

# Evaluation of Gentamicin Dosage Regimen and Route of Administration Based on Achieved Serum Concentrations in Neonates

Chuan Poh Lim (✉ [limcp87@gmail.com](mailto:limcp87@gmail.com))

Singapore General Hospital

Samuel Rocky Candra

Singapore General Hospital

Priyantha Ebenezer Edison

Singapore General Hospital

Mary Grace Tan

Singapore General Hospital

Amanda Mei Hui Yong

Singapore General Hospital

Yufei Chen

Cheo Lian Yeo

Singapore General Hospital

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## Research Article

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# Abstract

**Purpose:** Combination antibiotics consisting beta-lactam and aminoglycoside are commonly utilized in the treatment of neonatal septicaemia. The aims of this study were (1) to determine safety and efficacy of the revised gentamicin dosage regimen and (2) to compare intravascular (IV) versus intramuscular (IM) route of gentamicin administration, in term of attaining peak and trough serum concentration targets.

**Methods:** This was a retrospective study from 2012 to 2017. All neonates who received gentamicin with therapeutic drug monitoring performed were included in this study. Data for all eligible neonates were collected from electronic medical records and included demographics, serum creatinine levels, the complete gentamicin dosing and concentration history.

**Results:** A total of 737 neonates who received the correct institutional gentamicin dosage regimen ( $\pm 5\%$  of the intended dose) were included in this study. There were 635 trough concentrations (within 30 minutes prior to subsequent dose) and 430 peak concentrations (60 to 90 minutes post administration) included in the comparison of IV and IM route of administration. With the revised dosage regimen, 91% of peak and 98% of trough concentrations were found within therapeutic range. There was no difference in terms of proportion of trough concentrations within therapeutic range for IV as compared to IM (97.8 vs 98.6%,  $p = 0.556$ ) while IM resulted in a higher proportion of peak concentrations within therapeutic range (86.1 vs 97.0%,  $p < 0.001$ ).

**Conclusions:** The current institutional gentamicin dosage regimen is safe and effective in attaining therapeutic targets. Intramuscular injection can be an alternative route of administration for gentamicin in neonates.

## Introduction

Neonatal sepsis remains a major cause of morbidity and mortality in new-borns; with an incidence of up to 170/1000 live births [1]. Immaturity of the immune system, combined with the use of invasive procedures such as insertion of venous catheter and endotracheal intubation, renders a higher risk of nosocomial infection in neonates [2]. Combination antibiotics consisting of beta-lactam and aminoglycoside are commonly utilised in neonatal septicaemia (includes both early onset and late onset sepsis). The spectrum of activity of aminoglycoside include coverage for both gram negative bacilli as well as synergistic activity for gram positive organism when used in combination with a beta-lactam.

Gentamicin is the most commonly prescribed antibiotic to neonates in the United Kingdom (UK) [3]. It was found in an American study that 57.5% of all neonates discharged from the neonate intensive care unit had received gentamicin treatment [4]. The UK National Institute of Health and Care Excellence (NICE) guideline recommends the use of gentamicin (in combination with a penicillin) as first line therapy in neonates with suspected early onset sepsis [5]. Gentamicin exhibits concentration-dependent kill properties as well as post-antibiotic effect. Target peak concentration of  $> 5\text{mg/L}$  and trough

concentration of < 2mg/L has been quoted in literature as a measure of efficacy and safety for gentamicin. While the risk of aminoglycoside induced nephrotoxicity and ototoxicity remains controversial in the neonatal population, it remains prudent to monitor for the levels to ensure nil drug accumulation. Based on current literature, dosing of gentamicin is based on postmenstrual age (PMA) and postnatal age [6]. Additionally, current evidence suggest for the use of aminoglycoside extended dosing interval (dosage interval typically 24 hours in term and 36–48 hours in preterm neonates) as compared to traditional dosing (dosage interval typically 8–12 hours in term and 12–24 hours in preterm neonates) so as to reduce the risk of serum drug concentrations outside the therapeutic range [7]. At the Singapore General Hospital, the institutional dosage regimen for gentamicin was revised in year 1999 to once daily dosing primarily being aimed at reducing drug toxicity. The empiric dosing of gentamicin used by the institution is based solely on PMA, with peak and trough levels obtained pre and post-3rd dose to guide subsequent dosing.

