Clinical Pharmacokinetics of Once Daily IV Bolus Gentamicin in Paediatric Patients with Severe Pneumonia at the Kenyatta National Hospital

BY
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REGISTRATION NUMBER U59/7691/06

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A THESIS SUBMITTED IN PARTIAL FULFILMENT FOR THE AWARD OF THE DEGREE OF MASTER OF CLINICAL PHARMACY.

SEPTEMBER 2008

DECLARATION

This thesis is my original work and has not been presented for a degree in any university or any other award.

Signature.....Date...7/10/08...

SUPERVISORS' APPROVAL

We confirm that the work reported in this thesis was carried out by the candidate under our supervision.

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DEDICATION

To my family.

ACKNOWLEDGEMENTS

I wish to acknowledge individuals and institutions that invariably contributed to the successful completion of this study.

My special thanks to my supervisors Prof. Gilbert O. Kokwaro and Prof. Omu Anzala for their guidance and encouragement.

My appreciation is extended to Prof. David Scott, Dr. Karimi and Mr. Isaac Muriithi of School of pharmacy for their advice on aspects of this project.

I am grateful to the following staff at the Paediatric Filter Clinic, Kenyatta National Hospital (KNH) for their assistance with the collection of some of the data: Mr. Paul Kariuki, Mr. Jared Orina and Mr. John Kinyanjui. I am also thankful to the staff at Ward 3, KNH for their support.

My gratitude also goes to the following: Mr. Stanley Kinge Waithaka of Biochemistry Laboratory 16, Kenyatta National Hospital; Mrs. Beatrice Museve of Dept. of Medical Microbiology, University of Nairobi for assistance with microbiology analysis and to Mr Francis Njiri for advice on statistical analysis of the data. I am particularly grateful to Dr. Simon Ndirangu of KEMRI-Wellcome Trust Programme, Kilifi, for assistance with assay of gentamicin.

The study was partly sponsored by Prof. Gilbert O. Kokwaro. Am grateful for the help.

Finally, my gratitude to the study subjects and their families for accepting to participate in the study.

TABLE OF CONTENTS

LIST OF TABLES

List of Figures

ACRONYMS AND ABBREVIATIONS

1. KNH- Kenyatta National Hospital
2. UON- University of Nairobi
3. IV- Intravenous
4. TDM- Therapeutic drug Monitoring
5. OD- Once daily dosing
6. RCTS- Randomized controlled trials
7. MIC- Minimum inhibitory concentration
8. PFC- Paediatric Filter Clinic
9. UON- University of Nairobi
10. CrCl- Creatinine Clearance
11. TB- Tuberculosis
12. GFR- Glomerular filtration rate
13. PAE- Post antibiotic effect
14. $t_{1/2}$ - Half life
15. ke - Elimination rate constant
16. Vd - Volume of distribution
17. Cl- Clearance
18. Cp_o - Peak concentration
19. S_{cr}- Serum creatinine

ABSTRACT

Treatment of pneumonia using antibiotics at the Kenyatta National Hospital (KNH) is guided by clinical context, severity assessment and epidemiological data as well as antibiotic resistance patterns. High dose extended interval administration of gentamicin is the accepted empirical treatment for suspected gram negative pneumonia in children at KNH. Due to its narrow therapeutic range there is a need for routine therapeutic drug monitoring (TDM) to optimise the clinical use of gentamicin. However, TDM is expensive and is not a common practice at KNH. Hence, and there are limited data on pharmacokinetics of gentamicin in African children that can be used to rationalize its dosing in this population of patients. This prospective study describes the pharmacokinetics following "once daily" bolus administration (6.93+/- 1.35 mg/kg/24 hr) to African children with severe pneumonia. Sixteen children were enrolled into the study after obtaining written informed consent from the parents/guardians. Venous blood samples were collected for bacteriological culture and determination of gentamicin concentrations.

The median age and weight, respectively, were 35 months and 12 kgs. One blood culture was positive for *Coagulase negative staphylococcus.* There were two treatment failures (12.5%) and two cases of nephrotoxicity. Peak gentamicin concentrations ranged from 4.80 to 21.57 μg/mL, while troughs concentrations ranged from 1.07 μg/mL to below 0.27 μg/mL. Gentamicin was undetectable in one patient (7.7%) approximately 8 hours after the bolus administration. At approximately 12 hours post dose, 5 patients (38.5%) had undetectable levels of gentamicin. Just before the next dose, 13 patients (81.25%)

had gentamicin concentrations < 2 μg/mL. The median elimination half life was 2.1 hr while the median volume of distribution was 0.49 L/Kg.

In conclusion, although 87.5% of the children recovered, the efficacy and safety of once daily dosing in children needs to be explored further in a larger patient population.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

Pneumonia is one of the most common infections in the paediatric age group and one of the leading diagnosis that result in overnight hospital admission for children [1]. It accounts for almost one-fifth of childhood deaths world-wide [2]. Acute respiratory infections cause more than 2·7 million child deaths worldwide each year; most of these are pneumonia, and 99% occur in less-developed countries [3]. The major causes of pneumonia are *Streptococcus pneumoniae* and *Haemophilus influenzae* [3]. Although the common causes of pneumonia are well established, the causes of very severe pneumonia, and pneumonia that is fatal despite standard treatment, are less certain. However, enteric gram-negative bacilli, *Staphylococcus aureus*, beta lactamase producing antibiotic-resistant strains of Haemophilus, and penicillin-resistant pneumococci have been implicated [4].

To manage severe pneumonia in children, administration of "once daily" gentamicin has been adopted in many countries. This approach has been recently introduced at the Kenyatta National Hospital (KNH). Children with suspected pneumonia receive empirical once a day intravenous (IV) bolus dosing with gentamicin and six hourly benzyl penicillin. When combined with beta lactam antibiotics, there is synergistic activity against most commonly encountered pathogens [5].

1.1 The Rationale for Traditional /Conventional (multiple) Dosing of antibacterial agents

Multiple daily dose regimen is based on the assumption that therapeutic efficacy requires that the serum level of the antimicrobial agent be maintained above the minimum

inhibitory concentration (MIC) for the target organism at all times during the course of therapy. Even so, several underlying disease conditions may alter the pharmacokinetics of aminoglycosides such as gentamicin. For example, patients with pleural effusions have been reported to possess altered pharmacokinetics for aminoglycosides which result in lower peak and higher trough concentrations [5]. This is of importance since para-pneumonic effusions are a common complication of pneumonia [1, 2]. Hence, correct multiple daily dosing of aminoglycosides often requires pharmacokinetics information and close monitoring of drug serum levels and renal function [6]. This is vital since aminoglycosides are excreted unchanged in urine, and the rate of elimination is influenced by a patient's glomerular filtration. Hence, kidney function is a significant aspect in disease outcome as well as development of side-effects associated with use of aminoglycosides [6].

The reported ranges for peak gentamicin plasma concentration associated with clinical efficacy are 4-10mg/L [7]. Evidence suggests that high peak plasma concentrations must be achieved early in the course of treatment if gentamicin is to be effective, but prolonged high concentrations may cause ototoxicity and nephrotoxicity [8]. In order to choose any mode of dosing, correct interpretation of the initial dose is vital. Subsequent doses will then be chosen on the basis of the pharmacokinetic results of the first dose. This mode of multiple daily dosing is labour-intensive, often requires expertise in pharmacokinetics and close monitoring of drug serum levels and renal function. Nevertheless, little if any routine therapeutic drug monitoring (TDM) is done at most of the hospitals including KNH due to cost. It is also important to note that although aminoglycoside concentrations are sometimes measured by laboratories, they are seldom interpreted correctly [9].

1.2 The Rationale for Once Daily Dosing of Aminoglycosides

1.2.1 Concentration Efficacy Relationship

Gentamicin is the aminoglycoside used most often because of its low cost and reliable activity against gram-negative aerobes. However, local resistance patterns should influence the choice of therapy. Attainment of adequate peak concentrations is related to efficacy for some infections. Response to therapy in multiple dose regimens has been associated with achieving serum concentrations of above 5 mg/L measured one hour after the dose (peak concentration). However, when the same total daily dose is given as a single bolus (infused over 30-60 minutes), much higher peak concentrations (>10 mg/L) are obtained. The pharmaco-dynamic properties of gentamicin in support of this mode of dosing are as follows:

a) Rapid concentration-dependent killing action. This means that increasing concentrations with higher dosages increases both the rate and the extent of bacterial cell death [10]. Hence peak plasma concentration is important because response to gentamicin is concentration dependent;

b) Gentamicin has a significant post antibiotic effect (PAE). This is persistent suppression of bacterial growth after short exposure to the drug [10]. The duration of this effect depends on several factors; chief among them is the magnitude of the preceding peak concentration which will be higher in single extended dosing compared to multiple dose regimens. Research has demonstrated that increased peak aminoglycoside concentrations lengthen the duration of PAE and that the PAE duration is variable for different types of bacteria [11]. This phenomenon suggests that the aminoglycoside serum concentration may be allowed to fall below the MIC

for the pathogen without comprising antimicrobial efficacy. Other factors that affect the duration of PAE include host factors, presence of penicillin and neutropenia. The duration of PAE in the paediatric population, however, population remains unclear;

c) *In vitro* studies indicate that frequent dosing of aminoglycosides tends to reduce their uptake into the bacterial cell. This phenomenon, which is referred to as adaptive post-exposure resistance, is observed as an apparent increase in the MIC_{90}. Thus, longer dosing intervals appear to shorten the time required for the MIC to revert to its original value. These observations may have significant clinical implications. For example, persistent low level exposure of the target organism as occurs with multiple daily dosing may markedly reduce the antimicrobial activity of aminoglycosides [6]. Extending the dosing interval allows time for the adaptive resistance to resolve.

