PATTERN OF ANTIBACTERIAL USE: A CASE STUDY OF THE SURGICAL AND MEDICAL EMERGENCY UNIT OF KORLE BU TEACHING HOSPITAL, ACCRA, GHANA.

BY

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DECLARATION

I hereby declare that this submission is my own work towards the MSc and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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ABSTRACT

The use of antimicrobials has contributed to the dramatic fall in morbidity from communicable and infectious diseases over the last 50 years globally, as to increasingly high levels of expenditure on and consumption of antimicrobials. A substantial proportion of the total drug budget in many countries is dedicated to antibiotics and they are often the largest single group of drugs purchased in developing countries.

In developing countries like Ghana, relatively high levels of availability and consumption have led to disproportionately higher incidence of inappropriate use and greater levels of resistance compared to developed countries. This study tends to look at the pattern of antibacterial use in Surgical and Medical Emergency Unit of the Korlebu Teaching Hospital to serve as a baseline for further work. The unit where the work is taking place is the last referred point for the southern part of Ghana for most non-trauma emergencies.

The work was to determine whether antibiotics are used in response to microbiological tests and also whether prescriptions conform to acceptable standards.

A prospective study of patients admitted at the three wards of the Surgical and Medical Emergency Unit was undertaken from 14th January 2009 to 14th March 2009. Data Collection Sheets were used to collect data from patients' medical records while on admission over the period. Patients' records were reviewed once daily for 5 days until they were transferred to other units, discharged or died.

The main findings are:

1. Only 39 (39%) Prescribers requested for Culture and Sensitivity test during the period.
2. Of the number that requested Culture and Sensitivity test, only 2 (5.1 %) had their results before antibacterial therapy was initiated.

3. 62.4% (63) of the patients received more than one antibacterial drug during the period.
4. The highest frequently used antibacterial was ciprofloxacin 48 (23.3%) followed closely by metronidazole 46 (22.3%) and then by Co-Amoksiclav 40 (19.4%).
5. 83.7% (164) of the used drugs were generic with 16.3% (32) branded.
6. 54.4% of drugs were administered through the parenteral route, 45% through the oral route and 0.6% by the topical route.

Ciprofloxacin was the highest used drug and many of its prescriptions were for 'blind' therapy. Culture and sensitivity test results were hardly used in the selection of antibacterial therapies. The study therefore concluded that antibacterials were mostly used without basis for their choices.

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To my wife and daughter, Victoria and Acelynn.

ACKNOWLEDGEMENT

‘Thanks be to God who always causes us to triumph in Christ Jesus.’ To God be the glory, great things He has done.

My sincere gratitude also goes to my family for the sacrifice made during the long hours spent away from home. To my father, I express my heartfelt gratitude for the foundation he gave. Finally, my special thanks to my supervisor, Dr. Mrs. Frances Owusu- Daaku for her patience and guidance for a successful completion of this work. I am forever grateful.

CHAPTER ONE: LITERATURE REVIEW

1.1 Overview

The use of antimicrobials has contributed to the dramatic fall in morbidity from communicable and infectious diseases over the last 50 years globally, as to increasingly high levels of expenditure on and consumption of antimicrobials. A substantial proportion of the total drug budget in many countries is dedicated to antibiotics and they are often the largest single group of drugs purchased in developing countries[1].

However, despite the vast advancements brought about since the development of antibiotics and antimicrobials, their widespread availability and use have had several negative implications on global health care, among these the inappropriate use by health care providers and consumers and the increase of drug resistance. The primary economic implication of resistance on the diminishing efficacy of antibiotic treatment includes the need to rely on more expensive drugs that may be practically unaffordable for most primary health care programmes.

In developing countries like Ghana, relatively high levels of availability and consumption have led to disproportionately higher incidence of inappropriate use and greater levels of resistance compared to developed countries. These indicate the continuing need to curb the irrational, or inappropriate, use of antimicrobial agents and to identify effective interventions to improve drug use. Inappropriate drug use is characterized by any of the following: over prescription (prescribing drugs when none are needed clinically); omission (when required drugs for certain conditions are not prescribed); the use of inappropriate dosages (too high or too low); incorrect duration (too short or too long); incorrect selection (mismatch between organisms); unnecessary expense (the selection of newer and more expensive drugs when older, cheaper drugs are clinically adequate); and unnecessary risk (use of injections or

intravenous antibiotics when oral forms would be suitable). Participants in drug use decisions include not only clinically trained health care providers, and authorized and other dispensers, but also consumers who engage in self-initiated purchasing of drugs without contact with prescriber or dispenser and the use of drugs left over from previous treatments. For antimicrobials, these characteristics of inappropriate drug use cause particular concern for the development of resistance. There is a strong correlation between inappropriate prescribing and inappropriate self-medication, but generally drug use within these groups is rooted in a complex and multilayered mix of medical, psychosocial, cultural, economic, and even geopolitical factors. Within this complex, a number of factors have been associated with suboptimal use of antibiotics, particularly within the context of prescribing and dispensing health care provider groups. These include insufficient prescriber knowledge about differential diagnosis, the kinds of conditions treatable with antibiotics and appropriate therapies for bacterial infections; patient demands and preferences for treatment, sometimes real, sometimes based on misperceptions by health providers; fear of loss of economic incentives due to patient dissatisfaction arising from non-response to perceived patient demands; fear of negative clinical outcomes in the absence of therapy; influence of social and cultural norms or opinion leaders on practice; promotional pressures of pharmaceutical companies; and wish to maximize profits. To a lesser extent, inadequate drug supply infrastructure, inappropriate or outdated treatment guidelines, lack of access to correct clinical information, and work environment factors also contribute in varying measure to inappropriate use of antibiotics by prescribers and dispensers[2]. Attempts to improve antibiotic use should aim to identify the key factors that promote overuse, such as those described above, and develop interventions that address the identified factors.

1.2 Antibacterial drugs

In a study by Ali M.H et al (2006), titled 'Failure to implement hospital antimicrobial prescribing guidelines: a comparison of two UK academic centres' the authors concluded that there are inadequacies in the implementation and promotion of local guidelines, and demonstrate the potential for widely varying antimicrobial practices in the two comparable UK cities[2]. This shows that prescribers' behaviour towards antibiotic use can be influenced by the environment in which they practise. The Llor C et al (2005) study also emphasised this point. Their research showed the substantial differences in RTI management between the participating GPs. The discrepancies disclosed may indicate dissimilarities in recommendations, traditions, habits, or antibiotic pressures between the counties studied[3]. Many authors on antibiotic use have thus recommended that local guidelines should not only be made but all efforts should be made to make prescribers familiar and easily adapt and use them. This will prevent the variations. In addition, self-medication of antibiotics should not be encouraged. It has been shown in this study that, community pharmacies are failing their task in enhancing rational use of medicines[4]. The study found out that unnecessary and irrational self-medication with antibiotics was common in southern Spain among Finnish immigrants[5]. It was recommended that countries take the responsibility in promoting public health goals in their national policy, for example, in minimising the antibiotic resistance.

The URANO study found out that 19% of patients receive chemotherapy although 42% do not comply with treatment and 29% also self-medicated[6]. The study also recommended like other studies had done, surveillance of antibiotics resistance and improvement in the training of health professionals and health information for patients about risks of self-medication. The author also commented that development of antibiotics resistance was reaching epidemic proportions. Due to increased transportation of persons and goods across continents, some bacterial clones have disseminated over several countries. To increase benefits and reduce

risk, and therefore improve quality of prescription, the rational use of antibiotics should be promoted.

1.2.1 Choice of Antibacterial [7]

Ideally, antibacterial treatment of infections should be chosen after the infecting organisms have been identified and the results of sensitivity tests are known. In practice, empirical treatment is often necessary initially, bearing in mind local patterns of infection and resistance. Other factors such as site of infection and tissue penetration are also important in deciding which antibacterial to give. The prophylactic use of antibacterial agent is restricted mainly to patients undergoing some types of surgery. Other groups requiring infection prophylaxis include patients at special risk of developing endocarditis and those who have had rheumatic fever, or who are immunocompromised.

In selecting an antibacterial, two factors are considered: the patient and the known or likely causative organism. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection, ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking oral contraceptive.

Anaerobic bacteria predominate in the normal microbial flora of man and are a common cause of infections, especially those arising from the gastrointestinal tract, upper respiratory tract, skin, or vagina. Common anaerobic pathogens are *Bacteroides, Prevotella* (formerly non-fragilis *Bacteroides*), *Fusobacterium, Clostridium, Peptostreptococcus, and Actinomyces spp*. Apart from single species infections such as tetanus, gas gangrene, pseudomembranous colitis, and actinomycosis, most anaerobic infections are of mixed aetiology. Abscesses are often a feature. Infections include: brain abscess; acute necrotising gingivitis and other

periodontal infections; chronic otitis media and chronic sinusitis; aspiration pneumonia and lung abscess; peritonitis and intra-abdominal abscess; bacterial vaginosis and pelvic inflammatory disease; cellulitis, ulcers, bites, and other wound infections.

Sensitivity testing in vitro is often impractical and treatment is usually empirical. Benzylpenicillin was traditionally considered the antibacterial of choice when *B. fragilis* was unlikely (infections above the diaphragm) although resistance is increasingly a problem. Antibacterials with activity against the *B. fragilis* group and other anaerobic pathogens include metronidazole and other 5-nitroimidazole derivatives, chloramphenicol, clindamycin, cefoxitin, antipseudomonal penicillins, imipenem-cilastatin, and combinations of a beta lactam and a beta-lactamase inhibitor.

