CEFTRIAXONE VERSUS CHLORAMPHENICOL FOR THE TREATMENT OF SEVERE PNEUMONIA IN CHILDREN AT MULAGO HOSPITAL: A RANDOMIZED CLINICAL TRIAL

By

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DECLARATION

I declare that this work is original. It has not been presented anywhere either partially or in total for any award unless otherwise stated.

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This work is dedicated to my beloved parents Justice and Mrs. Bart Katureebe.
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LIST OF ABBREVIATIONS:

ACU: Acute care unit
ALRI: Acute lower respiratory tract infections
ARI: Acute respiratory tract infections
CBC: Complete blood count
CI: Confidence interval
CXR: Chest radiograph
G: Gram
Hib: Haemophilus influenzae type b
IM: Intramuscularly
IMCI: Integrated Management of Childhood Illness
IV: Intravenously
Kg: Kilogram
Mg: Milligram
ml: Milliliter
WHO: World Health Organisation
PI: Principal Investigator
HMIS: Health Management Information Systems
NCCLS: National Committee For Clinical Laboratory Standards
ESBL: Extended Spectrum beta-lactam
NMF: Normal mouth flora
OPERATIONAL DEFINITIONS:

Under-five is a child from 6 to 59 months.

Chest in drawing is continuous sub costal recessions observed while the child is breathing.

Hepatomegally is >2 centimeters or more of palpable liver below the sub costal margin or if it’s span is >8cm.

Tachypnea is a respiratory rate of 50 or more per minute in a child 6-12 months of age or 40 or more in a child 12-59 months.

Treatment success: by day 2 (48 hours) and day 7, refers to normalization of the respiratory rate (to below 50 per minute in a child 6-12 months of age and below 40 per minute for the child aged 12-59 months), oxygen saturation and disappearance of lower chest in drawing.

Treatment failure: (by day 2 (48 hours) and day 7.): is when the patient while on appropriate antibiotic treatment has failure to normalization of: the respiratory rate, temperature, oxygen saturation; or death.

Severe pneumonia: Cough or difficulty in breathing, fast breathing, chest in drawing.

POSITIVE CHEST X-RAY: Presence of any pathological findings related to pneumonia on chest X-ray regardless of the extent of the disease.

Efficacy: The maximum ability of a drug or treatment to produce a result regardless of dosage.

WHZ -2z: This is the weight for height Z score and a measure of children who are under weight.

Partly immunized: These were children who for their given age had not received the required vaccine at that point in time.
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ABSTRACT:

Background
Acute lower respiratory tract infections are a leading cause of morbidity and mortality in Sub-Saharan Africa. The World Health Organization (WHO) still recommends intravenous chloramphenicol for the treatment of severe pneumonia in children aged less than five years. However, up to 20% of children fail treatment due to the emergence of resistance by bacteria. Several centers now use ceftriaxone a third generation cephalosporin, which is reported to be efficacious in the treatment of severe pneumonia. However the high cost of ceftriaxone is too prohibitive to allow for its routine use in resource constrained countries like Uganda. We compared the efficacy of Ceftriaxone versus Chloramphenicol in the treatment of severe pneumonia in children aged 6-59 months admitted to Acute Care Unit Mulago hospital.

Methods
From September 2006 to March 2007, a double-blinded randomized placebo controlled trial of 352 children with severe pneumonia and whose caretakers gave informed consent, were randomized to receive either intravenous ceftriaxone (75mg/kg/day) or intravenous chloramphenicol (100mg/kg/day) for seven days.
The primary outcomes measured were: mortality, treatment success or failure (measured as time to normalization or no normalization of respiratory rate, temperature, and oxygen saturation). Secondary outcome measures were short term complications. Adverse effects associated with ceftriaxone and chloramphenicol were reported.
Data was entered into Epi-info 6.4 software and analyzed using an SPSS package. The chi-square test with corresponding risk or odds ratios and 95% confidence intervals were used for categorical variables and the student’s t or other appropriate test was used for continuous variables. Kaplan-Meier survival curves measured time to the event; and logistic regression for factors predicting outcome in both treatment groups.

Results:
Mortality was similar in the two groups: 8.5% in the chloramphenicol group and 7.5% in the ceftriaxone group; RR 1.15 (95% CI 0.57-3.35); p = 0.69. This difference was not statistically significant.
The fever clearance time, time to normalization of respiratory rate, oxygen saturation, and disappearance of chest in drawing were similar in both treatment groups. There were minor adverse events observed in both drugs.

**Conclusions:**
Intravenous ceftriaxone is as efficacious as intravenous chloramphenicol in the treatment of severe pneumonia in children.

**Recommendations:**
Intravenous chloramphenicol should still be considered as the first line drug for treatment of severe pneumonia for children in Uganda.
CHAPTER ONE

1.0 INTRODUCTION

1.1 Definition
Pneumonia is inflammation of lung parenchyma\(^2\), but is also defined as a condition associated with fever, respiratory symptoms and evidence of lung parenchyma involvement either by physical examination or the presence of infiltrates on chest radiography\(^3\). It is considered severe when the signs are accompanied by chest in drawing\(^4\). Features of very severe pneumonia include lethargy, refusal to eat/breast feed, grunting and cyanosis\(^5\).

1.2 Epidemiology and burden
Acute lower respiratory tract infections (ALRIs) are a major cause of morbidity and mortality in children less than 5 years worldwide\(^6^,\!^7\). A report from the World Health Organization in 2004 showed that pneumonia was the leading cause of death in children less than 5 years and contributed up to 19% of the overall childhood mortality worldwide. In developing countries, pneumonia accounts for 10% -30% of deaths in children less than five years\(^8^,\!^9\).

In 1999, hospitalized Zimbabwean children with severe pneumonia had a case fatality rate of 21%\(^10\). Another study from Durban, South Africa also showed a high case fatality rate of 16%\(^11\).

The 2006 Uganda Demographic Health Survey (UDHS) estimated that ALRI accounted for 15.5% of the overall morbidity among children less than five years but were the leading cause of childhood deaths\(^12\). In Mulago hospital ALRI account for 23-24% of all admissions on general pediatric wards with case fatality rates ranging between 10-25%\(^13^,\!^14\).

1.3 Treatment of severe Pneumonia
In Africa, choice of antibiotics for severe pneumonia depends on cost, availability, pattern of causative pathogens and antibiotic resistance\(^15\).

The World Health Organization (WHO) has defined protocols for management of severe pneumonia in under fives as in appendix IV\(^10^,\!^16\). It recommends intravenous chloramphenicol 25mg/kg six hourly as the first line drug for the treatment of severe pneumonia in the under fives.

However, there are reports of emergence of resistance to this drug by bacterial pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae* commonly implicated in
childhood pneumonia\textsuperscript{16,17}. Resistance of \textit{Streptococcus pneumoniae} to chloramphenicol ranges from 7.2\% to 15\%, that of \textit{Haemophilus influenzae} 50\% to 100\% and to \textit{Staphylococcus aureus} 40\%-45\%\textsuperscript{17}. A recent study in Mulago hospital by Nantanda in 2006 found resistance of \textit{Streptococcus pneumoniae} to chloramphenicol at 10\% and to \textit{Haemophilus influenzae} 100\% in vitro\textsuperscript{18}. The efficacy of chloramphenicol in the treatment of severe pneumonia in various studies ranges from 80\%-84\%\textsuperscript{19,20}. There is evidence supporting that empirical treatment with chloramphenicol may still be effective and that, unlike in meningitis, in vitro resistance of the pathogen in severe Pneumonia does not always translate into treatment failure. In another study, chloramphenicol was found safe, much cheaper and not inferior to cefotaxim a cephalosporin or Penicillin\textsuperscript{20}.

Ceftriaxone, a third generation cephalosporin is effective therapy for pneumonia caused by virtually all isolates of \textit{Streptococcus pneumoniae}. The advantages include high efficacy in community acquired pneumonia, a low incidence of severe adverse effects and shorter duration of stay in hospital\textsuperscript{21}. It’s efficacy in treatment of pneumonia ranges from 85\% to 97\%\textsuperscript{22-24}.

A study that compared penicillin G plus chloramphenicol and ceftriaxone in the treatment of severe pneumonia in 2004 in Turkey found that both regimens had equal efficacy\textsuperscript{22}. The problem with use of ceftriaxone as first line treatment for community acquired pneumonia is the increased risk of resistance and this may limit its effective life-span for less common but very important indications like bacterial meningitis.\textsuperscript{25}
1.4 LITERATURE REVIEW

1.4.1 Burden and mortality of Pneumonia

Acute respiratory tract infections are the major causes of death in children less than 5 years globally\textsuperscript{6,7}. They account for approximately a third of the deaths that occur annually in children less than five years worldwide, of which 75\% are due to pneumonia not associated with measles\textsuperscript{26}.

The deaths from ALRI show a striking difference between developing and developed countries. In developing countries, mortality is 10-20 times higher than in developed countries. Studies in developing countries have shown the case fatality rates ranging between 10-30\%\textsuperscript{8,9}.

In Africa, ALRI have been reported to account for 12\% of all childhood deaths, most of them due to bacterial pneumonia or a mixture of both viral and bacterial pneumonia\textsuperscript{27}.

Wafula et al found pneumonia to be the most common cause of childhood death in Kenya\textsuperscript{28}. This was related to severity of illness and delay in seeking appropriate care.

The Health Management Information Systems for 2004 Mulago hospital indicated a case fatality rate of 10\%\textsuperscript{14}.

In 2000, Namagala found 12\% of children admitted with severe pneumonia in Mulago hospital, died within the first week of admission and another high proportion of 28\% developed complications\textsuperscript{29}. A recent study by Bakeera, also in Mulago hospital showed that 23.1\% of the children with severe pneumonia died while 9.1\% developed complications such as pleural effusion and pneumothorax\textsuperscript{30}.

The main predictors of death among children less than five years include hypoxemia, malnutrition, and age 2-11months\textsuperscript{28}.

1.4.2 Etiology

The commonest causes of pneumonia are bacteria and viruses but other causes include fungi and protozoa. The etiological organism can be established in 54\% of cases\textsuperscript{2}. Most cases of severe pneumonia among children in developing countries are caused by bacteria\textsuperscript{31}. The probability of bacterial infection increases with increasing severity of the episode and decreasing age of the child\textsuperscript{32}. For children aged between 2 months to 5 years, the most common organisms identified include \textit{Streptococcus pneumonia} (65-75\%), less frequently \textit{Haemophilus} species 6\%-20\% (both typable and non-typable), \textit{Mycoplasma}
pneumoniae and Staphylococcus aureus about 10%\textsuperscript{32}. Other less common organisms include group A Streptococcus, Moraxella catarrhalis and Pseudomonas aeruginosa\textsuperscript{32}.

1.4.3 Diagnosis

This is mainly clinical involving a thorough history and physical examination then confirmation by Chest X-ray.

1.4.3.1 Clinical features

The clinical diagnosis of pneumonia has traditionally been made using auscultatory findings such as bronchial breath sounds and crepitations in children with cough. However the sensitivity of auscultation has been shown to be poor and varies between 33% - 60% with an average of 50% in children\textsuperscript{33,34}.

Tachypnea is the best single predictor in children of all ages and its sensitivity ranges between 85%-86\%\textsuperscript{35}. Observation of chest retractions has been found to have a sensitivity of 79\%\textsuperscript{36}.

1.4.3.2 Laboratory and Radiological Diagnosis

Children with bacterial pneumonia cannot be reliably distinguished from those with viral disease on the basis of any single parameter, clinical, laboratory or chest radiograph findings\textsuperscript{37}.

The chest radiograph is indicated when clinical criteria suggests pneumonia however it lags behind symptoms by 24-48 hours but it will not identify the etiological agents\textsuperscript{37}. However, the chest radiograph is not always necessary if the facilities are not available or the pneumonia is not severe\textsuperscript{38}.

Blood culture remains the non-invasive proxy for determining the precise etiology of pneumonia. However the sensitivity of this test is very low. Positive blood cultures are found only in 10% to 30% of patients with pneumonia\textsuperscript{39,40}.

The presence of leucopenia can either suggest a viral cause or severe overwhelming infection and leucocytosis also shows evidence of bacterial infection especially with a left shift and toxic granulations\textsuperscript{41}.

Sputum induction helps mobilize secretions from the lower respiratory tract in children where sputum production is usually difficult. It is usually well tolerated\textsuperscript{42}. The sensitivity ranges from 24\% to 90\% and is dependant on specimen collection and analysis by experienced personnel\textsuperscript{42}. 
1.4.4 Ceftriaxone

Ceftriaxone is a third generation semi-synthetic cephalosporin with a broad antibacterial spectrum, for intramuscular and intravenous use. The therapeutic form of its disodium salt (sodium content per gram of active ceftriaxone: 83 mg (3.6 Eq) is stored in vials of 250mg, 500mg and 1gram. The dry compound is stable for 3 years when it is stored at a temperature below 30°C. The reconstituted solution remains stable for 24 hours at 2-8°C and for 6 hours at ambient temperature

It possesses potent in vitro activity against most of the common aerobic gram positive and gram-negative pathogens. Numerous common anaerobic species are also susceptible. Like other B-lactam antibiotics, ceftriaxone inhibits the growth of bacteria by inactivating the Penicillin-Binding Proteins (PBPs) in the cytoplasmic membrane upon intravenous administration, whether by bolus dose or short infusion, high plasma concentration are instantly achieved and maintained.