1.2.2 Concentration Toxicity Relationship

Therapeutic range is defined in terms of peak concentration (to monitor effectiveness) and trough concentration (to avoid toxicity) [12]. The risk of side-effects are thought to increased if peak levels are consistently maintained above 12 mg/L and trough levels consistently exceed 2 mg/l [13]. Toxicity is also associated with prolonged therapy (more then 10 days), but not with high peak concentrations according to some researchers [11]. Indeed some researchers report that peaks as high as 25 mg/L do not increase toxicity [14]. Other risk factors for toxicity include co-administration of other drugs, liver disease and age.

Sick infants have low glomerular filtration rates which lead to slower clearance of drugs like gentamicin. Once a day dosing provides more time for clearance and may avoid the toxic effects of gentamicin due to slower clearance. Increasing the interval between doses

has the potential to maintain maximal antibacterial activity, while minimizing side-effects [14]. Aminoglycoside uptake into renal tubule cells and the inner ear appears to be saturated at relatively low serum levels, suggesting that higher peaks do not necessarily result in a greater risk of toxicity [6]. This is the basis for the once daily dosing of gentamicin.

1.3 Evidence supporting use of Once Daily Extended Dose Regimen over Multiple Daily Regimens.

There is limited evidence regarding the safety of once daily gentamicin in our setting (KNH). Moreover, studies in other settings give conflicting results. For example, a meta analysis of aminoglycoside dosing in children reported that an extended dose aminoglycoside regimen provides similar or potentially improved efficacy and safety, compared to multiple daily doses regimen [15]. Another meta analysis concluded that there is no significant difference in either efficacy or safety between the single-dose and the multiple-dose regimes [16]. A recently published audit in neonates in one hospital showed that a 'multiple dose a day' regimen resulted in sub-therapeutic levels. In contrast, the extended dosage schedules achieved safe and adequate levels [17]. Another meta analysis of the ten studies involving a total of 440 infants showed that 'once a day' regimen achieved higher peak levels and lower trough levels compared to 'multiple doses a day regimen'[14]. These findings are consistent with those in adults and older children that have shown that 'once a day' gentamicin achieves better pharmacokinetic profile compared to a 'multiple daily regimen [18, 19, 20].

These results need to be interpreted with caution and the appropriate dose and dose interval for gentamicin is still a matter of debate. The choice of a 24-hour dosage interval

is somewhat arbitrary, and the optimal interval may not necessarily be 24 hours. No studies have included dosage adjustment based on pharmacokinetic modelling, and the effect of this on treatment outcome needs to be assessed. The best method of administering aminoglycosides can be facilitated through appropriate pharmacokinetic analysis.

CHAPTER 2

CLINICAL PHARMACOKINETICS OF GENTAMICIN IN CHILDREN AT KNH

2.1 Justification

Gentamicin dosing at KNH is still empirical, and does not take into account the range of variables that may alter its pharmacokinetics and impact on treatment outcome. There is a need to evaluate the current dosage regimen for gentamicin and use pharmacokinetic principles to design optimal dosage regimen for various categories of patients at KNH. This study focused on severely sick children.

2.2 Hypothesis

This was an exploratory study; hence no hypothesis was being tested.

2.3 Study Objectives

The objectives of this study were to assess the clinical pharmacokinetics of once daily IV bolus dose gentamicin in selected children with suspected pneumonia and relate this to clinical outcome.

2.4 Study Site

The study was carried out between March and May 2008 at the Kenyatta National Hospital (KNH), which is the main teaching and referral hospital in Kenya.

2.5 Study Design

This was a prospective exploratory study whose purpose was to investigate the clinical pharmacokinetics of a bolus dose of gentamicin in children empirically diagnosed with

pneumonia at the paediatric filter clinic (PFC) at KNH. The study was approved by the KNH Ethics Committee (Appendix 3).

2.6 Study Population

Children selected for this study were identified at the paediatric filter clinic (PFC) with signs and symptoms suggestive of severe pneumonia.

2.6.1 Inclusion Criteria

- Children aged between 2 and 11 years admitted with suspected severe pneumonia. Children 2-11 years were chosen to exclude immature renal function.
- Children had suspected severe pneumonia as defined in the Ministry of Health Basic Paediatric protocols (2004) of severe pneumonia.
- Children whose parents gave informed consent on collection of blood samples for the study.
- Children for whom IV gentamicin was prescribed for treatment at the standard dose of 7.5mg/kg once a day.

2.6.2 Exclusion Criteria

- Patients who had been administered gentamicin before admission.
- Patients with major life-threatening congenital malformations
- Patients with a history of anuria for 24 hours on admission.
- Those with detectable gentamicin on the blank (admission) plasma sample (excluded at the data analysis stage).
- Those whose parents declined to sign the consent form.

2.7 Clinical Management

Empiric management of suspected severe pneumonia in this hospital is with gentamicin 7.5mg/kg OD and benzyl penicillin 50,000IU/kg QID.

2.8 Monitoring Parameters

Gentamicin trough concentrations of less than or equal to 2 μg/mL were considered to be essential to declare that this particular dosing regimen is pharmacologically safe. Trough concentrations were determined 24 hours after the drug was given and just before the next dose.

Peak concentrations of at least 5 μg/mL were considered to be essential for this particular dosing regimen to be pharmacologically effective. Peak levels were taken 30 minutes after the drug was administered.

Nephrotoxicity was defined as any increase in serum creatinine levels (or decrease in creatinine clearance) assessed by a rise in the serum creatinine concentration of greater than 0.5 mg/dL (44.2 μmol/L).

Clinical efficacy was be defined as clearance of positive blood cultures without the need for changing antibiotic.

Ototoxicity was not evaluated because of the lack of equipment and the short duration of stay in the hospital by most patients.

2.9 Sample Size Determination

These being an exploratory study, a total of 16 patients were enrolled into the study, based on resources and time available for the study.

2.10 Enrolment Procedure

Patients who met the inclusion criteria were enrolled consecutively into the study after informed consent from the parents or guardians (Appendix 1).

2.10.1. Collection of Blood Samples

After obtaining informed consent from their parents/guardians, a venous cannula was inserted after cleaning the skin with surgical spirit. A blood sample (1ml) was collected into Peads Plus/F bottles enriched with soya bean casein digest broth with CO_2 for microbiology analysis, and another sample (3 ml) was collected into vacutaneous bottles for determination of creatinine clearance. This sample was repeated at discharge. Further bloods samples (1ml) were collected into EDTA-coated sample collection bottles pre-dose and at 0.5, 4, 8, 12 and 24 hours after gentamicin administration. Gentamicin was administered as a bolus intravenous (IV) dose over a period of 30 seconds. The cannula was flushed with heparinised normal saline (0.5ml) after each blood sample collection. The blood samples were then centrifuged as soon as possible at 3000 rpm (approximately 1,500 g) for ten minutes at room temperature to obtain plasma. The plasma was separated and stored frozen at -70^0 C until analysed for gentamicin.

2.10.2 Patient Demographics

A special study form (Appendix 2) was used to collect relevant patient demographics and clinical laboratory data. The following data were recorded for each patient: identification number (ID), weight (kg), actual dose administered, date and time; sex, height (cm), co-morbid conditions and other drugs in use.

2.11 Laboratory Procedures and Clinical Methods

2.11.1 Microbiology

BACTEC 9050(Becton Dickinson Ltd) blood culture system was used to process blood cultures. The Peads Plus/F bottles enriched with soya bean casein digest broth with CO_2 into which 1ml of patients' venous blood was injected were entered into BACTEC 9050 as soon as possible. Incubation was done at room temperature (25^0C) for five days. Those that turned positive were further processed by standard methods.

2.11.2 Creatinine Clearance Determination

Olympus AU 640 was used to determine serum creatinine levels.

The instrument was controlled using standard Olympus quality control. Levy Jennings control charts are attached (Appendix 5). The reaction absorbance was monitored by the system at 520nm and the results are expressed in μmol/L.

Creatinine clearance was calculated from creatinine concentration using two formulae (Appendix 6).

2.11.3 Gentamicin Plasma Level Determination

Plasma gentamicin concentrations were determined with Abbott TDxFLx®. This system uses fluorescence polarization technology, competitive binding immunoassay and radiative energy attenuation. The following procedures were performed:

a. Calibration
b. Gentamicin plasma level determination
c. Treatment of high readings
d. Treatment of low readings
e. Gentamicin injection dilution

f. Gentamicin quality control

Calibration

- A carousel was loaded with 15 sample cartridges and an equal number of cuvettes.
- 55 µL of 6 calibrators (A-F), corresponding to gentamicin concentrations of 0.0, 0.5, 1.5, 3.0, 6.0 and 10 µg/mL were loaded in pairs into the sample wells.
- The remaining wells (position 13-15) were loaded with 55 µL of controls corresponding to low (L), medium (M) and high (H) values, with a target range of gentamicin concentrations of 1.0(0.85-1.15) µg/mL; 4.0(3.60-4.40) µg/mL and 8.0(7.20-8.80) µg/mL, respectively.
- Filling of the wells was done with a pipette using individual tips for each solution while avoiding splashing, foaming and bubbles. Any bubbles formed were removed with a different tip for each sample well.
- The carousal was locked and loaded into the Abbot TDx.
- The reagent pack was gentle shaken and checked for bubbles before loading it into the machine. The reagent pack consists of three reagents:
  I. S- < 1% gentamicin antiserum (sheep) in buffer with protein stabilizer.
  II. T- < 0.01% gentamicin fluorescein tracer in buffer containing surfactant and protein stabilizer.
  III. P- Pre-treatment solution. Surfactant in buffer containing protein stabilizer.

Gentamicin Plasma Level Determination

- The plasma samples were removed from the fridge and allowed to thaw.
- Each sample was mixed vigorously and 55 µL sampled with an individual pipette tip and put into the sample well.

- The carousal was loaded with the samples and one or two positions loaded with controls.
- The carousal was locked and put into the Abbot TDx.
- The reagent pack was gently shaken and loaded as discussed above. Then the access door was shut.
- An operation identification and carousal number were fed in and the run was performed. Results were printed and the control was checked to ensure that it was within range.

