AMINOGLYCOSIDE DOSING AND MONITORING - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Once daily dosing is the recommended method of administration for aminoglycosides in most clinical settings at CHW.
- Once daily dosing applies to immunocompromised patients (e.g. oncology, solid organ transplant and haematology patients).
- In suspected sepsis, particularly in immunocompromised patients, the first dose of aminoglycoside therapy should not be delayed pending results of blood tests.
- EUCs must be monitored at commencement and during aminoglycoside therapy.
- Initial starting dose should not exceed the maximum dose for that age group as specified in Table 1.
- Dosage should be based on the patient's ideal body weight (IBW) if BMI >30. Refer to Appendix I.
- Dosing in empirical therapy should not continue beyond 48 hours (i.e. a maximum of three empirical doses at 0, 24 and 48 hours); given the 'post-antibiotic effect' of aminoglycosides, this effectively provides 72 hours of therapy.
- Monitoring of aminoglycoside plasma concentrations is not required if therapy is ceased within 48 hours of commencement.
- Aminoglycosides are indicated for more prolonged directed therapy in only a few circumstances. If continued beyond 48 hours, plasma concentrations of aminoglycosides are required.
- Gentamicin should be administered by direct IV injection over 3 – 5 minutes irrespective of final concentration and volume of administered dose (*except in patients with neuromuscular disorders such as myasthenia gravis who should ideally receive aminoglycosides via 30 minute infusion)*.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st January 2015	**Review Period:** 3 years
Team Leader:	Antimicrobial Stewardship Pharmacist	**Area/Dept.:** Infectious Diseases

Date of Publishing: 16 December 2015 6:34 PM Date of Printing: 16 December 2015

- Clinicians administering neuromuscular blocking agents in the first few hours after aminoglycoside dosing, while plasma levels are high, should be aware that there is a theoretical possibility of enhanced or prolonged paralysis.

CHANGE SUMMARY

- Once daily aminoglycoside dosing now applies to immunocompromised patients (e.g. oncology, solid organ transplant, and haematology patients)
- All aminoglycoside doses have been updated to adhere with the most recent Australian consensus guidelines
- Dosing recommendations updated
- Amikacin is no longer recommended for bolus intravenous administration
- Further clarification of therapeutic drug monitoring of aminoglycosides
- New dosing information of aminoglycosides in patients with renal impairment
- New additional information of monitoring of otoxicity and vestibular toxicity

READ ACKNOWLEDGEMENT

- Local manager to determine which nursing/medical or pharmacy staffs are to read and acknowledge they understand the contents of this document.

TABLE OF CONTENTS

Introduction **4**
The available parenteral aminoglycosides at CHW: *4*
Initial dose for empirical and directed intravenous therapy **4**
Dosing and administration **6**
Dosing 6
Administration 7
Monitoring for patients on aminoglycosides **7**
Renal function 7
Therapeutic drug monitoring 8
Area Under the Curve calculations [5, 41-43]: 9
Amikacin for Mycobacterial infections [12]: 10
Ototoxicity and vestibular toxicity [5, 12, 44-46]: 11
Appendix I: Weight for age Percentiles **12**

Introduction

Aminoglycoside antibiotics are used to treat serious infections caused by Gram-negative bacteria. The bactericidal effect is related to inhibition of protein synthesis and also to their effect on bacterial cell wall integrity.

The primary indication for aminoglycosides is as **short-term empirical therapy** pending the outcome of microbiological investigations. Their value as empirical drugs relates to their rapid bactericidal activity and the comparatively low levels of resistance in many community and health care–associated Gram-negative pathogens.

Aminoglycosides given beyond 48 hours (i.e. more than three empirical doses at 0, 24 and 48 hours) are only indicated for directed therapy in only a few circumstances. These include:

- Multi-resistant infections that are not susceptible to alternative antimicrobial classes
- Patients with allergies or other contraindications to first-line agents.
- Initial combination therapy for *Pseudomonas aeruginosa* until susceptibility to alternative antibiotics are known
- Combination therapy for brucellosis and mycobacterial infections

Longer courses of aminoglycosides, usually in combination with a beta-lactam antibiotic, may be utilised for synergistic activity in a few specific clinical settings such as endocarditis, cystic fibrosis, and serious enterococcal and group B streptococcal (*Streptococcus agalactiae*) infections.

