Pharmacotherapy of pneumonia in children under five years in two hospitals in the Ashanti Region of Ghana

BY

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A thesis submitted to the department of pharmacology, faculty of pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, in partial fulfillment of the requirements for the award of master of philosophy in clinical pharmacology, 2016.

DECLARATION

I declare that this work is my own towards the award of Master of Philosophy in Clinical Pharmacology. I duly acknowledge information from other sources as in the text and it is not a material that has been previously submitted for another degree.

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DEDICATION

I dedicate this work to my family, especially my lovely wife, for their support and to my colleague and friend, Dr. Albert Akumani, for his encouragement to complete this work.

ACKNOWLEDGEMENT

My gratitude goes first and foremost to the Almighty God for giving me the strength and grace throughout this project. Secondly, I am grateful to Dr. K. Ohene Buabeng (Clinical Pharmacologist), Rev. Prof. Charles Ansah (Professor of Toxicology) and Dr. Theresa Reteig (Paediatrician, Agogo Presbyterian Hospital) for their immense guidance and encouragement to complete this research. Also, I am most grateful to the management and staff of Agogo Presbyterian Hospital and Kumasi South Hospital respectively for their support towards a successful data collection. My gratitude also goes to the entire staff of Pharmacology Department, KNUST for imparting to me the knowledge needed for this project. Last but not least, I am grateful to Dr. Richard Boadi and Miss Rhoda Akuye-Shika (both of Mathematics and Statistics Department, KNUST) who helped with the data analysis.

ABSTRACT

Pneumonia is a major cause of morbidity and mortality in children under five years of age globally with a record of 2 million deaths per year. Africa alone accounts for about half of global childhood mortality cases. In Ghana, pneumonia is the third leading cause of childhood mortality. This study was aimed at determining the responses of patients to the antibiotics and the relevance of adjunctive therapies in the management of pneumonia in children under five years at Kumasi South Hospital (KSH) in Kumasi metropolis and Agogo Presbyterian Hospital
(APH) in the Asante-Akyem North District both in the Ashanti Region of Ghana from January, 2015 to November, 2015.

A prospective non-randomized observational study was conducted on a total of 189 children with confirmed pneumonia. Ninety-nine children were involved at KSH and 90 children at APH. A pneumonia case was selected after re-examination of the patient previously seen by resident clinicians during the day. Data collected include patient's demographic information, type of pneumonia diagnosed, investigations and antibiotic and adjunctive therapies of the study subjects. The effectiveness of the treatments were measured using the length of stay on admission, and the overall health status and wellbeing of the patients after pneumonia therapy. Safety of antibiotics was assessed with reports of adverse reactions.

At APH, 60% (n=54) were males and 40% (n=36) were females while 52% (n=52) were females and 47.5% (n=47) were males at KSH. Total out-patients were 50% (n=45) and in-patients were 50% (n=45) at APH. At KSH, total out-patients were 14.1% (n=14) and in-patients were 85.9% (n=85). At APH, oral cefuroxime or oral amoxicillin were the first-line antibiotics and oral erythromycin and oral co-amoxiclav were the second-line antibiotics for out-patients. For inpatients, iv ampicillin or iv cefuroxime combined with iv gentamicin were the first-line

antibiotics while iv co-amoxiclav was the second-line antibiotics administered to in-patients. At KSH, first-line antibiotics were oral cefuroxime or oral amoxicillin for out-patients. For inpatients, iv cefuroxime combined with iv gentamicin were the first-line antibiotics while iv ceftriazone or iv co-amoxiclav were the second-line antibiotics. The main adjunctive treatments at APH were analgesics and antipyretics (paracetamol and ibuprofen) and oxygen. Others were ephedrine nasal drops, haematinics, saline nasal drops, multivitamin, ORS, iv fluids, steroids, vitamin K and blood and vitamin A. Adjunctive treatments at KSH include saline nasal drops, cough mixture, haematinics, ventolin inhaler and prednisolone. Others were ORS, zinc and vitamin C. At APH, the lengths of stay of patients on admission were one day (8.9%, n=8), two days (7.8%, n=7), three days (13.3%, n=12), four days (8.9%, n=8), five days (6.7%, n=6) and more than five days (4.4%, n=4). For KSH, the lengths of stay on admission were one day (4.7%, n=4), two days (18.8%, n=16), three days (24.7%, n=21), four days (10.6%, n=9), five days (10.6%, n=9) and more than five days (30.6%, n=26). At APH, clinical improvement recorded for first-line antibiotic therapy was 96.7%(n=87) and for second-line antibiotic therapy was 1.1%(n=1). Mortality recorded was 2.2%(n=2). At KSH, 89.9%(n=89) improved on first-line antibiotic therapy while 10.1%(n=10) improved on second-line antibiotic therapy.

Oral amoxicillin and oral cefuroxime were effective first-line antibiotics for out-patient treatment of pneumonia. Intravenous ampicillin or iv cefuroxime combined with gentamicin were used as first line antibiotics for in-patient treatment of pneumonia. Co-amoxiclav, ceftriazone and erythromycin were effective second-line antibiotics.

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CHAPTER ONE

INTRODUCTION

Background

Globally, pneumonia has been identified as one of the top causes of morbidity and mortality in children less than five (5) years old. It was identified as a forgotten killer of children as much attention was not given to it (Wardlaw T M et al, 2006) until 2001 when the World Health Organization (WHO) constituted the Child Health Research Epidemiology Group (CHERG) with the core duty to review and enhance data on the causes of under-five mortality for the year 2000. It is estimated that globally pneumonia accounts for nearly one million (920,136) deaths in the under-five every year accounting for 15% of total under five mortality. Africa accounts for about 50%of these deaths with Sub-Saharan Africa being the major contributor (WHO, 2015). In Ghana, mortality due to pneumonia in 2010 was estimated at 13% after malaria (18%) and prematurity (16%) (Commonwealth Health Online, 2016).

The prevalence of pneumonia is highest in the developing world with 0.28 episodes per child year in the face of high prevailing risk factors such as malnutrition, poor measles immunization coverage, over-crowding, indoor and outdoor air pollution, low level of maternal education, low level of exclusive breast-feeding among others compared to 0.05 episodes per child year for advanced countries (Singh V et al, 2011).

The causes of childhood pneumonia in the developing world are *Streptococcal pneumoniae* (3050% of cases) and *Haemophilus influenzae* (10-30% of cases) followed by *S. aureus* and *K. pneumoniae* (Shann F et al, 1998; Adegbola et al, 1994). In Sub-Saharan Africa, another important cause, non-typhoidal Salmonella (NTS), has been identified in children with sepsis presenting with

symptoms of pneumonia (Norbert G. Schwarz et al, 2010). Fifteen to forty percent of viral pneumonia cases are caused by Respiration Syncytial Virus. Other viral causes include Influenza A and B, Parainfluenza, Human metapneumovirus and adenovirus (Weber MW et al, 1998). It is projected that with the introduction of the pneumococcal and *H. influenzae* type b (Hib) vaccines, the emergence of antibiotic resistance and the prevalence of HIV infection may change the aetiological pattern of childhood pneumonia in developing countries and this may pose a challenge to the effective treatment of pneumonia (Richard A. Adegbola; clinical infectious disease, 2012).

The WHO treatment guideline (2011) for childhood pneumonia is high dose oral penicillin (amoxicillin) as first line drug for uncomplicated community-acquired pneumonia. Where penicillin is ineffective, oral levofloxacin is recommended for children more than 6months old. Macrolides are recommended for pneumonia caused by atypical bacteria *(Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*). A cephalosporin or a macrolide is indicated in children with known allergy to penicillin. In the case of type 1 hypersensitivity reaction, a macrolide, vancomycin or clindamycin is suggested. Linezolid, an oxazolidinone is recommended where vancomycin or clindamycin is contra-indicated in some children. For severe and very severe pneumonia, hospitalization is recommended for administration of parenteral antibiotics (penicillin or cephalosporin). In suspected *S. aureus* infection in hospitalized children, vancomycin or clindamycin together with a beta-lactam drug is recommended. Aminoglycosides or fluoroquinolones in addition to beta-lactams is indicated in pseudomonas infections in hospitalized children (Bradley J S et al, 2011).

The Ghana Standard Treatment Guideline (2010) approves oral amoxicillin for uncomplicated pneumonia. For patients allergic to penicillin or suspected of atypical pneumonia erythromycin or azithromycin is recommended. For severe and very severe pneumonia cases on admission iv

ceftriaxone or iv cefotaxime or iv co-amoxiclav are recommended as initial therapy followed by oral cefuroxime or oral co-amoxiclav when patient can tolerate oral therapy.

Non-antibiotic drugs (adjunctive therapy) in addition to antibiotics for pneumonia are commonly used. Simple analgesics and/or antipyretics are used in the management of pleuritic pain and fever if present (Sarrell M E et al, 2006). The use of cough mixtures in childhood pneumonia is unequivocal. Some clinicians prescribe cough mixtures as component of treatment for pneumonia while others do not. Oxygen, blood and intravenous fluids are administered to severely ill patients when necessary.

The millennium development goal 4 (MDG4) target of two-thirds reduction in child mortality between 1990 and 2015 was not met in Ghana as under-five mortality rate stood at 61.60 per 1,000 live births as of 2015 far below the national target of 43 deaths per 1,000 live births (Commonwealth Health Online, 2016).

In the face of the emerging factors threatening the effective treatment of pneumonia such as increasing antibiotic resistance to most current antibiotics (Walker B, et al, 2009) and the increasing number of substandard antibiotics on the market, further reduction in child mortality from pneumonia requires a more critical review of the effectiveness of the antibiotics for pneumonia and the relevance of the adjunctive therapies.

Study Aim

The aim of this study was to determine the responses of children with pneumonia to the antibiotics in use and the relevance of adjunctive therapies for pneumonia in children under-five years of age.

Specific Objectives

1. To determine the antimicrobials used in clinical practice for the treatment of pneumonia in under patients at the study sites

2. To determine patients' responses to the antimicrobials for under five pneumonia treatment

3. To determine the frequency of side effects of the antimicrobials prescribed for the treatment of pneumonia in children under five

4. To investigate the relevance of adjunctive therapy for pneumonia in under five patients

5. To assess the adherence of prescribers to the standard treatment guideline (STG) for pneumonia therapy

CHAPTER TWO

LITERATURE REVIEW

Background

Pneumonia is an inflammatory condition of the lung tissue caused by infections. The infectious agents are viruses, bacteria, fungi and parasites. Mortality due to pneumonia is high in the extremes of ages (under 5years and above 75years) globally (Ruuskanen O, et al, 2011).

Pneumonia is broadly classified into community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) depending on where it is acquired (Dunn L, 2005). Community-acquired pneumonia, the most common type of pneumonia, is diagnosed in a person from the community and who has not been recently hospitalized. The aetiology of community-acquired pneumonia varies depending on the child's age. For children between 2 months and 24 months the most common causes are viruses and these include Respiratory syncytial virus (RSV), Human metapneumovirus, Bocaviruses, Para-influenza viruses, Influenza A and B, Rhinovirus, Adenovirus and Enterovirus. The bacterial causes include Streptococcus pneumoniae, Chlamydia trachomatis; less common ones include *Mycoplasma pneumoniae*, *Haemophilus influenzae* (type b and non-typable) and Chlamydophilapneumoniae. Common viral causes of pneumonia in ages 2 to 5 years include RSV, Human metapneumovirus, Para influenza virus, Influenza A and B, Rhinovirus, Adenovirus and Enterovirus. Bacterial causes include *S. Pneumoniae, M. Pneumoniae, H. influenzae* (type b and non-typable) and *C. Pneumoniae*. Less common causes include Staphylococcus aureus (including MRSA) and Group A streptococcus (Jadavji T et al, 1997; Kumar S et al 2008). The multi-drug resistant non-typhoidal Salmonella is emerging as one of the causes of acute pneumonia in Malaria and TB endemic regions (Graham S.M. et al, 2010).

Viral pneumonia commonly affects children under 2years of age and accounts for 30-67% of cases of CAP (Harris M et al, 2011). *Strep pneumoniae* remains the leading cause of bacterial

pneumonia. *Chlamydophila pneumoniae*, *S. pneumoniae* and *Mycoplasma pneumoniae* are prevalent in pre-school and school children. Bacterial pneumonia usually follows viral pneumonia and are mostly caused by pathogenic microorganisms colonizing the nasophorynx **(**Streptococcus pneumoniae, H. influenzae and Moraxella catarrhalis). Nasopharyngeal natural microflora like *Streptococcus mitis* and *Peptostreptococcus anaerobius* offer some protection against pathogenic strains (Harris M et al, 2011, Michelow I.C. et al, 2004).

Risk factors for developing pneumonia

Risk factors for developing CAP depend on environmental factors such as exposure to other children with pneumonia, indoor air pollution caused by use of biomass fuels, crowded conditions and parental smoking.

Host factors include male sex, prematurity and infants (David M le Roux, et al, 2015), immunization status, underlying co-morbidities like diabetes mellitus, asplenia/splenic dysfunction, chronic cardiac disease, nephrotic syndrome, severe liver disease, asthma, and otitis media treated with tympanocentesis. Others include immunological deficits (primary/secondary), malnutrition, mucocilliary dysfunction, (cystic fibrosis, cilliary dyskinesia), congenital malformation of airways, impaired swallowing, microaspiration.

Prior antibiotic exposure can alter the bacterial microflora in the airway destroying commensals like alpha-hemolytic streptococci predisposing to pneumococcal and staphylococcal pneumonia (Van der Poll T et al, 2009).

In viral infections like influenza infections the viruses release neuraminidase and other enzymes onto the host cells to induce the expression and adherence of pneumococcal receptors which predisposes to secondary bacterial infection (Van der Poll T et al, 2009; Talbot T R et al, 2005).

Diagnosis of CAP depends on clinical signs and symptoms with or without chest x-ray. Clinical presentations are not specific especially in young infants less than 2 months old. Mortality increases with severity of the disease and hence early case detection is the cornerstone for reducing complications and mortality from pneumonia. WHO, since the 1980s, has been developing case management strategies aimed at reducing pneumonia-related deaths e.g. the acute respiratory infection (ARI) program which later was developed into the Integrated Management of Childhood Illnesses (IMCI) for resource-poor countries. The rationale for this is for early case detection and for appropriate management of pneumonia. Pneumonia is diagnosed clinically by the use of respiratory rate and chest in-drawing (Shann F et al, 1995). Other clinical parameters are cough with or without fever. Tachypnoea is the most sensitive clinical marker of pneumonia. It has a sensitivity of 74% and specificity of 67% for radiologically confirmed pneumonia but not reliable in the first three days of illness (Palafox M et al, 2000). Clinical manifestations of pneumonia are classified into general (non-specific) and respiratory (specific) signs and symptoms. The respiratory manifestations include cough, dyspnoea and tachypnoea (Table 2.1).General clinical manifestations include fever, lethargy, chest pain, abdominal pain, headache and cyanosis.

Table 2.1 Diagnosis of tachypnoea in the various paediatric age groups

Age	Respiration Rate (breaths/min)
0-2months	≥ 60
2-12months	≥ 50
1-4years	≥ 40

≥ 5years	≥ 30

Examination findings include dullness to percussion, crackles, reduced air entry, bronchial breath sounds, reduced or absent breath sounds, pleural rub (if there is pleuritis), wheeze (usually present in viral and *Mycoplasma pneumoniae* infections), prolonged capillary refill time more than 2seconds(Harris M et al, 2011).

Classification of pneumonia

Based on clinical presentation, pneumonia is sub-classified into uncomplicated/non-severe pneumonia, severe pneumonia and very severe pneumonia (Singh V et al, 2011; Harris M et al, 2011).

Uncomplicated pneumonia presents with cough, tachypnoea and dyspnoea.

Severe pneumonia presents with all clinical manifestations of uncomplicated pneumonia plus at least one of the following: nasal flaring, lower chest in-drawing and expiratory grunting.

Very severe pneumonia is diagnosed with all clinical manifestations of severe pneumonia plus at least one of the following: inability to feed, cyanosis, severe respiratory distress and impaired consciousness or convulsion.

Investigations for pneumonia

It is unnecessary for routine laboratory investigations for aetiology to be carried out in uncomplicated CAP treated as outpatient. Simple tests such as pulse-oximetery can be done for all

pneumonia cases and should always be performed in children with severe and very severe pneumonia on admission (J. Anthony G. Scott, et al, 2012).

Sputum, induced by inhalation of 5% hypertonic saline, has high bacterial yield for culture and sensitivity. Blood cultures are positive in less than 10% of pneumonia cases (Clements H, et al. 2000). Other samples for culture and sensitivity are tracheal aspirate in children on mechanical ventilation and pleural fluid aspirate. Viral detection can be done using nasopharyngeal aspirates or nasal lavage samples.

Serology (ELISA) is useful for detecting infections with Mycoplasma (anti-mycoplasma IgM antibody titre), *Chlamidophila pneumoniae* and *Legionella pneumoniae*. Urine for *Legionella pneumophilla* antigen detection has 80% sensitivity and 99-100% specificity (Harris M et al, 2011; Requejo H I et al, 1997).

Real time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) measures bacterial load and helps to predict the prognosis of pneumonia. Pneumolysin based PCR has a high sensitivity and specificity for detection of *Streptococcus pneumoniae* in blood and pleural fluid (Harris M et al, 2011).

Chest x-ray (CXR) is done routinely to confirm consolidation and to check for complications like pleural effusions, empyema or lung abscess. However, there is wide variation of opinion among radiologists about what radiological changes constitute pneumonia (Davies H, et al, 1996).

CT-Scan is not advised for routine diagnosis of pneumonia but useful for confirmation of complications of pneumonia.

Management of pneumonia

Most part of this section is limited to the discussion of the clinical pharmacology of the various drugs for the management of pneumonia.