Ceftriaxone is eliminated unmetabolised at a rate of about two-thirds in the urine and one third in bile with 50% to 60% of the drug excreted via the urine, 40% to 50% via the bile. The total plasma clearance of ceftriaxone is 10-22 ml/min; renal clearance is 5-12 ml/min. The non-significant excretion by the distal tubule contributes to the long elimination half life of ceftriaxone.

After intramuscular administration, there is 100% bioavailability with rapid and complete absorption.

1.4.4.1 Efficacy of ceftriaxone in the treatment of severe pneumonia:

Ceftriaxone has a broad-spectrum activity that covers the commonest etiological agents of childhood pneumonia. *S. pneumoniae* and *H. influenzae* are highly susceptible to ceftriaxone and has had success rates in previous studies at doses between 50 and 100mg/kg. In Israel, Leibovitz et al also found a favourable response in 147 cases (97%). In an analysis conducted on 629 children hospitalised with pneumonia who had received ceftriaxone (169 cases), cefuroxime (412 cases) or cefotaxime (48 cases), there was a shortened duration of treatment in the ceftriaxone group.

In another study by Toyonaga in children in Japan, at a dose of 50mg/kg an efficacy of 93.7% was found.
1.4.4.2 Adverse effects of ceftriaxone in the treatment of severe pneumonia
The incidence of adverse effects occur in less than 1% and include hypersensitivity reactions like urticarial or maculopapulous skin rashes, crythema, itching and edema. The common side effects are minor and include those affecting the gastrointestinal tract (2%) such as loose stools or diarrhoea, nausea, vomiting, and abdominal pain. Other side effects include ceftriaxone induced haemolysis (immune mediated)⁴². The local effects included phlebitic reactions after intravenous administration.
Moskovitz et al⁵⁶ described the incidence of adverse effects in 8,565 cases. They included gastrointestinal disorders (2.88%), haematological disorders (2.32%), hepatic (1.93%) and renal (0.13%) dysfunction.

1.4.5 Chloramphenicol
This is a broad spectrum antibiotic that possesses in vitro activity against infections caused by Bacteriodes, Haemophilus influenzae, Streptococcus pneumoniae, among others.
It is available for intravenous and intramuscular use. The dosage forms appear as injection, powder for reconstitution, as sodium succinate. One gram contains 52mg sodium (2.25.mEq/g). The reconstituted parenteral solution is stable for 30 days at room temperature. For pneumonia it is given in a dose of 100 mg/kg/day divided every six hours intravenously. Excretion occurs in the kidneys; 5-15% unchanged and 4% in the bile⁵⁷.
It reversibly binds to the 50S ribosomal subunits of susceptible organisms preventing amino acids from being transferred to growing peptide chains thus inhibiting protein synthesis⁵⁷. It readily crosses the placenta; appears in breast milk; distributes to most tissues and body fluids with good CSF and brain penetration. Sixty percent is bound to protein and is 90% metabolised extensively in the liver into inactive metabolites by glucuronidation into an active base⁵⁸,⁵⁹.

1.4.5.1 Adverse effects associated with chloramphenicol
Three major toxicities associated with the drug include aplastic anaemia occurring as an idiosyncratic reaction 3 weeks to 12 months after exposure and is very rare occurring in one in 25,000 people. Bone marrow suppression which causes a hypoplastic anemia is dose related and therefore reversible⁵⁷. The Gray baby syndrome has also been observed in children below three months. Additional adverse effects include GIT disorders, dermatologic, ocular, CNS, and hypersensitivity reactions.
1.4.5.2 Efficacy of chloramphenicol in treatment of pneumonia

Chloramphenicol has a broad spectrum activity that covers the majority of the isolates of *Streptococcus pneumoniae* implicated in pneumonia. However, up to 20% of children receiving chloramphenicol for severe pneumonia fail treatment. Efficacy rates in previous trials range between 80-85%\(^{19,22}\).

Studies comparing chloramphenicol alone to a combination of benzyl penicillin and chloramphenicol showed no difference in efficacy\(^{22}\). Another study comparing chloramphenicol to a combination of benzyl penicillin with gentamicin found that efficacy was the same\(^{60}\).

1.4.6 Ceftriaxone and chloramphenicol in treatment of pneumonia.

Only one study has compared ceftriaxone and a combination of penicillin G and chloramphenicol. Cetinkaya et al in Turkey, Istanbul(2004) found that a combination of penicillin G and chloramphenicol was as effective as ceftriaxone for the treatment of severe community pneumonia of young children\(^{22}\).

1.4.7 Susceptibility patterns to antimicrobial therapy

Several studies have been done to determine the sensitivity patterns of the common organisms causing pneumonia particularly *Streptococcus pneumoniae*, and have revealed different degrees of antimicrobial susceptibility\(^{61-63}\). About 10% of *Streptococcus pneumonia* and 80% of *Hemophilus influenzae* isolates in Mulago hospital were resistant to chloramphenicol and 61.9% of *Enterobacter* species were resistant to chloramphenicol while 35.2% were resistant to gentamycin\(^{64,65}\). Resistance of *Staphylococcus aureus* to chloramphenicol ranges between 40% and 45%.

Thirteen percent of *Haemophilus influenza* isolates in Mulago hospital are resistant to ceftriaxone\(^{64}\). Resistance of *Streptococcus pneumoniae* to ceftriaxone is reported to range between 2% - 15%. On the other hand, *Streptococcus pneumoniae* susceptibility to chloramphenicol was found to be 87.2% and 88.1% while that of ceftriaxonc was 95%.

1.4.8 Management of children with severe pneumonia

All children with cough or difficulty in breathing should be assessed for pneumonia using two criteria: fast breathing and lower chest in-drawing. Two additional signs; cyanosis and inability to drink are used to distinguish children with severe pneumonia from those with very severe pneumonia. Children with severe pneumonia may be managed without oxygen where it is scarce while those with very severe pneumonia always require oxygen
therapy \(^\text{66}\). The World Health Organization (WHO) has defined protocols for management of severe pneumonia in under fives as in appendix IV\(^\text{10,16}\). It recommends intravenous chloramphenicol 25mg/kg six hourly as the first line drug for the treatment of severe pneumonia in the under fives and ceftriaxone as a second line drug.

However, there are reports of the emergence of resistance to this drug by bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae* commonly implicated in childhood pneumonia\(^\text{16,17}\).

Ceftriaxone, a third generation cephalosporin is effective therapy for pneumonia caused by virtually all isolates of *Streptococcus pneumoniae*. The advantages include high efficacy in community acquired pneumonia, a low incidence of severe adverse effects and shorter duration of stay in hospital\(^\text{21}\). It’s efficacy in treatment of pneumonia ranges from 85% to 97\(^\%\)\(^\text{22-24}\). However, resistance to this drug is reported and the current cost still remains high. A study that compared penicillin G plus chloramphenicol and ceftriaxone in the treatment of severe pneumonia in 2004 in Turkey found that both drugs were equally effective\(^\text{22}\).

The problem with use of ceftriaxone as first line treatment for community acquired pneumonia will be increased risk of resistance and may mean its effective life-span for less common but very important indications like bacterial meningitis will be shorter\(^\text{25}\). The outcome largely depends on promptness of detecting the disease and institution of appropriate treatment. The main outcomes of bacterial pneumonia usually include cure, local or systemic complications and death\(^\text{30,67}\).

1.4.9 Treatment of Pneumonia and HIV infection

The reduction of immunity predisposes HIV infected children to higher risks of serious and recurrent bacterial, viral, and opportunistic pulmonary infections. The spectrum of bacteria is similar in both HIV infected and uninfected children, however, the incidence, response to standard treatment, course and prognosis is worse in HIV infected children.

The variety of pathogens that cause pneumonia in these children is wide and includes agents not normally seen in immunocompetent patients such as *Pneumocystis jiroveci pneumoniae* and *Penicillium marneffei*. Conventional pathogens like *Streptococcus pneumoniae* are more likely to cause severe infection\(^\text{68}\).
The WHO has designed guidelines for treatment of pneumonia in HIV infected children as shown in appendix V, however these have been found to be inadequate in areas of high HIV prevalence and associated with high failure rates\(^1\).

Other studies in Zimbabwe and South Africa revealed a higher incidence of bacteraemia (14.9\%) in HIV infected children compared to 6.5\% in the HIV-1 uninfected. There were also higher levels of resistance to antibiotics, longer duration of illness and higher case fatality rate.(13.1\% versus 2.1\%)
CHAPTER TWO

2.0 Statement of the problem

Pneumonia is a leading cause of morbidity and mortality in under fives worldwide\textsuperscript{5,8,69,70}. In Uganda, pneumonia accounts for 10% of the overall annual mortality in the under fives\textsuperscript{12}. In Mulago Hospital ALRI account for 23-25% of all admissions on general Paediatric wards with case fatality rates ranging between 10-25%\textsuperscript{13}. The consequences of severe pneumonia include increased morbidity and mortality and a strain on personal and national economies.

The main bacterial agents implicated in pneumonia in children in Uganda are \textit{Streptococcus pneumonia} and \textit{Haemophilus influenzae} which are showing increased resistance to chloramphenicol, the drug of choice\textsuperscript{4}.

One strategy recommended by WHO for reducing morbidity and mortality associated with ARI is the provision of cheap and effective antibiotics\textsuperscript{71}. However misuse of antibiotics and the heavy burden of bacterial infections have undermined the effectiveness of most of the cheap and historically effective antibiotics such as chloramphenicol.\textsuperscript{64,65} Other alternatives like ceftriaxone are still expensive.

Reduced effectiveness of the standard drugs is probably contributing to reduced clinical response in children treated for severe pneumonia as observed in Mulago hospital\textsuperscript{18,72}. In addition, there is wide spread and rapid development of resistance to commonly used antimicrobial agents like chloramphenicol, especially among HIV- infected children\textsuperscript{1}, which further compounds the challenge of appropriate management of severe bacterial pneumonia among the affected children.
2.1 Justification for the study

Due to emerging resistance to chloramphenicol by *H.influenzae* and *Streptococcus pneumoniae*\(^\text{64,65}\), the pathogens commonly implicated in pneumonia in under five children presenting at Mulago Hospital, there is variation in the choice of antibiotics given to children with severe pneumonia.

There are few randomized controlled trials that have been done to show the best treatment for pneumonia, current practice largely relies on empirical treatment with chloramphenicol. Recently there has been a tendency to use other antibiotics including ceftriaxone based on the reported increasing resistance to chloramphenicol\(^\text{17}\).

While the efficacy of ceftriaxone in the treatment of pneumonia in children ranges from 85% to 97%\(^\text{22-24}\), there is no study comparing ceftriaxone and chloramphenicol for the treatment of severe pneumonia in children world wide.

In Uganda, the efficacy of ceftriaxone or chloramphenicol in the treatment of severe pneumonia in children is unknown. In addition, ceftriaxone is still unaffordable as standard treatment in public health care facilities in Uganda.

This study was designed to compare the efficacy of ceftriaxone with chloramphenicol in the treatment of severe pneumonia in under fives attending Mulago hospital.

The findings from this study would be used to determine the need to revise current standard treatment of severe pneumonia with chloramphenicol.
2.2 Study Hypothesis

2.2.1 Null Hypothesis
There is no difference in the proportion of children with severe pneumonia surviving after seven days of treatment with intravenous chloramphenicol in a dose of 25mg/kg 6 hourly compared to those on intravenous ceftriaxone at a dose of 75mg/kg daily.

2.2.2 Alternate Hypothesis
There is a 12.5% difference in survival in the children receiving intravenous ceftriaxone compared to those receiving intravenous chloramphenicol after seven days of follow up.

2.3 Research questions
I. What is the efficacy of ceftriaxone compared to chloramphenicol in the treatment of severe pneumonia in children aged 6-59 months?
II. What are the immediate adverse effects associated with ceftriaxone or chloramphenicol in the treatment of severe pneumonia in children aged 6-59 months?

2.4 Objectives
2.4.1 General objective
To compare the efficacy and safety of ceftriaxone and chloramphenicol in the treatment of severe pneumonia in the under five children aged 6-59 months in Mulago hospital.

2.4.2 Specific objectives
I. To compare the immediate clinical outcome of severe pneumonia in children aged 6-59 months treated with ceftriaxone or chloramphenicol.

