patient Factors

a) Age: _____ b) Weight: _____

c) Gender: M ☐ F ☐

d) Invasive devices:

Endotracheal tube	
IV lines	
Urinary catheter	
Other catheter (type)	

e) Underlying diseases: _____

_____

f) Drug allergies:

_____

g) Concurrent medicine use

Medicine	Date		Dose	Frequency	Route	Indication
	Start	Stop				

h) Medical history		
Date	Diagnosis	Treatment
h) Previous antibiotic use in the 3 months preceding admission		
Date	Diagnosis	Antibiotic treatment

3. Section C: Antibiotic Factors

a) Antibiotics used before admission in PICU and referred with

Hospital / ward antibiotic was started	Antibiotic (& class)	Date		Dose	Frequency	Route	Indication
		Start	Stop				

b) Antibiotics used during first 3 days of admission in PICU

Antibiotic (& class)	Date		Dose	Frequency	Route	Indication
	Start	Stop				

c) Antibiotics used after 3 days of admission in PICU (including where antibiotic therapy was stopped and changed after 3 days of therapy)

Antibiotic (& class)	Date		Dose	Frequency	Route	Indication
	Start	Stop				

Appendix B: Admission characteristics

Table B1: Patient admissions and study sample

Year	Total Admissions (1998-2007)	Total Admissions excluding 2002 & 2005	Pt Records Retrieved	Study Sample (Pts on Antibiotics)
1998	175	175	114	75
1999	147	147	109	70
2000	157	157	115	81
2001	141	141	122	90
2002	52	excluded	excluded	excluded
2003	135	135	130	100
2004	105	105	96	75
2005	32	excluded	excluded	excluded
2006	141	141	118	88
2007	220	220	163	106
Total	**1305**	**1221**	**967**	**685**

Table B2: Yearly and monthly admissions for the study sample (n=685)

Month	Year								Total per month	Mean	SD	Median
	1998	1999	2000	2001	2003	2004	2006	2007				
Jan	2	8	4	7		6	10	12	**49**	**7**	**3.42**	**7**
Feb	4	4	6	14	8	7	2	9	**54**	**6.75**	**3.73**	**6.5**
Mar	6	4	7	6	6	14	3	12	**58**	**7.25**	**3.81**	**6**
Apr	4	3	5	7	6	9	2	9	**45**	**5.63**	**2.62**	**5.5**
May	3	6	5	6	10	9	15	8	**62**	**7.75**	**3.69**	**7**
Jun	9	5	7	4	8	7	11	8	**59**	**7.38**	**2.20**	**7.5**
Jul	10	5	6	5	14	8	12	5	**65**	**8.13**	**3.52**	**7**
Aug	11	12	11	8	11	8	2	12	**75**	**9.38**	**3.38**	**11**
Sep	4	7	5	9	9	1	2	9	**46**	**5.75**	**3.24**	**6**
Oct	6	5	10	8	8	4	4	7	**52**	**6.50**	**2.14**	**6.5**
Nov	9	7	5	11	11	1	12	10	**66**	**8.25**	**3.73**	**9.5**
Dec	7	4	10	5	9	1	13	5	**54**	**6.75**	**3.81**	**6**
Total per year	**75**	**70**	**81**	**90**	**100**	**75**	**88**	**106**	**685**	**85.63**	**12.75**	**84.5**
Mean	**6.25**	**5.83**	**6.75**	**7.5**	**9.09**	**6.25**	**7.33**	**8.83**	**57.08**	**7.21**	**3.27**	**7.13**
SD	**2.96**	**2.44**	**2.34**	**2.81**	**2.34**	**3.93**	**5.21**	**2.44**	**8.90**	**1.07**	**0.61**	**1.60**
Median	**6**	**5**	**6**	**7**	**9**	**7**	**7**	**9**	**56**	**7.13**	**3.47**	**6.75**

Table B3: Patients admitted per age group per year

Year	Age								Total Pts
	Children 1-15 years		Infants 1-11 months		Neonates 1-29 days		Not recorded		
	Pts	%	Pts	%	Pts	%	Pts	%	
1998	32	42.67	33	44	10	13.33		0	75
1999	41	58.57	19	27.14	10	14.29		0	70
2000	41	50.62	31	38.27	9	11.11		0	81
2001	48	53.33	39	43.33	3	3.33		0	90
2003	43	43	47	47	8	8	2	2	100
2004	38	50.67	28	37.33	9	12		0	75
2006	41	46.59	40	45.45	5	5.68	2	2.27	88
2007	53	50	44	41.51	9	8.49		0	106
Total	**337**	**49.2**	**281**	**41.02**	**63**	**9.2**	**4**	**0.58**	**685**
Mean	42.13	49.43	35.13	40.5	7.88	9.53	2	0.53	
SD	6.29	5.31	9.19	6.34	2.53	3.82	0	0.99	
Median	41	50.31	36	42.42	9	9.8	2	0	

Table B4: Annual gender profiles of the patients on admission

Year	Gender						Total Pts
	Male		Female		Not recorded		
	Pts	%	Pts	%	Pts	%	
1998	37	49.33	38	50.67			75
1999	41	58.57	28	40	1	1.43	70
2000	58	71.6	23	28.4			81
2001	39	43.33	51	56.67			90
2003	64	64	36	36			100
2004	41	54.67	34	45.33			75
2006	45	51.14	43	48.86			88
2007	60	56.6	46	43.4			106
Total	**385**	**56.2**	**299**	**43.65**	**1**	**0.15**	**685**
Mean	48.13	56.16	37.38	43.67			
SD	10.75	8.82	9.26	8.89			
Median	43	55.64	37	44.37			

Table B5i: Distribution of patient weight in the children group

Weight (kg)	No. of Pts								
	Year								Total
	1998	1999	2000	2001	2003	2004	2006	2007	
1-5.								1	**1**
6-10.	4	6	8	8	12	11	9	7	**65**
11-15.	13	14	18	16	9	9	12	16	**107**
16-20	4	7	3	7	7	2	4	11	**45**
21-25	3	3	8	6	3	3	6	8	**40**
26-30	4	2	2	3	7	6	4	2	**30**
31-35		1	1	3	2	2	3	3	**15**
36-40				1		2	2	3	**8**
41-45		1		1		1	1		**4**
46-50	1			1		1			**3**
>50								1	**1**
Not recorded	3	7	1	2	3	1		1	**18**

Table B5ii: Distribution of patient weight in the infants group

Weight (kg)	No. of Pts								
	Year								Total
	1998	1999	2000	2001	2003	2004	2006	2007	
1-1.4							1		**1**
1.5-2.4	1		1		3	7	5	2	**19**
2.5-3.4	7	8	7	5	9	5	9	12	**62**
3.5-4.4	3	2	2	12	9	6	6	8	**48**
4.5-5.4	5	2	5	11	8	5	2	7	**45**
5.5-6.4	5	2	6	1	3		3	5	**25**
6.5-7.4	4	1	6	4	4	2	8	3	**32**
7.5-8.4			3	3	3		4	2	**15**
8.5-9.4	1	1	1		3	1			**7**
9.5-10.4	1	2		2	1		1	2	**9**
>10.5	1			1	1			1	**4**
Not recorded	5	1			3	2	1	2	**14**

Table B5iii: Distribution of patient weight in the neonates group

Weight (kg)	No. of Pts								
	Year								Total
	1998	1999	2000	2001	2003	2004	2006	2007	
1-1.4	1		1						**2**
1.5-2.4	3	2	1	2	2	2		1	**13**
2.5-3.4	5	3	6	1	4	5	3	6	**33**
3.5-4.4	1	2				1	2	2	**8**
4.5-5.4		2	1						**3**
Not recorded		1			2	1			**4**

Table B6: Patients admitted with one or more problem

Year	1 Problem		>1 Problem		Total Pts
	No. of Pts	%	No. of Pts	%	
1998	34	45.33	41	54.67	75
1999	26	37.14	44	62.86	70
2000	26	32.1	55	67.9	81
2001	30	33.33	60	66.67	90
2003	32	32	68	68	100
2004	15	20	60	80	75
2006	24	27.27	64	72.73	88
2007	22	20.75	84	79.25	106
Total	**209**	**30.51**	**476**	**69.49**	**685**
Mean	26.13	30.99	59.5	69.01	
SD	6.06	8.37	13.61	8.37	
Median	26	32.05	60	67.95	

Table B7: Problem groups on admission

Problem-groups	No. of problems	%
Respiratory	406	23.40
Gastro-intestinal	381	21.96
Cardiovascular	330	19.02
Genito-urinary	107	6.17
Malignancies	105	6.05
Central nervous system	92	5.30
Haematological	77	4.44
HIV	40	2.31
Endocrine	30	1.73
Musculo-sceletal	23	1.33
Trauma	22	1.27
Toxicology/Poisoning	18	1.04
Dermatological	18	1.04
Multi-system	10	0.58
Nutritional	9	0.52
Auricular	7	0.40
Ocular	5	0.29
Auto-immune	5	0.29
Other	50	2.88
Total	**1735**	

Table B8: Patients admitted via casualty and wards/theatre

Year	Patients admitted via						
	Casualty		Ward / Theatre		Not recorded		Total Pts
	Pts	%	Pts	%	Pts	%	
1998	31	41.33	40	53.33	4	5	75
1999	18	25.71	52	74.29		0	70
2000	27	33.33	53	65.43	1	1	81
2001	21	23.33	63	70	6	7	90
2003	29	29	63	63	8	8	100
2004	28	37.33	46	61.33	1	1	75
2006	26	29.55	62	70.45		0	88
2007	43	40.57	63	59.43		0	106
Total	**223**	**32.55**	**442**	**64.53**	**20**	**2.92**	**685**
Mean	27.88	32.52	55.25	64.66	4	2.82	
SD	7.45	6.74	8.94	6.81	3.08	3.31	
Median	27.5	31.44	57.5	64.22	4	1.28	

Table B9i: Patients with invasive devices

Year	Pts with invasive devices		Total Pts
	Pts	%	
1998	72	96	75
1999	70	100	70
2000	81	100	81
2001	89	98.89	90
2003	98	98	100
2004	75	100	75
2006	88	100	88
2007	106	100	106
Total	**679**	**99.12**	**685**

Table B9ii: Patients with different invasive devices

Year	Invasive devices								Total Pts
	Intravenous line		Endotracheal tube		Urinary catheter		Other		
	Pts	%	Pts	%	Pts	%	Pts	%	
1998	72	100	34	47.22	18	25	6	8.33	75
1999	70	100	32	45.71	24	34.29	10	14.29	70
2000	81	100	39	48.15	38	46.91	18	22.22	81
2001	89	100	50	56.18	50	56.18	16	17.98	90
2003	98	100	47	48	39	39.8	17	17.35	100
2004	74	98.67	47	62.67	11	14.67	7	9.33	75
2006	88	100	44	50	17	19.32	13	14.77	88
2007	106	100	46	43.4	19	17.92	19	17.92	106
Total	**678**	**99.85**	**339**	**49.93**	**216**	**31.81**	**106**	**15.61**	**685**

Table B10: Patients with antibiotic allergies

Year	Pts with antibiotic allergy		Total Pts	Antibiotic allergy	
	Pts	%		Antibiotic allergy	No.
1998	1	1.33	75	Penicillin	1
1999	3	4.29	70	Co-trimoxazole	3
2000	0	0	81		
2001	1	1.11	90	Penicillin	1
2003	0	0	100		
2004	0	0	75		
2006	1	1.14	88	Vancomycin	1
2007	4	3.77	106	Vancomycin	1
				Cefotaxime	1
				Penicillin/Cefotaxime	1
				Penicillin	1
Total	**10**	**1.46**	**685**	**Penicillin**	**3**
				Co-trimoxazole	**3**
				Vancomycin	**2**
				Cefotaxime	**1**
				Penicillin/Cefotaxime	**1**

Table B11: Outcomes for patients treated in the PICU

Year	Outcome						Total Pts
	Alive		Death		Not recorded		
	Pts	%	Pts	%	Pts	%	
1998	71	94.67	4	5.33			75
1999	66	94.29	4	5.71			70
2000	79	97.53	2	2.47			81
2001	84	93.33	5	5.56	1	1.11	90
2003	89	89	10	10	1	1	100
2004	67	89.33	7	9.33	1	1.33	75
2006	83	94.32	5	5.68			88
2007	103	97.17	3	2.83			106
Total	**642**	**93.72**	**40**	**5.84**	**3**	**0.44**	**685**
Mean	80.25	93.71	5	5.86	1	1.15	
Median	81	94.31	4.5	5.62	1	1.11	
SD	12.43	3.16	2.51	2.68	0.00	0.17	

Table B12: Length of stay in the PICU

Year	Days admitted in the PICU								Total Pts
	1-3 days		4-9 days		10 days and longer		Not recorded		
	Pts	%	Pts	%	Pts	%	Pts	%	
1998	23	30.67	33	44	19	25.33		0	**75**
1999	15	21.43	38	54.29	17	24.29		0	**70**
2000	20	24.69	37	45.68	23	28.4	1	1.23	**81**
2001	20	22.22	46	51.11	22	24.44	2	2.22	**90**
2003	30	30	50	50	19	19	1	1	**100**
2004	19	25.33	40	53.33	15	20	1	1.33	**75**
2006	24	27.27	49	55.68	15	17.05		0	**88**
2007	27	25.47	55	51.89	23	21.7	1	0.94	**106**
Total	**178**	**25.99**	**348**	**50.8**	**153**	**22.34**	**6**	**0.88**	**685**
Mean	22.25	25.89	43.50	50.75	19.13	22.53	1.20	0.84	
SD	4.77	3.32	7.62	4.08	3.31	3.75	0.45	0.8	
Median	21.5	25.4	43	51.5	19	22.99	1	0.97	