The primary aim of the study was to evaluate adequacy of the current hospital gentamicin dosing protocol in achieving the target peak and trough serum concentrations. The secondary aim of the study was to compare intramuscular (IM) versus intravenous (IV) route of administration for gentamicin, as well as to evaluate and correlate the peak and trough concentrations with clinical outcomes in terms of efficacy and safety.

## Materials And Methods

All neonates managed in the Department of Neonatal and Developmental Medicine, Singapore General Hospital over the period of Nov 2012 and Oct 2017 who received gentamicin were included in this retrospective chart review. Approval to conduct this study was granted by the SingHealth Centralised Institutional Review Board (reference 2018/2546). Gentamicin doses were administered via IV infusion over a nominal duration of 30 minutes or IM injection as once daily dosing based on the neonate's postmenstrual age; 2.5mg/kg, 3.5mg/kg, and 4.5mg/kg in neonates < 30 weeks, 30–36 weeks and  $\geq$  37 weeks respectively.

Therapeutic drug monitoring was typically performed at the third dose of the dosing regimen where steady state was assumed to be attained. Trough concentrations were taken within 30 min preceding a dose, whereas peak concentrations were taken 1 h after IM injection or 30 minutes after the end of an intravenous infusion. Random concentrations were also considered if the timings of blood sampling were documented.

Data for all eligible neonates were collected from electronic medical records using Redcap and included demographics, serum creatinine (sCr), the complete gentamicin dosing and concentration history, indications for gentamicin use, culture results, and information regarding concomitant nephrotoxic agents. Neonates with ambiguous gentamicin dosing and serum concentrations, congenital kidney disease, major congenital heart disease (diagnosis other than ventricular septal defect, atrial septal defect, or patent ductus arteriosus), acute kidney injury, or unstable renal function and those on

extracorporeal membrane oxygenation during gentamicin therapy were excluded. The weight of the neonate at gentamicin initiation was recorded. The last measured weight would be carried forward if no measurement was done on the day of gentamicin therapy initiation. Serum creatinine levels around the time ( $\pm 48$  hours) of all gentamicin concentration measurements were recorded and updated throughout the gentamicin course. Where the sCr readings within  $\pm 48$  hours of assay of gentamicin concentrations were unavailable, the closest available sCr reading was imputed.

We defined correct gentamicin dose as  $\pm 5\%$  of the calculated dose based on the weight at gentamicin therapy initiation. Appropriate trough concentration sampling time was defined as  $\leq 30$  minutes preceding a dose, while appropriate peak sampling time was defined as 60–90 minutes after an IM injection or initiation of an IV infusion. Both peak and trough concentrations were deemed appropriate when done on or after the 3rd dose of gentamicin. The serum concentration targets were 5–12mg/L for peak and  $< 2$ mg/L for trough concentration.

In the analysis, categorical data were reported as number (percentages). Normally distributed data were reported as mean  $\pm$  standard deviation while non-normally distributed data were reported as median (interquartile range). For comparison between IM versus IV route of administration, Chi-square test or Fisher's Exact test was used for categorical data while continuous data was analysed using independent sample t-test. A  $p$  value of  $< 0.05$  was considered statistically significant.

## Results

A total of 825 neonates fulfilled the inclusion and exclusion criteria of this study, 737 neonates received the recommended institutional gentamicin dosage regimen with serum concentration monitored at appropriate timing (Fig. 1). Patient demographics and characteristics were summarised in Table 1. Median (interquartile range) gestational age was 34 weeks (31 to 39 weeks) and 2,200g (1,413 to 3,065g) for birth weight. There were 635 trough concentrations and 430 peak concentrations performed at the appropriate timing and included in the comparison between IV and IM route of administration. Of these serum concentrations, 91% of the peak and 98% of the trough levels were within the targeted therapeutic ranges of 5–12mg/L and  $< 2$ mg/L respectively (Fig. 2).

