Clinical and Medical Investigations

Review Article ISSN: 2398-5763

Clinical pharmacology of tobramycin in infants and children

Gian Maria Pacifici*

Associate Professor of Pharmacology, via Sant'Andrea 32, 56127 Pisa, Italy

Abstract

Tobramycin is an aminoglycoside antibiotic, binds to polysomes and interferes with bacterial protein synthesis causing misreading and premature termination of mRNA translation, it is bactericidal, has post-antibiotic effect on bacterial killing, and antimicrobial effect is concentration-dependent. This antibiotic may be administered orally, intravenously (either by slow injection or intravenous infusion), intramuscularly, applied to skin, and lung infections may be treated by inhalation. Tobramycin intravenous doses are: 5 mg/kg every 36 hours in infants, with a postmenstrual age < 32, and once-daily in older infants, and in children, doses are 2.5 and 3.5 mg/kg thrice-daily. Tobramycin effects are: increase of sodium excretion in the urine, tubular injury, and bronchoconstriction. This antibiotic well diffuses through all body organs, including the central nervous system, and successfully treated lung, kidney, ear, mouth, throat, eye, skin infections, rhinopharyngitis, and meningitis. Tobramycin peak and trough concentrations should be > 10 and < 2 μg/ml, respectively, in order to yield antimicrobial effect and to keep toxicity low. Optimization of treatment has been recommended in order to keep serum concentrations within the therapeutic-interval as they vary in infants and children. Tobramycin half-life is longer in infants (about 10 hours) than in children. Some organisms may become resistant to tobramycin. The aim of this study is to review published data on tobramycin dosing, efficacy, safety, effects, adverse-effects, drug-interactions, treatment optimization, trials, meningitis, pharmacodynamics, pharmacokinetics, and bacterial-resistance in infants and children.

Introduction

Tobramycin is an alternative to gentamicin in the management of gram-negative bacterial infections. It is particularly useful in the treatment of Pseudomonas aeruginosa infection in the lungs of children with cystic fibrosis and this drug was administered by either an inhalator or nebulizer. Tobramycin is a bactericidal antibiotic, related to kanamycin, which is handled by the body in much the same way as netilmicin. All the aminoglycoside antibiotics have a relatively low therapeutic ratio; there is little to choose between amikacin, gentamicin, netilmicin, and tobramycin in this regard. Tobramycin has certain theoretical advantages over gentamicin in the treatment of Pseudomonas infection because of greater in-vitro sensitivity, and aggressive high-dose treatment (10 mg/kg once-daily in children aged > 6 months) is often used when this pathogen colonizes the lung of children with cystic fibrosis. Twice-daily inhalation (300 mg in 2 to 5 ml of 0.9% sodium chloride) for four weeks is an alternative strategy that also has been used in this condition eliminating both lung infection and pseudomonas carriage. Repeat this, if necessary, after four weeks of treatment. Like gentamicin, tobramycin may be given either as an 'extended interval dose regimen' or as a 'multiple daily-dose-regimen' although very few of studies of once-daily versus thrice-daily aminoglycosides (see reference 6) treatment in neonates have actually involved the use of tobramycin. Check that blood levels can be measured by the local laboratory before starting treatment. Tobramycin crosses the placenta and whilst there are reports of total, bilateral congenital deafness after use other aminoglycosides, this has not been reported after tobramycin use. Systemic levels are much lower after nebulizer or ophthalmic administration compared to parenteral routes. Small amounts of tobramycin pass into breast-milk, however as oral bioavailability is poor, no effects would be expected in the breastfed infant. Aminoglycosides are capable of combining chemically with equimolar amounts of most penicillins. Such inactivation has been well documented in-vitro, and is the basis for the advice threat these antibiotics should never mixed together. Leaving a two- to four-hour gap between aminoglycoside and β-lactam antibiotic administration has been shown to enhance bactericidal potency in-vitro by an unaltered mechanism, but the clinical relevance remains far from clear. The blood levels is all that usually needs to be monitored in infants on treatment, and even this is probably only necessary as a routine in infants in possible renal failure or aged < 10 days. Aim for a through level of about 1 μg/ml (1 μg/ml=2.14 nanomoles/ml). In the multiple daily doses-regimens the one-hour ('peak') serum concentration should not exceed 10 μg/ml; and the pre-dose ('trough') concentration should be < 2 μg/ml [1].

Measure serum concentration when treating for more than 48 hours. Dosing recommendations are based on: (1) higher peak concentration increase concentration-dependent bacterial killing; (2) there is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) 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 infants. Inactivation of tobramycin by penicillin-

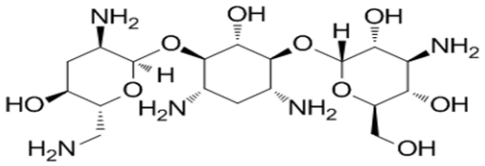
Correspondence to: Gian Maria Pacifici, Associate Professor of Pharmacology, via Sant'Andrea 32, 56127 Pisa, Italy, E-mail: pacifici44@tiscali.it

Key words: *tobramycin, dosing, efficacy, safety, effects, adverse-effects, development, drug-interactions, treatment, optimization, central nervous system, cerebrospinal fluid, meningitis, trials, pharmacokinetics, bacterial-resistance, infants, childre*

Received: November 14, 2020; **Accepted:** December 02, 2020; **Published:** December 09, 2020

containing compounds appears to be a time-, temperature-, and concentration depended processes. 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 the assay is performed. Tobramycin is incompatible with ampicillin, azithromycin, cefepime, imipenem/cilastatin, indomethacin, heparin, (concentration > 1 unity/ml), mezlocillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate [2].

Bacterial killing is concentration-dependent: the higher the concentration, the greater the bacterial killing-rate. The peak concentration to the organism's MIC ratio is a key predictor of aminoglycoside efficacy. Tobramycin diffuses through aqueous channels formed by porin proteins in the outer membrane of gram-negative bacteria to enter the periplasmic space. Transport of tobramycin across the cytoplasmic (inner) membrane depends on a transmembrane electrical gradient coupled to electron transport to drive permeation of tobramycin. This energy-dependent phase is rate limited and can be blocked or inhabited by divalent cations (e.g., Ca^{2+} and Mg^{2+}), hyperosmolarity, a reduction in pH, and anaerobic conditions. Thus, tobramycin antimicrobial activity is markedly reduced in the anaerobic environment of an abscess and in hyperosmolar acidic urine [3]. Once inside the cell, tobramycin binds to polysomes and interfere with protein synthesis by causing misreading and premature termination of mRNA translation. The primary intracellular site of tobramycin action is the 30S ribosomal subunit. At least three of these ribosomal proteins, and perhaps contributes to the streptomycin-binding protein. Tobramycin interferes with the protein synthesis initiation, leading to the accumulation of abnormal initiation complexes; the drug also can cause misreading of the mRNA template and incorporation of incorrect amino acids into the growing polypeptide chains [4]. The resulting aberrant proteins may be inserted into the bacterial cell membrane, leading to altered permeability and further stimulation of tobramycin transport [5].



Molecular structure of tobramycin (molecular weight=467)

Results

Tobramycin administration schedules in infants and children

Tobramycin administration schedules in infants

Extended interval dosing-regimen: Infants: give 5 mg/kg by intravenous injection over three to five min or by intravenous infusion. Give a dose once every 36 hours in infants with a postmenstrual age < 32 weeks and an once-daily dose in infants more mature than this [1].

Older infants: give 7 mg/kg once-daily; then adjust the dose according to serum tobramycin concentration [1].

Multiple daily dosing-regimens: infants give 2 mg/kg intravenously over three to five min or by intravenous infusion twice-daily during the first week of life. Reduce the dosing-interval to eight hours after that [1].

Older infants: give 2 to 2.5 mg/kg intravenously over three to five min or by intravenous infusion thrice-daily [1].

Tobramycin administration schedules to children

Administration by inhalation of nebulised solution

Chronic Pseudomonas aeruginosa infection in children with cystic fibrosis: children aged 6 to 17 years: give 300 mg twice-daily for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution [6].

Administration by inhalation of powder

Children aged 6 to 17 years: give 112 mg twice-daily for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder [6].

Pseudomonal lung infection in cystic fibrosis children

Administration by slow intravenous injection

Children: give 8 to 10 mg/kg daily in three equal divided doses, to be given as a multiple daily dosing-regimens over 3 to 5 min [6].

Administration by intravenous infusion

Children: give an initial dose of 10 mg/kg (maximum per dose 660 mg), to be given by intravenous infusion, subsequent doses should be adjusted according to serum tobramycin concentration [6].

Administration schedules to treat: septicaemia, meningitis, and other central nervous infections, biliary tract infections, acute pyelonephritis, and pneumoniae in hospitalized children

Administration by slow intravenous injection

Children aged 1 month to 11 years: give 2 to 2.5 mg/kg thrice-daily, to be given as a multiple daily dosing-regimen over 3 to 5 min [6].

Children aged 12 to 17 years: give 1 mg/kg thrice-daily, to be given as a multiple daily dosing-regimens over 3 to 5 min. Increase the dose if necessary up to 5 mg/kg in 3 to 4 divided dose, to be reduced back to 3 mg/kg as soon clinically indicated [6].