Table B13: Length of stay in the PICU per age group

Age	Days admitted in the PICU								Total Pts
	1-3 days		4-9 days		10 days & longer		Not recorded		
	Pts	%	Pts	%	Pts	%	Pts	%	
1-15 years	97	54.49	186	53.45	51	33.33	3	50	**337**
1-11 months	67	37.64	131	37.64	81	52.94	2	33.33	**281**
1-29 days	13	7.3	30	8.62	20	13.07			**63**
Not recorded	1	0.56	1	0.29	1	0.65	1	16.67	**4**
Total	**178**		**348**		**153**		**6**		**685**

Appendix B1: Application of the Queuing Theory: Calculation for all admissions over the 8 years (1221 patients)

$$P_o = \frac{1}{\sum_{n=0}^{m-1} \frac{(\lambda/\mu)^n}{n!} + \frac{(\lambda/\mu)^m}{m!}\left(\frac{m\mu}{m\mu-\lambda}\right)} \qquad \text{Eq. 2}$$

Solving for the Left side of Equation 2

m = number of beds = **5 beds**
λ = average arrival rate = Total no admitted in 8 year/days of the 8 years = 1221/(360x8) = **0.424 pts/day**
μ = average service rate at each channel/bed = (patients per day) = 1/length of stay = 1/7.48 = **0.134 pts/day**
n = m - 1

m	λ	μ	(λ/μ)	(m - 1) n	A (λ/μ)^n	n!	B (1/n!)	A x B
5	0.424	0.134	3.164	0	**1**	1	**1**	1
5	0.424	0.134	3.164	1	**3.164**	1	**1**	3.164
5	0.424	0.134	3.164	2	**10.012**	2	**0.5**	5.006
5	0.424	0.134	3.164	3	**31.680**	6	**0.1667**	5.280
5	0.424	0.134	3.164	4	**100.241**	24	**0.0417**	4.177
5	0.424	0.134	3.164	5	**317.180**	120	**0.0083**	2.643
5	0.424	0.134	3.164	6	**1003.613**	720	**0.0014**	1.394
								22.664

Solving for the right side of Equation 2

C (1/m)	D (λ/μ)pw 'm'	C x D	mμ	mμ-λ	E mμ/mμ-λ	CD x E	Solve all: Rt + Left CDE + 16K	1/Rt+Left Po (1/CDE16K)
0.143	3175.61	**453.659**	0.67	0.246	**2.7236**	**1235.575**	**1258.239**	**0.00079476**

Probability of having no patient in the PICU is 0.000795 =- aprox. zero

Other calculations:

- Number of patients in the system (L) = (λ/μ) = 3.1642 **= 4 patients**
- Average time a patient spends in the ICU = (1/μ) = L/λ) = 7.462687 **≡ 7.5 days**
- Average number waiting for service (in queue (Lq) = (L - (λ/μ)) = 0 => **no patient waiting**
- Utilization rate (ρ) = (λ/mμ) = **0.632836** per service unit/bed. => at the arrival rate of 0.424/day => **63% bed utilisation**

Appendix C: Antibiotic use in the Paediatric Intensive Care Unit patients

Table C1: Patients on antibiotics at different times in the PICU

Year	Antibiotics initiated before admission & continued		Antibiotics initiated within the first 3 days		Antibiotics initiated after the first 3 days		Total Pts
	Pts	%	Pts	%	Pts	%	
1998	20	26.67	58	77.33	15	20	75
1999	19	27.14	58	82.86	18	25.71	70
2000	25	30.86	67	82.72	23	28.4	81
2001	20	22.22	75	83.33	24	26.67	90
2003	24	24	80	80	16	16	100
2004	21	28	60	80	20	26.67	75
2006	36	40.91	70	79.55	16	18.18	88
2007	34	32.08	78	73.58	25	23.58	106
Total	**199**	**29.05**	**546**	**79.71**	**157**	**22.92**	**685**
Mean	24.88	28.99	68.25	79.92	19.63	23.15	
Median	22.5	27.57	68.5	80	19	24.65	
SD	6.60	5.80	8.96	3.28	3.96	4.55	

Table C2: Total antibiotics used in the PICU

Antibiotic	No. of prescriptions												
	Year								Total	%	Mean	Median	SD
	1998	1999	2000	2001	2003	2004	2006	2007					
Cefotaxime	43	36	29	43	26	30	33	46	**286**	**18.20**	35.75	34.5	7.48
Amikacin	16	28	37	15	49	26	31	29	**231**	**14.70**	29	28.5	10.97
Vancomycin	13	14	14	28	23	17	14	31	**154**	**9.80**	19.25	15.5	7.13
Cefuroxime	1	3	19	27	13	20	21	23	**127**	**8.08**	16	19.5	9.43
Imipenem	10	10	5	20	16	17	16	24	**118**	**7.51**	15	16	6.11
Metronidazole	11	8	16	18	18	10	16	16	**113**	**7.19**	14.13	16	3.87
Penicillin G	10	10	15	7	30	13	10	7	**102**	**6.49**	12.75	10	7.48
Cloxacillin	11	9	8	9	8	4	9	6	**64**	**4.07**	8	8.5	2.14
Co-trimoxazole	0	4	4	5	8	2	10	10	**43**	**2.74**	5.38	4.5	3.66
Gentamicin	5	3	3	2	8	8	5	4	**38**	**2.42**	5	4.5	2.25
Ciprofloxacin	0	4	9	4	7	4	3	3	**34**	**2.16**	4	4	2.71
Co-amoxiclav	9	3	12	0	2	0	3	2	**31**	**1.97**	4	2.5	4.32
Piperacillin	2	8	5	0	9	2	1	2	**29**	**1.85**	3.63	2	3
Cefepime	1	0	1	2	3	3	7	4	**21**	**1.34**	2.63	2.5	2.20
Ampicillin	3	2	4	1	1	2	1	4	**18**	**1.15**	2.25	2	1.28
Cefoxitin	3	2	2	6	3	0	2	0	**18**	**1.15**	2.25	2	1.91
Ceftriaxone	0	5	3	4	2	0	4	0	**18**	**1.15**	2	2.5	2
Cefazolin	0	0	1	3	2	3	4	4	**17**	**1.08**	2.13	2.5	1.64
Meropenem	0	1	1	0	1	2	3	9	**17**	**1.08**	2.13	1	2.95
Tobramycin	2	2	1	0	3	2	4	3	**17**	**1.08**	2	2	1.25
Erythromycin	2	2	1	1	2	1	7	0	**16**	**1.02**	2.00	1.5	2.14
Clindamycin	2	1	1	0	1	0	1	2	**8**	**0.51**	1	1	0.76
Cefamandole	2	4	1	0	0	0	0	0	**7**	**0.45**	0.88	0	1.46
Ceftazidime	1	3	1	0	0	0	2	0	**7**	**0.45**	0.88	0.5	1.13
Amoxycillin	0	0	0	1	1	3	0	1	**6**	**0.38**	0.75	0.5	1.04
Chloramphenicol	0	0	2	2	0	1	0	1	**6**	**0.38**	0.75	0.5	0.89
Cefpodoxime	1	4	0	0	0	0	0	0	**5**	**0.32**	0.63	0	1.41
Penicillin V	1	0	0	2	0	0	0	1	**4**	**0.25**	1	0	0.76
Fusidic acid	0	1	1	1	0	0	0	0	**3**	**0.19**	0	0	0.52
Piperacillin / tazobactam	0	0	0	0	1	0	1	1	**3**	**0.19**	0.38	0	0.52
Cefalexin	0	0	0	1	0	0	0	1	**2**	**0.13**	0.25	0	0.46
Loracarbef	1	1	0	0	0	0	0	0	**2**	**0.13**	0.25	0	0.46
Doxycycline	0	0	0	0	0	0	0	1	**1**	**0.06**	0	0	0.35
Nalidixic acid	0	1	0	0	0	0	0	0	**1**	**0.06**	0	0	0.35
Neomycin	0	0	1	0	0	0	0	0	**1**	**0.06**	0.13	0	0.35
Oxytetracycline	0	0	1	0	0	0	0	0	**1**	**0.06**	0	0	0.35
Streptomycin	1	0	0	0	0	0	0	0	**1**	**0.06**	0.13	0	0.35
Teicoplanin	0	0	0	0	1	0	0	0	**1**	**0.06**	0.13	0	0.35
Total	**151**	**169**	**198**	**202**	**238**	**170**	**208**	**235**	**1571**		**196.38**	**200**	**31.39**
Types of antibiotics	**23**	**26**	**28**	**22**	**25**	**20**	**24**	**25**	**38**		**24.13**	**24.5**	**2.47**

Table C3: Bactericidal and bacteriostatic antibiotics used in the PICU

Antibiotic	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Bactericidal Antibiotics									**1539**	**97.96**
Cephalosporins	53	58	57	86	49	56	73	78	**510**	**32.46**
Aminoglycosides	24	33	42	17	60	36	40	36	**288**	**18.33**
Penicillins	36	32	44	20	52	24	25	24	**257**	**16.36**
Glycopeptides	13	14	14	28	24	17	14	31	**155**	**9.87**
Carbapenems	10	11	6	20	17	19	19	33	**135**	**8.59**
Metronidazole	11	8	16	18	18	10	16	16	**113**	**7.19**
Co-trimoxazole		4	4	5	8	2	10	10	**43**	**2.74**
Ciprofloxacin		4	9	4	7	4	3	3	**34**	**2.16**
Fusidic acid		1	1	1					**3**	**0.19**
Nalidixic acid		1							**1**	**0.06**
Bacteriostatic Antibiotics									**32**	**2.04**
Erythromycin	2	2	1	1	2	1	7		**16**	**1.02**
Clindamycin	2	1	1		1		1	2	**8**	**0.51**
Chloramphenicol			2	2		1		1	**6**	**0.38**
Tetracyclines			1					1	**2**	**0.13**
Total Prescriptions									**1571**	

Table C4: Patients admitted to the PICU while on antibiotics & patients continued with antibiotics

Year	Pts admitted while on antibiotics		Pts admitted while on antibiotics & continued			Total Pts
	Pts	%	Pts	% of total admissions	% of pts admitted on antibiotics	
1998	26	34.67	20	26.67	76.92	75
1999	22	31.43	19	27.14	86.36	70
2000	28	34.57	25	30.86	89.29	81
2001	29	32.22	20	22.22	68.97	90
2003	27	27	24	24	88.89	100
2004	25	33.33	21	28	84	75
2006	41	46.59	36	40.91	87.8	88
2007	42	39.62	34	32.08	80.95	106
Total	**240**	**35.04**	**199**	**29.05**	**82.92**	**685**
Mean	30	34.93	24.88	28.99	82.90	
Median	27.5	33.95	22.5	27.57	85.18	
SD	7.41	5.89	6.6	5.8	7.0	

Table C5: Antibiotics initiated before admission and continued in the PICU

Antibiotic	No. of prescriptions										Mean	Median	SD
	Year								Total	%			
	1998	1999	2000	2001	2003	2004	2006	2007					
Cefotaxime	13	8	6	9	5	7	12	11	**71**	**24.32**	8.88	8.5	2.90
Amikacin	1	6	9	3	7	7	4	3	**40**	**13.70**	5	5	2.67
Cefuroxime	1	1	1	4	2	3	6	6	**24**	**8.22**	3	2.5	2.14
Imipenem	0	2	0	1	5	3	6	7	**24**	**8.22**	3	2.5	2.73
Vancomycin	1	2	2	3	5	2	2	5	**22**	**7.53**	2.75	2	1.49
Penicillin G	2	2	4	1	3	3	1	2	**18**	**6.16**	2.25	2	1.04
Cloxacillin	1	2	2	2	3	0	2	2	**14**	**4.79**	2	2	0.89
Metronidazole	3	1	2	2	0	0	2	3	**13**	**4.45**	1.63	2	1.19
Co-trimoxazole	0	2	0	0	4	0	3	4	**13**	**4.45**	1.63	1	1.85
Co-amoxiclav	1	0	4	0	0	0	1	0	**6**	**2.05**	1	0	1.39
Piperacillin	0	3	1	0	1	1	0	0	**6**	**2.05**	0.75	0.5	1
Ceftriaxone	0	0	2	0	2	0	2	0	**6**	**2.05**	1	0	1
Cefepime	0	0	1	0	0	0	3	1	**5**	**1.71**	0.63	0	1.06
Gentamicin	1	1	0	0	0	1	1	0	**4**	**1.37**	1	0.5	0.53
Cefoxitin	2	0	0	0	0	0	1	0	**3**	**1.03**	0.38	0	0.74
Ampicillin	0	1	2	0	0	0	0	0	**3**	**1.03**	0.38	0	0.74
Meropenem	0	0	0	0	0	1	0	2	**3**	**1.03**	0.38	0	0.74
Ciprofloxacin	0	0	1	0	0	0	1	0	**2**	**0.68**	0	0	0.46
Tobramycin	1	0	0	0	0	0	0	1	**2**	**0.68**	0	0	0.46
Clindamycin	0	0	1	0	0	0	1	0	**2**	**0.68**	0	0	0.46
Cefazolin	0	0	0	1	0	0	0	0	**1**	**0.34**	0	0	0.35
Cefamandole	0	0	1	0	0	0	0	0	**1**	**0.34**	0	0	0.35
Chloramphenicol	0	0	0	1	0	0	0	0	**1**	**0.34**	0	0	0.35
Amoxycillin	0	0	0	0	0	0	0	1	**1**	**0.34**	0	0	0.35
Ceftazidime	0	0	0	0	0	0	1	0	**1**	**0.34**	0	0	0.35
Penicillin V	1	0	0	0	0	0	0	0	**1**	**0.34**	0	0	0.35
Cefpodoxime	0	1	0	0	0	0	0	0	**1**	**0.34**	0	0	0.35
Fusidic acid	0	0	0	1	0	0	0	0	**1**	**0.34**	0	0	0.35
Nalidixic acid	0	1	0	0	0	0	0	0	**1**	**0.34**	0	0	0.35
Doxycycline	0	0	0	0	0	0	0	1	**1**	**0.34**	0	0	0.35
Oxytetracycline	0	0	1	0	0	0	0	0	**1**	**0.34**	0	0	0.35
Total	**28**	**33**	**40**	**28**	**37**	**28**	**49**	**49**	**292**		36.5	35	**8.9**
Types of antibiotics	**12**	**14**	**16**	**11**	**10**	**9**	**17**	**14**	**31**		12.875	13	2.85