The management of pneumonia is based on the age of the child, the severity of pneumonia and the likely aetiology of pneumonia. Children presenting to the hospital with uncomplicated pneumonia are treated as out-patients with appropriate empiric oral antibiotics bearing in mind the local resistance of the suspected aetiological organism. Severe pneumonia and very severe pneumonia cases that are usually hypoxic (oxygen saturation <92%), dehydrated (due to poor feeding or vomiting), and respiratory distressed with/without complications are hospitalized for administration of parenteral antibiotics and supporting treatments like rectal antipyretics (paracetamol) for fever, intravenous fluids for dehydration and electrolyte correction, haemotransfusion, oxygen and mechanical ventilation. The use of cough mixtures is still unequivocal as there is little clinical evidence for or against its usage. The classical antitussive with CNS effects are not recommended for the management of cough in pneumonia in children as the body's own physiologic way of clearing the lungs and airways of infection is by coughing. However, newer agents which act peripherally with no CNS effects like Levodropropizine and moguisteine have been shown to be beneficial in children. They modulate sensory neuropeptide levels within the respiratory tract thereby suppressing cough reflex with no interference with CNS activity (Kim DS et al, 2002).

Presence of complications like pleural effusions and empyema require surgical drainage (by thoracocentesis or video-assisted thoracoscopic surgery (VATS) in more severe cases) and when necessary the addition of fibrinolytics like urokinase, streptokinase and tissue plasminogen activator to dissolve fibrin formation from exudates thereby enhancing clearance of the infection

and improve lung mechanics. Hospitalization should always be considered for infants less than 2 months old and the premature because of the risk of apnoea in this group (Willwerth BM et al, 2006).

ANTIBIOTICS OF CHOICE FOR PNEUMONIA

Several factors are considered when choosing appropriate antibiotic for the treatment of pneumonia, as with all infections, in a particular patient and these include the clinical state of the patient, the innate characteristics of the patient (e.g. hypersensitivity reactions), the pharmacokinetic and pharmacodynamic properties of the antibiotic, the adverse reactions of the drug, the susceptibility of the aetiological organism to the antibiotic and the affordability of the drug (antibiotic).

Penicillins

Penicillin is a 4-membered beta-lactam ring fused to a five-membered thiazolidine ring. This complex structure forms the core structure of the penicillin molecule referred to as the penam ring. In general, the molecular structure of penicillin is R-C9H11N2O4S. The variable side chain R- differentiates the penicillins from one another (Nicolaou, 1996). Originally, penicillin used to be synonymous with benzylpenicillin (penicillin-G) and its derivatives: procaine benzylpenicillin, benzathine benylpenicillin (Benzathine penicillin) and phenoxymethyl penicillin (penicillin V) (Garrod LP, 1960). Due to extensive usage, the once penicillinsusceptible bacteria have developed resistance to the original penicillins necessitating the development of more resistant penicillins such as the anti-staphylococcal penicillins (betalactamase resistant), aminopenicillins and the antipseudomonal penicillins. The **aminopenicillins** include ampicillin, amoxicillin and

bacampicillin.The **antipseudomonal** penicillins (extended spectrum penicillins) include carboxypenicillins and the ureidopenicillins. The carboxypenicilins are Ticarcillin (with clavulanate) and carbenicillin while the ureidopeniccilins are Azlocillin, Mezlocillin, Piperacillin and Mecillinam.

Penicillins are bactericidal. The four-membered beta-lactam ring of penicillin binds to the enzyme,DD-transpeptidase, thus inhibiting the formation of peptidoglycancross-links leading to peptidoglycan precursor build-up. This phenomenon leads to the activation of bacterial cell wall hydrolases which degrades the bacterial cell wall (FACM /Vanbambeke, 1993).

Penicillins exhibit different pharmacological properties due to their structural modifications but share many functional similarities as in pharmacokinetics, drug-drug interactions and adverse drug reactions. They differ markedly in their acid stability and oral absorption hence giving rise to variation in the route of administration. Generally, metabolism is hepatic and excretion is mainly renal with half-lives between 1.4h and 6.7h (Gian MP, 2010; Pharmaceuticals 2010).

Benzylpenicillin (penicillin G) is active against a narrow spectrum of gram-positive bacteria but not against beta-lactamases (Rossi S, 2013). Its main route of administration is either intravenous or intramuscular because it is acid unstable. Penicillin G has a short half-life compared to its salts, procaine and benzathine penicillins which have longer half-lives because of their wide tissue distribution. Co-administration of penicillin G with probenecid increases its half-life. Probenecid competitively blocks the renal tubular secretion of beta-lactam.

Phenoxymethylpenicillin (Penicillin V) is acid-stable hence orally active but less active than benzylpenicillin against gram-negative bacteria (Garrod LP, 1960). Penicillin V for oral treatment may follow parenteral penicillin G once the patient is clinically stable (Sweetman S, 2002).

Clinical study to assess the efficacy of benzylpenicillin for the treatment of pneumonia

In a randomized controlled trial to assess the efficacy of the classic penicillin (benzylpenicillin), benzathine penicillin was used for unilateral lobar pneumonia or segmental infiltrates presumably caused by Streptococcus pneumoniae in children 2-12 years. One-hundred and eighty-six children were screened. A single dose of benzathine penicillin was administered to 93 children at the pediatric emergency unit in Belo Horizonte, Brazil, followed by oral penicillin-V for seven days. Another group received procaine penicillin for 7days upon the diagnosis of severe pneumonia. As high as 92.3% and 95.1% of total radiological clearance was seen in the benzathine penicillin and procaine penicillin groups respectively. It was concluded that Benzathine penicillin is an effective alternative for treating pneumonia compared to the classic agents (Camargos PA, et al, 1997).

Aminopenicillins

Aminopenicillins share the same basic core structure as ampicillin (2-amino derivative of benzylpenicillin). They feature a positively charged amino group that makes it easy to enter bacterial porin channels but does not protect it against the action of bacterial beta-lactamases (Golan, David E; Principles of Pharmacology). They have broad-spectrum activity against both gram-positive and gram-negative bacteria and their potency is enhanced by beta-lactamase inhibitors like clavulanic acid. They are very useful in the management of respiratory infections. The aminopenicillins include ampicillin, cyclacillin, amoxicillin, pivampicillin**,** andbacampicillin. Bacampicillin and pivampicillin are pro-drugs of ampicillin.

Ampicillin was the first aminopenicillin produced (1961). It is active against both Gram-positive and Gram-negative bacteria including S. pneumoniae and H. influenzae in respiratory tract infections. It is also effective against bacteria causing urinary tract infections, meningitis,

salmonellosis and endocarditis (Hauser A R, et al, 2013). Its spectrum of activity is enhanced by combination with sulbactam, a beta-lactamase inhibitor. It is available in oral and intravenous formulations. Oral bioavailability is 40%. About 15-20% of ampicillin is bound to plasma protein. About 12-50% of the drug undergoes hepatic metabolism. The biological half-life is about 1hour. Seventy-five to 85% of drug is excreted unchanged in the urine (Acred P et al, 1962).

Pivampicillin, a prodrug of ampicillin, is a pivaloyloxymethyl ester of ampicillin and has a better oral bioavailability and lipophilicity than ampicillin (Holme E et al, 1989). Peak plasma concentration occurs in about 56 minutes after oral administration and 67-73% of the administered dose is excreted in the urine (Roholt et al, 1974). Due to the release of pivalic acid when metabolized it depletes blood carnitine levels by forming conjugate with carnitine. Short term use does not appear to have any significant clinical effect with respect to carnitine depletion (Brass EP, 2002). However, long term use is not recommended (Holme E et al, 1992).

Bacampicillin, also a prodrug of ampicillin, is an ethoxycarbonyloyethyl ester of ampicillin that is rapidly converted to ampicillin in the gut wall and serum, has a better pharmacologic profile than ampicillin. It is more rapidly absorbed in the upper GIT than ampicillin with fewer side effects such as diarrhoea. It peaks in the plasma within 0.7-1.1 hours compared to 2.5 hours of ampicillin and has a 2-3 times higher bioavailability than ampicillin (Magni L, et al, 1978). It has a long half-life hence reduced dosing frequency (12 hourly) compared to both amoxicillin and ampicillin (George M, et al, 1982).

Cyclacillin, an aminopenicillin, is similar in its spectrum of activity to ampicillin but less susceptible to beta-lamases. Route of administration of cyclacillin is oral with higher bioavailability than ampicillin. Plasma protein binding is less than 25%. It is eliminated renally

(Warren G H, 1976). Side effects of cyclacillin are fewer and milder than ampicillin (McLinn S E, et al, 1983).

Amoxicillin is a 6-aminopenicillanic acid (6-APA) and usually the drug of choice within the aminopenicillin class for the treatment of respiratory infections because of its better absorption when taken orally (95% absorbed). Parenteral preparation is available for intramuscular and intravenous use. Less than one-third is metabolized in the liver and more than half is excreted unchanged in the urine. It has a half-life of 61.3 minutes (amoxicillin monograph, 2012).

Amoxicillin is a moderately broad spectrum antibiotic against susceptible Gram-positive and Gram-negative bacteria including Streptococcus, *Baccilus subtilis*, Enterococcus, Haemophilus, Helicobacter and Moraxella. *Citrobacter, Klebsiella, Pseudomonas aeroginosa,* some *E. coli* and *Staphylococcus aureus* are resistant to it. Combination of Amoxicillin with a beta- lactamase inhibitor like clavulanic acid (Co-Amoxiclav) improves its spectrum of activity. Drug-drug interactions with anticoagulants (e.g. Warfarin), allopurinol, methotrexate, uricosuric drugs and typhoid vaccine have been observed with Amoxicillin. It comes in oral suspension (for young children) and capsule. It is also available as salt for parental administration.

Clinical study to assess the effectiveness of oral amoxicillin for the treatment of severe pneumonia

A cluster randomized trial of community management of severe pneumonia with oral amoxicillin in children 2-59 months of age in Haripur District, Pakistan, one thousand, nine-hundred and ninety-five children were put in the intervention group and 1,477 in the control group. One thousand, eight hundred and fifty-seven children in the intervention group and 1,354 in the control group were analyzed. The intervention group received oral amoxicillin and the control group

received co-trimoxazole and then referred to a hospital. Treatment failure of 8.9% (165/1,857) was observed in the intervention group compared to 17.8% (241/1354) in the control group. Three deaths occurred and only one was from the intervention group. It concluded that community case management of severe pneumonia with oral amoxicillin is more effective thanWHO recommended treatment with first dose oral co-trimoxazole followed by referral (Abdul Bari, et al, 2013).

Beta-lactamase resistant penicillins

The **beta-lactamase resistant (antistaphylococcal)** penicillins (flucloxacillin, nafcillin, oxacillin, cloxacillin, dicloxacillin) are isoxazole penicillins which have narrow spectrum of activity against Gram-positive bacteria especially for staphylococcus but not against MRSA
(Pham P et al, 2009). They are effective against bacteria resistant to the other penicillins. Combinations with other penicillins like aminopenicilins (e.g. amoxicilin+flucloxacilin) increase the spectrum of antimicrobial activity (Carlone NA, et al, 1975). This may be useful for empirical treatment at a cheap cost.

Flucloxacillin possesses an isoxazoyl group on the side chain of the penicillin nucleus which enhances its resistance to beta-lactamase. It is effective against susceptible Gram-positive bacteria but not against MRSA. Clinical uses include pneumonia, tonsillitis, ear and throat infections, skin and soft tissue infections, endocarditis, osteomyelitis, meningitis and septicaemia. It is however less potent than benzyl penicillin against non-beta-lactase Grampositive organisms. Flucloxacillin is acid stable and therefore administered orally. It is also available for intramuscular and intravenous use. Oral bioavailability is 50-70%. Biological halflife ranges from 0.75hrs to 1hr. It undergoes hepatic metabolism and excreted renally. Adverse drug reactions are generally those of

the penicillins including diarrhoea, nausea, rash, urticaria, pain and inflammation at site of injection. Transient increase in liver enzymes and bilirubin is also noted (Rossi S, et al 2006).

Dicloxacillin is similar to flucloxacillin in terms of microbiological coverage, clinical use, pharmacokinetics and adverse reactions except it has higher renal effect and a lower hepatic effect than flucloxacillin (Rossi S et al, 2006).

Nafcillin resembles methicillin and oxacillin in microbiological activity, clinical use and pharmacokinetics. They are administered parenterally. Nafcillin is 90% bound to plasma protein. Less than 30% undergoes hepatic metabolism. It has a biological half-life of 30min. Excretion is both biliary and renal. Notable side effects include hypoglycaemia (JA Mohr, 1979), agranulocytosis and neutropenia.

Cloxacillin is a semi-synthetic beta-lactamase penicillin. Its large R-chain makes it impossible for beta-lactamases to bind. It is available for oral and intramuscular use. Oral bioavailability ranges from 37-90%. About 95% of the drug is protein-bound and has a biological half-life of 30mins to 1hr. Excretion is via biliary and renal. Aside allergic reactions common with all penicillins, it is devoid of serious toxicity (Rossi S, et al, 2006).

Antipseudomonal penicillins

Carboxypenicillin (Carbenicillin, Ticarcillin,), **Ureidopenicillin**and **Mecillinam**are termed antipseudomonal penicillin because of their antibacterial activity against P. aeroginosa. They are broad spectrum penicillin retaining most of the antibacterial activities of the natural penicillin and aminopenicillin with added activity against P. aeroginosa. They are however hydrolyzed by beta-lactamases and so susceptible to staphylococcus, some gram-negative rods and anaerobes. The

clinical usefulness of the antipseudomonal antibiotics is limited as agents for monotherapy if empirical treatment becomes necessary when the infecting organism is not known. The susceptibility to beta-lactamase is overcome when combined with a beta-lactamase inhibitor such as clavulanic acid, sulbactam, tazobactam or moxalactam. Combination with an aminoglycoside, such as gentamicin, also improves its activity (Fainstein V et al, 1984). The ureidopenicillins have a polar side chain that enhances penetration into Gram-negative bacteria which enhances their activity against Enterococcus, Klebsiella and P. aeroginosamore than the carboxypenicillins. Other advantages of the ureidopenicillins over the carboxypenicillins include lower risk of hypernatremia and hypokalemia, reduced platelet dysfunction, more tolerable in patients with renal failure and broader antibacterial spectrum (Tan JS et al, 1995).

Ureidopenicillins

Mezlocillin is similar to **azlocillin** (an acylampicillin) in microbiology and pharmacology. They are broad spectrum and useful for biliary tract infections as they are excreted by the liver (W. Schroeck et al, 1973). They come as parenteral preparations only for intravenous and intramuscular use. Mezlocillin is 16-59% protein-bound and 20-30% is metabolized in the liver. The biological half-life is 1.3 to 4.4hrs. Fifty percent of mezlocillin is excreted in the urine and the rest in the bile (Rohde B et al, 1997).

Piperacillin, an ureidopenicillin, is not active against certain Gram-positive bacteria including MRSA hence combined with tazobactam, a beta-lactamase inhibitor to make it resistant to betalactamase producing bacteria. It is not active against MRSA as it cannot bind to the penicillinbinding protein of this bacteria (Zhanel GG et al, 2008). Piperacillin is recommended for use in hospital-acquired pneumonia and infections caused by anaerobic Gram-positive rods

(Kasper DL, Harrison's principle of internal medicine, 18th Ed.). Piperacillin is administered intramuscularly or intravenously. Protein binding of piperacillin is slightly less than amoxicillin. It has a biological half-life of 36-72mins and largely excreted unchanged (20% in the bile and 80% in the urine). Side effects are largely as penicillins in general (Tan JS et al, 1995).

The population pharmacokinetics of piperacillin/tazobactam was analyzed in Japanese patients with CAP using the non-linear mixed effect model. A one-compartment model analysis demonstrated that the volume of distribution of piperacillin/tazobactam in patients with CAP was higher compared with the value in healthy adults (Hamada Y et al, 2013) and this makes piperacillin/tazobactam combination valuable for the treatment of pneumonia.

Carboxypenicillins

Carbenicillin is a semi-synthetic analogue of benzyl penicillin and active against Gram-negative bacteria including *P. aeroginosa* but has limited Gram-positive coverage. It is better than ampicillin in terms of susceptibility to beta-lactamases. It is formulated for oral and parenteral (intravenous/intramuscular) use. Oral bioavailability is 30 to 40%. Protein binding is from 3060%. Biological half-life is 1hr and it is largely excreted unchanged in the urine (30-40%).
Notable side effects include hypokalaemia and bleeding disorders at high doses (Basker MJ et al, 1977).

Ticarcillin is similar to carbenicillin in terms of microbiological coverage. When combined with clavulanic acid it is resistant to beta-lactamase bacteria. It is administered only intravenously. Plasma protein binding is 45% and half-life is 1.1hrs. It is excreted in the urine. Side effects include hypokalemia and thrombocytopenia (Mostow et al, 1985).

Clinical study to assess the efficacy of ticarcillin/clavulanate for severe pneumonia

The clinical efficacies of ticarcillin/clavulanate for severe pneumonia (both CAP and HAP) in 11 patients were studied in an opened controlled trial. With infections due to *P. aeroginosa*, amikacin was added. Seventy-three percent of patients improved with pathogen eradication in all patients except in 2 cases with P. aeroginosa superinfection. It was concluded that ticarcillin/clavulanate is effective for the treatment of pneumonia infection (Lakovlev SV et al, 2000).

Cephalosporins

Cephalosporins arealso β-lactam antibiotics derived from the fungus Acremonium (Yan L et al, 2014). They have similar mode of action as the penicillins but more resistant to β-lactamases. Bacterial resistance to cephalosporins is by reduced affinity of existing penicillin binding protein (PBP) components or the possession of a supplementary β-lactam insensitive PBP (Anthony MS et al, 2001). Cephalosporins are classified into generations by their antimicrobial spectrum of activity.

First generation cephalosporins

The first generation cephalosporins have antimicrobial activity predominantly against Grampositive bacteria including penicillinase-producing gram positive bacteria, methicillinsusceptible *Staphylococcus aureus* and streptococci. Susceptible gram-negatives include Proteus mirabilis, some E.coli and Klebsiella pneumoniae. Clinically useful members include cefadroxil, cephalexin, cefaloridine, cefalotin, cefapirin, cefatrizine, cefazedone, cefazolin, cefradine, cefroxadine.