The available parenteral aminoglycosides at CHW:

- **Gentamicin** – 80 mg/2 mL ampoules
- **Tobramycin** – 80 mg/2 mL vials (used mainly for cystic fibrosis patients)
- **Amikacin** – 500 mg/2 mL vials (reserved for proven resistance to other aminoglycosides)

Initial dose for empirical and directed intravenous therapy

- The initial dose for empirical and directed therapy in infants, children, and adults with **normal renal function** is as follows (Table 1).
- For neonates, please refer to Table 2.
- For patients with renal impairment, please refer to Table 3.
- For obese patients (i.e. BMI >30), dose must be calculated based on ideal body weight (IBW) because aminoglycosides distribute minimally in adipose tissue.

  BMI = weight (kg) / height^2 (m)

  IBW may be estimated by the Moore method [1-3] (refer to Appendix I).

Table 1: Dosing recommendations for infants, children, and adults [4-8]

Age	Gentamicin or Tobramycin	Amikacin
1 month to 12 years old	7.5 mg/kg/dose 24 hourly (max. 320 mg/dose)	15-30 mg/kg/dose 24 hourly (max. 1.25 g/dose) [NB1]
12 to 16 years old	7.5 mg/kg/dose 24 hourly (max. 560 mg/dose)	15-30 mg/kg/dose 24 hourly (max. 1.5 g/dose) [NB1]
≥16 years old	5 mg/kg/dose 24 hourly (max. 560 mg/dose)	15-20 mg/kg/dose 24 hourly (max. 1.5 g/dose) [NB1]
Children with cystic fibrosis [NB2]	10-12 mg/kg/dose 24 hourly	30 mg/kg/dose 24 hourly
Children with endocarditis [NB2] [NB3]	1 mg/kg/dose 8-12 hourly	Seek ID advice

[NB1]: Doses of 15-25 mg/kg/dose 3x weekly are used for mycobacterial infections under ID advice [9-12].
[NB2]: There is no maximum dose.
[NB3]: Used only in combination with beta-lactam for enterococcal and streptococcal synergy. Consult ID Team for advice.

Table 2: Dosing recommendations for neonates <28 days old [4, 5]

Age	Postnatal age	Gentamicin or Tobramycin	Amikacin
Neonate <30 weeks postmenstrual age [NB4]	0-7 days	5 mg/kg/dose 48 hourly	20 mg/kg/dose 48 hourly
	8-28 days	4 mg/kg/dose 36 hourly	16 mg/kg/dose 36 hourly
	≥ 28 days	4 mg/kg/dose 24 hourly	16 mg/kg/dose 24 hourly
Neonate 30-34 weeks postmenstrual age [NB4]	0-7 days	4.5 mg/kg/dose 36 hourly	16 mg/kg/dose 36 hourly
	≥8 days	4 mg/kg/dose 24 hourly	16 mg/kg/dose 24 hourly
Neonate ≥35 weeks postmenstrual age [NB4]		4 mg/kg/dose 24 hourly	16 mg/kg/dose 24 hourly

[NB4]: postmenstrual age= gestational age + postnatal age

Table 3: Dosing recommendations for renal impairment [4, 13]

Age	eGFR [NB5]	Gentamicin or Tobramycin	Amikacin
Neonate (<1 month)	Seek infectious diseases advice for alternative antibiotic		
Infant, children and Adolescents (1 month-18 years)	≥50 mL/min/1.73m^2	Normal dosing (refer to Table 1)	
	30-50 mL/min/1.73m^2	2.5 mg/kg/dose 12 hourly	7.5 mg/kg/dose 12 hourly
	10-29 mL/min/1.73m^2	2.5 mg/kg/dose 24 hourly	7.5 mg/kg/dose 24 hourly
	<10 mL/min/1.73m^2	2.5 mg/kg/dose 48-72 hourly	7.5 mg/kg/dose 48-72 hourly

[NB5]: For children, the Bedside Schwartz formula is recommended for the estimated glomerular filtration rate (eGFR).

$$eGFR\ (mL/min/1.73\ \mathrm{m}^2) = \frac{36.5 \times height\ (cm)}{serum\ creatinine\ (micromol/L)}$$

Dosing and administration

Dosing

Once daily dosing of aminoglycosides is the recommended frequency of administration in patients with normal renal function in most clinical settings. Numerous adult and paediatric studies suggest that once daily dosing results in improved clinical efficacy and reduced toxicity compared to multiple daily dosing (e.g. 8-12 hourly)[14-26]. The difference in nephrotoxicity is more difficult to detect in paediatric populations due to the lower incidence of nephrotoxicity in children compared to adults <2% vs. 8% respectively [7].