1.2.2 Penicillins

Penicillin was the first antibacterial to be used therapeutically and was originally obtained from the mould *Penicillium notatum*. Better yields were achieved using *P. chrysogenum*. Penicillins are still widely used. Benzylpenicillin can be considered the parent compound of the penicillins and is active mainly against Gram-positive bacteria and *Neisseria spp*. [8]. It is inactivated by penicillinase-producing bacteria and because of its instability in gastric acid it is usually injected. Long-acting preparations include procaine benzylpenicillin and benzathine benzylpenicillin, which slowly release benzylpenicillin after injection. Phenoxymethylpenicillin is acid-stable and is therefore given orally but it is also inactivated by penicillinase. Ampicillin is acid-stable and can be given orally but is destroyed by penicillinase[8]. Amoxicillin differs from ampicillin by the addition of a hydroxyl group. Drugs in this group include ampicillin, bacampicillin, benethamine penicillin, benzathine

benzylpenicillin, benzylpenicillin, cloxacillin, dicloxacillin, flucloxacillin, mecillinam, phenoxymethylpenicillin, piperacillin, pivampicillin, pivmecillinam, procaine benzylpenicillin, propicillin, sulbactam, temocillin, ticarcillin etc. The beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam are used to extend the antimicrobial range of certain beta-lactam antibacterials.

Adverse Effects

The most common adverse effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes; anaphylaxis occasionally occurs and has sometimes been fatal. Gastrointestinal effects such as diarrhoea and nausea are the most common adverse effects after oral use of benzylpenicillin; Pseudomembranous colitis has been associated with the use of most antibiotics; ampicillin or amoxicillin are the most frequently implicated penicillins.

Hypersensitivity to penicillin gives rise to immediate reactions including anaphylaxis, angioedema, urticaria, and some maculopapular rashes. Late reactions may include serum sickness-like reactions and haemolytic anaemia.

Precautions

Patients known to be hypersensitive to penicillins should be given an antibacterial of another class. However, sensitised patients may also react to the cephalosporins and other beta lactams. Penicillins should be given with caution to patients with a history of allergy, especially to drugs [8]. Renal, hepatic, and haematological status should be monitored during prolonged and high-dose therapy. Penicillin therapy changes the normal bacterial flora and can lead to superinfection with penicillin-resistant organisms including *Clostridium difficile* or *Candida*, particularly with prolonged use[8].

Antimicrobial Action

Benzylpenicillin is a beta-lactam antibiotic and has a bactericidal action against Gram-positive bacteria, Gram-negative cocci, some other Gram-negative bacteria, spirochaetes, and actinomycetes.

Mechanism of action: It exerts its killing action on growing and dividing bacteria by inhibiting bacterial cell-wall synthesis, although the mechanisms involved are still not precisely understood. Bacterial cell walls are held rigid and protected against osmotic rupture by peptidoglycan. Benzylpenicillin inhibits the final cross-linking stage of peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins on the inner surface of the bacterial cell membrane. Its action is inhibited by penicillinase and other beta-lactamases that are produced during the growth of certain micro-organisms.

Spectrum of activity[8]

The following pathogenic organisms are usually sensitive to benzylpenicillin:

Gram-positive aerobes and anaerobes including *Bacillus anthracis, Clostridium perfringens, Cl. tetani, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Listeria monocytogenes, Peptostreptococcus spp.,* non-beta-lactamase-producing *staphylococci,* and *streptococci* including *Streptococcus agalactiae , Str. pneumoniae , Str. pyogenes ,* and some *viridans streptococci; enterococc*i are relatively insensitive.

Gram-negative cocci including *Neisseria meningitidis (meningococci)* and *Neisseria gonorrhoeae (gonococci),* although beta-lactamase-producing strains are common.

Gram-negative bacilli including *Pasteurella multocida, Streptobacillus moniliformis,* and *Spirillum minus*; most Gram-negative bacilli, including *Pseudomonas spp.* and *Enterobacteriaceae,* are insensitive although some strains of Proteus mirabilis and Escherichia coli may be inhibited by high concentrations of benzylpenicillin.

Gram-negative anaerobes including non-fragilis *Bacteroides and Fusobacterium spp.*

Other organisms including *Actinomyces* and the *spirochaetes, Borrelia, Leptospira,* and *Treponema spp.* Mycobacteria, fungi, mycoplasmas, and rickettsias are however not sensitive.

Activity with other antimicrobials

Its activity may be enhanced by clavulanic acid and other beta-lactamase inhibitors, and both enhancement and antagonism have been demonstrated for beta-lactam combinations.

Resistance

Susceptible Gram-positive bacteria acquire resistance to beta lactams mainly through the induction of beta-lactamases, including penicillinases. These enzymes are liberated extracellularly and hydrolyse the beta-lactam ring. Most strains of *Haemophilus influenzae and Moraxella catarrhalis* are now resistant. .

Pharmacokinetics

Benzylpenicillin rapidly appears in the blood after intramuscular injection of water-soluble salts, and maximum concentrations are usually reached in 15 to 30 minutes; peak plasma concentrations of about 12micrograms/mL have been reported after single doses of 600mg. The plasma half-life is about 30 minutes and approximately 60% is reported to be bound to plasma protein. Benzylpenicillin is metabolised to a limited extent and the penicilloic acid derivative has been recovered in the urine. Benzylpenicillin is rapidly excreted in the urine, principally by tubular secretion and about 20% of a dose given by mouth appears unchanged in the urine[7].

Uses

Benzylpenicillin is used in the treatment of infections due to susceptible organisms. They include abscess, actinomycosis, anthrax, bites and stings, diphtheria, endocarditis, gas gangrene, leptospirosis, Lyme disease, meningitis, meningococcal infections, pneumonia, skin infections, syphilis tetanus, toxic shock syndrome, and Whipple's disease. It is also used

for surgical infection prophylaxis in first trimester abortion in women at high risk of pelvic infection.

Flucloxacillin

It is bactericidal with a mode of action similar to that of benzylpenicillin, but is resistant to *staphylococcal penicillinase*. It is active therefore against penicillinase-producing and non-penicillinase-producing staphylococci. Its activity against *streptococci* such as *Streptococcus pneumoniae* and *Str. pyogenes* is less than that of benzylpenicillin, but sufficient to be useful when these organisms are present with penicillin-resistant *staphylococci*. Flucloxacillin is virtually ineffective against *Enterococcus faecalis*. The resistance of *staphylococci* to flucloxacillin and other penicillinase-resistant penicillins is described under meticillin.

Flucloxacillin is better absorbed from the gastrointestinal tract than cloxacillin, but absorption is reduced by the presence of food in the stomach[7,21].

Phenoxymethylpenicillin

Phenoxymethylpenicillin has a range of antimicrobial activity similar to that of benzylpenicillin and a similar mode of action. It may be less active against some susceptible organisms, particularly Gram-negative bacteria.

Specific indications for phenoxymethylpenicillin include anthrax, Lyme disease, pharyngitis or tonsillitis, rheumatic fever streptococcal skin infections, and pneumococcal infection prophylaxis.

1.2.3 Cephalosporins

The cephalosporins are semisynthetic antibacterials derived from cephalosporin C, a natural antibacterial produced by the mould *Cephalosporium acremonium*. The active nucleus, 7-aminocephalosporanic acid, is very closely related to the penicillin nucleus, 6-

aminopenicillanic acid, and consists of a beta-lactam ring fused with a 6-membered dihydrothiazine ring and having an acetoxymethyl group at position 3. The cephalosporins are bactericidal and, like the penicillins, they act by inhibiting synthesis of the bacterial cell wall.

Succeeding generations generally have increasing activity against Gram-negative bacteria.

Cefamandole was the first available second-generation cephalosporin. It has similar or slightly less activity than cefalotin against Gram-positive bacteria, but greater stability to hydrolysis by beta lactamases produced by Gram-negative bacteria and enhanced activity against many of the *Enterobacteriaceae* and *Haemophilus influenza* [9].

The third-generation cephalosporins are even more stable to hydrolysis by beta lactamases than cefamandole and cefuroxime. Compared with the earlier generations of cephalosporins they have a wider spectrum and greater potency of activity against Gram-negative organisms, including most clinically important *Enterobacteriaceae*. Their activity against Gram-positive organisms is said to be less than that of the first-generation drugs, but they are very active against streptococci. Ceftazidime is typical of a group of parenteral third-generation cephalosporins with enhanced activity against *Ps. aeruginosa*. Cefoperazone is similar in its activity to ceftazidime. Cefpiramide is structurally related to cefoperazone and has comparable activity. The newer cephalosporins cefepime and cefpirome are generally considered to be fourth-generation because of their broad spectrum of activity.

Ceftriaxone

Ceftriaxone is currently being used widely. It is highly protein bound and is able to displace bilirubin from albumin binding sites, causing hyperbilirubinaemia; its use should be avoided in jaundiced neonates. Neutropenia has been reported with most cephalosporins.

The half-life does not change appreciably in patients with moderate renal impairment, but it may be prolonged in severe impairment especially when there is also hepatic impairment.

Ceftriaxone is widely distributed in body tissues and fluids. It crosses both inflamed and non-inflamed meninges, generally achieving therapeutic concentrations in the CSF. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations are achieved in bile. About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found in the faeces as unchanged drug and microbiologically inactive compounds[10].