Cefalexin is bacteriocidal and useful for the treatment of pneumonia and other infections including otitis media, pharyngitis, bone and joint infections, cellulitis and urinary tract infections but not effective against MRSA infections. It is only available in oral preparation and has a high oral bioavailability. Plasma protein binding is 15% and the half-life ranges from 0.5-1.2hrs. It is largely excreted (about 80%) unchanged in the urine.

Cefadroxil is the para-hydroxy derivative of cefalexin. It has similar clinical use as cefalexin. It is available for oral use only and completely absorbed after oral administration. About 20% is bound to plasma protein. Biological half-life is 1.5hrs and largely excreted unchanged in the urine (www.toku-e.com/assets/mic/cefadroxil).

Cefaloridine is effective for the treatment of pneumococcal pneumonia. It is given intramuscularly and widely distributed in tissues such as liver, lung, spleen and stomach wall. Cerebrospinal fluid (CSF) concentrations are however much lower than in the plasma (Charles H et al, 1975). Cefaloridine is excreted unchanged in the urine (Marvin T, 1982). Serum half-life is 1.1-1.5hrs.

Cefalotin has similar antibacterial coverage as cefalexin and cefazolin. It is available for intravenous use only. Sixty-five to 80% of the drug is bound to plasma protein and has a biological half-life of 30min to 1hr. It undergoes hepatic metabolism and excreted in the urine (AHFS/Drug.com).

Cefazolin is administered intramuscularly and intravenously only. It is useful for respiratory infections, urinary tract infections, bone and joint infections, genital infections and septicemia (Katzung et al, 2015). Biological half-life is 1.8hrs to 2hrs. It is excreted unchanged in the urine (AHFS/Drug.com).

Cefradine is indicated for use in respiratory infections, urinary tract infections and skin and skin structure infections. It is available for oral, intravenous and intramuscular use. Protein binding is less than 10%. Half-life is 0.9hrs. It is excreted unchanged in the urine (Dolfini J.E. et al, 1971).

Cefraxodine is similar in structure, pharmacology and microbiology to cefalexin. It is available for oral use only. Biological half-life is 1hr and excreted renally (Yasuda K et al, 1980).

Second generation cephalosporins

The secondgeneration cephalosporins include cefaclor, cefprozil, cefuroxime, cefuzonam, cefmetazole, cefotetan, cefoxitin. They have better Gram-negative coverage than the first generation.

Cefaclor is effective against bacteria causing pneumonia and other infections of the ear throat, skin and genitourinary tract. It comes as oral preparation only, formulated as sustained release due to its short half-life. It is well absorbed and independent of food intake. About 15-40% of the drug is metabolized and has a half-life of 0.6-0.9hrs. It is excreted in the urine (www.tokue.com/assets/MIC/cefaclor.pdf).

Cefprozil is also available in oral form only and has similar indications as cefaclor. It is not active against *Brucella abortus, Moraxella catarrhalis, Strep pneumonia, Enterobacter aerogenes, Morganella morganii* and *P.aeroginosa*. Cefproxil is well absorbed orally with a
95% bioavailability. Thirty-six percent of the drug is plasma protein bound. It has a half-life of 1-3hrs and is excreted renally (Drug.com monograph).

Cefuroxime is effective against some Gram-negative and Gram-positive bacteria including H. influenzae and N. gonorrhoea and lyme disease. Compared to most cephalosporins it is well tolerated after oral use with less side effects like diarrhoea, nausea, vomiting, headache, dizziness and abdominal pain. It is presented in both oral and parenteral forms. Oral bioavailability is 37-52% and this improves with meal. The biological half-life is 80minutes. Sixty-six to 100% of the drug is eliminated in the urine (gsk-india.com, 2013).

Cefmetazole, cefotetan and cefoxitin are cephamicin antibiotics classified as second generation cephalosporins due to similarity of chemical structure with cephalosporins. They possess the Nmethylthiotetrazole (NMTT) side chain as with other cephalosporins. Metabolism of these compounds leads to hypoprothrombinemia and inhibition of aldehyde dehydrogenase.

Cefmetazole is not clinically useful for respiratory tract infections. It is however used for urinary tract and skin infections. Cefotetan and cefoxitin on the other hand are effective for pneumonia, bone, skin and UTI (Stork CM, 2006). Cefoxitin is a strong beta-lactamase inducer (Philips I et al, 1993).

Third generation cephalosporins

The third generation cephalosporins have better Gram-negative coverage than the second generation cephalosporins but less effective against Staphylococcus and Streptococcus than the first and second generations. Members of the third generation include cefdinir, cefditoren, cefixime, cefmenoxime, cefpimizole, cefpodoxime, ceftibuten, ceftizoxime and ceftriaxone. Cefoperazone and cetazidime are the 3rd generation cephalosporins with antipseudomonal activity.

Cefdinir, an oral third generation cephalosporin, is effective for treating CAP and RTI, otitis media and other soft tissue infections. Oral bioavailability is 16-21%. Sixty to 70% of the drug is bound to plasma protein and to a large extent excreted unchanged in the urine (Gonzalez M et al, 2003).

Cefixime is also an oral third generation cephalosporin indicated forpneumonia, RTI, otitis media, biliary tract infections and typhoid fever. Forty to 50% of cefixime is absorbed after oral administration. Plasma protein binding is 60% and has a plasma half-life of 3-4hrs. It is eliminated in the urine and bile (www.toku-e.com/assets/MIC/cefiximetrihydrate.pdf).

Cefmenoxime is available as a parenteral preparation for intramuscular and intravenous administration only. Plasma protein binding is 50-70% and has a half-life of 1hr. It is largely excreted unchanged in the urine (Yokota N et al, 1995).

Cefodizine is effective for the treatment of RTIs, UTIs and gonorrhoea. It is available for only intramuscular and intravenous administration with a bioavailability of 90-100%. It is widely distributed in tissues and is 81% bound to plasma proteins. Biological half-life is 3.5hrs and is excreted unchanged by the kidneys (Barradell Lee B et al, 1993).

Cefotaxime is clinically useful against bacteria that cause pneumonia, genitourinary infections, septicaemia, osteoarthritis and CNS infections (USFDA, 2009). It is not active against Pseudomonas and Enterococcus. It is administered intramuscularly or intravenously onlyand undergoes hepatic metabolism. The biological half-life is 0.8-1.4hrs and fifty to 85% of cefotaxime is excreted in the urine.

Cefpodoxime and **ceftibuten** are also third generation oral cephalosporins effective for treating infections like pneumonia, RTIs, pharyngitis and tonsilitis and gonorrhoea. Cefpodoxime is formulated as cefpodoxime proxetiland has a bioavailability of 50% after oral administration.

Cefpodoxime proxetil is metabolized in the liver to the active drug, cefpodoxime. Twenty-one to 29% of cefpodoxime is bound to plasma protein. Biological half-life is 2hrs. It is excreted unchanged in the urine (Orelox-Drugs.com).

Ceftizoxime is a broad spectrum third generation cephalosporin resistant to beta-lactamase hydrolysis due to the removal of the whole C-3 side chain. It is available only for parenteral (intramuscular and intravenous) use (Takaya T. et al, 1978).

Ceftriazone is commonly used for the treatment of pneumonia, ear infections, skin infections, gonorrhoea, pelvic infections, septicemia, osteoarthritis, intra-abdominal infections and meningitis. It is not effective against P. aeroginosa and Enterobacter spp. infections (Katzung B et al, 2012). Ceftriazone is administered intramuscularly or intravenously. Ceftriazone is metabolized in the liver and by gut flora to the inactive compound and excreted in the bile. Thirty-three to 67% of ceftriazone is excreted unchanged (Balant L et al, 1985). It has an extensive tissue distribution including cerebrospinal fluid. Elimination half-life is 5.8 to 8.7hrs. Side effects include eosinophilia, thrombocytosis, elevated blood urea and nitrogen, biliary sludge, biliary pseudolithiasis and gallstones, pain at site of injection and rash (Shiffman ML et al, 1990).

Cefoperazone is a third generation cephalosporin active against *P. aeruginosa* infections. It is formulated with sulbactam, a beta-lactamase inhibitor for improved activity. It is administered only intramuscularly or intravenously and excreted hepatically.

Ceftazidime is also a third generation cephalosporin with antipseudomonal activity. It is clinically useful against bacteria causing RTIs, UTIs, septicaemia, peritonitis, arthritis and meningitis (Schaumburg I.L. et al, 2012). Ceftazidime is co-formulated with avibactam which is a non-beta-lactam beta-lactamase inhibitor to treat certain multi-drug resistant Gram-negative infections. It is

for intravenous or intramuscular administration and sometimes inhalational for cystic fibrosis. Bioavailability is 91% by intramuscular route and plasma half-life is 1.6-2hrs.

Ninety to 96% of the drug is excreted renally (Lagace-Wiens P et al, 2014).

Clinical study to assess the effectiveness of narrow-spectrum antibiotic therapy for severe and very severe pneumonia

A retrospective cohort study assessed the effectiveness of narrow-spectrum antibiotic therapy for children hospitalized with community-acquired pneumonia (CAP) between 2005 and 2011. Data from 43 children's hospitals included 15,564 children's records. The outcomes of two groups of children on two different treatment regimens respectively were assessed: children who received parenteral ampicillin / penicillin (narrow spectrum) and those who received ceftriaxone / cefotaxime (broad spectrum). In all 13,954 children received broad-spectrum therapy (89.7%) and 1,610 received narrow-spectrum therapy (10.3%). The median length of stay for the 2 groups was 3days. For those admitted to intensive care unit 156 children (1.1%) receiving broadspectrum therapy and 13 children receiving narrow-spectrum therapy respectively were admitted. Three hundred and twenty-one children (2.3%) receiving broad-spectrum therapy and 39 children (2.4%) receiving narrow-spectrum therapy were re-admitted respectively. The study concluded that the clinical outcomes for children hospitalized with CAP on narrow-spectrum antibiotic are not significantly different from treatment with broad-spectrum antibiotic (Derek JW, et al, 2013).

Comparing the efficacy and safety of ceftriazone/sulbactam with cefoperazone/sulbactam

In a multicenter clinical study the efficacy and safety of injection ceftriaxone/sulbactam and cefoperazone/sulbactam in the treatment of respiratory and urinary tract infections were compared in a total of 285 patients between 18-65 years. After three (3) days of treatment the bacteria isolated were either ceftriaxone-resistant or cefoperazone-resistant. In the ceftriaxone/sulbactam group the cure and effective rates were 39.55% and 85.07% respectively compared with 36.43% and 79.84% in the cefoperazone/sulbactam group. Bacterial eradication rates were 83.58% and 83.72% and adverse events rates were 7.48% and 7.80% for ceftriaxone/sulbactam and cefoperazone/sulbactam groups respectively. It was concluded that ceftriaxone/sulbactam is equally effective and as safe as cefoperazone/sulbactam for the treatment of moderate and severe bacterial infection caused by resistant strains (Xiaojuan X, et al, 2013).

Fourth generation cephalosporins

Cefipime, a fourth generation cephalosporin, has spectrum of activity against both Gramnegative and Gram-positive bacteria including Pseudomonas, Enterobacteriaceae and multi-drug resistant Streptococcus pneumoniae compared to the earlier generation cephalosporins. It is reserved for nosocomial infections including HAP and available for intramuscular or intravenous use only. Following intramuscular administration cefipime is rapidly absorbed with a bioavailability of 95.7%±7.44% and is 10.5-16.7% protein bound (Ismail MM, 2005). Fifteen percent of cefipime undergoes hepatic metabolism and plasma half-life is 2hrs. Seventy to 99% of the drug is excreted renally (Yahav D et al, 2007).

Other fourth generation cephalosporins include cefclidine, cefepime, cefluprenam, cefoselis, cefozopran and cefpirome.

Clinical study comparing cefepime and ceftriazone

Comparing cefepime and ceftriaxone for the treatment of hospitalized patients with CAP, eightysix patients were evaluated for clinical efficacy of these drugs respectively. One group (N=40) received cefepime 2g 12hrly, the other group (n=46) received ceftriaxone 1g 12hrly. Ninety-five percent of patients in the cefepime arm improved clinically compared to 97.8% of patients in the ceftriazone arm. *Streptococcus pneumoniae, H. influenzae* and *Staph aureus* were among the pathogens isolated in both groups. Results showed 100% eradication of the 32 pathogens for cefepime treated group compared to 97.4% (38 out of 39 pathogens) for the ceftriazone group. The resistant pathogen in the ceftriaxone group was Pseudomonas fluorescens. The conclusive result was that cefexime and ceftriazone have comparable efficacy and safety for the treatment of CAP in hospitalized patients (Zervos M et al, 1997).

Fifth generation cephalosporins

Ceftobiprole, a fifth generation cephalosporin, is active against MRSA, penicillin-resistant *Streptococcus pneumoniae, P. aeroginosa* and enterococci (Noel G J et al, 2008). It inhibits the 2aPBP of MRSA and the 2xPBP of *Strep pneumoniae* (Kollef M H, 2009). It is formulated for intravenous administration only.

Ceftaroline is similar to ceftobriprole microbiologically and pharmacologically. It has received approval for the treatment of CAP. It has a plasma protein binding of 20% and a biological halflife

of 2.5hrs. Eighty-eight percent of ceftaroline is excreted in the urine and 6% in the faeces (Kollef MH, 2009).

Ceftolozane, a new fifth generation cephalosporin, is acclaimed the most potent antipseudomonal antibiotic for clinical use. It is active against Gram-negative bacteria that have become resistant to existing antibiotics. The route of administration is intravenous only (Lang TE et al, 2014).

Aminoglycosides

The use of aminoglycosides against emerging antimicrobial resistance is being reconsidered in recent time due to evidence gathered that aminoglycosides still retain activity against most gramnegative bacteria (Falagas, et al, 2008). They are bactericidal against gram-negative aerobes and some anaerobic bacilli. They inhibit bacterial protein synthesis by binding irreversibly to the cytosolic, membrane-associated ribosome at the 30S subunit. This disturbs peptide elongation translating into an inaccurate protein synthesis. These aberrant proteins incorporated into the bacterial cell membrane results in changes in membrane permeability and eventual cell death. (Levison MD, et al, 2012).

Aminoglycosides are polar compounds and therefore not absorbed orally, hence administered intravenously or intramuscularly. They are also valuable as topical agents e.g. neomycin. Their oral use is clinically employed in gut decontamination prior to gut surgery. They are excreted by the kidney. Main side effects include ototoxicity and nephrotoxicity. They are contraindicated in patients with myasthenia gravis (Gautam M, et al, 2010) and mitochondrial diseases (Bindu LH, et al, 2008). Members in this class include **kanamycin A, amikacin, tobramycin, dibekacin, gentamicin, sisomicin, netilmicin, neomycin, streptomycin.**

Gentamicin is the drug of choice for paediatric hospital acquired pneumonia (HAP) and when with beta-lactams produces synergy. Gentamicin is broad-spectrum, mostly against Gramnegative bacteria including *Pseudomonas, Proteus, E. coli, Klebsiella pneumoniae, Enterobacter aerogenes* and Serratia and a few Gram-positives including Staphylococcus but not effective against Chlamydia and *Neiserria gonorrhoea*. It is therefore used for treating RTIs, UTIs, septicaemia and bone and soft tissue infections. Gentamicin is administered intravenously, intramuscularly and topically. Plasma protein binding ranges from 0-10% and a half-life of 2hrs. Caution should be used during therapy in pregnancy, children and the aged (Gentamicin, Baxter corporation, 2015).

Amikacin, kanamycin and tobramycin are similar to gentamicin pharmacologically and active against multi-drug resistant Gram-negative bacteria that may be resistant to gentamicin.

Netilmicin is also similar to gentamicin but less active against P. aeruginosa than gentamicin. Netilmicin is generally reserved for serious infections resistant to gentamicin and because of its less ototoxicity it is recommended for patients requiring longer than 10days treatment with aminoglycoside (Klingenberg C, et al, 2004).

Streptomycin is active against a wide range of bacteria and mycobacteria. It is reserved for bacteria resistant to gentamicin. Bioavailability is 84-88% following intramuscular or intravenous administration. The plasma half-life is 5hrs to 6hrs.

Macrolides

The macrolide antibiotics belong to the polyketides class of natural products that are a class of antibiotics possessing the macrocyclic lactone ring (macrolide ring) to which one or more deoxy sugars (cladinose and desosamine) may be attached. The macrolide ring may be 14-, 15-, or 16membered. They include **Azithromycin, Clarithromycin, Erythromycin, Fidaxomicin,**

Telithromycin. Others are **Carbomycin A, Josamicin, Kitasamycin, Midecamycin, Oleandomycin, Solithromycin, Spiramycin, Troleandomycin** and **Roxithromycin.**

Azithromycin has additional methyl substituted nitrogen in the lactone ring that improves its pharmacologic profile in terms of acid stability, tissue penetration and antibacterial spectrum.

Macrolides inhibit bacterial protein synthesis by inhibiting peptidyltransferase from catalyzing the addition of amino acids to the growing peptide chain attached to the tRNA (Gray Kaiser, 2009). Another possible mechanism proposed is premature dissociation of peptidyl tRNA from the ribosome (Tenson T, et al, 2009).This is made possible by the macrolide molecule binding reversibly to the P-site on the 50S subunit of the bacterial ribosome.

Macrolide antibiotics are generally bacteriostatic and are actively concentrated in leucocytes facilitating their transport to the site of infection (S Baily et al, 1991).

Microbiological activity

Macrolides are active mostly against Gram-positive bacteria (e.g. *S. pneumoniae*) and limited Gram-negatives (*Bordetella pertussis, H. influenzae*). They have a wider range of antibiotic spectrum than the penicillins against β-haemolytic streptococci, pneumococci, staphylococci and enterococci and also include *Legionella pneumophila, Mycoplasma, Mycobacteria*, Rickettsia and Chlamydia.