Treatment of High Readings

- High readings were noted to be those whose concentration exceeded 10µg/mL since the accepted calibration range was 0.0-10.0 µg/mL.
- Those samples noted to indicate a high reading were diluted to a ratio of 1:2 or 1:3 of the plasma sample to diluent buffer and re-assayed. The diluent buffer was 0.1M phosphate buffer containing 0.1% sodium azide as a preservative.
- Resulting concentrations were corrected for the dilution factor.

Treatment of Low Readings

Samples recording low results were below the lowest measurable concentration which can be distinguished from zero with 95% confidence.

Determination of Gentamicin in the Injection solution.

One vial from batch number 20961102 (Sinochem Ningbo Limited; China) was assayed for gentamicin content, and found to contain 87.5% of the stated amount of gentamicin.

Gentamicin Quality Control

The gentamicin assay kit manufacturer's recommended control requirement was performed as specified, i.e., one gentamicin control level tested once every 8 hours, and no less than two different controls per 24 hours. The controls were run together with patient samples.

2.12 Data Management and Analysis

Data collected was coded and entered into Statistical package for Social Science (SPSS) and Excel. Statistical analysis was done using SPSS PC+ Programme Version 13.

Pharmacokinetic parameters were determined as follows:

- The half life was obtained graphically from the line of best fit (Appendix 8.)
- Elimination rate constant was calculated as per the following equation;

$$Ke = (ln \text{ concentration } 2 - ln \text{ concentration } 1) / (\text{time } 2 - \text{time } 1)$$

- The volume of distribution was determined as follows;

$$Vd = Dose / Cp_o$$

Vd was corrected for weight of each patient.

- Clearance was obtained using the following equation;

$$Cl = Ke \times VD$$

Where;

$t_{1/2}$ = half life

ke = elimination rate constant

Vd = volume of distribution (corrected for body weight for each subject)

Cl= clearance

Cp_o = initial (peak) concentration at the end of the infusion period, assuming that negligible gentamicin was eliminated during this period.

Standard equations were used to calculate creatinine clearance (Appendix 6).

CHAPTER THREE

RESULTS

3.1 Patient Demographics and Clinical Outcome.

Twenty patients were screened consecutively for the study. Three withdrew consent during sample collection and one was discharged before data collection was complete. Data from sixteen patients who met the inclusion criteria are presented in Table 1.

Eight children received the drug for five days. Of these, six children received the drug for five days and their clinical conditions improved. The remaining two patients had treatment failure after five days on the gentamicin/ benzyl penicillin regimen and were switched to amikacin and ceftrioxone. Of the eight children who took the drug for five days and longer, five had underlying conditions. One had rheumatic heart disease and anaemia, one had rickets and TB (tuberculosis), one had TB and pleural effusion, one had clinical malaria and one had severe anaemia.

Table 1: Demographic Characteristics of the Patients

Patient Code	Sex (M/F)	Bactec results	Days of Treat-ment	Dose (mg)	Weight (kg)	Dose/ weight (mg/kg)	Height (cm)	Age (months)	Underlying Conditions
1	M	Negative	1	82.5	11	7.50	85	27	None
2	F	Negative	1	116	15.5	7.48	102	66	None
3	M	Negative	2	90	12	7.50	77.5	26	None
4	M	Negative	2	110	15	7.33	115	72	TB
6	F	Negative	2	90	12	7.50	107	48	Broncho-spasms
7	M	Negative	1	70	11	6.36	78	24	Broncho-spasms
8	F	Negative	5	45	6.2	7.26	76	24	Rickets and TB
11	F	Negative	5	160	32	5	157	132	Infective endocarditis, Rheumatic heart disease, severe anaemia
12	M	Negative	2	150	20.5	7.32	105	72	Broncho-spasms
13	M	Negative	5	52	8.9	5.84	65	24	None
14	F	Negative	5	200	19.5	10.26	135	96	None
15	M	Positive	5	120	18	6.67	116	86	TB, pleural effusion
16	F	Negative	2	56	7.5	7.5	78	24	None
17	M	Negative	5	40	8.9	4.49	81	24	None
18	F	Negative	5	40	7.5	5.33	70	24	Clinical malaria
20	F	Negative	5	82	10.9	7.52	101	42	Severe anaemia
Range			1-5	40-200	6-32	4.49-10.26	65-157	24-132	
Median			4	86.3	12	7.33	93	35	
Mean			3	94	14	6.93	97	51	
SD				46.53	6.56	1.35	25.34	33.25	

3.2 Microbiology and Clinical Efficacy

16 cultures were undertaken at enrolment. One child had *Coagulase negative staphylococcus* isolated and the rest of the cultures were negative. No sample met the defined criteria for clinical efficacy which was defined as clearance of positive blood cultures without the need for changing antibiotic.

3.3 Serum Creatinine and Creatinine Clearance

3.3.1 Serum Creatinine

Table 2 shows the serum creatinine values before and after treatment. Two (12.5%) patients met the criteria for nephrotoxicity which was an increase in serum creatinine after treatment by 0.5mg/dl while fourteen (87.5%) patients did not experience any change in serum creatinine.

One child had start serum creatinine outside the normal range before treatment while 15(93.8%) patients had the baseline creatinine within the normal range. After treatment with gentamicin, 2(12.5%) children had serum creatinine outside the expected range. The remaining 14(87.5%) children maintained creatinine within the normal range.

Table 2: Comparison of Serum Creatinine Values Before and After Treatment

Patient code	Days of treatment	Start Serum Creatinine (mg/dl)	End Serum Creatinine (mg/dl)	Change in serum creatinine	Nephrotoxicity outcome
1	1	0.49	0.49	0.00	Not Nephrotoxic
2	1	0.44	0.44	0.00	Not Nephrotoxic
3	2	0.33	0.33	0.00	Not Nephrotoxic
4	2	0.34	2.31	1.97	Nephrotoxic
6	2	0.79	0.86	0.07	Not Nephrotoxic
7	1	0.57	0.57	0.00	Not Nephrotoxic
8	5	0.43	0.52	0.09	Not Nephrotoxic
11	5	0.42	0.48	0.06	Not Nephrotoxic
12	2	0.55	0.55	0.00	Not Nephrotoxic
13	5	0.29	0.39	0.01	Not Nephrotoxic
14	5	0.53	0.66	0.13	Not Nephrotoxic
15	5	0.61	0.69	0.08	Not Nephrotoxic
16	2	0.41	1.63	1.22	Nephrotoxic
17	5	0.40	0.40	0.00	Not Nephrotoxic
18	5	0.50	0.50	0.00	Not Nephrotoxic
20	5	0.43	0.45	0.02	Not Nephrotoxic

Normal serum creatinine range was taken to be 0.339-0.904mg/dl [12].

3.3.2 Creatinine Clearance

Two methods were used to calculate creatinine clearance (Appendix 6). The results are shown in Table 3. The medium creatinine clearance at the start was 107.4 ml/min/1.73 m^2 and 83.9 ml/min/ 1.73 m^2 using Schwartz and Counahan-Barratt methods, respectively. The medium creatinine clearance at the end of treatment was 93.4 ml/min/ 1.73 m^2 and 73.1 ml/min/ 1.73 m^2. There was therefore a percentage decrease in creatinine clearance of 6.45%.

Only two patients had abnormally high creatinine clearances before treatment (above 160 ml/min/1.73 m^2) and one patient maintained the high level after treatment using the Schwartz equation. The normal creatinine clearance in children (2-12 years) is 133.0 +/- 27.0 ml/min/1.73 m^2 [28].

Table 3: Results of Creatinine Clearance using Schwartz and Counahan-Barratt Equations

Patient code	Start creatinine clearance by Schwartz (ml/min/1.73 m^2)	End creatinine clearance by Schwartz (ml/min/1.73 m^2)	Start creatinine clearance Counahan-Barratt (ml/min/1.73 m^2)	End creatinine clearance Counahan-Barratt ml/min/1.73 m^2)
1	93.9	93.9	73.4	73.4
2	127.2	127.2	99.4	99.4
3	125.6	125.6	98.2	98.2
4	186.4	27.4	145.7	21.4
6	74.3	68.5	58.1	53.5
7	74.4	74.7	58.1	58.1
8	97.2	80.3	76.0	62.8
11	206.3	181.8	161.3	142.1
12	104.2	104.2	81.4	81.5
13	121.6	93.0	95.0	72.7
14	139.7	113.2	109.2	88.5
15	104.4	92.5	81.7	72.3
16	105.3	26.3	82.4	20.6
17	109.4	109.4	85.5	85.5
18	75.6	75.6	59.1	59.1
20	129.2	122.8	101.0	96.0
Range	74.3-206.3	26.3-181.8	58.1-161.3	20.6-142.1
Median	107.4	93.4	83.9	73.1
Mean	117.2	94.8	91.6	74.1

3.3.3 Comparison of Schwartz and Counahan-Barratt

All patients were within the accepted clearance of above 60ml/min/1.73 m^2 before dosing with gentamicin [6]. Hence, they were considered to have adequate renal function. Using the Schwartz equation, 2(12.5%) patients had a creatinine clearance of less than 60ml/min/1.73 m^2 after treatment. The Counahan-Barratt equation had 5(31.3%) patients showing a creatinine clearance of less than 60ml/min/1.73 m^2 after treatment (Table 4).

Table 4: Comparison of Renal Compromise using Schwartz and Counahan-Barratt Equations

	Above 60ml/min/1.73 m^2		Less than 60ml/min/1.73 m^2	
	Count	%	Count	%
Patients with suspected renal compromise by Schwartz after treatment	14	87.5%	2	12.5%
Patients with suspected renal compromise by Counahan-Barratt after treatment	11	68.8%	5	31.3%

3.4 Gentamicin Quality Control Concentrations

The assay control values were found to be within the concentration ranges specified by the manufacturer and are shown in table 5.