Administration by intravenous infusion

Children: give initially 7 mg/kg, to be administered according to serum tobramycin concentration [6].

Indication and doses: local treatment of eye infections

Children aged 1 to 17 years: apply twice-daily for 6 to 8 days [6].

Eye severe infections

Children aged 1 to 17 years: apply 4 times-daily for first day, then apply twice-daily for 5 to 7 days.

Literature search

The literature search was performed electronically using PubMed database as search engine and the cut-off point was July 2020. The following key words: "tobramycin infants effects", "tobramycin children effects", "tobramycin infants metabolism", "tobramycin children metabolism", "tobramycin infants pharmacokinetics", "tobramycin children pharmacokinetics", and "tobramycin resistance", were used. In addition, the books Neonatal Formulary [1], NEOFAX® by Young and Mangum [2], The Pharmacological Basis of Therapeutics [3] and The British National Formulary for Children [6], were consulted. The manuscript is written according to "Instructions for authors".

Tobramycin efficacy and safety in children

Konstan *et al.* [7] evaluated the efficacy and safety of inhaled tobramycin powder versus tobramycin inhalation solution in treating 553 children, aged ≥ 6 years, suffering from cystic fibrosis and had their lung infected by Pseudomonas aeruginosa. Children were randomized 3:2 to tobramycin inhalation powder (total dose=12 mg) twice-daily or 300 mg/5 ml of nebulizer twice-daily for 3 treatment cycles (28 days on-drug, 28 days off-drug). Cough-rate was 26.9% for inhalation powder (5.6 min) versus 18.2% for inhalation solution (19.7 min, P-value < 0.0001), and both treatments were effective and safe, but inhaled tobramycin powder was more efficient.

Pai and Nahata [8] observed that tobramycin improved pulmonary function and decreased Pseudomonas aeruginosa density in sputum, but this organism became resistant to tobramycin.

Di Cicco *et al.* [9] assessed tobramycin tolerability and efficacy in 27 children, aged 15 years (range, 5 to 26), with cystic fibrosis who received nasal spray formulation containing hyaluronate and tobramycin 3% (N=14) or hyaluronate alone (N=13) for 14 days. The formulation containing tobramycin was more effective in improving ear, nose and throat symptoms, and treatment with tobramycin was safe.

Treggiari *et al.* [10] enrolled 304 children, aged 1 to 12 years, who had lung infected by Pseudomonas aeruginosa and were randomized to receive either tobramycin inhalation solution (300 mg twice-daily) or oral ciprofloxacin (15 to 20 mg/kg twice-daily) for 28 days. No difference was observed in exacerbation-rate and Pseudomonas aeruginosa re-infection.

Tobramycin effects in infants and children

Rothberg and Andronikou [11] measured the fractional sodium excretion in 25 infants with a postmenstrual age and birth-weight of 34.3 weeks and 1,830 grams, respectively, who were treated with tobramycin during the first 2 days of life. Mean fractional sodium excretion was persistently elevated during treatment and decreased to normal range within 2 days of stopping treatment.

Leititis *et al.* [12] noted that tobramycin treatment caused a transient disturbance of proximal tubular cell function, and decreased tubular reabsorption.

Glass *et al.* [13] stated that tobramycin is used to treat respiratory exacerbations in 22 children with cystic fibrosis, aged 10.9 years (range, 31.0 to 16.4), who were treated with 3 mg/kg tobramycin intravenously. Urinary excretion of N-acetyl-β-D-glucosaminidase and retinol-binding protein rose significantly (P-value < 0.0001). Tobramycin produced acute tubular injury which resolved 4 weeks after stopping treatment.

Gibson *et al.* [14] assessed tobramycin efficacy in decreasing Pseudomonas aeruginosa density in the bronchial lavage of children, aged < 6 years, and treatment lasted for 28 days. This organism was eradicated from bronchi in all children.

Alothman *et al.* [15] evaluated the risk of bronchoconstriction using inhaled tobramycin solution of either 80 mg/2 ml or 300 mg/5 ml saline in 19 children, aged 7 to 16 years, who had cystic fibrosis and their lung was infected by Pseudomonas aeruginosa. Both formulations caused significant bronchoconstriction.

Varricchio *et al.* [16] enrolled 155 children, aged 3 to 6 years, who were suffering from acute bacterial rhinopharyngitis, and were treated with 15 mg of aerosolized tobramycin or 50 mg/kg amoxicillin/clavulanate twice-daily for 10 days. Both treatments improved nasal obstruction, mucopurulent rhinorrhoea, post-nasal drip, adenoidal hypertrophy, tympanic inflammation, tympanogram, rhinomanometry, and reduced bacterial-density. Tobramycin is a valid antibiotic to treat acute rhinopharyngitis.

Ramagopal and Lands [17] determined incidence of bronchoconstriction with inhaled tobramycin (80 mg/2 ml of saline) in 10 children, and 16 children who were pre-treated with salbutamol. All children were, aged 7 to 17 years, and had cystic fibrosis. Bronchoconstriction did not occur in many children, and pre-treatment with salbutamol reduced tobramycin-exposure.

Tobramycin adverse-effects in infants and children

Tobramycin is a safe drug and in literature there are only three studies dealing with adverse-effects caused by this antibiotic. Abdulhamid *et al.* [18] reported a case of a preterm infant with numerous congenital and acquired disorders who was treated with tobramycin for 60 days of hospital stay. Tobramycin was inhaled at a dose of 80 mg, successively with 300 mg, and tobramycin cumulative dose was 1,300 mg over a 6-day of treatment. The infant developed several pulmonary infections caused by various bacteria, and died on the 60th day of hospitalization.

Howard-Thompson and Christensen [19] reported a case of a preterm infant, aged 1 month, who had compromised renal impairment and received tobramycin (300 mg twice-daily) endotracheally via a nebulizer, and also was treated with intravenous tobramycin (2.5 mg/kg) every18 hours. Tobramycin serum concentrations was 11.5 μg/ml 45 hours after the last intravenous dose, and 17.6 μg/ml after the second nebulized dose, suggesting that tobramycin decays slowly in preterm infant with renal failure.

Thomsen and Friis [20] assessed adverse-effects caused by tobramycin in 53 children with cystic fibrosis who also had lower respiratory-tract infection caused by Pseudomonas aeruginosa. Only one child had transient high tone impairment which was attributed to tobramycin treatment. High tobramycin dose implies only minimal ototoxic adverse-effects.

Effects of postmenstrual age and body-weight on tobramycin pharmacokinetics

In literature there is only one study concerning effects of postmenstrual, postnatal ages and body-weight on tobramycin pharmacokinetics in infants and was reported by Nahata *et al.* [21]. Twenty-six infants with bacterial sepsis received tobramycin intramuscularly at a dose of 2.5 mg/kg twice-daily. Infants were clustered into three groups according to postmenstrual age (PA): group A consisted of 9 infants with PA of 28 to 30 weeks; group B had 11 infants with PA > of 30 to 34 weeks; and group C had 6 infant with PA > 34 to ≤ 40 weeks. Tobramycin peak serum concentrations at steady-state averaged to 6.5, 7.2, and 7.1 μg/ml in groups A, B, and C, respectively; and the corresponding trough concentrations averaged to 3.0, 2.3, and 1.3 μg/ml. The frequency of trough concentration > 2 μg/ml was 44%, 45% and 0% in these groups, respectively. Total body clearance averaged to 1.04, 1.13, and 1.28 ml/min/kg, respectively; the distribution volume was 0.84. 0.81, and 0.61 L/kg, respectively; and elimination half-life averaged to 9.3, 8.9, and 5.6 hours in groups A, B, and C, respectively. Group D consisted of 7 infants with 1,000 to 1,250 grams of body-weight; group E had 6 infants with a body-weight of 1,260 to 1,500 grams; group F had 6 infants with body-weight 1,260

to 1,500 grams; group G had 6 infants with body-weight of 1,510 to 2,000 grams; and group H had 6 infants with body-weight of 2,100 to 3,500 grams. Steady-state peak serum concentration averaged to 5.7, 7.3, 7.8, and 7.1 μg/ml; and trough concentration averaged to 2.2, 2.4, 1.9, and 1.3 μg/ml in groups D, E, F, and G, respectively. The frequency of trough concentration exceeding 2 μg/ml was 43%. 50%, 43%, and 0% in these groups, respectively. Total body clearance averaged to 1.02, 1.12, 1.10, and 1.28 ml/min/kg; the distribution volume averaged to 1.02, 0.74, 0.69, and 0.61 L/kg; and elimination half-life averaged to 11.3, 8.2, 7.5, and 5.6 hours in these four groups respectively. Infants with < 34 weeks of postmenstrual age, particularly those weighing < 1,500 grams of body-weight required a longer dosing-interval than currently recommended. Total body clearance and half-life increased and decreased, respectively, according to both postmenstrual age and body-weight indicating that tobramycin clearance from the body increases with intrauterine development and infant maturation.

Tobramycin is a safe antibiotic and induces only limited toxicity in infants and children

Raine *et al.* [22] administered tobramycin intramuscularly, intravenously, and intraperitoneally at a dose of 5 mg/kg daily to 38 infants and children who were infected by gram-negative organisms and staphylococcal species. Microorganisms were eradicated by tobramycin and serum concentrations ranged from 2 to 10 μg/ml. Clinical and bacteriological assessments indicated that only two failures occurred. Renal, hepatic, and haematological impairments were transient and reversible and those occurred in only one subject. Tobramycin treatment was rapid and satisfactory and had limited adverse-effects.

