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Clinical Pharmacology of Gentamicin in Infants and Children

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Abstract

Gentamicin is an aminoglycoside antibiotic and it is active against aerobic gram-negative bacilli such as Pseudomonas, Klebsiella, and Escherichia coli. Gentamicin should be co-administered with a β-lactam antibiotic. This antibiotic is rapidly bactericidal as it inhibits bacterial cell protein synthesis. Bacterial killing is concentration dependent: the higher the concentration, the greater the rate of bacterial killing. Dosing recommendations are based on: (1) higher gentamicin peak concentrations, (2) post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic, and (3) less toxicity with less frequent gentamicin dosing, due to low renal gentamicin accumulation. When gentamicin trough concentration is > 2 µg/ml, intervals among gentamicin doses should be extended to yield gentamicin trough concentration < 2 µg/ml. In infants, gentamicin dose should be 4 – 5 mg/kg. Once-daily gentamicin dosing is preferred than twice- or thrice-daily gentamicin administration. Once-daily gentamicin dosing yields lower trough and higher peak gentamicin concentrations. The recommended peak and trough gentamicin serum concentrations range from 5 to 12 µg/ml, and from 0.5 to 1 µg/ml, respectively. In very-low-birth weight, gentamicin half-life and distribution volume are 12.9 hours and 0.72 l/kg, respectively. In small-for-gestational age infants, with an age ≤ 7 days of life, gentamicin half-life is longer, and clearance is lower than in infants appropriate-for-gestational age. Gentamicin increases the risk of hearing loos, and causes renal dysfunction. Ototoxicity rate in preterm infant's runs at 2-15% compared to 0.3% in full-term infants and it is permanent in 2-3% of cases, whereas nephrotoxicity is transient. Some bacteria may become resistant to gentamicin. The aim of this study is to review the published data on effects, pharmacokinetics, and bacterial-resistance of gentamicin in infants and children.

Keywords: Gentamicin, Gentamicin-dosing, effects, Pharmacokinetics, Bacterial-resistance, Infants, Children

Introduction

Gentamicin is widely used to treat gram-negative bacterial infection, but it is of variable efficacy for known staphylococcal sepsis. It has been given intravenously or intramuscularly. Gentamicin crosses the placenta, producing foetal levels that are about half of the maternal levels, but it has never been known to have caused ototoxicity in utero. Absorption from the gut it is too limited to disallow maternal use during lactation. Gentamicin is passive filtered unchanged by the glomerulus and concentrated in the urine. In healthy neonates the half-life decreases by more than 50% in the first 7-10 days after birth. Renal tubular damage is progressive with time and can even produce a Bartter-like syndrome (see reference 38). Cochlear impairment is uncommon in young children, but gentamicin can cause balance problems as well as high-tone deafness, and these can become permanent if early symptoms go unrecognized. Blood levels should always be measured in order to minimize these risks where facilities exist. It is at least as important to avoid simultaneous treatments with furosemide and to try to stop treatment after 7-10 days [1].

Aminoglycosides are only effective against many bacteria when the serum level is high enough to be potentially toxic. A high peak level (at least eight times the MIC) enhances the drug's bactericidal effect. Gram-negative organisms stop taking up the drug after an hour and only do so again 2-10 hours later ("adaptive resistance"); therefore, repeat treatment during this time is ineffective. Serious toxicity is predominantly seen with treatment longer than 7-10 days where there are sustained high trough serum levels and/or co-exposure to other ototoxic drugs. In children with normal renal function, treatment is optimized, and adverse effects are minimized, by following a once a day ("high peak low trough") policy. An increasing number of studies have now suggested that this is the right strategy to adopt in infants and children. When aminoglycosides are given more than once a day in children, the serum level will remain sub-therapeutic for many hours if an initial loading dose is not given (because of the large distribution volume). Gentamicin is frequently used in infants undergoing therapeutic hypothermia. These infants typically

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have renal impairment, and dose adjustment is frequently needed. A 4 mg/kg dose and a 36 hourly regimen are reported as best for these infants [1].

Gentamicin is an important agent for the treatment of many serious gram-negative bacillary infections. It is the aminoglycoside of first choice because of its lower cost and reliable activity against all but the most resistant gram-negative aerobes. Gentamicin preparations are available for parenteral, ophthalmic, and topical administration. The typical recommended intramuscular or intravenous dose of gentamicin sulphate, when used for the treatment of known or suspected gram-negative organisms, as a single agent or in combination therapy for adults with normal renal function is 5-7 mg/kg daily given over 30-60 min infusion. For patient's renal dysfunction, the interval may be extended. Several dosage schedules have been suggested for newborns and infants: 3 mg/kg once-daily for preterm newborns < 35 weeks of gestation; 4 mg/kg once-daily for newborns > 35 weeks of gestation; 5 mg/kg daily in two divided doses for neonates with severe infections; and 2-2.5 mg/kg every 8 hours for children up to 2 years of age. Peak plasma concentrations range from 4 to 10 µg/ml (dosing: 1.7 mg/kg every 8 hours) and 16-24 µg/ml (extended-interval dosing: 5 mg/kg once-daily). It should be emphasized that the recommended doses of gentamicin do not always yield desired concentrations. Periodic determination of the plasma concentration of gentamicin is recommended strongly. Gentamicin is absorbed slowly when it is applied as a cream. When gentamicin is applied to large areas of denuded body surface, as may be the case in burn patients, plasma concentrations can reach 4 µg/ml, and 2%-5% of the drug may appear in the urine [2].

Gentamicin is used in the treatment of infections caused by aerobic gram-negative bacilli (e.g. Pseudomonas, Klebsiella, and Escherichia coli). Gentamicin is used in combination with a β-lactam antibiotic. Dosing recommendations are based on: higher peak concentrations. There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic. There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Distribution volume is increased and clearance is decreased in infants with patent ductus arteriosus. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of gentamicin by penicillin-containing compounds appears to be a time, temperature-, and concentration dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in intravenous solutions or when the blood is at room temperature for several hours before the assay is performed. Transient and reversible tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity medications (e.g. furosemide and vancomycin) may increase these adverse effects. Increased neuromuscular blockade (i.e. neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in children with hypermagnesemia. Gentamicin is incompatible with amphotericin B, ampicillin, azithromycin, furosemide, imipenem-cilastatin, heparin, (concentrations > 1 unit/ml), indomethacin, mezlocillin, nafcillin, oxacillin, propofol, and ticarcillin-clavulanate [3]. Table 1 shows the dosing chart of gentamicin in infants. The recommended therapeutic serum concentrations of gentamicin in infants should be as follows: peak concentrations 5 to 12 µg/ml (or Cmax/MIC ratio greater than 8:1). Trough concentrations should range 0.5 to 1 µg/ml [3].

Literature Search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was April 2019. The following key words: "gentamicin infants effects", "gentamicin children effects", "gentamicin infants metabolism", "gentamicin children metabolism", "gentamicin infants pharmacokinetics", "gentamicin children pharmacokinetics", "gentamicin infants resistance", and "gentamicin children resistance" were used. In addition, the books "Neonatal Formulary" [1] and "NEOFAX" by Young and Mangum [3] were consulted. The manuscript was prepared according to the "Instructions for Authors".

Results

Mechanism of action of gentamicin

Gentamicin is rapidly bactericidal as it inhibits bacterial cell protein synthesis. Bacterial killing is concentration dependent: the higher the concentration, the greater the rate of bacterial killing. The ratio of the peak concentration to the organism's MIC is thus a key predictor of gentamicin efficacy. The inhibitory action of gentamicin persists after the serum concentration has fallen below the MIC, a phenomenon known as the "postantibiotic effect". These properties probably account for the efficacy of high-dose, extended-interval dosing regimens. Aminoglycosides, and thus gentamicin, diffuse through aqueous channels formed by porin proteins in the outer membrane of gram-negative bacteria to enter periplasmic space. Transport of aminoglycosides across the

Table 1: Doses and intervals among doses of gentamicin in infants of various postmenstrual and postnatal ages, by Young and Mangum [3]

Postmenstrual age (weeks)	Postnatal age (days)	Dose (mg/kg)	Intervals among doses (hours)
≤ 29*	0 to 7 8 to 28 ≥ 29	5 4 4	48 36 24
30 to 34	0 to 7 ≥ 8	4.5 4	36 24
≥ 35	All	4	24
*or significant asphyxia, patent ductus, treatment with indomethacin.			

cytoplasmic (inner) membrane depends on a trasmembrane electrical gradient coupled to an electric transport to drive permeation of these antibiotics. This energy-depended phase is rate limiting and can be locked or inhibited by divalent cations (e.g., Ca^{2+} and Mg^{2+}), hyperosmolarity, a reduction in pH, and anaerobic conditions. Thus, the antimicrobial activity of aminoglycosides is reduced markedly in the anaerobic environment of an abscess and in hyperosmolar acidic urine. Once inside the cell, aminoglycosides, and thus gentamicin, bind to polysomes and interfere with protein synthesis by causing misreading and premature termination of mRNA translation. The primary intracellular site of action of the aminoglycosides is the 30S ribosomal subunit. At least three of these ribosomal proteins and perhaps the 16S ribosomal RNA as well, contribute to the streptomycin-binding site. Aminoglycosides, and thus gentamicin, interfere with the initiation of protein synthesis, loading to the accumulation of abnormal initiation complexes; aminoglycosides also can cause misreading of the mRNA template and incorporation of incorrect of amino acids into the growing polypeptide chains [4]. The resulting aberrant proteins may be inserted into the cell membrane, leading to altered permeability and further stimulation of aminoglycoside transport [5].