Table 5: Gentamicin Quality Control Concentrations

Controls	Low 1.0(0.85-1.15)	Medium 4.0(3.60-4.40)	High 8.0(7.20-8.80)
Day 1	1.21 1.08	4.10 4.09 4.05	7.87 8.13
n	2	3	2
Mean	1.145	4.08	8
Standard deviation	0.092	0.026	0.184
CV%	8.034	0.637	2.3
Day 2	1.15 0.96 0.90 0.83 0.76 0.78	3.90 4.00 4.00 4.04	8.20 7.23 7.36 7.16 7.49 7.26
n	6	4	6
Mean	0.897	3.985	7.45
Standard deviation	0.145	0.060	0.385
CV%	16.167	1.505	5.167

The results from the two days were analysed in Table 6.

Table 6: Comparison of Controls (Day 1 vs. Day 2)

	Day1 gentamicin control levels	Day 2 gentamicin control levels
1	1.08	0.78
2	1.21	0.96
3	4.05	4.00
4	4.09	4.00
5	4.10	7.16
6	7.87	7.23
7	8.13	7.26
n	7	7
Mean	4.36	4.48
SD	2.812	2.858

P value for paired t-Test for controls done between the two days to test the reliability of the measurements was found to be 0.938 meaning the measurements done over the two days were comparable. The correlation coefficient was 0.991; p value < 0.001 meaning the measurements were highly correlated.

The repeatability of the results was calculated using R for windows version 2.7.2. The correlation coefficient was 0.8903; p value was calculated as 0.9367 meaning the measurements were highly repeatable between the two days.

3.5 Plasma Gentamicin Concentrations

Data on gentamicin concentrations from the 16 patients are summarized in Table 7. The peak concentrations ranged from 4.80 to 21.57 µg/mL while trough concentrations ranged from 1.07µg/mL to below 0.27 µg/mL (the limit of detection).

Table 7: Plasma Gentamicin Concentrations

Patient code	Treatment outcome	Sampling date	Sampling time	Sample time (hrs)	Gentamicin concentration (µg/mL)
1	Treated and discharged	09.03.08	14:10	0:00	Low
		09.03.08	14:43	0:33	15.93
		09.03.08	18:15	4:05	3.86
		09.03.08	22:20	8:10	0.97
		10.03.08	2:10	12:00	0.57
		10.03.08	14:00	23:50	Low
2	Treated and discharged	12.03.08	8:25	0:00	Low
		12.03.08	9:00	0:35	14.36
		12.03.08	13:15	4:50	1.48
		12.03.08	17:30	9:05	0.45
		12.03.08	21:00	12:35	Low
		13.03.08	9:00	24:35:00	Low

3	Treated and discharged	11.03.08	21:35	0:00	Low
		11.03.08	22:27	0:52	21.57
		12.03.08	1:57	4:22	3.15
		12.03.08	6:09	8:34	1.04
		12.03.08	22:00	23:33	1.07
4	Treated and discharged	10.03.08	12:20	0:00	0.27
		10.03.08	13:20	1:00	15.82
		10.03.08	17:18	4:58	2.75
		10.03.08	22:15	9:55	0.69
		11.03.08	0:23	12:03	0.42
		11.03.08	13:00	24:40:00	0.72
5	Withdrew	14.03.08	10:00	0:00	Low
		14.03.08	10:35	0:35	14.85
		14.03.08	14:00	4:00	No Sample
		14.03.08	18:00	8:00	No Sample
		14.03.08	22:00	12:00	No Sample
		15.03.08	10:00	24:00:00	No Sample
6	Treated and discharged	15.03.08	15:55	0:00	Low
		15.03.08	16:30	0:35	10.5
		15.03.08	19:50	3:55	1.4
		16.03.08	0:00	8:05	Low
		16.03.08	3:56	12:01	Low
		16.03.08	15:55	24:00:00	Low
7	Treated and discharged	15.03.08	23:05	0:00	Low
		15.03.08	23:36	0:31	14.52
		16.03.08	3:10	4:05	1.2
		16.03.08	7:45	8:40	0.7
		16.03.08	11:09	12:04	Low
		16.03.08	23:10	24:05:00	Low
8	Treatment failure	15.03.08	15:17	0:00	0.7
		15.03.08	16:45	1:28	4.8
		15.03.08	19:36	4:19	1.23
		15.03.08	0:00	8:43	No Sample
		16.03.08	3:05	11:48	0.28
		16.03.08	16:00	24:43:00	Low
9	Early discharge	15.03.08	9:30	0:00	Low
		15.03.08	10:05	0:35	15.12

		15.03.08	13:30	4:00	1.89
		15.03.08	17:30	8:00	No Sample
		15.03.08	21:30	12:00	No Sample
		16.03.08	9:30	24:00:00	No Sample
10	Withdrew				
11	Treated and discharged	17.03.08	15:10	0:00	Low
		17.03.08	15:40	0:30	7.98
		17.03.08	19:40	4:30	5.68
		17.03.08	2:24	11:14	No Sample
		18.03.08	3:15	12:05	Low
		18.03.08	15:20	24:10:00	Low
12	Treated and discharged	18.03.08	9:15	0:00	Low
		18.03.08	9:50	0:35	15.09
		18.03.08	13:20	4:05	1.57
		18.03.08	17:20	8:05	0.44
		18.03.08	21:15	12:00	Low
		19.03.08	9:15	24:00:00	Low
13	Treated and discharged	19.03.08	20:45	0:00	Low
		19.03.08	21:15	0:30	19.36
		20.03.08	1:15	4:30	1.31
		20.03.08	5:15	8:30	0.45
		20.03.08	9:20	12:35	0.47
		20.03.08	21:20	24:35:00	Low
14	Treated and discharged	24.03.08	14:10	0:00	Low
		24.03.08	14:55	0:45	13.14
		24.03.08	18:55	4:45	2.47
		24.03.08	23:00	8:50	0.67
		25.03.08	2:10	12:00	No Sample
		25.03.08	16:30	26:20:00	Low
15	Treated and discharged	24.03.08	14:00	0:00	No Sample
		24.03.08	14:50	0:50	10.92
		24.03.08	18:30	4:30	1.72
		24.03.08	23:00	9:00	0.76
		25.03.08	2:00	12:00	No Sample
		25.03.08	16:00	26:00:00	No Sample
16	Treatment failure	23.03.08	19:30	0:00	Low

		23.03.08	20:05	0:35	8.91
		24.03.08	1:12	5:42	6.56
		24.03.08	4:05	8:35	6.75
		24.03.08	9:00	13:30	3.84
		24.03.08	20:05	24:35:00	No Sample
17	Treated and discharged	23:03:08	19:45	0:00	Low
		23:03:08	20:20	0:35	6.03
		24.03.08	0:20	4:35	0.98
		24.03.08	4:20	8:35	0.92
		24.03.08	21:40	25:55:00	Low
18	Treated and discharged	23.03.08	20:00	0:00	2.89
		23.03.08	20:40	0:40	16.89
		24.03.08	0:40	4:40	4.33
		24.03.08	4:40	8:40	3.85
		24.03.08	9:20	13:20	4.17
		24.03.08	20:40	24:40:00	Low
19	Withdrew	21.03.08	15:00	0:00	Low
		21.03.08	15:35	0:35	14.46
		21.03.08	19:35	4:35	1.32
		21.03.08	23:35	8:35	No Sample
		22.03.08	3:35	12:35	No Sample
		22.03.08	15:35	24:35:00	No Sample
20	Treated and discharged	27.03.08	18:00	0:00	Low
		27.03.08	18:45	0:45	9.00
		27.03.08	22:20	4:20	3.92
		28.03.08	2:00	8:00	No Sample
		28.03.08	6:00	12:00	No Sample
		28.03.08	19:00	25:00:00	Low

Concentrations below 0.27ug/mL were recorded as low.

Three patients had detectable levels of gentamicin on the pre-dose plasma sample, while in another; gentamicin was undetectable approximately 8 hours after the bolus dose. At approximately 12 hours post dose, gentamicin was undetectable in five of the patients,

while 24 hours post dose, thirteen patients had undetectable gentamicin in plasma (Table 8).

Table 8: Gentamicin concentrations at different times post administration

Average sampling time	Low(below 0.27 µg/mL)		Above 0.27µg/mL		Total
	Patients	%	Patients	%	Patients
0 minutes	12	80.0%	3	20.0%	15
35 minutes	0	0.0%	16	100.0%	16
270(approximately 4hrs)	0	0.0%	16	100.0%	16
518 (approximately 8 hrs)	1	7.7%	12	92.3%	13
724(approximately 12 hrs)	5	38.5%	8	61.5%	13
1475(approximately 24hrs)	11	78.6%	3	21.4%	14

Figure 1 depicts the average gentamicin levels(µg/mL) drawn at median sampling times of 35 minutes, 270 minutes, 518 minutes and 724 minutes and 1475 minutes (just before the next dose). Mean gentamicin levels are shown in figure 2.