Uses and Administration

Ceftriaxone is used for the treatment of susceptible infections. They include chancroid, endocarditis, gastro-enteritis, gonorrhoea, Lyme disease, meningitis (including meningococcal meningitis prophylaxis), pneumonia, septicaemia, syphilis, typhoid fever, and Whipple's disease. It is also used for surgical infection prophylaxis.

The usual adult dose is 1 to 2g daily as a single dose or in two divided doses; in severe infections up to 4g daily may be given. A single intramuscular dose of 250mg is recommended for the treatment of uncomplicated gonorrhoea. For surgical infection prophylaxis, a single dose of 1g may be given 0.5 to 2 hours before surgery; a 2-g dose is suggested before colorectal surgery. For the prevention of secondary cases of meningococcal meningitis, a single intramuscular dose of 250mg may be used for adults and 125mg for children.

A reduction in dosage of ceftriaxone may be necessary in patients with severe renal impairment (creatinine clearance below 10mL/minute), in whom the daily dose should not exceed 2g. In patients undergoing dialysis, and in those with both renal and hepatic impairment, plasma concentrations of ceftriaxone should be monitored to determine whether dose adjustment is needed[9].

Carbapenems

Carbacephems are structurally related to the cephalosporins, but the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by a methylene group.

Imipenem was the first of the carbapenem group of antibacterials to become available. It is bactericidal, and, similarly to the cephalosporins, acts by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of antimicrobial activity including Gram-positive and Gram-negative aerobic and anaerobic organisms; it has good activity against both *Ps. aeruginosa* and *B. fragilis*. Two other carbapenems include ertapenem and meropenem.

The antimicrobial activity of aztreonam, however, differs from imipenem and the newer cephalosporins in that it is restricted to Gram-negative aerobic organisms. It has good activity against *Ps. aeruginosa* [11].

1.2.4 Tetracyclines

The tetracyclines are a group of antibacterials, originally derived from certain Streptomyces spp., having the same tetracyclic nucleus, naphthacene, and similar properties. Unlike the penicillins and aminoglycosides they are usually bacteriostatic at the concentrations achieved in the body but act similarly to the aminoglycosides by interfering with protein synthesis in susceptible organisms.

Tetracyclines all have a broad spectrum of activity which includes Gram-positive and Gram-negative bacteria, chlamydias and chlamydophilas, rickettsias, mycoplasmas, spirochaetes, some mycobacteria, and some protozoa, but the emergence of resistant strains and the

development of other antimicrobials have often reduced their value. Adverse effects have also restricted their usefulness. Gastrointestinal disturbances are common and other important toxic effects include deposition in bones and teeth, precluding their use in pregnancy and young children; anti-anabolic effects, especially in patients with renal impairment; fatty changes in the liver; and photosensitivity, especially with demeclocycline. Allergic reactions are relatively uncommon. Because of these adverse effects tetracyclines should be avoided in pregnant women, children, and, apart from doxycycline and minocycline, patients with renal impairment[12].

Tetracyclines are not generally the antibacterials of choice in Gram-positive or Gram-negative infections because of the emergence of resistant organisms and the discovery of drugs with narrower antimicrobial spectra. However, they have a place in the treatment of chlamydial infections, rickettsial infections such as typhus and the spotted fevers, mycoplasmal infections such as atypical pneumonia, pelvic inflammatory disease, Lyme disease, brucellosis, tularaemia, plague, cholera, periodontal disease, and acne. The tetracyclines have also been useful in the treatment of penicillin-allergic patients suffering from venereal diseases, actinomycosis, bronchitis, and leptospirosis. Minocycline may sometimes be used in multidrug regimens for leprosy. Doxycycline may be used for the treatment and prophylaxis of malaria; it is also used in the management of anthrax.

1.2.5 Aminoglycosides

The aminoglycosides are a closely related group of bactericidal antibacterials derived from bacteria of the genus Streptomyces (framycetin, kanamycin, neomycin, paromomycin, streptomycin, and tobramycin) and the genus Micromonospora (gentamicin).

The aminoglycosides have broadly similar toxicological features[13]. Ototoxicity is a major limitation to their use; streptomycin and gentamicin are generally considered to be more toxic to the vestibular branch of the eighth cranial nerve and neomycin and kanamycin to be more toxic to the auditory branch. Other adverse effects common to the group include nephrotoxicity, neuromuscular blockade, and allergy, including cross-reactivity.

The aminoglycosides have a similar antimicrobial spectrum and appear to act by interfering with bacterial protein synthesis, possibly by binding irreversibly to the 30S and to some extent the 50S portions of the bacterial ribosome. The manner in which they bring about cell death is not fully understood. They are most active against Gram-negative rods. *Staphylococcus aureus* is susceptible to the aminoglycosides but otherwise most Gram-positive bacteria, and also anaerobic bacteria, are naturally resistant. Aminoglycosides show enhanced activity with penicillins against some enterococci and streptococci. Bacterial resistance to streptomycin may occur by mutation, whereas with the other aminoglycosides it is usually associated with the plasmid-mediated production of inactivating enzymes which are capable of phosphorylation, acetylation, or adenylation. Gentamicin has an antimicrobial spectrum very similar to that of gentamicin and is reported to be more active against *Ps. aeruginosa*. Amikacin, a semisynthetic derivative of kanamycin, has a side-chain rendering it less susceptible to inactivating enzymes. It has a spectrum of activity like that of gentamicin but Gram-negative bacteria resistant to gentamicin, tobramycin, and kanamycin are often sensitive.

1.2.6 Macrolides

The macrolides are a large group of antibacterials mainly derived from Streptomyces spp. and having a common macrocyclic lactone ring to which one or more sugars are attached. The macrolides are bacteriostatic or bactericidal, depending on the concentration and the type of micro-organism, and are thought to interfere with bacterial protein synthesis. Their antimicrobial spectrum is similar to that of benzylpenicillin but they are also active against such organisms as *Legionella pneumophila, Mycoplasma pneumoniae,* and some rickettsias, chlamydias, and chlamydophilas. Drugs in this group include azithromycin, clarithromycin, erythromycin, roxithromycin, etc.

Erythromycin is used as an alternative to penicillin in many infections, especially in patients who are allergic to penicillin. It has similar uses to tetracycline in the treatment of infections due to *Mycoplasma pneumoniae* and *Chlamydia trachomatis,* and in acne vulgaris. It is also used in the treatment of infections caused by *Legionella pneumophila*.

These drugs all appear to have similar properties to erythromycin although they may differ in their pharmacokinetics.

Gastrointestinal disturbances are the most frequent adverse effect of azithromycin but are usually mild and less frequent than with erythromycin. Headache, somnolence, and taste disturbances may occur. Severe hypersensitivity reactions occur rarely but may be prolonged. Thrombocytopenia and mild transient neutropenia have been rarely reported in patients receiving azithromycin. Pain and inflammation may occur at the site of intravenous infusions particularly at high concentrations.

Antimicrobial Action

Azithromycin is less active than erythromycin against streptococci and staphylococci, but has greater activity than erythromycin in vitro against some Gram-negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis*, as well as having activity against some of the Enterobacteriaceae such as *Escherichia coli* and *Salmonella* and *Shigella spp*. Azithromycin is also more active than erythromycin against *Chlamydia trachomatis* and *Ureaplasma urealyticum*, and some opportunistic mycobacteria, including Mycobacterium avium complex. It has activity against the protozoa *Toxoplasma gondii* and *Plasmodium falciparum*.

Pharmacokinetics

Azithromycin given orally is rapidly absorbed and about 40% bioavailable. Absorption from capsules, but not tablets or suspension, is reduced by food. Peak plasma concentrations occur 2 to 3 hours after an oral dose and 1 to 2 hours after intravenous dosage. High concentrations are taken up into white blood cells.

Uses and Administration

Azithromycin is a nitrogen-containing macrolide with actions and uses similar to those of erythromycin. It is given in the treatment of respiratory-tract infections (including otitis media), in skin and soft-tissue infections, and in uncomplicated genital infections. It is also used in the management of trachoma and typhoid[14]. Erythromycin and its salts and esters are generally well tolerated and serious adverse effects are rare. Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are fairly common after both oral and parenteral use[13].

Interactions

Erythromycin and other macrolides have the potential to interact with a large number of drugs through their action on hepatic cytochrome P450 isoenzymes, particularly CYP1A2 and CYP3A4. Macrolides inhibit drug metabolism by microsomal cytochromes by competitive inhibition and by the formation of inactive complexes.

1.2.7 Lincosamides

Lincomycin is an antibacterial produced by a strain of Streptomyces. Clindamycin is the 7-chloro-7-deoxy derivative of lincomycin. Lincosamides have similar antimicrobial activity and act at the same site on the bacterial ribosome to suppress protein synthesis.

The lincosamides are bacteriostatic or bactericidal, depending on the concentration, and are active mainly against Gram-positive bacteria, and against *Bacteroides spp*. They also appear to have some antiprotozoal activity. Clindamycin and lincomycin have qualitatively similar activity but clindamycin is more active than lincomycin in vitro. Cross-resistance occurs between the lincosamides, macrolides, and streptogramins.