Table C6: Bactericidal & bacteriostatic antibiotics initiated before admission and continued in the PICU

Antibiotic	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Bactericidal Antibiotics									**287**	**98.29**
Cephalosporins	16	10	11	14	9	10	25	18	**113**	**38.7**
Penicillins	5	8	13	3	7	4	4	5	**49**	**16.78**
Aminoglycosides	3	7	9	3	7	8	5	4	**46**	**15.75**
Carbapenems		2		1	5	4	6	9	**27**	**9.25**
Glycopeptides	1	2	2	3	5	2	2	5	**22**	**7.53**
Metronidazole	3	1	2	2			2	3	**13**	**4.45**
Co-trimoxazole		2			4		3	4	**13**	**4.45**
Ciprofloxacin			1				1		**2**	**0.68**
Nalidixic acid		1							**1**	**0.34**
Fusidic acid				1					**1**	**0.34**
Bacteriostatic Antibiotics									**5**	**1.71**
Clindamycin			1				1		**2**	**0.68**
Tetracyclines			1					1	**2**	**0.68**
Chloramphenicol				1					**1**	**0.34**
Erythromycin									**0**	**0**
Total Prescriptions									**292**	

Table C7: Antibiotics used within the first three days in the PICU

Antibiotic	No. of prescriptions												
	Year								Total	%	Mean	Median	SD
	1998	1999	2000	2001	2003	2004	2006	2007					
Cefotaxime	26	26	22	31	20	18	19	31	**193**	**20.17**	24.13	24	5.17
Amikacin	10	17	19	8	38	16	23	19	**150**	**15.67**	18.75	18	9.19
Cefuroxime	0	1	15	21	11	14	13	16	**91**	**9.51**	11.38	13.5	7.31
Metronidazole	7	6	14	13	16	9	12	11	**88**	**9.20**	11.00	11.5	3.46
Penicillin G	8	8	10	6	26	10	8	5	**81**	**8.46**	10.13	8	6.64
Vancomycin	6	7	5	8	8	8	10	13	**65**	**6.79**	8.13	8	2.47
Cloxacillin	5	7	6	7	5	4	6	1	**41**	**4.28**	5.13	5.5	1.96
Imipenem	7	2	1	5	4	6	6	8	**39**	**4.08**	4.88	5.5	2.42
Co-amoxiclav	8	3	7	0	2	0	2	2	**24**	**2.51**	3.00	2	2.98
Gentamicin	2	2	2	0	7	5	2	4	**24**	**2.51**	3.00	2	2.20
Co-trimoxazole	0	2	2	4	3	2	5	5	**23**	**2.40**	2.88	2.5	1.73
Piperacillin	1	4	2	0	6	1	1	1	**16**	**1.67**	2.00	1	2.00
Cefazolin	0	0	1	2	2	3	4	4	**16**	**1.67**	2.00	2	1.60
Cefoxitin	1	2	2	6	3	0	1	0	**15**	**1.57**	1.88	1.5	1.96
Cefepime	1	0	0	0	2	3	4	3	**13**	**1.36**	1.63	1.5	1.60
Ampicillin	3	1	2	1	0	0	1	3	**11**	**1.15**	1.38	1	1.19
Ceftriaxone	0	4	0	3	0	0	2	0	**9**	**0.94**	1.13	0	1.64
Ciprofloxacin	0	1	3	0	3	1	0	1	**9**	**0.94**	1.13	1	1.25
Erythromycin	2	1	0	1	1	0	3	0	**8**	**0.84**	1.00	1	1.07
Meropenem	0	0	1	0	1	1	2	2	**7**	**0.73**	0.88	1	0.83
Cefamandole	2	4	0	0	0	0	0	0	**6**	**0.63**	0.75	0	1.49
Tobramycin	0	1	0	0	1	1	2	0	**5**	**0.52**	0.63	0.5	0.74
Chloramphenicol	0	0	2	1	0	1	0	1	**5**	**0.52**	0.63	0.5	0.74
Clindamycin	1	1	0	0	1	0	0	1	**4**	**0.42**	0.50	0.5	0.53
Amoxycillin	0	0	0	1	0	2	0	0	**3**	**0.31**	0.38	0	0.74
Ceftazidime	1	1	1	0	0	0	0	0	**3**	**0.31**	0.38	0	0.52
Penicillin V	0	0	0	2	0	0	0	0	**2**	**0.21**	0.25	0	0.71
Cefpodoxime	0	1	0	0	0	0	0	0	**1**	**0.10**	0.13	0	0.35
Fusidic acid	0	0	1	0	0	0	0	0	**1**	**0.10**	0.13	0	0.35
Piperacillin / tazobactam	0	0	0	0	0	0	1	0	**1**	**0.10**	0.13	0	0.35
Cefalexin	0	0	0	0	0	0	0	1	**1**	**0.10**	0.13	0	0.35
Neomycin	0	0	1	0	0	0	0	0	**1**	**0.10**	0.13	0	0.35
Teicoplanin	0	0	0	0	1	0	0	0	**1**	**0.10**	0.13	0	0.35
Total	**91**	**102**	**119**	**120**	**161**	**105**	**127**	**132**	**957**		119.63	119.5	21.59
Types of antibiotics	**17**	**22**	**21**	**17**	**21**	**18**	**21**	**20**	**33**		19.625	20.5	2

Table C8: Bactericidal and bacteriostatic antibiotics used within the first three days in the PICU

Antibiotic	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Bactericidal Antibiotics									**940**	**98.22**
Cephalosporins	31	39	41	63	38	38	43	55	**348**	**36.36**
Aminoglycosides	12	20	22	8	46	22	27	23	**180**	**18.81**
Penicillins	25	23	27	17	39	17	19	12	**179**	**18.7**
Metronidazole	7	6	14	13	16	9	12	11	**88**	**9.2**
Glycopeptides	6	7	5	8	9	8	10	13	**66**	**6.9**
Carbapenems	7	2	2	5	5	7	8	10	**46**	**4.81**
Co-trimoxazole		2	2	4	3	2	5	5	**23**	**2.4**
Ciprofloxacin		1	3		3	1		1	**9**	**0.94**
Fusidic acid			1						**1**	**0.1**
Bacteriostatic Antibiotics									**17**	**1.78**
Erythromycin	2	1		1	1		3		**8**	**0.84**
Chloramphenicol			2	1		1		1	**5**	**0.52**
Clindamycin	1	1			1			1	**4**	**0.42**
Tetracyclines									**0**	**0**
Total Prescriptions									**957**	

Table C9: Antibiotics used after three days in the PICU

Antibiotic	No. of prescriptions												
	Year								Total	%	Mean	Median	SD
	1998	1999	2000	2001	2003	2004	2006	2007					
Vancomycin	6	5	7	17	10	7	2	13	**67**	**20.81**	8.38	7	4.78
Imipenem	3	6	4	14	7	8	4	9	**55**	**17.08**	6.88	6.5	3.56
Amikacin	5	5	9	4	4	3	4	7	**41**	**12.73**	5.13	4.5	1.96
Ciprofloxacin	0	3	5	4	4	3	2	2	**23**	**7.14**	2.88	3	1.55
Cefotaxime	4	2	1	3	1	5	2	4	**22**	**6.83**	2.75	2.5	1.49
Cefuroxime	0	1	3	2	0	3	2	1	**12**	**3.73**	1.50	1.5	1.20
Metronidazole	1	1	0	3	2	1	2	2	**12**	**3.73**	1.50	1.5	0.93
Gentamicin	2	0	1	2	1	2	2	0	**10**	**3.11**	1.25	1.5	0.89
Tobramycin	1	1	1	0	2	1	2	2	**10**	**3.11**	1.25	1	0.71
Cloxacillin	5	0	0	0	0	0	1	3	**9**	**2.80**	1.13	0	1.89
Erythromycin	0	1	1	0	1	1	4	0	**8**	**2.48**	1.00	1	1.31
Co-trimoxazole	0	0	2	1	1	0	2	1	**7**	**2.17**	0.88	1	0.83
Piperacillin	1	1	2	0	2	0	0	1	**7**	**2.17**	0.88	1	0.83
Meropenem	0	1	0	0	0	0	1	5	**7**	**2.17**	0.88	0	1.73
Ampicillin	0	0	0	0	1	2	0	1	**4**	**1.24**	0.50	0	0.76
Penicillin G	0	0	1	0	1	0	1	0	**3**	**0.93**	0.38	0	0.52
Ceftazidime	0	2	0	0	0	0	1	0	**3**	**0.93**	0.38	0	0.74
Ceftriaxone	0	1	1	1	0	0	0	0	**3**	**0.93**	0.38	0	0.52
Cefepime	0	0	0	2	1	0	0	0	**3**	**0.93**	0.38	0	0.74
Cefpodoxime	1	2	0	0	0	0	0	0	**3**	**0.93**	0.38	0	0.74
Amoxicillin	0	0	0	0	1	1	0	0	**2**	**0.62**	0.25	0	0.46
Piperacillin / tazobactam	0	0	0	0	1	0	0	1	**2**	**0.62**	0.25	0	0.46
Clindamycin	1	0	0	0	0	0	0	1	**2**	**0.62**	0.25	0	0.46
Loracarbef	1	1	0	0	0	0	0	0	**2**	**0.62**	0.25	0	0.46
Penicillin V	0	0	0	0	0	0	0	1	**1**	**0.31**	0.13	0	0.35
Co-amoxiclav	0	0	1	0	0	0	0	0	**1**	**0.31**	0.13	0	0.35
Cefalexin	0	0	0	1	0	0	0	0	**1**	**0.31**	0.13	0	0.35
Streptomycin	1	0	0	0	0	0	0	0	**1**	**0.31**	0.13	0	0.35
Fusidic acid	0	1	0	0	0	0	0	0	**1**	**0.31**	0.13	0	0.35
Total	**32**	**34**	**39**	**54**	**40**	**37**	**32**	**54**	**322**		40.25	38	8.99
Types of antibiotics	**13**	**16**	**14**	**12**	**16**	**12**	**15**	**16**	**29**		14.25	14.5	1.75

Table C10: Bactericidal and bacteriostatic antibiotics used after three days in the PICU

Antibiotic	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Bactericidal Antibiotics									**312**	**96.89**
Glycopeptides	6	5	7	17	10	7	2	13	**67**	**20.81**
Carbapenems	3	7	4	14	7	8	5	14	**62**	**19.25**
Aminoglycosides	9	6	11	6	7	6	8	9	**62**	**19.25**
Cephalosporins	6	9	5	9	2	8	5	5	**49**	**15.22**
Penicillins	6	1	4		6	3	2	7	**29**	**9.01**
Ciprofloxacin		3	5	4	4	3	2	2	**23**	**7.14**
Metronidazole	1	1		3	2	1	2	2	**12**	**3.73**
Co-trimoxazole			2	1	1		2	1	**7**	**2.17**
Fusidic acid		1							**1**	**0.31**
Bacteriostatic Antibiotics									**10**	**3.1**
Erythromycin		1	1		1	1	4		**8**	**2.48**
Clindamycin	1							1	**2**	**0.62**
Chloramphenicol									**0**	**0**
Tetracyclines									**0**	**0**
Total Prescriptions									**322**	

Table C11: Patients treated with antibiotic combinations in the PICU

Year	Pts treated with antibiotic combinations		Total Pts
	Pts	%	
1998	41	54.67	75
1999	44	62.86	70
2000	50	61.73	81
2001	54	60	90
2003	77	77	100
2004	48	64	75
2006	58	65.91	88
2007	62	58.49	106
Total	**434**	**63.36**	**685**
Mean	54.25	63.08	
Median	52	62.3	
SD	11.52	6.61	

Table C12: The common two-combination antibiotic regimens used within the first three days in the PICU

Antibiotic Combination	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Penicillin G / Amikacin	6	5	8	3	16	4			**42**	**14**
Imipenem / Vancomycin	5	3		4	7	8	5	10	**42**	**14**
Cefotaxime / Amikacin		2	1	1	6	7	6	2	**25**	**8.33**
Cefuroxime / Amikacin			2	3	5	4	5	6	**25**	**8.33**
Cefotaxime / Metronidazole	5	4	5	4	1		1	1	**21**	**7**
Cefotaxime / Cloxacillin	2	2		5	2		1	3	**15**	**5**
Piperacillin / Amikacin		4	1		5	2	1	1	**14**	**4.67**
Cefotaxime / Vancomycin	1	4	1	2	1		1	1	**11**	**3.67**
Cefepime / Vancomycin			1		1	1	4	2	**9**	**3**
Co-amoxiclav / Amikacin		2	3						**5**	**1.67**
Cloxacillin / Amikacin		1			2		2		**5**	**1.67**
Cefuroxime / Co-trimoxazole			1	1		1	1	1	**5**	**1.67**
Penicillin G / Gentamicin		1	1			1	1		**4**	**1.33**
Cefotaxime / Gentamicin	2				1		1		**4**	**1.33**
Cefotaxime / Chloramphenicol			2	1		1			**4**	**1.33**
Cefuroxime / Metronidazole				4					**4**	**1.33**
Other	8	3	10	11	9	2	12	10	**65**	**21.37**
Total Combinations	**29**	**31**	**36**	**39**	**56**	**31**	**41**	**37**	**300**	