Efficacy and safety of gentamicin in infants and children

Tantiprabha, et al. [6] determined the pharmacological efficacy and safety of the gentamicin regimen in 49 Thai neonates aged ≤ 7 days. Neonates were stratified into four groups by gestational age: ≤ 29, 30-33, 34-37, and ≥ 38 weeks of gestation. Gentamicin doses were 5, 4.5, 4, and 4 mg/kg every 48, 36, 36, and 24 hours, respectively. Forty-four (89.7%) had peak of serum gentamicin concentration within the desirable range 5-12 μg/ml). All neonates had trough serum gentamicin concentration below 2 μg/ml. This gentamicin regimen yielded good pharmacological efficacy and safety in Thai neonates during the first week of life and no renal function impairment.

Tiwari, et al. [7] compared the clinical efficacy and the safety of once-daily dosing and multiple-daily dosing of gentamicin in 400 Indian hospitalized children. Children were randomized to once-daily dosing or multiple-daily dosing. Clinical efficacy was determined by comparing the proportion of patients with favourable response, and the safety of the two regimens was compared, besides according any symptoms due to side effects. A favourable response was observed in 89% of Indian children treated with once-daily dosing of gentamicin and 76% of children treated with multiple-daily dose of gentamicin. A 100% of children in the once-daily dosing group and 87% of children in the multiple-daily dosing group had favourable gentamicin peak. The undesirable range of trough gentamicin concentration was 17% in the multiple-daily dosing group and 0% in the once-daily dosing group. The present findings support the extended-interval (single-daily) dosing in Indian children due to its efficacy and safety with added advantage needing fewer infections.

Peak and trough serum gentamicin concentrations in neonates and infants

The peak and trough gentamicin concentrations were determined in 50 cases of neonates and infants [8]. The peak levels in neonates and infants were 5.98 ± 0.48 and 4.63 ± 0.31 μg/ml, respectively. The trough levels of gentamicin in the corresponding groups were 1.06 ± 0.19 and 0.94 ± 0.23 μg/ml. There was a significant (*P*-value < 0.05) lower peak concentration in infants than in neonates. A significantly (*P*-value < 0.05) higher peak concentration of gentamicin was observed in neonates aged < 7 days than in those above 7 days. The intravenous or intramuscular gentamicin route had any effect on the peak and trough levels of gentamicin.

Forty infants were randomized to receive either 2.5 or 4 mg/kg once-daily gentamicin [9]. Initial peak serum gentamicin concentration was > 5 μg/ml in only 6% of neonates receiving 2.5 mg/kg, versus 94% of neonates receiving 4 mg/kg. The initial trough gentamicin concentration after the first dose was < 2 μg/ml in 100% of neonates receiving 2.5 mg/ml and only 39% of neonates receiving 4 mg/ml. Thus, the standard treatment of 2.5 mg/kg gentamicin yields initial peak and trough serum gentamicin concentrations lower than those obtained after the administration of 4 mg/kg in neonates.

Gentamicin dosage intervals in infants

Davies and Cartwright [10] determined the incidence of toxic through serum gentamicin levels in infants in the first week of life, with different dosage intervals. A trough serum gentamicin level ≥ 1.5 μg/ml was considered toxic. Twenty-one neonates in group one (24-29 gestational weeks) received gentamicin with a dosage interval of 24 hours. Sixteen (76%) infants had toxic trough serum gentamicin levels. In group two (30-34 gestational weeks) 8 infants had gentamicin every 12 hours and all (100%) had toxic trough serum gentamicin levels. Fourteen infants had gentamicin every 18 hours and 13 (93%) had toxic trough serum gentamicin levels. Sixty-one infants had gentamicin every 24 hours and 25 (41%) had toxic trough serum gentamicin levels. In group three (≥ 35 gestational age) 29 infants had gentamicin every 12 hours and 25 (86%) had toxic trough serum gentamicin levels. Six infants had gentamicin every 18 hours and 2 (33%) had toxic trough serum gentamicin levels. Thirty-one infants had gentamicin every 24 hours and 4 (13%) had toxic trough serum gentamicin levels. The difference in proportions comparing infants having gentamicin every 12 hours with those having it every 24 hours were statistically significant. A starting gentamicin dosage interval of 12 hours in infants of any gestational age, or a starting dosage interval of 24 hours for infants of less than 30 weeks gestational age, leads to most having toxic trough serum gentamicin levels. In infants of 30 weeks gestational age or greater, most have safe non-toxic trough serum gentamicin levels if started on a dosage interval of 24 hours.

El-Chaar, et al. [11] hypothesized that one uniform gentamicin dose for infants of all gestational ages will reduce the incidence of elevated trough levels from 50% to 10%. Infants were stratified according to gestational age (group 1, ≤ 34 gestational age) and (group 2, > 35 gestational age). Infants in the study arm received 5 mg/kg intravenously every 36 hours, whereas infants in the control arm received traditional dosage.

Fifty infants in group 1 (N = 25 per arm) and 46 infants in group 2 (N = 23 per arm) were enrolled. Elevated serum gentamicin trough were reduced by 66% in group 1 (*P*-value = 0.61) and 100% in group 2 (*P*-value < 0.0001). A standardized gentamicin dosage of 5 mg/kg every 36 hours to infants of all gestational ages is safe and results in serum gentamicin concentrations in goal therapeutic ranges.

Infants were treated with 4 mg/kg gentamicin intravenously once-daily [12]. In infants with gestational age between 32 and 36 weeks, 14 of 65 (22%) had trough gentamicin serum concentration > 2 μg/ml. Only 39 (60%) had peak and trough gentamicin serum concentrations within the therapeutic range. Among term neonates, only 2 out of 50 (4%) had the trough serum gentamicin concentration < 2 μg/ml and the peak level was < 10 μg/ml. A dose of 4 mg/kg gentamicin once-daily produces serum gentamicin levels outside the therapeutic range in two-fifths of infants between 32±6 and 36±6 weeks of gestation. A single dose of 4 mg/kg once-daily is appropriate for term neonates and probably excessive for 32-36 gestational weeks' neonates.

Once-daily gentamicin dosing in infants and children

In a previous study, 22% of infants who received a once-daily gentamicin dosage of 5 mg/kg per day had unacceptably high trough gentamicin levels (i.e. > 2 μg/ml). Kiatchoosakun, et al. [13] studied 105 infants (of ≥ 34 gestational age and ≥ 2,000 gram body weight) receiving a once-daily gentamicin dosing of 4 mg/kg intravenously. Peak (i.e. efficacy) and trough (i.e. toxicity) serum gentamicin concentrations were collected on day 3 of therapy. Infants treated with 4 mg gentamicin/kg once-daily had a mean steady-state peak versus trough concentration of 7.33±2.77 versus 0.99±0.57 μg/ml in 102 infants (97%), while 7 (6.67%) had an undesirable gentamicin through level (> 2 μg/ml); notwithstanding, no nephrotoxic or ototoxic effects were identified. Gentamicin once-daily at 4 mg/kg/dose in infants at ≥ 34 gestational age achieved appropriate trough levels. This regimen is convenient and does not increase renal toxicity or ototoxicity.

McDade, et al. [14] estimated an appropriate once-daily gentamicin dose and dosing interval for 114 non-critical care infants aged > 3 months. Once-daily doses were extrapolated for each infant to achieve goal peak and trough gentamicin concentrations. Theoretical once-daily peak and trough concentrations were calculated for each infant. Mean±SD pharmacokinetic parameters were as follows: elimination rate constant was 0.32±0.06 $hour^{-1}$, half-life was 2.26±0.54 hours, and the distribution volume was 0.24±0.08 l/kg. The following age-specific once-daily doses were calculated: 3 months to < 2 years, 9.5 mg/kg; 2 years to < than 8 years, 8.5 mg/kg; and 8-18 years, 7 mg/kg. Age was the primary factor in determining the once-daily dose of gentamicin in this paediatric population.