Hennig *et al.* [23] administered tobramycin twice-daily, to infants and children, aged 0 to 5 years, who had lung infected by Pseudomonas aeruginosa. Subjects were treated with either aminoglycosides or tobramycin (N=39) with intravenous tobramycin alone (N=36) and with both intravenous and inhaled tobramycin (N=67). Pseudomonas aeruginosa was eradicated from the lung of all subjects, and estimation of audiological and glomerular filtration rate were assessed prior to and after treatments. Alteration of audiometry and renal function were not different among treatments suggesting that tobramycin does not cause ototoxicity and nephrotoxicity.

Tobramycin drug-interactions

Kaushik *et al.* [24] assessed tobramycin effects co-administered with bicarbonate to subjects who had lung infected by Pseudomonas aeruginosa. Bicarbonate associated with tobramycin enhanced Pseudomonas aeruginosa killing-rate. In contrast, bicarbonate antagonised tobramycin antimicrobial effect in promoting better biofilm growth. Caution should be used when bicarbonate is co-administered with tobramycin.

Tré-Hardy *et al.* [25] performed a study to assess tobramycin efficacy in children whose lung was infected by Pseudomonas aeruginosa. Tobramycin was administered twice-daily for 28 days and was co-administration with clarithromycin or with azithromycin. Administration of tobramycin and clarithromycin resulted in a synergistic effect against Pseudomonas aeruginosa which was more pronounced than that of tobramycin and azithromycin.

Nichols *et al.* [26] tested the hypothesis that azithromycin reduced the clinical benefits of tobramycin against Pseudomonas aeruginosa, and also assessed MexXY efflux pumps. Azithromycin selectively reduced anti-bactericidal effects of against Pseudomonas aeruginosa in-vitro and up-regulated antibiotic resistance through increasing MexXY efflux.

Vidaillac *et al.* [27] evaluated anti-microbial effect of tobramycin in-vitro, in presence of ceftaroline or vancomycin. Ceftaroline and vancomycin displayed significant greater activity of tobramycin against methicillin-resistant Staphylococcus aureus (P-value < 0.01, for both drugs).

Dupuis *et al.* [28] studied the interaction of tobramycin and gentamicin, 22 subjects had therapeutic serum levels of both drugs and 22 subjects served as controls. No statistically significant differences were found in onset-time, whereas hospital stay duration and recover-time were significantly longer in patients who received vecuronium or atracurium co-administered with tobramycin or gentamicin compared to controls (P-value < 0.01, for both drugs) and for hospital stay duration (P-value < 0.0005 for recovery).

Tobramycin penetration into cerebrospinal fluid and treatment of meningitis of infants and children

Eiland *et al.* [29] measured tobramycin concentration into the cerebrospinal fluid of an infant, aged 70 days, suffering from meningitis caused by Pseudomonas aeruginosa. Tobramycin was injected intraventricularly and also intravenously at doses of 2 mg daily and subsequent doses were adjusted to maintain concentrations of 20 to 30 μg/ml in the cerebrospinal fluid which was sterilized after three days over 24-days of systemic treatment. No acute complications were noted with addition of intraventricular injections.

Tessin *et al.* [30] administered tobramycin intravenously combined to ampicillin to 17 infants with meningitis caused by enterococci and Listeria monocytogenes. Tobramycin concentrations were measured on the third, fourth, and fifth injections. In 13 of 17 infants (76.5%), tobramycin concentration in cerebrospinal fluid was < 0.5 μg/ml and such concentration was sufficient to cure meningitis.

Schneeberger *et al.* [31] reported a child, aged 2 years, with meningitis caused by Listeria meningitis and treatment with tobramycin co-administered with amoxicillin intravenously quickly cured meningitis.

Tobramycin treatment in infants and children

Kaplan *et al.* [32] stated that tobramycin is active against a wide range of bacteria and > 90% of coliform organisms and Pseudomonas species are susceptible to 5 μg/ml concentration in-vitro. Following a dose of tobramycin 2 mg/kg twice-daily, peak concentration ranged from 4 to 6 μg/ml in all infants, and elimination half-life was inversely related to creatinine clearance. Tobramycin should be used only for treatment of neonatal infections caused by gram-negative organisms resistant to both kanamycin and gentamicin.

de Hoog *et al.* [33] assessed occurrence of hearing loos in 9 children who were exposure to long courses of tobramycin (> 7 days) and measured tobramycin serum concentrations in children. Control group consisted of 9 children without tobramycin-exposure and all children were aged 3 to 4 years. In the treated group, both evoked optoacoustic emission and distortion oto-acoustic emissions were normal, and no hearing loos were detected. Three of 9 children (33.3%) had tobramycin serum concentrations ranging from 84 to 92 μg/ml 20 to 24 days of exposure. No relation was detected between hearing loss and tobramycin-exposure.

Wientzen *et al.* [34] performed placebo-controlled study to determine response to tobramycin therapy in 11 children suffering from acute pulmonary exacerbations caused by Pseudomonas species, and the control group consisted of 11 children. All children were suffering from cystic fibrosis, and no treated child died, whereas 2 children who received placebo died. Symptoms decreased in 15% or more in treated children, and density of this organism decreased of 1 logarithm or greater in 6 of 7 treated children (85.7%) whereas it decreased in only 2 of 8 children (25.0%) who received placebo. Tobramycin is beneficial in treatment of acute pulmonary exacerbations.

Andreacchio *et al.* [35] evaluated efficacy of tobramycin-impregnated with calcium sulfate pellets in 12 skeletally immature children with chronic osteomyelitis. Single-stage surgery associated with systemic antibiotic therapy yielded satisfactory outcomes by reducing the risk of comorbidity occurrences.

de Velde *et al.* [36] reported elevated serum tobramycin concentrations in an 11-year-old child with renal failure who received inhaled tobramycin for treatment of respiratory-tract infection caused by Staphylococcus aureus and Candida albicans. Extracorporeal membrane oxygenation was performed for 4 days. Continuous veno-venous hemofiltration was started on day 6th day of hospitalization and atelectasis was detected in the right lobe. Tobramycin was inhaled, and 7 days after starting treatment, serum concentrations were 13.8 μg/ml and after 6 hours of dosing concentration were 17.1 μg/ml. Tobramycin concentration decayed slowly in a child with renal failure.

Bothra *et al.* [37] observed that tobramycin is effective in management of lower respiratory-tract infected by gram-negative bacilli in infants. Inhaled tobramycin provided advantages for easy administration at home for prolonged period, improved outcomes, decreased need of hospitalization and prevented systemic re-infection.

Stelmach *et al.* [38] administered tobramycin by inhalation to 12 children, aged 6 to 18 years, with lung infected by Pseudomonas aeruginosa. Treatment significantly reduced organism density in lung compared to children who did not receive treatment (P-value=0.049) in a follow-up of 2 years.

Clavel *et al.* [39] compared tobramycin lung absorption; 300 mg of tobramycin was delivered by inhalator or by nebulisation in 10 children, in two separate sessions. The amount tobramycin excretion in the urine was low and variable and accounted for 47.6 mg/g (range, 14.9-79.6) delivered by the nebuliser and 42.6 mg/g (6.3-112.8) by the inhalator. Tobramycin dose was delivered in 22 and 11 min with nebuliser and inhalator, respectively (P-value=0.005), and inhalator was more efficient.

Optimization of tobramycin administration in order to optimize tobramycin clinical outcomes in infants and children

de Hoog *et al.* [40] individualized tobramycin dosing-regimens in 247 infants, with different postmenstrual ages, who received tobramycin by intravenous infusion at a dose of 4 mg/kg. Serum peak and trough target concentrations were: 5 to 10 and 0.5 μg/ml, respectively, which were taken 1- and 6-hours after the first dose. The effect of sampling-time was investigated in a second group of infants and peak and trough serum specimens were sampled after a second dose on 3- and 8-hours. Peak serum concentrations were > 5 μg/ml in 90.8% infants, and trough serum concentrations were < 1 μg/ml in 25.5% infants. The 3- to 8-hour linear model had a bias of -0.31 μg/ml and a precision of 0.48 μg/ml, and it was significantly better than the 1- to 6-hour model.

Turner *et al.* [41] determined optimal tobramycin dosing-regimen for treatment of pulmonary exacerbations in children with cystic fibrosis. Once-daily dosing-regimen was performed in 44 and twice-daily dosing-regimen was carried-out in 15 children. Once-daily dosing-regimen achieved higher peak concentration than twice-daily dosing-regimen (29.5+11.0 versus 19.0+4.9 μg/ml, P-value < 0.001), and greater time to achieve peak concentration equivalent to MIC of the infective agent (13.4+1.7 versus 3.9+3.1 hours, P-value < 0.001). Twice-daily dosing-regimen failed to achieve higher peak*MIC for MICs > 1 μg/ml. Twice-daily dosing-regimen may be a viable alternative to once-daily dosing-regimen for treating organisms with MICs ≤ 1, however for organisms with MICs > 1 μg/ml once-daily achieves goal Peak/MIC ratio.

