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Research Article

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

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- Gentamicin
- Dosage regimen
- Neonates
- Serum concentration
- Route of administration

Abstract

Background: Combination antibiotics consisting beta-lactam and aminoglycoside are commonly utilized in the treatment of neonatal septicemia. 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 (± 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.

ABBREVIATIONS

AABR: Automated Auditory Brainstem Response; AKI: Acute Kidney Injury; DNA: Deoxyribonucleic Acid; ER: Endoplasmic Reticulum; IV: Intravenous; IM: Intramuscular; KDIGO: Kidney Disease Improving Global Outcomes; MIC: Minimal Inhibitory Concentration; NICE: National Institute of Health and Care Excellence; OAE: Otoacoustic Emissions; PAE: Post-antibiotic Effect; PMA: Postmenstrual Age; RNA: Ribonucleic Acid; sCr: Serum Creatinine; UK: United Kingdom

INTRODUCTION

Neonatal sepsis remains a major cause of morbidity and mortality in newborns; 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 utilized in neonatal septicemia (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]. Previous studies showed similar serum concentration attainment for both intramuscular and intravenous gentamicin in neonates [6,7]. Intramuscular route allows timely administration of first dose gentamicin in neonates without vascular access. Gentamicin exhibits concentration-dependent kill properties as well as post-antibiotic effect. Target peak concentration of > 5mg/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 [8]. 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 [9]. 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) on 27 June 2018. 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 ≥ 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 (± 48 hours) of all gentamicin concentration measurements were recorded and updated throughout the gentamicin course. Where the sCr readings within ± 48 hours of assay of gentamicin concentrations were unavailable, the closest available sCr reading was imputed.

We defined correct gentamicin dose as ± 5% of the calculated dose based on the weight at gentamicin therapy initiation. Appropriate trough concentration sampling time was defined as ≤ 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 < 2mg/L for trough concentration.

In the analysis, categorical data were reported as number (percentages). Normally distributed data were reported as mean ± 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 analyzed 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 (Figure 1). Patient demographics and characteristics were summarized 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 < 2mg/L respectively (Figure 2).

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

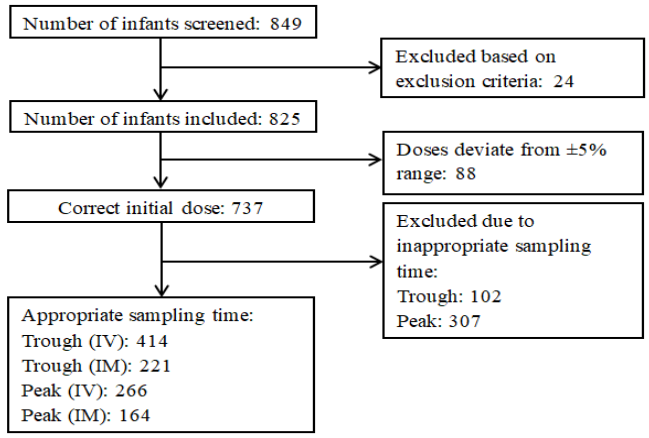

Figure 1 Flow chart of study subjects.

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

Variables	n (%)
Male	423 (57.4)
Race	
Chinese	338 (45.9)
Malay	219 (29.7)
Indian	108 (14.6)
Others	72 (9.8)
Postmenstrual age at therapy initiation, weeks	
< 24^{+0}	2 (0.3)
24^{+0} – 32^{+6}	262 (35.5)
33^{+0} – 36^{+6}	157 (21.3)
≥ 37^{+0}	316 (42.9)
Weight at therapy initiation, kg	
< 1.0	104 (14.1)
1.0 – 1.49	102 (13.9)
≥ 1.5	531 (72.0)
SGA	101 (13.7)
SCr at initiation, µmol/L	71 (60,81)#
Concomitant nephrotoxic agent	70 (9.5)
Aciclovir	1
Ibuprofen	33
Indomethacin	2
Fluconazole	34
Indication	
Presumed sepsis	642 (87.1)
Bacteremia	
E. coli	4 (0.5)
Pneumonia	93 (12.6)
Intra-abdominal infection^	7 (0.9)
Meningitis	
Acinetobacter sp.	2 (0.3)
E. coli	1 (0.1)
Empiric	1 (0.1)

SCr, serum creatinine; SGA, small for gestational age
#median (IQR)
^ includes both confirmed and presumed intestinal infections

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 automated auditory brainstem response (AABR) and/or otoacoustic emissions (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.