A total of 79 children aged 1 month to 16 years (median age 5.6 years) received an once-daily dose of 7 mg/kg gentamicin per day and had 106 episodes of therapy [15]. In all, 61% of these episodes were for febrile neutropenia. Two children (1.88%) experienced permanent hearing loss. One child (0.94%) experienced transient nephrotoxicity. In this paediatric cohort receiving once-daily dose of 7 mg/kg gentamicin, nephrotoxicity was uncommon and reversible, but irreversible ototoxicity occurred more frequently. Therapeutic drug monitoring using a monogram neither predicted nor prevented toxicity, which was only observed in those with risk factors.

Once-daily versus twice-daily gentamicin dosage in infants

Hagen and Oymar [16] evaluated once-daily or twice-daily gentamicin dosage in infants with a gestational age ≥ 34 weeks. Sixty-two infants received 2.5 mg/kg twice-daily and 73 infants received 4 mg/kg once-daily. In both groups, levels of gentamicin were obtained before and after the third dose. Mean peak levels were lower and trough levels were higher in the twice-daily regimen compared to the once-daily regimen (P-value < 0.001 for both). The trough gentamicin level was > 2 μg/ml in 16 infants who were treated with twice-daily regimen compared to 2 infants treated with once-daily regimen (P-value < 0.001). High peak levels (> 10 μg/ml) were achieved in one child in the twice-daily regimen compared to 8 children in the once-daily regimen (P-value = 0.04). In infants with suspected sepsis, gentamicin 4 mg/kg once-daily provided higher peak and lower trough gentamicin levels compared to administering gentamicin 2.5 mg/kg twice-daily.

Twenty-seven infants were given 2.0-2.5 mg/kg of gentamicin twice-daily while 27 infants were given 4.0-5.0 mg/kg of gentamicin once-daily [17]. The twice-dose and the once-daily dose group had mean steady-state gentamicin peak concentrations of 5.94±1.57 μg/ml and 8.92±1.59 μg/ml, respectively (P-value < 0.05) while their trough concentrations were 1.44±0.49 μg/ml and 0.90±0.35 μg/ml, respectively (P-value < 0.05). Three (11.1%) infants in the twice-daily dose group, peak and trough levels were not in the desirable therapeutic range, two infants with too high trough level (> 2 μg/ml) and one with subtherapeutic level (4 μg/ml). Only one patient in the once-daily regimen had undesirable trough level that was > 1.5 μg/ml. All infants in the twice-daily and in once-daily dosage groups showed improvement in clinical outcome. A once-daily dose with 4.0-5.0 mg/kg gentamicin could be an appropriate regimen in term neonates during the first 7 days of life. This regimen produces peak concentration that may have greater clinical efficacy and trough concentration with less toxicity than conventional dosing regimen.

Once-daily versus thrice-daily gentamicin dosage in infants and children

Chong, et al. [18] examined the safety and efficacy of once-daily gentamicin treatment compared to conventional 8-hourly dosing (thrice-daily) for urinary tract infection in children aged 1 month to 13 years (median age was 7 months). Children received 5 mg/kg gentamicin once-daily and 6 mg/kg gentamicin divided 8 hourly (thrice-daily). Eighty-four children were treated with once-daily gentamicin and 88 children were treated with thrice-daily gentamicin. The majority of infections were due to Escherichia coli (89%), of which 5.2% were bacteraemic. All children had negative

urine cultures after 2-3 days of treatment, demonstrating 100% microbiological efficacy. Once-daily gentamicin dosage is as efficacious as thrice-daily dosing in the treatment of urinary tract infection in children, with no difference in ototoxicity and nephrotoxicity.

Fifty children aged 3 months to 16 years with infections caused by gram-negative pathogens were enrolled. Twenty-six children received 4.5 mg/kg gentamicin once-daily, and 24 children received 4.5 mg/kg divided in three doses (thrice-daily) [19]. Serum through gentamicin concentrations were significantly lower in the once-daily regimen. Clinical cure was obtained in 88.8% children who received gentamicin once-daily and 91% of children treated thrice-daily. Microbiological cure was obtained in 100% and 92% of the evaluated cases, respectively. These results show a similar outcome in children receiving 4.5 mg/kg/day whether administered once or thrice daily.

Risk of hearing loos in infants and children exposed to gentamicin

Infants with a mitochondrial genetic variant (m.1555 > G), have permanent hearing loss can occur even when gentamicin blood levels are within therapeutic values. Bitner-Glindzicz et al. [20] investigated the burden of the m.1555 > G mitochondrial mutation which yields deafness in very preterm infants. Children in the control group were not treated with gentamicin. Saliva samples were taken in gentamicin treated infants and controls; DNA were extracted and tested for mutation. If there is an increased burden of hearing loss with m.1555A > G and aminoglycoside use, consideration will be give to genetic testing during pregnancy, postnatal testing prior to drug administration, or the use of an alternative first-line antibiotic.

Hearing loss rates preterm infants run at 2-15%, compared to 0.3% in full-term births. Garinis et al. [21] examined whether the level of ambient sound and/or cumulative gentamicin exposure affect infants, and/or gentamicin dosing, increase the risk of referral on the distortion product otoacoustic emission assessments and/or automated auditory brainstem response screens. The mean level of ambient sound was 62.9 dBA (range, 51.8-70.6 dBA). More than 80% of 82 infants received gentamicin. Distortion product otoacoustic emission referrals were significantly greater for infants receiving > 2 days of gentamicin compared to fewer doses (P-value = 0.004). All infants were exposed to higher levels of ambient sound that exceed American Academy of Paediatrics guidelines. More referrals were generated by distortion product otoacoustic emission assessment than with auditory brainstem response screens, with significantly more distortion product otoacoustic emission assessments than with automatic auditory brainstem response screens, with significantly more distortion product otoacoustic emission referrals with a high-frequency F2 range, consistent with sound- and/or gentamicin- induced cochlear dysfunction. Adding higher frequency distortion product otoacoustic emission assessments to existing neonatal intensive cure unity hearing screening protocols could better identify infants at-risk for ototoxicity.

A total of 8,333 children examined for hearing disorders, 134 (1.6%) had received previous treatment with gentamicin [22]. Only 8 (6.0%) children suffered from various extents of sensorineural hearing impairment, and all 8 had a history of other risk factors. In another study, 30 children (mean age, 13.2 months) with normal hearing had received gentamicin during the newborn phase, and 30 healthy children of similar age without previous gentamicin treatment were examined for vestibular function. These results indicate that gentamicin, in controlled therapeutic doses, has less ototoxic and vestibulotoxic effects in newborns than it does in older children.

Echeverria et al. [23] examined the incidence of clinical ototoxicity in 374 children who had serum gentamicin concentration determined 30 min before (trough value) and at the pharmacologic peak after parenteral administration of gentamicin. Thirty-seven of these children, aged 9 to 17 years, had two or more audiograms; of these, 9 children developed objective evidence of hearing loss; in 2 children the impairment was severe and permanent. Risk factors associated with ototoxicity were renal failure, concomitant administration of diuretics and serum peak gentamicin > 12 μg/ml (all were significant at P-value < 0.01). The minimum incidence of overt hearing loss secondary to gentamicin therapy is approximately 2.4%.

A total of 69 children were treated with continuous gentamicin intravenous infusion during neonatal intensive care [24]. A hearing loss of 20 dB was found in 2 (3%) children. Thus there is no indication that continuous 24 hours intravenous infusion of gentamicin causes more hearing impairment than intermittent intravenous or intramuscular administration.

Brainstem auditory evoked potential recording was used to screen presymptomatically the hearing of 200 infants, with mean post-conceptional 42.36 weeks, treated with ampicillin (100 mg/kg daily) and gentamicin sulphate (5 mg/kg daily) [25]. The infants were divided into 2 groups according to duration of antibiotic treatment; group 1 (179 infants) received antibiotic agents for ≤ 7 days. Fifteen (8.4%) infants initially manifested abnormal brainstem auditory evocated potential recordings, only 8 of these brain-damage infants (4.5%) (6 with peripheral and 2 with central dysfunction) later manifested abnormal recordings. Group 2 (21 infants) who were treated for 10 to 30 days; brainstem auditory evocated potential recordings were abnormal in 7 infants (33.3%) (4 with peripheral and 3 with central dysfunction). In this group, infants so treated usually had underlying disease or severe infection all of which were clinically significant indicators of high risk for auditory pathway dysfunction.

Seven healthy term infants who received gentamicin starting on the first day of life were compared to nine healthy term infants to determine whether gentamicin induces alterations in the auditory pathway [26]. The auditory pathway was studied on the third day of life by analyzing brainstem auditory evoked potentials elicited by a click stimulus presented at the infant's ears. Latencies of components III and V, interval I-III, and

interval I-V were significantly prolonged in the gentamicin group, indicating impairment of the central component of the auditory pathway. These findings indicate that short course gentamicin therapy in healthy infants can lead to abnormality of auditory function.