II. To describe the immediate adverse effects associated with use of ceftriaxone or chloramphenicol in the treatment of severe pneumonia in children aged 6-59 months.
CHAPTER THREE

3.0 METHODS

3.1 Study setting

The study was conducted in acute care unit (the pediatric emergency care unit) and one general pediatric ward of Mulago National Referral hospital in Kampala, Uganda. Mulago Hospital is the main National referral and Teaching Hospital in Uganda and receives patients mainly from the population around Kampala. Some patients are referred from upcountry hospitals while some are self-referred. It has a total bed capacity of 1500 beds, an inpatient turnover of 120,000 patients and attends to over 480,000 outpatients annually.

Acute care unit (ACU) acts as the pediatric emergency ward and the assessment centre as the screening unit for all pediatric medical patients. It admits children with medical conditions from birth to 12 years. Children who fall into this age group are admitted overnight and transferred to the general pediatric wards for continuity of care if needed. Otherwise, they are discharged and followed up as outpatients. The unit alone admits 30 to 50 patients daily of which 8-10 have pneumonia.

An average of 23,890 children are hospitalized annually, and 4,556 of these with pneumonia, accounting for 8-20%. In children the average mortality among hospitalized pneumonia cases is 8.7% in Mulago Hospital^{73-75}.

3.2 Study design

The study was a randomized double blinded placebo controlled trial.

3.3 Population

3.3.1 Reference population

All children aged 6 months to 59 months.

3.3.2 Accessible population

All children aged 6 months to 59 months attending acute care unit of Mulago National referral hospital.

3.3.3 Study population

Children presenting with pneumonia aged 6-59 months and meeting the criteria for study.
3.3.4 Study unit
A child aged 6 months to 59 months with a diagnosis of severe pneumonia. (According to WHO criteria; Cough, fast breathing, plus lower chest in drawing) admitted to ACU Mulago hospital that fulfilled the inclusion criteria.

3.3.5 Selection criteria

3.3.5.1 Inclusion criteria
I. A child aged 6-59 months that fulfilled the WHO criteria for severe pneumonia; Cough, fast breathing, plus lower chest in drawing(Appendix VIII)
II. Those who consented to the study.

3.3.5.2 Exclusion criteria
I. Children who are known asthmatics or have bronchiectasis
II. Signs of meningitis.(kernig’s sign, brudzinski’s sign, neck stiffness)
III. Known allergy to any of the study drugs or penicillins.
IV. Those with a probable diagnosis of Pneumocystis Jirovecei Pneumoniae and already on therapeutic doses of cotrimoxazole.
V. A child with a probable diagnosis of tuberculosis.

3.3.6 Sample size estimation
The assumptions made in the calculation of the sample size were as follows:
From a study done by Bakeera in 2004 on children with severe pneumonia admitted to Mulago hospital and treated with intravenous chloramphenicol, 80.2% of the children survived\(^1\). There are no studies available where ceftriaxone was compared to chloramphenicol, therefore an adult study was used where ceftriaxone was compared to ertapenem and survival was noted in 92.7% of the participants\(^2\). Therefore a 12.5% difference in survival would be expected. The desired sample size therefore, was calculated using the following formula by Joseph and Fleiss\(^3\):

\[ n = \left( \frac{Z_1 + Z_2}{2} \right)^2 \times \frac{2 \times \text{P} (1-\text{P})}{(\text{P}_2 - \text{P}_1)^2} \]

Where:

\( n \) = the sample size in each arm.
\( \text{P}_1 \) = percentage of success expected on the chloramphenicol arm.
\( \text{P}_2 \) = percentage of success expected on the ceftriaxone arm.
\( \text{P} \) = the average of \( \text{P}_1 \) and \( \text{P}_2 \)
\( Z_1 \) = 1.96 at 95% CI
Z \_2 = 1.28 at a power of 90%

Sample size therefore was:

\[ n = (1.96 + 1.28)^2 \times 2 \times 0.8645 \times (1 - 0.8645) \]

\[ (0.927 - 0.802)^2 \]

\[ n = 158 \] the sample size for each cohort.

Assuming 10% loss to follow up of the calculated sample size, the total number of study participants would be 348. We enrolled 352 children.

3.4 Data Collection:

3.4.1 Study instrument

This was a pre-coded, pre-tested standardized questionnaire in English and translated into the main local language, Luganda. (Appendix I). It was administered by the Principal Investigator or the Research assistants.

3.4.2 Study measurements/ Variables

Variables included socio-demographic characteristics, clinical and laboratory information.

Socio- demographic features

These included name, age, sex, address, and next of kin.

Clinical History

This included a history of cough, difficulty in breathing, fever, past medical history and drug history prior to admission.

Clinical examination

The following were measured or sought among others:

Body weight which was taken with a Salter scale

Mid- arm circumference (MAC).

The Length measured (cm) for children less than 2 years and height in those above 2 years.

Axillary temperature in degrees Celsius

Oxygen saturation. This was measured using a well calibrated pulse oximeter after ensuring that the child had warm extremities. The probes were put on the thumb or middle finger and a reading taken.
Respiratory rate was taken by a trained research assistant over a period of one minute using a stop clock. An average of two was recorded. Other signs like presence of nasal flaring, cyanosis and chest in drawing were looked for and recorded.

The clinical history and physical examination sought to look out for a diagnosis of asthma, bronchiectasis, Tuberculosis and these children were then excluded if a probable diagnosis of these conditions was made.

3.4.3 Laboratory and radiological investigations

On admission or within 24 hours of admission, the following were done:

**Hematology and microbiology testing:**

Blood was collected aseptically from an accessible vein in the cubital fossa after cleaning the site with an antiseptic (70% alcohol) in a concentric fashion. Using a Gauge 23 hypodermic needle and a 5ml syringe, 2ml of blood was drawn and placed in a sequestrene bottle and rolled gently to prevent clotting. This was sent to the Paediatric Hematology laboratory for complete blood count (CBC). The CBC was done with the help of a coulter counter and the film report was read manually.

For the blood cultures, 3ml of blood were drawn. Of this 1.5ml was placed in each of two blood culture bottles containing 15ml of Brain heart infusion prepared in the Medical School Microbiology laboratory to give a ratio of 1:10 using separate needles, and sterilizing their tops with alcohol. The blood samples for culture were transported in a box immediately to the Makerere University Medical School Microbiology laboratory accompanied with filled laboratory request forms. In the laboratory, specimens were received and recorded by a laboratory technician into a records book.

Bottles were incubated at 35°-37° C for 18-24 hours after which a gram stain was done and subcultures on chocolate agar, 5% sheep blood Agar and Mackonkey done. The plates were incubated at 35-37 ° C for 18-24 hours after which growth, if any, was observed. Growth monitoring was done after 18-24 hours of incubation and thereafter 48 hrs if no growth after 18-24 hours. Thereafter monitoring was done every after two days of incubation till seven days. A significant isolate was growth of *Streptococcus pneumoniae, Haemophilus species, and Staphylococcus aureus.*

a) Susceptibility testing was done using the Disc-diffusion method as per NCCLS with controls.
b) The antimicrobial susceptibility of the isolated organism was then tested against chloramphenicol, ceftriaxone, augmentin, oxacillin, erythromycin, clindamycin, gentamicin, and cefuroxime where appropriate. Susceptibility was recorded as sensitive or resistant and the intermediate group was considered resistant.

A thick blood smear for malarial parasites was prepared using a drop of blood obtained from the sequestrene bottle. The blood smear was examined for malaria parasites in the Paediatric hematology laboratory.

Following counseling for HIV testing and informed consent (Appendix IV), blood was tested for HIV using Determine HIV I & II stat pack according to the Mulago algorithm. DNA-PCR was requested for and done for children less than 18 months who tested positive on the antibody test.

A total of 7ml of blood was drawn from the study participants for all investigations.

**Chest X-ray:** A CXR was done with in 48 hours for stable patients or later in unstable ones to aid in the confirmation of severe pneumonia and to assess for any complications.

**Sputum Induction:** Induction of sputum was done by an experienced nurse physiotherapist. This was done on all children after nebulization with salbutamol 0.1mg/kg in 3ml of N/saline. Three mls of 3% sterile saline was then administered through a facemask nebuliser for about 10-15 minutes. Sputum was obtained by nasopharyngeal suction. Collected sputum was put in sterile containers and transported to the laboratory to be analyzed. A gram stain for organisms was done. Cultures were done on 5% sheep blood, chocolate agar and MacConkey Agar. Significant growths positive for organisms were tested against the selected antibiotics ceftriaxone, chloramphenicol, amoxicillin-clavulvin, oxacillin and others as necessary.

Interpretation of the findings from sputum induction and blood cultures were as follows:

i) growth of similar organisms in both blood and sputum were considered significant.

ii) Organisms grown on blood were considered more significant than those grown on sputum since some organisms are normal flora of the nasopharynx. Significance of organisms from induced sputum was assessed using laboratory protocol, appendix X.

**3.5 Outcome Measures**

The primary outcome measures were:

i) Mortality
ii) Treatment success: refers to normalization of the respiratory rate (to below 50 per minute in a child 6-12 months of age and below 40 per Minute for the child aged 12-59 months), temperature, oxygen saturation and disappearance of lower chest in drawing by day 2 (48 hours) and day 7.

iii) Treatment failure: is when the patient while on appropriate antibiotic treatment has failure to normalization of: the respiratory rate, temperature, oxygen saturation; or death by day 2 (48 hours) and day 7.

iv) Adverse effects were measured as the occurrence of an unexpected event during the course of treatment with the study drugs that was attributable directly to the drugs as shown in appendix VII.

Secondary outcome measures were the short term complications such as pleural effusions, lung collapse observed by day 7 of treatment.

3.6 Sampling procedure
3.6.1 Enrollment
A study nurse at the triage station of acute care unit was aided by a screening form to identify children aged between 6-59 months who fulfilled the inclusion criteria. Verbal consent was then sought at this point after explaining the study to the caregiver as children were too sick for us to obtain written consent.

The identified child was transferred to the resuscitation room where the PI or research assistant resuscitated accordingly. Oxygen saturation was then assessed by pulse oxymetry before the child was put on oxygen.

A clinical history and examination was done, and a diagnosis of severe pneumonia made and classified according to WHO guidelines.

The principal investigator or the research assistant then obtained written consent from the caregivers (Appendix II) after explaining the study to them. Patient information was filled in a pre-tested questionnaire. Blood samples were drawn for cultures, smear for malaria parasites, HIV serology and CBC, before initiation of treatment. Chest X-rays and sputum induction were done with in 48 hours.

3.6.2 Randomization
Eligible children were randomized to receive either intravenous chloramphenicol or ceftriaxone. Randomization was achieved using a set of random numbers generated by a
computer. To ensure equal distribution, randomization was done in blocks of four to 12. Treatment was based on the randomization list.

3.6.3 Blinding
Labeling and preparation of study drugs was done by a nurse not involved in the study following instructions from a pharmacist. This was done in the hospital central pharmacy. Each participant’s study drugs for 24 hours were prepared and packed daily in to a plastic container and stored in a fridge. This container was labeled with a sticker bearing the dosage schedule and a study number consistent with the random number.

The vials inside the container consisted of either active ceftriaxone with chloramphenicol placebo or active chloramphenicol with ceftriaxone placebo. The active chloramphenicol and chloramphenicol placebo vials were similar. The active ceftriaxone and ceftriaxone placebo vials were also similar. The two study drugs were packaged in the same way each with a corresponding placebo. The containers were identified based on the patient’s study number. The treatment nurse recorded the study number of the patient in to a log book on a daily basis.

The principal investigator, research assistants and parents/guardians were blinded to the treatment being given. The randomization list was kept by an independent person not involved in the study.

3.6.4 Drugs and their administration
Ceftriaxone is a once daily dose while chloramphenicol is a six hourly dose. Each day a child received active drug and a placebo to ensure that every child received six hourly treatments. This was done for the whole duration of treatment.

Doses were given based on the weight of the child. The study intervention consisted of intravenous ceftriaxone, 75mg/kg given once a day for seven days and intravenous chloramphenicol placebo 25mg/kg given six hourly for seven days. The chloramphenicol group therefore received intravenous chloramphenicol, 25 mg/kg given 6-hourly for seven days and ceftriaxone-placebo 75mg/kg once a day.

Therefore, each day:

(i) In the ceftriaxone arm, the 1st dose consisted of ceftriaxone plus chloramphenicol placebo. Subsequent doses that are 2, 3 and 4 consisted of chloramphenicol placebo only.
(ii) In the chloramphenicol arm, the 1st dose consisted of chloramphenicol plus ceftriaxone- placebo. Subsequent doses that are 2, 3 and 4 consisted of chloramphenicol only.

These were given by the study nurse in ACU. After 48 hours of stabilization the patients were transferred to one general pediatric ward for further management. Children were followed up and received treatment for seven days.