Resistance to macrolides is by post-transcriptional methylation of the 23S bacterial ribosomal RNA which is either plasmid-mediated or chromosomal (mutation). This results in cross resistance to macrolides, lincosamides and streptogramins. Other modes of resistance are production of drug inactivity enzymes (esterases or kinases) and production of active ATPdependent efflux proteins that transports the drug out of the cell.

Pharmacokinetics

Macrolides are basic compounds and are therefore unstable in acidic medium except roxithromycin and azithromycin. The small intestine is the main site of absorption. Macrolides are highly lipid-soluble and therefore have a high tissue penetration especially into bronchial secretions, prostatic tissue, middle ear exudates and bone tissue. However, they have poor penetration into CSF. The tissue concentrations ofmacrolides in respiratory tissues and extracellular fluids are mostly higher than the serum concentrations hence useful for respiratory infections (Jain R et al, 2004). The liver is the main site of metabolism of macrolides and elimination is via the billiary system. The metabolites of macrolides have no antimicrobial activity with the exception of a few (e.g. miocamycin). Plasma protein binding is variable; plasma protein binding for erythromycin is 80-90% and 95% for roxithromycin, protein binding is 15% for midecamycin and josamycin. The half-lives of erythromycin, oleandomycin, josamycin and miocamycin range from 1-2h. Spiramycin, erythromycin stearate, the mercaptosuccinate salt of propionyl erythromycin and rosaramicin have intermediate half-lives of 4.5h to 7h. Roxithromycin and azithromycin have long half-life values of 11h and 41h

respectively (Periti P et al, 1989).

Side effects

Macrolides are generally inhibitors of cytochrome P450 system (CYP3A4 especially) with the exception of azithromycin, hence their combination with statins cause debilitating myopathy (Sathasivam S et al, 2008). They also produce torsade de pointes by QT elongation especially with azithromycin and clarithromycin (British Medical Journal, 2008). Pyloric stenosis in infants has

also been noted hence contraindicated in this age group (Sanfilippo A, 1976). Others include nausea associated with entero-hepatic circulation (Honein MA, et al, 1999) and cholestasis (Hautekeete ML, et al, 1995).

Clinical study comparing the intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin and cefuroxime

A study comparing the intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin and cefuroxime was conducted in 68 volunteers. Single doses of oral azithromycin 500mg, clarithromycin 500mg, ciprofloxacin 500mg and cefuroxime 500mg were administered to four different groups. Broncho-alveolar lavage fluid concentrations of the drugs in each group were determined at different time intervals. The maximum observed concentrations (mean ± standard deviation) of azithromycin, clarithromycin, 14-hydroxyclarithromycin (14H), ciprofloxacin and cefuroxime in serum were 0.13±0.07, 1.0±0.6, 0.60±0.41, 0.95±0.32 and 1.1±0.3mg/ml respectively at 6h. Only clarithromycin was detected at 6h in epithelial lining fluid (ELF) at concentration of 39.6±41.1mg/ml. However, at 120h azithromycin reached its highest concentration in alveolar cells with the greatest area under the curve. Clarithromycin recorded the highest peak concentration but lower area under the curve than azithromycin. Ciprofloxacin recorded its peak concentration in the alveolar cells at 6 hours with the least area under the curve. The result concluded that azithromycin, clarithromycin and ciprofloxacin after a single dose administration penetrated alveolar cells at therapeutic concentrations except clarithromycin which was present in ELF (John E, et al, 1996).

Clinical study to compare the effectiveness of azithromycin with cefuroxime alone or

cefuroxime plus erythromycin

In a clinical study, iv azithromycin plus oral azithromycin was compared with cefuroxime with or without erythromycin. The mean duration of treatment for azithromycin group was 3.6 days for iv and 8.6 days for iv and oral and that for the comparator was 4 days for iv and 10.3 days for the iv and oral. A total of 268 patients were evaluated at the end of the trial at 10-14 day visit with 106/137 (77%) of patients who received azithromycin were cured or improved and 97/131 (74%) of patients who received cefuroxime with or without erythromycin also improved. It concluded that therapy with azithromycin is effective (Joseph P et al, 2000).

Ketolides

Ketolides are structurally related to macrolides. They are derived from structural modification of erythromycin by replacing the cladinose sugar with a keto-group and adding a cyclic cabamate to the lactone ring. Because they have two ribosomal binding sites and are poor substrates for efflux-pump mediated resistance they are more effective than macrolides. Ketolidesinclude telithromycin, cethromycin and solithromycin. Fluoroketolides (solithromycin) have three ribosomal binding sites. They are effective against respiratory infections caused by macrolideresistant bacteria (Bertram G.Katzung et al, 2009; Basic and Clinical Pharmacology).

Cethromycin and solithromycin are currently undergoing clinical trials for approval.

Telithromycin is acid stable so does not need enteric coating. It is available in oral form only. Bioavailability is 57% and has a high volume of distribution. It is more concentrated in phagocytes like all macrolides and ketolides making it effective against microbes. The plasma protein binding is 60-70%. About 50% of the drug undergoes hepatic metabolism mediated by CYP3A4.

Approximately, one-third of telithromycin is excreted unchanged. Biological half-life is 10hrs. Telithromycin is to a large extent excreted in the bile and to a minimal extent in the urine. Side effects include diarrhoea, nausea and vomiting, abdominal pain, headache and taste disturbance. Other rare side effects include palpitation, blurred vision and rashes. On electrocardiogram it prolongs QTc interval (Bertram G. Katzung et al, 2009).

Fluoroquinolones

Fluoroquinolones are a class of broad spectrum antibiotics effective against both Gram-positive and Gram-negative bacteria and are valuable for the treatment of respiratory infections. Until recent studies demonstrating the safety of fluoroquinolone antibiotics in children they were contra-indicated in pediatrics (Sung L et al, 2012; Rosanova MJ et al, 2010).

Fluoroquinolones are derived from the parent molecule, quinolone, where fluorine atom is attached to the quinolone ring at the 6^{th} or 7^{th} position. Their antibacterial effect is exerted through prevention of unwinding of bacterial DNA and duplication by inhibiting DNA gyrase in gram-negative bacteria and topoisomerase IV in gram-positive bacteria (Hooper DC, 2001).

The first generation drug differs from the subsequent generations by the absence of the fluorine atom in the quinolone ring (Schaumann R et al, 2007).

The first and second generation fluoroquinolones are active against mostly Gram-negative organisms. They selectively inhibit the topoisomerase II ligase domain leading to DNA fragmentation via the nuclease enzyme activity. The first generation fluoroquinolone include nalidixic acid, norfloxacin and the second generations are ciprofloxacin and ofloxacin.

The third and fourth generations inhibit topoisomerase IV ligase domain hence have improved coverage against Gram-positive bacteria. Due to their easy access into host cells via porins, fuoroquinolones are effective against Legionella pneumophilla and Mycoplasma pneumniae (Bergan T et al, 1988; Suto MJ et al, 1992).The third and fourth generations are used more for respiratory infections due to their broad-spectrum antibacterial activity (American Thoracic Soceity, 2005). Third generation fluoroquinolones include balofloxacin, grepafloxacin, levofloxacin, pazufloxacin, temafloxacin and tosufloxacin. Fourth generation fluoroquinolones include cinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin, trovafloxacin and prulifloxacin. Novel fuoroquinolones in clinical trials are delafloxacin, JNJ-Q2, nemonoxacin.

Pharmacokinetics and pharmacodynamics of fluoroquinolones

The oral bioavailability of the fluoroquinolones is moderate to excellent. Products containing multivalent cations like Fe, Zn, Mg, Ca markedly reduce absorption. They have extensive tissue penetration with concentration often exceeding plasma concentration. The central nervous systempenetration is moderate only when there is inflammation of the meninges. Plasma protein binding varies among the fluoroquinolones. Elimination is predominantly renal but some e.g. moxifloxacin undergo hepatic metabolism. Elimination half-life is between 50-98 min (Turnidge J, 1999). The bioavailability of levofloxacin, moxifloxacin and gatifloxacin is high (90-99%) with extensive tissue penetration. Levofloxacin and gatifloxacin are excretedin the urine unchanged. Moxifloxacin is excreted in the bile (Rodvold KA et al, 2001).

Adverse effects

The side effects range from mild to occasionally serious side effects (De Sarro A et al, 2001; Owens RC, et al, 2005). Nausea and vomiting, diarrhoea, headache and insomnia are common side effects associated with fluoroquinolone usage. More serious adverse effects include tendonitis and tendon rapture in all ages and torsades de pointes in rare cases (Hall MM et al, 2011), seizure, psychosis andperipheral neuropathy (Galatti L et al, 2005).

Drug-drug interactions with fluoroquinolones occur with the following drugs: sucrafate, probenecid, cimetidine, theophylline, warfarin, antiviral agents, phenytoin, cyclosporine, rifampin, pyrazinamide and Cycloserine (Fish DN, 2001).

Clinical study comparing the efficacy and safety of levofloxacin with ceftriazone and/or cefuroxime axetil

In a multicenter, prospective, randomized study to compare the efficacy and safety of levofloxacin with ceftriazone and/or cefuroxime axetil for adults with CAP, five hundred and fifty-six patients were evaluated for clinical efficacy. Two hundred and twenty-six received either intravenous levofloxacin followed by oral levofloxacin or only oral levofloxacin 500mg once daily while the other 230 received ceftriazone 1g 12hly or 2g daily followed by cefuroxime axetil 500mg twice daily. Erythromycin or doxycycline was added to the ceftriazone or cefuroxime for patients with infection with atypical bacteria. Microbiological evaluation was done 5-7days and 3-4 weeks after treatment respectively. Clinical success at 5-7days posttherapy for the levofloxacin group was 96%compared to 90% for the ceftriazone and/or cefuroxime axetil group. Both levofloxacin and ceftriaxone/cefuroxime eradicated 100% of both H. influenzae and S. pneumoniae isolated. For

atypical organisms (Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophilla) levofloxacin eradication was 98% compared to 85% for ceftriazone and/or cefuroxime axetil therapy (Thomas M. File Jr et al, 1997).

Clinical study to compare the treatment outcome of fluoroquinolones with those of beta-lactams and macrolides for community-acquired pneumonia

A meta-analysis to investigate whether the use of fluoroquinolones for the treatment of CAP was associated with better clinical outcomes compared with beta-lactams and macrolides was conducted with 23 trials. Evidence revealed that pneumonia patients who received fluoroquinolones recovered more compared with those on beta-lactams plus macrolides but found no difference in mortality between the two groups. It concluded that fluoroquinolones are superior to beta-lactam plus macrolide for pneumonia treatment (Konstantinos Z. Vardakas et al, 2008).

Clinical study to assess the efficacies of azlocillin, ciprofloxacin and tobramycin

The efficacies of azlocillin, ciprofloxacin and tobramycin used alone and in combination in experimental Pseudomonas sepsis were compared. Ciprofloxacin alone in all doses reduced mortality significantly. Tobramycin at higher doses also reduced mortality significantly. In contrast, at all doses of azlocillin and lower doses of tobramycin mortality was not improved. However, a combination of ciprofloxacin and azlocillin improved mortality more than ciprofloxacin alone (Johnson M et al, 1987).

Co-trimoxazole (Trimethoprim/Sulphamethoxazole)

Co-trimoxazole is a broad spectrum antibiotic consisting of one part of Trimethoprim to five parts of Sulfamethoxazole. The two antibacterial components have a synergistic effect (bactericidal) when combined. Individually, they are bacteriostatic. It is a folate synthesis inhibitor. The sulfamethoxazole inhibits the de novo synthesis of folate in the bacterial cell (protozoa and fungi as well) by competing with P-aminobenzoic acid (PABA) for the synthesis of dihydrofolate. Trimethoprim is a competitive inhibitor of dihydrofolate reductase (DHFR) resulting in tetrahydrofolate synthesis (Womser GP et al, 1982).

Due to its wide spectrum of antibacterial activity it is indicated for respiratory infections, urinary tract infections, GIT infections, skin and wound infections and septicaemia (Falagas ME et al, 2008).

Pharmacokinetics

Co-trimoxazole has a peak serum concentration between 1-4h after oral administration. The volume of distribution is 20L for sulfamethoxazole and 130Lfor trimethoprim. Protein binding is 66% for sulfamethoxazole and 42-45% for trimethoprim. Half-life for both components is between 8-10hrs. Excretion is by renal route.

Co-trimoxazole is contra-indicated in patients with hypersensitivity to the components of the drug, severe liver disease, severe haematological disorders, porphyria, severe renal insufficiency, and in neonates (≤ 6 weeks old) (Brumfitt W et al, 1994). Bramfelt et al, 1994, showed that trimethoprim alone could be used for common infections which co-trimoxazole is used to reduce the adverse effects seen with the combination of sulfamethoxazole/trimethoprim in cotrimoxazole.

Clinical study comparing the efficacy of co-trimoxazole with amoxicillin for the treatment of pneumonia

In a randomized controlled, double blind, multicenter study to compare the clinical efficacy of co-trimoxazole with twice daily dosing of amoxicillin for the treatment of pneumonia in Pakistan 1,459 children with non-severe pneumonia were recruited. Seven hundred and twenty-five randomly received amoxicillin and 734 received co-trimoxazole. Treatment failure of 16.8% was recorded for amoxicillin group compared to 18.9% for the Co-trimoxazole group. Based on multivariate analysis in both groups, treatment failure was shown to be more likely in infants with history of difficulty in breathing or those who had been ill for more than 3 days before presentation. It was therefore concluded that amoxicillin was as effective as co-trimoxazole for the treatment of non-severe pneumonia (Arch Dis Child, 2002).

Clinical study to assess the effectiveness of co-trimoxazole for the treatment of bacterial infections

The resistance of *Streptococcus pneumoniae* isolated from children to antibiotics in a crosssectional community study in a general practice setting in Canberra (1998) was analyzed. Four hundred and sixty-one children less than 3yrs were enrolled. One hundred and seventy-one of the 461 nasal swabs collected isolatedS. pneumoniae. Of the isolates, 12.3% showed resistance to penicillin, 44.4% to co-trimoxazole, 18.1% to erythromycin and 19% were multi-drug resistant. It was shown that co-trimoxazole was losing its effectiveness against most organisms but as shown

in another study by Jihad B et al (1997) on the susceptibility of bloodstream MRSA isolated from adult patients in one hospital to co-trimoxazole, susceptibility increased progressively from 31% in 1988 to 92% in 1997. These results were observed to correlate with a decline in the usage of co-trimoxazole in that institution. By inference, co-trimoxazole could be made more effective as a cheaper alternative to treating MRSA hospital-acquired infections if its usage is minimized to reduce bacterial resistance.

Co-trimoxazole, penicillin G and benzathine penicillin plus procaine penicillin compared for the treatment of pneumonia

In a clinical trial comparing co-trimoxazole, procaine penicillin and benzathine penicillin plus procaine penicillin in the treatment of childhood pneumonia, 151 patients aged 4months to 14years were recruited in Capa Children's Hospital in Istanbul. One group (N=46) received cotrimoxazole orally for 10 days, the second group (N=63) received intramuscular procaine penicillin G for 10 days and the 3rd group (N=42) received benzathine penicillin G combined with procaine penicillin G given as a single dose. Clinical outcome for procaine penicillin therapy was the most impressive (Sidal M, et al, 1994).

Chloramphenicol

Chloramphenicol, a once broad-spectrum antibiotic has been relegated to the background due to bacterial resistance and serious side effects. However, the recent global concerns about the continuous rise in bacterial resistance to newer antibiotics have rekindled the interest for research to improve this drug (Falagas ME et al, 2008).

Pharmacodynamics

Chloramphenicol is a protein synthesis inhibitor and bacteriostatic antibiotic. It inhibits peptidyl transferase activity by binding to A2451 and A2452 residuesin the 23S ribosomal RNA of the 50S ribosomal sub-unit (Schifano JM et al,2013).

Pharmacokinetics

It is administered orally, intravenously or intramuscularly. It is absorbed rapidly following oral administration and has 75-90% oral bioavailability. Plasma protein binding is 60% and a half-life of 1.6-3.3hrs. The liver is the main site of metabolism. Chloramphenicol inhibits cytochromeP450 isoforms (CYP3A4 andCY2C19) hence interacts with several drug metabolisms (Park JY et al, 2003). About 5-15% is excreted in the urine.

Adverse effects

The major adverse effect is bone marrow suppression as a result of direct toxicity of the drug (Yunnis AA, 1989). Others are leukemia (Shu X et al, 1987), gray baby syndrome and hypersensitivity reaction. Headache, mild depression, mental confusion and delirium have also been reported.

Clinical study comparing chloramphenicol with ampicillin/gentamicin combination

The SPEAR study compared treatments for very severe community acquired pneumonia with chloramphenicol versus ampicillin and gentamicin combination in children age 2-59months in poor resource settings in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen and Zambia. A total of 958 children were enrolled in the study from all the centers together. One group (n=479) received injectable ampicillin and gentamicin and the other group (n=479) received

chloramphenicol (two children were lost to follow up in the chloramphenicol group). At 48-60h assessment 447 improved in the ampicillin and gentamicin group and 425 in the chloramphenicol group. At day 5 assessment, 428 improved and 9 failed treatment in the ampicillin-gentamicin group while 402 improved and 8 failed treatment in the chloramphenicol group. At days 10-12, four hundred and seventeen (417) were cured in the ampicillin-gentamicin group and 393 cured in the chloramphenicol group. 407 children in the ampicillin-gentamicin group compared with 382 in the chloramphenicol group were cured at day's 21-30 assessment. It was therefore concluded that injectable ampicillin plus gentamicin is more effective than chloramphenicol for the treatment of very severe community acquired pneumonia in children age 2-59months (Rai A, et al, 2008).