Thirty-two infants (18 full-term and 14 premature) who had been treated with gentamicin were examined to ascertain whether gentamicin induces hearing loss [27]. Objective thresholds to clicks were obtained using auditory nerve and brain stem evoked responses. Serum gentamicin before and after gentamicin treatment were at therapeutic concentrations. All infants were examined at least 1 and ¼ months after cessation of therapy. Normal thresholds were obtained in all ears, with the exception of two with demonstrable middle ear effusion. Gentamicin in therapeutic doses and serum concentrations does not cause hearing loss in infants.

Cooper et al. [28] characterized the extent that serum gentamicin concentrations are associated with hearing loss indicated by otoacoustic emission screen failure in critically ill neonates receiving gentamicin in accordance with a single-dose, extended-interval dosing protocol. A total of 528 critically ill neonates were stratified into two groups: very-low-birth-weight (≤ 1,500 gram) and non-very-low-birth-weight (> 1,500 gram). Gentamicin was administered intravenously to achieve the peak serum concentration of 7-10 μg/ml and a target trough serum concentration < 2 μg/ml. The overall rate of otoacoustic emission screen failure was 13.1%. The rate of otoacoustic emission screen failure was 34.1% in very-low-birth-weight infants, which was significantly higher than the failure rate in non-very-low-birth-weight infants 9.0% (P-value = 0.001). Multivariate analysis of non-very-low-birth-weight infants determined that 1-μg/ml increase in gentamicin peak is associated with an increase risk of otoacoustic emission screen failure (P-value = 0.003). Infants weighing > 1,500 gram at birth and whose peak exceeded 10 μg/ml are at an increased risk for otoacoustic screen failure. Maintaining serum gentamicin peak concentration at, or below 10 μg/ml, may minimize hearing impairment.

A total of 255 children aged 6 months to 3 years were divided into two groups. One hundred and twenty-five (49%) children were exposed to gentamicin during 0-2 months of life, and 130 (51%) children were not treated with gentamicin (controls) [29]. The outcome measure was hearing loss, which was assessed by brainstem evoked response audiometry. Children in the gentamicin exposed group were not at increased risk for hearing loss compared to controls. Children with history of ear of discharge and children with family history of deafness were more at risk for having hearing loss.

Fuchs et al. [30] evaluated the impact of gentamicin exposure on sensorineural hearing loss in 25 infants weighing < 1,500 gram and with a gestational age < 32 weeks during the first 5 days of life. For each case, two controls were selected. Twenty-five infants affected by sensorineural hearing loss, leading to an incidence of sensorineural hearing loos was 1.58%. The proportion of infants treated with gentamicin was 76% in the study group and 70% in controls. The total cumulated dose of gentamicin administered did not differ between the study group (median, 10.2 mg/kg) and the control group (median, 7.9 mg/kg). The median duration of gentamicin treatment was 3 days both in the study group and the control group. Peak and trough gentamicin serum concentrations, AUC, and gentamicin clearance were not different between cases and controls. The impact of gentamicin on sensorineural hearing loss can be minimized with treatments of short duration, monitoring of gentamicin blood levels and dose adjustment.

E-Barbary et al. [31] assessed the extended interval regimen gentamicin associated ototoxicity in infants using hearing tests. A total of 220 infants were enrolled; 110 infants who had received gentamicin and 110 infants had not received gentamicin (controls). Gentamicin group were further subdivided according the duration of treatment. Fifty infants who had received gentamicin for 5 days or less, and 60 infants received gentamicin for more than 5 days. Auditory brain response was performed 3 months later for failed cases to confirm the hearing impairment. Three infants failed TEOAEs screening in each group but hearing impairment was confirmed in one neonate only (0.9%) in each group. Infants who received gentamicin for more than 5 days showed comparable results as regard TEOAEs or ABR results with those who received gentamicin for 5 days or less, and control group. Extended interval dosing of gentamicin therapy in infants does not increase the incidence of hearing loss.

Gentamicin causes renal dysfunction in infants

Gentamicin causes natriuresis, magnesuria, and calciuria in infants. Tugay, et al. [32] determined the acute effects of trough and peak levels of gentamicin on the values of serum creatinine, urine albumin/urine creatinine, fractional excretion of sodium and potassium, and urine calcium/urine creatinine in 61 preterm infants treated with gentamicin for suspected infection on the third gentamicin dose and 48-72 hours after the cessation of the gentamicin therapy. Trough and peak levels of gentamicin were positively correlated with serum creatinine, albumin/urine creatinine, fractional excretion of sodium and potassium, urine calcium/urine values. The albumin/urine creatinine, fractional excretion of sodium and urine calcium/urine creatinine values recorded during treatment were statistically significantly different from sub-therapeutic, therapeutic, and high peak gentamicin levels. Gentamicin was found to have a serum peal level-dependent microalbuminuric, natriuric and calciuric effect in preterm infants. These results suggest that when the monitoring of serum gentamicin is not possible, the monitoring of urine albumin/urine creatinine, the fractional excretion of sodium, urine calcium/urine creatinine can be useful as a non-invasive alternative.

Giapros, et al. [33] determined the acute effect of gentamicin administration on renal electrolyte handling in 33 preterm and full-term infants. Serum and 3-hours urine electrolytes were measured before and immediately after gentamicin infusion on the 1st, 3rd, 4th, and 7th day of treatment. Gentamicin caused a statistically significant post-infusion increase in fractional

excretion of sodium and magnesium and in the urine calcium to urine creatinine ratio. The disturbances in electrolyte excretion were observed in full-term as well as in preterm infants. Therapeutic doses of gentamicin result in urinary loss of sodium, calcium, and magnesium in infants immediately after the infusion of gentamicin. These electrolyte changes may be of clinical importance, especially for sick preterm infants.

Thirteen infants, 8 term and 5 preterm were treated for between 3 and 7 days with gentamicin and ampicillin or cloxacillin because suspected bacterial infection [34]. Urinary alanine aminopeptidase, urinary β-2-microglobulin, serum urea, and β-2-microglobulin were measured during and after the end of treatment to detect signs of renal toxicity. Levels of urinary aminopeptidase increased in 12 infants, indicating damage to cells of the proximal tubuli. Changes in urinary β-2-microglobulin followed the normal physiological course seen in infants after birth. Serum levels of urea and β-2-microglobulin did not indicate any drug-associated depression of glomerular filtration rate.

Ten infants were treated with gentamicin and 10 infants not-treated served as controls. Changes in the glomerular filtration rate and the fractional excretion of β-2-microglobulin in urine were used as indicators of renal dysfunction [35]. The glomerular filtration rate was statistically lower in 5/10 and 6/10 of infants on the first and the last days of gentamicin treatment, respectively. Three weeks after gentamicin treatment, 8/10 had a normal glomerular filtration rate. The fractional excretion of β-2-microglobulin was statistically higher in 4/10 of infants on their first day of gentamicin treatment and 7/10 on their postnatal age. Gentamicin influences filtration and proximal reabsorption in gentamicin treated infants by decreasing the glomerular filtration rate and increasing the fractional excretion of β-2-microglobulin. However, the observed renal dysfunction is reversible.

Toxic effects of gentamicin in infants

Mulhall, et al. [36] investigated the putatively toxic effects serum concentrations and the factor influencing their occurrence in 91 infants treated with parenteral gentamicin twice-daily at a dose of 5.5±0.1 mg/kg per day. Potentially toxic trough concentration (> 2 µg/ml) of gentamicin were recorded in 57 of 91 (63%) infants; 24 of these concentrations were 3 µg/ml. These infants were of a significantly lower gestational age and were younger than the remainder of the population. Toxic trough concentrations were not accompanied by raised peak serum values. A wide variance in all pharmacokinetic variables was observed. Peak serum concentration was most highly correlated with the dose, while trough concentration, AUC, and clearance were more dependent on postnatal age. Clearance of gentamicin decreased significantly with increasing serum urea and creatinine concentrations. Preterm infants in the first week of life are likely to develop potentially toxic serum concentrations when receiving the currently recommended dose of gentamicin (5-6 mg/kg per day). To prevent accumulation, the dosage interval may need to be increased to 18 hours in these infants.