The lincosamides have been used, like erythromycin, as an alternative to penicillin, but reports of severe and sometimes fatal pseudomembranous colitis in association with lincomycin and clindamycin have led to the recommendation that they should only be used when there is no suitable alternative[15]. Both lincomycin and clindamycin can be given orally and parenterally, but clindamycin is much better absorbed from the gastrointestinal tract and less affected by the presence of food in the stomach. They both penetrate well into bone and have been used successfully in osteomyelitis. They have also been used topically in the

treatment of acne vulgaris. The main indication for the use of lincosamides is now in the treatment of severe anaerobic infections, although metronidazole or some beta lactams may be a more suitable choice in such infections. Clindamycin also has a role in the prophylaxis of endocarditis in penicillin-allergic patients and has been used, usually with other antiprotozoals, in chloroquine-resistant malaria, toxoplasmosis, and pneumocystis pneumonia[16].

1.2.8 Anti-tuberculous drugs

The antimycobacterials are group of antibacterials whose spectrum of activity includes Mycobacterium spp. and which are used in the treatment of tuberculosis, leprosy, and other mycobacterial infections. They include the rifamycins. The main antibacterial in this group, rifampicin, is a mainstay of regimens for the treatment of tuberculosis and leprosy, and is increasingly being used for other infections[17].

Another antimycobacterial widely used for tuberculosis is isoniazid, a derivative of isonicotinic acid; it is invariably used with other drugs to avoid or delay emergence of resistance. Pyrazinamide, a nicotinamide derivative, is also an important component of regimens for tuberculosis, while ethambutol and the aminoglycoside streptomycin are added when resistance to first-line drugs is likely. The thiosemicarbazone derivative thioacetazone is now less widely used in tuberculosis because of its toxicity and because more effective drugs are available, but is sometimes used in developing countries.

Other drugs that have been used to treat tuberculosis including aminosalicylic acid and its salts, capreomycin, cycloserine, ethionamide, protionamide, and kanamycin are regarded as

secondary drugs and are reserved for patients in whom resistance or toxicity to first-line drugs is a problem.

1.2.9 Metronidazole and Tinidazole

Metronidazole

Antimicrobial Action

Metronidazole is active against several protozoa including *Balantidium coli, Blastocystis hominis, Entamoeba histolytica, Giardia intestinalis (Giardia lamblia),* and *Trichomonas vaginalis*. It is bactericidal. It also has activity against the facultative anaerobes Gardnerella vaginalis and Helicobacter pylori and against some spirochaetes. Metronidazole has well established bactericidal activity against obligate anaerobic bacteria in vitro, including the Gram-negative organisms Bacteroides fragilis and other *Bacteroides spp., Fusobacterium spp.,* and the Gram-positive organisms *Clostridium difficile, Cl. perfringens,* and other *Clostridium spp., Eubacterium spp., Peptococcus spp.,* and *Peptostreptococcus spp.; Propionibacterium* and *Actinomyces spp.* are often resistant. It also has activity against the facultative anaerobe Gardnerella vaginalis, although its bactericidal effect is reported to be much slower than against obligate anaerobes, against some strains of *Campylobacter spp.* including *C. fetus*, and against *Helicobacter pylori*.

The oxidative metabolites of metronidazole also have antibacterial activity; the hydroxy metabolite has been reported to be consistently more active than metronidazole against strains of G. vaginalis. The mode of action of metronidazole is not entirely clear, but is thought to involve reduction by bacterial `nitroreductases' to an unstable intermediate which interacts with DNA, effectively preventing further replication. Metronidazole is a 5-nitroimidazole

derivative with activity against anaerobic bacteria and protozoa. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced[18].

Resistance to metronidazole has developed in sensitive species. Although no resistance among the *B. fragilis* group was observed over several years, there have been occasional reports of resistance in this group and in other *Bacteroides spp.*

Metronidazole is readily and almost completely absorbed after oral doses. It also crosses the placenta and rapidly enters the fetal circulation. No more than 20% is bound to plasma proteins[19].

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. Small amounts of reduced metabolites, acetamide and N-(2-hydroxyethyl) oxamic acid (HOA), have also been detected in urine and are probably formed by the intestinal flora.

The elimination half-life of metronidazole is about 8 hours; that of the hydroxy metabolite is slightly longer. The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

Adverse Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastrointestinal disturbances, especially nausea and an unpleasant metallic taste. Vomiting, and diarrhoea or constipation may also occur. Weakness, dizziness, ataxia, headache, drowsiness, insomnia, and changes in mood or mental state such as depression or confusion have also been reported. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures has been associated with high doses of metronidazole or prolonged treatment.

Temporary moderate leucopenia and thrombocytopenia may occur in some patients receiving metronidazole. Skin rashes, urticaria, and pruritus occur occasionally and erythema

multiforme, angioedema, and anaphylaxis have been reported rarely. Other adverse effects include urethral discomfort and darkening of the urine. Raised liver enzyme values, cholestatic hepatitis, and jaundice have occasionally been reported. Thrombophlebitis may follow intravenous use of metronidazole.

Metronidazole is distributed into breast milk giving it a bitter taste which may impair feeding.It is recommended that breast feeding should be stopped for 12 to 24 hours when single-dose therapy is used; no specific recommendations are given for long-term treatment.

Metronidazole is mutagenic in bacteria and carcinogenic in rodents. It readily crosses the placenta achieving similar concentrations in the placental cord and maternal plasma and its use in pregnancy is controversial. Meta-analyses of studies involving the use of metronidazole in the first trimester of pregnancy concluded that there did not appear to be an increased risk of teratogenicity.

Interactions

Metronidazole impairs the metabolism or excretion of several drugs including warfarin, phenytoin, lithium, ciclosporin, and fluorouracil, with the consequent potential for an increased incidence of adverse effects.

Metronidazole may provoke a disulfiram-like reaction in some individuals when given with alcohol; reactions have occurred after the use of preparations formulated with alcohol, including injections, as well as after drinking alcohol[20].

Uses and Administration

Metronidazole is used in the treatment of susceptible protozoal infections such as amoebiasis, balantidiasis, Blastocystis hominis infections, giardiasis, and trichomoniasis; it has also been tried in leishmaniasis and microsporidiosis. Metronidazole is also used in the treatment and prophylaxis of anaerobic bacterial infections. Specific bacterial infections treated with

metronidazole include bacterial vaginosis, acute necrotising ulcerative gingivitis, pelvic inflammatory disease, tetanus, and antibiotic-associated colitis. Metronidazole is used to eradicate Helicobacter pylori in peptic ulcer disease (with other antimicrobials, and either bismuth compounds or proton pump inhibitors) and in the management of malodorous tumours and ulcers where there is anaerobic infection.

For the treatment of most anaerobic bacterial infections, metronidazole is given orally in an initial dose of 800mg followed by 400mg every 8 hours, usually for about 7 days. A regimen of 500mg every 8 hours is alternatively used. For the prevention of postoperative anaerobic bacterial infections, especially in patients undergoing abdominal or gynaecological surgery, metronidazole is given orally, intravenously, or rectally in doses similar to those used for treatment, usually with a beta-lactam or an aminoglycoside antibacterial.

In peptic ulcer disease, metronidazole is used in combination therapy to eradicate Helicobacter pylori[21].

Tinidazole

Tinidazole may produce a disulfiram-like reaction with alcohol. Tinidazole is rapidly and almost completely absorbed after oral doses and, typically, a peak plasma concentration of about 40micrograms/mL is achieved 2 hours after a single 2-g dose, falling to about 10micrograms/mL at 24 hours and 2.5micrograms/mL at 48 hours.

Tinidazole is widely distributed and concentrations similar to those in plasma have been achieved in bile, breast milk, CSF, saliva, and a variety of body tissues; it crosses the placenta readily. Unchanged drug and metabolites are excreted in the urine and, to a lesser extent, in the faeces.

Uses and Administration

Tinidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly .in the treatment of susceptible protozoal infections and in the treatment and prophylaxis of anaerobic bacterial infections. It has also been used in regimens for the eradication of Helicobacter pylori in peptic ulcer disease. Tinidazole is usually given as a single daily oral dose with or after food; it is also given by intravenous infusion and as vaginal pessaries[22].

1.2.10 Quinolones

The quinolonecarboxylic acids, carboxyquinolones, or 4-quinolones are a group of synthetic antibacterials structurally related to nalidixic acid. Nalidixic acid is active against Gram-negative bacteria but has little activity against Pseudomonas and Gram-positive organisms. Because bactericidal concentrations can only be achieved in urine its use has generally been limited to the treatment of urinary-tract infections. The types include ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nadifloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, rufloxacin, sparfloxacin, and trovafloxacin. The fluoroquinolones are very active against aerobic Gram-negative bacilli and cocci including the Enterobacteriaceae, Haemophilus influenzae, Moraxella catarrhalis and Neisseria gonorrhoeae and are also active against Pseudomonas aeruginosa. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as Streptococcus pneumoniae, although some fluoroquinolones now developed have increased activity against these organisms. They also

have activity against mycobacteria, mycoplasmas, and rickettsias. Some, for example ofloxacin, have useful activity against Chlamydia trachomatis. Activity against anaerobic bacteria is generally poor[23]. Drugs in this group include ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, nalidixic acid, norfloxacin, ofloxacin, pefloxacin, sparfloxacin,etc.

Adverse Effects

Ciprofloxacin is generally well tolerated but there are some adverse effects which most often involve the gastrointestinal tract, CNS, or skin. Gastrointestinal disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia and are the most frequent adverse effects. Other adverse effects reported with ciprofloxacin include crystalluria, transient increases in serum creatinine or blood urea nitrogen and, rarely, acute renal failure secondary to interstitial nephritis. Elevated liver enzyme values, jaundice, and hepatitis have occurred, as have haematological disturbances including eosinophilia, leucopenia, thrombocytopenia and, very rarely, pancytopenia, haemolytic anaemia or agranulocytosis. Cardiovascular adverse effects include tachycardia, hypotension, oedema, syncope, hot flushes, and sweating[8].