Dopfer *et al.* [42] optimized tobramycin dosing-regimen with two inhalation techniques. Tobramycin was inhaled at doses of 300 or 150 mg twice-daily for three days either in controlled and conventional inhalation types in 16 children, aged 13 to 39 years, whose respiratory-tract was infected and had cystic fibrosis. Optimization of treatment was investigated by measuring tobramycin serum concentration one hour after the end of inhalation and no difference was observed in serum concentrations according to two methods. Exposition to tobramycin was double with conventional infusion; variation coefficient and required inhalation time were shorter in controlled inhalation (42% versus 65% 7 and 8 min versus 20 min, respectively). Controlled inhalation significantly reduced tobramycin amounts required for therapy, inhalation time for drug deposition, variability of pulmonary exposition, and prevented re-infection.

Tobramycin trials in children

Ratjen *et al.* [43] performed a placebo-controlled trial and compared eradication-rate of Pseudomonas aeruginosa from lung using 300 mg tobramycin inhaled twice-daily to that of placebo in children, aged < 7 years, with cystic fibrosis. On 29th day of therapy, 84.6% children had sputum free from this organism compared to 47.8% in children who received placebo. Inhaled tobramycin eradicated bacteria more efficiently than placebo, and adverse-effects caused by tobramycin were similar to those caused by placebo.

Stanojevic *et al.* [44] conducted a study consisting in tobramycin inhaled at doses of 300 mg/5 ml or 80 mg/2 ml twice-daily for 28 days. Sixty-five children, aged < 18 years, were enrolled, their lung were infected by Pseudomonas aeruginosa and had cystic fibrosis. Seven children (10.8%) failed to eradicate organism, and failure-rate was similar in both treatments. Four children (6.2%) developed chronic infection at 12 months after end of therapy. Female gender, older age, pancreatic insufficiency, lower lung function and worse nutritional status were identified as risk factors for recurrent of Pseudomonas aeruginosa infection. Both dosing-regimens had similar antibacterial effectiveness and prevented Pseudomonas re-infection.

Sung *et al.* [45] conducted a tobramycin trial in 60 children, aged ≤ 18 years, who had fever and neutropenia undergoing stem cell transplantation, who were assigned to receive intravenous tobramycin, either a single-daily dose (N=29, group A) or thrice-daily (N=31, group B) and all children were co-administered either with intravenous piperacillin or ceftazidime. Average percent increase of serum creatinine concentration was 32% in children of group A and 51% in children of group B. Treatment efficacy was observed in 12 children (46.1%) of group A and 5 children of group B (P-value=0.03). There was only one death in each dosing-regimen, and tobramycin is less nephrotoxic and more efficacious when administered once-daily.

Wientzen *et al.* [46] performed a tobramycin trial to test eradication-rate of Pseudomonas aeruginosa from lung in 11 children, whereas other 11 children received placebo, and all had cystic fibrosis. Two children died in the placebo group whereas no child died in the treatment group, and this organism was eradicated from lung in 6 of 11 treated children (54.5%). In 6 of 7 treated children (85.7%), Pseudomonas species density decreased of 1 logarithm in sputum compared to 2 of 8 children (25.0%) who received placebo. Tobramycin is beneficial in treatment of acute pulmonary exacerbations.

Tobramycin pharmacokinetics in infants

de Hoog *et al.* [47] established tobramycin dosing-regimens in 470 infants, with suspected septicaemia in the first week of life, and dosing-regimens were performed according to the following postmenstrual ages (PA): infants with PA < 28 weeks were treated with 3.5 mg/kg once-daily, at a PA from ≤ 28 to < 32 weeks infants received 2.5 mg/kg every 18 hours, and at a PA > 37 weeks infants received 2.5 mg/kg twice-daily, and treatment lasted 10 days in all cases. Tobramycin was co-administered with amoxicillin at a dose of 50 or 100 mg/kg. For prospective study, tobramycin was administered according to the following PA: 4 mg/kg every 48 hours (PA < 32 weeks) 4 mg/kg every 36 hours (PA ≤ 32 and < 37 weeks), and 2.5 mg/kg twice-daily (PA > 37 weeks). Table 1 summarizes measured serum trough and peak concentrations, Table 2 shows the predicted trough and peak concentrations, and Table 3 gives trough and peak concentrations with the use of revised dosing-regimens. Acceptable therapeutic tobramycin peak and trough concentrations were achieved in three separate PA groups. Trough concentrations are not toxic with ≤ 1 and < 2 μg/ml and guarantee bacteria regrowth. Tobramycin elimination half-live are longer in infants, especially in preterm infants; this is due to higher percentage of body water and consequently larger distribution volume and reduced clearance, and total body clearance increases with infant maturation. Peak concentrations of > 4 to 5 μg/ml are necessary for antibacterial efficacy which is related to MIC/AUC ratio and should be kept 1:10 to prevent emergence of resistant pathogens. Dosing-regimens used in this study showed that most peak concentrations were in the required range (Table 2). The prospective evaluation showed that trough and peak serum concentrations are in the desired therapeutic-range (Table 3).

Nahata *et al.* [48] assessed tobramycin pharmacokinetics in 8 infants with a postmenstrual age, and body-weight of 28.4+2.0 weeks and 8,050+1.105 grams, respectively. Tobramycin was intravenously infused at a dose of 2.2+0.44 mg/kg, and the dose-interval was 18.0+3.0 hours (range, 18 to 24). Total body clearance, distribution volume and

Table 1. Measured tobramycin serum trough and peak concentrations[§] in 470 infants with different postmenstrual ages. Figures are the number of infants and (percentage) and are arranged according to postmenstrual age, by de Hoog *et al.* [47]

	Postmenstrual age (PA, weeks)				
Tobramycin conc. (μg/ml)	**PA<28**	**PA ≤ 28<32**	**PA ≤ 32<37**	**PA>37**	**Total**
Trough ≤ 2	42 (51.3%)	103 (61.7%)	104 (81.2%)	67 (72.1%)	316 (67.2%)
Trough>2	40 (48.8%)	64 (38.3%)	24 (18.8%)	26 (28.0%)	154 (32.8%)
Peak>5	4 (4.9%)	37 (22.2%)	32 (25.0%)	17 (18.3%)	90 (19.1%)
Peak ≤ 5 ≤ 10	75 (91.5%)	128 (76.6%)	96 (75.0%)	74 (79.6%)	373 (79.4%)
Peak>10	3 (.37%)	2 (1.2%)	0 (0.0%)	2 (2.2%)	7 (1.5%)
Total	82 (17.4%)	167 (35.5%)	128 (27.2%)	93 (19.8%)	470 (100%)

Conc.=concentration. [§]Tobramycin doses were: 3.5 mg/kg once-daily (PA<28 weeks), 2.5 mg/kg every 18 hours (PA=28 to 32 weeks), and 2.5 mg/kg twice-daily (PA>37 weeks). Amoxicillin was administered at doses of 50 or 100 mg/kg once-daily to all infants.

Table 2. Predicted tobramycin trough and peak concentrations[§] in 470 infants with different postmenstrual ages. Figures are the number of infants and (percentage) and are arranged according to postmenstrual age, by de Hoog *et al.* [47]

	Postmenstrual age (PA, week)				
Tobramycin conc. (μg/ml)	**PA<28**	**PA ≤ 28<32**	**PA ≤ 32<37**	**PA>37**	**Total**
Trough ≤ 1	75 (91.5%)	161 (96.4%)	116 (90.6%)	82 (88.2%)	434 (92.3%)
Trough <1 ≤ 2	6 (7.3%)	5 (3.0%)	9 (7.0%)	7 (7.5%)	27 (5.7%)
Trough>2	1 (1.2%)	1 (0.6%)	3 (2.3%)	4 (4.3%)	9 (1.9%)
Peak<5	11 (13.4%)	10 (6.0%)	2 (1.6%)	0 (0.0%)	23 (4.9%)
Peak ≤5 ≤ 10	69 (84.1%	149 (89.2%)	92 (71.9%)	6 (6.5%)	316 (67.2%)
Peak>10	2 (2.4%)	8 (4.8%)	34 (26.6%)	87 (93.5%)	131 (27.9%)
Total	82 (17.4%)	167 (35.5%)	128 (27.2%)	93 (27.2%)	470 (100%)

Conc.=concentration. [§]Tobramycin doses were: 3.5 mg/kg once-daily (PA<28 weeks), 2.5 mg/kg every 18 hours (PA=28 to 32 weeks), and 2.5 mg/kg twice-daily (PA>37 weeks). Amoxicillin was administered at doses of 50 or 100 mg/kg once-daily to all infants.