Musiime, et al. [37] assessed the risk of gentamicin toxicity and potential number of infants exposed annually to this risk, through treatment with WHO-recommended first line antibiotics (gentamicin with penicillin) for 6.9 million infants with possible serious bacterial infection. Eleven studies (946 infants) were included (nine randomized controlled trials and two prospective cohort studies). Six trials reported consistently measured ototoxicity outcomes in infants treated with gentamicin, and the pooled estimate for hearing loos was 3%. Nephrotoxicity could not be assessed due to variation in case definitions used. Estimates of the number of infants potentially affected by gentamicin toxicity were not undertaken due to insufficient data. Given wider scale-up of outpatient-based and lower-level treatment of possible serious bacterial infection, improved data are essential to better assess the risk from neonatal gentamicin treatment without assessment of blood levels, to maximise benefit and reduce harm.

A Bartter-like syndrome is a toxic manifestation of gentamicin which includes nephrotoxic syndrome. Four children aged 4 months to 17 years demonstrated evidence of renal tubulopathy, primarily affecting the distal nephron [38]. Hypocalcaemia, hypomagnesaemia, alkalosis, and hypokalemia were the main manifestations in these children. After discontinuation of gentamicin, recovery of the tubular functions and resolution of the electrolyte abnormalities were complete in all children.

The susceptibility to gentamicin and typical minimal concentrations that will inhibit 90% (MIC_{90}) of clinical isolates of 7 bacteria are reported in table 2, by Sader, et al. [39]. The % susceptibility ranges from 37.0 to 97.0 and the MIC_{90} ranges from 1 and > 128 µg/ml. Enterobacter species have the highest % susceptibility and the lowest MIC_{90} whereas Acinetobacter baumannii have the lowest % susceptibility and the highest MIC_{90}.

Gentamicin is not metabolized and is excreted unchanged in the urine [1, 3]. In literature, there are not studies on the metabolism of gentamicin in infants and children.

Pharmacokinetics of Gentamicin in Infants

Comparison of twice-daily versus once-daily gentamicin administration

Fifty full-term infants (gestational age 37-42 weeks, and birth weight ≥ 2.500 gram, post-natal age ≤ 7 days) received 2.5 mg/kg/dose intravenously every 12 hours, and 50 infants

Table 2: Susceptibility to gentamicin and typical minimal concentrations that will inhibit 90% (MIC_{90}) of clinical isolates of 7 bacteria, by Sader, et al. [39]

Species	% susceptibility (MIC_{90} µg/ml)
Enterobacter species	97.0% (1)
Escherichia coli	88.2% (8)
Klebsiella pneumoniae	89.2% (8)
Pseudomonas aeruginosa	88.0% (16)
Serratia species	97.0% (1)
Acinetobacter baumannii	37.0% (> 128)
Staphylococcus aureus	95.0% (0.5)

were given 4 mg/kg every 24 hours [40]. The peak and trough gentamicin concentrations are summarized in table 3. Once-daily dosing had the highest peak and the lowest trough gentamicin concentrations. The number of gentamicin level in therapeutic concentration was higher in the once-daily dosing.

Gentamicin pharmacokinetics in low-birth weight

Nakae, et al. [41] studied the gentamicin pharmacokinetics in 41 preterm low-birth weight infants (20 infants with birth weight of < 1,500 gram and 21 with birth weight of ≥ 1,500 gram) in the first week of life. Gentamicin regimens, were 2.0 mg/kg every 24 hours for the < 1,500 gram group and 2.0 mg/kg every 12 hours for the ≥ 1,500 group. On the 4th day of treatment, the half-life and the total body clearance were higher in infants aged ≥ 1,500 gram. In a one-compartment pharmacokinetic analysis, a large variability among infants was observed on the 1st day of treatment. The gentamicin pharmacokinetic parameters are shown in table 4.

Gentamicin pharmacokinetics in very-low-birth weight

Very-low-birth weight preterm infants (N = 18) with suspected infection were administered gentamicin intramuscularly every 18 hours (2.5 mg/kg) or 24 hours (3.0 mg/kg) [42]. The gestational age and the body weight ranged from 26 to 32 weeks and 690 to 1,450 gram, respectively. Twelve of infants with estimated gestational age ranging from 26 to 32 weeks and birth weights ranging from 690 to 1,420 gram were administered 2.5 mg/kg gentamicin every 18 hours beginning on 1st day of life. All 12 infants had jaundice. The remaining 6 infants with estimated gestational age between 26 and 30 weeks and birth weights between 720 and 1,450 gram were administered 3.0 mg/kg of gentamicin every 24 hours beginning on 1st day of life and continuing to day 10 in 4 infants and to day 16 in 2 infants. Capillary (heel prick) blood samples were collected at 0, 0.5, 1, 8, 16, and 18 hours after the 4th, 9th, and 13th dose of gentamicin. For both dosage regimens plasma gentamicin levels were monitored during a dosage interval on three separate occasions over a 10 day period. Both regimens gave satisfactory plasma gentamicin concentrations and there was no important statistically significant difference between the two. The body clearance of gentamicin correlated significantly with gestational age ($r = 0.76$; P-value < 0.01). These results indicate that either regimen may be useful in the clinical situation but from a practical standpoint administration every 24 hours may be easier to comply with then every 18 hours. The gentamicin pharmacokinetic parameters are summarized in table 5.

Gentamicin pharmacokinetics in small-for-gestational age and appropriate-for-gestational-age infants

Lulic-Botica [43] compared gentamicin pharmacokinetics among infants born small-for-gestational age and appropriate-for-gestational age. These authors further compared gentamicin pharmacokinetics in subgroups of appropriate-for-gestational age and small-for-gestational age infants born preterm and term and treated within and after the initial week of age.

Table 3: Peak and trough gentamicin concentrations in infants, by Alsaedi [40]

Infants different serum drug level	Twice-daily dosing group	Once-daily dosing group
Number of infants	50	50
Peak gentamicin concentration (μg/ml)		
Mean±SD	6.7±2.0	8.4±1.8*
Range	1.3 -11	4.8 – 13
Number of serum drug level < 5 μg/ml (%)	7 (14)	2 (4)
Number of serum drug level 8-12 μg/ml (%)	12 (24)	29 (58)**
Number of serum drug level > 12 μg/ml (%)	0 (0)	1 (2)
Trough gentamicin concentration (μg/ml)		
Mean±SD	1.5±0.9	1.3±0.8
Range	< 0.5 – 3.4	< 0.5 – 1.9
Number of serum drug level > 2 μg/ml (%)	13 (26)	13 (6)**
Number of serum drug level in therapeutic range (%)***	30 (60)	44 (88)**

P*-value < 0.05 by unpaired t test, ***P*-value by X^2 analysis. * trough concentrations < 2 μg/ml and peak concentrations 5 -12 μg/ml.

Table 4: Gentamicin pharmacokinetic parameters in low-birth weight infants in the first week of life. The figures are the mean±SD, by Nakae, et al. [41].

Infants	Elimination rate ($hours^{-1}$)	Half-life (hours)	Distribution volume (L/kg)	Total body clearance (L/kg/h)
< 1,500 gram group				
1st day of treatment (N =19)	0.072±0.060	12.97±6.08	0.725±0.447	0.045±0.036
4th day of treatment (N = 20)	0.056±0.022	13.82±4.98	0.596±0.262	0.030±0.011
≥ 1,500 gram group				
1st day of treatment (N = 18)	0.083±0.044	10.89±6.45	0.780±0.393	0.058±0.014
4th day of treatment (N = 21)	0.091±0.024*	8.13±2.32*	0.503±0.150**	0.043±0.006**

**P*-value < 0.01 against values of the < 1,500 gram group on the 4th day of treatment. ***P*-value < 0.01 against values of the ≥ 1,500 gram group on the 1st day of treatment.

Table 5: Gentamicin pharmacokinetic parameters in very-low-birth weight infants. The figures are the mean±SD, by Hindmarsh, et al. [42].