Table C13: The common two-combination antibiotic regimens used after three days in the PICU

Antibiotic Combination	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Imipenem / Vancomycin	1	2	2	12	5	5	1	7	**35**	**35.71**
Cefotaxime / Amikacin				1		3			**4**	**4.08**
Imipenem / Amikacin			1		1		1		**3**	**3.06**
Piperacillin / Amikacin			1		1			1	**3**	**3.06**
Amikacin / Ciprofloxacin		2		1					**3**	**3.06**
Tobramycin / Ciprofloxacin					2			1	**3**	**3.06**
Vancomycin / Ciprofloxacin			2	1					**3**	**3.06**
Others	6	5	9	4	5	2	7	6	**44**	**44.9**
Total Combinations	**7**	**9**	**15**	**19**	**14**	**10**	**9**	**15**	**98**	

Table C14: The common three-combination antibiotic regimens used within the first three days in the PICU

Antibiotic Combination	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Penicillin G / Amikacin / Metronidazole	1	2		1	4	2	5	3	**18**	**18.56**
Penicillin G / Gentamicin / Metronidazole					5	3		1	**9**	**9.28**
Cefuroxime / Amikacin / Metronidazole				1		1	4	1	**7**	**7.22**
Cefotaxime / Amikacin / Metronidazole			1	1		1	1	2	**6**	**6.19**
Cefotaxime / Amikacin / Cotrimoxazole					1		1	3	**5**	**5.15**
Ampicillin / Gentamicin / Metronidazole							1	3	**4**	**4.12**
Cloxacillin / Cefotaxime / Metronidazole	1		1	1	1				**4**	**4.12**
Others	4	7	11	1	7	6		8	**44**	**45.36**
Total Combinations	**6**	**9**	**13**	**5**	**18**	**13**	**12**	**21**	**97**	

Table C15: The common three-combination antibiotic regimens used after three days in the PICU

Antibiotic Combination	No. of prescriptions									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Cefotaxime / Amikacin / Metronidazole				1			1	2	**4**	**17.39**
Imipenem / Vancomycin / Cotrimoxazole				1	1	1			**3**	**13.04**
Cloxacillin / Imipenem / Amikacin							1	1	**2**	**8.70**
Imipenem / Vancomycin / Metronidazole	1			1					**2**	**8.70**
Amikacin / Tobramycin / Cotrimoxazole							1	1	**2**	**8.70**
Others	3		1	2	3	1			**10**	**43.48**
Total Combinations	**4**	**0**	**1**	**5**	**4**	**2**	**3**	**4**	**23**	

Table C16i: Antibiotics used for pneumonia on admission and within the first three days in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Amikacin	5	5	10	2	9	9	7	10	**57**	**17.98**
Cefotaxime	7	6	2	4	5	9	12	7	**52**	**16.40**
Cefuroxime			3	6	3	6	9	7	**34**	**10.73**
Penicillin G	3	2	8	2	6	4	1		**26**	**8.20**
Co-trimoxazole		1	2	3	4	1	7	7	**25**	**7.89**
Vancomycin	1	2	2	2	3	4	5	6	**25**	**7.89**
Imipenem	1	1	1		2	4	7	5	**21**	**6.62**
Cloxacillin	1	2	4	2	2	1	3		**15**	**4.73**
Co-amoxiclav	2	1	4						**7**	**2.21**
Metronidazole	1	2	2				1	1	**7**	**2.21**
Erythromycin	1	1		1			3		**6**	**1.89**
Cefepime	1						3	1	**5**	**1.58**
Tobramycin		1				1	2	1	**5**	**1.58**
Chloramphenicol			2	1		1			**4**	**1.26**
Gentamicin			1			1	1	1	**4**	**1.26**
Piperacillin		1	1		1			1	**4**	**1.26**
Ceftriaxone			2				1		**3**	**0.95**
Ciprofloxacin			1		1	1			**3**	**0.95**
Meropenem						1		2	**3**	**0.95**
Ampicillin	1							1	**2**	**0.63**
Ceftazidime		1					1		**2**	**0.63**
Clindamycin		1					1		**2**	**0.63**
Amoxicillin				1					**1**	**0.32**
Cefoxitin				1					**1**	**0.32**
Cefpodoxime		1							**1**	**0.32**
Fusidic acid				1					**1**	**0.32**
Teicoplanin					1				**1**	**0.32**
Total	**24**	**28**	**45**	**26**	**37**	**43**	**64**	**50**	**317**	
Types of Antibiotics	**11**	**15**	**15**	**12**	**11**	**13**	**16**	**13**	**27**	

Table C16ii: Antibiotics used after three days for the same pneumonia on admission in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Vancomycin	1	1			2	2			6	16.67
Imipenem		1			3	1			5	13.89
Amikacin		1	1	1	1				4	11.11
Ciprofloxacin		1	1		1	1			4	11.11
Cefotaxime	1			1			1		3	8.33
Cefpodoxime	1	1							2	5.56
Cefuroxime						2			2	5.56
Co-trimoxazole			1		1				2	5.56
Ampicillin								1	1	2.78
Cefepime				1					1	2.78
Ceftazidime		1							1	2.78
Loracarbef	1								1	2.78
Erythromycin					1				1	2.78
Gentamicin			1						1	2.78
Meropenem		1							1	2.78
Tobramycin					1				1	2.78
Total	**4**	**7**	**4**	**3**	**10**	**6**	**1**	**1**	**36**	
Types of Antibiotics	**4**	**7**	**4**	**3**	**7**	**4**	**1**	**1**	**16**	

Table C16iii: Antibiotics used for new cases of pneumonia in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Amikacin	5	10	12	5	10	1	8	8	**59**	**15.73**
Vancomycin	4	5	5	10	12	2	3	12	**53**	**14.13**
Cefotaxime	6	10	5	9	2	2	4	7	**45**	**12.00**
Imipenem	3	3		5	8	3	5	9	**36**	**9.60**
Metronidazole	2	5	2	4	7	2	5	3	**30**	**8.00**
Cefuroxime		1	5	3	3	1	6	4	**23**	**6.13**
Ciprofloxacin		3	5	3	3		2	2	**18**	**4.80**
Penicillin G		2	2	2	8		2	2	**18**	**4.80**
Co-trimoxazole		2	1	2		1	1	6	**13**	**3.47**
Cloxacillin	2		2	3	1		2	2	**12**	**3.20**
Gentamicin	2				5	2	2	1	**12**	**3.20**
Tobramycin	1	1	1		2	1	3	2	**11**	**2.93**
Co-amoxiclav	3	1	3						**7**	**1.87**
Piperacillin	1	2	2		2				**7**	**1.87**
Erythromycin	1	1		1		1	2		**6**	**1.60**
Cefepime			1	1	1	1	1		**5**	**1.33**
Meropenem								5	**5**	**1.33**
Ceftriaxone		3			1				**4**	**1.07**
Ampicillin						1	1		**2**	**0.53**
Ceftazidime		1					1		**2**	**0.53**
Clindamycin	1				1				**2**	**0.53**
Cefazolin							1		**1**	**0.27**
Cefoxitin				1					**1**	**0.27**
Chloramphenicol				1					**1**	**0.27**
Fusidic acid			1						**1**	**0.27**
Piperacillin / tazobactam					1				**1**	**0.27**
Total	**31**	**50**	**47**	**50**	**67**	**18**	**49**	**63**	**375**	
Types of antibiotics	**12**	**15**	**14**	**14**	**16**	**12**	**17**	**13**	**26**	

Table C17i: Antibiotics used for septicaemia on admission and within the first three days in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Cefotaxime	2	3	2	2	1	1	3	6	**20**	**16.81**
Vancomycin	2	3	3		2		3	4	**17**	**14.29**
Amikacin	1	1	4		5	1	1	2	**15**	**12.61**
Penicillin G	11				2		1	1	**15**	**12.61**
Imipenem	2	1	1		1	1	3	5	**14**	**11.76**
Metronidazole	2			2	1		2	2	**9**	**7.56**
Cefepime			1		1		1	1	**4**	**3.36**
Cefuroxime			1			1	1	1	**4**	**3.36**
Cloxacillin		1		1	1				**3**	**2.52**
Co-trimoxazole					1			2	**3**	**2.52**
Meropenem					1	1		1	**3**	**2.52**
Piperacillin			1		2				**3**	**2.52**
Ciprofloxacin		1	1						**2**	**1.68**
Ampicillin			1						**1**	**0.84**
Cefoxitin	1								**1**	**0.84**
Ceftriaxone					1				**1**	**0.84**
Erythromycin							1		**1**	**0.84**
Fusidic acid			1						**1**	**0.84**
Gentamicin					1				**1**	**0.84**
Tobramycin							1		**1**	**0.84**
Total	**21**	**10**	**16**	**5**	**20**	**5**	**17**	**25**	**119**	
Types of Antibiotics	**7**	**6**	**10**	**3**	**13**	**5**	**10**	**10**	**20**	

Table C17ii: Antibiotics used for new cases of septicaemia in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Vancomycin		4	3	7	7	3		3	**27**	**25.00**
Imipenem		1	2	6	3	3		2	**17**	**15.74**
Amikacin		2	3	3		1	1	2	**12**	**11.11**
Cefotaxime	1	3		2	1	2	2		**11**	**10.19**
Ciprofloxacin		1	2	1	3	1			**8**	**7.41**
Metronidazole		1	2	2	1				**6**	**5.56**
Co-trimoxazole		1		1			2		**4**	**3.70**
Cefuroxime			1				1	1	**3**	**2.78**
Ampicillin	1				1				**2**	**1.85**
Cefepime					2				**2**	**1.85**
Cloxacillin							1	1	**2**	**1.85**
Co-amoxiclav	1		1						**2**	**1.85**
Gentamicin				1			1		**2**	**1.85**
Meropenem								2	**2**	**1.85**
Cefoxitin			1						**1**	**0.93**
Ceftazidime			1						**1**	**0.93**
Fusidic acid		1							**1**	**0.93**
Erythromycin				1					**1**	**0.93**
Penicillin G				1					**1**	**0.93**
Piperacillin								1	**1**	**0.93**
Piperacillin / tazobactam					1				**1**	**0.93**
Tobramycin					1				**1**	**0.93**
Total	**3**	**14**	**16**	**25**	**20**	**10**	**8**	**12**	**108**	
Types of antibiotics	**3**	**8**	**9**	**10**	**9**	**5**	**6**	**7**	**22**	

Table C18i: Antibiotics used for UTI on admission and within the first three days in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Cefotaxime	2	2	1	1	1			3	**10**	**29.41**
Vancomycin	1	1						4	**6**	**17.65**
Imipenem	1							4	**5**	**14.71**
Amikacin		1		1		2			**4**	**11.76**
Cefuroxime			1					1	**2**	**5.88**
Metronidazole	1		1						**2**	**5.88**
Ceftazidime							1		**1**	**2.94**
Cloxacillin								1	**1**	**2.94**
Nalidixic acid		1							**1**	**2.94**
Meropenem								1	**1**	**2.94**
Piperacillin						1			**1**	**2.94**
Total	**5**	**5**	**3**	**2**	**1**	**3**	**1**	**14**	**34**	
Types of antibiotics	**4**	**4**	**3**	**2**	**1**	**2**	**1**	**6**	**11**	

Table C18ii: Antibiotics used for new cases of UTI in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Amikacin			3	1	2	3	3	3	**15**	**19.23**
Cefotaxime		1	1	1		3	1	6	**13**	**16.67**
Vancomycin		1			7			2	**10**	**12.82**
Imipenem			1		2	1	2	1	**7**	**8.97**
Ciprofloxacin			2	1	1	1	1		**6**	**7.69**
Co-trimoxazole							1	4	**5**	**6.41**
Cefuroxime					1	1	1		**3**	**3.85**
Cefepime					2				**2**	**2.56**
Clindamycin								2	**2**	**2.56**
Cloxacillin				1				1	**2**	**2.56**
Meropenem								2	**2**	**2.56**
Metronidazole						1		1	**2**	**2.56**
Penicillin G					1	1			**2**	**2.56**
Piperacillin					1			1	**2**	**2.56**
Cefazolin				1					**1**	**1.28**
Ceftriaxone		1							**1**	**1.28**
Loracarbef		1							**1**	**1.28**
Piperacillin / tazobacatm								1	**1**	**1.28**
Tobramycin						1			**1**	**1.28**
Total	**0**	**3**	**7**	**5**	**17**	**12**	**9**	**24**	**78**	
Types of antibiotics	**0**	**3**	**4**	**5**	**8**	**8**	**6**	**11**	**19**	

