

**Prescribing patterns in adult patients with meningitis in internal medicine
wards, Dr George Mukhari Hospital**

A dissertation submitted by

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DECLARATION

I, **Wandisile Grootboom**, hereby declare that the work on which this study is based is original, except where acknowledgements indicate otherwise.

This dissertation is submitted for the degree Master of Science (Medical) in Pharmacy at the University of Limpopo. Neither the whole work nor any part of it has been before any degree or examination at this or any other university.

Signed

.....on the.....day of

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Even youths grow tired and weary, and young men stumble and fall; but those who hope in the LORD will renew their strength. They will soar on wings like eagles; they will run and not grow weary, they will walk and not faint (Isaiah 40:30:31).

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SUMMARY

Background

Information regarding disease epidemiology, treatment options and emerging infections and resistance constantly challenge the knowledge of the health care practitioner. Antibiotic prescribing patterns was identified by the Dr George Mukhari hospital antibiotics committee as an area of concern. Due to this concern it was decided to investigate the prescribing patterns in adult patients with meningitis admitted to the internal medicine wards at Dr George Mukhari hospital.

Objectives

To determine the current antimicrobial prescribing patterns in adult patients diagnosed with meningitis, to record the causative organisms and sensitivity patterns, to record the outcome, cost and length of treatment.

Method

Patient and prescriptions data were recorded prospectively on specially designed data sheets from five internal medicine wards for four months (May to August 2008). Patients were followed until discharged.

Results

Sixty-six patients were enrolled; 41 recovered, 22 died, 2 refused treatment and 1 absconded.

Ceftriaxone was prescribed the most frequently and was administered to 58 patients; four patients with confirmed cryptococcal meningitis received amphotericin B IVI, three patients were started on

Rifabutin® for suspected tuberculosis meningitis and one was started on cefuroxime. Specimens from only 22 patients were sent for culture and sensitivity tests; ten were positive for yeast-like organisms, three for *S pneumoniae* and one for *N meningitidis* and tuberculosis respectively.

The average duration of treatment of patients with meningitis was 9.2days. The total cost of anti-infectives used for treatment of meningitis amounted to R111, 292.53 and the average cost per patient was R1 686.25. The cost of all medicines prescribed for the 66 patients amounted to R116, 490.43.

Conclusion

Ceftriaxone was used frequently as empiric therapy. Specimens for culture and sensitivity were not sent routinely. Therefore it was difficult to monitor and observe any resistance patterns and to contain cost of treatment.

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CHAPTER 1: INTRODUCTION

Meningitis is one of the major causes of morbidity and mortality around the world. Hearing impairment, obstructive hydrocephalus and damage to the brain parenchyma are common neurological sequelae from meningitis (Leib and Täuber, 1999).

According to DiPiro *et al.*, (1997) Different types of meningitis have been identified; “purulent” (bacterial aetiology) and “aseptic” (acute meningeal irritation, usually benign and self-limiting, with complete recovery and sterile pleocytic CSF and at least 70% are caused by viruses). Most cases of meningitis are due to infection with viruses, followed by bacteria, fungi, and parasites (Helbok *et al.*, 2009). Viruses that can cause meningitis include various enterovirus subtypes, herpes simplex virus 2 (and less commonly HSV-1), *Varicella zoster* virus (known for causing chickenpox and shingles), mumps virus and HIV. The types of bacteria that cause bacterial meningitis vary by age group. In premature and newborn babies up to three months, common bacteria are group B streptococcus (subtype III)—especially in the first week of life—and bacteria that normally inhabit the digestive tract such as *Escherichia coli* (carrying K1 antigen). *Listeria monocytogenes* (serotype IVb) may affect the newborn and occurs in epidemics. Older children are more commonly affected by *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (serotypes 6, 9, 14, 18 and 23) and those under five by *Haemophilus influenzae* type B. In adults, *N. meningitidis* and *S. pneumoniae* together cause 80% of all cases of meningitis, with increased risk of *L. monocytogenes* in those over 50. In trauma, neurosurgery, or other contact between the skin and the meninges, staphylococci are more likely, as well as infections with pseudomonas and related Gram-negative bacilli. The same pathogens are also more common in those with an impaired immune system. Tuberculous meningitis due to infection with *Mycobacterium tuberculosis*, is more common in those from countries where tuberculosis is common, but is also encountered in those with immune deficiencies, such as AIDS (Katti, 2004).

According to (Steele, 2002) *Streptococcus pneumoniae* is the most frequent cause of meningitis in the United States, accounting for 47% of all cases, followed by *Neisseria meningitides*, the meningococcus (25%), group B streptococcus (12%), *Listeria monocytogenes* (8%), and *Haemophilus influenzae* (7%). The pneumococcus continues to exhibit the highest mortality and morbidity rates among these more common bacterial causes of meningitis, with a 4% to 16% mortality rate in children and a substantially higher rate in adults. Death is the result in more than half of the elderly adults (older than 70 years of age) infected with pneumococcal meningitis. *S pneumoniae* strains that are non-susceptible to penicillin and third-generation cephalosporins (i.e., ceftriaxone and cefotaxime) have been identified worldwide, with as many as 8% of pneumococci demonstrating this multiresistant pattern in some regions

Meningitis and intracranial tuberculoma are types of tuberculosis (TB) infection of the central nervous system (CNS). These types of infections are seen in regions where the incidence of tuberculosis is high and there is a prevalence of dissemination after primary TB infection. Treatment of CNS tuberculosis should begin as soon as possible when clinically suspected because patient outcome is improved when therapy is begun in the early stage of disease. For all types of CNS tuberculosis, treatment should begin with a combination of bactericidal drugs that penetrate the CSF (Katti, 2004; Be *et al.*, 2009).

The first line of therapy should include isoniazid (INH), rifampicin, and pyrazinamide, all of which are bactericidal and achieve effective levels in the CSF. Pyrazinamide is given with INH and rifampicin during the first 2 months of therapy, and then is stopped. A fourth drug should be used during the first 2 months of therapy when INH drug resistance is a concern. Drug resistance is a concern if the region has more than a 4% INH resistance rate, if the patient has received prior antituberculosis therapy, or if the patient has been exposed to a resistant case. Ethambutol or streptomycin are the medications recommended as the fourth agent. Ethambutol has moderate CSF penetration and streptomycin has

poor penetration, so it has been given as a combination of intramuscular and intrathecal delivery (Steele, 2002).

Pharmacotherapy in infectious diseases is constantly changing. The change is affected by the constant change in pathogen resistance to therapy and emerging infections (Drew *et al.*, 2004). The principles of antimicrobial therapy for acute meningitis include use of agents that penetrate well into cerebrospinal fluid and attain appropriate cerebrospinal fluid concentrations, are active in purulent cerebrospinal fluid, and are susceptible against the infecting pathogen.

In the hospital where the study was conducted certain antimicrobials were used for the treatment of various causes of meningitis. The guidelines of neurology department (2004) state that acute bacterial meningitis be treated with cefotaxime 3g 6hourly IV or ceftriaxone 2g 12 hourly IV. Meningococcal meningitis is treated with benzyl penicillin 6 million units 6 hourly IV for 10 days. Cefotaxime 3g 6 hourly IV or ceftriaxone 2g 12 hourly IV would also be effective. Pneumococcal meningitis, if it is penicillin sensitive is treated with benzyl penicillin 6 million units 6 hourly IV for 14 days or ceftriaxone 2g 12 hourly IV. If penicillin resistant, it is treated with cefotaxime 3g 6 hourly IV for 14 days or ceftriaxone 2g 12 hourly IV for 14 days. In practice meningococcal meningitis was treated with ceftriaxone 2g 12 hourly IV for 13 days in one case while pneumococcal meningitis with culture resistant to penicillin was treated with ceftriaxone 2g 12 hourly IV for 15 days in one case and for 16 days in another case. The current practice is therefore showing deviation from the hospital treatment guidelines. The hospital antibiotics committee has had concerns about the usage of antibiotics and their prescribing patterns in the hospital, hence the study. This study was therefore designed to determine the prescribing patterns for adult patients with meningitis in the medical wards of Dr. George Mukhari Hospital. The specific objectives were to record the prescribing patterns in patients diagnosed with meningitis, to record the

causative organisms and sensitivity patterns, to record the outcome of treatment, to determine the treatment cost, and to determine the length of treatment.

The following chapter will deal with the literature review.

CHAPTER 2: LITERATURE REVIEW

2.1 Meningitis

2.1.1 Epidemiology

Victor and Ropper (2001) state that pneumococcal, influenzal (*Haemophilus influenza*), and meningococcal forms of meningitis have a worldwide distribution, occurring mainly during the fall, winter, and spring and predominating in males. Each has a relatively constant yearly incidence, although epidemics of meningococcal meningitis seem to occur roughly in 10-year cycles. Drug-resistant strains occur with varying frequency. *H. influenzae* meningitis, formerly encountered mainly in infants and young children, has been nearly eliminated in this age group as a result of vaccination programmes in developed countries. It continues to be common in less developed nations and is now occurring with increasing frequency in adults. *Meningococcal meningitis* occurs mostly in children and adolescents but is also encountered throughout much of adult life, with a sharp decline in incidence after the age of 50. *Pneumococcal meningitis* predominates in the very young and in older adults. Perhaps the greatest change in the epidemiology of bacterial meningitis, aside from the one related to *H. influenza* vaccination, has been the increasing incidence of nosocomial infections. Gram-negative bacilli and *Staphylococcus spp.* account for a large proportion of these. The yearly incidence rate (per 100,000) of the responsible pathogens is as follows: *Streptococcus pneumoniae*, 1.1; *Nisseria meningitidis*, 0.6; group B streptococcus, 0.3; *Listeria monocytogenes*, 0.2; and *H. influenzae*, 0.2.