Doses	Peak concentration (µg/ml)	Trough concentration (µg/ml)	AUC (µg/ml/h)	Half-life (hours)	Gentamicin total body clearance (ml/h)	Gentamicin clearance average (µg/ml)
Gentamicin dose of 2.5 mg /kg every 18 hours						
4th dose	6.7±1.7	1.5±0.6	53.9±14.4	11.3±3.7	59.7±23.2	3.0±0.8
9th dose	6.7±2.1	1.7±0.6	57.0±14.2	11.7±3.4	50.9±17.2	3.2±0.8
13th dose	7.3±1.4	1.5±0.5	54.3±16.7	13.1±3.2	58.0±21.6	3.0±0.9
Gentamicin dose of 3.0 mg/kg every 24 hours						
3rd dose	6.4±2.2	1.4±0.6	69.0±21.7	13.8±5.2	53.8±19.8	2.9±0.9
7th dose	7.6±1.6	1.5±0.3	82.3±20.6	16.1±5.1	46.5±21.5	3.4±0.9
10th dose	7.5±2.9	1.5±0.4	75.0±25.2	13.9±1.7	49.2±20.9	3.1±1.1

Steady-state peak and trough serum gentamicin concentrations were used to calculate the clearance, elimination rate constant, distribution volume, and half-life in 236 infants who received gentamicin for ≥ 48 hours. Statistical analysis included X^2 and non-parametric Mann-Whitney-U-test. The dosing regimen for early (< 7 days of age) onset sepsis was 3 mg/kg every 36 hours for infants < 1.200 gram, 3 mg/kg every 36 hours for infants < 1,200 gram, 3 mg/kg every 24 hours for infants 1,200 – 2,000 gram and 3.5 mg/kg every 24 hours for infants > 2,000 gram at birth. For gentamicin use beyond 7 days, gentamicin doses of 3 – 4 mg/kg every 24 hours were administered for infants < 1,200 gram, 4 mg/kg every 24 hours for infants who weighed 1,200 – 2,000 gram and 4 – 5 mg/kg every 24 hours for those who weighed 1,200 – 2,000 gram, and 4 - 5 mg/kg every 24 hours for those who weighed > 2,000 gram. Gentamicin doses were infused intravenously over a 0.5-hour-period. Table 6 shows the median and IQR in infants at ≤ 7 days of life, and table 7 summarizes the median and IQR in infants at > 7 days of life. On the ≤ 7 days of life, infants small-for-gestational age had longer gentamicin half-life and

Table 6: Comparison of median (IQR) baseline and TDM parameters between groups of small-for-gestational age (N = 29) and appropriate-for-gestational age (N = 53) infants who underwent gentamicin TDM at ≤ 7 days of life, by Lulic-Botica [43].

Median (IQR)	Small-for-gestational infants (N = 29)	Appropriate-for-gestational age (N = 53)	P-value by Mann-Whitney U-test
Gestational age (weeks)	30 (27 – 38)	32 (27 – 38)	0.694
Birth-weight (gram)	770 (543 – 2,312)	1,850 (1,030 – 2,980)	0.0001
Gentamicin dose (mg/kg/dose)	3.1 (3.0 – 3.4)	3.3 (2.9 – 3.5)	0.082
Age at TDM (days)	4 (3.5 – 4)	4 (3 -5)	0.317
Weight at TDM (gram)	860 (535 – 2,300)	1.780 (920 – 2,940)	0.01
Elimination rate constant ($hour^{-1}$)	0.069 (0.050 – 0.081)	0.081 (0.064 – 0.106)	0.017
Half-life (hours)	10 (8.5 – 14.1)	8.6 (6.9 – 10.8)	0.008
Clearance (ml/kg/min)	0.58 (0.41 – 0.84)	0.68 (0.57 – 0.90)	0.036
Distribution volume (L/kg)	0.5 (0.41 – 0.84)	0.5 (0.42 – 0.62)	0.969
Peak gentamicin concentration (µg/ml)	7.7 (5.5 – 8.5)	7.6 (6.2 – 8.6)	0.645
Trough gentamicin concentration (µg/ml)	1.2 (1.1 – 1.6)	1.1 (0.8 – 1.6)	0.278
Serum creatinine (mg/dl)	0.8 (0.5 – 1.1)	0.8 (0.6 – 0.9)	0.524

Table 7: Comparison of median (IQR) baseline and TDM parameters between groups of small-for-gestational age (N = 19) and appropriate-for-gestational age (N = 53) infants who underwent gentamicin TDM at > 7 days of life, by Lulic-Botica [43].

Median (IQR)	Small-for-gestational infants (N = 19)	Appropriate-for-gestational age (N = 53)	P-value by Mann-Whitney U-test
Gestational age (weeks)	28 (25 – 31)	27 (26 – 30)	0.847
Birth-weight (gram)	750 (540 – 879)	1.030 (750 -1,380)	0.004
Gentamicin dose (mg/kg/dose)	3.1 (2.8 – 3.3)	3.1 (2.9 – 3.5)	0.599
Age at TDM (days)	44 (21 – 75)	22 (13 – 42)	0.021
Weight at TDM (gram)	1,420 – (1,020 – 1,75)	1,280 (980 – 1,703)	0.848
< 10th centile postmenstrual at TDM	18 (95%)	21 (40%)	0.001
Elimination rate constant ($hour^{-1}$)	0.107 (0.086 – 0.124)	0.095 (0.081 – 0.111)	0.195
Half-life (hours)	6.5 (6.5 – 8.1)	7.3 (6.25 – 8.6)	0.138
Clearance (ml/kg/min)	0.90 (0.77 – 1.05)	0.80 (0.67 – 0.95)	0.197
Distribution volume (L/kg)	0.5 (0.4 – 0.6)	0.5 (0.4 – 0.6)	0.919
Peak gentamicin concentration (µg/ml)	7 (5.5 – 8.4)	6.9 (5.4 – 8.05)	0.964
Trough gentamicin concentration (µg/ml)	0.5 (0.3 – 0.6)	0.7 (0.5 – 0.9)	0.013
Serum creatinine (mg/dL)	0.3 (0.3 – 0.5)	0.5 (0.34 – 0.60)	0.04

smaller clearance than infants appropriate-for-gestational age. In infants aged > 7 days of life, the only parameter different in the two groups was the trough concentration which was smaller in infants smaller-for-gestational age.

Extended-interval dosing of gentamicin in premature infants

Some authors suggested to extend intervals among gentamicin doses in premature infants when the trough gentamicin concentration is > 2 μg/ml to yield a trough gentamicin concentration < 2 μg/ml. The gentamicin concentrations and intervals among gentamicin doses are summarized in table 8 [44-46].

Bacterial resistance to gentamicin in infants and children

Research is lacking regarding the treatment of suspected sepsis in infants and children with hospital-acquired sepsis, despite rising antimicrobial resistance rates worldwide [47]. Current WHO guidelines supporting the use of gentamicin and penicillin for hospital-based patients or gentamicin intramuscularly or intravenously and oral amoxicillin when referral to a hospital is in accordance with currently available and other international guidelines, and there is no strong evidence to change this.

Almost one-third of the admitted infants (33.4%) were diagnosed as having neonatal sepsis. Early/late onset sepsis was found in 35.4% and 64.6%, respectively [48]. Gram-negative/gram-positive bacteria was found in 68% to 25.6%, respectively. Fungal infection was detected in 9% of isolates. Escherichia coli was the main pathogen isolated in both early-onset sepsis (41.2%) and late-onset sepsis (24.5%). Overall, 77% of isolates were multidrug-resistant (60% of gram-positive bacteria and 83.4% of gram-negative bacteria). The mortality rate was 79% caused by multidrug-resistant organisms. Gram-positive and gram-negative bacteria showed high resistance against commonly used antibiotics including gentamicin. There is an alarming increase in antibiotic resistance and continuous surveillance for antibiotic susceptibility is needed to ensure proper empirical therapy.

Lorenzoni, et al. [49] evaluated the antimicrobial susceptibility profile of 1,905 Klebsiella pneumoniae isolates. The resistance to gentamicin was 35.1%. Infection control measures in the hospitals are necessary for reducing the spread of multidrug-resistant microorganisms and preventing efficacy loss of antibiotics.

A total of 1,179 studies were screened and 82 articles were identified as eligible for inclusion. Most studies (78.7%) were reported from neonatal intensive care unities [50]. Among a total of 50,545 reported blood cultures, 14,794 (29.1%) were positive. Staphylococcus aurous (14.7%) and Klebsiella pneumonia (26%) were the commonest reported gram-positive and gram-negative pathogens, respectively. Approximately half of all Staphylococcus aureus isolates were methicillin-resistant. After age stratification, the median rate of resistance of common gram-negative bacteria to gentamicin/amikacin was extremely high (Klebsiella pneumoniae 75%, Escherichia coli/gentamicin 55.6%).

Kaur, et al. [51] determined the occurrence of uropathogens and their antimicrobial susceptibility pattern in infants aged < 1 year suspected with urinary tract infection. Culture positivity rate was found to be 15.7%. Most common bacterial isolate was Escherichia coli (45.4%) followed by Klebsiella (16.7%) and Enterococcus species (13.2%). Isolation of Candida was 21.1%, maximum from Intensive Care Unit (63.1%). Maximum gram-negative isolates (50%) showed high resistance to gentamicin and other antibiotics. These authors recommend continuous monitoring of changes in bacterial pathogens causing urinary tract infection and antibiotic sensitivity in each area for effective treatment of urinary tract infection.