Table C19: Antibiotics used in post-operative patients on admission in the PICU

Antibiotic	No. of prescriptions									
	Year									
	1998	1999	2000	2001	2003	2004	2006	2007	Total	%
Cefotaxime	17	10	12	20	8	8	12	16	**103**	**22.74**
Amikacin	1	2	8	5	21	8	13	8	**66**	**14.57**
Metronidazole	7	4	9	9	10	6	9	6	**60**	**13.25**
Cefuroxime			8	12	5	7	9	7	**48**	**10.60**
Penicillin G	1	3	2	4	16	7	6	2	**41**	**9.05**
Vancomycin	2		1	5	3	1	2	4	**18**	**3.97**
Cefoxitin	2	2	2	5	3		2		**16**	**3.53**
Cefazolin			1	2	2	3	4	4	**16**	**3.53**
Gentamicin		1			3	4	2	3	**13**	**2.87**
Imipenem	1			2	3	1	1	4	**12**	**2.65**
Co-amoxiclav	2	1	3		1		1	1	**9**	**1.99**
Cloxacillin		1	2	2	1	1		2	**9**	**1.99**
Ampicillin			3				1	2	**6**	**1.32**
Cefamandole	2	3	1						**6**	**1.32**
Ciprofloxacin			2		1		1	1	**5**	**1.10**
Ceftriaxone		1		1			3		**5**	**1.10**
Cefepime					1		2	1	**4**	**0.88**
Clindamycin			1		1			1	**3**	**0.66**
Piperacillin			1		1			1	**3**	**0.66**
Amoxicillin						2		1	**3**	**0.66**
Co-trimoxazole						1		1	**2**	**0.44**
Meropenem					1		1		**2**	**0.44**
Ceftazidime	1								**1**	**0.22**
Chloramphenicol				1					**1**	**0.22**
Cefalexin								1	**1**	**0.22**
Total	**36**	**28**	**56**	**68**	**81**	**49**	**69**	**66**	**453**	
Types of antibiotics	**10**	**10**	**15**	**12**	**17**	**13**	**16**	**20**	**25**	

Table C20i: Antibiotics used in the children group in the PICU

Antibiotic	No. of prescriptions												
	Year												
	1998	1999	2000	2001	2003	2004	2006	2007	TOTAL	%	Mean	Median	SD
Cefotaxime	15	21	13	24	13	12	14	19	**131**	**18.90**	16.38	14.5	4.41
Amikacin	5	14	15	6	16	9	11	14	**90**	**12.99**	11.25	12.5	4.20
Cefuroxime	0	1	12	16	7	7	8	15	**66**	**9.52**	8.25	7.5	5.90
Vancomycin	3	8	6	15	7	7	7	7	**60**	**8.66**	7.50	7	3.38
Metronidazole	7	5	7	8	8	4	7	4	**50**	**7.22**	6.25	7	1.67
Imipenem	2	5	1	11	3	6	7	8	**43**	**6.20**	5.38	5.5	3.34
Cloxacillin	7	6	3	7	4	1	6	3	**37**	**5.34**	4.63	5	2.20
Penicillin G	4	4	5	2	11	6	3	2	**37**	**5.34**	4.63	4	2.92
Piperacillin	0	6	3	0	6	2	1	2	**20**	**2.89**	2.50	2	2.39
Co-amoxiclav	7	1	5	0	2	0	3	1	**19**	**2.74**	2.38	1.5	2.50
Co-trimoxazole	0	3	1	1	4	1	3	2	**15**	**2.16**	1.88	1.5	1.36
Cefazolin	0	0	0	1	2	3	3	4	**13**	**1.88**	1.63	1.5	1.60
Ceftriaxone	0	3	2	4	1	0	3	0	**13**	**1.88**	1.63	1.5	1.60
Gentamicin	1	1	1	1	3	4	1	1	**13**	**1.88**	1.63	1	1.19
Cefepime	0	0	1	2	1	1	4	1	**10**	**1.44**	1.25	1	1.28
Cefoxitin	3	1	1	3	0	0	0	0	**8**	**1.15**	1.00	0.5	1.31
Ciprofloxacin	0	1	2	1	1	2	0	1	**8**	**1.15**	1.00	1	0.76
Ampicillin	1	0	2	1	0	0	1	1	**6**	**0.87**	0.75	1	0.71
Cefamandole	2	3	1	0	0	0	0	0	**6**	**0.87**	0.75	0	1.16
Clindamycin	1	1	1	0	1	0	1	1	**6**	**0.87**	0.75	1	0.46
Erythromycin	0	2	0	0	1	0	3	0	**6**	**0.87**	0.75	0	1.16
Amoxycillin	0	0	0	1	0	3	0	1	**5**	**0.72**	0.63	0	1.06
Cefpodoxime	1	4	0	0	0	0	0	0	**5**	**0.72**	0.63	0	1.41
Chloramphenicol	0	0	2	1	0	1	0	1	**5**	**0.72**	0.63	0.5	0.74
Meropenem	0	0	0	0	0	1	1	3	**5**	**0.72**	0.63	0	1.06
Penicillin V	1	0	0	2	0	0	0	1	**4**	**0.58**	0.50	0	0.76
Fusidic acid	0	1	1	1	0	0	0	0	**3**	**0.43**	0.38	0	0.52
Tobramycin	0	0	0	0	0	0	3	0	**3**	**0.43**	0.38	0	1.06
Cefalexin	0	0	0	1	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Doxycycline	0	0	0	0	0	0	0	1	**1**	**0.14**	0.13	0	0.35
Loracarbef	0	1	0	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Nalidixic acid	0	1	0	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Oxytetracycline	0	0	1	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Piperacillin / tazobactam	0	0	0	0	0	0	0	1	**1**	**0.14**	0.13	0	0.35
Total	**60**	**93**	**86**	**109**	**91**	**70**	**90**	**94**	**693**		**86.63**	**90.5**	**15.17**
Types of antibiotics	**15**	**22**	**22**	**21**	**18**	**17**	**20**	**23**	**34**		**19.75**	**20.5**	**2.82**

Table C20ii: Antibiotics used in the infants group in the PICU

Antibiotic	No. of prescriptions												
	Year												
	1998	1999	2000	2001	2003	2004	2006	2007	TOTAL	%	Mean	Median	SD
Cefotaxime	22	9	12	19	10	13	16	21	**122**	**17.21**	15.25	14.5	5.01
Amikacin	7	8	15	7	26	24	16	15	**118**	**16.64**	14.75	15.0	7.36
Vancomycin	8	2	7	10	10	7	5	20	**69**	**9.73**	8.63	7.5	5.29
Metronidazole	5	3	8	10	10	3	7	12	**58**	**8.18**	7.25	8	3.37
Cefuroxime	1	1	6	12	5	12	12	8	**57**	**8.04**	7.13	7	4.67
Imipenem	6	2	4	6	8	9	7	14	**56**	**7.90**	7.00	6.5	3.59
Penicillin G	3	2	6	3	15	5	6	4	**44**	**6.21**	5.50	5	4.11
Co-trimoxazole	0	1	3	4	4	1	5	8	**26**	**3.67**	3.25	4	2.60
Ciprofloxacin	0	2	7	2	5	1	2	2	**21**	**2.96**	2.63	2	2.26
Gentamicin	2	2	1	1	5	3	4	3	**21**	**2.96**	2.63	2.5	1.41
Cloxacillin	4	2	4	2	3	2	2	0	**19**	**2.68**	2.38	2.0	1.30
Co-amoxiclav	2	2	7	0	0	0	0	1	**12**	**1.69**	1.50	0.5	2.39
Tobramycin	2	2	1	0	2	1	1	3	**12**	**1.69**	1.50	1.5	0.93
Meropenem	0	1	0	0	1	1	1	6	**10**	**1.41**	1.25	1	1.98
Erythromycin	2	0	1	1	0	1	4	0	**9**	**1.27**	1.13	1	1.36
Ampicillin	1	2	1	0	0	1	0	3	**8**	**1.13**	1.00	1.0	1.07
Cefoxitin	0	1	1	3	3	0	0	0	**8**	**1.13**	1.00	1	1.31
Piperacillin	2	2	2	0	2	0	0	0	**8**	**1.13**	1.00	1	1.07
Ceftazidime	1	3	1	0	0	0	2	0	**7**	**0.99**	0.88	1	1.13
Cefepime	1	0	0	0	2	0	1	1	**5**	**0.71**	0.63	1	0.74
Ceftriaxone	0	2	1	0	1	0	1	0	**5**	**0.71**	0.63	1	0.74
Cefazolin	0	0	1	2	0	0	1	0	**4**	**0.56**	0.50	0	0.76
Clindamycin	1	0	0	0	0	0	0	1	**2**	**0.28**	0.25	0	0.46
Amoxycillin	0	0	0	0	1	0	0	0	**1**	**0.14**	0.13	0.0	0.35
Cefalexin	0	0	0	0	0	0	0	1	**1**	**0.14**	0.13	0	0.35
Cefamandole	0	1	0	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Chloramphenicol	0	0	0	1	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Loracarbef	1	0	0	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Neomycin	0	0	1	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Streptomycin	1	0	0	0	0	0	0	0	**1**	**0.14**	0.13	0	0.35
Teicoplanin	0	0	0	0	1	0	0	0	**1**	**0.14**	0.13	0	0.35
Total	**72**	**50**	**90**	**83**	**114**	**84**	**93**	**123**	**709**		**88.63**	**87**	**22.89**
Types of antibiotics	**19**	**20**	**21**	**15**	**19**	**15**	**18**	**17**	**31**		**18.00**	**19**	**2.20**

Table C20iii: Antibiotics used in the neonates group in the PICU

Antibiotic	No. of prescriptions												
	Year												
	1998	1999	2000	2001	2003	2004	2006	2007	TOTAL	%	Mean	Median	SD
Amikacin	4	6	7	2	6	4	3	0	**32**	**18.93**	4.00	4.0	2.33
Cefotaxime	6	6	4	0	3	5	1	6	**31**	**18.34**	3.88	4.5	2.36
Vancomycin	2	4	1	3	5	3	1	4	**23**	**13.61**	2.88	3.0	1.46
Penicillin G	3	4	4	2	4	2	1	1	**21**	**12.43**	2.63	3	1.30
Imipenem	2	3	0	3	4	2	2	2	**18**	**10.65**	2.25	2	1.16
Cloxacillin	0	1	1	0	1	1	1	3	**8**	**4.73**	1.00	1.0	0.93
Cefepime	0	0	0	0	0	2	1	2	**5**	**2.96**	0.63	0	0.92
Ciprofloxacin	0	1	0	1	1	1	1	0	**5**	**2.96**	0.63	1	0.52
Metronidazole	0	0	1	0	0	3	1	0	**5**	**2.96**	0.63	0	1.06
Ampicillin	1	0	1	0	1	1	0	0	**4**	**2.37**	0.50	0.5	0.53
Gentamicin	2	0	1	0	0	1	0	0	**4**	**2.37**	0.50	0.0	0.76
Cefuroxime	0	1	1	0	0	1	0	0	**3**	**1.78**	0.38	0.0	0.52
Cefoxitin	0	0	0	0	0	0	2	0	**2**	**1.18**	0.25	0.0	0.71
Piperacillin / tazobactam	0	0	0	0	1	0	1	0	**2**	**1.18**	0.25	0	0.46
Tobramycin	0	0	0	0	1	1	0	0	**2**	**1.18**	0.25	0	0.46
Co-trimoxazole	0	0	0	0	0	0	1	0	**1**	**0.59**	0.13	0.0	0.35
Erythromycin	0	0	0	0	1	0	0	0	**1**	**0.59**	0.13	0	0.35
Meropenem	0	0	1	0	0	0	0	0	**1**	**0.59**	0.13	0	0.35
Piperacillin	0	0	0	0	1	0	0	0	**1**	**0.59**	0.13	0	0.35
Total	**20**	**26**	**22**	**11**	**29**	**27**	**16**	**18**	**169**		**21.13**	**21**	**6.10**
Types of antibiotics	**7**	**8**	**10**	**5**	**12**	**13**	**12**	**6**	**19**		**9.13**	**9**	**3.04**

Table C21: The different routes used for administration of antibiotics in the PICU

Year	Route of administration						Total antibiotics prescribed
	Intravenous		Oral		Nebulise		
	Antibiotics prescribed	%	Antibiotics prescribed	%	Antibiotics prescribed	%	
1998	136	90.07	15	9.93		0	151
1999	160	94.67	8	4.73	1	0.59	169
2000	188	94.95	10	5.05		0	198
2001	185	91.58	17	8.42		0	202
2003	222	93.28	15	6.3	1	0.42	238
2004	161	94.71	9	5.29		0	170
2006	199	95.67	9	4.33		0	208
2007	224	95.32	11	4.68		0	235
Total	**1475**	**93.89**	**94**	**5.98**	**2**	**0.13**	**1571**
Mean	184.38	93.78	11.75	6.09	0.25	0.13	
Median	186.5	94.69	10.5	5.17	0	0	
SD	30.92	1.99	3.41	2.03	0.46	0.24	

Appendix D: The prevalence and pattern of antibiotic resistance in the Paediatric Intensive Care Unit

Table D1: Patients from whom specimens were taken for C/S

Year	Pts in whom C/S were requested		Pts in whom bacteria were cultured			Total Pts
	Pts	% of total Pts	Pts	% of total Pts	% of pts where specimens were taken	
1998	34	45.33	14	18.67	41.18	75
1999	35	50	24	34.29	68.57	70
2000	60	74.07	37	45.68	61.67	81
2001	65	72.22	30	33.33	46.15	90
2003	69	69	38	38	55.07	100
2004	35	46.67	19	25.33	54.29	75
2006	67	76.14	25	28.41	37.31	88
2007	86	81.13	51	48.11	59.3	106
Total	**451**	**65.84**	**238**	**34.74**	**52.77**	**685**
Mean	56.38	64.32	29.75	33.98	52.94	
SD	19.46	14.54	11.90	9.95	10.66	
Median	62.5	70.61	27.5	33.81	54.68	

Table D2: Specimens in which bacteria were cultured

Year	Specimens taken for C/S tests				
	No. of specimens in which bacteria were cultured	%	No. of specimens in which no bacteria were cultured	%	Total Specimens
1998	19	23.46	62	76.54	**81**
1999	42	31.11	93	68.89	**135**
2000	58	27.23	155	72.77	**213**
2001	59	20.14	234	79.86	**293**
2003	86	31.27	189	68.73	**275**
2004	28	26.17	79	73.83	**107**
2006	53	27.46	140	72.54	**193**
2007	107	31.47	233	68.53	**340**
Total	**452**	**27.61**	**1185**	**72.39**	**1637**
Mean	56.5	27.29	148.13	72.71	204.63
SD	28.96	4.05	67.19	4.05	93.32
Median	55.5	27.35	147.5	72.66	203