Table 1  
Demographics and characteristics of study subjects (n = 737)

Variables	n (%)
Male	423 (57.4)
Race	338 (45.9)
Chinese	219 (29.7)
Malay	108 (14.6)
Indian	72 (9.8)
Others	
Postmenstrual age at therapy initiation, weeks	2 (0.3)
< 24 <sup>+0</sup>	262 (35.5)
24 <sup>+0</sup> – 32 <sup>+6</sup>	157 (21.3)
33 <sup>+0</sup> – 36 <sup>+6</sup>	316 (42.9)
≥ 37 <sup>+0</sup>	
Weight at therapy initiation, kg	104 (14.1)
< 1.0	102 (13.9)
1.0–1.49	531 (72.0)
≥ 1.5	
SGA	101 (13.7)
SCr at initiation, μmol/L	71 (60,81) <sup>#</sup>
Concomitant nephrotoxic agent	70 (9.5)
Aciclovir	1
Ibuprofen	33
Indomethacin	2
Fluconazole	34

SCr, serum creatinine; SGA, small for gestational age

<sup>#</sup>median (IQR)

<sup>^</sup> includes both confirmed and presumed intestinal infections

Variables	n (%)
Indication	642 (87.1)
Presumed sepsis	4 (0.5)
Bacteremia	93 (12.6)
<i>E. coli</i>	7 (0.9)
Pneumonia	2 (0.3)
Intra-abdominal infection <sup>^</sup>	1 (0.1)
Meningitis	1 (0.1)
<i>Acinetobacter sp.</i>	
<i>E. coli</i>	
Empiric	
SCr, serum creatinine; SGA, small for gestational age	
#median (IQR)	
<sup>^</sup> includes both confirmed and presumed intestinal infections	

In terms of route of administration, there was no difference in the proportion of trough concentrations that were within therapeutic range for IV as compared to IM, while IM resulted in a higher proportion of peak concentrations within therapeutic range, as well as higher trough concentrations (Table 2). Sixty-two (8.4%) neonates required dosage adjustment for gentamicin and 20 (2.7%) neonates required change in antibiotic therapy: 14 of whom had antibiotic escalated to a broader spectrum antibiotic; 5 changed to culture directed antibiotic; 1 changed to an alternative antibiotic due to acute kidney injury. Forty-seven (6.4%) neonates failed hearing screening done using AABR and/or OAE: 1 had trough concentration of 2.2mg/L; 2 had peak concentrations of 12.8mg/L and 13.4mg/L while the remaining 44 neonates had normal gentamicin serum concentrations.

Table 2  
Comparison of trough and peak serum concentration levels of subjects on IV versus IM gentamicin

Serum concentration	IV	IM	<i>p</i>
Trough, mg/L (mean ± SD)	0.97 ± 0.44	1.19 ± 0.40	< 0.001 <sup>#</sup>
Within therapeutic range, %	97.8	98.6	0.556 <sup>∞</sup>
Peak, mg/L (mean ± SD)	9.09 ± 2.30	8.97 ± 1.77	0.562 <sup>#</sup>
Within therapeutic range, %	86.1	97.0	0.000 <sup>∞</sup>
<sup>#</sup> Independent sample t-test			
<sup>∞</sup> Chi-square test or Fisher's Exact Test where appropriate			

Records of 37 neonates (10 term and 27 preterm) who failed the initial hearing screen were available for review. Of the 10 term neonates who failed hearing screen, 6 had normal hearing on further evaluation or close developmental surveillance. Four neonates had significant hearing impairment and had pertinent risk factors such as Down syndrome, listeria meningitis, perinatal depression and congenital hydrocephalus. Of the 27 preterm neonates, 24 were very preterm infants with gestational age < 33 weeks. Of whom 3 had hearing impairment requiring further management. None of the neonates with significant hearing impairment or hearing impairment requiring further management had supra-therapeutic gentamicin levels.

Of all infants on gentamicin therapy, 2 neonates had renal impairment defined as rise in serum creatinine by at least 1.5 times the baseline. Renal function improved with hydration in the neonate with severe intra-ventricular haemorrhage. The other extreme preterm neonate had severe acute kidney injury following umbilical venous catheter extravasation and demised. The peak and trough concentrations of gentamicin were within the therapeutic range in both neonates.

## Discussion

Gentamicin is one of the most commonly used antibiotic in the treatment of neonatal sepsis. Early onset sepsis in neonates is usually due to vertical transmission during vaginal delivery or by ascending contamination of amniotic fluid, from bacteria colonization or infection of the mother's lower genital tract [8]. It is hydrophilic with a volume of distribution of 0.45L/kg in neonates, which suggests that it is mainly distributed in the intravascular compartment [9]. This property makes gentamicin an ideal agent for this indication as it is able to achieve bloodstream bacterial clearance effectively.