1.2.11 Other antibacterials

Chloramphenicols

Chloramphenicol has a relatively simple structure and is a derivative of dichloroacetic acid with a nitrobenzene moiety. The sensitivities of *Salmonella typhi, Haemophilus influenzae,* and *Bacteroides fragilis* to chloramphenicol have dictated the principal indications for its use.

Chloramphenicol is widely used for typhoid fever, although resistance is a problem in some countries[24]. For *Haemophilus influenzae* infections, especially meningitis, the emergence of ampicillin-resistant strains led to a reappraisal of the use of chloramphenicol, and suggestions that ampicillin and chloramphenicol should both be given empirically to patients with meningitis until the sensitivity of the infecting organisms was known, but the newer third-generation cephalosporins are increasingly preferred because of resistance. For proven *H. influenzae meningitis*, chloramphenicol is used as an alternative to the third-generation cephalosporins, which are now regarded as treatment of choice. Chloramphenicol is also effective against many anaerobic bacteria and may be valuable in such conditions as cerebral abscess where anaerobes such as *Bacteroides fragilis* are often involved, although metronidazole may be preferred.

Thiamphenicol is a semisynthetic derivative of chloramphenicol in which the nitro group on the benzene ring has been replaced by a methylsulfonyl group, resulting, in general, in a loss of activity in vitro. It has been claimed that thiamphenicol is less toxic than chloramphenicol and there have been fewer reports of aplastic anaemia but reversible bone-marrow depression may occur more frequently. It is also less likely to cause the `grey syndrome'. Unlike chloramphenicol, thiamphenicol is not metabolised in the liver to any extent and is excreted largely unchanged in the urine. It has been used similarly to chloramphenicol in some countries. Thiamphenicol can also be used to treat donovanosis[25].

Sulfonamides and Diaminopyrimidines

The sulfonamides are analogues of p-aminobenzoic acid. The first sulfonamide of clinical importance was Prontosil, an azo dye that is metabolised in vivo to sulfanilamide. Many

sulfonamides have since been synthesised; they differ only slightly in their antimicrobial activity, but vary in their pharmacokinetic properties. The sulfonamides have been classified according to their rate of excretion as short-, medium- or intermediate-, long-, and ultra-long-acting. The sulfonamides are usually bacteriostatic, and interfere with folic acid synthesis of susceptible organisms; their broad spectrum of antimicrobial activity has, however, been limited by the development of resistance. The clinical use of sulfonamides has therefore been greatly reduced; in general they are indicated only in the treatment of urinary-tract infections and a few other disorders such as nocardiosis.

Trimethoprim is a diaminopyrimidine that also inhibits folic acid synthesis but at a different stage in the metabolic pathway to that inhibited by the sulfonamides. It has a similar spectrum of antimicrobial activity to sulfonamides and often shows synergy in vitro with these drugs. Trimethoprim was initially available only in combination with sulfonamides, most commonly with sulfamethoxazole as co-trimoxazole. It is now used alone particularly in the treatment of infections of the urinary and respiratory tracts. Co-trimoxazole generally replaced use of sulfonamides alone in the treatment of systemic infections, although its use has also been restricted in some countries and trimethoprim may be preferred. Co-trimoxazole is however indicated for pneumocystis pneumonia and nocardiosis and may be useful in protozoal infections such as toxoplasmosis. Other sulfonamides which have been combined with trimethoprim include sulfadiazine , sulfamethoxypyridazine, sulfametopyrazine, sulfametrole, and sulfamoxole Sulfonamides have also been used with pyrimethamine in the treatment or prophylaxis of some protozoal infections. Common combinations are sulfadoxine and pyrimethamine for malaria, and sulfadiazine and pyrimethamine for the treatment of toxoplasmosis[26].

Precautions

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of skin rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects. Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Immunocompromised patients

An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in patients with AIDS being treated for Pneumocystis carinii pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS. Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and

hepatitis, may be 80% or more. Adverse reactions also appear to be unusually frequent when prophylactic doses are used[8].

Antimicrobial Action

The actions and spectrum of activity of co-trimoxazole are essentially those of its components, sulfamethoxazole and trimethoprim. Because they act at different points of the folate metabolic pathway a potent synergy exists between its components in vitro with an increase of up to about 10-fold in antibacterial activity, and a frequently bactericidal action where the components individually are generally bacteriostatic. The optimum effect against most organisms is seen at a ratio of 1 part trimethoprim to 20 of sulfamethoxazole; although co-trimoxazole is formulated as a 1 to 5 ratio, differences in the pharmacokinetics of the two drugs mean that the ratio of the peak concentrations is approximately 1:20. However, it is not clear that the optimum ratio is achieved at all sites and, given that both drugs are present in therapeutic concentrations, the contribution of synergy to the effects of co-trimoxazole in vivo is uncertain[27].

Its other uses have included the treatment of acne, biliary-tract infections, brucellosis (generally in combination with other drugs), infections in cystic fibrosis, some forms of AIDS-associated diarrhoea such as the protozoal infection isosporiasis, gonorrhoea, granuloma inguinale, listeriosis, melioidosis, mycetoma, otitis media, pertussis, typhoid and paratyphoid fever, and Whipple's disease. It has also been used for the prophylaxis of infections in immunocompromised patients[28].

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have

been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

Sulfonamide-like skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Disturbances of liver enzyme values and cholestatic jaundice have been associated with trimethoprim. Rises in serum creatinine and blood-urea nitrogen have been reported although it is unclear whether this represents genuine renal dysfunction or inhibition of tubular secretion of creatinine. Photosensitivity has been reported. Fever is not uncommon but occasionally hypersensitivity reactions may be severe and anaphylaxis and angioedema have been reported.

Vancomycin

Vancomycin has a glycopeptide structure; it acts by interfering with bacterial cell wall synthesis and is very active against Gram-positive cocci. Intravenous vancomycin is reserved for the treatment of severe staphylococcal infections and for the treatment and prophylaxis of endocarditis when other antibacterials cannot be used, either because of patient sensitivity or bacterial resistance. It is the treatment of choice for infections caused by meticillin-resistant staphylococci. Vancomycin hydrochloride is poorly absorbed when taken orally.

Adverse Effects

Hypersensitivity reactions may occur in about 5% of patients and include rashes, fever, chills, and rarely, anaphylactoid reactions, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Nephrotoxicity, including rare cases of interstitial

nephritis, may occur, particularly at high doses or in patients with predisposing factors, but has declined in frequency with greater awareness of the problem and appropriate monitoring of plasma concentrations and renal function.

Ototoxicity is also associated with vancomycin, and is more likely in patients with high plasma concentrations, or with renal impairment or pre-existing hearing loss. It may progress after drug withdrawal, and may be irreversible. Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment[26].

Precautions

Because the risk of ototoxicity and nephrotoxicity is thought to be increased at high plasma concentrations it may be desirable to adjust dosage requirements according to plasma-vancomycin concentrations. It has been suggested that dosage should be adjusted to avoid peak plasma concentrations above 30 to 40micrograms/mL and trough concentrations exceeding 10micrograms/mL, although uncertainty about the optimum methods and sampling times for monitoring, as well as some uncertainty about the degree of risk, means that there is less general agreement than for the aminoglycosides. It is generally agreed, however, that vancomycin should be avoided in patients with a history of impaired hearing and that particular care is necessary in patients with renal impairment, in neonates and in the elderly, all of whom may be at increased risk of toxicity. Renal function and blood counts should be monitored regularly in all patients, and monitoring of auditory function is advisable, especially in high-risk patients[26].

Mechanism of action

Vancomycin exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall. Unlike penicillins, which act primarily to prevent the cross-linking of

peptidoglycans which gives the cell wall its strength, vancomycin prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself. Vancomycin may also exert some effects by damaging the cytoplasmic membrane of the protoplast, and by inhibiting bacterial RNA synthesis[8].

Spectrum of activity

Staphylococci, notably *Staph. aureus* and *Staph. epidermidis*, *Streptococcus pneumoniae, Str. pyogenes,* and some strains *of Group B streptococci* are reported to be susceptible to vancomycin. *Clostridium difficile* is usually highly susceptible as are most other *clostridia*. *Actinomyces spp., Bacillus anthracis, Corynebacterium spp., some lactobacilli,* and *Listeria* are usually susceptible. Virtually all Gram-negative organisms, as well as mycobacteria and fungi, are intrinsically resistant.

Pharmacokinetics

Vancomycin is only poorly absorbed from the gastrointestinal tract, although absorption may be somewhat greater when the gastrointestinal tract is inflamed. Infusion of a 1-g dose intravenously over 60 minutes has reportedly been associated with plasma concentrations of up to about 60micrograms/mL immediately after completion of the infusion, and about 25micrograms/mL 2 hours later, falling to under 10micrograms/mL after 11 hours. About 55% is bound to plasma proteins, although large variations have been reported. Vancomycin diffuses into extracellular fluid, including pleural, pericardial, ascitic, and synovial fluid. Small amounts are found in bile. It is reported to cross the placenta. It is also distributed into breast milk. Little or no metabolism of vancomycin is thought to take place. It is excreted unchanged by the kidneys, mostly by glomerular filtration. Some 80 to 90% of the dose is excreted in urine within 24 hours.