Figure 1: Average gentamicin levels (μg/mL) vs. median sampling time in hours

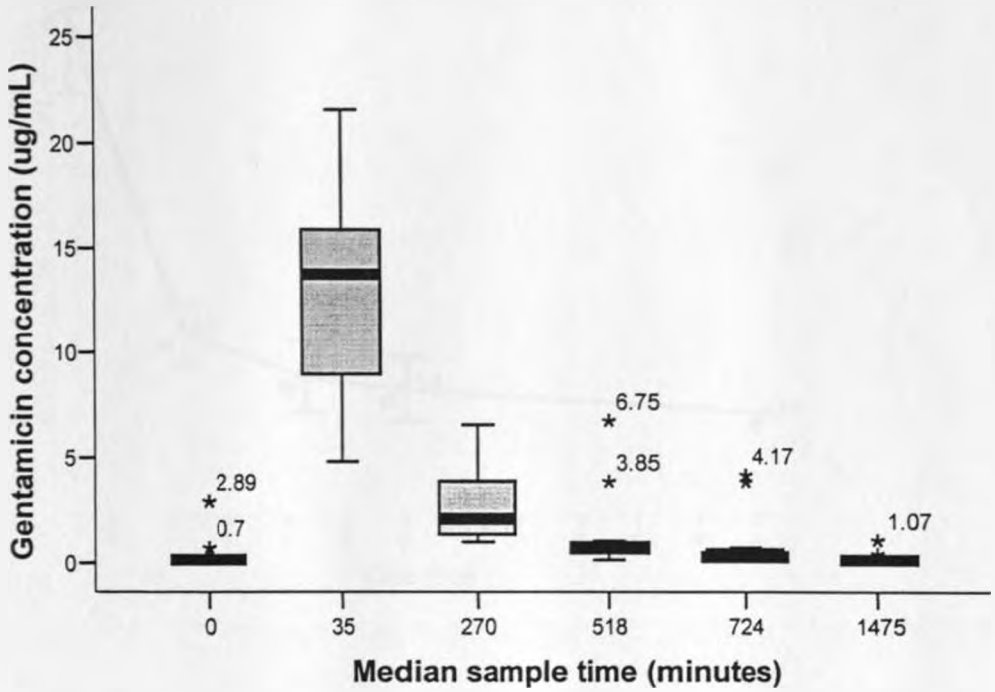
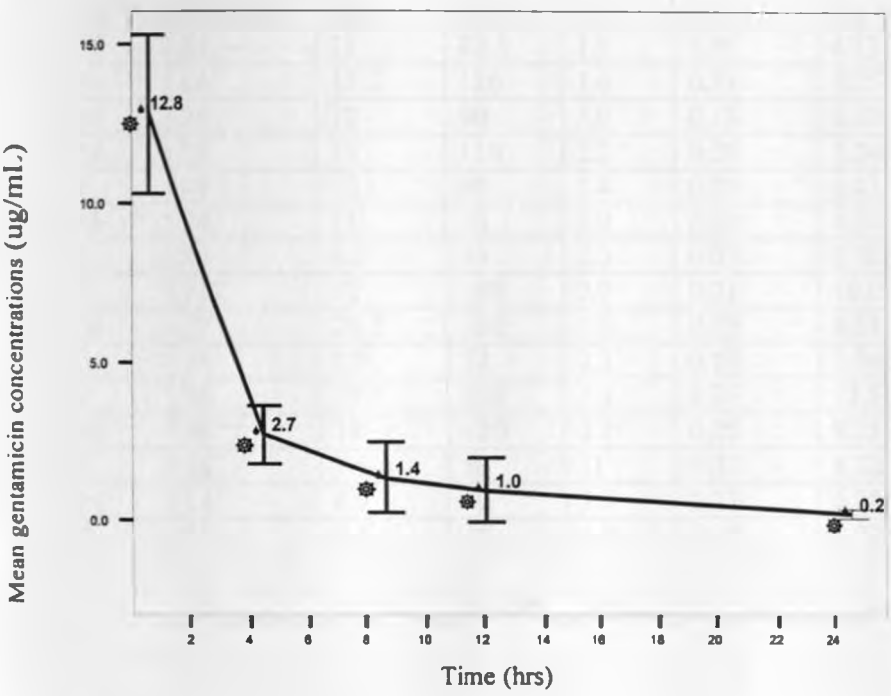


Figure 2: Mean gentamicin levels (μg/mL) in children dosed once daily (OD)



Error bars show 95% confidence interval.

3.6 Pharmacokinetic Parameters of Gentamicin in the Patients.

Table 9 summaries pharmacokinetic parameters in the patients studies as determined by methods discussed in section 2.12 above.

The median half-life was found to be 2.1 hr and the median volume of distribution was 0.49L/Kg.

Table 9: Pharmacokinetics of Gentamicin.

Patient code	Sex (M/F)	Age (months)	Weight (kg)	Dose (mg)	$t_{1/2}$ (hr)	Ke (hr^{-1})	Vd (L)	Vd (L/kg)	Cl (L/hr)
1	M	27	11	82.5	1.9	0.35	4.13	0.38	1.45
2	F	66	15.5	116	1.6	0.21	7.25	0.47	1.55
3	M	26	12	90	5.0	0.13	3.60	0.30	0.48
4	M	72	15	110	2.2	0.28	5.24	0.34	1.46
6	F	48	12	90	1.4	0.39	6.43	0.54	2.56
7	M	24	11	70	2.0	0.29	4.38	0.40	1.25
8	F	24	6.2	45	2.0	0.03	5.70	0.52	0.17
11	F	132	32	160	2.0	0.21	16.0	0.50	3.31
12	M	72	20.5	150	1.6	0.25	8.33	0.41	2.04
13	M	24	8.9	52	2.2	0.18	2.36	0.27	0.43
14	F	96	19.5	200	1.9	0.27	12.50	0.64	3.38
15	M	86	18	120	2.4	0.25	9.23	0.51	2.28
16	F	24	7.5	56	11	0.07	6.22	0.83	0.40
17	M	24	8.9	40	3.0	0.21	5.88	0.66	1.26
18	F	24	7.5	40	4.0	0.19	2.22	0.29	0.41
20	F	42	10.9	82	2.4	0.22	7.46	0.68	1.66
Range		24-132	6.2-32	40-200	1.4-11	0.03-0.39	2.22-16	0.27-0.83	0.17-3.38
Median		34.5	11.5	86.25	2.1	0.22	6.05	0.49	1.46
Mean		50.69	13.53	93.97	2.91	0.22	6.68	0.48	1.51
SD		33.25	6.56	46.53	2.35	0.09	3.60	0.16	1.01

Legends:
$t_{1/2}$ = half life
ke = elimination rate constant
Vd = volume of distribution
Cl= clearance

CHAPTER FOUR

DISCUSSION

4.1 Microbiology and Clinical Efficacy

Only one positive culture was obtained. This is in accordance with the various studies that have found the very low positivity rate of blood cultures in pneumonia [21, 22]. Studies that have attempted to evaluate the use of blood cultures in the diagnosis of pneumonia, yielded positive cultures in only 3% to 11% of cases [1]. Low yield in cultures despite the signs and symptoms may have been because the pneumonias were not of bacterial origin. In a recent study of children aged 2 months to 17 years who were hospitalized for pneumonia in the United States, 45% were found to have a viral etiology [23]. Pneumonia is usually caused by viruses or bacteria but most serious episodes are caused by bacteria [24]. However, a significant proportion of cases of paediatric pneumonia represent a mixed infection [25].

The organism isolated in his case was *Coagulase negative staphylococcus*. In a symptomatic child a pathogen identified in blood culture is widely regarded as the causal agent of pneumonia. However, this means of identifying organisms is only useful when pneumonia is associated with bacteraemia and the culturing technique used here is considerably less sensitive than other tests such as lung aspiration. This culture may have been a false positive since the bacteria implicated (*Coagulase negative staphylococcus*) could be considered a skin contaminant. There are three obvious sources of false-positive results: (1) contamination of the aspirate cultures; (2) detection of infection confined to the blood stream; and (3) culture of bacteria that are not primarily responsible for the

pneumonia. The laboratory did not regard the organism as a contaminant and left that decision to the discretion of the doctor who treated as a skin contaminant.

When symptoms persist despite empiric antibiotic therapy, bronchoscopy with bronchoalveolar lavage can be used as a diagnostic option in making a microbiological diagnosis but is not needed for routine cases and is not done in our set up. Bronchoscopy should be considered when patients fail to improve with standard therapy or when concern about antibiotic resistance or unusual organisms is high and recovery of the causative agents will change management. Early bronchoscopy may be critical for immuno-compromised patients, for whom the selection of empiric therapy is difficult because of the expanded list of potential causes. Another method that can be used to confirm the presence of pneumonia is consolidation or infiltrates on chest radiography. One child with treatment failure had pneumonia confirmed by this method.

4.2. Treatment failure

Clinical efficacy in this study was defined as clearance of positive blood cultures without the need for changing antibiotic. This could not be evaluated because of lack of positive cultures. Two treatment failures were obtained which necessitated the change of gentamicin/penicillin to amikacin/ceftriaxone. The children recovered.

Treatment failure may be attributed to resistance. Most resistance to aminoglycosides is caused by bacterial inactivation by intracellular enzymes. Because of structural differences, amikacin is not inactivated by the common enzymes that inactivate gentamicin. Therefore, a large proportion of the Gram-negative aerobes that are resistant to gentamicin are sensitive to amikacin [26]. In addition, with decreased use of amikacin

at KNH, a lower incidence of resistance may be observed compared to that of gentamicin which is more widely used.

4.3 Serum Creatinine and Creatinine Clearance

In this study, nephrotoxicity was defined as an increase in serum creatinine levels (or decrease in creatinine clearance) assessed by a rise in the serum creatinine concentration of greater than 0.5 mg/dL. The incidence of nephrotoxicity reported in adult studies is usually assessed by a rise in the serum creatinine concentration of greater than 0.5 mg/dL (44.2 μmol/L) [11]. This figure was chosen for this study because no paediatric assessment guide was located. Two patients (12.5%) experienced nephrotoxicity by this definition.

Nephrotoxicity results from renal cortical accumulation resulting in tubular cell degeneration and sloughing. An elevation of serum creatinine is more likely to reflect glomerular damage rather than tubular damage. Periodic monitoring of serum creatinine concentrations may alert the clinician to renal toxicity [12]. Nephrotoxicity normally occurs after five to seven days of treatment and presents as hypo-osmolar, non-oliguric renal failure with a slow rise in serum creatinine. Both these patients received the drug for two days. Hence the increase could be due to underlying disease states.

4.3.1 Serum Creatinine

Measurement of renal function is important to optimize drug dosing in critically ill paediatric patients and to prevent dose-related toxicities caused by medications that are eliminated or metabolized by the kidney. The KNH laboratory has not defined its ranges for serum creatinine and creatinine clearance in the paediatric population. Text book

ranges were therefore used to define ranges for this study. Normal serum creatinine range was taken to be 30-80 μmol/L (0.339-0.904 mg/dl) [13]. All but one patient had baseline serum creatinine within the normal range. However, two children had the end serum creatinine above this range. One of these patients was diagnosed as having TB and was discharged on anti-TBs while the second patient went into shock just before discharge. These may explain the rise of end serum creatinine. Other possible causes of increased serum creatinine are kidney disease, ingestion of cooked meat, ketoacidosis and drugs such as trimethoprim, cimetidine, flucytosine, some cephalosporins. Decrease in serum creatinine may be due to reduced muscle activity and malnutrition.