Glycopeptides

Glycopeptide antibiotics are glycosylated cyclic or polycyclic non-ribosomal peptides. They exert their bactericidal action by inhibiting peptidoglycan synthesis to disrupt bacterial cell wall formation. This is achieved by binding to the amino acids acyl-D-alanyl-D-alanine in the peptidoglycan. They include vancomycin, teicoplanin, telavancin, ramoplanin and decaplanin, and the anti-tumour,bleomycin. Only vancomycin, teicoplanin and telavancin are of clinical value with respect to pneumonia and other systemic infections. Their use is restricted to critically ill patients with beta-lactam resistant Gram-positive bacteria including MRSA and multi-drug resistant Staphylococcus epidermidis. Some Gram-negative bacteria like some non-gonococcal Neisseria spp. are however susceptible.

Vancomycin is the drug widely used in this class. It is a branched tricyclic glycosylated nonribosomal peptide, produced by the *Actinobacter spp*. It is indicated for the treatment of Grampositive septicaemia, complicated CAP and HAP, skin and bone infections. Other indications include pseudomembranous colitis since it is poorly absorbed orally. Lactobacillus spp. except *Lactobacillus acidophilus* and *L. delbruekii*, *Erysipelothrix rhusiopathiae*, *Weissella confusa* and *Clostridium innocuum* are intrinsically resistant to vancomycin (Hamilton-Miller JM, et al, 1998; Romney M, et al, 2001). Recently, some Enterococcus spp and some Staphylococcus have acquired resistance to vancomycin (McDonald LC, et al, 2005). Vancomycin is mainly administered intravenously. Biological half-life after intravenous administration is 4-11hrs in adults but prolonged in renally impaired individuals to 6-10days. It is excreted unchanged in the urine (Van Bambeke F, 2006). Side effects include pain at site of injection, thrombophlebitis, nephrotoxicity, ototoxicity. Other rare side effects include anaphylaxis, toxic epidermal necrolysis, erythema multiforme, redman syndrome, superinfection, thrombocytopenia and neutropenia (Dragalski A et al, 2007). Concomitant use with aminoglycoside increases nephrotoxicity and ototoxicity (Farber BF, et al, 1983).

Teicoplanin is a semi-synthetic glycopeptide similar inmechanism of action and antibacterial coverage as vancomycin but has improved pharmacokinetic properties over vancomycin. It is administered intramuscularly, intravenously or orally with a bioavailability of 90% after intramuscular administration. Plasma protein binding ranges from 90-95% and has a biological half-life of 70-100hrs. It is largely (97%) excreted unchanged in the urine (Jung HM, et al, 2009; Bernareggi A, et al, 1992).

Telavancin is a lipoglycopeptide and a semi-synthetic derivative of vancomycin (Huggins DL, et al, 2005). It is effective against complicated skin and skin structure infections and S. aureus

hospital-acquired and ventilator-associated pneumonia. Telavancin is administered intravenously with 90% bound to plasma proteins and has a biological half-life of 9hrs. It is excreted in urine (76%) and less than 1% in faeces. Telavancin comes with relatively fewer side effects than vancomycin. However, it has been shown to be more nephrotoxic than vancomycin (Saravolatz LD, et al, 2009). It is not approved for use in children and adolescents younger than 18yrs.

Oxazolidinones

The oxazolidinones are heterocyclic five-membered ring compounds which inhibit protein synthesis by inhibiting the initiation step involving the prevention of the formation of Nformylmethionyl-tRNA to the 50S ribosomal subunit for protein synthesis (Shinabarger D, 1999). They are active against a wide range of Gram-positive bacteria including MRSA, vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant enterococci (VRE), penicillin-resistant pneumococci and anaerobes (Sztanke K, et al, 2004). They have extensive tissue distribution and accumulate well in lung, haematoma, vegetion and cerebrospinal fluid (CSF) (Bozdogan B, et al, 2004). Oxazolidinones include**linezolid, posizolid, tedizolid, radezolid**. Linezolid and tedizolid are clinically approved for use with linezolid currently the only oxazolidinone approved for hospital acquired pneumonia treatment.

Linezolid (1,3-oxazolidinone) covers most Gram-positive bacteria including Streptococci, vancomycin-resistant enterococci (VRE) and MRSA but is not effective clinically against most Gram-negative bacteria including Pseudomonas and Enterobacteriaceae (Davaro RE et al, 2004). It binds to the 23S portion of 50S submit close to the binding sites of other antibiotics including chloramphenicol and lincomycin (Colca JR et al, 2003). Linezolid is administered orally and intravenously. Oral bioavailability is nearly 100%. Absorption is however slowed by meal. The peak serum concentration is 1-2hrs after drug administration. It does not penetrate into bone and

white adipose tissue (Barbachyn MR et al, 2003). It readily distributes to most tissue notably the lungs. The concentration in the epithelial lining fluid of the respiratory tract is usually more than in the serum and poorly crosses the blood-brain barrier hence its concentration in the CSF is lower than in the serum (Hermann DJ et al, 2008). Plasma protein binding is 31%. Fifty to 70% of the drug is metabolized in the liver without cytochrome-P450 system involvement. The biological half-life is 4.2 to 5.4hrs. The clearance of linezolid is dependent on age and gender and is fastest in children and faster in men than in woman (Sisson TL et al, 2002). It is eliminated to a large extent in the urine and to a less extent in feces. Adverse effects commonly encountered are headache, nausea and vomiting, rash, constipation, altered taste perception discoloration of tongue, oral thrush, and vaginal candidiasis (Lexi-comp, 2008). Less common but serious side effects include allergic reactions, pancreatitis, and elevated liver enzymes, pseudomembranous colitis, peripheral neuropathy, bone marrow suppression (Zabel LT et al, 2005). Linezolid should not be taken with mono-oxidase inhibitors like tyramine-rich foods such as pork, cheese, alcoholic beverages or smoked or pickled foods or co-administered with serotonergic drugs like paroxetine and sertraline, sympathomimetic drugs (pseudoephedrine or phenylpropanolamine) and meperidine (Stalker DJ et al, 2003; Lawrence KR, et al, 2006).

Tedizolid, a second generation oxazolidinone, is effective for the treatment of serious skin and skin structure infections. It is 4-16 times more potent than linezolid against Staphylococci and Enterococci. It is formulated as tedizolid phosphate (prodrug) and administered orally or intravenously. It is metabolized to the active drug, tedizolid, in the liver. Bioavailability is 91% and is 70-90% bound to plasma proteins. Tedizolid has a biological half-life of 12hrs and excreted in the faeces (US-FDA, 2014).

Clinical study to compare ceftobiprole with ceftazidime plus linezolid

In a phase 3 randomized double-blind multicenter study, ceftobiprole was compared with ceftazidime plus linezolid for the treatment of nosocomial pneumonia. Seven-hundred and eighty-one patients with HAP were recruited. Out of this 210 had ventilator-associated pneumonia (VAP). Intravenous ceftobiprole 500mg was administered every 8hly to one group and ceftazidime 2g 8hly plus linezolid 600mg 12hly were administered to the other group. The results showed that the overall cure rate for ceftobiprole was 49.9% compared with 52.8% for ceftazidime/linezolid. For clinical outcome the cure rates for ceftobiprole was 69.3% and 71.3% for ceftazidime/linezolid respectively. For HAP alone cure rate for ceftobiprole was 59.6% and 58.8% for ceftazidime/linezolid, while for VAP the cure rate for ceftobiprole was 23.1% as against 36.8% for ceftazidime/linezolid. The microbiological eradication rates in patients were 62.9% for cetobiprole and 67% for ceftadizime/linezolid. It was concluded that ceftobiprole is safe and effective for the empiric treatment of HAP excluding VAP (Samir S. Awad et al, 2014).

Streptogramins

Streptogramins are antibiotics that consist of one part with macrolactone structure and the other with hexadepsipeptide structure. The macrolactone molecules are classified as group A streptogramins and the hexadepsipeptide as group B streptogramins. Both inhibit protein synthesis by binding to the 50S ribosomal subunit to prevent the elongation process of protein synthesis. The combined effects of these molecules are synergy and prevention of bacterial resistance. Both group A and group B streptogramins concentrate in macrophages and bacterial vegetations (Khosla R, et al, 1999). They are broad-spectrum covering both Gram-positive and Gram-negative bacteria including vancomycin-resistant Staphylococcus aureus (VRSA) and vancomycin-resistant

Enterococcus (VRE). Antibiotics in this class are quinupristin/dalfopristin, pristinamycin, virginiamycinandNXL-103 (Baucheer HW, et al, 2009).

Quinupristin/dalfopristin is a combination antibiotic of two streptogramins: quinupristin and dalfopristin. Both are bacteriostatic independently but bacteriocidal when combined. Dalfopristin changes the conformation of 50S ribosomal subunit by binding to the 23S portion of it. This improves the binding of quinupristin to a site close to the 50S subunit to prevent polypeptide elongation. It is administered intravenously and has a half-life of 1-3hrs with a longer postantibiotic effect. It is eliminated by the liver and inhibits CYP-450 system. Side effects include arthralgia, nausea and vomiting, diarrhoea, rashes, headache, phlebitis and hyperbilirubinaemia. It interferes with the metabolism of the following drugs: terfenadine, astemizole, indinavir, midazolam, calcium-channel blockers, warfarin, cisapride and ciclosporin (William BH, et al, 2004).

Pristinamycin is composed of pristinamycin IA (a macrolide similar to erythromycin) and pristinamycin IIA (a depsipeptide). Both bind to the 50S ribosomal subunit and inhibit the elongation process of protein synthesis. Water-soluble formulation has made it possible, in recent time, to be used intravenously (William BH, et al, 2004).

Lincosamides

Clindamycin and lincomycin are lincosamide antibiotics which inhibit bacterial protein synthesis by binding to the 50SrRNA of the bacterial ribosome similar to macrolides. Clindamycin has largely replaced lincomycin due to its better pharmacologic profile.

Clindamycin has coverage against aerobic Gram-positive cocci including Staphylococcus and

Streptococcus spp., anaerobic gram-negative rod-shaped bacteria including some *Bacteroides sp, Fusobacterium* and *Prevotella.* In contrast, *Bacteroides fragilis, Pseudomonas, Legionella, H. influenzae, Moraxella* and the facultataive anaerobic Enterobacteriaceae are resistant to clindamycin (Bell EA, 2005; Gold et al, 1999).

Clindamycin is effective in the treatment of dental infections, respiratory infections, skin and soft tissue infections, peritonitis, bone and joint infections (Darley ES et al, 2004).

For methicillin-resistant staph aureus (MRSA) infections clindamycin is useful hence its use in hospital acquired pneumonia.

It may be used in place of penicillin in penicillin-allergic individuals. It isavailable for intravenous and oral administration. Bioavailability after oral administration is 90% and protein binding is 95%. The liver is the main site of metabolism. The half-life is 2-3hrs and is excreted mainly in the bile and about 20% in the urine.

Adverse reactions

Adverse effects include diarrhea, pseudomembranous colitis, nausea and vomiting, abdominal pain or cramps and or rash. Other rare side effects include anaphylaxis, blood dyscrasias, polyarthritis, jaundice, renal dysfunction, cardiac arrest, hepatotoxicity (Rossis, 2006; Australian Medicnes Handbook).

Drug-drug interactions

It should not be given together with macrolides and chloramphenicol because of similarity of actions and the resultant effect is antagonism (Bell EA, 2005).

It prolongs the effect of neuromuscular blocking agents such as succinylcholine and vecuronium (Fogdall RP et al, 1974; Sloan P.A et al, 2002).

Clinical studies to assess the efficacy of clindamycin for treating aspiration pneumonia

The efficacy of clindamycin in the treatment of aspiration pneumonia in children was investigated in 28 children with anaerobic pleuropulmonary infections treated with clindamycin alone or clindamycin with gentamicin. Sixteen children had pneumonitis, nine had necrotizing pneumonia, and 3 with lung abscesses. The predominant isolates were anaerobic gram-positive cocci (*Bacteroides melaninogenicus, Bacteroides fragilis*), *Fusobacterium nucleatum*, Alphahemolytic streptococci (Diplococcus pneumoniae), *Pseudomonas aeruginosa, Kletosiella pneumoniae,* Group A beta-hemolytic streptococci, *Staph aureus*, and *E. coli*. Cure rate was 100% with both treatments. It was concluded that clindamycin is effective in treating mixed aerobic and anaerobic infections alone or with an aminoglycoside (Itzhak Brook, 1979).

The ZEPHyR Study

Inconclusive results of several clinical trials and meta-analysis have resulted in different recommendations by various guidelines; the ATS/IDSA guideline on hospital-acquired pneumonia or ventilator-acquired pneumonia (HAP/VAP) does not recommend the use of linezolid in patients with HAP/VAP whereas the German sepsis guideline recommends linezolid in MRSA pneumonia and warns against vancomycin monotherapy.

In order to resolve this problem, Pfizer initiated a study to compare linezolid to vancomycin for the treatment of MRSA pneumonia.

Four hundred and forty-eight patients with MRSA pneumonia were enrolled but 339 patients met key protocol criteria; 165(68.3%) patients were treated with linezolid and 174 (74.5%) with vancomycin. Both groups were ventilated at baseline. Clinical success rate for patients receiving linezolid was 57.6% (95/165) compared to 46.6% (81/174) for patients receiving vancomycin. Linezolid was shown to achieve a statistically significant higher clinical success rate compared to vancomycin.

The evidence gathered showed that vancomycin, despite low resistance rate, should not be the drug of first choice in critically ill patients.In MRSA infections vancomycin can be combined with rifampin to overcome poor tissue penetration and slow bactericidal action (Jung YJ, et al, 2010) but cautions the risk of emerging resistance to rifampin and drug-drug interactions.

Other treatment options available are Tigecycline (± ceftazidime) but this is inferior to imipenem (± vancomycin) (Freire AT et al, 2010).

Quinupristin-dalfopristin is used against MRSA infections in some European countries but not in the USA due to its inferiority to vancomycin in clinical trials (Fagon JY et al, 2000).

Linezolid is currently the only drug superior to vancomycin for the treatment of MRSA pneumonia.

Novel antibiotics

The growing numbers of bacteria resistant to most antibiotics in clinical practice over the years has necessitated the search for a single agent that is immune to bacterial resistance. Few such antibiotics are under development and notable among them is the Human Alpha-lactalbumin Made Lethal to Tumor cells (HAMLET). This is a human milk lipid-protein complex which has anti-

tumor activities and also increases bacterial sensitivity to multiple classes of antibiotics (antibiotic adjuvant) such as methicillin, vancomycin, gentamicin and erythromycin (Marks LR, et al, 2013). It is bactericidal to *Streptococcus pneumoniae* employing a different mechanism different from conventional antibiotics which is immune to bacterial resistance. It has been shown that sub-lethal concentrations of HAMLET work synergistically with common antibiotics (penicillin, macrolides and aminoglycosides) below their MICs against pneumococci. A biofilm model in vitro and nasopharyngeal colonization in vivo were completely eradicated by the combinations of HAMLET and these antibiotics. Similar effects were observed against *Acinetobacter baumaniiand, Moraxella catarrhalis* (HAMLET-resistant respiratory species) (Laura R, et al, 2012). This finding also strongly supports the fact that breastfeeding decreases the incidence of infectious diseases including bacterial meningitis, bacteremia, diarrhoea, respiratory infections and otitis media (Rudan I, et al, 2008).

Another novel antibiotic, **teixobactam**, currently at its preclinical stage inhibits cell wall synthesis by binding to lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid). It was observed during a preclinical trial that Staph aureus and Mycobacterium tuberculosis were not able to show any mutant strains to teixobactam, which is likely to avoid development of resistance by bacteria to it (Losee L, et al, 2015).

Other antibiotics for respiratory infections in various stages of clinical trials are: Ceftobiprole, Cethromycin, Nemonoxacin, Radezolid and KPI-10 (Fluoroquinolone) (www.biocentury.com).

Viral pneumonia

Treatment of most viral pneumonia generally is by supportive treatment. Such viral pneumonias include those caused by SARS, coronavirus, adenovirus, Hantavirus, para-influenza virus or H1N1 virus.

In cases of pneumonia caused by influenza A or B, **Oseltamivir** or **Zanamivir** may be beneficial within 48hrs of onset of symptoms. Respiratory syncytial viral pneumonia responds to **ribavirin** treatment. **Acyclovir** is effective against herpes-simplex virus (HSV) and varicella-zoster virus (VZV) infections. **Ganciclovir** is indicated for cytomegalovirus (CMV) pneumonia.

Oseltamivir

Oseltamivir is a viral neuraminidase enzyme inhibitor hence blocks neuraminidase action on sialic acid (neuraminic acid) found on the surface of normal host cells thereby preventing the release of new viral particles (Agrawal R, et al, 2010). Oseltamivir is a prodrug converted to its active metabolite oseltamivir carboxylate. Oral bioavailability is over 80%. Volume of distribution is estimated between 23-26L. Half-life of active metabolite is between 6-10h, and that for the prodrug is 1-3h. It is excreted in the urine as the active metabolite (Davies B E, 2010).

Side effects include nausea and vomiting. Other uncommon side effects include hepatitis, rash, allergic reactions including anaphylaxis, toxic epidermal necrolysis, cardiac arrhythmia, seizure, confusion, aggravation of diabetes, hemorrhagic colitis and Steven-Johnson syndrome (Rossi S, Australian medicine handbook, 2006).

Zanamivir

Zanamivir is a neuraminidase inhibitor which binds to the active site of the viral neuraminidase enzyme thereby blocking the release of new virons from the host cell. It is indicated for the prevention and treatment of influenza A and B infections. It is administered intravenously and also available as inhalational powder but contraindicated in asthmatics and chronic obstructive pulmonary disease (COPD) patients (Hayden FG, 2001). Oral bioavailability is 2% and plasma protein binding is less than 10%. The biological half-life is 2.5-5.1hrs. It is excreted renally (Moscona A, 2005).