Uses and Administration

Vancomycin is a glycopeptide antibiotic that is used in the treatment of serious staphylococcal or other Gram-positive infections when other drugs such as the penicillins cannot be used because of resistance or patient intolerance. It is used particularly in the treatment of meticillin-resistant staphylococcal infections, in conditions such as brain abscess, staphylococcal meningitis, peritonitis associated with continuous ambulatory peritoneal dialysis, and septicaemia. It is used alone, or with another drug such as an aminoglycoside, in the treatment and prophylaxis of endocarditis, for the prophylaxis of surgical infection, and in intensive care and the management of immunocompromised patients. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax.

MUPIROCIN is an antibacterial produced by Pseudomonas fluorescens with activity against most strains of staphylococci and streptococci and also some Gram-negative bacteria[29]. The polymyxins are basic antibacterials produced by the growth of different strains of *Bacillus polymyxa (B. aerosporus). Polymyxin B* and colistin have been used clinically, but their systemic use has been more or less abandoned because of their toxicity, notably to the kidneys and nervous system. They are not absorbed when taken orally and have therefore been given in gastrointestinal infections for their bactericidal activity against Gram-negative bacteria. They continue to be widely used as components of topical preparations. Bacitracin, gramicidin, gramicidin S, and tyrothricin are polypeptide antibacterials also produced by certain strains of *Bacillus spp*. but they are active against Gram-positive bacteria. Like the polymyxins, they are toxic when used systemically and are therefore mainly used topically.

1.3 Antibacterial Policy[30]

There are local policies in institutions that should guide the use of antibacterials. However the following precepts should be considered before starting:

- Viral infections should not be treated with antibacterials. However, antibacterials are occasionally helpful in controlling secondary bacterial infection
- Samples should be taken for culture and sensitivity testing; 'blind' antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- Knowledge of prevalent organisms and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available;
- The dose of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection. An inadequate dose may increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- The route of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate. Whenever possible, painful intramuscular injections should be avoided in children;

- Duration of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly.

1.4 Resistance

Resistance is not a new phenomenon; it was recognized early as a scientific curiosity and then as a threat to effective treatment outcome. Resistance costs money, livelihoods and lives and threatens to undermine the effectiveness of health delivery programmes. It has recently been described as a threat to global stability and national security. A few studies have suggested that resistant clones can be replaced by susceptible ones; in general, however, resistance is slow to reverse or is irreversible[31].

Antimicrobial use is the key driver of resistance. Paradoxically this selective pressure comes from a combination of overuse in many parts of the world, particularly for minor infections, misuse due to lack of access to appropriate treatment and underuse due to lack of financial support to complete treatment courses. Resistance is only just beginning to be considered as a societal issue and, in economic terms, as a negative externality in the health care context. Individual decisions to use antimicrobials (taken by the consumer alone or by the decision-making combination of health care worker and patient) often ignore the societal perspective and the perspective of the health service.

The World Health Assembly Resolution of 1981 urged Member States to develop measures to encourage appropriate and cost-effective use of antimicrobials, to prohibit the dispensing of antimicrobials without the prescription of a qualified health care professional, to improve

practices to prevent the spread of infection and thereby the spread of resistant pathogens, to strengthen legislation to prevent the manufacture, sale and distribution of counterfeit antimicrobials and the sale of antimicrobials on the informal market, and to reduce the use of antimicrobials in food animal production. Countries were also encouraged to develop sustainable systems to detect resistant pathogens, to monitor volumes and patterns of use of antimicrobials and the impact of control measures[31].

1.5 The Research Problem

Inappropriate use of antimicrobial agents has been found to be common in various parts of the world, especially in developing countries[32]. There are more findings needed to address the challenging issues on the use of these agents and how they affect the health of the nation. The Surgical and Medical Emergency Unit, in a tertiary institution, Korlebu Teaching Hospital, is a very important one in the delivery of quality services in Ghana since it is the first point of most final referrals from other institutions. Consequently, its use of antimicrobial drugs should always conform to clearly documented policies to prevent resistance and enhance health care delivery.

1.6 Research Objectives

The objectives of the study include

1. The demographic distribution of patients
2. The different types of infectious diseases occurring
3. The percentage of requested and undertook Culture and Sensitivity tests
4. The percentage of changed prescriptions when the culture and sensitivity tests results are seen by physicians and recorded
5. The most frequently used antibacterial drug and the different types of dosage forms used
6. The percentage of branded and generic agents frequently used

CHAPTER TWO : RESEARCH METHODOLOGY

2.1 Setting

The Surgical and Medical Emergency unit (SME) of the Korlebu Teaching Hospital is the non-trauma emergency admission unit of the hospital and a major entry point. It has a high turn over rate of patients and is always congested. It has one male ward and two female wards with a total of 65 beds. The average intake for 2007 was 25 new cases daily. SME received a total of 9802 patients in 2008[33].

2.2 Methodology

A prospective study of patients admitted at the three wards of the Surgical and Medical Emergency Unit was undertaken from 14th January 2009 to 14th March 2009. Data Collection Sheets (appendix 1) were used to collect data from patients' medical records while on admission over the period. Patients' records were reviewed once daily for 5 days until they were transferred to other units, discharged or died. Data analysis was done using SPSS and MS Excel.

2.3 Inclusion criteria

Patients admitted at any of the three wards of the S.M.E unit receiving antibacterial drugs during the period.

2.4 Exclusion criteria

1. Patients that were seen at the Unit but were not admitted.
2. Patients whose medical records were not available throughout the period.
3. Patients who deserted their wards

2.5 Pilot Study

A pilot study was conducted to determine the clarity and reliability of the data collection sheet, to test the internal reliability of the measures used in this study and to discover any discrepant issues relating to the wording and administration of the instrument. Five randomly selected patients who were on admission at the wards were used in the pilot study. It was realised that weights of patients admitted at the unit were not measured and recorded in their medical records. It was also important to obtain data on the average number of days patients spent on admission. This was to inform the decision to set a cut-off point to exclude those patients who exceed such.

2.6 Results

2.6.1 Section A: Demography of Patients

N=101

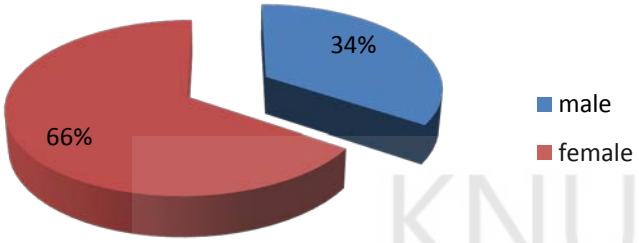


Figure 2.1. Sex Distribution

Table 2.1. Age Distribution

Age(yrs)	<21	21-40	41-60	>60
Frequency	9	41	33	18

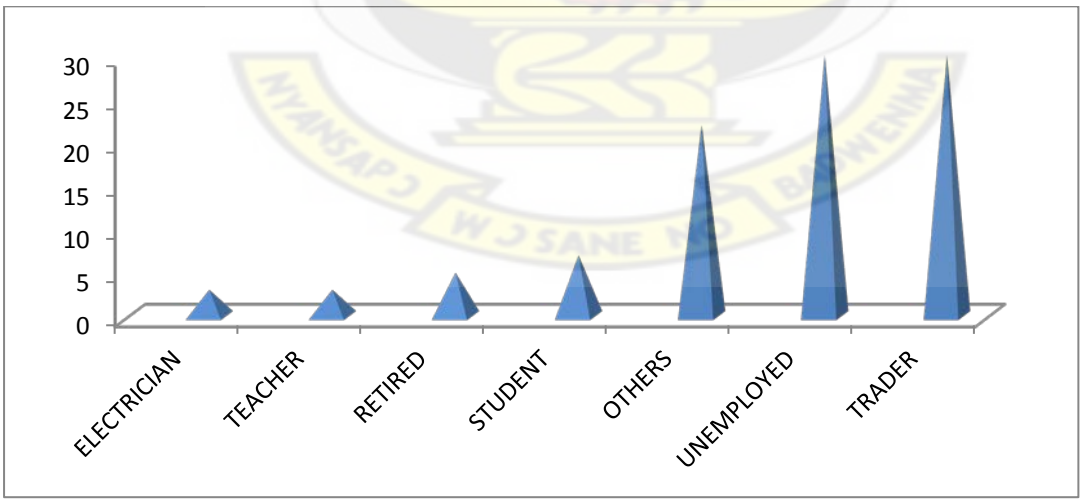


Figure 2.2 Occupation types

(Others include: accountant, researcher, footballer, waiter, managress, fishmonger, housewife, orderly, administrator, draughtman, farmer, driver, apprentice, credit officer, carpenter, foreman computer technician, business executive and secretary)

2.6.2 Section B: Infectious Disease and other co-morbid conditions

Classifications

a. Infections e.g pneumonia, meningitis, respiratory tract infections, etc
b. Cardiovascular (CVS) e.g hypertension, congestive cardiac failure, hemiplegias,etc
c. Diabetes Mellitus and glycaemic disorders (DM) e.g hyperglycaemia
d. Respiratory e.g asthma and chronic obstructive pulmonary disease
e. Malaria
f. Malignant diseases
g. Anaemia
h. Others including gastro-intestinal disorders, endocrine disorders, central system disorders,etc