Table 3. Measured tobramycin trough and peak concentrations[§] obtained with use of recommended revised dosing-regimes administered to 23 infants with different postmenstrual age. Figures are the number of infants and (percentage) and are arranged according to postmenstrual age, by de Hoog *et al.* [47]

	Postmenstrual age (PA, weeks)			
Tobramycin conc. (μg/ml)	**PA<32 weeks**	**PA ≤ 32<37**	**PA ≥ 37**	**Total**
Trough ≤ 1	6 (85.7%)	5 (62.5%)	---	---
Trough <1 ≤ 2	---	2 (25.0%)	2 (25.0%)	4 (17.4%)
Trough>2	1 (14.3%)	1 (12.5%)	1 (12.5%)	3 (13.0%)
Peak<5	1 (14.3%)	---	---	1 (4.3%)
Peak ≤ 5 ≤ 10	6 (85.7%)	7 (87.5%)	6 (75.0%)	19 (82.6%)
Peak<10	---	1 (12.5%)	2 (25.0%)	3 (13.0%)
Total	7 (30.4%)	8 (34.8%)	8 (34.8%)	23 (100%)

Conc.=concentration. [§]4 mg/kg (PA ≤ 32 weeks), 4 mg/kg every 36 hours (PA>32<37 weeks), 2.5 mg/kg twice-daily (PA>36 weeks). Amoxicillin was administered at doses of 50 or 100 mg/kg once-daily to all infants.

elimination half-life were: 0.69+0.10 ml/min/kg, 0.59+0.10 L/kg, and 9.9+1.5 hours (range, 9.4 to 12.6), respectively. Steady-state peak and trough tobramycin concentrations were: 7.6+1.5 and 1.7+0.4 μg/ml, respectively. Seven of 8 infants (87.5%) had a serum concentration > 2 μg/ml at 12 hours and two of 8 infants (25.0%) had a serum concentration > 2 μg/ml at 18 hours after dosing. Total body clearance increased and half-life decreased, respectively, according to postmenstrual age and body-weight. This variation may be explained by increasing of intrauterine development and infant maturation as tobramycin is mainly eliminated by kidney and renal function increases with infant maturation. Peak serum concentration was within therapeutic-range, and trough concentration should be < 2 μg/ml in order does not cause nephrotoxicity and ototoxicity. Tobramycin dosing-regimens should be 2.5 mg/kg every 18 hours or 3.0 mg/kg once-daily. Infant maturation increased tobramycin clearance from the body.

Changes of tobramycin pharmacokinetic parameters during human development

van den Anker *et al.* [49] described changes in drug pharmacokinetic parameters during human development. Distribution volume, total body clearance, and half-life are important pharmacokinetic parameters and these are influenced by human development. Half-life decreases during development and this may be explained by either and increase of total body clearance and a decrease of distribution volume. Absorption, distribution, metabolism and elimination display modifications during human development. Gastric emptying and intestinal mobility determines the extent-rate of drug absorption, the former undergoes developmental changes, is lower in infants aged < 6 to 8 months, and the latter is minimally influenced by development. Intestine contains several influx and efflux factors and drug transporters as well as drug-metabolizing enzymes which contribute to the overall drug bioavailability and undergo changes during development. Distribution of drugs depends on drug lipophilicity, water solubility, degree of ionization, protein binding, and tissue uptake, the last two parameters are influenced by human development; in particular plasma protein binding of drugs is decreased in infants. Age-dependent maturational in body composition changes the physiological space into which a drug distributes and amount of body-water/kg is 90% to 80%, 70%, and 60% in preterm, term, and children, respectively. Drug distribution in deep compartments, such as the central nervous system, is limited in infants due to reduced efflux transporters (P-gp) expression, and intrathecal administration may be an alternative option. Drug metabolism rate is reduced in infants and this is true for different CYP enzymes, particularly for CYP3A4 and CYP3A5, which metabolize 50 to 60% of all drugs. Expression of conjugating enzymes, such as sulfotransferases, glucuronyltransferase, glutathione-transferases, and N-acetyl transferases, are reduced in infants, and sulfotransferase and glucuronyltransferase metabolize all hydrolytic drugs. Drug elimination by kidney is depending on glomerular filtration, tubular excretion, tubular reabsorption and renal function increases with infant maturation. Glomerular filtration-rate (ml*min^2) is 20 to 30, 20 to 40, and 70 at birth, in the first weeks of life, and in children aged over 15 years, respectively.

Lam *et al.* [50] evaluated optimal tobramycin dosing-regimen for treatment of acute pulmonary exacerbation in 102 children patients with cystic fibrosis, aged 13.5+3.5 years, of whom 41 and 91 were males and females, respectively, and all children were infected by Pseudomonas aeruginosa. Tobramycin was intravenously infused at a dose of 3.3 mg/kg thrice-daily and ceftazidime was co-administered at a dose of 50 mg/kg 4 times-daily. Table 4 shows tobramycin pharmacokinetic parameters which were grouped according to both sex and age, and Table 5 summarizes simulated pharmacokinetic parameters obtained with once-daily dosing-regimen. Table 4 shows that peak concentration using the binary partitioning method, and the critical value for age was 13.7 years. Nutritional status and sex were significantly associated with distribution volume corrected per kg body-weight. About 49 to 67% of Pseudomonas aeruginosa had an MIC ≤ 4 μg/ml, with the majority (80%) having an MIC ≤ 2 μg/ml. The target peak concentration range should be 8 to 10-fold higher MIC for an organism in order to produce an adequate clinical response. Peak concentration ranged from 11.9 (in males) to 13.5 μg/ml (in females) thus was 3- and 3.4-fold higher the MIC=4 μg/ml and 5.9- and 6.7-fold higher than an MIC=2 μg/ml, thus this dosing-regimen produced 50% of children with peak concentration outside the therapeutic-range. Multi linear regression

Table 4. Tobramycin pharmacokinetic parameters obtained in 102 children, aged 13.5±3.5 years, with cystic fibrosis Parameters are arranged according to sex and age. Ceftazidime was co-administered at a dose of 50 mg/kg 4 times-daily. Figures are the mean±SD, by Lam *et al.* [50]

	Sex			Age (years)		Nutritional status	
Parameter	**Male (N=41)**	**Female (N=61)**	***P-value**	**MLR**	***P-value**	**MLR**	***(P-value)**
Peak (μg/ml)	11.9±2.9	13.5±3.8	0.0208	0.20	0.046	0.25	0.0099
TBC (μg/ml/kg)	---	---	---	0.51	<0.0001	0.26	0.0084
Distribution volume (L)	10.4±3.7	8.9±3.1	0.0291	0.54	<0.0001	0.21	0.035
Distribution volume (L/kg)	0.27±0.09	0.23±0.06	0.0369	0.22	0.026	-0.34	0.0004

TBC=total body clearance. *Student t test for unpaired data. MLR=multiple linear regression.

Table 5. Simulated tobramycin pharmacokinetic parameters obtained with once-daily dosing-regimen in 102 children, aged 13.5±3.5 years, with cystic fibrosis. Parameters are arranged according to age, sex. Ceftazidime was co-administered at a dose of 50 mg/kg 4 times-daily. Figures are the mean±SD, by Lam *et al.* [50]

	Dose (mg)	**Dose/kg (mg/kg)**	**Peak (μg/ml)**	**$AUC_{0-\infty}$ (μg/*h/ml)**	**DFI (hours)**
Age<13.7 (years)	288±106	9.15±0.30	32.1±9.5	102±29	15.9±1.3
Age ≥ 13.7 (years)	373±90	7.8±0.65	31.3±10.8	103±25	15.5±1.7
Male aged ≥ 13.7 years	412±105	8.51±0.26	31.1±8.9	105±21	15.3±2.0
Female aged ≥ 13.7 years	344±66	7.32±0.29	31.5±12.0	101±24	15.7±1.6
Desired target range	---	---	25 – 35	70 - 100	4 – 16
Under target (%)	---	---	22	8	0
Meeting target (%)	---	---	50	42	55
Over target (%)	---	---	28	50	45

DFI=drug free interval. AUC0-∞=Area under serum concentration versus time in the interval from 0 time to infinite.

revealed that peak concentration was significantly associated with age, sex, and distribution volume.

Vic *et al.* [51] compared tobramycin pharmacokinetic parameters obtained with once-daily with thrice-daily dosing-regimen for treatment of 10 children, aged 10.7+2.9 years (group A), and 12 children aged 11.4+4.2 years (group B). All children had pulmonary Pseudomonas aeruginosa exacerbations and cystic fibrosis. Tobramycin was intravenously infused at a dose of 15 mg/kg either in three divided equal doses (group A) or in once-daily dose (group B), and all children received ceftazidime intravenously at a daily-dose of 200 mg/kg. Table 6 shows serum tobramycin pharmacokinetic parameters and data are reported according to children of groups A and B. This table shows that peak and trough serum concentrations are significantly greater and lower, respectively, following once-daily dosing-regimen whereas total body clearance, distribution volume, and $AUC_{0-\infty}$ were not different in both dosing-regimens. Tobramycin once-daily dosing-regimen is preferable because increases peak concentration, thus increasing efficacy, and decreases trough concentration, thus decreasing tobramycin toxicity.