The ceftriaxone generic drug used in this study was “Powercef”, purchased from Star Pharmaceuticals Company, but manufactured from Workardt industries in India. The batch numbers for the ceftriaxone used were as follows: CEF 94055, CF10103, and CF10191. The chloramphenicol used in this study was purchased from Joint Medical stores but is a product of Flamingo industries. The batch numbers used were 302, 305, 306, 304 and 307. The placebo used in this study was normal saline locally manufactured from the Mulago Hospital central pharmacy.

3.6.5. Supportive Treatment

Standard guidelines for management of severe pneumonia were followed.

a) Oxygen saturations were done upon admission and before administering oxygen.

All children with peripheral oxygen saturation of less than 92% were given humidified oxygen by nasal prongs at 1L/min. During the study period there were no irregularities in oxygen supply.

b) All children received one dose of vitamin A according to IMCI guidelines.

c) Children unable to feed orally were fed via a Nasogastric tube, on milk, porridge, or locally available soups that the care giver may have had.

3.6.6 Monitoring

For the first 48 hours the study patients were examined six hourly to document the Respiratory rate, temperature, chest in drawing, cyanosis, and oxygen saturations. After 48 hours, 12 hourly monitoring was done and recorded in each patient’s follow up form.

Twice each day the principal investigator assisted by the research assistant examined the children to assess for treatment success or failure, the development of complications and adverse effects, and to measure peripheral oxygen saturation while the child breathed room air for 15 minutes.

Each child was followed up for seven days to assess for the immediate outcome or the development of short term complications.
Treatment success was assessed at 48 hours, by resolution of clinical signs and symptoms of pneumonia that included normalization of respiratory rate, resolution of fever, improved oxygen saturations, and absence of chest in drawing. Treatment failure at 48 hours was documented as persistence or deterioration in signs and symptoms of respiratory rate, Temperature, Oxygen saturations and chest in drawing. Mortality occurring at any time was also reported. The principal investigator and the research assistants ensured that the children received their treatment accordingly and that it was charted. Recording of information in the follow up forms was also ensured.

A monitoring board comprising of an epidemiologist, pharmacist and a statistician monitored the data generated from the study and reported to the Faculty of medicine, Research and Ethics committee for remedial action when necessary. This was done after three months of carrying out the study.

3.6.7 Follow up of cases
After the administration of the first dose of study drugs, each child was clinically assessed every six hours for the first 48 hours and observations made. There after clinical assessment and observations were made twice a day. The following were then assessed:

a) A child having persistent symptoms or deteriorating while on the study antibiotics at 48 hours was re-assessed, and considered as a treatment failure and then put on second line antibiotic treatment. The second line treatment for both treatment arms was cloxacillin combined with gentamicin according to current standard practice. (Appendix IV)

b) A child who was found HIV positive and did not respond to the study medications at 48 hours was reassessed for a possibility of Pneumocystis jiroveci pneumoniae and high dose cotrimoxazole was started after consultation with the attending pediatricians. This was considered a treatment failure. All children identified as being HIV positive were referred to the Paediatric infectious disease clinic for further follow up and care. Antibiotic choices were altered based on blood culture results whenever necessary. For a selected trial antibiotic, the necessity of such a change was considered a treatment failure. A child was discharged from the study after seven days of follow up.
3.7 Data management

The data was cleaned, edited, and stored by the principal investigator. The data was cleaned on a weekly basis and cross checked and then stored in a safe file cabinet which was kept locked.

3.8 Data analysis

Data entry and analysis was done with the help of a statistician using Epi-Info 6.4 and SPSS software. Intention to treat analysis was used. The results were summarized into tables, graphs. The primary outcome variables to be analyzed were mortality, treatment success or failure as well as adverse events. The strengths of association between the variables were determined using the Chi square test for categorical variables. Student’s T test was used to compare means of continuous variables of normal distribution. Factors affecting outcome were analyzed using univariate analysis and multivariate logistic regression analysis was done to predict factors independently predicting outcome. For the survival analysis, either success or failure was analyzed using Kaplan-Meier survival curves measured by time to normalization of respiratory rate, Oxygen saturation, temperature, chest in drawing and time to death. P values of below 0.05 were considered significant.

3.9 Quality control

i) The questionnaire was pre-tested by the principal investigator. The research assistants and nurses underwent 3-day training on data collection, patient diagnosis and management prior to the actual research and participated in pre-testing and refining the questionnaire which was back translated in English to ensure accuracy of the questions being asked.

ii) A pulse-oximeter of the model Omeda Biox 3700 with inbuilt automatic calibration was used to measure oxygen saturation and the probe attached to the thumb or middle finger of a child’s warm extremities.

iii) Body weight was taken to the nearest 100g with the child undressed using a 25kg salter scale (salter Weigh-Tronix, Birmingham, UK.) and axillary temperature was measured using a digital thermometer in °C.

iv) All the blood culture tests and sputum induction cultures were performed by an experienced Laboratory Technician under the supervision of a senior microbiologist in
the Makerere Medical School Microbiology laboratory and Chest X-rays were read by a radiologist not involved in the study.

3.10 Ethical considerations

3.10.1 Informed consent
   I. Voluntary informed consent by the child’s parent or guardian was a pre-requisite to enter the study.
   II. The parent or guardian retained the right to withdraw from the study anytime without penalty.

3.10.2 Permission to carry out the study
This was obtained from the Department of Paediatrics and child Health of Makerere University, Makerere University Faculty of Medicine Research and Ethics Committee, the Uganda National Council for Science and Technology and Mulago Hospital Ethics committee. The clinical trial was also registered with clinical trials.gov under registration number NCT00372541.

3.10.3 Limitations of the study
   I. We were unable to investigate fully for hypo plastic anemia as CBCs were not done after treatment. Also inability to perform CBCs after treatment limited our ability to detect other side effects associated with ceftriaxone use like leucopenia, eosinophilia and thrombocytosis.
   II. This study was not adequately powered to demonstrate a significant difference between the two drugs since the effect size found in this study was much smaller than what had been assumed in the calculation of the sample size.

3.11 Dissemination of the results
The results of this study will be distributed to the school of postgraduate studies of Makerere University, the department of Pediatrics’ and Child health, Albert Cook Library of Makerere Medical School and the Ministry of Health Uganda.
CHAPTER FOUR

4.0 RESULTS

4.1 DESCRIPTION OF STUDY PATIENTS

From September 2006 to March 2007, three hundred and fifty two patients with severe pneumonia were enrolled and randomly assigned to treatment with either intravenous (IV) ceftriaxone or intravenous (IV) chloramphenicol. A total of 420 children were screened for severe pneumonia and sixty eight did not fulfill the inclusion criteria as shown in fig 1.

Figure 1: Study Profile
4.2 Base line clinical characteristics of children with severe pneumonia.

The age range of children was 6 months to 59 months with a mean of 17.9(11.6SD) months for the chloramphenicol group and 18(12.3SD) months for the ceftriaxone group. The majority of children were between the ages of 6 months and 24 months 283(80.3%). The sex distribution of patients in the two treatment groups was similar. Of the 176 patients assigned to intravenous chloramphenicol, 104(59.1%) were males and 72(40.9%) were female. In those assigned to IV ceftriaxone arm, 94(53.4%) were males and 82(46.6%) were females (p=0.283).

The most common presenting symptoms of severe pneumonia were cough 174 (98.9%) in chloramphenicol group,175(99.4%) in ceftriaxone group, difficulty in breathing 168(95.5%) in both groups and fever 167 (94.9 %) in both groups as reported by guardians. The rest of the symptoms and signs are shown in Table 1. The most common sign was tachypnea 163 (92.6%) in chloramphenicol arm and 164(93.2%) in ceftriaxone arm. The rest of the symptoms and signs are shown in table 1 below:

Children in both treatment arms had an associated co-morbidity with pneumonia at admission. These accounted for 74 cases (21%). These included 36(10.2%) with malaria, 20(11.3%) in the chloramphenicol arm and 16(9%) in the ceftriaxone arm. Others included diarrhea, anemia, co-infection with HIV, post measles pneumonia.
Table 1: Baseline Clinical characteristics of children with severe pneumonia in both treatment arms on admission, September 2006-March 2007

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chloramphenicol N=176</th>
<th>Ceftriaxone N=176</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>104 (59.1%)</td>
<td>94 (53.4%)</td>
<td>1.26 (0.82-1.92)</td>
<td>0.282</td>
</tr>
<tr>
<td>Female</td>
<td>72 (40.9%)</td>
<td>82 (46.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>74 (42%)</td>
<td>70 (39.8%)</td>
<td>0.79 (0.22-2.77)</td>
<td>0.671</td>
</tr>
<tr>
<td>13-24</td>
<td>68 (38.6%)</td>
<td>71 (40.3%)</td>
<td>1.43 (0.39-5.33)</td>
<td>0.542</td>
</tr>
<tr>
<td>25-59</td>
<td>34 (19.3%)</td>
<td>35 (19.9%)</td>
<td>0.71 (0.06-7.94)</td>
<td>0.743</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>174 (98.9%)</td>
<td>175 (99.4%)</td>
<td>0.49 (0.04-5.53)</td>
<td>0.562</td>
</tr>
<tr>
<td>Difficulty Breathing</td>
<td>168 (95.5%)</td>
<td>168 (95.5%)</td>
<td>1.00 (0.37-2.72)</td>
<td>1.001</td>
</tr>
<tr>
<td>Fever</td>
<td>167 (94.9%)</td>
<td>167 (94.9%)</td>
<td>1.00 (0.38-2.58)</td>
<td>1.002</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>51 (29%)</td>
<td>50 (28.4%)</td>
<td>1.02 (0.64-1.63)</td>
<td>0.906</td>
</tr>
<tr>
<td>Grunting</td>
<td>86 (48.9%)</td>
<td>103 (58.9%)</td>
<td>0.66 (0.43-1.01)</td>
<td>0.063</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHZ-2z</td>
<td>38 (21.6%)</td>
<td>32 (18.2%)</td>
<td>1.23 (0.73-2.09)</td>
<td>0.423</td>
</tr>
<tr>
<td>Temp≥37.5</td>
<td>135 (76.7%)</td>
<td>133 (75.6%)</td>
<td>0.93 (0.57-1.53)</td>
<td>0.803</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>163 (92.6%)</td>
<td>164 (93.2%)</td>
<td>0.91 (0.40-2.07)</td>
<td>0.836</td>
</tr>
<tr>
<td>Oxygen sats ≤92%</td>
<td>29 (16.4%)</td>
<td>33 (18.7%)</td>
<td>1.67 (0.92-3.03)</td>
<td>0.087</td>
</tr>
<tr>
<td>Immunization status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully</td>
<td>109 (61.9%)</td>
<td>98 (55.7%)</td>
<td>1.29 (0.83-2.03)</td>
<td>0.232</td>
</tr>
<tr>
<td>partly</td>
<td>67 (38%)</td>
<td>78 (44.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Antibiotic use</td>
<td>18 (10.3%)</td>
<td>20 (11.4%)</td>
<td>0.89 (0.45-1.75)</td>
<td>0.745</td>
</tr>
<tr>
<td>Co-morbidity (n=74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasite density/ul (Median (IQR) *)</td>
<td>53,040(13,281-227,225)</td>
<td>30,160(1490-71,100)</td>
<td>N/A</td>
<td>0.091</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (4.5%)</td>
<td>11 (6.3%)</td>
<td>0.71 (0.25-1.97)</td>
<td>0.471</td>
</tr>
<tr>
<td>Others</td>
<td>10 (5.7%)</td>
<td>9 (5.1%)</td>
<td>1.23 (0.23-12.45)</td>
<td>0.234</td>
</tr>
<tr>
<td>HIV sero status *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=302</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22 (14.6%)</td>
<td>30 (20%)</td>
<td>0.70 (0.37-1.33)</td>
<td>0.243</td>
</tr>
</tbody>
</table>

- Values are number (%) unless otherwise stated. IQR = Interquartile range
- Numbers only for those whose results were available
4.3 Baseline hematological characteristics for children with severe pneumonia.

The range for Hemoglobin (Hb) levels in the study population was 2.5g/dl to 12.6g/dl. The mean Hb in the chloramphenicol group was 7.8g/dl (1.94Sd) and that in ceftriaxone was 8.12g/dl (1.79Sd) but this difference was not statistically significant.

Table 2: Baseline Hematological characteristics for children with severe pneumonia before treatment in both treatment arms Sept 2006-March 2007*.