According to Miller (2008) meningitis is an inflammation of the leptomeninges and underlying subarachnoid cerebrospinal fluid (CSF). It can be useful to divide symptom onset into acute, sub-acute, and chronic categories. Unlike sub-acute (1-7 days) or chronic (>7 days) meningitis, which have myriad

infectious and non-infectious aetiologies, acute meningitis (<24 hours) is almost always a bacterial infection caused by one of several organisms. Depending on age and general condition, these gravely ill patients present acutely with signs and symptoms of meningeal inflammation and systemic infection of less than 1 day's duration. Patients may deteriorate quickly and require emergency care, including antimicrobial therapy, within 30 minutes of emergency department (ED) presentation.

2.1.2 Pathogenesis and pathophysiology

To cause disease, the pathogen must, in the absence of a neurosurgical procedure or CSF leak, colonise the nasopharynx, traverse the nasopharynx into the blood stream, survive host defence mechanisms in the intravascular space, invade the blood-brain barrier (BBB), and survive and replicate in the subarachnoid space, producing disease. Various cell wall products of meningeal pathogens are well-known inducers of the inflammatory host responses. The inflammatory response in the subarachnoid space characteristic of acute purulent meningitis can be reproduced by the intracisternal challenge with whole heat-killed unencapsulated pneumococci, their isolated cell walls, lipoteichoic acid, or peptidoglycan, but not by the injection of heat-killed encapsulated strains or isolated capsular polysaccharide. For meningeal pathogens, the major inflammatory stimuli are lipopolysaccharide (LPS) and peptidoglycan for Gram-negative and Gram-positive organisms, respectively. Multiple cytokines play an important regulatory role in the control of inflammation (Trunkel and Scheld, 1996).

2.2 Bacterial meningitis

2.2.1 Clinical presentation

According to Razonable *et al.*, (2007) depending on the duration of symptoms, meningitis may be classified as acute or chronic. Mehlhorn and Sucher (2005) have pointed out that adults with meningitis

typically present with the classic triad of fever, neck stiffness and altered mental status. Other symptoms are headache, photophobia, nausea and vomiting, rash, and seizures. It was found that only 44% with meningitis presented with the triad of symptoms (indicating a low sensitivity), while 95% had at least two of four symptoms: fever, neck stiffness, altered mental status, and/ or headache. Infants often have nonspecific symptoms, e.g., irritability, crying, vomiting, seizures, or altered sleeping or eating patterns.

2.2.2 Aetiology

According to Trunkel and Scheld, (1996), Victor and Ropper (2001) and Beers and Berkow (2005) almost any bacterium gaining entrance to the body may produce meningitis, but, as already noted, by far the most common are *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, which account for about 75% of sporadic cases. Infection with *L. monocytogenes* is now the fourth common type of nontraumatic or nonsurgical bacterial meningitis in adults. The following are less frequent causes: *Staphylococcus aureus* and group A and group D streptococci, usually in association with brain abscess, head trauma, neurosurgical procedures or cranial thrombophlebitis; *E. coli* and group B streptococci in newborns; and the other *Enterobacteriaceae* such as *Klebsiella*, *Proteus*, and *Pseudomonas*, which are usually a consequence of lumbar puncture, spinal anaesthesia, or shunting procedures to relieve hydrocephalus. Rarer meningeal pathogens include *Salmonella*, *Shigella*, *Clostridium*, *Nisseria gonorrhoeae*, and *Acinetobacter calcoaceticus*, which may be difficult to distinguish from *Haemophilus* and *Neisseria*. In endemic areas, mycobacterial infections are as frequent as those due to other bacterial organisms. They have also assumed greater importance in developed countries as the number of immunosuppressed persons increases.

Kam *et al.*, (1995) in their study conducted in Hong Kong from January 1993 to May 1995 analysing two hundred and four strains of *Streptococcus pneumoniae* for their antibiotic susceptibilities and epidemiological patterns pointed out that emergence of multiple- antibiotic- resistant *S. pneumoniae* reflects recent changes in the pneumococcus itself and the general indiscriminate use of antibiotics in treatment of respiratory infections in Hong Kong. In the South East Asian region, the recent report of a penicillin resistance rate of 70% in Korea was one of the highest reported to date.

Canada Communicable Disease report (1997) states, 'the prevalence of isolates of *S. pneumoniae* with intermediate or high resistance to penicillin varies worldwide. Some of the highest incidences of these isolates have been reported from Spain (51%), Hungary (57, 8%), South Africa (62, 2%) and Korea (70%).'

2.2.3 Diagnosis

The suspicion of meningitis is generally based on the nature of the symptoms and findings on physical examination. According to Trunkel and Scheld (1996) meningitis is a medical condition that is caused by inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The inflammation is usually caused by infection with viruses, bacteria, or other microorganisms but may also arise due to certain drugs, or other diseases. Meningitis is potentially life threatening due to the inflammation's proximity to the brain and spinal cord; it is therefore a medical emergency. The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, and an inability to tolerate bright light (photophobia) or loud noises (phonophobia). Sometimes, especially in small children, only nonspecific symptoms may be present, such as irritability and drowsiness. If a rash is present, it may indicate a particular cause of

meningitis; for instance, meningitis caused by meningococcus bacteria may be accompanied by a characteristic rash.

Meningitis is a medical emergency, and referral to hospital is indicated. Investigations include blood tests and usually X-ray examination of the chest. The most important test in identifying or ruling out meningitis is analysis of the cerebrospinal fluid. However, if the patient is at risk for a cerebral mass lesion or elevated intracranial herniation, in such cases CT or MRI scan is generally performed prior to the lumbar puncture to exclude this possibility (Lazoff, 2007).

According to Roos (2005) the opening pressure is elevated and the CSF appears cloudy in patients with bacterial meningitis. In patients with extremely low CSF glucose concentrations (< 5mg/dl), usually a high number of microorganisms can be found on microscopy of the CSF. Diagnosis of acute bacterial meningitis is established by identification of the bacterial pathogen by microscopy of a Gram-stained smear or methylene blue- stained smear and by a positive bacterial CSF culture. Bacterial microorganisms are detectable in the CSF in 70 to 90 percent of patients by at least one of the above-mentioned methods. Blood cultures are positive in 50 percent of patients with bacterial meningitis. Blood and CSF cultures should be obtained prior to the start of antibiotic therapy. Antigen detection in the CSF using latex particle agglutination (e.g. antigen detection of *N. meningitides*, *S. pneumoniae*, *H. influenzae*, and *S. agalactiae*) can provide diagnostic confirmation or give additional information if there are suspected bacterial pathogens on a microscopically stained smear. The use of antigen detection tests to detect classic meningeal pathogens is indicated (1) to confirm unclear microscopic CSF results, (2) if the CSF shows marked pleocytosis but a negative microscopic bacterial result, and (3) if there is a history of antibiotic pre-treatment.

If there is clinical suspicion of meningococcal disease but negative microscopic and culture results, then the polymerase chain reaction (PCR) assay to detect meningococcal DNA in the CSF should be done. A broad-range PCR can detect small numbers of viable and nonviable organisms in CSF. When the broad-range PCR is positive, a PCR that uses specific bacterial primers to detect the nucleic acid of *S. pneumoniae*, *N. meningitidis*, *E. coli*, *L. monocytogenes*, *H. influenzae*, and *S. agalactiae* should be done.

2.2.4 Treatment

Antimicrobial agents are among the most dramatic examples of the advances of modern medicine. Many infectious diseases once considered incurable and lethal are now amenable to treatment (Trunkel and Scheld, 1996; Katzung, 2001). Of various classes of drugs used in the world, antibiotics receive special attention because more money is spent on them than any other drugs (Hasan *et al.*, 1997). Infectious diseases are said to account for approximately 30% of hospital admissions in the United States and an estimated 26- 53% of hospitalized patients receive at least one antibiotic (Gums *et al.*, 1999). Prevalence rates of meningitis are not known, despite the fact that in many countries public health bodies need to be notified of every episode; studies have shown that bacterial meningitis occurs in about 3 people per 100,000 annually in Western countries.

Beers and Berkow (2005) remarked that if the patient appears acutely ill, empiric therapy with multiple antibiotics should be started immediately after an IV line has been placed and blood for culture has been drawn. Lumbar puncture can be performed afterward. If the patient does not appear acutely ill, a lumbar puncture should be promptly performed before starting therapy, but after CT scan has excluded a mass lesion. Gram stain of CSF sediment can usually discriminate between meningococcus, *H. influenzae*, pneumococcus, staphylococcus, and gram-negative organisms. Antibiotics should be started

immediately after CSF, blood, nasopharyngeal secretions, and other body fluids have been sent for culture (Mark *et al.*, 2005). Fitch and van de Beek (2007) state that when initial choice of antibiotics is considered, practice guidelines and expert opinions recommend broad-spectrum coverage until bacterial identification can be obtained. According to Beers and Berkow (2005) and Prasad *et al.*, (2009) a 3rd- generation cephalosporin (e.g., ceftriaxone or cefotaxime) should be included because it is highly active against common meningeal pathogens in patients of all ages. Ceftriaxone is widely distributed after parenteral administration. It penetrates well into CSF, especially when the meninges are inflamed; CSF clearance is low (Gibbon, 2005). However, because pneumococcal strains resistant to ceftriaxone and cefotaxime are becoming increasingly prevalent, vancomycin, with or without rifampicin, is usually added. Ampicillin is added to cover *Listeria sp.* Herfindal and Gourley (2000), note that if a steroid is used, the preferred regimen is ceftriaxone IV plus rifampicin PO or IV. Short courses (i.e., first 2 days of therapy) of corticosteroid may be optimal. According to Fitch and van de Beek (2007) in newborns, gentamicin may be added to expand Gram-negative coverage. These recommendations are likely to change as new resistance patterns evolve and new antibiotics are developed. When lumbar puncture results become available, antibiotics are adjusted.