Continuous prospective target surveillance was conducted in two Polish Neonatal Surveillance Network. The study covered 386 infants with very-low-birth weight, among which 262 cases of invasive infection were detected with predominance of central nervous system (123; 47%) [52]. The resistance phenotypes were determined according EUCAST. Resistance genes: mecA, ermA, ermB, ermC, msrA, aac(6')/aph(2''), ant(4')-la, and aph(3')-IIIa were detected using multiplex PCR. The most common species was Streptococcus epidermidis (63%), then Streptococcus haemolyticus (28%) and other central nervous system pathogens (9%). Among Streptococcus epidermidis, 95% of isolates were resistant to gentamicin. Among Streptococcus haemolyticus isolates, 100% were resistant to gentamicin. The mecA gene was detected in 98% of Streptococcus epidermidis and Streptococcus haemolyticus. Of the aminoglycoside resistance genes, aac (6')/aph(2'') were present alone in 83% of Streptococcus epidermidis, whereas aac(6'')/aph(2'') with aph(3')-III were predominant in 84% of Streptococcus haemolyticus. Knowing the epidemiology and antibiotic resistance of central nervous system isolated from

Table 8: Gentamicin dosing intervals and gentamicin concentrations

Gentamicin concentration (μg/ml) at 22 hours	≤ 1.2	1.2 - 2.7	2.7 – 3.5	≥ 3.6	By Sundaram. et al. [44]
Dosing interval (hours)	24	36	48	Base dosing interval to achieve a concentration < 2 μg/ml	
Gentamicin concentration (μg/ml) at 22 hours	≤ 1.2	1.3 – 2.6	2.7 – 3.5	≥ 3.6	By Alshaikh, et al. [45]
Dosing interval (hours)	24	36	48	Base dosing interval to achieve a concentration < 2 μg/ml	
Gentamicin concentration (μg/ml) at 22 hours	≤ 1.2	1.3 – 2.6	2.7 – 3.5	≥ 3.6	By Dersch-Mills, et al. [46]
Dosing interval (hours)	24	36	48	Hold dose, repeat level in 24 hours	

invasive infection in very-low-birth weight infants is a key step in developing targeted prevention strategies and reducing antibiotic consumption.

Neonatal sepsis is characterized by bacteraemia and clinical symptoms caused by microorganisms and their toxic products. Gram-negative bacteria are the commonest causes of neonatal sepsis [53]. A total of 130 infants with sepsis who were found to be blood culture positive were enrolled. Out of 130 culture proven cases of neonatal sepsis, gram-negative bacteria were found in 71 (54.6%) all cases. Staphylococcus aureus was the most common bacteria found in 35 (26.9%) followed by Escherichia coli in 30 (23.1%) cases. Acinetobacter cloacae, Enterobacter species, Staphylococcus epidermidis, Klebsiella, Streptococci, Enterobacter cloacae, and Moraxella species were found in 13.1%, 13.1%, 10%, 5.4%, 4.6%, and 3.8% cases, respectively. Gentamicin had resistance in 55.1% cases.

Hammoud, et al. [54] investigated the incidence, etiological pattern, and the antimicrobial resistance of late-onset neonatal infections over a period of 5 years. The overall incidence was 16.9 episodes per 100 live births. The commonest pathogen was coagulase-negative Staphylococcus (37%), while Klebsiella was the most common gram-negative pathogen (18.8%), Escherichia coli, Enterococcus, and Enterobacter spices were each responsible for 6% of all infections. Candida caused 11.0% infections. Twenty percent of pathogens were resistant to gentamicin.

A one year retrospective hospital based study was carried out to analyze the results of neonatal blood, cerebrospinal fluid, urine, stool, and surfaces and to look into the sensitivity pattern of the commonly used antibiotics [55]. The positive yield of blood, urine, eye swab, and cerebrospinal fluid cultures were 19.5%, 38.5%, 60%, and 0.36%, respectively. The most common isolates in the blood were coagulase-negative Staphylococcus, Acinetobacter, and Enterobacter species. Among the gram-negative isolates more than 50% were resistant to gentamicin.

Viswanathan, et al. [56] reviewed aetiological agents of neonatal sepsis and their antibiotic resistance. Blood culture was done for 997 infants with suspected clinical sepsis. The incidence of culture proven neonatal sepsis among inborn infants was 14.8/1,000 live births. The proportion of culture positive sepsis for outborn infants was admitted in neonatal intensive care unit was 8.3%. Gram-negative aetiology was predominant (71.6%), with Klebsiella pneumoniae being the most common isolate. The aetiology of early-onset and late-onset sepsis was similar. The proportion of resistance to gentamicin was 84.4%.

Enterococci are important nosocomial agents and serious infections caused by them are often treated with a combination of cell wall inhibitor and aminoglycoside [57]. However, the presence of high level aminoglycoside resistance in these isolates makes this treatment combination ineffective. Fifty-one enterococcal strains were isolated from 21 infants, 9 young children, and 21 children with a clinical diagnosis of septicaemia. Sixty-eight percent of these isolates had high level of resistance to gentamicin.

Mahmood, et al. [58] studied the bacterial pathogens causing neonatal sepsis and their sensitivity pattern so that guidelines can be prepared for empirical antibiotic therapy. Blood specimens were drawn from 520 infants. A total of 212 organisms were isolated. These included Staphylococcus aureus (N = 22), Klebsiella pneumoniae (N = 18), Acinetobacter baumannii (N = 23), Escherichia coli (N = 22), Enterobacter cloacae (N = 18), Citrobacter diversus (N = 5), Pseudomonas aeruginosa (N = 4), and group B Streptococcus (N = 2). Resistance to gentamicin was as high as 90.4% for Klebsiella pneumoniae, and 60.87% for Acinetobacter baumannii.

Enterococci are one of the leading causes of nosocomial infections [59]. A study was conducted to determine the antimicrobial susceptibility of 50 isolates of enterococci from bacteraemic children. Seventh-two percent of isolates showed high-level of resistance to gentamicin.

A total of 561 stool cultures were obtained from children aged 1 to 60 months and presenting diarrhoea [60]. The children who were positive for bacterial culture were 33.9%. Most of the positive cultures (58%) were from children aged 1 to 12 months. The majority of the positive cultures were enteropathogenic Escherichia coli (58.4%) Salmonella species and Shigella species (20% each). The majority of the Salmonella was group C (60.5%) and group B (26%). Of the Shigella isolates, 34% was Shigella flexneri, and 18% was Shigella dysentrea. More than two-thirds of the Salmonella isolates were resistant to gentamicin. The tested Escherichia coli were resistant to gentamicin for 54%.

Escherichia coli sequence type 131 has emerged as a higher as a virulent and multidrug-resistant pathogen worldwide. Park, et al. [61] retrospectively reviewed culture-proven Escherichia coli bacteraemia cases of children aged ≤ 18 years. Escherichia coli isolates were analyzed using multilocus sequence typing, fimH typing, and CTX-M typing. Among 177 children with Escherichia coli bacteraemia, a total 21 (11.9%) had sequence type 131 isolates and 37 (20.9%) had extended spectrum β-lactamase-producing Escherichia coli. Nineteen (90.5%) isolates of sequence typing 131 Escherichia coli had the fimH gene, of which 3 were assigned to subclone H30. There was a significant difference in the prevalence of extended spectrum β-lactamase-production between sequence type 131 (N = 8.38%) and non-sequence type-131 (N = 29, 18.6%) isolates (P-value = 0.039). Five extended spectrum β-lactamase-producing sequence type 131 Escherichia coli isolates had the bla_{CTX-m} gene and $bla_{CTX-M-15}$. Sequence type 131 isolates had higher resistance to gentamicin 52.4% versus 28.8% (P-value < 0.05). The prevalence of sequence type 131 Escherichia coli causing bacteraemia in children was not different from that in adults or that causing urinary tract infection in children.

Heidary, et al. [62] investigated the frequency of virulence factors in the multidrug resistant strains of Pseudomonas aeruginosa from paediatrics hospitalized due to urinary tract infections. Seventy-one out of 143 samples (49.65%) were

positive for Pseudomonas aeruginosa. Bacterial strains were resistant to gentamicin for 92.95%. The most commonly detected virulence in cases of urethral infections was exoU and plcH while those of pyelonephritis and cystitis were exoS and lasB.

Enterococcal bacteraemia was identified in 2.1% of admissions, and in 15.3% of cases of culture-confirmed bloodstream infections [63]. The case-fatality rate in children with Enterococcus faecalis (28.6%) was not significantly different from those with Enterococcus faecium septicaemia (6.7%, P-value = 0.12). Enterococcus faecium isolates commonly had high-level gentamicin resistance (53%), while Enterococcus faecalis frequently displayed gentamicin resistance (40%). Multi-locus sequence-typing showed that the majority of Enterococcus faecium (58%) belonged to the hospital associated Bayesian Analysis of Population Structure group 3-3. Risk factors of enterococcal bloodstream infection in univariate analysis were hospital-acquired infection and clinical diagnosis of sepsis with unknown focus. In multivariate analysis, infants in general were relatively protected from enterococcal infection, while both prematurity and clinical sepsis was risk factors.