Table D3: Positive cultures for the different bacteria genera in the PICU

Bacteria genus	No. of cultures												
	Year								Total	%			
	1998	1999	2000	2001	2003	2004	2006	2007			Mean	Median	SD
Staphylococcus	9	19	20	30	26	10	17	34	**165**	**29.26**	20.63	19.5	8.94
Klebsiella	2	3	7	11	10	4	5	25	**67**	**11.88**	8.38	6	7.44
Acinetobacter	0	5	6	3	23	6	7	16	**66**	**11.7**	8.25	6	7.52
Pseudomonas	6	10	9	4	10	1	15	8	**63**	**11.17**	7.88	8.5	4.26
Escherichia	4	3	7	9	9	2	1	13	**48**	**8.51**	6	5.5	4.17
Enterococcus	1	1	1	6	7	2	5	10	**33**	**5.85**	4.13	3.5	3.40
Streptococcus	0	2	1	0	4	0	5	11	**23**	**4.08**	2.88	1.5	3.80
Enterobacter	0	0	6	1	2	6	4	4	**23**	**4.08**	2.88	3	2.47
Stenotrophomonas	0	0	1	0	8	0	2	8	**19**	**3.37**	2.38	0.5	3.54
Haemophilus	0	2	0	0	1	2	1	5	**11**	**1.95**	1.38	1	1.69
Serratia	0	0	1	3	0	0	2	1	**7**	**1.24**	0.88	0.5	1.13
Proteus	1	0	1	0	2	0	0	2	**6**	**1.06**	0.75	0.5	0.89
Bacillus	0	0	1	1	0	0	0	2	**4**	**0.71**	0.5	0	0.76
Moraxella	0	0	0	2	1	0	1	0	**4**	**0.71**	0.5	0	0.76
Micrococcus	0	0	0	1	1	0	1	0	**3**	**0.53**	0.38	0	0.52
Alcaligenes	0	0	0	0	2	0	1	0	**3**	**0.53**	0.38	0	0.74
Shigella	0	1	1	1	0	0	0	0	**3**	**0.53**	0.38	0	0.52
Clostridium	0	0	2	0	0	0	0	0	**2**	**0.35**	0.25	0	0.71
Citrobacter	0	0	0	0	2	0	0	0	**2**	**0.35**	0.25	0	0.71
Flavobacterium	0	0	0	0	1	0	0	1	**2**	**0.35**	0.25	0	0.46
Aerococcus	0	0	0	0	1	0	0	0	**1**	**0.18**	0.13	0	0.35
Eubacterium	0	0	0	0	0	0	0	1	**1**	**0.18**	0.13	0	0.35
Leuconostoc	0	0	1	0	0	0	0	0	**1**	**0.18**	0.13	0	0.35
Bacteroides	0	0	0	0	0	0	0	1	**1**	**0.18**	0.13	0	0.35
Branhamella	0	0	1	0	0	0	0	0	**1**	**0.18**	0.13	0	0.35
Fusobacterium	0	0	0	1	0	0	0	0	**1**	**0.18**	0.13	0	0.35
Kluyvera	0	0	0	0	1	0	0	0	**1**	**0.18**	0.13	0	0.35
Morganella	0	0	0	0	0	1	0	0	**1**	**0.18**	0.13	0	0.35
Pasteurella	0	0	0	0	0	1	0	0	**1**	**0.18**	0.13	0	0.35
Salmonella	0	0	0	1	0	0	0	0	**1**	**0.18**	0.13	0	0.35
Total	**23**	**46**	**66**	**74**	**111**	**35**	**67**	**142**	**564**		70.5	66.5	39.49
Total Gram+	**10**	**22**	**26**	**38**	**39**	**12**	**28**	**58**	**233**	**41.31**	29.13	27	15.72
Total Gram-	**13**	**24**	**40**	**36**	**72**	**23**	**39**	**84**	**331**	**58.69**	41.38	37.5	24.6

Table D4: Different types of specimens with positive bacteria cultures

Specimen Type	No. of specimens									
	Year								Total	%
	1998	1999	2000	2001	2003	2004	2006	2007		
Tracheal aspirate	6	16	27	22	40	13	23	45	**192**	**42.48**
Blood	7	12	16	15	23	9	12	18	**112**	**24.78**
Urine	3	3	7	4	9	4	5	19	**54**	**11.95**
Pus	2	3	3	5	7	2	5	8	**35**	**7.74**
Catheter point		6			4		3	6	**19**	**4.2**
CSF			1	3			2	4	**10**	**2.21**
Tissue			2	2	1		1	2	**8**	**1.77**
Pleural fluid				2				3	**5**	**1.11**
Eye		1	1		1			2	**5**	**1.11**
Stool		1	1	2					**4**	**0.88**
Ascites fluid				2					**2**	**0.44**
Fluid unspecified				1					**1**	**0.22**
Drain							1		**1**	**0.22**
Breast milk							1		**1**	**0.22**
Pericardial fluid					1				**1**	**0.22**
Peritoneal dialysis				1					**1**	**0.22**
Not stated	1								**1**	**0.22**
Total	**19**	**42**	**58**	**59**	**86**	**28**	**53**	**107**	**452**	

Table D5: Positive cultures for the different bacteria genera (top nine) in the different specimens (top five)

Specimen Type	No. of cultures of different Bacteria genus									Total Specimens
	Staph	**Enteroc**	**Strep**	**Kleb**	**Acine**	**Pseud**	**Esch**	**Enterob**	**Steno**	
Tracheal aspirate	39	2	4	30	49	46	17	14	17	**192**
Blood	70	2	10	13	2	5	6	4		**112**
Urine	9	15	2	12	3	1	11	2	1	**54**
Pus	20	4	1	7	6	4	7	1	1	**35**
Catheter point	14	3	1	2	5	3				**19**
CSF	2	2	4				4			**10**
Tissue		5	1	1	1			2		**8**
Pleural fluid	1			1			3			**5**
Eye	3					1				**5**
Stool										**4**
Ascites fluid	1					1				**2**
Drain	1					1				**1**
Breast milk	2									**1**
Pericardial fluid	1									**1**
Peritoneal fluid	1									**1**
Fluid unspecified	1									**1**
Not stated				1		1				**1**
Total cultures	**165**	**33**	**23**	**67**	**66**	**63**	**48**	**23**	**19**	

Key: Staph = *Staphylococcus*, Enteroc = *Enterococcus*, Strep = *Streptococcus*, Kleb = *Klebsiella*, Acine = *Acinetobacter*, Pseud = *Pseudomonas*, Esch = *Escherichia*, Enterob = *Enterobacter*, Steno = *Stenotrophomonas*

Table D6: The antibiotic resistance for *Staphylococcus* genus

Antibiotic	No. of cultures, R = Resistant & T = Total									Total Cultures	% Resistance
		1998	1999	2000	2001	2003	2004	2006	2007		
BETA-LACTAMS											
Penicillin G *	R T	3 (3)	1 (1)	5 (5)	4 (4)	2 (2)	1 (1)			16 (16)	**100**
Penicillin/Ampicillin *	R T	4 (4)	16 (16)	15 (16)	23 (23)	25 (25)	5 (5)	12 (13)	28 (28)	128 (130)	**98.46**
Co-amoxiclav	R T	1 (1)								1 (1)	**100**
Cloxacillin *	R T	0 (1)				22 (23)	0 (1)	10 (13)	23 (28)	55 (66)	**83.33**
Methicillin *	R T	6 (6)	13 (17)	12 (19)	25 (26)	24 (26)	4 (5)		1 (1)	85 (100)	**85**
Piperacillin	R T		0 (1)							0 (1)	**0**
Cefuroxime	R T				2 (2)	2 (2)				4 (4)	**100**
Cefotaxime *	R T	1 (1)	3 (3)	0 (1)	2 (3)	0 (1)				6 (9)	**66.67**
Ceftriaxone/Cefotaxime	R T				1 (1)					1 (1)	**100**
Cefepime	R T			0 (1)						0 (1)	**0**
Imipenem	R T	1 (1)			1 (1)					2 (2)	**100**
AMINOGLYCOSIDES											
Amikacin	R T		2 (3)	0 (1)	1 (3)					3 (7)	**42.86**
Gentamicin	R T			1 (1)					3 (3)	4 (4)	**100**
Tobramycin	R T			1 (1)						1 (1)	**100**
OTHERS											
Ciprofloxacin	R T		1 (1)	2 (2)					1 (1)	4 (4)	**100**
Vancomycin *	R T	0 (5)	0 (13)	0 (14)	0 (20)	0 (25)	0 (2)	0 (12)	0 (27)	0 (118)	**0**
Erythromycin *	R T	5 (6)	13 (15)	11 (19)	19 (26)	22 (27)	5 (6)	9 (12)	19 (23)	103 (134)	**76.87**
Clindamycin *	R T	3 (5)	10 (12)	5 (11)	12 (19)	8 (26)	4 (5)	4 (13)	8 (20)	54 (111)	**48.65**
Co-trimoxazole *	R T	2 (5)	14 (17)	11 (17)	19 (25)	20 (26)	4 (5)	6 (13)	13 (25)	89 (133)	**66.92**
Linezolid	R T							0 (3)	0 (2)	0 (5)	**0**
Chloramphenicol	R T		0 (1)	0 (1)	1 (3)					1 (5)	**20**
Fusidic acid *	R T	0 (2)	2 (10)	2 (5)	5 (9)	8 (26)	1 (2)			18 (54)	**33.33**
Nitrofurantoin	R T			0 (2)					0 (1)	0 (3)	**0**
Nalidixic acid	R T	1 (1)								1 (1)	**100**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D7: The antibiotic resistance for *Enterococcus* genus

Antibiotic	No. of cultures, R = Resistant & T = Total								Total Cultures	% Resistance
	1998	1999	2000	2001	2003	2004	2006	2007		
BETA-LACTAMS										
Penicillin/Ampicillin *	R T						0 (4)	4 (9)	4 (13)	**30.77**
Ampicillin *	R T	1 (1)	1 (1)	0 (1)	3 (6)	2 (6)	0 (2)	0 (2)	7 (19)	**36.84**
Co-amoxiclav	R T							0 (2)	0 (1)	0 (3)	**0**
Piperacillin/tazobactam	R T							0 (2)	0 (1)	0 (3)	**0**
Cefazolin/Cefalexin *	R T		1 (1)		2 (2)	6 (6)	1 (1)	1 (1)		11 (11)	**100**
Cefuroxime	R T				1 (1)			1 (1)		2 (2)	**100**
Cefotaxime	R T				1 (1)					1 (1)	**100**
Ceftriaxone/Cefotaxime	R T		1 (1)							1 (1)	**100**
Imipenem *	R T		1 (1)		3 (3)	2 (5)		0 (2)	0 (1)	6 (12)	**50**
AMINOGLYCOSIDES										
Amikacin	R T					0 (1)				0 (1)	**0**
Gentamicin	R T						0 (1)	1 (1)	2 (2)	3 (4)	**75**
OTHERS										
Ciprofloxacin	R T					1 (1)			4 (4)	5 (5)	**100**
Vancomycin *	R T		0 (1)	0 (1)	0 (4)	0 (5)	0 (2)	0 (1)	0 (7)	0 (22)	**0**
Erythromycin	R T				1 (1)			1 (2)	2 (2)	4 (4)	**100**
Clindamycin	R T				1 (1)					1 (1)	**100**
Co-trimoxazole	R T							1 (1)		1 (1)	**100**
Linezolid	R T								0 (2)	0 (2)	**0**
Tetracycline *	R T		1 (1)		2 (3)	5 (6)	2 (2)	0 (1)	3 (4)	13 (17)	**76.47**
Nitrofurantoin *	R T		1 (1)	0 (1)	0 (2)	1 (3)	0 (1)	0 (1)	0 (5)	2 (14)	**14.29**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D8: The antibiotic resistance for *Streptococcus* genus

Antibiotic	No. of cultures, R = Resistant & T = Total					Total Cultures	% Resistance
	1999	2000	2003	2006	2007		
BETA-LACTAMS							
Penicillin G	R T	0 (1)		0 (1)		0 (2)	**0**
Penicillin/Ampicillin *	R T	0 (1)	1 (2)		2 (7)	3 (10)	**30**
Ampicillin	R T		0 (2)			0 (2)	**0**
Cloxacillin	R T		0 (1)		1 (1)	1 (2)	**50**
Methicillin	R T		0 (1)			0 (1)	**0**
Cefazolin/Cefalexin	R T		0 (1)			0 (1)	**0**
Cefuroxime	R T	0 (1)	0 (1)			0 (2)	**0**
Cefotaxime	R T	0 (1)	0 (1)	0 (2)		0 (4)	**0**
Ceftriaxone/Cefotaxime	R T			0 (2)		0 (2)	**0**
Cefepime	R T		0 (1)			0 (1)	**0**
Imipenem	R T		0 (3)			0 (3)	**0**
AMINOGLYCOSIDES							
Amikacin	R T		0 (1)			0 (1)	**0**
Gentamicin	R T		0 (2)			0 (2)	**0**
OTHERS							
Vancomycin *	R T		0 (4)	0 (1)	0 (6)	0 (11)	**0**
Erythromycin *	R T	0 (1)	0 (1)	1 (2)	1 (3)	2 (4)	4 (11)	**36.36**
Clindamycin *	R T		0 (2)	1 (2)	2 (5)	3 (10)	**30**
Co-trimoxazole	R T		1 (2)	2 (2)	1 (1)	4 (5)	**80**
Tetracycline	R T		0 (4)			0 (4)	**0**
Chloramphenicol	R T		0 (1)	0 (1)		0 (2)	**0**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D9: The antibiotic resistance for *Klebsiella* genus