Neisseria meningitidis meningitis: When the CSF Gram stain reveals Gram-negative cocci, meningococcal meningitis is assumed and empiric therapy is directed at that organism. The drug of choice for the treatment of meningococcal meningitis is penicillin G administered 4 million units every 4 hours for 7 days for adults with normal renal function. Penicillin dose adjustment should be considered in patients with an estimated creatinine clearance of less than 30mL/min. Cefotaxime (2g every 4 to 6 hours) or ceftriaxone (2g every 12 to 24 hours) are used as second-line agents for patients with penicillin allergy, although cross-sensitivity is sometimes seen. Chloramphenicol may be used in patients with allergy to both penicillin and cephalosporins. Other alternatives include sulfonamides and

fluoroquinolones. Antimicrobial prophylaxis is indicated for intimate contacts of sporadic cases of meningococcal disease. Hospital staff do not require treatment unless they have given the patient mouth-to-mouth resuscitation. Options include rifampicin or ceftriaxone (adult, children), or ciprofloxacin (preferred option in adults). Ceftriaxone: adults, 250mg as a single dose. Children under 12 years, 125 mg. Ciprofloxacin: adults, 500mg as a single dose. Rifampicin: adults, 600mg 12 hourly for 4 doses. Children, 1- 12 years, 10mg/kg/dose; under 1 year, 5 mg/kg/dose. Patients who have had meningitis and recovered fully should also receive treatment as above for elimination of the nasopharyngeal carrier state, unless they received a third generation cephalosporin as treatment (Gibbon, 2005).

***Haemophilus influenzae* type b meningitis:** Given the tremendous success that conjugated Hib vaccines have had on reducing the incidence of Hib meningitis in the United States, all children > 2 months of age should receive the vaccination series (Koda- Kimble *et al.*, 2005).

According to Standard Treatment Guidelines and Essential Drugs List (1998) chloramphenicol , IV, 100mg/kg/day in 4- 6 divided doses is recommended, if there is resistance, a third generation cephalosporin, eg. cefotaxime,IV, 8- 12g in 4 divided doses, 6 hourly or ceftriaxone, IV, 4g/day divided in 12 hourly doses for at least 7 days.

***Listeria monocytogenes* meningitis:** When listeric meningitis occurs, the overall mortality may reach 70%; from septicemia 50%, from perinatal/neonatal infections greater than 80%. In infections during pregnancy, the mother usually survives. Reports of successful treatment with parenteral penicillin or ampicillin exist. Trimethoprim-sulfmethoxazole has been shown effective in patients allergic to penicillin (Wikipedia, 2008).

Enterobacteriaceae: A third generation cephalosporin, e.g. cefotaxime IV, 8-12g/day in 4 divided doses, 6 hourly or ceftriaxone, IV, 4 g/day divided in 12 hourly doses for 3 weeks (Standard Treatment Guidelines and Essential Drugs List,1998).

Pseudomonas aeruginosa: A third generation cephalosporin, eg. cefotaxime, IV, 8-12g/day in 4 divided doses, 6 hourly or ceftriaxone, IV, 4g divided in 12 hourly doses plus gentamicin, IV, 3-5 mg/kg/day in 3 divided doses, 8 hourly for 3 weeks (Standard treatment Guidelines and Essential Drugs list,1998).

Staphylococcus aureus:

S. aureus has become resistant to many commonly used antibiotics (Naesens *et al.*, 2009). In the UK, only 2% of all *S. aureus* isolates are sensitive to penicillin with a similar picture in the rest of the world, due to a penicillinase (a form of β -lactamase). The β -lactamase-resistant penicillins (methicillin, oxacillin, cloxacillin and flucloxacillin) were developed to treat penicillin-resistant *S. aureus* and are still used as first-line treatment. Methicillin was the first antibiotic in this class to be used (it was introduced in 1959), but only two years later, the first case of methicillin-resistant *S. aureus* (MRSA) was reported in England. Despite this, MRSA generally remained an uncommon finding even in hospital settings until the 1990s when there was an explosion in MRSA prevalence in hospitals where it is now endemic. First-line treatment for serious invasive infections due to MRSA is currently glycopeptide antibiotics (vancomycin and teicoplanin). There are a number of problems with these antibiotics, mainly centred around the need for intravenous administration, toxicity and the need to monitor drug levels regularly by means of blood tests. There are also concerns that glycopeptide antibiotics do not penetrate very well into infected tissues (this is a particular concern with infections of the brain and meninges and in endocarditis). Glycopeptides must not be used to treat methicillin-sensitive *S. aureus* as outcomes are

inferior. When the infection is confirmed to be due to a methicillin-susceptible strain of *S. aureus*, then treatment can be changed to flucloxacillin.

Hospital acquired meningitis, organism unknown: A third generation cephalosporin, e.g. cefotaxime, IV, 8- 12g/day in 4 divided doses, 6 hourly or ceftriaxone, IV, 4g/day divided in 12 hourly doses plus tobramycin, IV, 5mg/kg/day in 3 divided doses for 3 weeks (Standard Treatment Guidelines and Essential Drugs List, 1998).

2.3 Viral Meningitis

2.3.1 Definition

According to Trunkel and Scheld, (1996) and Ramachadran (2007) aseptic meningitis syndrome is not caused by pyogenic bacteria, but can be caused by multiple conditions including infectious viral and non-viral causes and many non-infectious aetiologies. Acute viral infections of the nervous system may manifest clinically in three forms: viral (aseptic) meningitis, encephalitis, or myelitis, the latter of which is infrequent. Viral meningitis is usually a self-limiting illness characterized by signs of meningeal irritation, such as headache, photophobia, and neck stiffness. Encephalitis entails involvement of parenchymal brain tissue, as indicated by convulsive seizures, alterations in the state of consciousness, and focal neurologic abnormalities. When both meningeal and encephalitis are present, the term meningoencephalitis may be used. Viral infection may also localize to the parenchyma of the spinal cord, resulting in myelitis. Myelitis may occur from infection of spinal motor neurons, sensory neurons, autonomic neurons, or demyelination of white matter. When both encephalitis and myelitis occur, the term encephalomyelitis is used. The CSF findings in these three acute viral syndromes are usually

similar, consisting of an increase in pressure, pleocytosis of varying degree, a moderate protein content elevation, and normal sugar content (Rowland, 2005).

According to Parasuram *et al.*, (2000) concerns about the costs of viral meningitis (VM) are growing, and accurate estimates of the economic impact of VM are becoming increasingly relevant. Based on a conservatively estimated 300,000 annual cases in the United States, the economic impact in direct costs to payers exceeds \$1.5 billion per year.

2.3.2 Pathogenesis and pathophysiology

After the colonization of mucosal surfaces throughout the body by various viruses, the host possesses numerous barriers to prevent viral entry. For example, the respiratory tract contains a thin film of mucus and mucociliary elevator that moves viral particles away from the lower respiratory tract; even if this barrier is crossed, alveolar macrophages are actively phagocytic for viral particles. Gastric acidity inactivates most swallowed viruses and gastrointestinal enzymes and bile also disrupts viral envelopes, capsid proteins, and lipoprotein membranes; however, some nonenveloped, acid-resistant viruses (e.g., enteroviruses, adenoviruses, reoviruses, and parvoviruses) are adapted for replication in the gastrointestinal tract. If certain viruses are able to escape initial host defence mechanisms, they may replicate and disseminate with the potential for CNS invasion. CNS invasion by viruses may occur via several mechanisms. Most viruses invade directly across cerebral capillary endothelial cells, the major site of the blood-brain-barrier (BBB). Some viruses directly infect cerebral microvascular endothelial cells before infection of adjacent glia and neurons, whereas others initially infect glia without evidence of endothelial cell infection. Still other viruses may be carried between cerebral endothelial cells in infected leukocytes after BBB disruption. Another site of virus entry is the choroids plexus epithelium (Trunkel and Scheld, 1996; Mandell, *et al.*, 2000).

According to Lo Re III (2004) enteroviruses remain the most common cause of aseptic meningitis in those cases in which diagnosis has been made. Approximately two thirds of all culture-negative CSF from patients with aseptic meningitis will be positive for enteroviruses by polymerase chain reaction (PCR). The most common enteroviruses causing meningitis include coxsackieviruses A and B, echovirus, and enterovirus 68 to 71. Poliovirus is also classified as an enterovirus, but its incidence has declined greatly since vaccination.

2.3.3 Antiviral therapy

Walker and Edwards (2003) pointed out that it is fortunate that most cases of viral meningitis are self-limiting since none of the currently available antiviral agents have useful activity against the viruses that commonly cause this condition. CNS infections with herpes simplex viruses tend to present as encephalitis rather than meningitis. Herpes simplex meningoencephalitis is treated with high doses acyclovir injection, 10mg/kg three times daily.

Symptomatic control with antipyretics, analgesics, and antiemetics is usually all that is needed in the management of uncomplicated viral meningitis. Anti-HIV therapy is initiated when the history is strongly suggestive and/or confirmatory tests have proven an infection. Ganciclovir for cytomegalovirus, CMV-related infections is reserved for severe cases with positive CMV culture, congenital infection, or immunocompromised patients. Pleconaril is an antipicornavirus drug that held potential for treatment of enteroviral meningitis. However, to date, no study has demonstrated clear efficacy, and pleconaril trials have now shifted focus to treatment of rhinovirus upper respiratory infections (Vokshoor and Wan, 2007)

2.4 Cryptococcal meningitis (Fungal)

2.4.1 Background

The most common cause of fungal meningitis is cryptococcal meningitis. *Cryptococcus neoformans* is an encapsulated yeast. In 1984, a pathologist named Busse first described the yeast in a paper he presented to the Greifswald Medical Society (King, 2007). Cryptococcal meningitis is the third most neurological condition that people with acquired immune deficiency syndrome (AIDS) present with (Harrison *et al.*, 1998).