<table>
<thead>
<tr>
<th>variable</th>
<th>Chloramphenicol N=176</th>
<th>Ceftriaxone N=176</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb(SD)</td>
<td>7.89(1.94)</td>
<td>8.12(1.79)</td>
<td>N/A</td>
<td>0.270</td>
</tr>
<tr>
<td>Neutrophils(SD)</td>
<td>56.9(20.12)</td>
<td>63.2(68.9)</td>
<td>N/A</td>
<td>0.322</td>
</tr>
<tr>
<td>Parasite density/ul</td>
<td>53,040(13,281-227,225)</td>
<td>30,160 (1490-71,100)</td>
<td>N/A</td>
<td>0.091</td>
</tr>
<tr>
<td>Presence of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12(8.2%)</td>
<td>8(4%)</td>
<td>1.72(0.63-4.77)</td>
<td>0.244</td>
</tr>
</tbody>
</table>

* Values are number (%) unless otherwise stated.
4.4 Chest Radiological findings of the children admitted with severe pneumonia.

Chest X-rays were done on 250 children and of these, the diagnosis of pneumonia was confirmed in 200 (80.2%) of them, 49 (19.8%) did not show radiological evidence of Pneumonia.
4.5 Bacterial organisms isolated in children with severe pneumonia.

Of the 302 samples where blood cultures were done, bacterial growth was seen in 53 (17.5%). In chloramphenicol arm 26/152 (17.1%) and in ceftriaxone arm 27/150(18%). There was no growth in 183/302(60.5%). The commonest causative organism for severe pneumonia isolated from blood in chloramphenicol arm was Staphylococcus aureus contributing 6/26(23 %) of total isolates. The commonest organism isolated from blood in ceftriaxone arm was Streptococcus pneumoniae contributing to 10/27(37.0%) of the total isolates.

The other organisms which were isolated in blood were Haemophilus influenza, Escherichia coli, Klebsiella pneumoniae species, Salmonella and Listeria Monocytogenes. The details are shown in table 3.

Fifty children did not have blood cultures done because some specimens were lost, children died before blood was drawn off and other caregivers refused to consent.

Table 3 Bacterial organisms isolated from Blood culture in children with severe pneumonia.

<table>
<thead>
<tr>
<th>Variable (Blood culture)</th>
<th>Chloramphenicol (N=152)</th>
<th>Ceftriaxone (N=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>4(2.6%)</td>
<td>10(6.0%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>6(3.9%)</td>
<td>3(2.0%)</td>
</tr>
<tr>
<td>H.influenza</td>
<td>2(1.3%)</td>
<td>1(0.6%)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1(0.6%)</td>
<td>1(0.6%)</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
<td>4(2.6%)</td>
<td>3(2.0%)</td>
</tr>
<tr>
<td>Coagulase negative staph</td>
<td>1(0.6%)</td>
<td>5(3.0%)</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>2(1.3%)</td>
<td>1(0.6%)</td>
</tr>
<tr>
<td>Others</td>
<td>6(3.9%)</td>
<td>3(2.0%)</td>
</tr>
<tr>
<td>No growth</td>
<td>93(61.2%)</td>
<td>90(60%)</td>
</tr>
<tr>
<td>Contaminant</td>
<td>33(21.7%)</td>
<td>23(15.3%)</td>
</tr>
</tbody>
</table>

30
Of the 271 samples where sputum induction was done, bacterial growth was seen in 151 (55.7%) of the children. In the chloramphenicol arm, 76(57%) and in ceftriaxone arm 65(47.8%). The commonest organism isolated from sputum in chloramphenicol arm was *Streptococcus pneumoniae* contributing (17)12.9% of patients and in ceftriaxone arm was *Klebsiella pneumoniae* in (18)12.9%. The other organisms which were isolated in sputum were *Escherichia coli*, *Acinobacter species*. The details are shown in table 4.

Eighty children did not have sputum inductions done because majority of the caregivers later refused to consent, while some children died before the sputum induction was done.

**Table 4: Bacterial organisms isolated from Sputum culture in children with severe pneumonia, in both treatment arms**

<table>
<thead>
<tr>
<th>Variable (Sputum culture)</th>
<th>chloramphenicol (N=132)</th>
<th>Ceftriaxone (N=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>17(12.8%)</td>
<td>12(8.6%)</td>
</tr>
<tr>
<td><em>E.coli</em></td>
<td>11 (8.3%)</td>
<td>6(4.3 %)</td>
</tr>
<tr>
<td><em>E.coli</em> (ESBL)</td>
<td>2(1.5%)</td>
<td>1(0.7%)</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>12(9.0%)</td>
<td>18(12.9%)</td>
</tr>
<tr>
<td><em>H.influenzae</em></td>
<td>7(5.3%)</td>
<td>0</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>6(4.5%)</td>
<td>5(3.5%)</td>
</tr>
<tr>
<td><em>Acinobacter</em></td>
<td>4(3.0%)</td>
<td>9(6.4%)</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>5(3.7%)</td>
<td>3(2.1%)</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>1(0.7%)</td>
<td>4(2.3%)</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>2(1.5%)</td>
<td>4(2.3%)</td>
</tr>
<tr>
<td><em>S. coagulase –ve</em></td>
<td>2(1.5%)</td>
<td>2(1.4%)</td>
</tr>
<tr>
<td>Normal Mouth Flora</td>
<td>24(18.2%)</td>
<td>28(20.1%)</td>
</tr>
<tr>
<td>No growth</td>
<td>32(24.2%)</td>
<td>46(33%)</td>
</tr>
<tr>
<td>Others</td>
<td>7(5.3%)</td>
<td>1(0.7%)</td>
</tr>
</tbody>
</table>
4.6 Antimicrobial sensitivity of organisms isolated from blood

Most of the gram negative and gram positive organisms were sensitive to ceftriaxone. *Streptococcus pneumoniae* sensitivity to chloramphenicol was 13/14(92.9%) and that to ceftriaxone was 14/14(100%). *H.influenza* sensitivity to chloramphenicol was 0/3(0%) and to ceftriaxone was 3/3(100%). Other sensitivities are as shown in table 5;

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Chloramphenicol (N=23)</th>
<th>Ceftriaxone (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Strep pneumoniae</em></td>
<td>13/14</td>
<td>14/14</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3/9</td>
<td>7/9</td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em></td>
<td>2/5</td>
<td>7/7</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0/3</td>
<td>3/3</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td>Coag –ve Staphylococcus</td>
<td>2/6</td>
<td>4/6</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>0/2</td>
<td>2/2</td>
</tr>
<tr>
<td>Others</td>
<td>1/2</td>
<td>5/5</td>
</tr>
</tbody>
</table>

*Data not expressed in percentages because numbers are too few.

The category of others included;

*Moraxella catarrhalis*
*Listeria monocytogenes*
*Candida albicans*
*Coagulase –ve Staphylococcus*
*Citrobacter sp*
*corrineform*
4.7 Antimicrobial sensitivity of organisms isolated from sputum.

*Streptococcus pneumoniae* sensitivity to chloramphenicol was 19/28 (67.8%) and that to ceftriaxone was 26/27 (96.2%). *H.influenza* sensitivity to chloramphenicol was 3/7 (42.8%) and to ceftriaxone was 6/7 (85.7%). *Klebsiella pneumoniae* sensitivity to chloramphenicol was 1/29 (3.4%) and to ceftriaxone was 7/30 (23.3%). Other percentage sensitivities are as shown in table 6:

Table 6 Anti-microbial sensitivity of organisms isolated from the Sputum of patients with severe pneumonia, Mulago Hospital Sept 2006-March 2007.

<table>
<thead>
<tr>
<th>Organisms</th>
<th>chloramphenicol (N=129)</th>
<th>ceftriaxone (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>19/28 (67.8%)</td>
<td>26/27 (96.2%)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4/11 (36.3%)</td>
<td>9/11 (81.8%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1/29 (3.4%)</td>
<td>7/30 (23.3%)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>3/7 (42.8%)</td>
<td>6/7 (85.7%)</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>1/12 (8.3%)</td>
<td>9/12 (69.2%)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1/6 (16.7%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td><em>E.coli</em></td>
<td>5/17 (29%)</td>
<td>0/3</td>
</tr>
<tr>
<td>others</td>
<td>5/15 (33%)</td>
<td>9/15 (60%)</td>
</tr>
</tbody>
</table>

The category of others included:

*Moraxella catarrhalis*

*Listeria monocytogenes*

*Candida albicans*

*Coagulase-ve staphylococcus*

*Citrobacter sp*

*corrineform*
4.8 TREATMENT OUTCOME

4.8.1 Outcome of children with severe pneumonia at day seven.

Of the 352 children who were enrolled, treated and followed up, 324 (92%) survived. In the chloramphenicol arm, survival was observed in 161 (91.4%) of the children and in the ceftriaxone group in 163 (92.6%) of the children. This difference was not statistically significant. The total mortality in both treatment arms was 7.9%, with 15 (8.5%) children in the chloramphenicol arm and 13 (7.3%) in the ceftriaxone arm. The differences in death observed in the chloramphenicol arm and the ceftriaxone arm was not statistically significant. P value = 0.69, risk ratio RR = 1.15 (95% CI, 0.57-3.35)

![Final outcome of children with severe pneumonia in both treatment arms](image)

**Figure 2 Outcome of children with severe pneumonia at day seven in both treatment arms**
4.9 MORTALITY:
Twenty eight (7.9%) children died. Fifteen (8.5%) were observed in the chloramphenicol arm and thirteen (7.3%) in the ceftriaxone arm. Causes of death were not established as post-mortem examinations were not done in this study because most care givers left the hospital immediately.

Factors that were compared with mortality at Bivariate analysis were Temp ≥37.5°C, age, treatment arm, co-morbidity, immunization status, sex, Oxygen saturations ≤92%, WHZ - 2sd.

Table 7: Bivariate analysis for factors associated with Death in children with severe pneumonia in both treatment arms.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>OR(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age(mo)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>14(9.7%)</td>
<td>0.42(0.07-2.45)</td>
<td>0.024*</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6(11.5%)</td>
<td>3.13(0.96-9.92)</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>17(11%)</td>
<td>2.10(0.95-4.64)</td>
<td>0.059</td>
</tr>
<tr>
<td><strong>Immunization status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fully</td>
<td>15(17.3%)</td>
<td>1.66(0.72-3.84)</td>
<td>0.19</td>
</tr>
<tr>
<td>Partly</td>
<td>11(13.1%)</td>
<td>2.22(0.99-4.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Temp ≥37.5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8(14.8%)</td>
<td></td>
<td>0.41(0.17-0.99)</td>
<td>0.046*</td>
</tr>
<tr>
<td><strong>Oxygen sat ≤ 92%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7(6.9%)</td>
<td></td>
<td>0.81(0.33-0.98)</td>
<td>0.043*</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7(6.9%)</td>
<td></td>
<td>122(0.50-2.98)</td>
<td>0.652</td>
</tr>
<tr>
<td><strong>WHZ ≤-2sd</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13(18.6%)</td>
<td></td>
<td>0.24(0.11-0.54)</td>
<td>0.000*</td>
</tr>
<tr>
<td><strong>Treatment arm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28(8%)</td>
<td></td>
<td>0.85 (0.39-1.85)</td>
<td>0.694</td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(7.1%)</td>
<td></td>
<td>3.73 (1.09-12.75)</td>
<td>0.044</td>
</tr>
<tr>
<td><strong>Sensitivity to Chloramphenicol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>2(3.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistant</td>
<td>2(2.7%)</td>
<td>0.74(0.01-5.39)</td>
<td>0.762</td>
</tr>
<tr>
<td><strong>Sensitivity to Ceftriaxone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>4(4.1%)</td>
<td>N/A</td>
<td>0.246</td>
</tr>
<tr>
<td>Resistant</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
To determine independent predictors of mortality, irrespective of the treatment arm, factors with p values < 0.02 at Bivariate level were entered into the logistic regression model and HIV status (positive), oxygen saturations ≤ 92%, still remained as independent predictors of death (table 8).

### Table 8 Logistic regression model for factors independently predicting death in severe pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex female</td>
<td>6.14</td>
<td>(0.72-52.29)</td>
<td>0.097</td>
</tr>
<tr>
<td>WHZ -2sd</td>
<td>0.91</td>
<td>(0.134-6.19)</td>
<td>0.082</td>
</tr>
<tr>
<td>Oxygen sats ≤92%</td>
<td>7.25</td>
<td>(1.22-43.47)</td>
<td>0.029*</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>5.93</td>
<td>1.027-34.24</td>
<td>0.047*</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>10.66</td>
<td>(0.932-121.82)</td>
<td>0.057</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1.29</td>
<td>(0.23-7.04)</td>
<td>0.773</td>
</tr>
</tbody>
</table>
4.9.1 Time to death among children with severe pneumonia.
Median survival time in both treatment arms was 2 days. Analysis by the log rank test showed no statistical significance in the two treatment arms. Log rank P-value=0.841
Twenty deaths (71.4%) occurred within the first 48 hours. Eight deaths (28.6%) occurred after 48 hours.

Figure 3 Kaplan Meier survival curve for time to death for children receiving Ceftriaxone or Chloramphenicol
4.10 Treatment outcome of children with severe pneumonia.