The rationale for once daily dosing is based on the pharmacokinetic and pharmacodynamic parameter of aminoglycosides. The bactericidal activity of aminoglycosides is concentration-dependent. Optimising the ratio of peak plasma concentrations over the minimum inhibitory concentration maximises the bactericidal activity of aminoglycosides[18] (Figure 1).

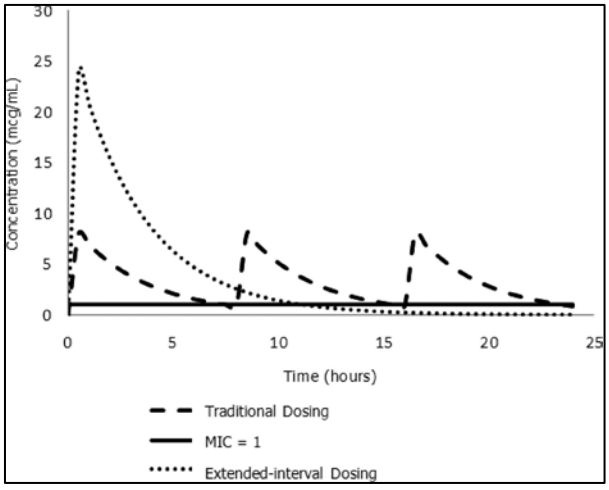


Figure 1: Traditional dosing (8 hourly dosing) versus extended-interval dosing (24 hourly) of aminoglycosides. MIC indicates minimum inhibitory concentration.
Source: Jenh, A. M., et al. (2011)." Pediatric Infectious Disease Journal 30(4): 338-339.

Administration

- Gentamicin and tobramycin (but NOT amikacin) can be safely administered **by IV bolus over 3-5 minutes** [27-34]. This is preferred over 30 minute infusions to take advantage of the concentration dependent bactericidal effects [35-38].
- **Dose may be diluted in 5-10 mL of normal saline** OR **injected directly undiluted.** (28, 32, 38, 39)
- Clinicians administering neuromuscular blocking agents in the first few hours after aminoglycoside dosing, while plasma levels are high, should be aware that there is a theoretical possibility of enhanced or prolonged paralysis.
- Aminoglycosides should be used with great caution in patients with neuromuscular disorders (e.g. myasthenia gravis). These patients should be infused over 30 minutes.

Amikacin MUST be administered by INFUSION

Amikacin must be diluted to a maximum concentration of 10 mg/mL and infused over at least 30 minutes.

Monitoring for patients on aminoglycosides

Renal function

- Accumulation of aminoglycosides within the kidneys results in reversible nephrotoxicity.
- Elevated trough concentrations, increased frequency, concurrent nephrotoxins (e.g. vancomycin and amphotericin), dehydration and prolonged duration of therapy (>5 days) are risk factors for nephrotoxicity [6, 14].
- Monitoring of plasma aminoglycoside levels is required to minimise the risk of accumulation and toxicity if therapy is continued beyond 48 hours.
- Before starting therapy, bloods should be collected for measurement of electrolytes, urea and creatinine.
- In suspected sepsis (particularly in immunocompromised patients) the first dose of aminoglycoside therapy should not be delayed pending results of these blood tests (urea, creatinine etc.), give doses recommended in Table 3.
- Electrolytes, urea and creatinine (EUC) must be monitored at baseline and during aminoglycoside therapy. An alternative antibiotic is to be considered if urea and/or creatinine are not within the normal range.
- **Twice weekly** EUC monitoring is required in clinically stable patients and should be performed more frequently if renal impairment exists.

- For patients on aminoglycoside therapy for more than a month, the frequency of EUC is the following:

1st month	Twice a week
2nd month	Weekly
3rd month until end of treatment	Fortnightly*
*Consider reducing to monthly if renal function remains stable. Consider increasing frequency of monitoring if evidence of renal impairment.	