According to Wilks *et al.*, (2003), fungal meningitis is usually associated with immunodeficiency such as HIV infection. Diagnosis is made by India ink staining of CSF and antigen detection in CSF and serum.

2.4.2 Pathophysiology and Pathogenesis

Meningitis, space-occupying intracranial lesions, and invasion into arterial or venous structures are the main manifestations of CNS fungal infection. The production of toxins and antigens may also be harmful to humans. The most important mechanism of disease production is the invasion of tissue. Invasive diseases caused by fungi are termed mycoses. Entrance into the body occurs from inhalation of fungal spores, and by penetration of the skin, the mouth, the gastrointestinal tract or nasal sinuses, as well as via indwelling arterial or venous catheters. Fungal infections of the central nervous system can produce meningitis, cerebritis, ventriculitis, brain abscess, granuloma, meningeal vasculitis with brain infarctions and, in rare instances, septic (mycotic) sinus venous thrombosis or intracranial haemorrhage in case of rupture of a mycotic aneurysm (Trunkel and Scheld, 1996; Noseworthy, 2003).

2.4.3 Antifungal therapy

According to Standard Treatment Guidelines and Essential Drugs List (2006) in human immunodeficiency virus negative patients the aim is to cure the infection, whilst in HIV infection the aim is to suppress the infection until the immune restoration occurs with antiretroviral therapy.

Katzung (2004) states that amphotericin B remains the antifungal agent with the broadest spectrum of action.

The recommended treatment of cryptococcal meningitis is divided into three stages. They are: induction phase, consolidation phase and maintenance phase. Amphotericin B given at 0.7mg/kg/day is the drug of choice in the induction phase. It can be used alone or in combination with 5-flucytosine given at 100mg/kg/day. An alternative to this regimen is fluconazole at 400- 800mg/day. Either alone or with 5-flucytosine. Treatment is to be continued for two weeks (Harrison,1998). In the consolidation phase of therapy, fluconazole is given at 400mg/day for 8 weeks or until the CSF cultures are sterile. Maintenance therapy is given to patients who were successfully treated to prevent relapse (Saag *et al.*, 2000). In AIDS-related extrapulmonary cryptococcosis, amphotericin B is administered for the initial 2 weeks, followed by fluconazole. In non- AIDS- related extrapulmonary cryptococcosis, amphotericin is continued for longer periods (4- 8 weeks), as the goal is to cure rather than long- term suppression. (Gibbon, 2005; Sloan, 2009).

2.5 Tuberculous Meningitis

Tuberculosis is the most prevalent infection in the world, infecting roughly one third of the world. The World health estimates that there are approximately 8 million new cases every year (Iseman, 2000). This increase is due mainly though not exclusively to the HIV epidemic. In developing countries,

particularly in sub-Saharan Africa, the incidence of tuberculosis is estimated to be more than 25 times that in the United States, again largely because of the prevalence of HIV infection (Victor and Ropper, 2001).

Ramachadran (2007) states that in a healthy host, CNS tuberculosis usually takes the form of a meningitis that causes an acute-to-subacute illness characterized by fever, headache, drowsiness, meningism, and confusion over a period of approximately 2-3 weeks. Less frequent presentations include atypical febrile seizures in children, isolated cranial nerve palsies, bilateral papilledema, and acute confusional states. Tuberculous meningitis (TBM) is difficult to diagnose, and a high index of suspicion is needed for making an early diagnosis. Establish the patient's recent contact with tuberculosis. The prodrome is usually nonspecific, including headache, vomiting, photophobia, and fever. In one study, only 2% of subjects reported meningitic symptoms. The duration of presenting symptoms may vary from 1 day to 9 months, although 55% of individuals presented with symptoms of fewer than 2 weeks' duration.

2.5.1 Anti-TB therapy

The treatment of tuberculous meningitis consists of the administration of a combination of drugs: isoniazid (INH), rifampicin (RMP), and a third and sometimes a fourth drug, which may be ethambutol (EMB), ethionamide (ETA), or preferably pyrazinamide (PZA). All of these drugs have a capacity to penetrate blood-brain-barrier, with INH, ETA, and PZA ranked higher than the others in this respect. Resistant strains are emerging, which require the use of PZA and ETA in addition to the two main drugs (INH, RMP). Antibiotics must be given for a prolonged period, 18 to 24 months as a general rule (although it may not be necessary to give all three or four drugs for the entire period). Isoniazid is the single most effective drug. It can be given in a single daily dose of 5mg/kg in adults and 10mg/kg in

children. The most important adverse effects of INH are neuropathy and hepatitis, particularly in alcoholics. Neuropathy can be prevented by the administration of 50mg pyridoxine daily. In patients who develop the symptoms of hepatitis or have abnormal liver function tests, INH should be discontinued. The usual dose of RMP is 600mg daily for adults, 15mg/kg in children. Ethambutol is given in a single daily dose of 15mg/kg. The dose of ETA is 15 to 25mg/kg daily for adults; because of its tendency to produce gastric irritation, it is given in divided doses, after meals. The latter two drugs (EMB and ETA) may cause optic neuropathy, so that patients taking them should have regular examinations of visual acuity and red-green colour discrimination. Pyrazinamide is given once daily in doses of 20 to 35 mg/kg. Rash, gastrointestinal disturbances and hepatitis are the main adverse effects. Except for INH, all these drugs can only be given orally, or by stomach tube. Isoniazid can be given parenterally, in the same dose as with oral use. Corticosteroids should be used only in patients whose lives are threatened by the effects of subarachnoid block or raised intracranial pressure, and only in conjunction with antituberculous drugs (Victor and Ropper, 2001).

2.6 Drug-induced aseptic meningitis

Kepa *et al.*, (2005) state that drug-induced aseptic meningitis (DIAM) is a relatively uncommon impairment of the CNS. It may be associated with autoimmune disorders- diseases of connective tissue and the use of some drugs and chemicals. Causative therapeutic agents potentially inducing DIAM are the following: nonsteroidal anti-inflammatory drugs (NSAIDs) - ibuprofen, naproxen, tolmetin, sulindac, diclofenac, ketoprofen; antimicrobials- co-trimoxazole, isoniazid, pyrazinamide, penicillin, ciprofloxacin, metronidazole, cephalosporins; intravenous immunoglobulins (IV IG); intrathecal agents; monoclonal antibodies; vaccines.

2.6.1 Pathophysiology

Aseptic meningitis caused by nonsteroidal anti-inflammatory drugs occurs primarily in patients with connective tissue disorders, especially those with systemic lupus erythematosus (SLE) and mixed connective tissue disease. Clinically, patients develop the classic signs of meningitis, usually including fever. In most cases, this reaction occurs within hours to 1 day of exposure and is reproducible upon re-exposure to the offending agent. CSF studies in general show lymphocyte- predominant pleocytosis unless the fluid was collected early in the course, at which time polymorphonuclear cells may predominate. Eosinophils may also be present. The CSF protein level is mildly elevated, and glucose concentration is normal in most patients. Generally, the symptoms resolve without sequelae, and only supportive therapy is needed (Samuels and Feske, 2003).

To avoid inducing drug- related meningitis, avoid antimicrobial treatment of respiratory tract infections (e.g., sinusitis and pneumonia) with oral antibiotics that do not have optimal activity against pneumococci. A substantial number of patients have acquired fatal pneumococcal sepsis and meningitis while taking such antibiotics (Wilson and Sande, 2001).

2.7 Prescribing patterns

2.7.1 Recommended meningitis prescribing patterns

Members of Antimicrobial Committee Johannesburg Hospital (2005) state the following about guidelines for treatment of acute bacterial meningitis:

Negative CSF Gram stain

Aetiological agents: Group B *streptococcus*, *E. coli*, *Listeria monocytogenes*, and other Gram negative bacilli.

Suggested regimen: ampicillin 50mg/kg q8h IV + cefotaxime 50mg/kg q8h IV x21 days .

Aetiological agents: *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *E. coli*, *S. agalactiae*

Suggested regimen: cefotaxime 50mg/kg q6- 8h IV + dexamethasone (0.15mg/kg q6h x 2- 4 days).

Aetiological agents: *S. pneumoniae*, *N. meningitidis*, *H. influenzae*

Suggested regimens: ceftriaxone 2g IV q 12h or cefotaxime 2g q4-6h IV + dexamethasone 0.15mg/kg IV q6 h x 2- 4 days, give with or just before 1st dose of antibiotics x 10 – 14 days.

Aetiological agents: *S. pneumoniae*, *Listeria monocytogenes*, Gram- negative bacilli

Suggested regimen: ampicillin 2g q4h IV+ ceftriaxone 2g q 12h or cefotaxime 2g q 6h+ vancomycin 500- 750mg q 6h IV + dexamethasone 0.15mg/kg q6 IV x2days.

Positive CSF Gram stain

Gram positive diplococci- *S. pneumoniae*- ceftriaxone 2g IV q 12h or cefotaxime 2g IV q6h x 10-14 days + dexamethasone 0.15mg/ kg q 6h IV x 2 days.

Gram negative diplococci- *N. meningitidis*- Pen G 4MU q4h IV x 7 days + dexamethasone 0.15mg/kg q6h IV x 2 days.

Gram positive bacilli or coccobacilli- *L. monocytogenes*- ampicillin 2g IV q4h x 21 days + gentamicin 1.7mg/kg q8h initially.

Gram negative bacilli- *H. influenzae*, *P. aeruginosa*, coliforms- ceftazidime 2g IV q8h x 21 days + gentamicin 1.7mg/kg q8h x initially.