Our institution dosage regimen was revised to once daily dosing in year 1999, as IM injection route. There were 248 neonates involved in the study and the dosage regimen was revised in 2 phases [10]. The same dosage regimen was utilised since, as attainment of therapeutic serum concentration has been observed

to be consistent. Findings of current study showed that 91% of peak and 98% of trough concentrations were within therapeutic range. As a result of findings from the present study, we have since revised our therapeutic drug monitoring practice in neonates to only monitor serum trough concentration prior to the 3rd dose of gentamicin. Monitoring of serum peak concentration is reserved for neonates who have inadequate clinical response toward antibiotic treatment at the discretion of physicians. The revised practice has significantly reduced the amount of logistic duties such as reduction in the number of blood sampling, reduction in the cost of laboratory tests as well as reduction in workload of medical staffs.

As gentamicin exhibits concentration dependent kill, its antimicrobial effect can be optimized through administration of a larger dose to achieve higher serum concentration. Once daily dosing of gentamicin has been found to be more efficacious as well as a better safety profile [11, 12]. However, the commonly used drug reference in neonates, Neofax, recommends gentamicin frequency to be prolonged to 36 or 48 hours for neonates with PMA < 35 weeks in their first week of life, with a slightly higher dosage recommendation for different age group [6].

Gentamicin dosage regimen recommended by Neofax is supported by results from 2 studies [13, 14]. Population pharmacokinetic parameter estimates from study by Stolk and colleagues were calculated from 725 serum gentamicin concentrations obtained in 177 neonates of 24 to 42 weeks' gestational age in their first week of life. The initial peak and trough concentrations were predicted to be 6 to 10mg/L and less than 1mg/L, respectively, based on population pharmacokinetic parameters [13]. In another larger study that involved 1854 neonates with birth weight 390–5200g, postnatal age 0–27 days, Monte Carlo simulations on the basis of validated models were undertaken to evaluate the attainment of target peak (5–12mg/L) and trough (< 0.5mg/L) concentrations. The above standard dosing regimen attained trough concentrations of 1mg/L or less and 0.5mg/L or less in 50% and 17%, respectively, of dose simulations (n = 5,000). Likewise, peak concentrations of 5 to 12mg/L, greater than 12mg/mL, and less than 5mg/L were attained in 75%, 20%, and 6%, respectively, of dose simulations [14].

Post-antibiotic effect (PAE) allows antibiotic doses to be administered less frequently. The PAE of gentamicin on *E. coli* was studied by Stubbings et al [15]. When exposed to gentamicin concentration of 5 times above the minimal inhibitory concentration (MIC) for 60 minutes, *E. coli* RNA synthesis remained inhibited for only 1 hour after gentamicin exposure while DNA synthesis recovered between 2–3 hours, before the onset of growth. Gudmundsson et al. investigated the PAE of beta-lactam and aminoglycosides combination on *S. aureus*, *P. aeruginosa*, *E. coli* and *K. pneumonia* [16]. When used against *S. aureus* and *P. aeruginosa*, the antibiotic combination prolonged PAE by 1.0–3.3 hours but no prolongation was observed against *E. coli* and *K. pneumonia*. It remains unknown if gentamicin serum concentration will drop to a sub-therapeutic level with the extended dosing frequency of more than 24 hours, thereby potentially affecting gentamicin efficacy. Future study should focus on developing a validated population pharmacokinetic model which can then be utilised to determine the most appropriate dosage regimen through Monte Carlo simulation.

A total of 47 (6.4%) neonates who received gentamicin failed inpatient hearing screening done using AABR and /or OAE. Aminoglycoside ototoxicity is associated with swelling of nerve terminals within 15–18 hours after exposure and death of inner ear hair cells 1–2 days post exposure [17, 18]. There were no association found between gentamicin dose measures and hearing screen failure, while another study suggests long course gentamicin may be responsible for the increased ototoxicity [19, 20]. Mitochondrial DNA mutations have been linked to sensitivity to aminoglycosides and associate with hearing loss in the absence of aminoglycosides exposure [21].

Aminoglycoside induced nephrotoxicity is characterised by selective targeting of the proximal tubule epithelial cells within the renal cortex. Approximately 5% of the administered dose accumulates within these cells after glomerular filtration [22]. Once inside the cell, aminoglycosides accumulate within lysosomes, the Golgi apparatus and endoplasmic reticulum (ER) causing lysosomal phospholipidosis [23–25]. Leakage of aminoglycosides from the lysosomal structures into the cytoplasm then acts on the mitochondria, activating the intrinsic pathway of apoptosis which in turn leads to formation of reactive oxygen species [25–27]. Renal impairment was found in 2 neonates who received gentamicin, 1 of whom received both gentamicin and amikacin during their hospital stay. The renal function improved with supportive management in one neonate while the other extreme preterm infant developed severe AKI as per the modified KDIGO classification due to umbilical venous catheter extravasation and demised within the first week of life [28]. A retrospective study of nephrotoxin exposure in preterm neonates documented gentamicin exposure in 86.0% of the 107 neonates, 26.2% of whom developed AKI [29].