Ribavirin

Ribavirin is a guanosine analog (nucleoside inhibitor) that interferes with viral RNA synthesis and mRNA capping. It is a prodrug metabolized in the liver to purine RNA nucleotides (Carter John et al, 2007). Ribavirin is indicated for RSV pneumonia, Hepatitis C, viral haemorrhagic fever, Hepatitis B and HIV (mediscape reference, 2014). Combined with ketamine, midazolam and amantadine it has been used for rabies treatment (Hemachudha T, et al, 2013). The routes of administration of ribavirin are oral and inhalational. The bioavailability after oral administration is 64%. It undergoes hepatic metabolism and has a plasma half-life of 43.6 hours after a single dose and 298 hours after multiple doses. It is excreted in the urine (61%) and about 12% in the faeces (Merck Sharp and Dohme Ltd, 2013).

Clinical study on the effect of antiviral treatment on the outcome of secondary bacterial

pneumonia

The effect of antiviral treatment on the outcome of secondary bacterial pneumonia after influenza was studied in mouse models with secondary pneumococcal pneumonia after influenza. Twenty-two (22) mice were studied. It was observed that treatment with oseltamivir improved survival from 0% to 75%. Treatment with rimantadine had no effect on survival.

Survival improved after oseltamivir treatment with ampicillin to 100%. It concluded that treating severe viral pneumonia with appropriate antiviral drugs improves the survival in persons with secondary bacterial pneumonia on antibacterials (McCullers JA, 2004).

ADJUNCTIVE THERAPY

Management of cough

Cough is usually one of the disturbing symptoms that prompts parents to seek medical care for their children. In most cases of mild coughs, over-the-counter cough medicines are used as first aids and when there is no remission they are prompted to visit the hospital for appropriate medical care. Although cough is not a cardinal symptom of pneumonia it defines conditions that heralds pneumonia such as upper respiratory tract infections, bronchitis and bronchiolitis (Redington A, et al, 2005). Cough is the body's natural mechanism for clearing the respiratory tract of 'debris' (Chung KF, et al, 2008). While there is no clinical evidence for or against the use of cough medicines they continue to be prescribed for symptomatic treatment of cough (Smith SM, et al, 2014). Currently, the cough medicines available are composed of one or more of the following compounds: Expectorants (guaifenesin), mucolytics(acetylcysteine and carbocisteine), cough

suppressants/antitussives(codeine, dextromethorphan, noscapine and cloperastine), antihistamines (e.g. diphenhydramine), decongestants (e.g. ephedrine), antipyretics (acetaminophen, ibuprofen).

Acetylcysteine(N-acetylcysteine or acetyl-L-cysteine) is a derivative of cysteine where acetyl group is attached to the nitrogen atom. It is used as a mucolytic for the management of cough that may be associated with pneumonia due to its ability to cleave the disulfide bonds in the mucoproteins in mucous secretion to reduce its viscosity for easy expectoration. (Tse HN, et al, 2013). Acetycisteine also has some anti-inflammatory activity possibly by inhibiting NF-kB and modulating cytokine synthesis (Berk M, et al, 2013). It is available for oral, injection and inhalation administration. Bioavailability after oral administration is 4-10% due to high first-pass metabolism and this limits its oral use. It has minimal CYP-450 induction. Half-life is 5-6 hours in adults and 11 hours in neonates. It is excreted in the urine (Borgstom L, et al, 1986).

Guaifenesin, derived from the guaiac tree, works by increasing the volume and reducing the viscosity of secretionsin the respiratory tree by dilution. This increases the efficiency of cilliary movement and the cough reflex to facilitate the removal of secretions (Gutierrez K, 2007). It is formulated in oral form and has a half-life of 1-5 hours. It is metabolized and excreted by the kidneys (Aluri JB, et al, 1993).

Codeine is a naturally occurring methylated morphine used as an anti-cough medicine (antitussive), analgesic and anti-diarrhoea. Its use in children is limited by its numerous unwanted side effects such as sedation and respiratory depression.

Dextromethorphan, a non-opiod antitussive, is the D-isomer of methorphan and in low doses is used in over-the-counter preparations for suppression of cough. In high doses, it is a dissociative hallucinogen. It is rapidly absorbed from the gut following oral administration and converted by

the liver to dextrorphan, the active metabolite. It enters the central nervous system (CNS) by raising the threshold for cough. The half-life is 8hours for dextromethorphan-hydrobromide and10-12hours for dextromethorphan-polistirex. Caucasians are slow metabolizers of dextromethorphan due to the lack of CYP2D6 enzyme activity resulting in prolonged drug effect (Morice AH, International society for the study of cough). Because of its ability to trigger histamine release it is contraindicated in atopic children.

Noscapine is also known as narcotine, nectodon, anarcotine or opiane. It is a benzylisoquinoline alkaloid derived from the poppy plant family and acts centrally via gamma- receptors to effect antitussive activity (Singh H, et al, 2013). Its numerous opiod side effects limit its use in children.

Diphenhydramine is a first generation antihistamine possessing antitussive, anticholinergic, antiemetic and sedative properties. Its stabilization of mast cells and consequent inhibition of histamine release is employed to reduce secretion in the respiratory tract. Other uses include the treatment of allergy, extrapyramidal symptoms caused by antipsychotics (Aminoff MJ, 2012). Others are insomnia, vomiting in motion sickness (Zachary Flake, et al, 2004). Its routes of administration are oral, intravenous, intramuscular, topical and rectal. Oral bioavailability is 4060% and plasma protein binding is 98-99%. It is metabolized in the liver under various CYP-450 liver enzymes. The biological half-life in children is 7hrs, 12hrs in adults and 17hrs in the elderly (Simons KJ, et al, 1990). Ninety-four percent of diphenhydramine is excreted renally and 6% in feces (Garnett WR, 1986). Side effects include dry mouth, palpitation, pupil dilation, urinary retention, constipation, and hallucination/delirium. Others are ataxia skin flush, blurred vision, photophobia, amnesia, warm hands and feet and erectile dysfunction. It is not recommended for children less than 6yrs and patients older than 60yrs; alternatively, loratadine, desloratadine,

fexofenadine, cetirizine, levocetirizine or azelastine may be used in these age groups (Brunton L, et al, 2011).

Novel antitussives

The unsatisfactory clinical effects of the current cough medicines available has necessitated the search for newer agents like **levodropropizine** and **moguisteine** which are peripherally acting antitussives devoid of CNS side effects (De Blasio et al, 2012).Both levodropropizine (Zanasi et al, 2015) and moguisteine (Del Donno M, et al, 2012) have been shown to be effective in both pediatric and adult populations.

Management of fever

Fever is a common symptom in paediatric patients and the most common cause of anxiety in parents that causes them to seek medical care for their children (NICE Clinical Guideline, 2007). Fever is present in 88-96% of all paediatric pneumonia cases (Don M, et al, 2010). It is known that fever to some extent is beneficial to the body's immune response (Schmitt BD, 1980). High fever should be treated for the comfort of the child and to relieve anxiety of the parent (Casteelsvan Daele M, et al, 1991).

Ibuprofenand **acetaminophen** are the recommended antipyretics for children. Studies have shown that both drugs are more effective than placebo (Chappini E, et al, 2009). Combined or alternating acetaminophen and ibuprofen is recommended by many articles (Pashapour N, et al, 2009) but according to a guideline on fever management combined acetaminophen and ibuprofen or alternating ibuprofen and acetaminophen is not recommended (Chiappini E, et al, 2009). The use

of antipyretics should not be routine in the management of the febrile child (Robinson JL, et al, 1998). Non-pharmacological methods like tepid sponging may be used instead (Casteels-van Daele M, et al, 1991). Antipyretics are recommended if the child is crying excessively, irritable, less active and there is sleeplessness (Hay AD, et al, 2008).

Corticosteroid Therapy

Antibiotic-induced immunopathology following bacterial cell wall lysis contributes to poor outcomes in secondary bacterial pneumonia. Adjunctive corticosteroid therapy was investigated to improve lung immunopathology and survival during severe secondary pneumococcal pneumonia in mice models of streptococcal pneumonia following influenza. Ampicillin treatment was observed to cure mice with mild pneumonia but treatment failure was observed in the mice with severe pneumonia despite bacterial eradication. It was however noted that those mice with severe secondary bacterial pneumonia treated with dexamethasone and ampicillin improved. It was suggested that it is beneficial employing adjunctive corticosteroid in severe community acquired pneumonia (Ghoneim HE, et al, 2014).

CHAPTER THREE

METHODOLOGY

StudyDesign and Site

This was a prospectivenon-randomized observational study done at two hospitals in the Ashanti regionof Ghana from January 2015 to November 2015. The hospitals were Agogo Presbyterian Hospital in the Asante-Akyem North District and Kumasi South Hospital in Kumasi Metropolis.

The criteria for selecting the study sites were based on location, size and level of care. For location, urban and rural settings were compared to see it had any influence on the prevalence of pneumonia and quality of care. The size of the hospital in terms of staff strength, logistics and patient attendance were also compared.

Agogo Presbyterian Hospital

Agogo Presbyterian Hospital is a faith-based hospital established in 1931 primarily to provide health care services to the rural communities in the Asante-Akyem district and neighboring districts. Although a district hospital, the range of services provided including tertiary education has elevated it to a teaching hospital status where nurses, physician assistants and house officers are trained. It has an average daily out-patient attendance of 285 patients per day (this excludes eye, dental and physiotherapy) with 57 patients per day being children less than five years and the average under five pneumonia cases per day is one per day (Hospital Records Unit, 2014). The hospital has a 215 bed compliment with 22 doctors and 142 nurses. The range of services provided include maternal and child health, pediatrics, gynecology, surgery, general medicine, ophthalmology, buruli ulcer care, pharmacy, laboratory (including a research laboratory- KCCR) and public health.

The pediatric unit is composed of a pediatric out-patient department with two consulting rooms and a 60 bed capacity ward. The pediatric ward is equipped with four (4) oxygen cylinders, one (1) nebulizer, thermometers, sphygmomanometers, an ambu-bag and one non-functional patient monitor. The unit is manned by one consultant pediatrician, three (3) resident pediatricians and two(2) house officers and 14 nurses.

The services provided by the laboratory include hematology and blood bank, chemistries and microbiology excluding culture and sensitivity tests. Culture and sensitivity tests are occasionally supported by KCCR.

The pharmacy has a staff strength of sixteen(16) made up of one pharmacist, two intern pharmacists, eleven(11) dispensary technicians and two(2) medicine counter assistants. The unit is stocked with a wide range of drugs for the treatment of various conditions. Antibiotics in stock were amoxicillin, co-amoxiclav, ampicillin and flucloxacillin. Others were cefuroxime, ceftriaxone, ciprofloxacin, clindamycin, streptomicin, gentamicin, tetracyclines, azithromycin, erythromycin, metronidazole, co-trimoxazole and chloramphenicol.

Kumasi South Hospital

Kumasi South Hospital is the designated regional hospital of Ashanti Region. It has 18 doctors and over 100 nurses. It is a 61 bed complement hospital. The average out-patient attendance is 283 patients per day with children under five years being 45 per day. The average under five pneumonia cases per day is1 per day (Hospital Records Unit, 2014).

Services provided include general medical care, surgery, maternal and child health, herbal medicine, pharmacy, laboratory, radiology (x-ray/ ultrasoundscan) and public health.The range of

services provided by the laboratory includes hematology and blood bank, chemistries and microbiology excluding culture and sensitivity. Culture and sensitivity is supported by the public health reference laboratory situated on the same premise of the hospital.The pharmacy, most of the time during the study, was stocked with a wide range of drugs including antibiotics such as crystalline penicillin, ampicillin, amoxicillin, co-amoxiclav and flucloxacillin. Others are cefuroxime, ceftriaxone, erythromycin, azithromycin, levofloxacin, ciprofloxacin, clindamycin, gentamicin, metronidazole and co-trimoxazole.

Estimation of Sample Size

The sample size was estimated based on the following:

1. The Study Design
2. Information on the incidence of pneumonia in the respective hospitals
3. The level of precision (allowable sampling error)
4. The confidence interval (The risk of selecting a 'bad' sample e.g. a misdiagnosis)
5. The degree of variability

The statistical formula below developed by Yamane (1967) was used to estimate the minimum size for this study.

$$\mathbf{n} = \frac{\mathbf{N}}{\mathbf{1} + \mathbf{N}(\mathbf{e})^2}$$

Where: **n**= Sample size **N**= Population size **e** = Level of precision at a confidence level of 90%

(Assumption: degree of variability= 0.5)

Therefore, using the average pneumonia casesfor the two hospitals i.e. 429, the minimum sample size calculated was as follows:

$$n = \frac{429}{1 + 429(0.1)^2}$$

$$n = 81.1$$

$$\therefore n \cong 82$$

From the above calculation, a minimum sample of 82 children with pneumonia were considered for the study.Ninety children were selected for Agogo Presbyterian Hospital and 99 for Kumasi South Hospital.

Inclusion criteria

A child is selected for the study if he/she meets the following criteria:

1. Child must be less than 5years
2. The diagnosis of pneumonia in a child must be confirmed clinically or radiologically
3. Confirmed pneumonia cases with co-morbidities like uncomplicated malaria, minor skin and ear/eye infections and other minor illnesses
4. Child must be resident in Kumasi or Agogo and its environs
5. The parent or guardian must have a telephone number and/or residential address

Exclusion criteria

A child with any of the following co-morbidities like HIV/AIDS, severe malaria, other concurrent severe bacterial infections includinginfective endocarditis, congenital heart disease, kidney disease, severe malnutrition etc which have profound confounding effects on the treatment outcome of pneumonia were excluded.

Data Collection

Research assistants including the clinicians, nurses and staff from the records departments in each facility were involved in case selection. Data collection and entry were done by independent clinicians. Questionnaire composed of structured and semi-structured questions on patient's demographic data, severity of pneumonia, investigations, antibiotic and adjunctive therapies for pneumonia, adverse effects of the antibiotics and treatment outcomesweresought for. The questionnaire drafted was pre-tested on two patientsin Agogo Hospital. One patient was an out-patient and the other an in-patient. A case selected was re-examined for inclusion and the folder kept in a box at the records department for data extraction and follow up for out-patients to check for adherence to the treatment given and to assess the clinical progress of child. For cases on admission, they were followed up on the ward to observe patients' medications and clinical progress. Patients were reviewed on the third day and fifth day respectively after discharge for all categories of pneumonia cases. The study ended with the second review when treatment was expected to end.

Assessment of treatment outcomes

Significant improvement in patients' condition by the third day of treatment with oral antibiotic at home was expected for out-patients with bacterial pneumonia and this was achieved by reviewing the patients after three days and five days respectively. Those that failed to come for review were contacted on phone and followed up at their residence. The effectiveness of treatment was measured by the rate of resolution of symptoms and signs of pneumonia between day one and day five for patients on admission. It was expected that a child with bacterial pneumonia should start responding to treatment within 24hrs after administration of antibiotics and should significantly improve by day five depending on the severity of pneumonia and the efficacy of the antibiotic. Discharged patients were reviewed after three days and five days of discharge respectively.

The clinical progress of patients were assessed using the rate of fall in body temperature to between 36ºC and 37ºC, the reduction of cough episodes and the reduction in respiratory rate. Examination for resolution of dullness to percussion, crackles and improvement of air entry to lungs and breath sounds were done periodically. When necessary, chest x-ray was used to check for resolution of consolidation of the lung. Also, parents or guardians were interviewed on their children's responses to treatment and adverse reactions of treatments if any.

Treatment failure was defined by failure of change in symptoms and signs of pneumonia in a child between 24 to 48hrs or a progressively worsening clinical condition after initiation of treatment within 24hrs. Patient is re-assessed if treatment failure is noted; the presence of complications are looked for and the antibiotic(s) is/are reviewed empirically or with aid of the results of blood culture and sensitivity.

Assessment of the relevance of adjunctive therapies

The significance of adjunctive therapies for the management of pneumonia was assessed by observing the frequency of their usage in addition to the antibiotics given at both study sites, and compare their effects on clinical progress of patients using the length of stay on admission of the patients at the study hospitals.

Data Analysis

Data obtained were coded, stored and analyzed with the aid of SPSS-16 computer software program. Independent T-test was used to compare the means of the length of stay on admission for both hospitals and Chi-square test to determine if there was any statistical difference in the treatment outcomes for the two hospitals.

Ethical Consideration

A copy of the proposal in addition to an introductory letter from the pharmacology department was presented to each of the hospitals for approval. The study in both facilities commenced after institutional approval. Informed consent was sought from parents or guardians to include their children or wards in the study after self-introduction and explanation of the purpose of the study to them. They were assured of anonymity of data and patient confidentiality.

CHAPTER FOUR

RESULTS

4.1 PROPORTION OF MALES AND FEMALES AND THEIR AGE CATEGORIES

Table 4.1a Agogo Presbyterian Hospital

AGE (Months)	MALE n(%)	FEMALE n(%)
0-11	**18**(60)	**12**(40)
12-23	**20**(62.5)	**12**(37.5)
24-35	**10**(58.8)	**7**(41.2)
36-47	**6**(66.7)	**3**(33.3)
48-59	**0**(0)	**2**(100)
TOTAL	**54**(60)	**36**(40)

In general, more males(60%) were seen with pneumonia than females(40%). Similarly, in all age groups the males out-number the females. Children in the 12-23 months age group formed the largest population (62.5% males and 37.5 % females), and those within 48-59months formed the least Table 4.1.

Table 4.1b Kumasi South Hospital

AGE (Months)	MALES **n(%)**	FEMALES **n(%)**
0-11	18**(34)**	35**(66)**
12-23	12**(63.2)**	7**(36.8)**
24-35	10**(71.4)**	4**(28.6)**
36-47	5**(55.6)**	4**(44.4)**
48-59	2**(50)**	2**(50)**
TOTAL	**47**(47.5)	**52**(52.5)

The females were 52(52.5%) and the males 47(47.5%). With the exception of children below 12 months (0-11), across the various age groups in general, the males were more than the females. Children from age 48-59months were the least seen.