Antifungal regimen

Aetiological agents: *C. neoforms*

Suggested regimen: amphotericin B 0.7- 1mg/ kg/day IV x 14 days followed by fluconazole 400mg q 24h PO x 10 wks followed by secondary prophylaxis: fluconazole 200mg q24h PO

Candida spp. - fluconazole 400mg PO q24h x 6 months

Antiviral regimen

Aetiological agents: HSV-

Suggested regimens: acyclovir 10mg/kg IV q8h x 14- 21 days.

Aetiological agents: Cytomegalovirus

Suggested regimens: ganciclovir 5mg/kg IV q12h x 3- 6wks.

2.8 Current recommended prescribing for meningitis in Dr George Mukhari Hospital

According to Neurology department Dr George Mukhari Hospital (2004) the following guide serves as an empiric therapy for treatment of suspected diagnosis of acute bacterial meningitis: cefotaxime 3g 6 hourly IV or ceftriaxone 2g IV 12 hourly.

Pneumococcal meningitis: If penicillin sensitive (MIC = 0.06 µg/ ml) benzyl penicillin 6MU 6 hourly for 14 days or ceftriaxone 2g IV 12 hourly. If penicillin intermediate resistant (MIC 0.12- 1 µg/ ml) cefotaxime 3g 6hourly IVI for 14 days or ceftriaxone 2g 12 hourly IVI for 14 days.

If penicillin resistant (MIC > 2µg/ ml) cefotaxime 3g 6 hourly IVI for 14 days or ceftriaxone 2g 12 hourly IVI for 14 days. If cefotaxime resistant (MIC = 4mcg/ml), as recommended by the microbiological pathologist.

Meningococcal meningitis: benzyl penicillin 6 MU 6 hourly IV for a period of 10 days. Cefotaxime 3g 6 hourly IV or ceftriaxone 2g IV 12 hourly would also be effective.

Prophylaxis – ciprofloxacin 500mg orally single dose. NB: Prophylaxis should be given only to those who had close contact with patient (household contacts, children at day care centre and health care workers who had examined the patient and those who had close contact with the patient). It is a notifiable disease.

Haemophilus influenzae meningitis: cefotaxime 3g 6 hourly or ceftriaxone 2g IV 12 hourly for 14 days

Gram negative bacterial meningitis: cefotaxime 3g 6 hourly IV or ceftriaxone 2g IV 12 hourly for 21 days or depending on the antibiotic susceptibility results.

TB meningitis: rifampicin, isoniazid, pyrazinamide, ethambutol or streptomycin plus 25 – 50 mg pyridoxine orally daily for 2 months. If there is satisfactory clinical improvement it may be followed by rifampicin plus isoniazid orally 5 times a week for 10 months. Tuberculoma may need 2 years of treatment.

Cryptococcal meningitis: amphotericin B 0.7 mg/kg IVI in 5% dextrose for 14 days to be given slowly as follows: amphotericin B 1mg in 5% dextrose solution infused slowly through a central venous line over 4- 6 hours on day 1. The rate of infusion may be varied according to the severity of the side effects. Increase the dose at an incremental rate at 5-15mg per day (according to the severity of the infection) and one aims usually at a treatment dose of approximately 50 mg per day. Switch over to fluconazole 400mg orally daily for 8 weeks followed by maintenance dose of 200mg orally per day for life. Or fluconazole 800mg orally stat followed by 400mg orally daily for 10 weeks, if there is associated HIV infection; one could consider the maintenance dose of 200mg daily thereafter.

In the following chapter the methodology of the study will be addressed.

CHAPTER 3: METHODOLOGY

3.1 *Aim*

To determine prescribing patterns for adult patients with meningitis in the medical wards of Dr. George Mukhari Hospital

3.2 *Study Objectives*

- To record prescribing patterns in patients diagnosed with meningitis
- To record causative organisms and sensitivity patterns
- To record the outcome of treatment
- To determine the length of treatment
- To determine the treatment cost

3.3 *Method and Materials*

Permission was obtained from the Research and Ethics Committee of Medunsa Campus, University of Limpopo, Department of Internal Medicine in University of Limpopo and the Superintendent of Dr George Mukhari Hospital before the study commenced (see Appendix 1).

3.4 Study site

The study was conducted in the following wards of internal medicine (36, 34, 37, 38 and 39) at Dr George Mukhari Hospital.

3.5 The study design

This was a prospective study. Adults patients 18 years and older admitted to the admission ward (ward 36) between May and August 2008 were included in the study. Patients with suspected and confirmed meningitis were included in the study and followed through until they were discharged from the hospital. Patients who were lost in the process due to wrong patients` hospital number capturing in the ward register or electronic patients` database were eliminated from the study.

3.6 Data collection

- Patients admitted to internal medicine admission ward (ward 36) with suspected or confirmed meningitis were included in the study. Both male and female patients were included.
- Patients` demographics, diagnosis and treatment the patients were put on were recorded on data collection sheets (see Appendix 2).
- Patients transferred from the admission ward to other wards were followed until they were discharged.
- Prescribed anti-infectives for different types of meningitis were recorded.

- All anti-infectives used in the study were assigned to an ATC codes (Anatomical Therapeutic Chemical Classification System code (WHO , 2009).
- Culture and sensitivity tests done on patients` blood or cerebrospinal fluid specimens were documented.
- Any change in any of the anti-infectives prescribed during patients` hospitalisation was noted.
- Dose, frequency and duration of treatment for each patient were recorded.
- The treatment outcome of each patient hospitalised was recorded.
- The Gauteng provisional code list was used to calculate daily cost of anti-infectives and other medicines used by patients during their hospital stay.

The following chapter will show results obtained during the study.

CHAPTER 4: RESULTS

4.1 *Introduction*

This chapter presents the findings of the study. For easy reference, the specific objectives are listed again below.

- To record the prescribing patterns in patients diagnosed with meningitis
- To record the causative organisms and sensitivity patterns
- To record the outcome of treatment
- To determine the treatment cost
- To determine the length of treatment

4.2 *Patient demographics*

4.2.1 Age and gender

There were 33 male and 33 female patients enrolled in the study. The distribution of patients per age group (years) is depicted in Figure 1. The age group of 31 to 40 years had the highest number of patients enrolled in the study with male patients showing the highest number in this age group as compared with other age groups. In the age group of 61 to 70 years there were no female patients represented.

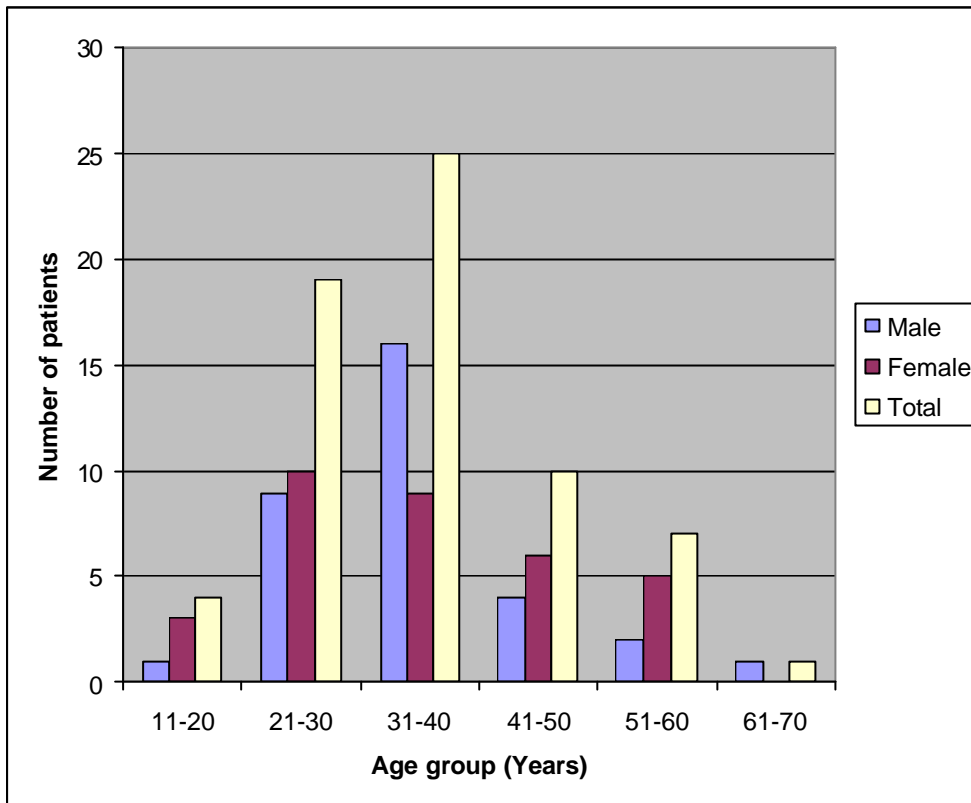


Figure 4.1: Patient demographics

4.3 Duration of stay in hospital

As shown in Table 1, the average duration of stay in hospital by female patients (n = 33) was 13.5 and that of male patients was 13.0 days. The average number of days in the hospital was 13.3 days, with a very wide range of 3 to 47 days.