4.3.2 Creatinine Clearance

In clinical practice, creatinine clearance is widely accepted as a simple measure of glomerular filtration rate (GFR) [27]. This is because clearance of drugs primarily eliminated by glomerular filtration is well correlated to GFR. Thus, estimation of the GFR gives a rough measure of the number of functioning nephrons. The main aim of determining creatinine clearance has been to reduce the dose in patients with impaired renal function so as to reduce toxicity. The normal creatinine clearance (2-12 years) was taken from references to be 133.0 +/- 27.0 ml/min/1.73 m^2 [29].

Once a day dosing is recommended for patients with a creatinine clearance of more then 60 ml/min/1.73 m^2 and the dose is adjusted on the basis of blood levels [6]. All patients were above this level before treatment using Schwartz formula, but after receiving gentamicin, two patients had clearances of 27.4 and 26.3 ml/min/1.73 m^2. Both patients

received the drug for only two days and were then discharged. Had treatment gone on for longer, OD dosing would no longer have been appropriate.

Creatinine clearance range was calculated using the Schwartz [28] and the Counahan-Barratt equations [29]. These two equations were used because they have been the most extensively validated and are commonly used. Both are both based on a constant multiplied by a child's height/length divided by serum creatinine. The Schwartz and Counahan-Barratt formulae (Appendix 6) can provide rapid and convenient estimates of GFR, although clinicians should be aware of their imprecision in this setting. The use of serum creatinine concentration to estimate GFR relies on the individual being in steady state and the ability to estimate the average rate of creatinine generation. GFR from any prediction equation will therefore be unreliable in the settings of acute renal failure, muscle breakdown or fluctuating dietary intake. Other disease states, such as malnutrition common in our setting and evident in some of the children would also likely undermine the performance of GFR prediction equations.

4.4 Gentamicin Pharmacokinetics

Three patients had recordable gentamicin concentrations at time zero. This was probably due to prior administration of the drug before this admission or errors in measurement. Peak levels of at least 5µg/mL were considered to be essential to declare that this particular dosing regimen was pharmacologically effective. The peak concentrations in this study ranged from 4.80 to 21.57µg/mL. The patient (number 8) with a peak below 5 µg/mL at 4.8 µg/mL was one of the two patients who had treatment failure. This low reading was in spite of the fact that she had recordable gentamicin levels at zero hours. This could have been due to loss of the drug from intravenous administration into

surrounding tissue. Creatinine clearances of this patient were also below the range of 133.0 +/- 27.0 ml/min/1.73 m^2 both before and after treatment with gentamicin at 97.2 and 80.3 ml/min/1.73 m^2 meaning that fast elimination could not have been the cause. Both patients who experienced treatment failure had among the lowest elimination rates and volumes of distribution and among the highest half lives.

Trough concentrations of less or equal to 2 μg/ml at the 24 hour sampling time, were considered to be essential to declare that this particular dosing regimen was pharmacologically safe. However, at approximately 8hours, one patient had undetectable levels while at approximately 12 hours, five patients (38.5%) had untraceable levels of gentamicin. By 24 hours, it can be stated that these patients had sub-therapeutic levels of gentamicin in their blood. These patients possibly experienced fast clearance of the drug.

The study showed that that despite the concepts in support of once daily dosing, a considerable portion of this particular population appears to have sub-therapeutic drug levels since tough levels were undetectable in some patients as early as 8 hours post-dose. Just before the next dose, 11 patients (78.6%) recorded low undetectable levels of plasma gentamicin. It may be necessary to have an additional sampling time between 12 and 24 hours to determine how many of these patients were below the therapeutic range long before the trough period. This is because although research has demonstrated that PAE causes the persistent suppression of bacterial growth following limited exposure to an antibiotic, it is variable for different types of bacteria and the duration of the PAE in different age groups of patients treated with extended-dosing interval regimens is uncertain[6, 11]. Indeed most literature state it to be between 6 to 8 hours.

The adjustment of aminoglycoside dosing interval may be necessary since how long the serum concentration can remain below detectable limits before a change in dosing interval is necessary is not known and must be determined before a nomogram can be developed and tested [11].

The median elimination half-life ($t_{1/2}$) was found to be 2.1 hr and the median volume of distribution (Vd) was 0.49L/Kg. The median elimination rate constant (ke) was calculated to be 0.22 L/kg. Although most studies focus on neonatal groups, these median results are similar to a study done on a similar paediatric period [30].

4.5 Study Limitations

1. The sample size was small hence it was difficult to make definite conclusions on larger populations.
2. The sample ages, weights and heights were very varied.
3. The serum creatinine concentration alone should not be used to assess the level of kidney function.
4. The allocated period for the study was only six months. This was inadequate.
5. Gentamicin analysis kits are expensive. Hence, no pairing of samples was done during analysis. Only one value was available for use.
6. The biochemistry laboratory could not provide laboratory ranges for expected serum creatinine for this population of children. Text book values of other populations were used to set the normal ranges.
7. Dosing of the children was not accurately done. Rounding off was applied.
8. The line of best fit was use for pharmacokinetic calculations. This line is subjective.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATION

This study has shown that 7.7% of patients had their gentamicin concentration at low levels as early as 8 hours post dose and at approximately 12 hours post dose, 5 patients (38.5%) had undetectable levels of gentamicin Once daily dosing may not be suitable for every patient within the age bracket studied due to the uncertainty of the duration of PAE. The use of TDM to individualize the dose may improve patient management. This would be safe for the patient because the dose calculation would be based on the clinical pharmacokinetic parameters. However, individualizing the dosing, though ideal, is expensive and is probably not practical within public health facilities without substantial subsidy. Moreover, given the busy nature of such facilities, the added complexity of TDM would make it unattractive even if the cost were to be subsidized. Nevertheless, these results can inform further studies on the efficacy and safety of once daily dosing in children, and may be useful in selected situations. This would address some of the limitations (section 4.5) associated with present study.

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APPENDIX 1

PATIENT INFORMED CONSENT DOCUMENT

PART I: INFORMATION SHEET AND CONSENT FORM

1. **CENTRE**: Kenyatta National Hospital

2. **PRINCIPAL INVESTIGATOR**:
   Dr. Irene Chege

3. **TITLE OF STUDY:** Clinical pharmacokinetics of once daily IV bolus Gentamicin in paediatric patients with severe pneumonia at KNH.

4. **INVITATION TO VOLUNTARY PARTICIPATION**

We are inviting you to allow your child to participate in this study being conducted by Dr. Irene Chege .We would like you to know that participating in this study is absolutely voluntary.

You can decide not to allow your child to participate or decide to withdraw your child from the study any time, whatever you choose you will still get the necessary attention. Before making your choice it is important to understand why the study is being done and what it will involve. Please take time to read the information (or have it read to you) very carefully and you can discuss, with friends and even your family doctor if you like. Feel free to ask us if there is anything you have not understood or if you need more explanation. We will appreciate if you will take your time to read (or ask somebody to read it to you), ask questions and even understand the following information.

BACKGROUND, AIM AND PROCEDURE OF STUDY

If you decide to allow your child to participate in the study we will request to take a total of 10 mls (two teaspoonfuls) of your child's blood over 24 hours to use in the study. If your child is found to have pneumonia, (s)he will be treated with a medicine called gentamicin. It is the way the child's body handles gentamicin that we are interested in so that we can better treat other children using this medicine

It is not a must that you participate in the study for your child (if she/he has malaria) to get treated for pneumonia. Your permission for your child to participate in the study is voluntary and you have a right to withdraw your consent any time without giving reasons.

If you agree to participate, your child's sample will be tested at our laboratories at KEMRI/Wellcome Trust Laboratories and also in laboratories University of Nairobi. The purpose of these tests is to determine the severity of the pneumonia and the levels of the medicine in the child's body.

What are my rights to participate or refuse to participate?

- Participation in this study is absolutely voluntary.
- If you agree to participate you will be requested to sign a consent form and you will get a copy of the form you have signed.
- Even if you decide to participate in the study you will be at liberty to withdraw from the study any time without giving reasons.

What am I supposed to do?

If you agree for your child to participate we will take a total of 10 mls (2 teaspoonfuls) of blood over 24 hours from the arm vein

Are there any risks/discomforts to the participants?

- Pricking a vein to obtain blood may cause pain and some discomfort.
- Little pain is experienced when the blood sample is being taken

Are there any benefits to the participants?

There are no direct benefits to you. However, your child's participation will provide the doctors with more information that can help them in the development of the best ways of using this medicine.

How about cost and compensation?

There is no compensation arising from participation in this study.

Is my participation assured of confidentiality?

- Your information or records during the study will be strictly confidential all the time and no unauthorized person(s) will be allowed to access these information/records
- After taking the blood, we will assign a study number to the sample. The blood sample will only be identified by this study number, and only the doctors from this clinic involved in the study will be able to link this number to your child. Thus, the

results of this study will be handled in such a way as not to reveal your identity or that of your child

Whom can I contract during the study?

- If you have any questions or doubts for now or any other time concerning this research, please ask your doctor or those concerned with this study whose names have been given below.
- If you participate in this study you can contact the following (in case of questions or worries concerning the treatment): Dr. Irene Chege who will be the principal investigator.

  Dr Irene Chege: Mobile Telephone 0727871188
- For any additional information regarding ethical issues, contact the chairman, KNH-ERC:

  Prof K.M. Bhatt, P.O. Box 20723, Nairobi. Tel 726300-9
- If you accept to participate in this study we will request you to sign a consent form.
- You will be given a copy of this record.

PART II
INFORMED CONSENT

Dear participant,
I am a final year master's student at the School of pharmacy, University of Nairobi. I am conducting a research study on the "Clinical pharmacokinetics of once daily IV bolus gentamicin in paediatric patients with severe pneumonia at KNH."