Antibiotic	No. of cultures, R = Resistant & T = Total								Total Cultures	% Resistance
		1999	2000	2001	2003	2004	2006	2007		
PENICILLINS										
Penicillin/Ampicillin	R					1			1	**100**
	T					(1)			(1)	
Ampicillin *	R	2	7	11	9	2	5	25	61	**100**
	T	(2)	(7)	(11)	(9)	(2)	(5)	(25)	(61)	
Co-amoxiclav *	R	0	0	1	0	1	1	7	10	**34.48**
	T	(1)	(2)	(6)	(3)	(1)	(1)	(15)	(29)	
Piperacillin *	R	1	6	8	6	3			24	**88.89**
	T	(1)	(6)	(10)	(7)	(3)			(27)	
Piperacillin/tazobactam*	R	0	0	0	1	1	1	3	6	**21.43**
	T	(2)	(1)	(3)	(6)	(1)	(1)	(14)	(28)	
CEPHALOSPORINS										
Cefazolin/Cefalexin *	R						4	21	25	**86.21**
	T						(4)	(25)	(29)	
Cefoxitin *	R		2	0	0				2	**22.22**
	T		(2)	(1)	(6)				(9)	
Cefuroxime *	R	1	3	5	3	2	3	21	38	**73.08**
	T	(2)	(5)	(8)	(7)	(2)	(3)	(25)	(52)	
Cefamandole	R		3	3					6	**100**
	T		(3)	(3)					(6)	
Cefotaxime *	R	1	4	1	6			0	12	**70.59**
	T	(2)	(5)	(2)	(7)			(1)	(17)	
Ceftriaxone/Cefotaxime*	R			1	5	1	2	17	26	**96.3**
	T			(1)	(6)	(1)	(2)	(17)	(27)	
Ceftazidime *	R	1	3	4	6	1	2	17	34	**94.44**
	T	(1)	(4)	(4)	(7)	(1)	(2)	(17)	(36)	
Cefepime *	R	1	3	0	0	0	1	17	22	**61.11**
	T	(2)	(4)	(2)	(6)	(1)	(1)	(20)	(36)	
CARBAPENEMS										
Imipenem *	R	0	0	0	0	0	0	1	1	**1.92**
	T	(2)	(3)	(7)	(8)	(4)	(5)	(23)	(52)	
Meropenem *	R	0	0	0	0	0	0	0	0	**0**
	T	(2)	(1)	(3)	(7)	(3)	(5)	(8)	(29)	
Ertapenem *	R						0	0	0	**0**
	T						(5)	(14)	(19)	
AMINOGLYCOSIDES										
Amikacin *	R	0	1	5	2	0	0	0	8	**15.69**
	T	(2)	(7)	(8)	(7)	(3)	(4)	(20)	(51)	
Gentamicin *	R	1	4	7	5	2	3	19	41	**69.49**
	T	(2)	(7)	(11)	(9)	(3)	(3)	(24)	(59)	
Tobramycin *	R	1	3	7	4	1	5	14	35	**77.78**
	T	(2)	(3)	(7)	(8)	(2)	(5)	(18)	(45)	
OTHERS										
Ciprofloxacin *	R	0	0	0	0	0	2	3	5	**15.15**
	T	(2)	(3)	(6)	(6)	(3)	(3)	(10)	(33)	
Co-trimoxazole *	R	1	6	5	5	2	5	20	44	**70.97**
	T	(2)	(7)	(11)	(9)	(3)	(5)	(25)	(62)	
Tetracycline	R							0	0	**0**
	T							(2)	(2)	
Nitrofurantoin	R		0					1	1	**25**
	T		(2)					(2)	(4)	
Nalidixic acid	R		0						0	**0**
	T		(2)						(2)	

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D10: The antibiotic resistance for *Pseudomonas* genus

Antibiotic	No. of cultures, R = Resistant & T = Total									Total Cultures	% Resistance
		1998	1999	2000	2001	2003	2004	2006	2007		
PENICILLINS											
Ampicillin *	R T	2 (2)	11 (11)	8 (8)	4 (4)			1 (1)		26 (26)	**100**
Co-amoxiclav *	R T		4 (4)	2 (2)	3 (3)	1 (2)				10 (11)	**90.91**
Piperacillin *	R T	0 (2)	3 (11)	2 (9)	0 (4)	2 (9)	0 (1)			7 (36)	**19.44**
Piperacillin/tazobactam*	R T		2 (3)	0 (1)		2 (8)	0 (1)	4 (12)	1 (8)	9 (33)	**27.27**
CEPHALOSPORINS											
Cefoxitin	R T		3 (3)	1 (1)	2 (2)	2 (2)				8 (8)	**100**
Cefuroxime *	R T		6 (6)	2 (2)	2 (2)					10 (10)	**100**
Cefotaxime *	R T	2 (2)	11 (11)	6 (7)	2 (2)	7 (9)	1 (1)			29 (32)	**90.63**
Ceftriaxone/Cefotaxime	R T					0 (2)			2 (2)	2 (4)	**50**
Ceftazidime *	R T		2 (6)	2 (5)	0 (1)	2 (10)	0 (1)	3 (4)	1 (2)	10 (29)	**34.48**
Cefepime *	R T	0 (1)	1 (6)	0 (2)	0 (1)	3 (8)	1 (1)	3 (10)	1 (6)	9 (35)	**25.71**
CARBAPENEMS											
Imipenem *	R T		4 (9)	1 (2)		6 (10)	0 (1)	4 (12)	2 (7)	17 (41)	**41.46**
Meropenem *	R T		2 (5)	0 (2)		2 (9)	0 (1)	4 (11)	1 (1)	9 (29)	**31.03**
AMINOGLYCOSIDES											
Amikacin *	R T		2 (11)	0 (8)	0 (2)	3 (10)	1 (1)	4 (11)	1 (5)	11 (48)	**22.92**
Gentamicin *	R T	0 (2)	10 (11)	6 (9)	1 (4)	3 (10)	1 (1)	4 (15)	1 (6)	26 (58)	**44.83**
Tobramycin *	R T	0 (2)	4 (10)	2 (8)	1 (3)	3 (10)	1 (1)	4 (11)	1 (7)	16 (52)	**30.77**
OTHERS											
Ciprofloxacin *	R T		1 (9)	0 (5)		2 (10)	1 (1)	3 (6)	1 (5)	8 (36)	**22.22**
Co-trimoxazole *	R T	2 (2)	11 (11)	9 (9)	4 (4)	9 (10)	0 (1)	9 (10)	1 (1)	45 (48)	**93.75**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D11: The antibiotic resistance for *Escherichia* genus

Antibiotic	No. of cultures, R = Resistant & T = Total									Total Cultures	% Resistance
		1998	1999	2000	2001	2003	2004	2006	2007		
PENICILLINS											
Penicillin/Ampicillin	R T						1 (1)			1 (1)	**100**
Ampicillin *	R T	1 (1)	2 (2)	6 (7)	9 (9)	8 (9)	1 (1)	1 (1)	11 (12)	39 (42)	**92.86**
Co-amoxiclav *	R T		0 (2)	0 (4)	4 (5)	0 (5)	1 (2)		1 (10)	6 (28)	**21.43**
Piperacillin *	R T	1 (1)		3 (3)	7 (7)	6 (7)	2 (2)			19 (20)	**95**
Piperacillin/tazobactam*	R T				0 (2)	1 (8)	0 (1)		0 (7)	1 (18)	**5.56**
CEPHALOSPORINS											
Cefazolin/Cefalexin *	R T							1 (1)	6 (8)	7 (9)	**77.78**
Cefoxitin *	R T			1 (2)	0 (1)	0 (8)				1 (11)	**9.09**
Cefuroxime *	R T			1 (5)	5 (7)	3 (9)	1 (2)	1 (1)	5 (9)	16 (33)	**48.48**
Cefamandole	R T	1 (1)		1 (1)	2 (2)					4 (4)	**100**
Cefotaxime *	R T	1 (1)	0 (1)	1 (4)	5 (7)	3 (8)			0 (1)	10 (22)	**45.45**
Ceftriaxone/Cefotaxime*	R T				2 (2)	3 (8)	1 (1)	1 (1)	4 (6)	11 (18)	**61.11**
Ceftazidime *	R T	1 (1)		1 (1)	5 (6)	4 (9)	1 (1)	1 (1)	4 (4)	17 (23)	**73.91**
Cefepime *	R T			1 (1)	1 (2)	0 (8)	0 (1)	1 (1)	3 (7)	6 (20)	**30**
CARBAPENEMS											
Imipenem *	R T	0 (1)	0 (1)	0 (2)	0 (7)	0 (9)	0 (2)	0 (1)	0 (10)	0 (33)	**0**
Meropenem *	R T				0 (4)	0 (8)	0 (1)	0 (1)	0 (5)	0 (19)	**0**
Ertapenem	R T							0 (1)	0 (6)	0 (7)	**0**
AMINOGLYCOSIDES											
Amikacin *	R T	1 (1)	0 (2)	1 (4)	2 (8)	1 (9)	1 (2)	0 (1)	2 (4)	8 (31)	**25.81**
Gentamicin *	R T	1 (1)	0 (2)	1 (7)	7 (9)	4 (9)	1 (2)	0 (1)	5 (11)	19 (42)	**45.24**
Tobramycin *	R T	1 (1)	0 (1)	1 (3)	6 (7)	5 (9)	1 (2)	1 (1)	4 (6)	19 (30)	**63.33**
OTHERS											
Ciprofloxacin *	R T		0 (1)	0 (3)	0 (8)	0 (9)	0 (1)		1 (1)	1 (23)	**4.35**
Co-trimoxazole *	R T	1 (1)	2 (2)	5 (6)	9 (9)	9 (9)	2 (2)	0 (1)	9 (11)	37 (41)	**90.24**
Tetracycline	R T			1 (1)					1 (1)	2 (2)	**100**
Chloramphenicol	R T			0 (1)						0 (1)	**0**
Nitrofurantoin	R T		0 (1)	0 (2)					0 (2)	0 (5)	**0**
Nalidixic acid	R T		0 (1)	0 (2)						0 (3)	**0**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D12: The antibiotic resistance for *Enterobacter* genus

Antibiotic	No. of cultures, R = Resistant & T = Total							Total Cultures	% Resistance
		2000	2001	2003	2004	2006	2007		
PENICILLINS									
Penicillin/Ampicillin	R T				1 (1)			1 (1)	**100**
Ampicillin *	R T	6 (6)	1 (1)	2 (2)	5 (5)	3 (3)	4 (4)	21 (21)	**100**
Co-amoxiclav *	R T	6 (6)	1 (1)	2 (2)	6 (6)	1 (1)	4 (4)	20 (20)	**100**
Piperacillin *	R T	3 (6)		1 (2)	2 (3)			6 (11)	**54.55**
Piperacillin/tazobactam	R T	0 (2)		0 (2)			0 (1)	0 (5)	**0**
CEPHALOSPORINS									
Cefazolin/Cefalexin	R T					2 (2)	2 (2)	4 (4)	**100**
Cefoxitin *	R T	6 (6)	1 (1)	1 (2)	4 (4)			12 (13)	**92.31**
Cefuroxime *	R T	4 (4)		1 (1)	3 (3)	1 (1)		9 (9)	**100**
Cefotaxime	R T	3 (4)		1 (2)	1 (1)			5 (7)	**71.43**
Ceftriaxone/Cefotaxime	R T			1 (2)	1 (1)			2 (3)	**66.67**
Ceftazidime	R T	3 (3)		0 (2)	3 (3)			6 (8)	**75**
Cefepime *	R T	2 (3)		0 (2)	0 (4)	0 (3)	0 (4)	2 (16)	**12.5**
CARBAPENEMS									
Imipenem *	R T	0 (2)		0 (2)	0 (6)	0 (4)	0 (2)	0 (16)	**0**
Meropenem *	R T	0 (2)		0 (2)	0 (6)	0 (3)		0 (13)	**0**
Ertapenem	R T					0 (3)	0 (2)	0 (5)	**0**
AMINOGLYCOSIDES									
Amikacin *	R T	2 (3)	0 (1)	0 (2)	0 (4)	0 (3)	0 (1)	2 (14)	**14.29**
Gentamicin *	R T	2 (6)	0 (1)	0 (2)	3 (6)	2 (3)	1 (4)	8 (22)	**36.36**
Tobramycin *	R T	0 (2)		0 (2)	2 (3)	2 (3)	1 (1)	5 (11)	**45.45**
OTHERS									
Ciprofloxacin *	R T	0 (3)	0 (1)	0 (2)	0 (3)			0 (9)	**0**
Co-trimoxazole *	R T	2 (6)	1 (1)	1 (2)	4 (4)	3 (3)	1 (4)	12 (20)	**60**
Nitrofurantoin	R T				1 (1)			1 (1)	**100**
Nalidixic acid	R T				1 (1)			1 (1)	**100**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D13: The antibiotic resistance for *Acinetobacter* genus