4.2 INVESTIGATIONS

Table 4.2aAgogo Presbyterian Hospital

	CXR n(%)	FBC n(%)	Blood C/S n(%)	Others n(%)
Uncomplicated Pneumonia	**1**(1.1)	**6**(6.7)	**0(0.0)**	**12**(13.3)
Severe Pneumonia	**7**(7.8)	**18**(20.0)	**2**(2.2)	**15**(16.7)
Very Severe Pneumonia	**12**(13.3)	**18**(20.0)	**7**(7.8)	**17**(18.9)
TOTAL	20(22.2)	42(46.7)	9(10)	44(48.9)

CXR-Chest X-Ray **FBC**-Full Blood Count **C/S**-Culture and sensitivity **Others**-Investigations carried out to rule out other conditions

A total of 20(22.2%) children out of 90 children had CXR done to confirm diagnosis of pneumonia. Most of them were those with very severe pneumonia representing 60% of the CXR done. Forty-two children (46.7%) did FBC and most of them were children with severe pneumonia (42.9%) and very severe pneumonia (42.9%). Blood C/S was done for only 9(10%) children. A total of 44(48.9%) children did other investigations (Table 4.2)

Table 4.2b Kumasi South Hospital

	CXR **n(%)**	FBC **n(%)**	Blood C/S **n(%)**	Others **n(%)**
Uncomplicated Pneumonia	**1**(1.0)	**21**(21.2)	0(0.0)	**17**(17.2)
Severe Pneumonia	**4**(4.0)	**57**(57.6)	0(0.0)	**39**(39.4)
Very Severe Pneumonia	**4**(4.0)	**11**(11.1)	0(0.0)	**9(9.1)**
TOTAL	**9(9.1)**	**89(89.9)**	**0(0.0)**	**65(65.7)**

CXR-Chest X-Ray **FBC**-Full blood count C**/S**-Culture and sensitivity Others-Investigations carried out to rule out other conditions.

CXR was conducted for 9(9.1%) patients, FBC for 89(89.9%) and other investigations for 65(65.7%) patients. No blood C/S was done for any case (table 4.2b).

4.3 PNEUMONIA CASES MANAGED AS OUT-PATIENT OR IN-PATIENT

Table 4.3aAgogo Presbyterian Hospital

	Out-Patient n(%)	**In-Patient n(%)**
Uncomplicated Pneumonia	**28**(62.2)	**0**(0.0)
Uncomplicated Pneumonia with co-morbidity	**14**(31.1)	**5**(11.1)
Severe Pneumonia	**3**(6.7)	**9**(20.0)
Severe Pneumonia with comorbidity	**0**(0.0)	**9**(20.0)
Very Severe Pneumonia	**0**(0.0)	**8**(17.8)
Very Severe Pneumonia with co-morbidity	**0**(0.0)	**14**(31.1)
TOTAL	**45(50)**	**45(50)**

Fifty percent of cases were managed as out-patient and in-patient respectively. Most of the out-patients had uncomplicated pneumonia with only 3(6.7%) of the out-patient cases being severe pneumonia. Twenty-two (48.9%) cases of very severe pneumonia were managed as in-patients. Five in-patients (11%) were uncomplicated pneumonia with co-morbidity. All cases of uncomplicated pneumonia only were managed as out-patients (Table 4.3a).

Table 4.3b Kumasi South Hospital

	Out-Patient **n(%)**	In-Patient **n(%)**
Uncomplicated Pneumonia	**13**(92.9)	**0 (0.0)**
UP with Co-morbidity	**1**(7.1)	**8**(9.4)
Severe Pneumonia	**0(0.0)**	**50**(58.8)
SP with Co-morbidity	**0(0.0)**	**15**(17.6)
Very Severe Pneumonia	**0(0.0)**	**4**(4.7)
VSP with Co-morbidity	**0(0.0)**	**8**(9.4)
TOTAL	14**(14.1)**	85**(85.9)**

Fourteen (14.1%) pneumonia cases were managed as out-patients and 85(85.9%) were in-patients. The out-patients were uncomplicated pneumonia cases only. However, 8 cases of uncomplicated pneumonia with co-morbidity were managed on admission. All severe and very severe pneumonia cases were managed on admission (Table 4.3b).

4.4 ANTIBIOTIC THERAPY FOR PNEUMONIA

Table 4.4aAgogo Presbyterian Hospital

	CFX(iv) n(%)	**CFX (oral)** n(%)	**GMN** n(%)	**AMXCLAV (iv)** n(%)	**AMXCLAV (oral)** n(%)	**AMX (oral)** n(%)	**AMP (iv)** n(%)	**ERY (oral)** n(%)	**FLU (oral)** n(%)
Uncomplicated Pneumonia	**1**(1.1)	**22**(24.4)	**1**(1.1)	**0**(0)	**1**(1.1)	**17**(18.9)	**0**(0)	**5**(5.6)	**1**(1.1)
Severe Pneumonia	**15**(16.7)	**11**(12.2)	**14**(15.6)	**0**(0)	**0**(0)	**1**(1.1)	**0**(0)	**1**(1.1)	**0**(0)
Very Severe Pneumonia	**20**(22.2)	**11**(12.2)	**20**(22.2)	**2**(2.2)	**0**(0)	**0**(0)	**1**(1.1)	**0**(0)	**0**(0)
TOTAL	**36(40)**	**44(48.9)**	**35(38.9)**	**2(2.2)**	**1(1.1)**	**18(20)**	**1(1.1)**	**6(6.7)**	**1(1.1)**

CFX-Cefuroxime GMN-Gentamicin AMX-Amoxicillin CLAV-Clavulanic acid AMP-Ampicillin ERYErythromycin FLU-Flucloxacillin

Oral cefuroxime was prescribed to 44(48.9%) of the total pneumonia cases. This is closely followed by 36(40%) for iv cefuroxime and 35(38.9%) for gentamicin. Amoxicillin-clavulanic acid, ampicillin and flucloxacillin were the least prescribed (table 4.4).

Table 4.4bKumasi South Hospital

	CFX (iv) n(%)	**CFX (oral)** n(%)	**CTZ**n(%)	**GMN**n(%)	**AMX-CLAV(iv)** n(%)	**AMX-CLAV(oral)** n(%)	**AMX(oral)** n(%)
Uncomplicated Pneumonia	**9**(9.1)	**15**(15.2)	0(0.0)	**8**(8.1)	0(0.0)	**1**(1.0)	**2**(2.0)
Severe Pneumonia	**63**(63.6)	**24**(24.2)	**2**(2.0)	**61**(61.6)	**2**(2.0)	**2**(2.0)	0(0.0)
Very Severe Pneumonia	**11**(11.1)	**4**(4.0)	**1**(1.0)	**10**(10.1)	**1**(1.0)	**2**(2.0)	0(0.0)
TOTAL	**83(83.8)**	**43(43.4)**	**3(3.0)**	**79(79.8)**	**3(3.0)**	**5(5.0)**	**2(2.0)**

The number of cases that received iv cefuroxime were 83(83.8%).Seventy-nine (79.8%) of all cases that received iv cefuroxime were given gentamicin. Oral cefuroxime was prescribed for 43(43.3%) of cases. Ceftriazone and iv amoxicillin-clavulanic acid were given to 3(3%) respectively, oral amoxicillin-clavulanic acidto 5(5%) and oral amoxicillin to 2(2%) patients (Table 4.12).

4.5 ADVERSE DRUG REACTIONS

Table 4.5aAgogo Presbyterian Hospital

	Diarrhea n(%)	Vomiting n(%)	Rash n(%)	Others n(%)
Cefuroxime	3**(5.2)**	2**(3.4)**	0(0.0)	0(0.0)
Ceftriazone	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Amoxicillin-Clavulanate	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Amoxicillin	2**(11.1)**	0(0.0)	1**(5.6)**	1**(5.6)**
Gentamicin	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Erythromycin	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Flucloxacillin	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ampicillin	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Adverse drug reactions observed were for cefuroxime and amoxicillin. For cefuroxime 3 out of 57 (5.3%) patients exposed to cefuroxime had diarrhoea and 2(3.5%) vomited. Eighteen patients received amoxicillin: two (11.1%) had diarrhoea, 1(5.6%) developed rashes and 1(5.6%) had haematuria (Table 4.5a).

Table 4.5bKumasi South Hospital

	Diarrhoea n(%)	Vomiting n(%)	Rash n(%)	Others n(%)
Cefuroxime	3**(3.4)**	0(0.0)	0(0.0)	0(0.0)
Ceftriazone	0(0.0)	1**(33.3)**	0(0.0)	0(0.0)
Amoxicillin-Clavulanate	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Gentamicin	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Erythromycin	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Flucloxacillin	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ampicillin	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Out of 89 patients exposed to cefuroxime 3(3.4%) had diarrhoea. One out of 3 patients (33.3%) exposed to ceftriazone vomited. No adverse reaction was observed with the rest of the antibiotics (Table 4.5b).

4.6 ADJUNCTIVE THERAPY

Table 4.6aAgogo Presbyterian Hospital

	Uncomplicated Pneumonia	Severe Pneumonia	Very Severe Pneumonia	TOTAL N(%)

Haematinic n**(%)**	**2**(2.2)	**6**(6.7)	**10**(11.1)	**18**(20)
Multivit. **n(%)**	**2**(2.2)	**1**(1.1)	**0**(0.0)	**3**(3.3)
Vit. A n**(%)**	**1**(1.1)	**0**(0.0)	**0**(0.0)	**1**(1.1)
Vit. K n**(%)**	**0**(0.0)	**0**(0.0)	**2**(2.2)	**2**(2.2)
END n**(%)**	**33**(36.7)	**2**(2.2)	**8**(8.9)	**43**(47.8)
SND n**(%)**	**9**(10.0)	**1**(1.1)	**2**(2.2)	**12**(13.3)
P'mol **n(%)**	**48**(53.3)	**18**(20.0)	**22**(24.4)	**88**(97.8)
Ibuprofen n**(%)**	**0**(0.0)	**0**(0.0)	**2**(2.2)	**2**(2.2)
Neb. Salbutamol **n(%)**	**4**(4.4)	**5**(5.6)	**6**(6.7)	**15**(16.7)
Prednisolone n**(%)**	**0**(0.0)	**2**(2.2)	**0**(0.0)	**2**(2.2)
Dexamethasone **n(%)**	**0**(0.0)	**0**(0.0)	**1**(1.1)	**1**(1.1)
IVF n**(%)**	**0**(0.0)	**0**(0.0)	**8**(8.9)	**8**(8.9)
ORS n**(%)**	**2**(2.2)	**5**(5.6)	**4**(4.4)	**11**(12.2)
Zinc n**(%)**	**2**(2.2)	**2**(2.2)	**0**(0.0)	**4**(4.4)
Blood n**(%)**	**0**(0.0)	**2**(2.2)	**0**(0.0)	**2**(2.2)
Oxygen n**(%)**	**0**(0.0)	**4**(4.4)	**8**(8.9)	**12**(13.3)
Adrenaline n**(%)**	**0**(0.0)	**0**(0.0)	**1**(1.1)	**1**(1.1)

END-Ephedrine nasal drops SND-Saline nasal drops IVF-Intravenous fluid ORS-Oral rehydration salt P'molParacetamol(acetaminophen).

Eighty-eight (97.8%) cases received paracetamol in general followed by 43(47.8%) for ephedrine nasal drops and more of these were prescribed for uncomplicated pneumonia cases. Children with very severe pneumonia i.e. 10(55.6%) were the most given haematinics. Two patients received blood and all had severe pneumonia. Oxygen was administered to 12(13.3%) children with severe pneumonia and very severe pneumonia. Dexamethasone was administered to only one (1.1%) patient with very severe pneumonia as with adrenaline (Table 4.6a).

Table 4.6bKumasi South Hospital

	Hm **n(%)**	Vit C **n(%)**	ORS **n(%)**	Ps **n(%)**	VI **n(%)**	Dzp **n(%)**	Zn **n(%)**	Bld **n(%)**	SND**n(%)**	ACM **n(%)**
Uncomplicated Pneumonia	**2**(2.0)	**0**(0.0)	**2**(2.0)	**0**(0.0)	**0**(0.0)	**0**(0.0)	**0**(0.0)	**0**(0.0)	**17**(17.2)	**4**(4.0)
Severe Pneumonia	**0**(0.0)	**1**(1.0)	**2**(2.0)	**0**(0.0)	**0**(0.0)	**0**(0.0)	**2**(2.0)	**0**(0.0)	**54**(54.5)	**4**(4.0)
Very Severe Pneumonia	**2**(2.0)	**0**(0.0)	**2**(2.0)	**2**(2.0)	**2**(2.0)	**2**(2.0)	**1**(1.0)	**2**(2.0)	**6**(6.1)	**0**(0.0)
TOTAL	**4**(4.0)	**1**(1.0)	**6**(6.1)	**2**(2.0)	**2**(2.0)	**2**(2.0)	**3**(3.0)	**2**(2.0)	**77**(77.8**)**	**8**(8.1**)**

H(haematinic) **Vit C**(Vitamin C) **ORS**(oral rehydration salt) **VI**(ventolin inhaler) **Dzp**(diazepam) **Zn**(zinc) Bld(blood) **SND**(saline nasal drops) **ACM**(anti-cough mixture)

Saline nasal drops was prescribed to 77(77.8%) of all cases. Anti-cough mixture was prescribed to 8(8.1%) cases. Two (2%) very severe pneumonia cases were transfused. Generally, other treatments compared to SND were rarely prescribed (Table 4.6b)

4.7 LENGTH OF STAY ON ADMISSION

Table 4.7aAgogo Presbyterian Hospital

	1day n(%)	2days n(%)	3days n(%)	4days n(%)	5days n(%)	>5days n(%)
UP+ Co-morbidity	**4**(4.4)	**0**(0.0)	**1**(1.1)	**0**(0.0)	**0**(0.0)	**0**(0.0)
SP	**3**(3.3)	**6**(6.7)	**7**(7.8)	**2**(2.2)	**0**(0.0)	**0**(0.0)
VSP	**1**(1.1)	**1**(1.1)	**4**(4.4)	**6**(6.7)	**6**(6.7)	**4**(4.4)
TOTAL n(%)	8**(8.9)**	7**(7.8)**	12**(13.3)**	8**(8.9)**	6**(6.7)**	4**(4.4)**

The average length of stay on admission was 3days. Two (2.2%) children were admitted for less than one day and 4(4.4%) children for more than 5days. For uncomplicated pneumonia with co-morbidity and severe pneumonia, the maximum number of days on admission 3days respectively. The minimum length of stay on admission for very severe pneumonia was 3days (table 4.7a).

Table 4.7bKumasi South Hospital

	1 day n(%)	**2 days n(%)**	**3 days n(%)**	**4 days n(%)**	**5 days n(%)**	**>5 days n(%)**
UP with Comorbidity	3(37.5)	3(37.5)	2(25.0)	0(0.0)	0(0.0)	0(0.0)
Severe pneumonia	1(1.5)	10(15.4)	18(27.7)	7(10.8)	9(13.8)	20(30.8)
Very severe pneumonia	0(0.0)	3(25.0)	1(8.3)	2(16.7)	0(0.0)	6(50.0)
TOTAL	**4(4.7)**	**16(18.8)**	**21(24.7)**	**9(10.6)**	**9(10.6)**	**26(30.6)**

In all, 26(30.6%) were admitted for more than 5days comprising of 20(30.8%) severe pneumonia cases and 6(50%) very severe pneumonia cases. Four (4.7%) cases were admitted for only one day and these were 3(37.5%) uncomplicated pneumonia cases with co-morbidity and 1(1.5%) severe pneumonia case. The rest were 16(18.8%) for 2days, 21(24.7%) for 3days, 9(10.6%) for 4days and 5days respectively. The maximum length of stay for uncomplicated pneumonia with co-morbidity was 3days and the minimum period of admission for very severe pneumonia was 2days (Table 4.7b).

4.8 TREATMENT OUTCOME

Table 4.8aAgogo Presbyterian Hospital

	Improved with First-line Antibiotic(s) **n(%)**	Improved with Secondline Antibiotic(s) **n(%)**	Death **n(%)**
Uncomplicated Pneumonia	46**(97)**	1**(2.1)**	0**(0.0)**
Severe Pneumonia	21**(100)**	0**(0)**	0**(0)**
Very Severe Pneumonia	20**(90.9)**	0**(0)**	2**(9.1)**
TOTAL	**87(96.7)**	**1(1.1)**	**2(2.2)**

For uncomplicated pneumonia 97.9% improved with first-line antibiotic therapy and 2.1% were switched to secondline antibiotic. All severe pneumonia cases improved with first-line antibiotic. Twenty (90.7%) with very severe pneumonia improved with first-line antibiotic(s) and 2(9.1%) died even with second line antibiotic therapy. In all, 87(96.7%) children improved clinically with initial antibiotic therapy and 1(1.1%) improved with second-line antibiotic therapy (Table 4.8a).

Table 4.8b Kumasi South Hospital

	Improved with First-line Antibiotic(s) **n(%)**	Improved with Secondline Antibiotic(s) **n(%)**	Death **n(%)**
Uncomplicated Pneumonia	21**(95.5)**	1**(4.5)**	0(0.0)
Severe Pneumonia	59**(90.8)**	6**(9.2)**	0(0.0)
Very Severe Pneumonia	9**(75.0)**	3**(25.0)**	**0**(0.0)
TOTAL N(%)	**89(89.9)**	**10(10.1)**	**0(0)**

In general 89.9% of all pneumonia cases improved with initial (first-line) antibiotic(s) and 10.1% improved with second-line antibiotic therapy. For uncomplicated pneumonia, 95.5% improved with first-line antibiotic therapy and 4.5% had to be managed with second-line antibiotic therapy. For severe pneumonia 90.8% improved with first-line antibiotic therapy while9.2% improved with second-line antibiotic therapy. Nine(75%) cases of very severe pneumonia improved with first-line antibiotic therapy while 25% failed with fist-line antibiotic therapy. There were no mortalities (Table 4.8b).