Table 4.1: Duration of stay in hospital

	Female	Male	Total
N=	33	33	66
Average (days)	13.5	13.0	13.3
Range	3-47	4-29	3-47
Median	9	13	11.5

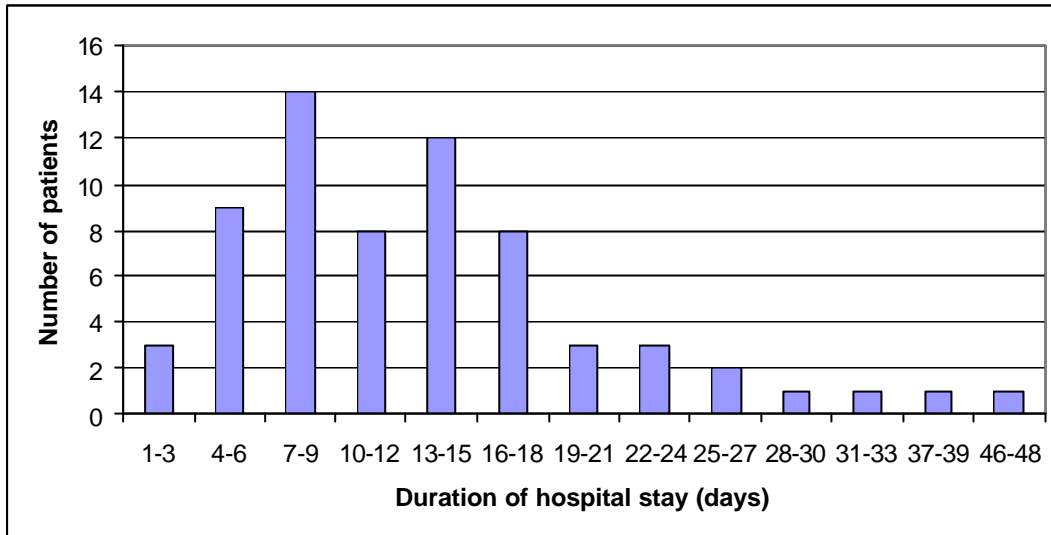


Figure 4.2: Distribution of the duration of hospital stay by study patients (n=66)

4.4 Outcomes

From a total number of 66 patients who were enrolled in the study, one female patient absconded, 13 female patients and nine male patients died, 17 female patients and 24 male patients recovered with two female patients refusing hospital treatment.

Table 4.2: Outcomes

Outcome	Female	Male	Total
Absconded	1		1
Death	13	9	22
Recovered	17	24	41
Refusal of hospital treatment	2		2
Total	33	33	66

The diagnoses are shown in Table 3.

Table 4.3: Diagnoses

Diagnosis	Female		Male		Total	
	Count	Percentage	Count	Percentage	Count	Percentage
Meningitis	31	94%	32	97%	63	95%
RVD	16	48%	22	67%	38	58%
TB	10	30%	7	21%	17	26%
Pneumonia or bronchopneumonia	2	6%	2	6%	4	6%
Diarrhoea	2	6%	1	3%	3	5%
Headache	3	9%	0	0%	3	5%
Hypertension	1	3%	1	3%	2	3%
Otitis media	2	6%	0	0%	2	3%
Pleural effusion	1	3%	1	3%	2	3%
Other (one patient each)*	5	15%	6	18%	11	17%
Total	33	100%	33	100%	66	100%

* Patients could have more than one diagnoses.

* Other conditions included genital ulcer, nephrotic syndrome, *Herpes zoster*, systemic lupus erythematosus (SLE), hyperosmolar nonketoacidosis (HONK), *Herpes labialis*, upper respiratory tract infection (URTI), cavernous sinus thrombosis (CST), nodular rash, chronic obstructive pulmonary disease (COPD), oropharyngeal thrush, and lung cancer.

Table 4.4: Treatment outcomes

Type of meningitis	RVD	Died	Recovered	Total
Tuberculosis	No RVD	2	4	6
	RVD	1	6	7
	Total	3 (23%)	10 (77%)	13
Fungal	RVD	2	8	10
	Not known	1	1	2
	Total	3 (25%)	9 (75%)	12
Bacterial	No RVD	1	1	2
	RVD	0	1	1
	Total	1 (33%)	2 (67%)	3
Not specified	No RVD	6	10	16
	RVD	8	9	17
	Not known	0	2	2
	Total	14 (40%)	21 (60%)	35
Grand total		21 (33%)	42 (67%)	63

Two patients refused hospital treatment (one with fungal and one with unspecified meningitis). One patient with unspecified meningitis absconded. Three patients did not have meningitis. These patients were excluded from further analysis

4.5 Types of meningitis

From the 63 patients with the diagnoses of meningitis, five patients were tested for bacterial meningitis (four patients were tested positive and one patient tested negative). From the four patients who were tested positive, three of them had *S. pneumoniae* and one had *N. meningitides*. Specimens were sent from 16 patients for fungal meningitis. Ten were positive for fungal meningitis and six were negative. One patient tested positive for TB meningitis. No tests were done for non-specific meningitis.

Table 4.5: Types of meningitis

Suspected cause of meningitis	No. of patients with lab test	Lab results			Total no. of patients	% of patients
		Positive	Negative	Not tested		
Bacterial	5	4 3 (<i>S.pneumoniae</i>) 1 (<i>N. meningitides</i>)	1	2	7	11.1%
Fungal	16	10	6	2	18	28.6%
Tuberculosis	1	1	0	8	9	14.3%
Non-specific	0	0	0	29	29	46.0%
Total	22	15	7	41	63	100%

- Viral and drug-induced meningitis were not included as differential diagnosis.
- From 66 subjects, three cultures were identified to have *Streptococcus pneumoniae*, one was found to be resistant to cloxacillin, penicillin and ampicillin respectively with high level sensitivity to gentamicin and sensitive to ceftriaxone and cefotaxime, two cultures were not tested for sensitivity.
- *Neisseria meningitidis* culture was found to be sensitive to both cefotaxime and ceftriaxone

Table 4.6: All anti-infectives given to patients during hospitalisation

ATC Code	Lookup	Prescriptions for anti-infectives				Total (n=63 patients)
		Tuber- culous meningitis (n=13 patients)	Other bacterial meningitis (n=3 patients)	Fungal meningitis (n=12 patients)	Meningitis not further specified (n=35 patients)	
J01AA02	Doxycycline				1	1
J01DA06	Cefuroxime			3	2	5
J01DA13	Ceftriaxone	11	3	8	33	55
J01DH02	Meropenem				1	1
J01EE01	Co-trimoxazole	4		8	8	20
J01FA01	Erythromycin	1		1		2
J01GA01	Streptomycin	3			1	4
J01HB02	Cloxacillin				2	3
J01MA02	Ciprofloxacin	1				1
J01XE01	Nitrofurantoin				1	1
J02AA01	Amphotericin B			10		10
J02AC01	Fluconazole	8	2	9	19	38
J04AK02	Ethambutol	1				1
J04AM02	Rifinah®	2				2
J04AM06	Rifafour®	12	2	3	24	41
J05AB01	Aciclovir				1	1
J05AB11	Valaciclovir			1		1
J05AF01	Zidovudine				1	1
J05AF04	Stavudine	2			1	3
J05AF05	Lamivudine	3			2	5
J05AG03	Efavirenz	2			2	4
Total		50	7	43	99	199

4.6 Duration of treatment

This section presents results on the duration with the different types of medicines (Tables 4.7 and 4.8).

Table 4.7: Duration of treatment

Drug class	System	Number of prescriptions	Mean duration (days)	Range (days)	Median (days)
A	Alimentary tract	77	9.8	1-39	7
B	Drugs affecting the blood	9	7.9	2-24	6
C	Cardiovascular drugs	9	6.6	2-13	7
D	Dermatologicals	4	14.8	10-19	15
H	Systemic hormonal preparations	9	5.8	2-10	6
J	General anti-infectives for systemic use	210	9.8	1-39	8.5
M	Musculoskeletal system	12	6.7	1-16	5.5
N	Central nervous system	49	9.6	1-44	9
P	Antiparasitic products	5	5.6	2-8	6
R	Respiratory system	2	6.0	4-8	6
All		386	9.4	1-44	8

Ceftriaxone was the most prescribed anti-infective with meropenem, cloxacillin, and ethambutol being the least prescribed. The anti-infective with the highest average duration of treatment was Rifinah® with streptomycin having the least average duration of treatment. With the total patients days of 1660 the average duration of treatment was 9.2 days.

Table 4.8: Duration of treatment with anti-infectives for meningitis

ATC code	Anti-infective	Total patient-days	Number of treatment courses	Average duration of treatment (days)
J01DA06	Cefuroxime	41	5	8.2
J01DA13	Ceftriaxone	539	58	9.3
J01DH02	Meropenem	11	1	11.0
J01GA01	Streptomycin	20	4	5.0
J01HB02	Cloxacillin	11	1	5.5
J01MA02	Ciprofloxacin	14	2	7.0
J02AA01	Amphotericin B	126	10	12.6
J02AC01	Fluconazole	425	41	10.4
J04AK02	Ethambutol	8	1	8.0
J04AM02	Rifinah®	28	2	14.0
J04AM06	Rifafour®	437	43	10.2
Total		1660	168	9.2

4.7 Cost of treatment**Table 4.9: Cost of treatment**

Drug class (ATC code)	System	Number of prescriptions	Number of patients (n=66)	Total cost (ZAR)
A	Alimentary tract	77	49	245.33
B	Drugs affecting the blood	9	9	1,812.04
C	Cardiovascular drugs	9	4	48.00
D	Dermatologicals	4	3	203.90
H	Systemic hormonal preparations	9	8	346.76
J	General anti-infectives for systemic use	210	66	113,174.95
M	Musculoskeletal system	12	10	30.97
N	Central nervous system	49	34	368.65
P	Antiparasitic products	5	5	253.65
R	Respiratory system	2	2	6.19
All drug classes		386	66	116,490.43