Therapeutic drug monitoring

- Accurate documentation of **sample collection time** and **time of last dose MUST** always be recorded on the request form.
- Trough levels are measured within 30 minutes before the next dose
- Inpatients on a stable aminoglycoside regimen should continue to be monitored **twice weekly** if renal function is normal and stable and more frequently when impaired renal function exists or is potentially unstable.
- Trough level monitoring should be done following each dosing adjustment.
- Trough levels are used **only** to monitor toxicity, not efficacy.

Table 5: Therapeutic drug monitoring of aminoglycosides [4, 5, 30]:

Indication	Level	How often	Target level	
			Gentamicin or Tobramycin	Amikacin
Empirical therapy ≤48 hours	Not required	Not required	Not applicable	Not applicable
Empirical therapy >48 hours	Review use ***(e.g. cease, switch to a less nephrotoxic agent, or seek ID advice)***	Twice a week	Trough < 1 mg/L	Trough < 5 mg/L
	If empirical therapy continues >48 hours, before the 4th dose			
Febrile neutropenia	Before the 2nd dose	Twice weekly	Trough < 1 mg/L	Trough < 5 mg/L
Neonate	Before the 2nd dose	Twice weekly	Trough < 1 mg/L	Trough < 5 mg/L
Pre-existing renal impairment	Before the 2nd dose *Consider ceasing or changing antibiotic. Seek ID advice*.	At least twice weekly	Trough < 2 mg/L*	Trough < 10 mg/L*
			**The target troughs are higher due to multiple daily dose regimens.*	
Directed therapy	Before the 2nd dose	Twice weekly	Trough < 1 mg/L	Trough < 5 mg/L
	Measure Area Under the Curve (see below)	Twice weekly	AUC: 80-100 mg.hr/L	Not applicable
Cystic fibrosis	Measure Area Under the Curve (see below)	Twice weekly	AUC: 80-100 mg.hr/L	Not applicable
Endocarditis [5, 8, 40]	Before the 4th dose	At least twice weekly	Trough < 1 mg/L	Not applicable
Amikacin for Mycobacterial infections [9-11]	Measure peak and troughs (see below)			

Area Under the Curve calculations [5, 41-43]:

Achieving adequate Area Under the Concentration-time curve (AUC) of aminoglycosides is associated with clinical efficacy and minimises toxicity. AUC calculations are recommended for the following patients:

- Directed therapy
- Cystic fibrosis (CF)

The calculation of AUC requires two levels within the same dosage interval:

1st level	5 minutes - 2 hours after completion of the dose
2nd level	6 - 8 hours after completion of the dose

Record the **EXACT** time of collection and dose on the collection tube **AND** the request form to allow accurate interpretation of results.

The AUC is calculated through a computer program within *PowerChart* and is used to recommend dose adjustments. The target AUC is 80 – 100 mg.hr/L. Please contact the Antimicrobial Stewardship Pharmacist on (ext. 53226/pager 6658) for advice.

Amikacin for Mycobacterial infections [12]:

- Amikacin is a **RED** restricted antibiotic and requires Antimicrobial Stewardship (AMS) approval. Please discuss with ID/AMS for advice or alternative therapy.
- The rationale for monitoring amikacin for mycobacterial infection is to ensure therapeutic efficacy and avoid accumulation due to drug-induced renal impairment.
- Record the **EXACT** time of collection and dose on the collection tube **AND** the request form to allow accurate interpretation of results.

Target level	Timing	Frequency
Peak: 25 - 35 mg/L	Within 60 minutes after the end of the infusion	Peak level in the 1st week only
	If the peak level is high, reduce the **dose**. If the peak level is low, increase the **dose**.	
Trough: <5 mg/L	Pre-dose	Weekly for 4 weeks then fortnightly (Consider reducing to monthly if renal function remains stable)
	If the trough level is high, the dosing **interval** should be extended	

If the timing of levels is logistically difficult, the peak and trough levels may be calculated using 2 levels (similar to the AUC method). Please contact the Antimicrobial Stewardship/ID Pharmacist on (ext. 52696/pager 6698) for advice.