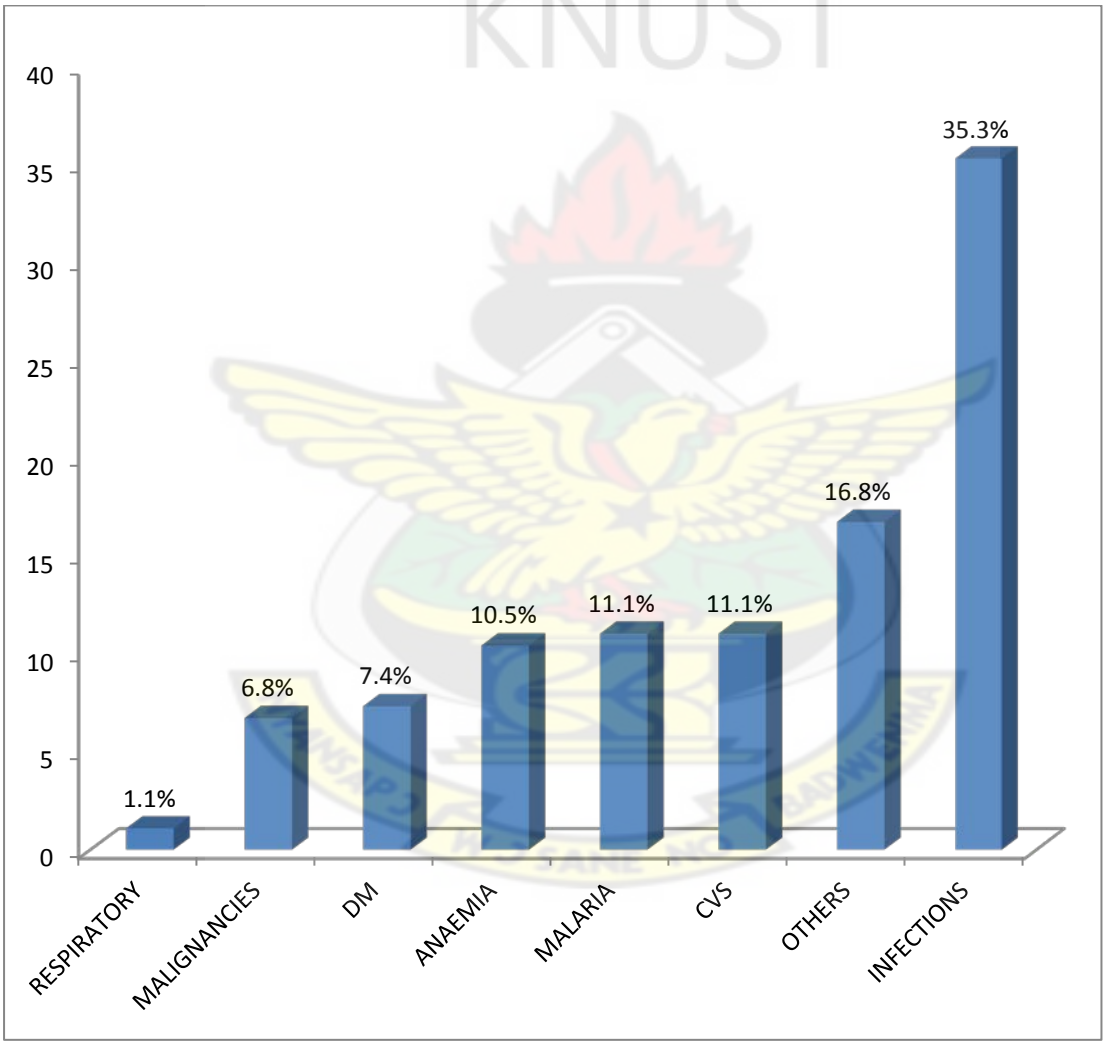


Figure 2.3 Infectious Disease and other co-morbid conditions

The various infectious diseases recorded and their degrees of occurrences were as follows:

Table 2.2 Infectious Diseases and the Frequencies of their Occurrence

Types of infectious disease	**Occurrence**	**Percentage**
Pyelonephritis	6	6%
Gastroenteritis	11	11%
Urinary Tract Infections	12	12%
Peritonitis	3	3%
Septicaemia	10	10%
Enteric Fever	10	10%
Pelvic Inflammatory Disease	11	11%
Meningitis	4	4%
Pneumonia	23	22%
Tuberculosis	9	9%
Cellulitis	2	2%
Appendicitis	1	1%
Endocarditis	1	1%

2.6.3 Section C: Culture and Sensitivity test

1. Of the number that had Culture and Sensitivity test requested by the prescriber, 39 (39%), only 2 (5.1 %) had their results before antibacterial therapy was initiated
2. Moreover, of the number that had Culture and Sensitivity test requested by the prescriber, 39 (39%), only 3(7.7%) of them had their results seen at all by their physicians during the period.
3. Of the number 3(7.7%) that had their results seen at all by their physicians during the period, only 1 of them changed the therapies of those patients.

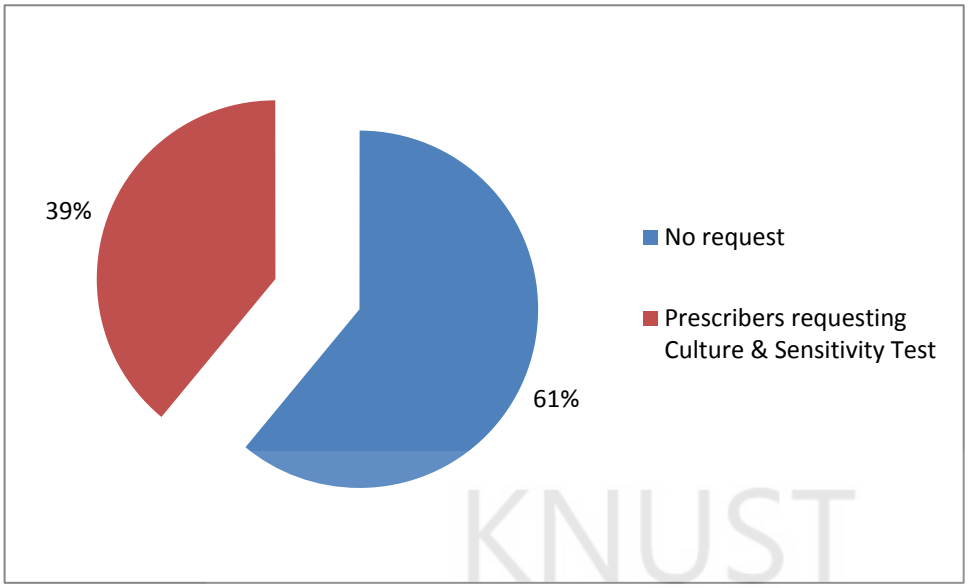


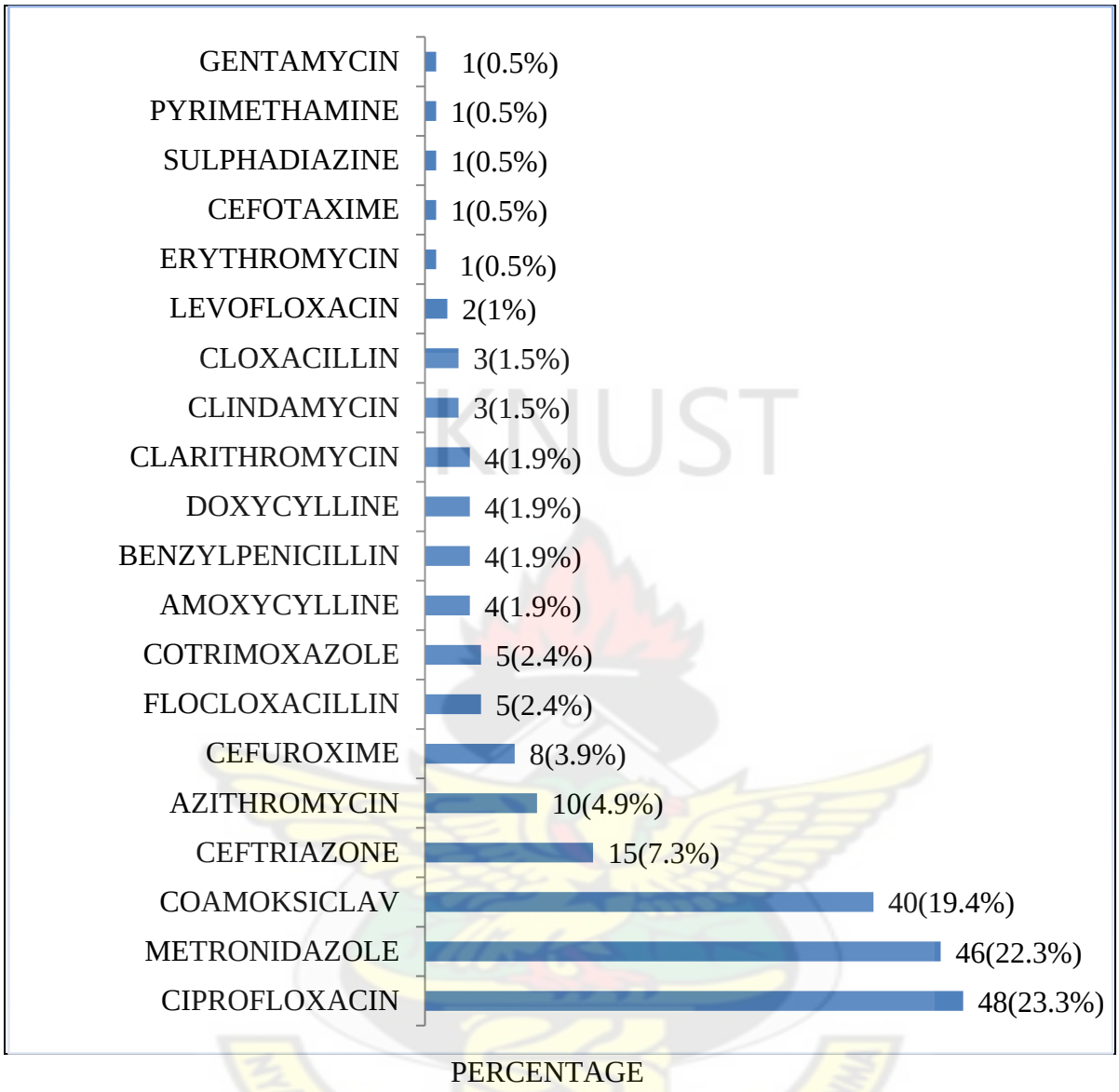
Figure 2.4 Requesting Culture and Sensitivity test