Turner *et al.* [52] delineated optimal tobramycin dosing-regimens in children, aged 12 years (interquartile range, 10 to 17), and had pulmonary exacerbations caused by Pseudomonas aeruginosa and cystic fibrosis, who were treated with tobramycin either at a dose of 11.3±1.9 mg/kg once-daily (N=44) or 11.7±2.4 mg/kg, divided in two equal divided doses, which were administered twice-daily (N=15). Optimal pharmacodynamics attainment-rate was defined as: a peak/MIC ratio ≥ 8, $AUC_{0\text{-}24\ hours}$/MIC ≥ 80 and a *f*T < MIC for 10 hours in a 24 hours treatment. Standardized MICs for Pseudomonas aeruginosa were: 1, 2, and 4 μg/ml and were used for determining pharmacodynamic indices. Table 7 summarizes pharmacodynamic attainment-rate in once-daily and twice-daily dosing-regimens, respectively, and Table 8 shows pharmacokinetic parameters obtained with both dosing-regimens. Table 7 shows that tobramycin once-daily dosing-regimen was more likely to achieve the goal peak/MIC ratio but less likely to achieve AUC/MIC ratio and *f*T < MIC target attainment. In almost all children, peak concentration was consisted with an MIC=1 to 2 μg/ml, whereas in only 36% children with an MIC=4 μg/ml; twice-daily dosing-regimen failed to achieve goal peak/MIC ratio for MICs > 1 μg/ml. Table 8 reveals that tobramycin twice-daily dosing-regimen was associated with lower distribution volume and total body clearance, in 38% compared to once-daily dosing-regimen. Tobramycin efficacy expressed as peak/MIC ratio was similar in two dosing-regimens for a MIC=1 μg/ml, whereas for MICs=2 and 4 μg/ml this parameter was higher in the once-daily dosing-regimen, in addition peak and trough concentrations were higher and lower, respectively in only once-daily dosing-regimen, thus once-daily regimen is preferably, and this result is consistent with those above reporter by Vic *et al.* [51].

Mechanisms of bacterial-resistance to tobramycin

Jacoby *et al.* [53] stated that in Pseudomonas aeruginosa, resistance to tobramycin was transferable by the IncP-2 plasmid pMG77, while in Escherichia coli and Klebsiella pneumonia resistance was carried by a transferable plasmids pMG221, pMG22, and pMG222 belonging to the IncM group. Isolates and transconjugants produced an enzyme adenyltransferase activity with substrates having a 4'-hydroxyl group, such as amikacin, kanamycin, neomycin, Sch 21768, isepamicin (Sch 21420) or tobramycin, but not with aminoglycosides lacking this target, such as dibekacin, netilmicin, sisomicin, or gentamicin. Genes encoding the 4'aminoglycosides nucleotidyltransferase [ANT(4')] activity were

Table 6. Tobramycin pharmacokinetic parameters obtained in 10 children, aged 10.7±2.9 years, who received 15 mg/kg daily tobramycin divided in three doses (group A) and in 12 children, aged 11.4±4.2 years, who received tobramycin in a single daily-dose of 15 mg/kg (group B). All children had cystic fibrosis and were co-administered with ceftazidime at a single daily dose of 200 mg/kg. Figures are the mean±SD, by Vic *et al.* [51]

	Children of group A	Children of group B	*P-value
Serum peak concentration on day 1 (μg/ml)	13.2±7.1	42.5±11.2	< 0.001
Serum peak concentration on day 14 (μg/ml)	12.4±3.9	39.4±20.0	< 0.001
Serum trough concentration on day 1 (μg/ml)	1.1±0.8	0.3±0.2	< 0.01
Serum peak concentration on day 14 (μg/ml)	0.9±0.5	0.4±0.3	< 0.01
Total body clearance (ml/h/kg)	3.7±1.4	4.7±2.4	0.4
Distribution volume (L/kg)	0.54±0.88	0.97±0.44	0.6
$AUC_{0-\infty}$ (μg*ml/ml)	121±42	98.6±32.5	0.6

Total body clearance and distribution volume were corrected for body-weight. $AUC_{0-\infty}$=Area under serum concentration versus time in the interval from 0 time to infinite. *Non-parametric Wilcoxon signed rank test for paired samples.

Table 7. Attainment target-rates obtained in 59 children, who were treated with tobramycin at doses of 11.3±1.9 mg/kg once-daily (children number=44) or 11.7±2.4 mg/kg twice-daily (children number=15). All children were aged 12 years (interquartile range, 10 - 17), and had pulmonary exacerbations caused by Pseudomonas aeruginosa and cystic fibrosis. Figures are the median (interquartile rang), by Turner *et al.* [52]

	Once-daily dosing-regimen (N=59)	**Twice-daily dosing-regimen (N=44)**	***P-value**
MIC for Pseudomonas aeruginosa=1 μg/ml			
Peak/MIC ratio>8	58 (98.3)	44 (100)	1.0
AUC/MIC ratio>80	39 (66.1)	42 (95.5)	< 0.001
*f*T<MIC<10 hours	1 (1.7)	42 (95.5)	< 0.001
MIC for Pseudomonas aeruginosa=2 μg/ml			
Peak/MIC ratio>8	54 (91.5)	27 (61.4)	< 0.01
AUC/MIC ratio>80	1 (1.7)	12 (27.3)	< 0.001
*f*T<MIC<10 hours	0 (0.0)	33 (75.0)	<0.01
MIC for Pseudomonas aeruginosa=4 μg/ml			
Peak/MIC ratio>8	21 (35.6)	0 (0.0)	< 0.01
AUC/MIC ratio>80	0 (0.0)	0 (0.0)	1.0
*f*T<MIC<10 hours	0 (0.0)	5 (11.4)	0.012

*Fishers Exact text. MIC=minimum inhibitory concentration. AUC=area under serum concentration versus time.

Table 8. Tobramycin pharmacokinetic parameters obtained in 59 children, who were treated with tobramycin at doses of 11.3±1.9 mg/kg once-daily (children number=44) or 11.7±2.4 mg/kg twice-daily (children number=15). All children were aged 12 years (interquartile range, 10 - 17), and had pulmonary exacerbations caused by Pseudomonas aeruginosa and cystic fibrosis.. Figures are the mean±SD, by Turner *et al.* [52]

Pharmacokinetic parameters	Once-daily dosing-regimen (N=59)	Twice-daily dosing-regimen (N=44)	*P-value
Peak concentration (µg/ml)	29.5±11.0	19.0±4.8	< 0.01
Trough concentration (µg/ml)	0.02±0.03	0.6±0.4	<0.001
Distribution volume (L/kg)	0.41±0.21	0.31±0.08	0.04
Total body clearance (L/h/kg)	0.13±0.04	0.09±0.03	< 0.001
$AUC_{0\text{-}24\ hours}$ (µg*h/ml)	92±27.7	128±34.6	<0.01

*Student t test for unpaired data. $AUC_{0\text{-}24\ hours=}$area under serum concentration versus time interval from 0 to 24 hours.

cloned from pMG77, pMG221, and pM222. A DNA probe prepared from the ANT(4') found in Pseudomonas aeruginosa hybridized with the ANT(4') determinant found in Escherichia coli. A probe for the ANT(4') from Staphylococcal species, which differs in its modification of substrates, like dibekacin, that has a 4" but not a 4'hydroxyl group, failed to hybridize with the gram-negative ANT(4') determinant, which consequently has been termed ANT(4')-II.

McCaughey *et al.* [54] determined whether fosfomycin and tobramycin could delay or prevent the resistance-onset compared to either fosfomycin or tobramycin alone under aerobic and anaerobic conditions. Pseudomonas aeruginosa and methicillin resistant Staphylococcus aureus isolates had a lower frequency of spontaneous mutations to fosfomycin and tobramycin compared to fosfomycin and tobramycin under both aerobic and anaerobic conditions. There was a maximum two-fold increase in MICs of fosfomycin and tobramycin when Pseudomonas aeruginosa and methicillin resistant Staphylococcus aureus were passed in sub-inhibitory fosfomycin and tobramycin for 12 days. In contrast, sequential resistance to fosfomycin and tobramycin developed quickly (3 days for both drugs) after a passage in sub-inhibitory concentrations. Both fosfomycin and tobramycin developed resistance and was not associated with a biological fitness cost to either isolates of Pseudomonas aeruginosa or methicillin resistant Staphylococcus aureus. The development of resistance compared to fosfomycin and tobramycin alone under aerobic and physiologically relevant anaerobic conditions.

Barclay *et al.* [55] enrolled 7 patients with cystic fibrosis who were treated with inhaled tobramycin and determined whether adaptive resistance occurred in Pseudomonas aeruginosa in their sputum. Adaptive resistance of Pseudomonas aeruginosa was assessed 1 to 4 hours after dosing. Moderate resistance was present at 24 hours and full susceptibility returned between 24 to 48 hours after stopping treatment. In 4 patients on long-term twice-daily of inhaled tobramycin, adaptive resistance was seen before, and 4 hours after 80 mg inhaled tobramycin. The adaptive resistance in humans may have implications for improving tobramycin dosing-regimen.

Miller [56] reviewed the epidemiology of antibiotic-resistant in ophthalmology. Resistance high-rate was observed for several antibiotics, including tobramycin, for treatment of ophthalmologic disease. Resistance was assessed for Staphylococcus aureus and epidermis, Streptococcus pneumoniae and viridians, Haemophilus influenzae, and Pseudomonas aeruginosa. Collectively, the resistance-rate for gentamycin and tobramycin was 74%. Combination therapy with a fluoroquinolone, vancomycin, and vancomycin co-administered aminoglycoside proved coverage for 99% of isolates. Some authors [8,57,58] observed the antibiotic consumption, including tobramycin, is associated with increasing resistance-rate to different organisms.