Ototoxicity and vestibular toxicity [5, 12, 44-46]:

- Aminoglycosides can cause **irreversible** ototoxicity and vestibular toxicity
- Ototoxicity and vestibular toxicity are **NOT** predicted by plasma concentrations
- Loss of hearing usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances are also signs of ototoxicity.

Audiograms and vestibular testing should be performed for patient on aminoglycosides longer than 5 days.

Prolonged therapy should be discussed with ID/Micro

SEEK ID/Micro advice for alternative therapy.

- Audiograms require cooperation of the subject and reliable results are difficult to obtain for children younger than 2 years of age. Brain-stem-evoked response audiometry (BERA) may be considered in infants as an option.
- Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies.
- If this occurs, aminoglycoside should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.
- We recommend that patients have **baseline** audiometry and then **monthly** reviews until treatment with aminoglycoside ceases.
- For patients on aminoglycosides longer than 1 month, audiometric and vestibular testing should be performed 4 months after cessation to detect delayed impairments.
- For vestibular toxicity seek ENT for advice.

Additional Information

Contacts

- Antimicrobial Stewardship Pharmacist on pager 6658
- Antimicrobial Stewardship Consultant on pager 7092.
- Infectious Diseases Fellow on pager 6675 or
- After hours or on weekends, Microbiologist on-call via switchboard.

Quick links to Drug Therapy – Drug Dose Therapy:

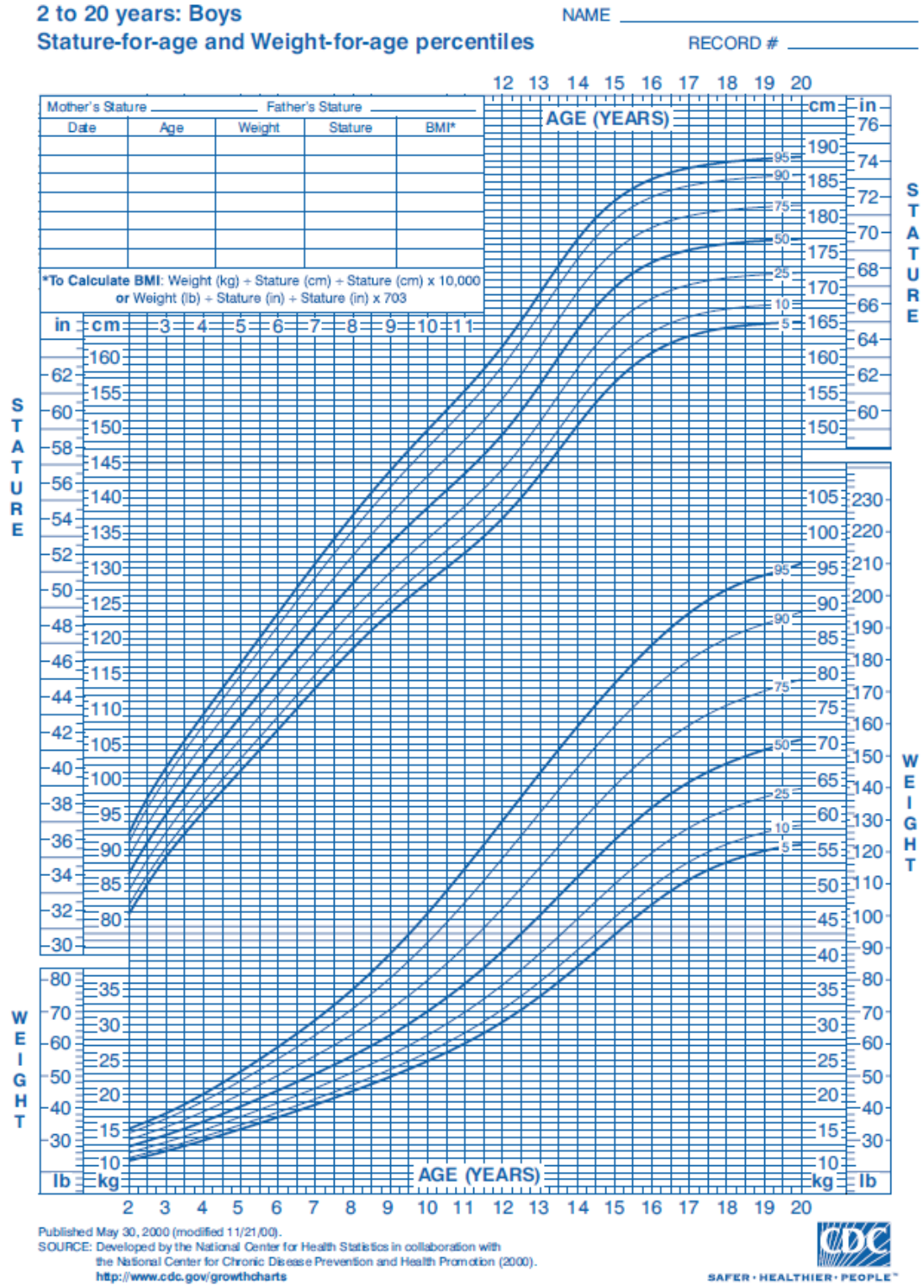
- Gentamicin: CHW Intranet - Paediatric Intensive Care Unit
- Tobramycin: CHW Intranet - Paediatric Intensive Care Unit
- Amikacin: CHW Intranet - Paediatric Intensive Care Unit