The mean respiratory rate observed in the chloramphenicol arm was 63.4 (16.83Sd) and in the ceftriaxone arm was 65.9 (14.46Sd). Normalization of respiratory rate at 48 hours was observed in 123 (74.5%) of children in the chloramphenicol arm and 109 (64.8%) in the ceftriaxone arm but this difference was not statistically significant. P-value=0.055.

The differences in time to normalization of Temperature, oxygen saturation, and chest in drawing were also not statistically significant.

Children who improved on first line therapy in the chloramphenicol arm were 146 (82.9%) and 154 (87.5%) in the ceftriaxone group. This difference was not statistically significant.

A total of 32 (9%) of the children failed on first line therapy and were switched to second line therapy. These were considered treatment failures.

Twenty four (75%) children of those who failed first line therapy survived and 8(25%) of those who failed first line therapy died.

Twenty children 20/352 (5.6%) died with in 48 hours. See table 9.
Table 9 Treatment Outcome of children with severe pneumonia at 48 hours in both treatment groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chloramphenicol N=176</th>
<th>Ceftriaxone N=176</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>123(74.5%)</td>
<td>109(64.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>24(14.5%)</td>
<td>59(35.1%)</td>
<td>1.58(0.98-2.54)</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>Oxygen sats</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤92%</td>
<td>15(9.2%)</td>
<td>16(9.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;92%</td>
<td>148(90.7%)</td>
<td>153(90.5%)</td>
<td>0.96(0.46-2.03)</td>
<td>0.934</td>
</tr>
<tr>
<td><strong>Temp</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37.5°C</td>
<td>20(12.1%)</td>
<td>14(83.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37.5°C</td>
<td>144(87.8%)</td>
<td>154(91.6%)</td>
<td>1.52(0.74-3.13)</td>
<td>0.282</td>
</tr>
<tr>
<td><strong>Chest in drawing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>80(48.7%)</td>
<td>89(52.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>84(51.2%)</td>
<td>79(47%)</td>
<td>1.18(0.76-1.82)</td>
<td>0.445</td>
</tr>
<tr>
<td><strong>Treatment success</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>146(82.9%)</td>
<td>154(87.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>21(11.9%)</td>
<td>11(6.2%)</td>
<td>0.50(0.22-1.13)</td>
<td>0.068</td>
</tr>
<tr>
<td>n= (332)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>9(5.1%)</td>
<td>11(6.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>167(94.8%)</td>
<td>165(93.7%)</td>
<td>0.81(0.30-2.17)</td>
<td>0.645</td>
</tr>
</tbody>
</table>
4.11 Clinical responses observed in children with severe Pneumonia at 48 hours and 7 days.

Temperature at 48 hrs
The median time taken to normalization of temperature in the chloramphenicol group was 30 hours (95% CI; 29-31) and that in the ceftriaxone group was 30 hours (95%CI; 29-31) Analysis by Log Rank test showed no statistical significance. Log rank p-value= 0.788

Figure 4 Time to normalization of Temperature at 48 hours

Temperature at 7 days
Median time to normalization of temperature in chloramphenicol arm was 60 hrs (95% CI; 70-75) and in ceftriaxone arm 60 hrs (95% CI; 70-74) Analysis by Log Rank p value=0.915

Figure 5 Time to normalization of Temperature at day 7
Respiratory rate at 48 hours

The median time taken to normalization of respiratory rate in the chloramphenicol group was 24 hours (95% CI; 23-25) and that in the ceftriaxone group was 25 hours (95% CI; 24-26). Analysis by Log Rank test showed statistical significance. Log rank p-value = 0.046

Figure 6 Time to Normalization of Respiratory rate at 48 hours

The median time taken to normalization of respiratory rate in the chloramphenicol group was 48 hours (95% CI; 43-53) and that in the ceftriaxone group was 60 hours (95% CI; 54-56). Analysis by Log Rank test showed statistical significance. Log rank p-value = 0.014.

Figure 7 Time to Normalization of Respiratory rate at day 7
The median time taken to normalization of Oxygen saturation in the chloramphenicol group was 39 hours (95% CI; 38-40) and that in the ceftriaxone group was 39 hours (95% CI; 38-39). Analysis by Log Rank test showed no statistical significance. Log rank p-value = 0.723

Figure 8 Time taken to Normalization of Oxygen saturation at 48hrs

The median time taken to normalization of Oxygen saturation in the chloramphenicol group was 141 hours (95% CI; 138-143) and that in the ceftriaxone group was 140 hours (95% CI; 137-142) Analysis by Log Rank test showed no statistical significance. Log rank p-value = 0.674

Figure 9 Time taken to Normalization of Oxygen saturation at day 7
The median time taken to disappearance of chest in drawing in the chloramphenicol group was 48 hours (95% CI; 46-50) and that in the ceftriaxone group was 48 hours (95% CI; 46-50).

Analysis by Log Rank test showed no statistical significance. Log rank p-value = 0.460

Figure 10 Time to disappearance of chest in drawing in both treatment arms at 48 hrs

The mean time taken to disappearance of chest in drawing in the chloramphenicol group was 108 hours (95% CI; 98-102) and that in the ceftriaxone group was 108 hours (95% CI; 97-102).

Analysis by Log Rank test showed no statistical significance. Log rank p-value = 0.477

Figure 11 Time to disappearance of chest in drawing in both treatment arms, day 7
4.12 ADVERSE EVENTS

Drug adverse effects such as hypersensitivity reactions including urticaria, maculopapular skin rashes, and edema were not observed in any treatment arm. Common minor side effects such as diarrhea, vomiting and abdominal pain were observed in some children. Vomiting occurred in children that were in the ceftriaxone group 10 (5.6%) and this occurred with in ten minutes of drug administration. No phlebitic reaction was observed after IV administration in the children randomized to the ceftriaxone arm or chloramphenicol arm.

Diarrhea mainly occurred with in 72 hrs of therapy in both treatment arms 7 (1.9%) with 4 (2.2%) in the chloramphenicol group and 3 (1.7%) in the ceftriaxone arm. These side effects had improved by day six of treatment. The seven day follow up was too short to assess for bone marrow suppression as a result of treatment with chloramphenicol.

Ceftriaxone has also been associated with other side effects including eosinophilia, trombocytosis, leucopenia however we were unable to perform complete blood counts. However, all children were seen twice daily but no jaundice or anemia was observed clinically especially in the HIV positive children who are likely to get ceftriaxone induced hemolysis. There were no deaths associated with severe hemolysis. Other side effects related to chloramphenicol use like optic neuritis, mental confusion, peripheral neuritis could not be assessed in this age group.
CHAPTER FIVE

5.0 DISCUSSION

5.1 Introduction

This study was undertaken to compare the efficacy of intravenous chloramphenicol and intravenous ceftriaxone in the treatment of severe pneumonia in children age 6-59 months. It specifically looked at the following as outcome measures: mortality and clinical response (normalization of respiratory rate, chest in drawing, temperature and oxygen saturation). The study also sought to identify adverse effects that might occur with both drugs.

5.2 Mortality:

Overall, (7.9%) of the patients died. This mortality is lower than the 20% reported by Bakeera et al\textsuperscript{30}, and 15.3% found by Nantanda et al\textsuperscript{18} in the same hospital. Several factors could explain this low mortality such as: effect of being in a trial, awareness of the role of co-morbidity and adherence to the indications for changing antibiotics. The fact that these children were promptly started on antibiotics and were closely monitored 6 hourly could also explain the low mortality.

There was no statistically significant difference in mortality between patients on chloramphenicol (8.5%) and ceftriaxone (7.3%) RR=1.15 (95% CI=0.57-3.35); p=0.69. Although there was no difference between the two drugs in this study, the expected effect size (difference in mortality) observed in this study was much smaller than the assumption made in the calculation of the sample size. In order to detect a meaningful difference, this would require an equivalence study with much larger numbers. This was not an equivalence study.

The mortality in the chloramphenicol group in this study was higher than the 6% observed by Duke et al\textsuperscript{60} in Papua New Guinea but is lower than what others have observed in Mulago\textsuperscript{18,30}. This could also be explained by the fact that this study and that done in New Guinea were randomized trials while those done here were not. However we could not find any study comparing the efficacy of ceftriaxone with that of chloramphenicol in children.
While the WHO recommends chloramphenicol for the treatment of severe pneumonia, the tendency has been to use third generation cephalosporins without adequate evidence. The majority of deaths occurred with in 48 hours 20/28 (71.4%), eight in the chloramphenicol arm and twelve in the ceftriaxone arm. The majority of deaths were associated with presence of co-morbidity and severity of illness, or other etiology like viral, fungal and delay in seeking care. In less developed countries, some children with severe pneumonia are going to die even with the best possible therapy. Analysis for the effect of in-vitro resistance on outcome showed that only 3.6% of children who had organisms resistant to either drug died, (3.6% in the chloramphenicol arm and none in the ceftriaxone arm). Analysis for the effect of in-vitro resistance on outcome showed that only 7% of children who had organisms sensitive to either drug died. (3.6% in the chloramphenicol arm and 4.1% in the ceftriaxone arm) These findings compare with those observed else where that in-vitro resistance to organisms does not correlate to treatment failure in severe pneumonia. However there were very few numbers to make such conclusions and further more, blood cultures are only positive in about 15% to 30% of the children therefore the effect of antibiotic sensitivity in predicting outcome may not be accurate.\textsuperscript{60,80} In this study the commonest organisms causing pneumonia were \textit{Streptococcus pneumoniae, Staphylococcus aureus, and Klebsiella pneumoniae}. \textit{Haemophilus influenzae} isolates were very few and this could be explained by the fact that introduction of the pentavalent vaccine in 2002 in Uganda could be responsible for the reduction in \textit{Haemophilus influenzae} organisms isolated and therefore not being a major cause of severe pneumonia. The majority of children in this study had received the pentavalent vaccine (59%).

5.3 Clinical responses of children with severe pneumonia.

Survival was observed in 91.5% of the children treated with chloramphenicol and in 92.5% of the children treated with ceftriaxone.

The observed survival noted in this study was higher than that observed in this hospital previously by Nantanda et al\textsuperscript{18} and Bakeera et al\textsuperscript{30}, where children who were treated with intravenous chloramphenicol also showed success rates in 82.8%, and 80.2% respectively, but these were not randomized trials. The observed survival was similar to that found by Trevor duke in Papua New Guinea, who compared chloramphenicol to a combination of benzyl penicillin and gentamicin and found survival in the
chloramphenicol arm of 91.2%⁶⁰. This could be explained by the nature of the study where children were strictly observed and received appropriate and early treatment. Shann F et al in a study comparing chloramphenicol versus a combination of chloramphenicol plus penicillin found clinical success in the chloramphenicol arm of 86.2%¹⁹. This study however also found almost similar success rates in the ceftriaxone group like in other studies. Leibovitz et al⁵⁴ found 96.6% cure in children who received once daily intramuscular ceftriaxone for five days and by Toyonaga et al of 93.7% in Japan²⁴.

5.3.1. Time to normalization of Temperature

In this study, the median time to normalization of temperature was similar in both treatment arms 60 hours, (95%CI; 70-75). p-value=0.915. This finding is similar to the study from Turkey, Istanbul where the median time to normalization of temperature was observed by 72 hours²². No other study has compared the median time to normalization of temperature between the two drugs.

5.3.2. Time to normalization of respiratory rate

The median time to achieving normal respiratory rate in the chloramphenicol arm was 48 hours (95% CI; 43-53) while that in the ceftriaxone arm was 60 hours (95% CI; 54-66). The difference however was statistically significant, p-value = 0.014. This is explained by the fact that peak values of chloramphenicol occur with in three hours which is faster than that in ceftriaxone. These findings also compare with those observed in the Turkey study²² where the median time to achieve normal respiratory rate was between the third and fourth day. In a study done here on children receiving chloramphenicol, more than 80% of the children had achieved a normal respiratory rate by day 4 which also compares with the findings in this study¹⁸.

5.3.3. Time to normalization of oxygen saturation.

Children in both treatment arms achieved normal oxygen saturations with median times in chloramphenicol group being 141 hours(95% CI;138-143) and in the ceftriaxone arm being 140 hours (95% CI;137-142). This difference was not statistically significant. P-Value = 0.674. No significant fluctuations were reported in the following days.

In the study done in Turkey²², the mean oxygen saturation values were over 95% on the second day in all groups which was also observed in this study.
5.3.4. Time to Disappearance of chest in drawing

Children in both treatment groups achieved disappearance of chest in drawing similarly, median time being by 108 hours, (95% CI; 98-102). This difference was not statistically significant. P-value = 0.477

In a study by Nantanda, chest in drawing had disappeared by 3-4 days in 90% of the patients.\textsuperscript{18}

5.4 Observed Treatment Failure

In total, treatment failure was observed in 32 children (10.8%). These were children who were changed to second line antibiotics. The second line antibiotic according to WHO is a combination of gentamicin and cloxacillin, however a number of children were also given anti-Tb treatment, high dose cotrimoxazole for PJP and others were put on treatment for heart failure. Common clinical co-morbidities observed included tuberculosis, PJP, Measles developed while on treatment, malaria, and diarrhea. Two children had severe anemia warranting blood transfusion but despite this one child died.