Table 4.10: Cost of anti-infectives

Class of anti-infectives	ATC code	Medicine	Number of treatment courses	Total cost (ZAR) ²	Average cost per treatment course (ZAR) ⁴	
Antibacterials	Tetracyclines	J01AA02	Doxycycline	1	1.61	1.61
	Cephalosporins	J01DA06	Cefuroxime	5	1,189.04	237.81
		J01DA13	Ceftriaxone	58	22,594.88	389.57
	Carbapenems	J01DH02	Meropenem	1	9,457.80	9,457.80
		Sulphonamide/trimethoprim	J01EE01	Co-trimoxazole	21	98.77
	Macrolides	J01FA01	Erythromycin	2	49.51	24.76
	Aminoglycosides	J01GA01	Streptomycin	4	61.88	15.47
	Penicillins	J01HB02	Cloxacillin	2	877.20	438.60
	Quinolones	J01MA02	Ciprofloxacin	2	2,219.63	1,109.81
	Other antibacterials	J01XE01	Nitrofurantoin	1	83.57	83.57
	Antimycotics	J02AA01	Amphotericin B	10	3,559.18	355.92
		J02AC01	Fluconazole	39 ¹	70,116.24 ¹	1,797.85
	Antimycobacterials	J04AK02	Ethambutol	1	3.50	3.50
J04AM02		RIFINAR®	2	94.94	47.47	
J04AM06		Rifafour®	43	1,278.56	29.73	
Antivirals	J05AB01	Aciclovir	1	933.60	933.60	
	J05AB11	Valaciclovir	1	272.31	272.31	
Antiretrovirals	J05AF01	Zidovudine	1	25.99	25.99	
	J05AF04	Stavudine	3	19.42	6.47	
	J05AF05	Lamivudine	5	53.92	10.78	
	J05AG03	Efavirenz	4	183.38	45.85	
All anti-infectives			207	113,174.95	546.74	

Notes:

- 1 Excluding fluconazole tabs (donated by Pfizer, prescribed to two patients)

Fluconazole was the most costly anti-infective that was used. It was used on patients with fungal meningitis. Cloxacillin was the least costly anti-infective that was used. It was used as combination therapy together with streptomycin and ethambutol on patients with TB re-infection.

Table 4.11: Eight most costly medicines for meningitis treatment

Medicine	Number of prescriptions	Cost (ZAR)	Percentage of Total cost
1 Fluconazole	41	70,116.24	63.00%
2 Ceftriaxone	58	22,594.88	20.30%
3 Meropenem	1	9,457.80	8.50%
4 Amphotericin B	10	3,559.18	3.20%
5 Ciprofloxacin	2	2,219.63	1.99%
6 Rifafour®	43	1,278.56	1.15%
7 Cefuroxime	5	1,189.04	1.07%
8 Cloxacillin	3	877.20	0.79%
All medicines	163	111,292.53	100%

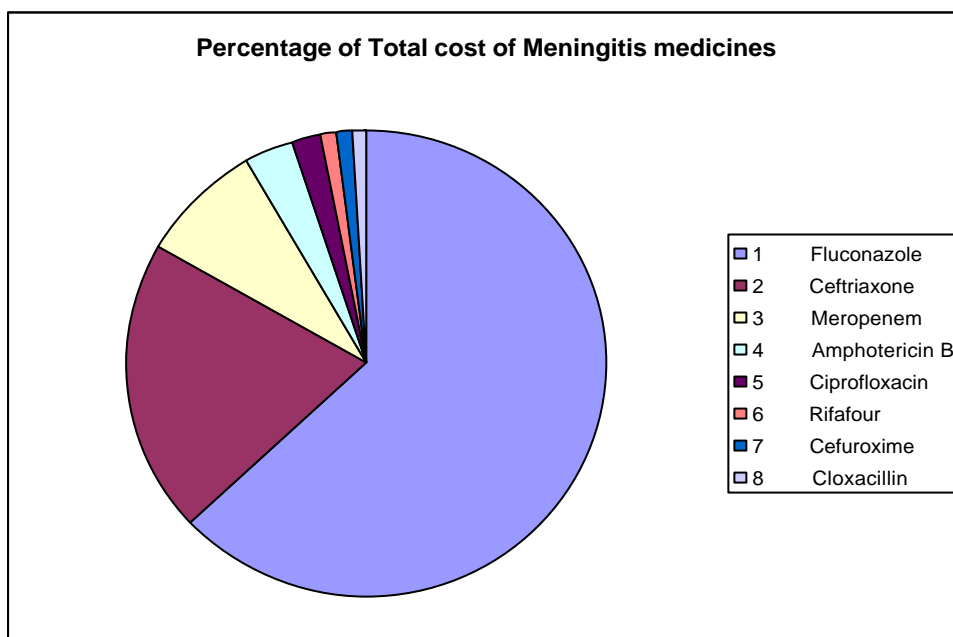


Figure 4.3: Percentage of total cost of meningitis medicines

Table 4.12: Duration of treatment with anti-infectives for meningitis

ATC code	Anti-infective	Total patient-days	Number of treatment courses	Average duration of treatment (days)
J01DA06	Cefuroxime	41	5	8.2
J01DA13	Ceftriaxone	539	58	9.3
J01DH02	Meropenem	11	1	11.0
J01GA01	Streptomycin	20	4	5.0
J01HB02	Cloxacillin	11	1	5.5
J01MA02	Ciprofloxacin	14	2	7.0
J02AA01	Amphotericin B	126	10	12.6
J02AC01	Fluconazole	425	41	10.4
J04AK02	Ethambutol	8	1	8.0
J04AM02	Rifinah®	28	2	14.0
J04AM06	Rifabutin®	437	43	10.2
Total		1660	168	9.2

The following chapter will deal with the discussion of the results obtained during the study.

CHAPTER 5: DISCUSSION

5.1 *Age and gender*

During the course of the study that was conducted from February to August 2008; 66 patients were enrolled and 33 patients were male and 33 of them female. The largest number of patients was between ages 31 and 40. After provisional diagnosis; 63 patients were later confirmed as meningitis cases and only three were confirmed otherwise. In all the subjects of the study no differential diagnosis of viral meningitis was made. This is different from findings according to Morbidity and Weekly Report (2003) which states that aseptic or viral meningitis is the most common type of meningitis and is associated with an estimated 26,000-42,000 hospitalizations each year in the United States. Enteroviruses are the most common cause of aseptic meningitis. Echovirus 9 (E9) and echovirus 30 (E30) have been associated frequently with outbreaks of aseptic meningitis. During March 2003, several state public health departments noted increased reports of aseptic meningitis and, as of August 7, seven states (Arizona, California, Georgia, Idaho, Oregon, South Carolina, and Texas) had reported outbreaks associated with either E9 or E30.

5.2 *Duration of stay in hospital*

The average stay in hospital for patients was 13.3 days. Recommendations regarding length of therapy depend on the offending organism. Patients with meningococcal meningitis or meningitis caused by *H. influenzae* should be treated for 7 days. Patients with pneumococcal meningitis are treated for 10 to 14 days, and those with meningitis caused by *L. monocytogenes* or *S. agalactiae* are treated for 14 to 21 days. Therapy for patients with *Listeria* meningitis may need to be individualized, since some patients

require longer courses. Meningitis caused by Enterobacteriaceae or *P. aeruginosa* requires 21 days of treatment (Aronin and Qualiarello, 2003).

According to the treatment guideline for treatment of different bacterial meningitis the number of treatment days in the hospital is as follows; for community acquired with unknown bacterial aetiology; ceftriaxone, IV, 2g 12 hourly is given for 10 days. For confirmed meningococcal disease only: benzyl penicillin (Penicillin G), IV, 20- 24 million units daily in 4-6 divided doses for one week. For pneumococcal meningitis, if sensitive, the following is given; benzyl penicillin (Penicillin G), IV, 20-24 million units daily in 4-6 divided doses for 10 days. If any degree of resistance is present or cannot be excluded: the following is given; ceftriaxone, IV, 2g 12 hourly for at least 10 days (Standard Treatment Guidelines and Essential Drug List, 2006).

Tuberculosis is the most prevalent infection in the world, infecting roughly one third of the world. The World Health Organization estimates that there are approximately eight million new cases every year. Exposure to HIV significantly increases susceptibility to tuberculosis (Iseman, 2000). Treatment of CNS tuberculosis should begin as soon as possible when clinically suspected because patient outcome is improved when therapy is begun in the early stage of disease. For all types of CNS tuberculosis, treatment should begin with a combination of bactericidal drugs that penetrate into the CSF. The first line of therapy should include isoniazid (INH), rifampicin, and pyrazinamide, all of which are bactericidal and achieve effective levels in the CSF. Pyrazinamide is given with INH and rifampicin during the first two months of therapy, and then is stopped. A fourth drug should be used during the first two months of therapy when INH drug resistance is a concern (Bajaj, 2002). In the ward a patient with confirmed TB meningitis was treated with Rifafour®. For the first two months patients are treated with Rifafour® and then switched to Rifinah®; the total duration of treatment is 12 months. However, after TB meningitis patients have been discharged, they are referred to their local clinic for further management. Treatment

for tuberculous meningitis, intracranial tuberculoma, or tuberculoma with meningitis should be given for 12 months when the tuberculosis strain is sensitive to the antibiotics. Treatment should be lengthened to 18 months if the patient does not receive pyrazinamide during the first two months of therapy. If a patient has a multidrug-resistant strain of CNS tuberculosis, therapy is often extended to 24 months. It is also recommended that patients with active tuberculosis have directly observed therapy to insure compliance, reduce the development of a resistant organism, and monitor clinical response (Bajaj, 2002).

In the study most patients who were on antituberculosis therapy were started on Rifafour®, two were started on Rifinah® (combination of rifampicin and isoniazid), later during the course of treatment Rifafour® was added to the therapy of one patient but there was an overlap of six days between the two drugs and the 2nd one only continued with Rifinah®. Another patient was started on Rifafour® which was stopped after four days of therapy and streptomycin injection was added to the therapy one day later but was subsequently stopped after one day of therapy. The reason for stopping antituberculosis treatment was because of the fact that the patient was confirmed TB negative. One patient was started on both Rifafour® and streptomycin injection for 8 days. Another patient was put on Rifafour® for 15 days and was later given ciprofloxacin oral, ethambutol oral, and streptomycin injection, until the patient was discharged. Patients with confirmed TB meningitis and other forms of TB were given Rifafour® on discharge and referred to local clinic for further management. It must be noted that there was not consistency in the treatment of TB as is shown in the above-mentioned remarks.