A total of 1,493 uropathogens were isolated. Escherichia coli was the leading cause, followed by Enterobacter species and other negative bacilli [64]. It was observed high resistance rate of Escherichia coli to gentamicin.

Discussion

Gentamicin is an aminoglycoside antibiotic and it is active against aerobic gram-negative bacilli such as Pseudomonas, Klebsiella, and Escherichia coli. Gentamicin should be co-administered with a β-lactam antibiotic. This antibiotic is rapidly bactericidal as it inhibits bacterial cell protein synthesis. Bacterial killing is concentration dependent: the higher the concentration, the greater the rate of bacterial killing [3]. Aminoglycosides, and thus gentamicin, are only effective against many bacteria when the serum concentration is high enough to be potentially toxic. A high peak level (at least eight times the MIC) enhances the drug's bactericidal effect. Gram-negative organisms stop taking up the drug after an hour and only do so again 2-10 hours later; therefore, repeat treatment during this time is ineffective. Serious toxicity is predominantly seen with treatment longer than 7-10 days where there are sustained high trough serum levels and/or co-exposure to other ototoxic drugs [1].

The ratio of the gentamicin peak concentration to the organism's MIC is a key predictor of gentamicin efficacy. The inhibitory of gentamicin persists after the serum concentration has fallen below the MIC, a phenomenon known as the "postantibiotic effect". Gentamicin diffuses through aqueous channels formed by porin proteins in the outer membrane of gram-negative bacteria to enter periplasmic space. Transport of gentamicin across the cytoplasmic (inner) membrane depends on a trasmembrane electrical gradient coupled to an electric transport to drive permeation of this antibiotic. One inside the cell, gentamicin binds to polysomes and interfere with protein synthesis by causing misreading and premature termination of mRNA translation. The primary intracellular site of action of gentamicin is the 30S ribosomal subunit. At least three of these ribosomal proteins and perhaps the 16S ribosomal RNA as well, contribute to the streptomycin-binding site. Gentamicin interferes with the initiation of protein synthesis, loading to the accumulation of abnormal initiation complexes, and also can cause misreading of the mRNA template and incorporation of amino acids into the growing polypeptide chains [4]. The resulting aberrant proteins may be inserted into the cell membrane, leading to altered permeability [5].

Several dosage schedules have been suggested for newborns and infants: 3 mg/kg once-daily for preterm newborns < 35 weeks of gestation; 4 mg/kg once-daily for newborns > 35 weeks of gestation; 5 mg/kg daily in two divided doses for newborns with severe infections; and 2-2.5 mg/kg every 8 hours for children up to 2 years of age [2]. Gentamicin is an efficacy and safe antibiotic in infants and children [6, 7]. In infants, gentamicin peak concentration should range between 5 and 10 μg/ml and the trough concentration should be < 2 μg/ml [8, 9]. A lower gentamicin was observed in infants than in neonates [8]. In infants aged < 7 days the peak gentamicin concentration was higher than in those above 7 days. Gentamicin was administered at a single daily dose of 2.5 or 4 mg/kg. Initial peak serum gentamicin concentration > 5 μg/ml was observed in 6% infants who received 2.5 mg/kg, versus 94% of infants who received 4 mg/kg gentamicin. Trough gentamicin < 2 μ/ml was observed in 100% and in 39% in infants who received 2.5 and 4 mg/kg, respectively [9]. Some authors determined the appropriate dosing intervals to obtain the correct therapeutic gentamicin concentrations in infants [10, 11, 12]. Dose intervals of 24 hours and 12 hours yielded 76% and 100%, respectively, toxic trough gentamicin concentrations [10]. Infants were administered 5 mg/kg gentamicin every 36 hours or every 24 hours. Toxic trough gentamicin concentration was found higher after 24 hours dosing than after 36 hours dosing intervals [11]. Infants with gestational age between 32 and 36 weeks, received 4 mg/kg gentamicin once-daily. Only 60% had peak and trough gentamicin concentrations within the therapeutic range [12]. Once-daily gentamicin dosing in infants and children was explored by some authors [13, 14, 15]. This dosing regimen was preferred than twice-daily [16, 17] and thrice-daily [18, 19] regimens. Once-daily regimen yielded higher peak and lower trough gentamicin concentrations.

Gentamicin causes ototoxicity [20-31] and nephrotoxicity [32-35]. Infants with a mitochondrial genetic variant (m.1555 > G), causes permanent hearing loss permanent hearing loss can occur even when gentamicin blood levels are within the therapeutic concentrations [20]. Hearing loss rate in preterm infants runs at 2-15%, compared to 0.3% in full-term births, and may be permanent in 2-3% of cases. Nephrotoxicity is transient.

Toxicity of gentamicin is greater infants with low gestational age [36]. The risk of gentamicin toxicity, and the potential

number of infants exposed annually to this risk is 6.9 million infants with possible serious bacterial infection [37]. A Bartter-like syndrome is a toxic manifestation of gentamicin [38]. Hypocalcaemia, hypomagnesaemia, alkalosis, and hypokalemia are the main manifestation of this syndrome. After discontinuation of gentamicin, recovery of the tubular functions and resolution of the electrolyte abnormalities were obtained.

The pharmacokinetic parameters of gentamicin were measured after the administration of 4 mg/kg once-daily and 2.5 mg/kg twice-daily gentamicin in 50 full-term infants [40]. The mean gentamicin peak concentration was higher in once-daily regimen. No difference of gentamicin through concentration was observed in these two regimens. The number of infants who had serum therapeutic gentamicin concentrations was greater in once-daily regimen. Low-birth weight infants were stratified on body weight. Infants with a body weight < 1,500 gram had a longer half-life and a greater distribution volume than infants with a body weight ≥ 1,500 gram [41]. Gentamicin pharmacokinetic parameters were measured in very-low-birth weight [42]. Infants received 2.5 mg/kg every 18 hours or 3.0 mg/kg every 24 hours. The gentamicin pharmacokinetic parameters were not different in these two regimens. The gentamicin pharmacokinetic parameters were measured in infants at ≤ 7 days of life and at > days of life in small-for-gestational age and in appropriate-for-gestational age [43]. At ≤ 7 days of life, the half-life was longer and the clearance was smaller in infant's small-for-gestational age than in infant's appropriate-for-gestational age. At > days of life, the trough gentamicin concentration was lower in infants small-for-gestational-age than in infants appropriate-for-gestational age. The other gentamicin pharmacokinetic parameters were not significantly different in both groups of infants.

Some authors suggested extending intervals among gentamicin doses when the gentamicin concentrations at 22 hours are higher than 1.2 μg/ml [44-46]. When the gentamicin concentration (μg/ml) is ≤ 1.2, 1.2-2.7, 2.7-3.5 intervals among gentamicin dose should be 24, 36, and 48 hours, respectively. When the gentamicin concentration at 22 hours is ≥ 3.6 μg/ml the dosing interval should be based to achieve a concentration < 2 μg/ml.

Several bacteria are resistant to gentamicin [48-64]. The mechanisms of bacterial resistance are: (1) inactivation of gentamicin by microbial enzymes, (2) failure of gentamicin to penetrate into the intracellular bacteria, and (3) low affinity of gentamicin for the bacterial ribosome [2].

In conclusion, gentamicin is an aminoglycoside antibiotic and is used to treat infections caused by aerobic gram-negative bacilli such as Pseudomonas, Klebsiella, and Escherichia coli. Gentamicin is rapidly bactericidal as it inhibits bacterial cell protein synthesis. The antimicrobial activity of gentamicin is based on peak concentration. The greater the peak concentration the greater the antimicrobial activity. The dose of gentamicin is 4 mg/kg given once-daily in full-term infants. In younger infants the gentamicin dose is reduced. Once-daily gentamicin administration is preferred than twice- or thrice-daily. The number of serum gentamicin concentration in therapeutic range is greater after once-daily than twice-daily. In infants, the gentamicin peak concentration ranges from 5 to 12 μg/ml and the trough concentration should be < 2 μg/ml. When the gentamicin trough concentration is > 2 μg/ml, intervals among doses should be extended to yield a trough concentration < 2 μg/ml. The gentamicin half-life is longer in premature than in full-term infants. At an age of ≤ 7 days of life, gentamicin half-life is longer and the clearance is lower in infants small-for-gestational age than in infants appropriate-for-gestational age. Several bacteria are resistant to gentamicin. Mechanisms of bacterial resistance to gentamicin are the inactivation of gentamicin by microbial enzymes, failure of gentamicin to penetrate into the intracellular bacteria, and low affinity of gentamicin for the bacterial ribosome.

Conflict of interests

The author declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

This article is a review and drugs have not been administered to men or animals.

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