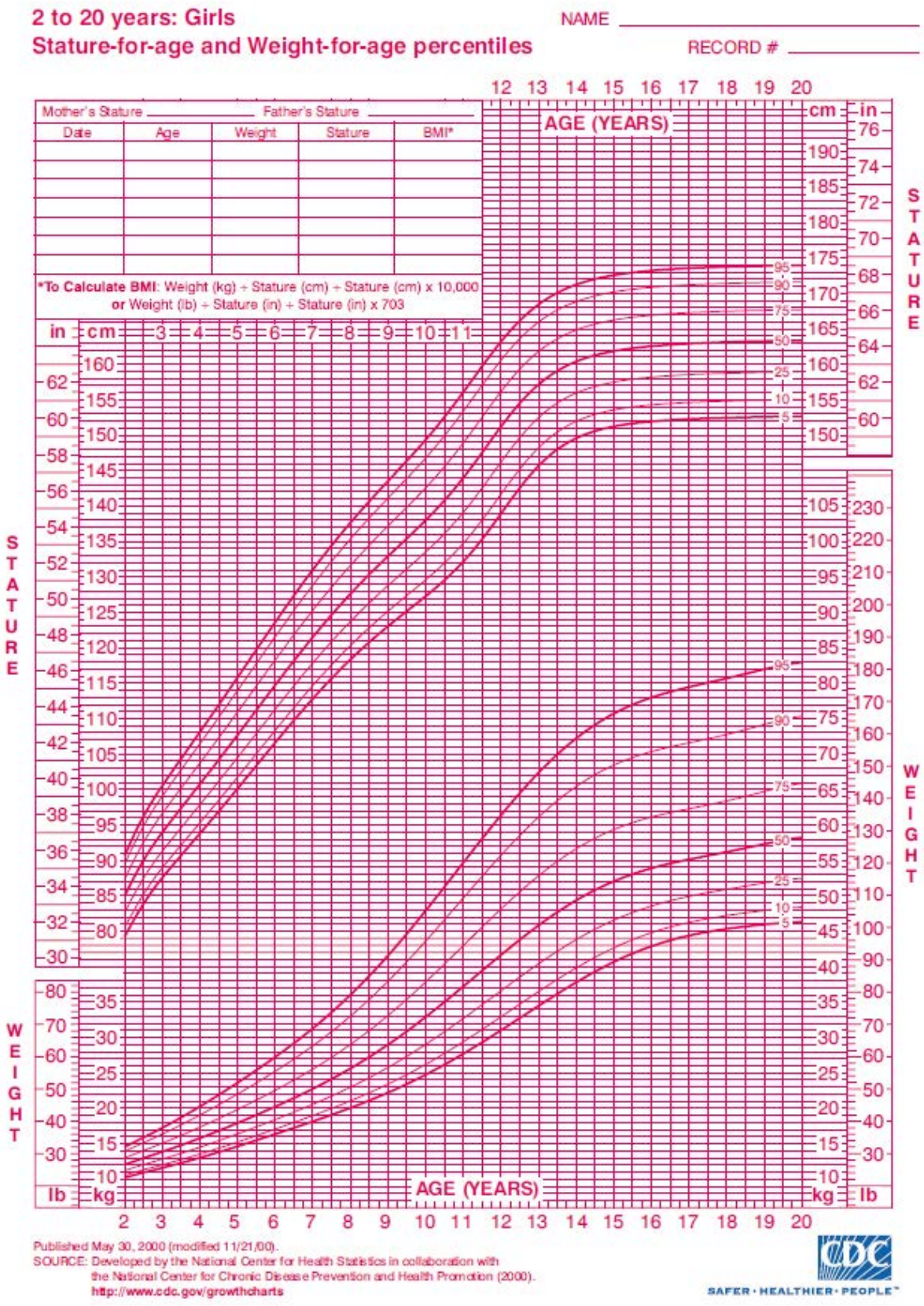
Appendix I: Weight for age Percentiles

The Ideal Body Weight (IBW) can be estimated by using the Moore method. There are 2 CDC growth charts: one for boys 2-20 years of age **(blue)** and one for girls 2-20 year of age **(pink).**

Step 1: Go to patient's age on x axis and find the percentile for their height

Step 2: Use the same percentile, go to the corresponding age for weight.




2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
SAFER · HEALTHIER · PEOPLE™

References

1. Kendrick JG, Carr RR, Ensom MH. Pharmacokinetics and drug dosing in obese children. J Pediatr Pharmacol Ther. 2010;15(2):94-109.
2. Moore DJ, Durie PR, Forstner GG, Pencharz PB. The assessment of nutritional status in children. Nutrition Research. 1985;5(8):797-9.
3. Le Grange D, Doyle PM, Swanson SA, Ludwig K, Glunz C, Kreipe RE. Calculation of expected body weight in adolescents with eating disorders. Pediatrics. 2012;129(2):e438-46.
4. Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, [Internet]. Lexi-Comp, Inc. 2015 [cited 11/12/2015].
5. Therapeutic Guidelines Limited. Antibiotic Expert Group. Therapeutic guidelines: antibiotic. 15 ed. Melbourne, Vic.: Therapeutic Guidelines Limited; 2014. xxxi 687 p. p.
6. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis. 2007;45(6):753-60.
7. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics. 2004;114(1):e111-8.
8. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30(19):2369-413.
9. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis. 2004;38(11):1538-44.
10. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.
11. Treatment of tuberculosis. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2003;52(Rr-11):1-77.