Discussion

Tobramycin is an aminoglycoside antibiotic, is active against gram-negative bacteria, the primary bacterial intracellular site of tobramycin action is the 30S ribosomal subunit, tobramycin binds to polysomes and interferes with bacterial protein synthesis causing misreading, premature termination of mRNA translation causing incorrect amino acids incorporation into growing polypeptide chains, and is bactericidal [4]. Tobramycin may be administered orally, intravenously (either by low injection or intravenously infused), intramuscularly, applied to skin, and by inhalator or nebuliser to treat lung infection [7,10,15-19,38,39,42-44,55], and nebuliser delivers tobramycin more rapidly [39]. Intravenous tobramycin doses are: 5 mg/kg every 36 hours in infants with a postmenstrual age < 32 weeks, once-daily in older infants [1], and in children these are 2.5 and 3.5 mg/kg given thrice-daily [6]. Tobramycin well diffuses into all body organs [2,3], including the central nervous system and the cerebrospinal fluid [29-31]. This drug is efficacy and safe in infants and children [7-10], and causes few adverse-effects. Tobramycin effects are: increase of sodium excretion in the urine [11], tubular injury resulting in renal impairment [12,13], bronchoconstriction [15], eradicates Pseudomonas aeruginosa from lung [14], and cures rhinopharyngitis [16] and meningitis, the latter was caused by Pseudomonal aeruginosa, enterococci, Listeria monocytogenes and Listeria meningitis [29-31] in infants and children. In infants, tobramycin half-life depends on both postmenstrual, postmenstrual ages and body-weight and is about 10 hours [21] and in children is shorter. Tobramycin interacts with drugs, it has synergistic effect when co-administered with clarithromycin [25] or ceftaroline [27], whereas azithromycin reduces the clinical benefit of tobramycin [26] and also influences the duration of hospital stay and recover-time of vecuronium and atracurium administration [28]. Tobramycin treatment yields eradication of Pseudomonas aeruginosa [32,38], reduces acute pulmonary exacerbations caused by Pseudomonas aeruginosa [34], decreases the risk of comorbidities in skeletally immature children [35], and does not cause hearing loss [33]. Optimization of tobramycin treatment has been recommended in order to assure that peak and trough concentrations should be > 10 and < 2 µg/ml [47,50-52] in order to yield antimicrobial effect and to keep toxicity low, respectively [40-42]. Optimization also concerns (1) to keep peak and trough concentrations within the therapeutic-interval and (2) and addresses the variation of these concentrations in both infants and children. In addition, peak/MIC ratio and AUC/MIC ratio should be > 8 and > 80, respectively, and tobramycin serum concentration should be > MIC for at least 10 hours of 24 hours dosing-interval [52]. Once-daily dosing-regimen yields higher peak and lower trough concentrations compared to twice-daily [41,42] and thrice-daily [45,50] dosing-regimens. Thus once-daily dosing-regimen increases efficacy and keeps toxicity low. Inhaled tobramycin was more efficacy than placebo in eradicating Pseudomonas aeruginosa from lung even in children with cystic fibrosis [43,46], and tobramycin inhaled at a dose of 300 mg/5 ml is as effective as a dose of

80 mg/2 ml [44]. Tobramycin peak concentration is higher in female than male children, and peak concentration, total body clearance, and distribution volume are age-dependent [50]. Resistance to tobramycin in Pseudomonas aeruginosa is transferred by plasmid pMG77, whereas in Escherichia coli and Klebsiella pneumonia resistance is transferred by pM221, pM22, pM222 [53] and also resistance may be caused by increased MIC of Staphylococcus aureus [54]. Adaptive resistance to pseudomonas aeruginosa was developed after 28 hours of tobramycin inhaled and is transitory and disappears 48 hours after stopping treatment [55]. Different antibiotics, including tobramycin, were used in treatment of ophthalmology and caused high-rate of resistance in Staphylococcus aureus and epidermis, Streptococcus pneumoniae and viridians Haemophilus influenzae, and Pseudomonas aeruginosa [56] and antibiotic consumption, included tobramycin, was associated with increased resistance-rate [8,58,59].

In conclusion, tobramycin is an aminoglycoside antibiotic, causes inhibition of protein synthesis in bacterial cell and is bactericidal. This antibiotic well diffuses through all body-organs, including the central nervous system, and successfully treated infections of respiratory-tract, renal-tract, mouth, throat, eye, ear, skin, and meningitis caused by gram-negative organisms. Meningitis caused by Pseudomonas aeruginosa, enterococci, Listeria monocytogenes and Listeria meningitis was successfully treated with tobramycin. Inhalation has been used for treating respiratory-tract infections caused by Pseudomonas aeruginosa even in children with cystic fibrosis. As for all aminoglycosides, tobramycin has post-antibiotic effect on bacterial killing, and its antibacterial effect is concentration-dependent. Peak and trough serum concentrations should be > 10 and < 2 μg/ml, respectively, to yield antibacterial effect and to keep toxicity low. Optimization of treatment has been recommended for keeping tobramycin serum tobramycin concentrations within the therapeutic-interval. In addition, optimization of treatment requires a peak/MIC ratio > 8, AUC/MIC ratio > 80, and serum concentration should be > MIC for at least 10 hours of 24 hours dosing-interval. In infants, tobramycin total body clearance and half-life increases and decreases, respectively, according to postmenstrual, postnatal ages and body-weight as this antibiotic is mainly eliminated by renal route and renal function increases with intrauterine development and infant maturation. Some organisms may become resistant to tobramycin, and mechanisms of resistant are: either transfer of plasmids into the bacterial cell or by increasing bacterial MIC, antibiotic consumption is associated to increased resistance, and adaptive resistance have implications for improving tobramycin dosing-regimen.

Conflict of interests

The authors declare 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.

Acknowledgments

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

References

1. Neonatal Formulary (2020) Tobramycin, 8th Edition Oxford University Press. Great Clarendon Street, Oxford, OX2, 6DP, UK, pp: 789-791.
2. Young TE, Mangum B (2010) NEOFAX®. Piperacillin/tazobactam, Thomas Reuters Clinical Editorial Staff, 23rd Edition USA, pp: 90-92.
3. MacDougal C (2020) Aminoglycosides. In the Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 13th Edition. Brunton Hilal-dandan LL, Knollmann BC, editors. Mc Graw Hill, New York, pp: 1040-1045.
4. Davis BB (1988) The lethal action of aminoglycosides *J Antimicrob Chemother* 22: 1-3. [Crossref]
5. Busse HJ, Wöstmann C, Bakker EP (1992) The bactericidal action of streptomycin: membrane permeabilization caused by the insertion of mistranslated proteins into the cytoplasmic membrane of Escherichia coli and subsequent caging of the antibiotic inside the cells due to degradation of these proteins. *J Gen Microbiol* 138: 551-561. [Crossref]
6. British national formulary for children. Cefuroxime. 78th Edition, Macmillan, Hampshire International Business Park, Hampshire, Lime Three Way, Basingstoke, Hampshire, UK, pp: 323-324.
7. Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, et al. (2011) Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cyst Fibros* 10: 54-61. [Crossref]
8. Pai VB, Nahata MC (2001) Efficacy and safety of aerosolized tobramycin in cystic fibrosis. *Pediatr Pulmonol* 32: 314-327. [Crossref]
9. Di Cicco M, Alicandro G, Claut L, Cariani L, Luca N, et al. (2014) Efficacy and tolerability of a new nasal spray formulation containing hyaluronate and tobramycin in cystic fibrosis patients with bacterial rhinosinusitis. *J Cyst Fibros* 13: 455-460. [Crossref]
10. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, Khan U, Kulich M, et al. (2011) Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. *Arch Pediatr Adolesc Med* 165: 847-856. [Crossref]
11. Rothberg AD, Andronikou S (1984) Effect of tobramycin on fractional sodium excretion in neonates. *Pediatr Pharmacol (New York)* 4: 49-52.
12. Leititis JU, Zimmerhackl LB, Burghard R, Gordjani N, Brandis M (1991) Evaluation of local renal function in newborn infants under tobramycin therapy. *Dev Pharmacol Ther* 17: 154-160.
13. Glass S, Plant ND, Spencer DA (2005) The effects of intravenous tobramycin on renal tubular function in children with cystic fibrosis. *J Cyst Fibros* 4: 221-225.
14. Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, et al. (2003) Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care Med* 167: 841-849. [Crossref]
15. Alothman GA, Alsaadi MM, Ho BL, Ho SL, Dupuis A, et al. (2002) Evaluation of bronchial constriction in children with cystic fibrosis after inhaling two different preparations of tobramycin. *Chest* 122: 930-934.
16. Varricchio A, Tricarico D, De Lucia A, Utili R, Tripodi MF, et al. (2006) Inhaled tobramycin in children with acute bacterial rhinopharyngitis. *Int J Immunopathol Pharmacol* 19: 131-140.
17. Ramagopal M, Lands LC (2000) Inhaled tobramycin and bronchial hyperactivity in cystic fibrosis. *Pediatr Pulmonol* 29: 366-370. [Crossref]
18. Abdulhamid I, Wise TL, Andrews S, Biglin K, Tutag Lehr V (2008) Elevated serum tobramycin concentrations after treatment with tobramycin inhalation in a preterm infant. *Pharmacotherapy* 28: 939-944.
19. Howard-Thompson A, Christensen ML (2008) Elevated tobramycin concentrations following endotracheal administration in a premature infant. *J Pediatr Pharmacol Ther* 13: 88-92.
20. Thomsen J, Friis B (1997) High dosage tobramycin treatment of children with cystic fibrosis. Bacteriological effect and clinical ototoxicity. *Int J Pediatr Otorhinolaryngol* 1: 33-40.
21. Nahata MC, Powell DA, Durrell DE, Miller MC, Glazer JP (1984) Effect of gestational age and birth-weight on tobramycin kinetics in newborn infants. *J Antimicrob Chemother* 14: 59-65. [Crossref]
22. Raine PA, Young DG, McAllister TA, Tait SC (1976) Tobramycin in pediatric use. *J Infect Dis* 134: 165-169.
23. Hennig S, McKay K, Vidmar S, O'Brien K, Stacey S, et al. (2014) Safety of inhaled (Tobi®) and intravenous tobramycin in young children with cystic fibrosis. *J Cyst Fibros* 13: 428-434.