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

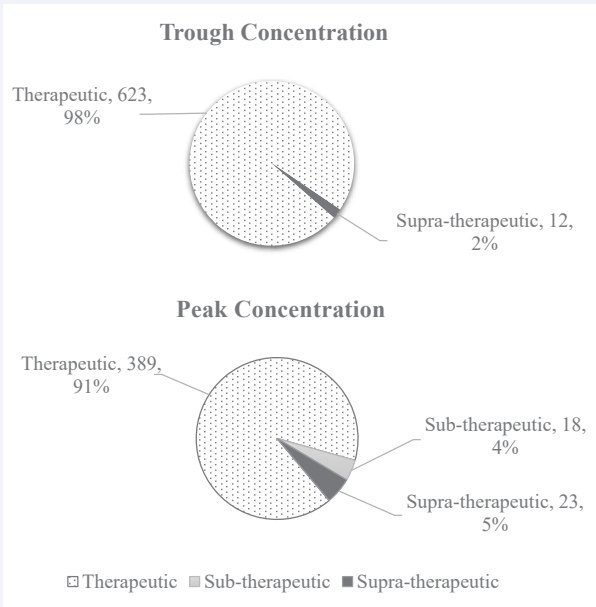

Figure 2 Gentamicin serum concentrations.

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

Serum concentration	IV	IM	*p*
Trough, mg/L (mean ± SD)	0.97 ± 0.44	1.19 ± 0.40	<0.001#
Within therapeutic range, %	97.8	98.6	0.556∞
Peak, mg/L (mean ± SD)	9.09 ± 2.30	8.97 ± 1.77	0.562#
Within therapeutic range, %	86.1	97.0	<0.001

Independent sample t-test
∞Chi-square test or Fisher's Exact Test where appropriate

in the neonate with severe intra-ventricular hemorrhage. 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 [10]. 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 [11]. 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 [12]. The same dosage regimen was utilized 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 [13,14]. 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 [8].

Gentamicin dosage regimen recommended by Neofax® is supported by results from 2 studies [15,16]. 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 [15]. 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 [16].

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. [17]. When exposed to gentamicin concentration of 5 times above the minimal inhibitory concentration (MIC) for 60 minutes, *E. coli* ribonucleic acid (RNA) synthesis remained inhibited for only 1 hour after gentamicin exposure while deoxyribonucleic acid (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* [18]. 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 utilized 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 [19,20]. 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 [21,22]. Mitochondrial DNA mutations have been linked to sensitivity to aminoglycosides and associate with hearing loss in the absence of aminoglycosides exposure [23].

Aminoglycoside induced nephrotoxicity is characterized 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 [24]. Once inside the cell, aminoglycosides accumulate within lysosomes, the Golgi apparatus and endoplasmic reticulum (ER) causing lysosomal phospholipidosis [25-27]. 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 [25,28,29]. 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 acute kidney injury (AKI) as per the modified Kidney Disease Improving Global Outcomes (KDIGO) classification due to umbilical venous catheter extravasation and demised within the first week of life [30]. 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 [31].

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 [6,7]. Chow-Tung et al., compared pharmacokinetic profile of gentamicin after IV and IM administration in 16 neonates during their first week of life [6]. 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. [7]. Intravenous and intramuscular routes of administration for gentamicin were alternated in 11 infants, the resultant serum concentrations did not differ significantly.

Our study included a large number of subjects over a 5-year period. It is one of the largest studies that examined gentamicin dosage regimen in neonates. However, 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.

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.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were performed by Chuan Poh Lim, Samuel Rocky Candra, Ebenezer Priyantha Edison, Mary Grace Sy Tan, Mei Hui Amanda Yong and Yufei Chen. Data analysis was performed by Chuan Poh Lim, Samuel Rocky Candra. The first draft of the manuscript was written by Chuan Poh Lim. All authors commented on previous versions of the manuscript, read and approved the final manuscript.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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.