12. Potter J, Capstick T. A UK based resource to support the monitoring and safe use of anti-tuberculosis drugs and second line treatment of multidrug-resistant tuberculosis2014 [cited 2014 18/12/14]. Available from: http://www.tbdrugmonographs.co.uk/uploads/2/8/9/4/28941471/mdrtb_adr_monitoring_guidancefinal.pdf.
13. Aronoff GB, WM; Berns, JS;. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children. 5th ed. Philadelphia, PA: American College of Physicians; 2007.
14. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother. 1999;43(7):1549-55.
15. Prescott WA, Jr., Nagel JL. Extended-interval once-daily dosing of aminoglycosides in adult and pediatric patients with cystic fibrosis. Pharmacotherapy. 2010;30(1):95-108.
16. Nestaas E, Bangstad H-J, Sandvik L, Wathne K-O. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2005;90(4):F294-FF300.
17. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. Journal of Antimicrobial Chemotherapy. 1996;37(4):645-63.
18. Jenh AM, Tamma PD, Milstone AM. Extended-interval aminoglycoside dosing in pediatrics. [Review]. Pediatric Infectious Disease Journal. 2011;30(4):338-9.
19. Inparajah M, Wong C, Sibbald C, Boodhan S, Atenafu EG, Naqvi A, et al. Once-daily gentamicin dosing in children with febrile neutropenia resulting from antineoplastic therapy. Pharmacotherapy. 2010;30(1):43-51.
20. Kirkpatrick CM, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. Br J Clin Pharmacol. 1999;47(6):637-43.
21. Rao SC, Srinivasjois R, Hagan R, Ahmed M. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2011(11):CD005091.
22. Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. Cochrane Database Syst Rev. 2014;2:CD002009.
23. Tiwari S, Rehan HS, Chandra J, Mathur NN, Singh V. Efficacy and safety of a single daily dose of gentamicin in hospitalized Indian children: a quasi-randomized trial. J Antimicrob Chemother. 2009;64(5):1096-101.
24. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995;39(3):650-5.