24. Kaushik KS, Stolhandske J, Shindell O, Smyth HD, Gordon D (2016) Tobramycin and bicarbonate synergise to kill planktonic Pseudomonas aeruginosa, but antagonise to promote biofilm survival. *npj Biofilms and Microbiomes* 2: 160062. DOI: 10.1038. [Crossref]

25. Tré-Hardy M, Nagant C, El Manssouri N, Vanderbist F, Traore H, et al. (2010) Efficacy of the combination of tobramycin and a macrolide in an in vitro pseudomonas aeruginosa mature biofilm model. *Antimicrob Agents Chemother* 54: 4409-4415.

26. Nichols DP, Happoldt CL, Bratcher PE, Caceres SM, Chmiel JF, et al. (2017) Impact of azithromycin on the clinical and antimicrobial effectiveness of tobramycin in the treatment of cystic fibrosis. *J Cyst Fibros* 16: 358-366. [Crossref]

27. Vidaillac C, Leonard SN, Rybak MJ (2010) In vitro evaluation of ceftaroline alone and in combination with tobramycin against hospital-acquired meticillin-resistant Staphylococcus aureus (HA-MRSA) isolates. *Int J Antimicrob Agents* 35: 527-530. [Crossref]

28. Dupuis JY, Martin R, Tétrault JP (1998) Atracurium and vecuronium interaction with gentamicin and tobramycin. *Can J Anaesth* 36: 407-411.

29. Eiland LS, Luedtke SA, Chuachingco JC (2004) Intraventricular tobramycin in a premature infant with pseudomonas meningitis. *J Pediatr Pharmacol Ther* 9: 55-62.

30. Tessin I, Trollfors B, Thiringer K, Thörn Z, Larsson P (1989) Concentrations of ceftazidime, tobramycin and ampicillin in the cerebrospinal fluid of newborn infants. *Eur J Pediatr* 148: 679-681. [Crossref]

31. Schneeberger P, Sluiter E, van Doorn LJ, Spanjaard L (1996) Listeria meningitis during treatment of a meningococcal meningitis in an immunocompetent infant. *Scand J Infect Dis* 28: 525-526.

32. Kaplan JM, McCracken GH Jr, Thomas ML, Horton LJ, Davis N (1973) Clinical pharmacology of tobramycin in newborns. *Am J Dis Child* 125: 656-660.

33. de Hoog M, van Zanten GA, Hoeve LJ, Blom AM, van den Anker JN (2002) A pilot case control follow-up study on hearing in children treated with tobramycin in the newborn period. *Int J Pediatr Otorhinolaryngol* 65: 225-232. [Crossref]

34. Wientzen R, Prestidge CB, Kramer RI, McCracken GH, Nelson JD (1980) Acute pulmonary exacerbations in cystic fibrosis. A double-blind trial of tobramycin and placebo therapy. *Am J Dis Child* 134: 1134-1138.

35. Andreacchio A, Alberghina F, Paonessa M, Cravino M, De Rosa V, et al. (2019) Tobramycin-impregnated calcium sulfate pellets for the treatment of chronic osteomyelitis in children and adolescents. *J Pediatr Orthop B* 28: 189-195.

36. de Velde F, Marieke Emonts M, Sascha Verbruggen S, van der Sijs H (2014) High tobramycin serum concentrations after tobramycin inhalation in a child with renal failure. *J Antimicrob Chemother* 69: 3163-3164. [Crossref]

37. Bothra M, Lodha R, Kabra SK (2012) Tobramycin for the treatment of bacterial pneumonia in children. *Expert Opin Pharmacoth* 13: 565-571.

38. Stelmach I, Korzeniewska A, Stelmach W (2008) Long-term benefits of inhaled tobramycin in children with cystic fibrosis: first clinical observations from Poland. *Respiration* 75: 178-81.

39. Clavel A, Boulaméry A, Bosdure E, Luc C, Lanteaume A, et al. (2007) Nebulisers comparison with inhaled tobramycin in young children with cystic fibrosis. *J Cyst Fibros* 6: 137-143.

40. de Hoog M, Mouton JW, Schoemaker C,Verduin M, van den Anker JN (2002) Extended-interval dosing of tobramycin in neonates: implications for therapeutic drug monitoring. *Clin Pharmacol Ther* 71: 349-358. [Crossref]

41. Turner RB, Elbarbry FE, Biondo L (2016) Pharmacokinetics of once and twice daily dosing of intravenous tobramycin in paediatric patients with cystic fibrosis. *J Chemother* 28: 304-307.

42. Dopfer R, Brand P, Müllinger B, Hunger T, Häussermann S, et al. (2007) Inhalation of tobramycin in patients with cystic fibrosis: comparison of two methods. *J Physiol Pharmacol* 58: 141-154.

43. Ratjen F, Moeller A, McKinney ML, Asherova I, Alon N, et al. (2019) Eradication of early P. aeruginosa infection in children <7 years of age with cystic fibrosis: The early study. *J Cyst Fibros* 18: 78-85. [Crossref]

44. Stanojevic S, Waters V, Mathew JL, Taylor LT, Ratjen F (2014) Effectiveness of inhaled tobramycin in eradicating Pseudomonas aeruginosa in children with cystic fibrosis. *J Cyst Fibros* 13: 172-178.

45. Sung L, Dupuis L, Bliss B, Taddio A, Abdolell M, et al. (2003) Randomized controlled trial of once- versus thrice-daily tobramycin in febrile neutropenic children undergoing stem cell transplantation. *J Natl Cancer Inst* 95: 1869-1877.

46. Wientzen R, Prestidge CB, Kramer RI, McCracken GH, Nelson JD (1980) Acute pulmonary exacerbations in cystic fibrosis. A double-blind trial of tobramycin and placebo therapy. *Am J Dis Child* 134: 1134-1138. [Crossref]

47. de Hoog M, Schoemaker RC, Mouton JW, van den Anker JN (1997) Tobramycin population pharmacokinetics in neonates. *Clin Pharmacol Ther* 62: 392-399.

48. Nahata MC, Powell DA, Durrell DE, Miller MA (1986) Tobramycin pharmacokinetics in very low birth-weight infants. *Br J Clin Pharmacol* 21: 325–327.

49. van den Anker J, Reed MD, Allegaert K, Kearns GL (2018) Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol* 58: S10-S25. [Crossref]

50. Lam W, Tjon J, Seto W, Dekker A, Wong C, et al. (2007) Pharmacokinetic modelling of a once-daily dosing-regimen for intravenous tobramycin in paediatric cystic fibrosis patients. *J Antimicrob Chemother* 59: 1135-1140. [Crossref]

51. Vic P, Ategbo S, Turck D, Husson M, Launay V, et al. (1998) Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Arch Dis Child* 78: 536-539.

52. Turner RB, Elbarbry F, Biondo L (2016) Pharmacokinetics of once and twice daily dosing of intravenous tobramycin in paediatric patients with cystic fibrosis. *J Chemother* 28: 304-307. [Crossref]

53. Jacoby GA, Blaser MJ, Santanam P, Hächler H, Kayser FH, et al. (1990) Appearance of amikacin and tobramycin resistance due to 4'-aminoglycoside nucleotidyltransferase [ANT(4')-II] in gram-negative pathogens. *Antimicrob Agents Chemother* 34: 2381-2386.

54. McCaughey G, Diamond P, Elborn JS, McKevitt M, Tunney MM (2013) Resistance development of cystic fibrosis respiratory pathogens when exposed to fosfomycin and tobramycin alone and in combination under aerobic and anaerobic conditions. *PLoS One* 8: e69763. Doi: 10.1371. [Crossref]

55. Barclay MJ, Begg EJ, Chambers ST, Thornley PE, Pattemore PK, et al. (1996) Adaptive resistance to tobramycin in Pseudomonas aeruginosa lung infection in cystic fibrosis. *J Antimicrob Chemother* 37: 1155-1164.

56. Miller D (2017) Update on the epidemiology and antibiotic resistance of ocular infections. *Middle East Afr J Ophthalmol* 24: 30-42. [Crossref]

57. Sánchez-Ramírez C, Hípola-Escalada S, Cabrera-Santana M, Hernández-Viera MA, Caipe-Balcázar L, et al. (2018) Long-term use of selective digestive decontamination in an ICU highly endemic for bacterial resistance. *Crit Care* 22: 141.

58. Hsueh PR, Chen WH, Luh KT (2005) Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991-2003 at a university hospital in Taiwan. *Int J Antimicrob Agents* 26: 463-472. [Crossref]