Causative organisms and sensitivity patterns

According to the specimens that were cultured the following micro-organisms were identified; *Streptococcus pneumonia* (3) and *Neisseria meningitides* (1) (Table 4.5). This is in line with the

findings of Razonable, Keating, (2007) which state the following in terms of the causative micro-organisms in adult patients: age 18-50 years;(1) *Streptococcus pneumonia*, *Neisseria meningitides* and *H. influenzae*, age older than 50 years;(2) *Streptococcus pneumonia*, *Neisseria meningitides*, *Listeria monocytogenes* and aerobic Gram- negative bacilli.

Out of 18 patients with suspected fungal meningitis, 10 were positive with cryptococcus and six were negative. Out of nine patients treated for TB meningitis only one patient had a positive result for TB. The rest were not tested. There were 29 non-specified meningitis cases that were not tested for micro-organisms and sensitivity. Because there was no routine testing of specimens from patients, it was difficult to record causative organisms and sensitivity patterns. This, therefore, made it difficult to establish any level of resistance to ceftriaxone that is being used as the antibiotic of choice in the treatment of bacterial meningitis in the internal medicine wards of Dr George Mukhari Hospital. This also had a negative effect in containing the cost of anti-infectives used as there was no consistent tailoring of anti-infectives used even when the final diagnosis was pointing to other than bacterial meningitis.

5.3 Treatment cost

The total cost of anti-infectives used for treatment of meningitis amounted to R111, 292.53; and the average cost per patient was R1 686.25. All anti-infectives prescribed for the patient cost R113, 174.95 with an average cost of R546.74 per patient. Cost of all medicines prescribed for the 66 patients amounted to R116, 490.43. Ceftriaxone was the most prescribed anti-infective; 58 patients out of 66 were started on ceftriaxone. This is due to the fact that ceftriaxone is an anti-infective of choice to patients suspected with meningitis in the internal medicine wards of Dr George Mukhari Hospital. According to (Steele 2002) *S pneumoniae* strains that are non-susceptible to penicillin and third-

generation cephalosporins (i.e., ceftriaxone and cefotaxime) have been identified worldwide, with as many as 8% of pneumococci demonstrating this multi-resistant pattern in some regions. Fluconazole was the second most prescribed anti-infective, and though it was prescribed to only 41 patients it was the most expensive anti-infective used.

5.4 Outcomes

One female patient absconded treatment. The patient was on the ninth day of treatment when she absconded. She was still on ceftriaxone, IV, 2g q12h that was started on the day she was admitted and Rifafour®, four tablets daily from the second day of her admission. According to her blood specimen, meningitis was confirmed though no mention of the type of meningitis was made. This poses a question to the addition of Rifafour® to her treatment. But it has been established in the study that patients who were admitted with provisional meningitis diagnosis and who were very sick with concomitant diseases like retroviral disease were put on different anti-infectives ranging from antibacterials, anti-TB drugs and antifungals. It was only when the differential diagnosis has been made that the medication would be tailored. There was, however, no routine blood or cerebrospinal fluid specimens taken to establish whether the current treatment given to a patient was relevant. Sputums for TB would also be sent for testing but were not part of the sample types that were identified to be recorded for the purpose of the study.

In two patients therapy was initiated but they refused hospital treatment. One patient had unspecified meningitis and was put on ceftriaxone, IV, 2g q12h and fluconazole, IV, 400mg q12h, and the second patient had a confirmed cryptococcal meningitis and was put on amphotericin B, IV, 50mg daily. These two patients were then discharged from the hospital.

A total number of 41 (62%) patients recovered. All the patients were started on ceftriaxone, IV, 2g q12h except for one patient who had a final diagnosis of severe headaches. It is advised that treatment of bacterial meningitis should be initiated as soon as possible as it is a medical emergency, and patients should be hospitalized. They can deteriorate as rapidly as in less than 24 hours. Empiric treatment is advised according to the likely organisms, until the organism has been identified (Spiro *et al.*,2004) According to Mark *et al.*, (2005) if the patient appears acutely ill, empiric therapy with multiple antibiotics should be started immediately after an IV line has been placed and blood for culture has been drawn. Lumbar puncture can be performed afterwards. A third generation cephalosporin (e.g., ceftriaxone or cefotaxime) should be included because it is highly active against common meningeal pathogens in patients of all ages. During the study severely ill patients were put on multiple anti-infectives with the addition of Rifabactin® and amphotericin B to ceftriaxone. It was observed that there was no routine drawing of blood for culture before initiating anti-infectives that was observed. Lumbar puncture was performed on some patients suspected of meningitis and some of the CSF results were not available in the patients` files. There was no evidence of routine de-escalation of anti-infective therapy noted as culture sensitivity was not prescribed for most of the patients` specimens. It was only in one case where there was a tailoring of antibiotics, with ceftriaxone stopped after one day of commencement and switched over to fluconazole, IV, 400mg bd and amphotericin, IV; 50mg daily after the patient was confirmed with cryptococcal meningitis, which was not the case with other differential meningitis diagnoses. From the 24 males that recovered, two were confirmed with cryptococcal meningitis and the first one was started on amphotericin B,IV, 50mg and the second one was started on both amphotericin B, IV, 50mg daily and fluconazole, IV, 400mg bd respectively after one day of ceftriaxone, IV, 2g bd. In two other cases where cryptococcal meningitis was confirmed on admission, one patient was started on amphotericin B, IV, 50mg daily for 13 days and the second patient was started on amphotericin B, IV, 50mg daily for 14 days and later during the course of treatment

fluconazole, IV, 400mg bd for six days but overlapped with amphotericin B treatment for six days. one patient was started on anti-TB drugs. All other male patients were started on ceftriaxone, IV, 2g bd. The concomitant conditions in male patients who recovered were the following; hypertension, nephritic syndrome, LRTI, retroviral disease, pulmonary TB, herpes labialis, pneumonia, pleural effusion, oropharangeal thrush, diffused nodular rash, multi- drug resistant tuberculosis (MDR), chronic diarrhoea.

5.5 Limitations

Several factors contributed to the limitations of the study. The following were the limitations observed:

Following-up of some patients was not easy as there was no consistency in updating the list of patients in some of the wards. It must be explained that some patients would be moved from the admission ward (ward 36) to one of the other internal medicine wards and if the patient is diagnosed to have TB he will be moved to a TB ward (ward 39).

Some of the patients who were discharged or demised their files would be taken to the filing room before final information is obtained from the files. This was due to the fact that in the beginning of the study only one clerk was involved in keeping the files for final recording of information for all the internal medicine wards. It was also very difficult to get files that were taken to the filing room as some of them were taken to finance department for billing which took a long time for them to be returned to the filing room. The files of the patients who were demised were not filed in any particular order and it made it very difficult to access them.

The following chapter will deal with conclusion and recommendations.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Most patients in the study were put on ceftriaxone which is the anti-infective of choice for empiric treatment in patients with meningitis. There was no consistent tapering down of empiric therapy as the culture and sensitivity tests were not done for most of the patients.

The lack of culture and sensitivity results made it difficult to establish which type of meningitis is prevalent and also to understand resistance patterns in the internal medicine wards.

From a total number of 66 patients who were enrolled in the study, one female patient absconded, 13 female patients and nine male patients died, 17 female patients and 24 male patients recovered with two female patients refusing hospital treatment.

The total cost of anti-infectives used for treatment of meningitis amounted to R111, 292.53; and the average cost per patient was R1 686.25. All anti-infectives prescribed for the patient cost R113, 174.95 with an average cost of R546.74 per patient. Cost of all medicines prescribed for the 66 patients amounted to R116, 490.43.

The anti-infective with the highest average duration of treatment was Rifinah® with streptomycin having the least average duration of treatment. With the total patients days of 1660 the average duration of treatment was 9.2 days.

To be able to address issues of culture and sensitivity results in future a researcher will need to involve clinicians at the beginning of the study in making sure that for every suspected meningitis case a request is made to get the culture and sensitivity tests done. The researcher can also play a proactive role in accessing the results from the microbiology laboratory. This will also make it easy for him to

inform the clinicians about any resistance patterns picked up in the process and to suggest an appropriate alternative. This will also help to draft a new treatment protocol should it be necessary to do so.

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APPENDICES

Appendix 1:

UNIVERSITY OF LIMPOPO Medunsa Campus	
MEDUNSA RESEARCH & ETHICS COMMITTEE	
CLEARANCE CERTIFICATE	
MEETING: 04/2008	P O Medunsa Medunsa 0204 SOUTH AFRICA
PROJECT NUMBER: MREC/H/53/2008: PG	Tel: 012 - 521 4000 Fax: 012 - 560 0086
PROJECT :	
Title:	Prescribing patterns in adult patients with Meningitis in Internal Medicine wards, Dr George Mukhari Hospital
Researcher:	Mr W.M. Grootboom
Supervisor:	Prof A.G.S. Gous
Hospital Superintendent:	Dr M.P.E Ddungu
Other Involved H.O.D's:	Prof M.O. Mzileni
School:	Health Care Sciences
Department:	Pharmacy
Degree:	MSc (Med) Pharmacy
DECISION OF THE COMMITTEE:	
MREC approved the project.	
DATE:	May 07, 2008
 PROF GA OGUNBANJO DIRECTOR: RESEARCH & CHAIRPERSON MREC	
Note: i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee. ii) The budget for the research will be considered separately from the protocol. PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.	
<i>African Excellence - Global Leadership</i>	