Despite considerable efforts to primarily exclude such patients, clinical complications included conditions like bacterial meningitis (2), Tuberculosis (pulmonary and tuberculous meningitis) in (5), Empyema thoracis (3), Heart failure (3), and Pneumocystis jiroveci pneumoniae(3) among others. Some children developed measles (7) after being recruited and were considered treatment failures. The findings of other comorbidities in this study also demonstrate similar findings observed in a study by Trevor Duke where 130 children out of 1116 (11.6%) had similar co-morbidities and were put on second line antibiotics.\textsuperscript{60} Presence of co-morbidity was responsible for most of the observed treatment failures.

We did not exclude these children from the primary analysis if these infections were diagnosed during the treatment course. To have done so would reduce the applicability of the study for other similar settings in other developed countries, where children present apparently with a single disease but often have multiple pathology that contribute to outcome. The observed treatment failures described provide information about the complexity of treatment failure in severe pneumonia; and to emphasize that children with severe pneumonia who do not respond to treatment may have more than one disease process. The treatment failures that were observed requiring change to second line
antibiotics were comparable in both treatment arms and any differences observed were not statistically significant.

5.5 Adverse events

In this study both drugs had no reported major adverse events noted. This shows that both drugs are tolerated quite well and that the noted side effects observed occur rarely which could explain why they were not observed in this study.

The incidence of adverse effects due to ceftriaxone occur in less than 1% and include hypersensitivity reactions like urticaria or maculopapulous skin rashes, erythema, itching and edema. The common side effects are minor and include those affecting the gastrointestinal tract (2%) such as loose stools or diarrhea, nausea, vomiting, and abdominal pain. Only three patients reportedly had loose stools however vomiting occurred in 5.6% of the patients in the ceftriaxone arm. In this study it was difficult to observe for any adverse events due to chloramphenicol as the idiosyncratic aplastic anemia that occurs in 1/30,000 people is a very rare occurrence. We also followed up these children for only seven days and we were unable to do full blood counts on day seven to look for any evidence of bone marrow suppression in relation to the hypoplastic anemia that occurs.

Ceftriaxone has also been associated with other side effects including eosinophilia, trombocytosis, leucopenia, however we were unable to perform complete blood counts. However, all children were seen twice daily but no jaundice or anemia was observed clinically especially in the HIV positive children who are likely to get ceftriaxone induced hemolysis. There were no deaths associated with severe hemolysis or anemia during the course of treatment.

Other side effects related to chloramphenicol use like optic neuritis, mental confusion, peripheral neuritis could not be assessed in this age group because the children were too young to report them.

In this study, the inability to perform further hematological studies to document the immediate side effects associated with either drug limited our ability to conclude that actually no adverse events were observed.
CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1) Intravenous ceftriaxone was as efficacious as intravenous chloramphenicol in the treatment of severe pneumonia in children

2) There was no significant difference in mortality and clinical responses between the two treatment arms.

3) The study also shows that both ceftriaxone and chloramphenicol did not show serious adverse events for the seven days duration of follow up.

6.2 Recommendations

1) Intravenous chloramphenicol should still be considered as the first line drug for severe pneumonia in Ugandan children according to the WHO recommendations.

2) An equivalence study based on a larger sample size should be done to test for the efficacy of either drug and also a longer follow up period to ascertain the adverse events associated with either drug.
REFERENCES:


57. Chloramphenicol Drug Information, version 12.3 ed, Up to Date, 2006.


64. Mulago Hospital, Bacterial isolates, October 1st 2001 to April 6th, 2002. Mulago Hospital Microbiology Laboratory records.
APPENDIX I

Questionnaire
CEFTRIAXONE VERSUS CHLORAMPHENICOL FOR THE TREATMENT OF SEVERE PNEUMONIA IN CHILDREN AGED 6-59 MONTHS ADMITTED TO ACU MULAGO HOSPITAL

A. Study Identification

1. Serial number: .................................................................
2. Study Identification number: ........................................
3. IP Number: ........................................................................
4. Date of Admission: .............................................................
5. Date of Discharge/Death/Ran away: .................................
6. Duration of Hospital stay (days): ........................................

B. Socio-Demographic Details

7. Name of patient: .................................................................
8. Date of Birth: ......................................................................
9. Age (months): ......................................................................
10. Sex
   1. Male  2. Female [ ]
11. Relationship of Caretaker/Parent to patient
    1. Mother
    2. Father
    3. Grandmother [ ]
    4. Aunt
    5. Other
12. District of origin
    1. Kampala
    2. Wakiso
    3. Mukono [ ]
    4. Mpiigi
    5. Luweero
    6. Other
13. Distance from Hospital (kilometres): ..............................

C. Symptoms of present illness and duration

14. Drug used for treating the patient
    1. S  2. T [ ]
15. Cough
   1. Yes  2. No  [ ] Duration (days): .....................

16. Fever
   1. Yes  2. No  [ ] Duration (days): .....................

17. Difficulty in breathing
   1. Yes  2. No  [ ] Duration (days): .....................

18. Grunting respiration
   1. Yes  2. No  [ ] Duration (days): .....................

19. Inability to feed on solids/breast feed/formula feeds
   1. Yes  2. No  [ ] Duration (days): .....................

20. Convulsion/seizures
   1. Yes  2. No  [ ] Duration (days): .....................

21. Vomiting
   1. Yes  2. No  [ ] Duration (days): .....................

22. Diarrhoea
   1. Yes  2. No  [ ] Duration (days): .....................

D. Past Medical History

23. Recurrent cough
   1. Yes  2. No  [ ] Duration (days): .....................

24. Cardiac disease
   1. Yes  2. No  [ ] Duration (days): .....................

25. Use of study antibiotics in the last one month
   1. Yes  2. No  [ ] Duration (days): .....................

   Specific antibiotic(s) used if any
   1. Chloramphenicol  2. Ceftriaxone  3. CAF  4. Other  [ ]

26. Use of study antibiotics in the last 24 hour
   1. Yes  2. No  [ ] Duration (days): .....................

   Specific antibiotic(s) used if any
   1. Chloramphenicol  2. Ceftriaxone  3. CAF  4. Other  [ ]

27. HIV sero-status
   1. Positive  2. Negative  3. Unknown  [ ]

28. Immunization status
   1. Fully immunized  2. Partly immunized  3. Not immunized  [ ]
29. Card available
   1. Yes    2. No [ ]

Which vaccines:

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<th>BC</th>
<th>Poli</th>
<th>Penta</th>
<th>Penta</th>
<th>Penta</th>
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</tr>
</tbody>
</table>

E. General examination

30. Pallor

31. Jaundice
   1. Yes    2. No [ ]

32. Dehydration
   1. None 2. Some 3. Severe [ ]

33. Grunting
   1. Yes    2. No [ ]

34. Cyanosis
   1. Yes    2. No [ ]

35. Extremities
   1. Warm 2. Cold [ ]

36. Capillary refill time (seconds/minute): ......................

F. Respiratory system examination

37. Respiratory rate (breaths/minute): ......................

38. Flaring of alae nasi
   1. Present 2. Absent [ ]

39. Chest retractions
   1. Present 2. Absent [ ]

40. Percussions

41. Air entry
   1. Normal 2. Reduced [ ]

42. Crepitations/rales
1. Yes  2. No  [  ]

43. Bronchial breathing
   1. Yes  2. No  [  ]

G. Cardiovascular system

44. Pulse rate (beats/minute) .................................

45. Heart sounds
   1. Normal  2. Abnormal  [  ]

46. Murmurs
   1. Yes  2. No  [  ]

H. Central nervous system

47. Consciousness
   1. Abnormal  2. Normal  [  ]

48. Behaviours
   1. Abnormal  2. Normal  [  ]

49. Lethargy
   1. Present  2. Absent  [  ]

50. Seizures
   1. Yes  2. No  [  ]

I. Abdominal examination

51. Hepatomegaly
   1. Yes  2. No  [  ]

52. Tenderness
   1. Yes  2. No  [  ]

J. Skin examination

53. Rashes
   1. Yes  2. No  [  ]

54. Other lesions
   1. Yes  2. No  [  ]

K. Pulse Oximetry (%) .................................

L. Laboratory investigations

55. Thin blood film
   1. No malaria  2. Malaria  [  ]
56. Hb Level (g/dl) .....................

57. Differential counts (initial/final)
   Neutrophils (%) ..................
   Lymphocytes (%) ................
   Monocytes (%) .................
   Basophils (%) ..................
   Eosinophils (%) ...............

58. Chest radiograph appearances
   a. Date when radiograph appearances were taken ................
   b. Chest X-ray findings

   1. No Pneumonia
   2. Broncho pneumonia          [  ]
   3. Lobar pneumonia
   4. Lobar pneumonia and pleural effusions
   5. Broncho pneumonia and pleural effusions

M. Diagnosis

59. Diagnosis

   1. Severe Broncho pneumonia
   2. Lobar Pneumonia
   3. Pneumonia and Malaria
   4. Pneumonia and Diarrhoea
   5. Pneumonia and HIV            [  ]
   6. Pneumonia and Anaemia
   7. Pneumonia and Post measles
   8. Pneumonia and TB
   9. Pneumonia and Malnutrition
  10. Pneumonia, Malaria and Anaemia
  11. Pneumonia and Others

60. Other treatments administered other than Chloramphenicol or Ceftriaxone

   1. Analgesia
   2. Oxygen
   3. Anti-malarial
   4. Blood transfusion           [  ]
   5. ORS
   6. Vitamin A
   7. Dextrose
   8. Other

61. Other treatments administered other than Zinc

   1. Vitamin A
   2. Analgesia                    [  ]
   3. Anti-malarial
62. Classification of the severity of the pneumonia

1. Severe pneumonia  2. Very severe pneumonia  [ ]

63. Outcome of treatment

1. Treatment success
2. Treatment failure  [ ]
3. Death
4. Ran away

64. Treatment failure

(i) Clinical complication  1. Yes  2. No  [ ]

(ii) Nature of clinical complication
1. Malaria  2. Measles  3. PTB  4. Other  [ ]

(iii) Death  1. Yes  2. No  [ ]

(iv) Date of death: ......................

(v) Cause of death 1. Respiratory failure  2. Severe pneumonia

(vi) Second line drugs  1. Yes  2. No  [ ]

N. Nutrition

Dietary history: Feeding

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<tr>
<th></th>
<th>Breast feeding</th>
<th>Breast/complementary feeding</th>
<th>Solid feeding</th>
<th>Others</th>
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</table>

Appetite improved  
1. Yes  2. No  [ ]

Vitamin A supplementation  
1. Yes  2. No  [ ]

O. Physical examination

Nutritional assessment

Birth weight (kgs)  ..........  
Weight today (kgs)  ..........  
Length/height (cms)  ..........  

60
Mid upper arm circumference (cms) ..............

Assessment of Micronutrients status

Skin rashes
   1. Yes  2. No  [  ]

Signs of vitamin A deficiency
   1. Yes  2. No  [  ]

Axillary temperature (°C) ..............
Respiratory rate (beats/min) ..............
Pulse rate (beats/min) ..............
Oxygen saturation (%) ..............

P Laboratory and CXR results sheet

Laboratory investigations

HIV Antibody
   1. Positive  2. Negative  [  ]

DNA PCR
   1. Positive  2. Negative  [  ]
APPENDIX II

Doctor’s follow up form.

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<td>Yes 2. No [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest indrawing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAY 6</td>
<td>Ability to feed</td>
<td>Temperature</td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>-------------</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>DAY 6</th>
<th>Oxygen saturation</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>DAY 6</th>
<th>Cyanosis</th>
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<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>DAY 6</th>
<th>Chest indrawing</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 7</th>
<th>Ability to feed</th>
<th>Temperature</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 7</th>
<th>Oxygen saturation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 7</th>
<th>Cyanosis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 7</th>
<th>Chest indrawing</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Yes 2. No [ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX III

CEFTRIAXONE VERSUS CHLORAMPHENICOL IN THE TREATMENT OF SEVERE PNEUMONIA IN CHILDREN AGED 6-59 MONTHS ADMITTED TO ACU MULAGO HOSPITAL.

Consent form

Introduction

Dr. Katureebe Cordelia of the department of Paediatrics and Child Health, Makerere Medical School, is conducting a study on ceftriaxone, an antibiotic, for the treatment of severe pneumonia in Ugandan children aged from 6 months to 5 years. This drug will be compared with Chloramphenicol, which currently is the standard treatment for this condition. Relevant authorities have approved this study. I am requesting you to participate in this study by allowing your child to be enrolled.