Intramuscular gentamicin administration was found to be similar to intravenous route, in term of the serum concentration achieved in this study. This finding is in agreement with previous gentamicin pharmacokinetic studies in neonates [30, 31]. Chow-Tung et al. compared pharmacokinetic profile of gentamicin after IV and IM administration in 16 neonates during their first week of life [31]. Mean serum concentration obtained from both IV and IM route were similar ( $p > 0.05$ ). Similar findings were reported in the kinetic study by Paisley et al [30]. Intravenous and intramuscular routes of administration for gentamicin were alternated in 11 infants, the resultant serum concentrations did not differ significantly.

Our study was not without limitations. First, the retrospective nature of this study, implies a huge reliance on the documentation of dose administration and blood sampling time by the nurses. Second, missing data for serum creatinine was imputed using last observation carried forward technique. However, most of the neonates had their renal panel checked at least once during the course of gentamicin treatment.

In conclusion, the current institutional gentamicin dosage regimen is safe and effective in attaining therapeutic targets. Intramuscular injection can be an alternative route of administration for gentamicin in neonates.

## Abbreviations

ER                      Endoplasmic reticulum

IV	Intravenous
IM	Intramuscular
MIC	Minimal inhibitory concentration
NICE	National Institute of Health and Care Excellence
PAE	Post-antibiotic effect
PMA	Postmenstrual age
sCr	Serum creatinine
UK	United Kingdom

## Declarations

### Funding Sources

None to declare

### Competing interests

The authors have no competing interests to declare

### Ethics approval

Approval to conduct this study was granted by the SingHealth Centralised Institutional Review Board (reference 2018/2546).

### Consent to participate

Waiver of informed consent was granted by the SingHealth Centralised Institutional Review Board