The findings of the study will be useful in helping formulate policies and guidelines in the treatment of pneumonia in children. The research will be in the form of a questionnaire and blood samples will be required from your child. Strict confidentiality will be maintained. To confirm that you have accepted to take part in the research, you will be required to complete the form below.

YOUR CONSENT

(1) I .....confirm that I have read and understood the information sheet about the above-mentioned study and I have had the opportunity to ask questions. I am aged 18 years or above.
(2) The study has been explained to me by----------
in---------- ---------- -- language.
(3) I understand that my participation is voluntary and that I am free to withdraw my child at any time without giving any reasons or without my medical and legal rights being affected.

(4) I agree for blood samples to be taken from my child and used for the pneumonia study.

(5) I accept not to restrict the use of any results/records, which may arise from this study.

Signature or thumb print of parent/guardian.....Date.....

Signed by investigator .....Date.....

APPENDIX 2

QUESTIONNAIRE

Clinical pharmacokinetics of IV bolus Gentamicin in paediatric patients with suspected pneumonia at KNH

Respondent Code_____ Date of admission ___ / ____2007

Ward_____

SOCIO-DEMOGRAPHIC DATA		
No.	**Questions and filters**	**Coding categories**
1.	Identification number	
2.	Sex	1. Male 2. Female
3.	Age	[ ] Years
4.	Weight(Kg)	
5.	Co-morbid conditions	
6.	Con-current drugs in use	
7.	Date and time of blood sample collection for microbiology analysis	
8.	Date and time of first administered dose of Gentamicin (one hour after bolus administration).	
9.	Actual dose of Gentamicin administered	
10.	Results of serum levels of Gentamicin detected 30 minutes after bolus dose	Peak……..

11.	Results of serum blood levels at specific times	(4hrs after)Time of collection..... Seru reading..... (8hrs after)Time of collection..... Seru reading..... (12hrs after)Time of collection..... Seru reading.....
12.	Results of serum levels immediately prior to the second dose (24hours later).	Trough.....
13.	Date and time of second administered dose	
14.	Blood culture results	
15.	Renal function test results prior to treatment	
16.	Renal function tests after treatment	

APPENDIX 3

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP" Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ 01/ 181

15th February 2008

Dr. Chege Irene Njeri
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
University of Nairobi

Dear Dr. Chege

RESEARCH PROPOSAL: "CLINICAL PHARMACOKINETICS OF ONCE DAILY IV BOLUS GENTAMICIN IN PEDIATRIC PATIENTS WITH SEVERE PNEUMONIA AT KENYATTA N.HOSPITAL" (P367/12/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your revised research proposal for the period 15th February 2008 – 14th February 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Pharmacy, UON
The Chairman, Dept. of Pharmaceutics & Pharmacy Practice, UON
Supervisors: Prof. G. Kokwaro
Prof. O. Anzala

APPENDIX 4

Dr. Chege Irene Njeri
U59/7691/06
Department of Pharmaceutics and
Pharmacy Practice
School of Pharmacy
University of Nairobi
25/2/2008

The director,
Kenyatta National Hospital
P.O. Box 20723,
Nairobi.

Attention: Deputy Director Clinical Services

Through: Research supervisors:
Prof. G. Kokwaro (School of Pharmacy and KEMRI-Wellcome Trust Programme
Prof. A. O. Anzala (Kenya AIDS Vaccine Initiative)

Dear Sir,

RE: AUTHORITY TO CONDUCT REASEACH AT KNH

I am a final year clinical pharmacy student at the University of Nairobi. I would kindly like to request you to grant me permission to conduct research on **"Clinical pharmacokinetics of once daily IV bolus gentamicin in pediatric patients with severe pneumonia at KNH."** The patients will be followed from casualty to wards 3 and 4. The findings from this research will assist in setting up guidelines and policies in the treatment of pneumonia in the paediatric population. This research will be undertaken in the partial fulfilment of the requirements of Master of Clinical Pharmacy degree.

I look forward to your positive response. Thank you in advance.

Yours sincerely

Dr. Chege Irene Njeri

APPENDIX 5

Creatinine Measurement Controls

PAGE 2

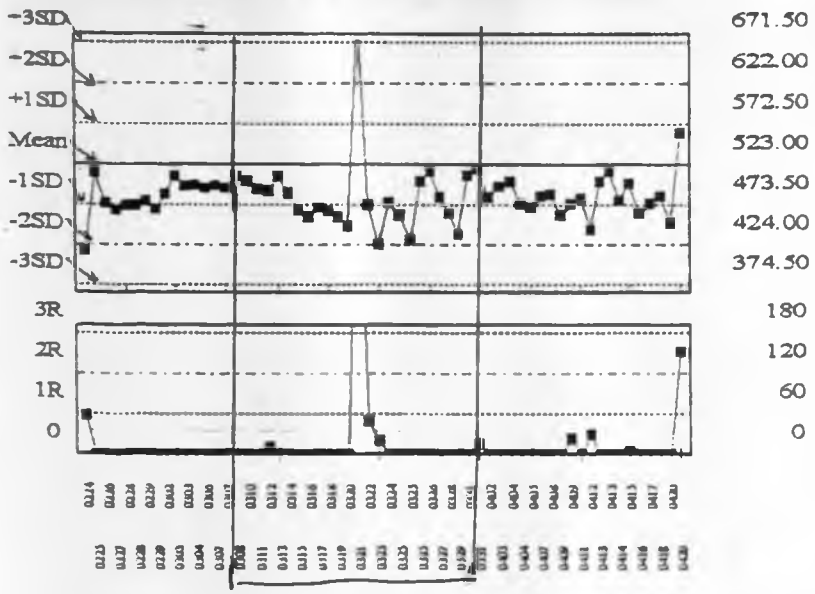
TO DAY SERUM

PRINT TIME [21/04/2008 14:20]

INDEX [27/02/2006 10:25] - [21/04/2008 10:50]

2 OLYMPUS CONTROL 2

97	470.8	36.14	7.68	291
	(523.0)	(49.50)	(9.46)	(60)



5 Data-Trol N

33	321.3	27.69	8.62	124
	(270.0)	(25.00)	(9.26)	(100)

APPENDIX 6

Equations used to calculate Creatinine Clearance

Equation 1: Schwartz equation

Standard Cl_{cr} (ml/min/1.73m^2) = k x height (cm)/ S_{cr} (mg/dl) Where: k = 0.55

Equation 2: Counahan-Barratt equation.

Cl_{cr} (ml/min/1.73m^2) = k x height (cm)/ S_{cr} (mg/dl) Where; k= 0.43

APPENDIX 7

Patient Results

code	SAMPLING DATE	SAMPLING TIME	SAMPLE TIME (min)	GENTAMICIN CONCENTRATION	GENDER	DOSE	DAYS
1	09.03.08	2:10:00 PM	0	LOW	M	82	1
	09.03.08	3:-16:-59 PM	33	15.93			
	09.03.08	6:15:00 PM	245	3.86			
	09.03.08	10:20:00 PM	490	0.97			
	10.03.08	2:10:00 AM	720	0.57			
	10.03.08	2:00:00 PM	1,430	LOW			
2	12.03.08	8:25:00 AM	0	< 0.27	F	116	1
	12.03.08	9:00:00 AM	35	14.36			
	12.03.08	1:15:00 PM	290	1.48			
	12.03.08	5:30:00 PM	545	0.45			
	12.03.08	9:00:00 PM	755	LOW			
	13.03.08	9:00:00 AM	1,475	LOW			
3	11.03.08	10:-24:-59 P	0	LOW	M	90	2
	11.03.08	10:27:00 PM	52	21.57			
	12.03.08	2:2:59 AM	262	3.15			
	12.03.08	6:09:00 AM	514	1.04			
	12.03.08	10:00:00 AM	745	5.43			
	12.03.08	2:15:00 PM	1,000	2.34			
	12.03.08	10:00:00 PM	1,413	1.07			
4	10.03.08	0:20:00 PM	0	0.27	M	110	2
	10.03.08	1:20:00 PM	60	15.82			
	10.03.08	5:18:00 PM	298	2.75			
	10.03.08	10:15:00 PM	595	0.69			
	11.03.08	0:23:00 AM	723	0.42			
	11.03.08	1:00:00 PM	1,480	0.72			
5	14.03.08(early discharge)	10:00:00 AM	0	LOW	F		
	14.03.08	11:-24:-59 A	35	14.85			
	14.03.08	2:00:00 PM	240	No Sample			
	14.03.08	6:00:00 PM	480	No Sample			
	14.03.08	10:00:00 PM	720	No Sample			
	15.03.08	10:00:00 AM	1,440	No Sample			
6	15.03.08	4:-4:-59 PM	0	LOW	F	90	2
	15.03.08	5:-29:-59 PM	35	10.5			
	15.03.08	8:-9:-59 PM	235	1.4			
	16.03.08	12:00:00 AM	485	< 0.27			
	16.03.08	4:-3:-59 AM	721	LOW			
	16.03.08	4:-4:-59 PM	1,440	LOW			
7	15.03.08	11:05:00 PM	0	LOW	M	70	1
	15.03.08	0:-23:-59 PM	31	14.52			
	16.03.08	3:10:00 AM	245	1.2			
	16.03.08	8:-14:-59 AM	520	0.7			
	16.03.08	11:09:00 AM	724	LOW			
	16.03.08	11:10:00 PM	1,445	LOW			
8	15.03.08	3:17:00 PM	0	0.7	F	45	5
	15.03.08	5:-14:-59 PM	88	4.8			
	15.03.08	8:-23:-59 PM	259	1.23			
	15.03.08	12:00:00 PM	523	No Sample			