Methods

During this study, the following will be done:

i. You will be asked questions about your child’s current and past medical history.

ii. Your child will receive a complete physical examination.

iii. A small amount of blood (7ml) will be taken from the child for a number of important investigations.

iv. Your child will be allocated to receive one of the study drugs using a standard method recommended for this kind study.

v. A chest X-ray will be taken to diagnose pneumonia and to determine the presence of chest complications.

vi. The child will receive additional treatment, as his/her condition will warrant.

Risks and benefits.

The process of drawing blood and introducing a canula for medicines will cause pain when the needle enters the skin. The amount of blood drawn will be too small to affect your child’s health. Precaution will be taken so as not to introduce infection in the process of blood collection. The drugs in this study are generally safe. The incidence of severe side effects for either drug is less than 1%.
Your child will receive a careful examination and will be put on treatment for pneumonia and for other concurrent illness. The child will be followed up daily for one week or longer if his/her condition warrants it. The treatments and investigations will be done free of charge. The results of this study are needed to improve the management of severe pneumonia in children in Uganda.

The patient's rights

Refusal to participate in this will not carry a penalty. If you have any problems or questions relating to the study you may ask them at any time during the course of the study. You may contact Dr. Katureebe at the Department of Child health, Mulago Hospital. Tel No 0772372411

STATEMENT OF CONSENT

The purpose and nature of this study has been explained to me. I understand that my participation in this study is voluntary and that no consequence will result if I refuse to participate. I am free to withdraw from the study at any time. I have the right to know the results of the laboratory tests.

Name of Subject………………………… Name, Signature/Finger………………………… Date
Print of parents/caretaker…………………………

Name of investigator or Authorized representative………………………… Signature………………………… Date
## APPENDIX IV

### WHO Guidelines on the Treatment of severe Pneumonia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Pneumonia</td>
<td>IV/IM chloramphenicol 25mg/kg every 6 hours until the child improves then continues with oral chloramphenical for a total of 10 days. If no improvement after 2 days or deteriorates, switch to gentamycin 2.5mg/kg every 12 hours plus cloxacillin 50mg/kg every 6 hours for a total of 2 weeks. Give oxygen by nasal catheter</td>
</tr>
<tr>
<td>Very severe pneumonia</td>
<td>IV/IM chloramphenical 25mg/kg every 6 hrs until the child improves then continues with oral chloramphenical for a total of 10 days. If no improvement after 2 days or deteriorates, switch to gentamycin 2.5mg/kg every 12 hrs plus cloxacillin 50mg/kg every 6hrs a total of 2 weeks. Oxygen by nasal catheter</td>
</tr>
<tr>
<td>Pneumonia in severe malnutrition</td>
<td>IV/IM Ampicillin 100mg/kg/day + Gentamycin 2-5mg/kg/day for 14 days Oxygen by nasal catheter</td>
</tr>
</tbody>
</table>
### APPENDIX V

**WHO Guidelines on the treatment of severe pneumonia in HIV infected children.**

<table>
<thead>
<tr>
<th>Severe pneumonia</th>
<th>2 – 11 months</th>
<th>IV/IM Ampicillin 100mg/kg/day + Gentamycin 2 – 5mg/kg/day for 7 – 10 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>If no improvement after 48 – 72 hours, switch to ceftriaxone 75 – 100mg/kg/day for 7 days. PCP therapy with IV cotrimoxazole or suspension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroids.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe pneumonia</th>
<th>12 – 39 months</th>
<th>Ampicillin/penicillin + gentamycin (as above)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>If no improvement after 48 – 72 hours, switch to ceftriaxone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCP treatment if clinically indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very severe pneumonia</th>
<th>2 – 11 months</th>
<th>Treat as in severe pneumonia</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Very severe pneumonia</th>
<th>12 – 59 months</th>
<th>Treat as in severe pneumonia</th>
</tr>
</thead>
</table>
APPENDIX VI:

Consent for HIV serology

I am a counselor from the department of Paediatrics and child Health Makerere medical school. I am conducting a study for Dr Katureebe cordelia. She is comparing Ceftriaxone to Chloramphenicol in the treatment of severe pneumonia in children less than five years and HIV testing is one among other investigations to be done. Other investigations to be done include CXR, blood cultures, CBC & ESR.

I will talk to you about doing the HIV test, why it’s done, the benefits and risks. You will also be allowed to ask any questions on this subject and I will respond to them accordingly.

Benefits
Knowing the HIV status of your child is beneficial in terms of future management and follow-up of the child and family.

Risks
The child will feel slight pain when the blood is being obtained with a needle. You and your child may have some psychological trauma.

Confidentiality
The results obtained shall be confidential. Any other person other than the principal investigator, counselor and research assistant will not know them. The doctors and nurses participating in the care of your child will not know them unless we see that by doing so it will aid in the management of your child and you have accepted us to release this information.

The purpose and nature of the HIV test has been explained to me. I am aware that the results of the test will be confidential but I have a right to know them. I therefore sign below as proof of my consent.

........................................  .................  ........................................
Study Identification No  Date  signature of caretaker

........................................  .................  ........................................
Name Counselor  Date  signature of counselor

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APPENDIX VII

Adverse event report form

CEFTRIAXONE VERSUS CHLORAMPHENICOL IN THE TREATMENT OF SEVERE PNEUMONIA IN CHILDREN AGED 6-59 MONTHS ADMITTED TO ACU MULAGO HOSPITAL.

Day 1  [ ] 2  [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ]

Patients Initials: [ ] study id no [ ] Date: [ ]/ [ ]/2006
Investigator: Name [ ] Signature: [ ]
Serial number [ ]

Adverse drug experience form

Describe the event.

Date of onset. [ ]/ [ ]/2006
Day of onset.
4. Duration of event. (To date) [ ] days

5. Maximum intensity:
   [ ] MILD. (awareness of signs or symptoms, but easily tolerated)
   [ ] MODERATE. (Causes interference with usual activity)
   [ ] SEVERE. (Incapacitating, inability to do usual activity)

Was the adverse effect serious?
   [ ] NO: Any mild or reversible adverse events. Includes changes, which produce no
   Hazard to health, will not hinder the patient in continuing their normal life;
   and will not lower the patient’s life expectancy.

   [ ] YES: Any adverse event which is a definite hazard to the patient’s well-being. In
   general, vital organ-system, functional or physicochemical impairment
   which at the time of diagnosis appears irreversible or is known to be
   Irreversible for a significant period of time.

Action taken:
   [ ] Patient withdrawn. (Fill out patient withdrawal form)
   [ ] Patient continued.
   [ ] Other. (Any temporary cessation of treatment).

Follow-up:
   [ ] Patient recovered – no residual effects observable
   [ ] Adverse experience still present – no treatment
   [ ] Adverse experience still present – being treated

Details: ________________________________

   [ ] Residual effects present – no treatment/being treated
Details: ________________________________

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### APPENDIX VIII

**WHO guidelines for clinical features of severe pneumonia.**

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Cough or difficult breathing (RR&gt;60bpm in children 1 week - 2 months &gt;50bpm in children 2-12 months and &gt;40bpm in children 12 – 59 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Pneumonia</td>
<td>Cough or difficult breathing, fast breathing plus lower chest in drawing.</td>
</tr>
<tr>
<td>Very severe pneumonia</td>
<td>Cough or difficult breathing, fast breathing, chest in drawing, cyanosis and/or inability to feed.</td>
</tr>
</tbody>
</table>
APPENDIX IX

Identification of isolates from sputum
Sputum microscopy and culture are the most common investigations for the identification of the cause of lower respiratory infections. Expectorated sputum is inevitably contaminated with upper respiratory tract and oral normal flora. Organism such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* which are the commonest causes of acute bacterial pneumonia often colonize the upper respiratory tract of healthy people, making interpretation of culture results difficult. However, in true bacterial pneumonias, the pathogen is usually recovered almost pure from the cultures.

Processing of specimen

1. Macroscopic examination: Note the amount, consistence, colour, purulence and the presence of blood and classify a specimen as
   a. Salivary if it consists of mainly saliva
   b. Mucoid if it consists of mainly mucous
   c. Purulent if it appears yellow or greenish as pus
   d. Muco-purulent if it has visible yellow particles in mucus
   e. Bloody if it contains blood
   f. Blood stained if it contains stains or streaks of blood

2. Microscopy:
   a. Gram staining:
      i. Perform a gram stain on a smear made from the most purulent or mucoid part of the sputum (Check appendix 1 for Gram staining procedure)
      
      ii. Examine the smear under low power (x10 objective) to determine the acceptability of the specimen for culture (Q-score as in the table below). Specimens scoring ≤0 should not be cultured
<table>
<thead>
<tr>
<th>Type of cell and no./low power (x10 objective)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils:</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>0</td>
</tr>
<tr>
<td>10-25</td>
<td>+1</td>
</tr>
<tr>
<td>&gt;25</td>
<td>+2</td>
</tr>
<tr>
<td>Mucous present</td>
<td>+1</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td></td>
</tr>
<tr>
<td>10-25</td>
<td>-1</td>
</tr>
<tr>
<td>&gt;25</td>
<td>-2</td>
</tr>
</tbody>
</table>

*Sputum from children (≤12 years of age) or patients with neutropenia e.g. cancer patients should not be rejected based on the above criteria*

iii. Examine the slide under oil objective for presence of bacteria and fungi

3. **Culture for pyogenic bacteria**

   **Day 1:**
   1. Homogenize sample by adding N-acetyl-L cysteine (NALC). (5 parts of sputum to one part of NALC).

   2. Vortex for 30 seconds and leave to stand for 30 minutes.

   3. Add 0.5ml of the sputum to 4.5ml of sterile normal (0.9%) saline and mix thoroughly.
4. Inoculate 10μl onto plates of blood, chocolate and MacConkey agar using a calibrated wire loop

5. Incubate in a CO₂ incubator or candle jar at 35-37°C

Day 2: Plate reading and follow up

1. Check plate for predominant growth, particularly colonies suggestive of *Streptococcus pneumoniae, Haemophilus spp, Moraxella catarrhalis, Klebsiella pneumoniae, Staphylococcus aureus and Escherichia coli, β-hemolytic streptococci, Acinetobacter spp*
   Significant organisms are those that are dominant in the growth and are seen on the specimen Gram-stain.

2. Perform identification tests and antimicrobial susceptibility testing for organisms considered significant
   (Check SOPs on identification and antimicrobial susceptibility testing)

3. If colonies are not very discrete, make purity plates before the identification and susceptibility testing

4. If colonies are too small or no growth is seen or there is only growth of normal flora, re-incubate the plates for a further 24 hours then follow up as in 2-3 above

Day 3-5: Reporting of results

- Record the following:
  - Macroscopic appearance
  - Findings on Gram-stain (quantity of pus cells and bacteria)
  - Findings on ZN stain (See appendix 2)
Growth:

- Report with quantification all significant pathogens and their susceptibility profiles. *Significant isolates are those that Predominate on plates and are seen in large numbers on Gram-stain

- In case growth only oral flora is present, report with quantification: Growth of oro-pharyngeal flora.

Mycological cultures

- Performed when yeasts and hyphae are seen on Gram-stain
<table>
<thead>
<tr>
<th>Isolate</th>
<th>Identification</th>
<th>Antibiotics to set</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Optochin on 5% TSA-sheep Blood agar</td>
<td>1. Oxacillin (1μg)</td>
</tr>
<tr>
<td></td>
<td>&gt;14mm (<em>S. pneumoniae</em>)</td>
<td>2. Erythromycin</td>
</tr>
<tr>
<td></td>
<td>&gt;6mm but ≤ 14mm do bile solubility)</td>
<td>3. Cotrimoxazole</td>
</tr>
<tr>
<td></td>
<td>6mm Not <em>S. pneumoniae</em></td>
<td>4. Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Ceftriaxone</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>• Translucent colonies</td>
<td>1. Ampicillin (10 μg)</td>
</tr>
<tr>
<td></td>
<td>• Small Gram-ve bacilli</td>
<td>2. Augmentin</td>
</tr>
<tr>
<td></td>
<td>• X&amp;V factors</td>
<td>3. Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Cotrimoxazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Cefuroxime/ cefaclor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Ciprofloxacin</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>• Hockey puck sign (moveable colonies)</td>
<td>1. Ampicillin (10 μg)</td>
</tr>
<tr>
<td></td>
<td>• Oxidase test (+ve)</td>
<td>(??? Moraxella uniformly resistant to penicillins /Ampicillin)</td>
</tr>
<tr>
<td></td>
<td>• DNAse (+ve)</td>
<td>2. Augmentin</td>
</tr>
<tr>
<td></td>
<td>• Catalase (+ve)</td>
<td>3. Cotrimoxazole</td>
</tr>
<tr>
<td></td>
<td>• Nitrate reduction (+ve)</td>
<td>4. Cefuroxime/cefaclor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Erythromycin/Azithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: Only need to routinely test nitrocefin for β-lactamases and cotrimoxazole</td>
</tr>
</tbody>
</table>