Antibiotic	No. of cultures, R = Resistant & T = Total								Total Cultures	% Resistance
		1999	2000	2001	2003	2004	2006	2007		
PENICILLINS										
Ampicillin *	R T	5 (5)	6 (6)	3 (3)					14 (14)	**100**
Co-amoxiclav	R T	2 (2)	1 (1)	2 (2)					5 (5)	**100**
Piperacillin *	R T	5 (5)	3 (4)	3 (3)	19 (23)	1 (2)			31 (37)	**83.78**
Piperacillin/tazobactam*	R T	1 (2)	3 (4)	2 (2)	16 (21)	0 (1)	7 (7)	5 (5)	34 (42)	**80.95**
CEPHALOSPORINS										
Cefoxitin	R T	2 (2)	2 (2)	2 (2)					6 (6)	**100**
Cefuroxime *	R T	3 (3)	4 (4)	2 (2)					9 (9)	**100**
Cefotaxime *	R T	5 (5)	5 (5)	3 (3)	15 (19)	1 (2)			29 (34)	**85.29**
Ceftriaxone/Cefotaxime	R T							8 (8)	8 (8)	**100**
Ceftazidime *	R T	4 (5)	3 (4)	3 (3)	15 (22)	1 (2)	4 (4)	9 (9)	39 (49)	**79.59**
Cefepime *	R T	1 (2)	3 (5)	2 (2)	12 (20)	0 (1)	6 (6)	14 (15)	38 (51)	**74.51**
CARBAPENEMS										
Imipenem *	R T	1 (4)	1 (3)	1 (2)	13 (22)	0 (2)	6 (6)	12 (13)	34 (52)	**65.38**
Meropenem *	R T	0 (1)	3 (5)	1 (1)	13 (20)	0 (2)	7 (7)	6 (6)	30 (42)	**71.43**
AMINOGLYCOSIDES										
Amikacin *	R T	4 (5)	3 (6)	3 (3)	18 (24)	0 (1)	7 (7)	14 (14)	49 (60)	**81.67**
Gentamicin *	R T	4 (5)	3 (6)	3 (3)	18 (23)	0 (3)	7 (7)	9 (13)	44 (60)	**73.33**
Tobramycin *	R T	4 (5)	1 (6)	3 (3)	4 (23)	0 (2)	3 (7)	1 (16)	16 (62)	**25.81**
OTHERS										
Ciprofloxacin *	R T	3 (5)	3 (5)	3 (3)	16 (22)	0 (1)	7 (7)	12 (12)	44 (55)	**80**
Co-trimoxazole *	R T	4 (5)	3 (6)	3 (3)	18 (23)	1 (2)	7 (7)	15 (16)	51 (62)	**82.26**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

Table D14: The antibiotic resistance for *Stenotrophomonas* genus

Antibiotic	No. of cultures, R = Resistant & T = Total					Total Cultures	% Resistance
		2000	2003	2006	2007		
PENICILLINS							
Ampicillin	R T	1 (1)				1 (1)	**100**
Co-amoxiclav	R T	1 (1)		1 (1)		2 (2)	**100**
Piperacillin	R T	1 (1)	3 (7)			4 (8)	**50**
Piperacillin/tazobactam	R T	1 (1)	2 (6)	1 (1)		4 (8)	**50**
CEPHALOSPORINS							
Cefoxitin	R T	1 (1)				1 (1)	**100**
Cefuroxime	R T	1 (1)				1 (1)	**100**
Cefotaxime	R T	1 (1)	3 (5)			4 (6)	**66.67**
Ceftriaxone/Cefotaxime	R T				5 (5)	5 (5)	**100**
Ceftazidime *	R T	0 (1)	2 (7)	1 (1)	2 (3)	5 (12)	**41.67**
Cefepime *	R T		2 (8)	1 (1)	5 (5)	8 (14)	**57.14**
CARBAPENEMS							
Imipenem *	R T	1 (1)	8 (8)	2 (2)	6 (6)	17 (17)	**100**
Meropenem *	R T	1 (1)	8 (8)	2 (2)		11 (11)	**100**
AMINOGLYCOSIDES							
Amikacin *	R T	1 (1)	4 (5)	1 (2)	4 (4)	10 (12)	**83.33**
Gentamicin *	R T	1 (1)	8 (8)	2 (2)	3 (3)	14 (14)	**100**
Tobramycin *	R T	1 (1)	8 (8)	2 (2)	2 (2)	13 (13)	**100**
OTHERS							
Ciprofloxacin *	R T	0 (1)	2 (7)	0 (1)	3 (4)	5 (13)	**38.46**
Co-trimoxazole *	R T	0 (1)	1 (8)	1 (2)	0 (8)	2 (19)	**10.53**

Key: R = Resistant cultures, T= Total no. cultures tested, * = Antibiotics with ≥9 cultures that were selected for resistance prevalence

SUMMARY

Key terms: Antibiotics, Paediatric intensive care, Bacteria, Resistance, Antibiotic factors, Bacterial factors, Host factors, Broad-spectrum antibiotics, Nosocomial infections, Intensive care unit performance

Many antibiotics have been developed and are available on the market. An increase in the use of antibiotics in hospitals was observed and antibiotics are among the medicines most commonly prescribed to paediatric patients. Resistance to antibiotics is increasing and is a major problem not only in the Paediatric Intensive Care Unit at Universitas Hospital in Bloemfontein, but in South Africa in general. The continued value and effectiveness of antibiotics depend on careful use to avoid bacterial resistance from developing. Thus, guidelines for rational antibiotic use and prevention of resistance should be developed and implemented. This requires an understanding of the factors influencing antibiotic use in a particular setting, in this case the Paediatric Intensive Care Unit at Universitas Hospital. Therefore, the aim of this study is to describe the factors that influence the use of antibiotics in the Paediatric Intensive Care Unit from 1998 to 2007.

This research consisted of a retrospective study of the records of patients admitted to the Paediatric Intensive Care Unit from 1998 to 2007. Using a datasheet, the following information was captured and evaluated: patients' demography, indication for admission, co-morbid conditions, antibiotic and other drug therapy, culture and sensitivity and other relevant parameters.

Of the 1 221 patients admitted during the study period, information could only be retrieved for 967 patients, and of these 685 patients (385 males and 299 females) met the study criteria. The Paediatric Intensive Care Unit performance, measured as Intensive Care Unit utilisation, was optimal at 63%, implying that no patient needing intensive care was denied. The most common conditions on admission were respiratory (23.4%), gastro-intestinal (22%) and cardiovascular (19%) related problems.

Pneumonia (8.9%) was the most common infective condition. The most common infective complications while in the Paediatric Intensive Care Unit were pneumonia (35.6%), septicaemia (11.1%) and urinary tract infection (8.8%). Broad-spectrum antibiotics were prescribed the most widely. The top ten antibiotics included cefotaxime (18.2%), amikacin (14.7%), vancomycin (9.8%), cefuroxime (8.1%) imipenem (7.5%), metronidazole (7.2%), penicillin G (6.5%), cloxacillin (4.1%), co-trimoxazole (2.7%) and gentamicin (2.4%).

The top ten bacteria genera cultured were *Staphylococcus* (29.3%), *Klebsiella* (11.9%), *Acinetobacter* (11.7%), *Pseudomonas* (11.2%), *Escherichia* (8.5%), *Enterococcus* (5.9%), *Streptococcus* (4.1%), *Enterobacter* (4.1%), *Stenotrophomonas* (3.4%) and *Haemophilus* (2%). There was high resistance of the *Staphylococcus* genus to penicillins and penicillin-allergy substitutes (>80%, with methicillin-resistance of 85%), but no resistance to vancomycin was observed. The *Klebsiella* and *Pseudomonas* genera exhibited considerable resistance to most aminoglycosides (40–78%) and cephalosporins (70–100%), but *Klebsiella* remained sensitive to imipenem (1.9%), while *Pseudomonas* was moderately sensitive to amikacin (22.9%). The nosocomial bacteria genera *Acinetobacter* and *Stenotrophomonas* were resistant (>70%) to almost all antibiotics excluding tobramycin (25.8%) for *Acinetobacter* and co-trimoxazole (10.5%) for *Stenotrophomonas*.

Lastly, the persistently challenging factors that influenced antibiotic use in the Paediatric Intensive Care Unit from 1998 to 2007 were common bacteria cultured from specific specimens, bacterial innate resistance, interaction of bacterial and host factors (multiple and severe infections), disease pattern, new antibiotics, overuse of antibiotics, length of stay, personal preferences and treatment guidelines. In conclusion, it was illustrated that bacterial resistance to antibiotics is increasing, and that antibiotic use in the Paediatric Intensive Care Unit at Universitas Hospital was greatly influenced by the efforts to contain antibiotic resistance.

OPSOMMING

Sleutelbegrippe: Antibiotika, Pediatriese intensiewe sorg, Bakterieë, Weerstandigheid, Antibiotiese faktore, Bakteriële faktore, Gasheer-faktore, Breë-spektrum-antibiotika, Nosokomiale infeksies, Intensiewe Sorgeenheid-prestasie

Baie antibiotika is al ontwikkel en is in die handel beskikbaar. ’n Toename in die gebruik van antibiotika in hospitale is waargeneem en antibiotika is van die algemeenste medisyne wat aan pediatriese pasiënte voorgeskryf word. Antibiotika-weerstandigheid is aan die toeneem en is ’n groot probleem in die Pediatriese Intensiewe Sorgeenheid van Universitas Hospitaal in Bloemfontein, sowel as in Suid-Afrika in die algemeen. Die volgehoue waarde en effektiwiteit van antibiotika is onderworpe aan die sorgvuldige gebruik daarvan ten einde te voorkom dat bakteriële weerstandigheid ontwikkel. Riglyne vir die rasionele gebruik van antibiotika moet dus ontwikkel en geïmplementeer word om weerstandigheid te verhoed. Dit vereis begrip van die faktore wat die gebruik van antibiotika in ’n spesifieke omgewing beïnvloed, in hierdie geval die Pediatriese Intensiewe Sorgeenheid van Universitas Hospitaal. Gevolglik is die doel van hierdie studie om die faktore te beskryf wat die gebruik van antibiotika in die Pediatriese Intensiewe Sorgeenheid vanaf 1998 tot 2007 beïnvloed het.

Hierdie navorsing behels ’n retrospektiewe studie van pasiëntrekords wat vanaf 1998 tot 2007 in die Pediatriese Intensiewe Sorgeenheid opgeneem is. Die volgende inligting is deur middel van ’n datavel versamel en geëvalueer: demografie van die pasiënt, aanduiding vir opname, ko-morbiede toestande, antibiotika en ander geneesmiddel terapie, kultuur en sensitiwiteit en ander toepaslike parameters.

Van die 1 221 pasiënte wat tydens die studieperiode opgeneem is, kon inligting vir slegs 967 van die pasiënte verkry word, waarvan 685 pasiënte (385 manlike- en 299 vroulike pasiënte) aan die studie-kriteria voldoen het. Die Pediatriese Intensiewe Sorgeenheid-

prestasie, gemeet as Intensiewe Sorgeenheidbenutting, was optimaal teen 63%, wat daarop dui dat geen pasiënt wat intensiewe sorg benodig het, weggewys is nie. Die algemeenste siektetoestande tydens opname was respiratoriese (23.4%), gastro-intestinale (22%) en kardiovaskulêre (19%) verwante probleme. Pneumonie (8.9%) was die algemeenste infektiewe toestand. Die algemeenste infektiewe komplikasies gedurende verblyf in die Pediatriese Intensiewe Sorgeenheid was pneumonie (35.6%), septisemie (11.1%) en urienweginfeksie (8.8%). Breë-spektrum antibiotika is die meeste voorgeskryf. Die toptien antibiotika was kefotaksiem (18.2%), amikasien (14.7%), vankomisien (9.8%), kefuroksiem (8.1%), imipenem (7.5%), metronidasool (7.2%), penisillien G (6.5%), kloksasillien (4.1%), ko-trimoksasool (2.7%) en gentamisien (2.4%).

Die toptien gekweekte bakterie genera was *Staphylococcus* (29.3%), *Klebsiella* (11.9%), *Acinetobacter* (11.7%), *Pseudomonas* (11.2%), *Escherichia* (8.5%), *Enterococcus* (5.9%), *Streptococcus* (4.1%), *Enterobacter* (4.1%), *Stenotrophomonas* (3.4%) en *Haemophilus* (2%). Daar was hoë weerstandigheid van die *Staphylococcus*-genus teen penisilliene en penisillien-allergieplaasvervangers (>80%, met metisillien-weerstandigheid van 85%), maar vankomisien-weerstandigheid is nie waargeneem nie. *Klebsiella*- en *Pseudomonas*-genera het aansienlike weerstand teen die meeste van die aminoglikosiede (40–78%) en kefalosporiene (70–100%) getoon, maar *Klebsiella* het sensitief vir imipenem (1.9%) gebly, terwyl *Pseudomonas* matig sensitief vir amikasien (22.9%) was. Die hospitaalverworwe bakterie genera *Acinetobacter* en *Stenotrophomonas* was weerstandig (>70%) teen amper alle antibiotika behalwe tobramisien (25.8%) vir *Acinetobacter* en ko-trimoksasool (10.5%) vir *Stenotrophomonas*.

Laastens, die steeds uitdagende faktore wat die gebruik van antibiotika in die Pediatriese Intensiewe Sorgeenheid beïnvloed het, was algemene bakterieë wat van spesifieke monsters gekweek is, ingebore bakteriële weerstandigheid, interaksie van bakteriële faktore met gasheerfaktore (veelvoudige en erge infeksies), siektepatroon, nuwe antibiotika, oorgebruik van antibiotika, duur van opname, persoonlike voorkeure

en behandelingsriglyne. Ten slotte is geïllustreer dat bakteriële weerstandigheid teen antibiotika toeneem, en dat die gebruik van antibiotika in die Pediatriese Intensiewe Sorgeenheid in Universitas Hospitaal grootliks beïnvloed is deur die pogings om antibiotika-weerstandigheid in bedwang te hou.

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13 Februarie 2013

VIR WIE DIT MAG AANGAAN

Hiermee verklaar ek dat die teksversorging van die meegaande verhandeling van me. Riana van Wyk deur opgeleide taalpraktisyns van ons Eenheid gedoen is.

Die uwe

.....

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