CHAPTER FIVE

DISCUSSION OF RESULTS

Demography

At Agogo Presbyterian Hospital (APH), more male children were seen with pneumonia than female children as opposed to Kumasi South Hospital (APH) where the females were more than the males. Generally, for each age group, the males were more than the females at APH. A similar trend was observed at KSH except for children below 12months where the females formed 66% of the group population and this was the group with the largest population. This observation is similar to the Drakenstein Child Health Study in South Africa which observed that more male infants are vulnerable to pneumonia (David M le Roux, et al, 2015). The incidence of pneumonia decreased progressively in successive older age groups (tables 4.1a and 4.1b) and this shows that as children grow, they acquire immunity to infection hence become less vulnerable to pneumonia.

Investigations

At both hospitals, the diagnosis of pneumonia was more clinical than with the aid of chest x-ray (CXR). Comparatively, at Agogo Presbyterian Hospital few cases of pneumonia (a little above 20%) were confirmed with CXR while fewer cases (less than 10%) were confirmed with CXR at Kumasi South Hospital. At both institutions, more CXRs were requested for severe pneumonia and very severe pneumonia cases than for uncomplicated pneumonia cases. CXR was mainly requested to rule out differentials like pulmonary tuberculosis and asthma and to check for complications of pneumonia.

Full blood count (FBC) was the investigation mostly done in both institutions to check for white cell count and differentials and haemoglobin levels but not as a diagnostic tool for pneumonia.

However, it may indicate the presence of an infection (American Association for Clinical Chemistry, 2016).At APH, a little less than half of the cases did FBC compared to KSH where majority of the cases did FBC (Tables 4.2a and 4.2b).

Blood for culture and sensitivity (blood C/S) test was done for critically ill patients on admission who were not responding to treatment. This was only done in APH for 10% of the cases. The results of the test helped with switching to alternative (second line) antibiotic. On the other hand, KSH relied solely on empirical treatment.

Since it is not uncommon for a child to present to hospital with more than one morbidity other investigations like blood film for malaria parasites, urine or stool routine examinations, serology for HIV, renal function test, etc. to check for other conditions that may be present were carried out at both centers. Most of these investigations are routine in both facilities. More than half of the cases at KSH and less than half of the cases at APH went through other investigations. The results of these investigations were not principal findings but came as additional findings in the study subjects (Tables 4.2a and 4.2b).

Management of pneumonia

Uncomplicated pneumonia cases were generally managed as out-patients at both centers except for a few cases with co-morbidities such malaria with vomiting and/or fever of 38.0ºC or more that were admitted for management. Generally, severe and very severe pneumonia cases were managed on admission. At APH, few children with severe pneumonia only were managed successfully as out-patients on oral antibiotics (cefuroxime, amoxicillin and erythromycin respectively)as demonstrated by the MASS study (Addo-Yobo, et al, 2011) and in another study by Abdul Bari et al, 2013 that severe pneumonia can be managed successfully in the community. On the contrary,

all severe pneumonia cases were managed on admission at KSH. At both centers, very severe pneumonia cases were managed exclusively on admission.

Antibiotic therapy

Antibiotic therapies for pneumonia at both hospitals were almost similar. At APH, the spectrum of antibiotics for pneumonia were amoxicillin, ampicillin, cefuroxime, co-amoxiclav, gentamicin, erythromycin and flucloxacillin. At KSH, the antibiotics were amoxicillin, cefuroxime, ceftriazone, co-amoxiclav and gentamicin.

For uncomplicated pneumonia cases treated as out-patients at APH, a little more than half of them received oral cefuroximeand a little less than half received oral amoxicillin. Oral erythromycin was prescribed to a few cases with suspected atypical pneumonia. Oral flucloxacillin was only prescribed empirically to a child diagnosed with uncomplicated pneumonia and impetigo. Oral co-amoxiclav was given as a second-line treatment to a case that did not respond well to oral amoxicillin. A few uncomplicated pneumonia cases were however managed on admission out of which one case received a combination of iv cefuroxime and iv gentamicin followed by oral cefuroxime. Similarly, at KSH, most of the cases of uncomplicated pneumonia received oral cefuroxime. Those uncomplicated pneumonia cases on admission received a combination of iv cefuroxime and iv gentamicin followed by oral cefuroxime. Oral amoxicillin was prescribed to just a few cases. Oral co-amoxiclav was prescribed as a secondline antibiotic to a case that did not respond well to oral amoxicillin.

For treatment of severe pneumonia, a few cases were treated with oral antibiotics as out-patients. Generally, almost all severe pneumonia cases were treated on admission with a combination of iv cefuroxime and iv gentamicin followed by oral cefuroxime when stable. Intravenous coamoxiclav

was used in place of iv cefuroxime when one patient was not responding to treatment. A similar situation was observed at KSH, but here, all cases of severe pneumonia were treated on admission and almost all also received a combination of iv cefuroxime and iv gentamicin. There were a few cases that did not respond well to the cefuroxime and gentamicin combination and so were switched on to iv ceftriazone followed by oral cefuroxime or iv co-amoxiclav followed by oral co-amoxiclav and the treatment outcome in all were good.

There was no significant difference between the antibiotic treatment of severe pneumonia and very severe pneumonia. At APH, almost all the cases of very severe pneumonia received a combination of iv cefuroxime and iv gentamicin as first-line treatment. Intravenous ampicillin was used as first-line treatment for one case less than 2months old. Two cases received iv coamoxiclav in place of cefuroxime/gentamicin when their conditions were not improving. A similar pattern was observed at KSH where iv cefuroxime/iv gentamicin combination was also used as first-line antibiotics for all cases. Intravenous co-amoxiclav was used as second-line treatment for one case of poor improvement on the first-line treatment and the outcome was good.

Higuera F, et al compared oral cefuroxime with oral amoxicillin/clavulanic acid in the management of CAP in a multicenter, investigator-blinded clinical trial and showed that oral cefuroxime given twice daily was as effective as oral co-amoxiclav given three times daily (Higuera F, et al, 1996) . Despite treatment failure of cefuroxime in isolated cases in this study, cefuroxime was still effective for the treatment of CAP.

The clinical outcome for the cefuroxime/gentamicin combination treatment was good at both centers. The early empiric combination of beta-lactam and aminoglycoside or fluoroquinolone or

macrolide/clindamycin compared with beta-lactam monotherapy was shown to be associated with a decrease in mortality (36% vs. 25%, p=0.0002) (Kumar A, et al, 2010).

Adverse drug reaction

Adverse drug reactions of some of the antibiotics were recorded in a few study subjects soon after commencing treatment. Cefuroxime was associated with diarrhoea in less than 5%, and vomiting in about 2% of the cases exposed to cefuroxime. Vomiting was noted in one out of three cases that received ceftriazone. For amoxicillin, two cases of diarrhoea, one case of skin rash and another case ofhaematuria were noted. Adverse drug reactions such as diarrhoea and vomiting did not affect treatment compliance as they were managed accordingly. On the other hand, the presence of rashes and haematuria influenced the replacement of amoxicillin with erythromycin as recommended by the standard treatment guideline.

Adjunctive therapy

The adjunctive therapies were directed towards the symptomatic relief of symptoms associated with pneumonia. At APH, no medicine was prescribed to relieve cough but 8 cases received cough mixtures at KSH. This observation was however not found to have any significant effect on treatment outcome in spite of the minimal reduction in cough episodes by these cough mixtures.

Fever management at APH was largely pharmacological and almost all the cases were given paracetamol. Only about 2% received ibuprofen and these were all cases of very severe pneumonia. Contrarily, at KSH, the management of fever was non-pharmacological; tepid sponging and expectant management were employed. It was recommended by Hay AD, et al in a randomized

control trial that to reduce the duration of fever in a child, supplementary antipyretics (ibuprofen or ibuprofen plus paracetamol) in addition to non-pharmacologic measures should be used (Hay AD, et al, 2008).

A few children with worsening dyspnoea were given oxygen at APH. No child at KSH required oxygen. The management of wheeze in about 15% of cases at APH was by the administration of nebulized salbutamol due to the presence of wheezes. At KSH, ventolin inhaler was used instead due to the absence of a nebulizer. Prednisolone or dexamethazone was given to the patients with wheeze but these were patients with no diagnosis of asthma at both centers. Other treatments like ephedrine nasal drops and saline nasal drops were administered to children with nasal congestion to clear the airways of nasal mucus seen in upper respiratory tract infections to improve breathing. Upper respiratory tract infections usually precede pneumonia. Ephedrine nasal drops was used in APH compared to saline nasal drops in KSH. Other general supportive treatments not specific to pneumonia were haematinics, intravenous fluids, blood, adrenaline, zinc, vitamins A and K at APH. At KSH, other general supportive treatments were haematinics, zinc, vitamin C, ORS, diazepam and blood.

Length of stay on hospital admission

The length of stay on admission was a measure of the effectiveness of treatment. The length of stay was measured from less than one day to more than 5days on admission. At APH, uncomplicated pneumonia with co-morbidities cases were admitted for less than one day to a maximum of 3 days. Similarly, at KSH, uncomplicated pneumonia cases spent from a minimum of one day to maximum of 3 days. Patients with severe pneumonia spent from a minimum of one day to a maximum of 4days on admission at APH. The situation was different for KSH; severe

pneumonia cases stayed longer on the ward to more than 5 days compared to APH. For very severe pneumonia cases, the minimum length of stay on admission was 3days with a few spending more than 5 days on admission at APH. A similar trend was seen at KSH where very severe pneumonia cases spent from 2days to more than 5days on admission. It was apparent that more patients spent less time on admission at APH than at KSH. This difference was due to faster resolution of symptoms and signs such as reduction in fever and improved feeding.

Independent T-test, used to compare the mean length of stay on admission for both hospitals shows no significant statistical difference (p=0.802).

Treatment outcome

The treatment outcomes of the antibiotic therapies for pneumonia for both hospitals were good. At both APH and KSH, almost all the patients improved clinically with first-line antibiotic therapy. Only a few did not respond to treatment,but recovered on second-line antibiotic therapy at both sites. There were two deaths due to very severe pneumonia at APH while no death was recorded at KSH.

At APH, first-line antibiotics were oral cefuroxime which was administered to half of uncomplicated pneumonia cases, oral amoxicillin to more than one-third of cases and erythromycin and flucloxacillin to just a few cases.The second-line antibiotics for uncomplicated pneumonia were oral co-amoxiclav and erythromycin.At KSH, most of the uncomplicated pneumonia cases were treated mainly with oral cefuroxime and just about 2% received oral amoxicillin as first line treatment.

At APH, all the severe pneumonia cases recovered on first-line antibiotic therapy i.e. iv cefuroxime and gentamicin combination followed with oral cefuroxime. The few cases of severe pneumoniatreated with oral amoxicillin and oral erythromycinall responded to treatment. At KSH, most of the severe pneumonia cases on iv cefuroxime and iv gentamicin combination followed by oral cefuroxime responded well to treatment. The few that did not respond well on the first-line treatment recovered on either iv co-amoxiclav or iv ceftriazone.

For very severe pneumonia, most of the cases at APH responded well toiv cefuroxime and iv

gentamicin combination followed with oral cefuroxime. Two cases died irrespective of treatment with eitheriv cefuroxime and iv gentamicin combination or withiv co-amoxiclav. At KSH, treatment was successful with iv cefuroxime and iv gentamicin combination followed with oral cefuroxime in more than 70% of very severe pneumonia cases. The rest responded to treatment to either iv co-amoxiclav or iv ceftriazone as second-line therapy.

Chi-square test, comparing treatment outcomes in both hospitals for pneumonia indicates no significant difference (p=0.171).

CHAPTER SIX

CONCLUSION

The antibiotics used commonly were oral amoxicillin and cefuroxime as first-line antibiotics for the out-patient treatment of community-acquired pneumonia. Erythromycin was also used for a

few cases for atypical bacterial pneumonia. Oral co-amoxiclav and erythromycin were the second-line antibiotics used for out-patient management of CAP. Co-amoxiclav was used for severe pneumonia cases resistant to cefuroxime or amoxicillin. Erythromycin was used either for suspected cases of atypical bacterial pneumonia or as a substitute in the case of penicillin allergy. For in-patients, iv ampicillin or cefuroxime alone or in combination with gentamicin were firstline antibiotic therapies. Intravenous co-amoxiclav and iv ceftriazone were the second-line antibiotics used for patients not responding to the first-line therapy.

Amoxicillin was as effective as cefuroxime in the management of uncomplicated pneumonia and for some of the severe pneumonia cases at both study sites. Generally, the patients responded well to the antibiotics used.

Less frequent adverse reactions were seen with the usage of the antibiotics at both study sites making them relatively safe in children less than five years.

The main adjunctive therapies were paracetamol and ibuprofen and/or non-pharmacological methods such as tepid sponging for fever management, cough medicines for cough in a few cases and oxygen for hypoxaemia for the management of pneumonia.

Adherence to the standard treatment guideline for the treatment of pneumonia in both hospitals was not strictly followed.

RECOMMENDATIONS

More chest x-rays should be encouraged to help in the diagnosis of pneumonia and complication of pneumonia. Blood culture and sensitivity should also be encouraged for in-patients to determine the right choice of antibiotics in the event of treatment failure.

The use of penicillins as first-line antibiotic treatment should be encouraged as recommended by the standard treatment guideline.

The use of cefuroxime in combination with gentamicin should be reviewed due to the increased risk of nephrotoxicity.

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APPENDIX

APPENDIX 1: APPROVAL LETTERS

PRESBYTERIAN HEALTH SERVICES
AGOGO HOSPITAL

BANKERS:
Ghana Commercial Bank
Agogo, Ashanti-Akim
Barclays Bank
Prempeh II Street, Adum Kumasi

P. O. Box 27
Agogo, Ashanti - Akim
Ghana-W/Africa
E-mail:info@agogopresbyhospital.org
Website:www.agogopresbyhospital.org

Our Ref: APH/ADM/HRD-06/16

Your Ref:.....

26TH JUNE, 2014

.....20.....

DR. EBENEZER OBU
P.O. BOX UP 751
KNUST
KUMASI

Dear Sir,

APPROVAL FOR CLINICAL RESEARCH

The Management of the Agogo Presbyterian Hospital have given approval for your Clinical Research on the Pharmaceutical Management of Childhood Pneumonia in a District Hospital Setting in Rural and Urban Ghana which you intend to carry out in our hospital.

You will be given all the necessary assistance in your work.

Yours faithfully,

MEDICAL ADMINISTRATOR
PRESBY HOSPITAL
AGOGO

DR. WILLIAM N.A. THOMPSON
MEDICAL ADMINISTRATOR

A MEMBER OF CHAG

CHRISTIAN HEALTH ASSOCIATION OF GHANA

In case of reply the number
and the date of this letter
should be quoted

My Ref. No: KSH./GEN- 53
Your Ref. No:
Tel. . 0501266827/0501297292
Fax :03220 35169
E-mail: Kumasisouth@yahoo.com

GHANA HEALTH SERVICE
KUMASI SOUTH HOSPITAL
P. O. BOX 1908
KUMASI

20th November, 2014

PERMISSION TO CONDUCT RESEARCH

This serves to formally inform you that the under mentioned student of Clinical Pharmacology College of Health Sciences, KNUST at the department of Pharmacology has been granted permissio by the Kumasi South Hospital to conduct the following study:

Title of study: **Pharmacotherapy of pneumonia in children under five years in two distri hospitals in the Ashanti Region.**

Period: January 2015 – November 2015.

Student Name: Dr. Ebenezer Obu

Thank you.

DR. KWAME OFORI BOADU
MEDICAL DIRECTOR

THE HEAD OF DEPARTMENT
PHARMACOLOGY
COLLEGE OF HEALTH SCIENCES
KNUST

APPENDIX 2: QUESTIONNAIRE

PHARMACOTHERAPY OF PNEUMONIA IN CHILDREN UNDER FIVE YEARS IN TWO HOSPITALS IN ASHANTI REGION

[A]

1. Name……..

2. Age…….…….

3. Sex [M] / [F]

4. Home Address ……...

5. Name of hospital

……

6. Date seen…….

[B]

1. Type of pneumonia diagnosed

(a) Uncomplicated Pneumonia [ ]

(b) Severe Pneumonia [ ]

(c) Very Severe Pneumonia [ ]

2. (a) Did the child present with other condition(s)? Yes [ ] No [ ]

(b) If yes, state the condition(s)

……..……

3. (a) What was the management schedule

(i) OPD [ ]

(ii)Admission [ ]

(b) If child was admitted, for how long? .....

4. Please, tick the investigation(s) carried out

(a) Chest x-ray [ ]

(b) Full blood count [ ]

(c) Blood for culture and sensitivity [ ]

(d) Other(s)…… (Specify)

5. (a) Please, state the antibiotic(s) prescribed including the route, frequency and duration of administration

……

……

(b) Did child show signs of clinical improvement with the treatment on review? Yes [ ] No [ ]

(c) If no, was there the need to review the antibiotic(s) prescribed? Yes [ ] No [ ] (d)

If yes, how did you review the antibiotic(s) therapy?

(i) By checking right dosage and dosing of drug and/or compliance [ ]

(ii) By Culture and Sensitivity results [ ] (for in-patients)

(e) How did the findings in (d) affect your decision on the antibiotic therapy?

(i) Added another antibiotic [ ]

(ii) Switched to a different antibiotic [ ]

(iii) Changed the brand of same antibiotic [ ]

(f) Please, state the second/substituted antibiotic(s)

……..

6. Please, state the adjunctive therapy prescribed

……

……

……

7. (a) Were there adverse effects of any treatment noted? Yes [ ] No [ ]

(i) If yes, state the significant reaction(s) noted
……
……

……...

(ii) Please, did you identify the culprit drug(s)? Yes [ ] No [ ]

(iii) If yes, state the drug(s)

……

(iv) Was treatment discontinued? Yes [ ] No [ ]

(v) If yes, state the alternative medicine(s) given

……

(vi) If no, state why

……

8. What was the treatment outcome?

(a) Child improved clinically on first choice antibiotic(s) [ ]

(b) Treatment failure with first choice antibiotic(s) but improved on additional/alternative antibiotic [ ]

(c)Patient died [ ]