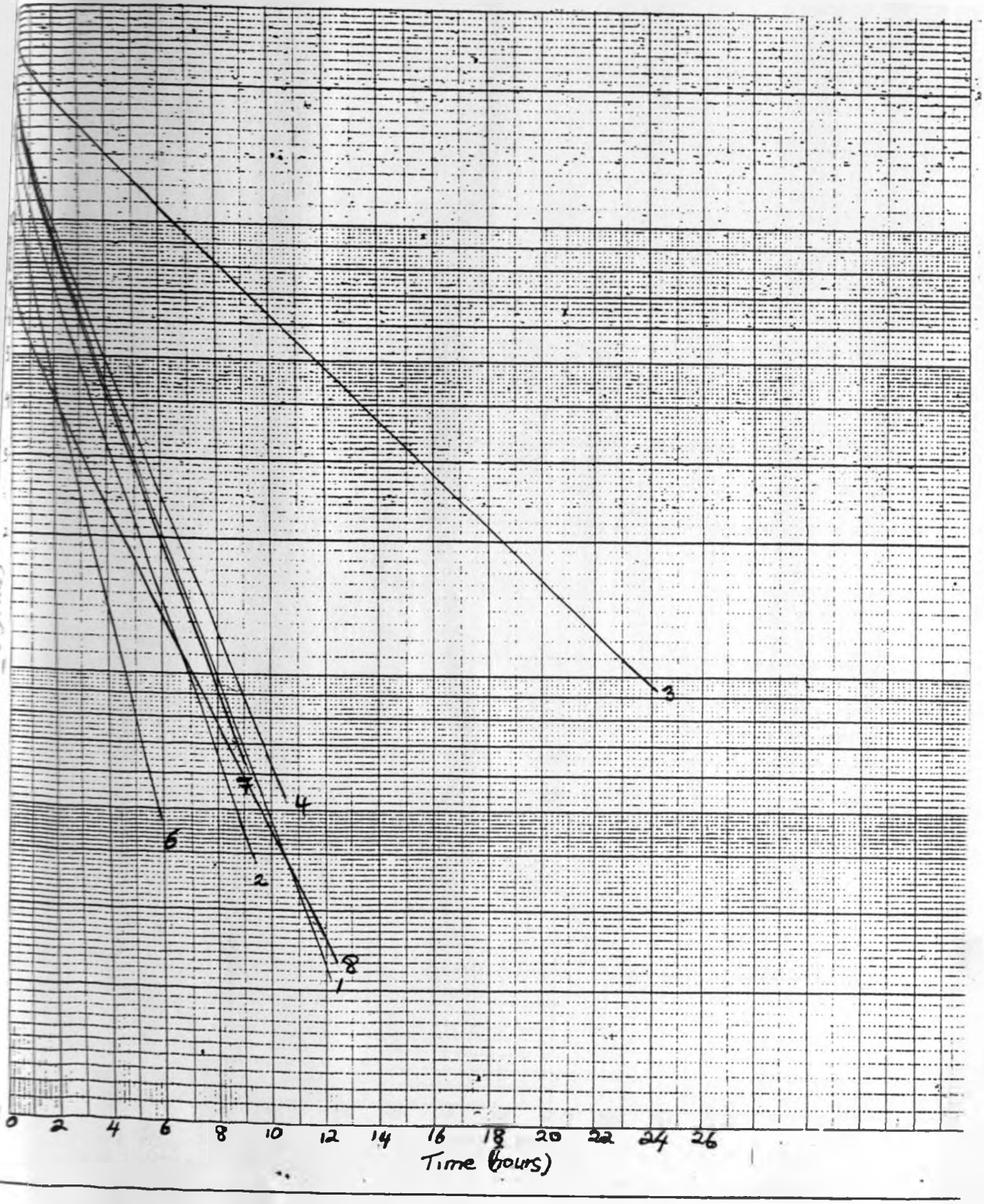
	16.03.08	3:05:00 AM	708	0.28			
	16.03.08	4:00:00 PM	1,483	LOW			
9	15.03.08(with drew)	9:30:00 AM	0	LOW	F	-	-
	15.03.08	10:05:00 AM	35	15.12			
	15.03.08	2:-29:-59 PM	240	1.89			
	15.03.08	5:30:00 PM	480	No Sample			
	15.03.08	10:-29:-59 P	720	No Sample			
	16.03.08	9:30:00 AM	1,440	No Sample			
10	DECLINED				M	-	-
11	17.03.08	3:10:00 PM	0	LOW	F	160	5
	17.03.08	4:-19:-59 PM	30	7.98			
	17.03.08	8:-19:-59 PM	270	5.68			
	17.03.08	2:24:00 PM	674	No Sample			
	18.03.08	3:15:00 AM	725	< 0.27			
	18.03.08	3:20:00 PM	1,450	LOW			
12	18.03.08	9:15:00 AM	0	LOW	M	150	2
	18.03.08	10:-9:-59 AM	35	15.09			
	18.03.08	1:20:00 PM	245	1.57			
	18.03.08	5:20:00 PM	485	0.44			
	18.03.08	9:15:00 PM	720	LOW			
	19.03.08	9:15:00 AM	1,440	LOW			
13	19.03.08	9:-14:-59 PM	0	LOW	M	52.0	5
	19.03.08	9:15:00 PM	30	19.36			
	20.03.08	1:15:00 AM	270	1.31			
	20.03.08	5:15:00 AM	510	0.45			
	20.03.08	9:20:00 AM	755	0.47			
	20.03.08	9:20:00 PM	1,475	LOW			
14	24.03.08	2:10:00 PM	0	LOW	F	200	5
	24.03.08	3:-4:-59 PM	45	13.14			
	24.03.08	7:-4:-59 PM	285	2.47			
	24.03.08	11:00:00 PM	530	0.67			
	25.03.08	2:10:00 AM	720	No Sample			
	25.03.08	16:30	1,580	LOW			
15	24.03.08	2:00:00 PM	0	No Sample	M	120	5
	24.03.08	3:-9:-59 PM	50	10.92			
	24.03.08	7:-29:-59 PM	270	1.72			
	24.03.08	11:00:00 PM	540	0.76			
	25.03.08	2:00:00 AM	720	No Sample			
	25.03.08	4:00:00 PM	1,560	No Sample			
16	23.03.08	8:-29:-59 PM	0	< 0.27	F	56	2
	23.03.08	8:05:00 PM	35	8.91			
	24.03.08	1:12:00 AM	342	6.56			
	24.03.08	4:05:00 AM	515	6.75			
	24.03.08	9:00:00 AM	810	3.84			
	24.03.08	8:05:00 PM	1,475	No Sample			
17	11:03:08	8:-14:-59 PM	0	LOW	M	40	5
	11:03:08	8:20:00 PM	35	6.03			
	24.03.08	0:20:00 AM	275	0.98			
17	24.03.08	4:20:00 AM	515	0.92	M	40	5
	24.03.08	9:30:00 AM	825	2.01			
	24.03.08	10:-19:-59 P	1,555	< 0.27			
18	23.03.08	8:00:00 PM	0	2.89	F	40	5
	23.03.08	9:-19:-59 PM	40	16.89			

	24.03.08	1:-19:-59 AM	280	4.33			
	24.03.08	5:-19:-59 AM	520	3.85			
	24.03.08	9:20:00 AM	800	4.17			
	24.03.08	9:-19:-59 PM	1,480	6.44			
19	21.03.08(with drew)	3:00:00 PM	0	LOW	F	-	-
	21.03.08	4:-24:-59 PM	35	14.46			
	21.03.08	8:-24:-59 PM	275	1.32			
	21.03.08	0:-24:-59 PM	515	No Sample			
	22.03.08	4:-24:-59 AM	755	No Sample			
	22.03.08	4:-24:-59 PM	1,475	No Sample			
20	27.03.08	6:00:00 PM	0	LOW	F	82	5
	27.03.08	7:-14:-59 PM	45	9			
	27.03.08	10:20:00 PM	260	3.92			
	28.03.08	2:00:00 AM	480	No Sample			
	28.03.08	6:00:00 AM	720	No Sample			
	28.03.08	7:00:00 PM	1,500	< 0.27			

Appendix 7 (continued)

Patient code	Start Creatinine mg/dl	End Creatinine mg/dl	Bac-tec	Height (cm)	Weight (Kg)	Age (months)	Other Conditions	Other Drugs
1	0.4977	0.4977	0	85	11	27	None	x-pen
2	0.4411	0.4411	0	102	16	66	None	x-pen and paracetamol
3	0.3393	0.3393	0	78	12	26	None	x-pen and prednisolone
4	0.3393	2.3076	0	115	15	72	TB	rifater and x-pen
5	Withdrew	-	-	-	-	-	-	-
6	0.7918	0.8597	0	107	12	48	BRONCHOSPASMS	x-pen, salbutamol and prenisolone
7	0.5769	0.5769	0	78	11	24	BRONCHOSPASMS	x-pen, salbutamol and ascoril
8	0.4298	0.5203	0	76	6	24	RICKETS AND TB	rifater, x-pen, co-artem, flagyl, vit a, mebendazole,ascoril, multivit
9	Early discharge	-	-	-	-	-	-	-
10	Withdrew	-	-	-	-	-	-	-
11	0.4185	0.4751	0	157	32	132	INFECTIVE ENDOCARDITIS, RHD, SEVERE ANAEMIA	x-pen, brufen, lasix
12	0.5542	0.5542	0	105	21	72	BRONCHOSPASMS	x-pen
13	0.2941	0.3846	0	65	9	24	None	vit a, x-pen
14	0.5316	0.6561	0	135	20	96	None	x-pen, paracetamol, eftriaxone, levamisol
15	0.6108	0.6900	1	116	18	86	TB, PLURAL EFFUSSION	rifater, xpen
16	0.4072	1.6289	0	78	8	24	None	x-pen
17	0.4072	0.4072	0	81	9	24	None	x-pen
18	0.5090	0.5090	0	70	8	24	CLINICAL MALARIA	xpen, co-artem
19	Withdrew	-	0	-	-	-	-	-
20	0.4298	0.45248	0	101	11	42	SEVERE ANAEMIA	xpen, paracetamol

APPENDIX 8
Plasma Gentamicin Concentration (µg/mL) vs. Time (hours)



Plasma Gentamicin Concentration (µg/mL) vs. Time (hours)