REFERENCES

1. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014; 5: 170-178.
2. Schelonka RL, Infante AJ. Neonatal immunology. Semin Perinatol. 1998; 22: 2-14.
3. Turner MA, Lewis S, Hawcutt DB. Prioritising neonatal medicines research: UK Medicines for Children Research Network scoping survey. BMC Pediatr. 2009; 9: 50.
4. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. Pediatrics. 2006; 117: 1979-1987.
5. Team NGU. In: Evidence review for investigations before starting treatment for late-onset neonatal infection: Neonatal infection: antibiotics for prevention and treatment: Evidence review Ged. National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021.
6. Chow-Tung E, Malalis L, Lau A, Gurwich E. 1453 comparison of intravenous and intramuscular administration of gentamicin in neonates. Pediatr Res. 1981; 15: 685.
7. Paisley JW, Smith AL, Smith DH. Gentamicin in newborn infants. Comparison of intramuscular and intravenous administration. Am J Dis Child. 1973; 126: 473-477.
8. Truven Health Analytics I. Neofax® 2021. United States.
9. Nestaas E, Bangstad HJ, Sandvik L, Wathne KO. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2005; 90: F294-300.
10. Puopolo KM, Benitz WE, Zaoutis TE, Committee On F, Newborn, Committee On Infectious D. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics. 2018; 142.
11. Inc L. Lexi-drugs online Hudson (OH) 2021.
12. Lian WB, Yeo CL, Ho LY. Once-daily-dosing intramuscular gentamicin in neonates. Ann Acad Med Singap. 2012; 41: 227-229.
13. Miron D. Once daily dosing of gentamicin in infants and children. Pediatr Infect Dis J. 2001; 20: 1169-1173.
14. Rao SC, Srinivasjois R, Moon K. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2016; 12: CD005091.
15. Stolk LM, Degraeuwe PL, Nieman FH, de wolf MC, de Boer A. Population pharmacokinetics and relationship between demographic and clinical variables and pharmacokinetics of gentamicin in neonates. Ther Drug Monit. 2002; 24: 527-531.
16. Valitalo PA, van den Anker JN, Allegaert K, de Cock RFW, de Hoog Mathijs, Simons SHP, et al. Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates. J Antimicrob Chemother. 2015; 70: 2074-2077.
17. Stubbings W, Bostock J, Ingham E, Chopra I. Mechanisms of the post-antibiotic effects induced by rifampicin and gentamicin in Escherichia coli. J Antimicrob Chemother. 2006; 58: 444-448.
18. Gudmundsson S, Einarsson S, Erlendsdottir H, Moffat J, Bayer W, Craig WA. The post-antibiotic effect of antimicrobial combinations in a neutropenic murine thigh infection model. J Antimicrob Chemother. 1993; 31: 177-191.
19. Hirose K, Westrum LE, Cunningham DE, Rubel EW. Electron microscopy of degenerative changes in the chick basilar papilla after gentamicin exposure. J Comp Neurol. 2004; 470: 164-180.
20. Alharazneh A, Luk L, Huth M, Monfared A, Steyger PS, Cheng AJ, et al. Functional hair cell mechanotransducer channels are required for aminoglycoside ototoxicity. PLoS One. 2011; 6: e22347.
21. Cross CP, Liao S, Urdang ZD, Srikanth P, Garinis AC, Sterger PS. Effect

of sepsis and systemic inflammatory response syndrome on neonatal hearing screening outcomes following gentamicin exposure. Int J Pediatr Otorhinolaryngol. 2015; 79: 1915-1919.

22. Puia-Dumitrescu M, Bretzius OM, Brown N, Fitz Henley JA, Ssengonzi R, Wechsler CS, et al. Evaluation of gentamicin exposure in the neonatal intensive care unit and hearing function at discharge. J Pediatr. 2018; 203: 131-136.

23. Jing W, Zongjie H, Denggang F, Na H, Bin Z, Aifen Z, et al. Mitochondrial mutations associated with aminoglycoside ototoxicity and hearing loss susceptibility identified by meta-analysis. J Med Genet. 2015; 52: 95-103.

24. Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother. 1999; 43: 1003-1012.

25. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopes Hernandez AJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011; 79: 33-45.

26. Taber SS, Pasko DA. The epidemiology of drug-induced disorders: the kidney. Expert Opin Drug Saf. 2008; 7: 679-690.

27. Silverblatt FJ, Kuehn C. Autoradiography of gentamicin uptake by the rat proximal tubule cell. Kidney Int. 1979; 15: 335-345.

28. Regec AL, Trump BF, Trifillis AL. Effect of gentamicin on the lysosomal system of cultured human proximal tubular cells. Endocytotic activity, lysosomal pH and membrane fragility. Biochem Pharmacol. 1989; 38: 2527-2534.

29. Servais H, Van Der Smissen P, Thirion G, Tulkens PM. Gentamicin-induced apoptosis in LLC-PK1 cells: involvement of lysosomes and mitochondria. Toxicol Appl Pharmacol. 2005; 206: 321-333.

30. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr. 2012; 24: 191-196.

31. Rhone ET, Carmody JB, Swanson JR, Charlton JR. Nephrotoxic medication exposure in very low birth weight infants. J Matern Fetal Neonatal Med. 2014; 27: 1485-1490.