2.6.4 Section D: Antibacterial Usage

Table 2.3 Prescriptions with two antibacterial drugs

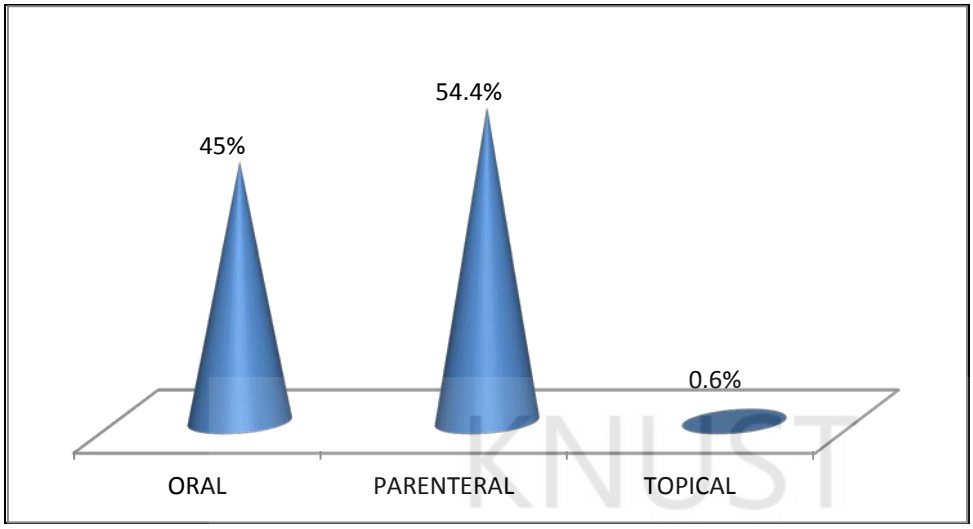
DRUG	NUMBER	(%)
CIPROFLOXACIN AND METRONIDAZOLE	44	32
METRONIDAZOLE AND COAMOKSICLAV	36	26
METRONIDAZOLE AND CEFTRIAZONE	13	10
CIPROFLOXACIN AND COAMOKSICLAV	7	5
METRONIDAZOLE AND AZITHROMYCIN	8	6
OTHER COMBINATIONS	28	21

Figure 2.5 Pattern of antibacterial drug use



1. 62.4% (63) of the patients received more than one antibacterial drug during the period.
2. The highest frequently used antibacterial was ciprofloxacin 48 (23.3%) followed closely by metronidazole 46 (22.3%) and then by Co-Amoksiclav 40 (19.4%).
3. 32% (44) of the patients received both ciprofloxacin and metronidazole together during the period.

Figure 2.6 Dosage Forms



Generic Prescribing

83.7% (164) of the used drugs were generic with 16.3% (32) branded. Of the branded, 93.7% (30) was for a brand of Co-Amoksiclav (Augmentin) and the rest 6.3% (2) was for a brand of Levofloxacin (Tavanic).

CHAPTER THREE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

3.1 Discussion

Introduction

Most patients were in the age group of between 21-40 years with females in the majority, representing 66%. This could be to the fact that the unit has two female wards and only one male. This result also compares with most research work done in the hospital[33]. The majority were workers 70% and the rest were unemployed.

Weight

The study showed that weights of patients admitted at the unit were not taken. Weights of patients are sometimes used in determining doses of some antibacterial drugs[30]. It is therefore essential for weights of patients to be measured.

Diseases Presented

Infectious diseases were the highest recorded (35.3%) during the study. This could be so because the study looked at antibacterials. However, the majority (74.7%) of the patients had other conditions other than infections but still received antibacterial drugs. These were Cardiovascular diseases, Diabetes Melitus, Respiratory Diseases, Malaria, malignancies, anaemia etc . Of the infectious diseases recorded, pneumonia was the highest.

Culture and Sensitivity(C/S) Test

C/S test included samples of urine, blood, sputum, ear, throat, wound and cerebrospinal fluid. It is recommended that in emergency situations, an antibacterial could be started based on the known or likely organism and its antibacterial sensitivity and then a final choice made depending on the microbiological properties[30]. The study confirmed the practice and only

5.1% received the C/S results before antibacterial therapy were initiated. Consequently, the majority (61%) of physicians did not request for C/S test at all though they initiated antibacterial therapy. This was against the recommendations and showed no basis for antibacterial use. In addition, results of majority (92.3%) of those that physicians requested C/S for, were not seen at all during the period. This could be attributed to the fact that the unit does not have its own laboratory facilities. Samples taken are sometimes left in the care of relatives to get the tests done outside the unit and results are only expected not earlier than 48 hours later.

Antibacterial Drugs Use

The study showed that the highly used antibacterial was ciprofloxacin followed by metronidazole. Ciprofloxacin and metronidazole have been the drug of choice for first line 'blind' treatment in both prophylaxis and treatment. This practice is of great concern to many health care professionals in the hospital because of the development of resistance. It is recommended that ciprofloxacin be reserved for the indications that it is specific for and not for 'blind' prophylaxis use[30].

The study also showed that the majority of the prescriptions were in parenteral forms. This conforms to protocols for managing severe acute infectious diseases which are mostly seen at the unit the study took place[34]. The majority of prescriptions were in generic forms but a few of prescribers are still prescribing branded products. Further studies would have to be performed to find out the reasons and prescribers should be encouraged to stop.

Importance of Findings

The importance of these findings cannot be overemphasised since the appropriate use of antibacterial drugs is very essential in avoiding resistance and achieving quality health care. It will also inform health care authorities on the compliance of practitioners to policies.

Comparisons with similar studies

A similar study was done in the medical wards of a university hospital, Bangkok, Thailand showed similar results of the use of antibacterials without evidence of infection. The Bangkok study also estimated the loss of $40,000 to the medical wards alone for that year[34].

Another survey of drug use practices and antibiotic prescribing pattern at a general hospital in Nigeria revealed that appreciable gaps in knowledge with respect to rational drug use, still exists among these cadre of healthcare professionals. It suggested an urgent need for review of current policies and systems in the hospital with the view of enhancing the drug use practices of the health providers[1].

3.2 Limitations

The study could not cover all patients receiving antibacterials who were seen at the unit. Some patients were seen, treated at other parts of the unit and discharged within 24 hours without being admitted at the wards. Further studies should be carried out, more comprehensively with more data collectors to provide a larger coverage. Moreover, the study could not determine the possible reasons why physicians do not probe for microbiological basis for their use of antibacterials and also why those requested could not be done.

CONCLUSIONS

The research questions posed concerning the pattern of antibacterial drug use have been fully answered. Ciprofloxacin was the highest used drug, followed by metronidazole, coamoksiclav, ceftriazone, azithromycin, cefuroxime, cotrimoxazole, and flucloxacillin, in that order. Many of the prescriptions were for 'blind' therapy. Culture and sensitivity test results were hardly used in the selection of antibacterial therapies. The study therefore concluded that antibacterials were used without sufficient basis for their choice.

RECOMMENDATIONS

1. Prescribers of antibacterial drugs should be continually reminded by hospital authorities through training of the need to abide by policies.
2. There is the need for the Surgical and Medical Emergency Unit to get its own laboratory facility to facilitate the performance of Culture and Sensitivity Tests.
3. There is the need for more studies on antibacterial drug use to inform the review of the policy on the management of infectious diseases.
4. The economic loss of poor antibacterial drug use can also be determined in future studies.

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3.5 Appendix 1

DATA COLLECTION SHEET

A. PERSONAL DETAILS

INITIALS ☐ **FOLDER NUMBER** ☐

AGE ☐ **WEIGHT** (Kg) ☐ **OCCUPATION** ☐

SEX M ☐ **F** ☐

DATE OF ADMISSION ☐ **TEAM** ☐

B. MEDICAL PROBLEM(S)

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C. CULTURE AND SENSITIVITY

1. Was culture and sensitivity test requested? YES ☐ NO ☐
2. Were the results seen before antibacterial therapy YES ☐ NO ☐
3. When the results were seen, was the therapy altered? YES ☐ NO ☐

4. Has the results been seen at all by a physician and recorded during the period?

YES ☐ NO ☐

D. ANTIBACTERIAL USAGE

NAME	**DOSAGE FORM**	**TYPE** B/G	**DOSAGE**	**COMMENTS**

4.6 Appendix 2

DATA COLLECTION MONITORING SHEET

DATA..... DATA COLLECTOR.....

PATIENT	WARD	DATE OF ADMISSION	DATE OF DISCHARGE