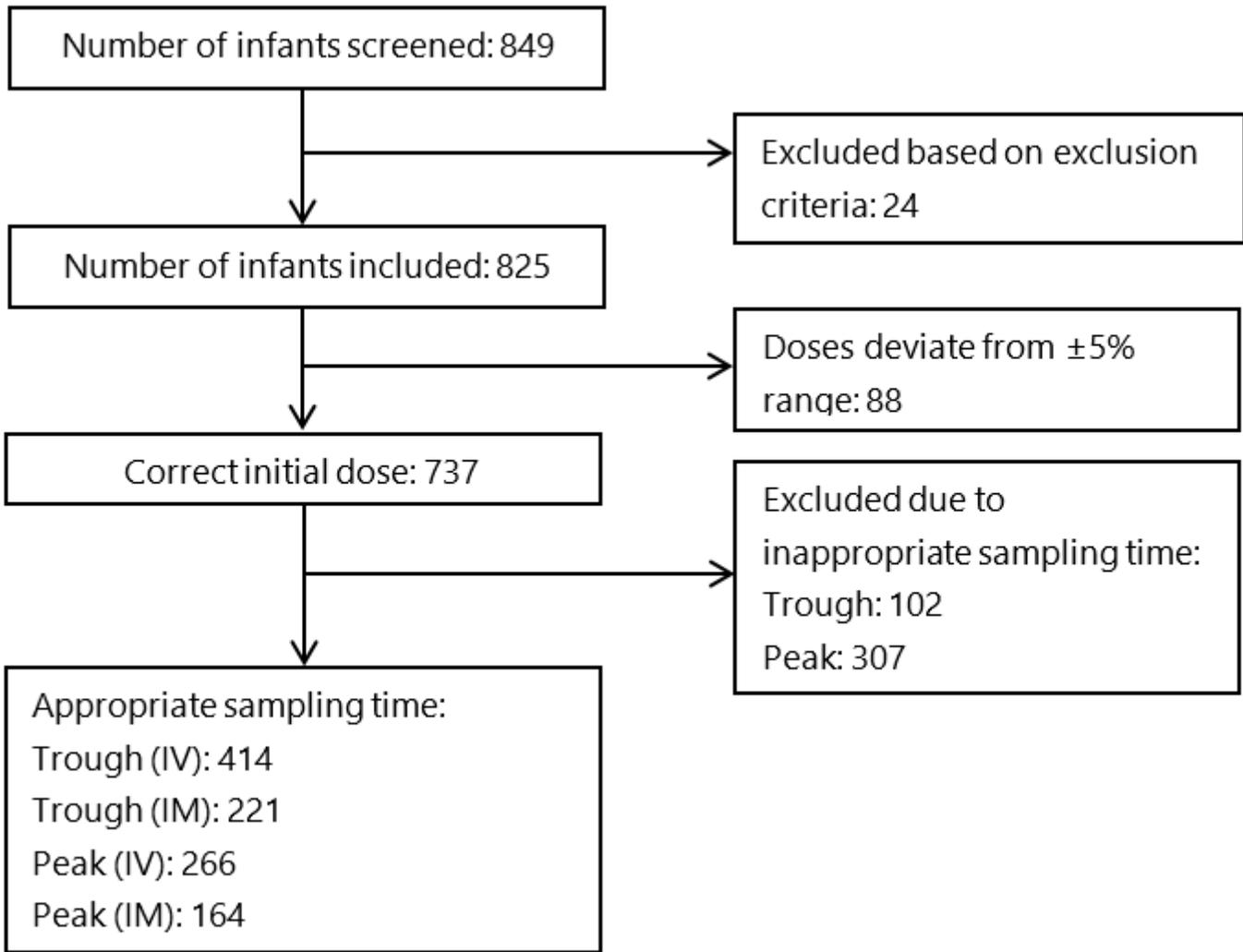
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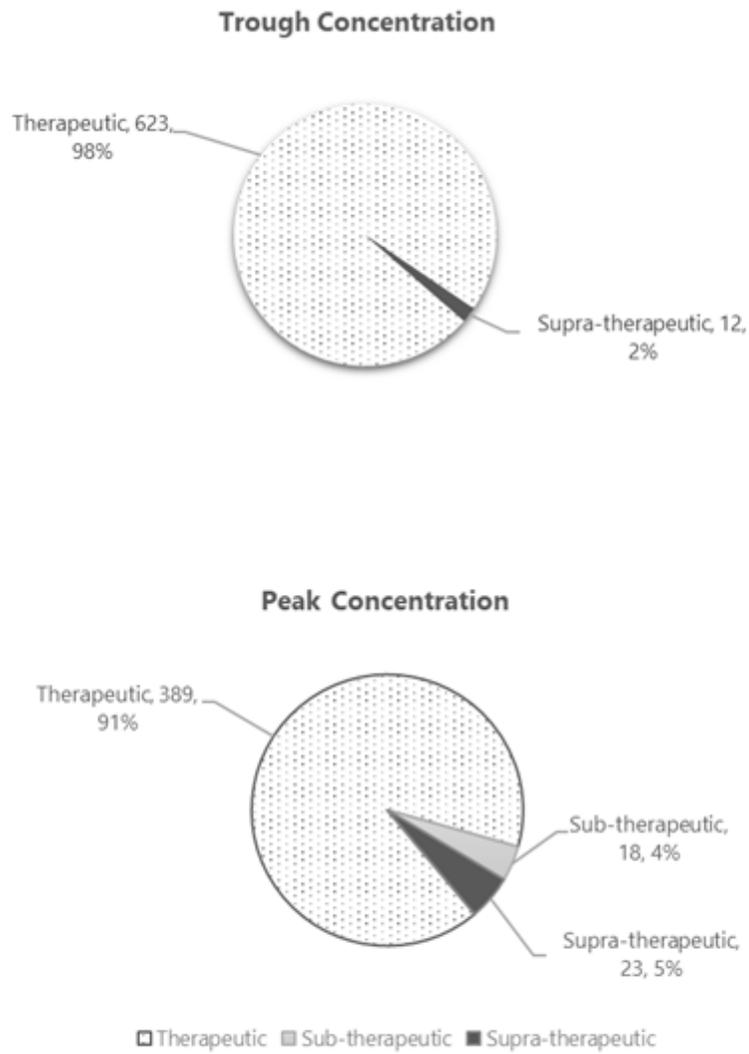
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## Figures



**Figure 1**

Flow chart of study subjects



**Figure 2**

Gentamicin serum concentrations