25. McDade EJ, Wagner JL, Moffett BS, Palazzi DL, Myers EJ. Once-daily gentamicin dosing in pediatric patients without cystic fibrosis: Pharmacotherapy. 30 (3) (pp 248-253), 2010. Date of Publication: March 2010.; 2010.
26. Zakova M, Pong S, Trope A, Atenafu EG, Papaioannou V, Bitnun SA, et al. Dose derivation of once-daily dosing guidelines for gentamicin in critically ill pediatric patients. Therapeutic drug monitoring. 2014;36(3):288-94.
27. Robinson RF, Nahata MC. Safety of intravenous bolus administration of gentamicin in pediatric patients. Ann Pharmacother. 2001;35(11):1327-31.
28. Loewenthal MR, Dobson PM. Tobramycin and gentamicin can safely be given by slow push. J Antimicrob Chemother. 2010;65(9):2049-50.
29. Phelps SJ. Pediatric injectable drugs the teddy bear book. Bethesda, Maryland: American Society of Health-System Pharmacists,; 2013.
30. BNF for Children [Internet]. Pharmaceutical Press. 2014.
31. Gillett AP, Falk RH, Andrews J, Wise R, Melikian V. Rapid intravenous injection of tobramycin: suggested dosage schedule and concentrations in serum. J Infect Dis. 1976;134 Suppl:S110-3.
32. Royal College of Paediatrics and Child Health (RCPCH) NaPPGN. Medicines for Children. London: RCPCH Publications Limited; 2003.
33. Mendelson J, Portnoy J, Dick V, Black M. Safety of the bolus administration of gentamicin. Antimicrob Agents Chemother. 1976;9(4):633-8.
34. Bromiker R, Adelman C, Arad I, Shapiro M, Levi H. Safety of gentamicin administered by intravenous bolus in the nursery. Clin Pediatr (Phila). 1999;38(7):433-5.
35. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987;155(1):93-9.
36. McLean AJ, IoannidesDemos LL, Li SC, Bastone EB, Spicer WJ. Bactericidal effect of gentamicin peak concentration provides a rationale for administration of bolus doses. J Antimicrob Chemother. 1993;32(2):301-5.
37. Bastone EB, Li SC, Ioannides-Demos LL, Spicer WJ, McLean AJ. Kill kinetics and regrowth patterns of Escherichia coli exposed to gentamicin concentration-time profiles simulating in vivo bolus and infusion dosing. Antimicrob Agents Chemother. 1993;37(4):914-7.
38. Roberts GW, Harbi GA, Khalessi-Rad M. Immediate Post-Administration Safety of Bolus Gentamicin. Journal of Pharmacy Practice and Research. 2012;42(3):200-3.
39. Guy's and St Thomas' Hospital, King's College and University Lewisham Hospitals Paediatric Formulary. London, : Guy's & St Thomas' NHS Foundation Trust; 2012.
40. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Jr., Bolger AF, Levison ME, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. 2005;111(23):e394-434.
41. Wong C, Kumar SS, Graham GG, Begg EJ, Chin PKL, Brett J, et al. Comparing dose prediction software used to manage gentamicin dosing. Internal medicine journal. 2013;43(5):519-25.
42. Bauer LA. Applied clinical pharmacokinetics. New York: McGraw-Hill Medical,; 2008. Available from: http://ezproxy.library.usyd.edu.au/login?URL=http://accesspharmacy.mhmedical.com/book.aspx?bookid=510.
43. Avent ML, Teoh J, Lees J, Eckert KA, Kirkpatrick CM. Comparing 3 methods of monitoring gentamicin concentrations in patients with febrile neutropenia. Therapeutic drug monitoring. 2011;33(5):592-601.
44. Best EJ, Gazarian M, Cohn R, Wilkinson M, Palasanthiran P. Once-daily gentamicin in infants and children: a prospective cohort study evaluating safety and the role of therapeutic drug monitoring in minimizing toxicity. Pediatr Infect Dis J. 2011;30(10):827-32.
45. McCracken GH, Jr. Aminoglycoside toxicity in infants and children. Am J Med. 1986;80(6B):172-8.
46. Management of Drug-Resistant Tuberculosis in Children: A Field Guide2012 18/12/2014. Available from: http://sentinel-project.org/.