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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.
Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Dosing of antibiotics and therapeutic drug monitoring

Aminoglycosides

Aminoglycosides exert a post-antibiotic effect: high peak levels are required to penetrate the bacterial cell wall, where the drug continues to have a bactericidal effect after systemic levels have declined. Monitoring is used to ensure adequacy of dosing, to delay or prevent the onset of nephrotoxicity and reduce the risk of vestibular and auditory ototoxicity. Initial gentamicin dosing is based on bodyweight to ensure an adequate peak concentration. Modified dose is needed with increasing age (as per the Therapeutic Guidelines Antibiotic, below). Clearance of aminoglycosides is increased in children, patients with sepsis, and patients with cystic fibrosis; these patient groups require increased initial doses.

Age	Initial dose (gentamicin, tobramycin)	Initial dose (amikacin)
10 to 29 years	6 mg/kg up to 560 mg	24 mg/kg up to 2.25 g
30 to 60 years	5 mg/kg up to 480 mg	20 mg/kg up to 2 g
> 60 years	4 mg/kg up to 400 mg	16 mg/kg up to 1.5 g

Subsequent dosing may be based either on trough levels or area under the curve (AUC) methods. There are a number of computer software programmes for AUC monitoring, which help to achieve/maintain adequate levels in younger patients with good renal function; yet the simplest method for elderly patients with impaired renal function is to not greatly reduce the starting dose, but to check trough levels before repeat/extended dosing. Since aminoglycosides are nephrotoxic, prolonged low levels of drug exposure are best avoided if possible; it is important for the kidneys to have a period of no exposure to the aminoglycoside. Trough levels taken immediately before the next dose ought to be below the limit of quantification, to guarantee complete clearance of aminoglycosides. Once-daily dosing is now well accepted for all indications (apart from endocarditis). For GFR <60 mL/min, single dosing every 24 hours is appropriate, while for GFR 30-40mL/min alternate day dosing may be necessary, and for GFR<30mL/min it is best to give subsequent doses when a zero trough level is confirmed. Renal failure does not preclude giving the original “stat” dose of aminoglycoside.

Vancomycin

Some antibiotics have been classified as time-dependent, however, because of their post-antibiotic effect, they also have concentration-dependent features. Vancomycin is an example, and while efficacy is best determined by the 24-hour AUC to MIC ratio, currently vancomycin monitoring is by trough levels for practical reasons. Monitoring is used to ensure adequate levels & reduce under-dosing, but is also useful to prevent accumulation in renal impairment. Steady-state levels are usually achieved after approximately five doses (normal renal function), i.e. on the third day if dosing 12-hourly. With impaired renal function therapeutic levels may be reached sooner & lower doses/less frequent dosing is required. The target therapeutic range for pre-dose trough levels is often reported as 15-20mg/L, although this varies slightly between references. For patients on continuous infusion, aim for steady-state concentration 20-25mg/L.

Creatinine clearance (mL/min)	Starting dose	Timing of trough concentration measurement
greater than 90	1.5 g 12-hourly	before the fourth or fifth dose
60 to 90	1 g 12-hourly	before the fourth or fifth dose
20 to less than 60	1 g 24-hourly	before the third dose
less than 20	1 g 48-hourly	before the second dose

Vancomycin should not be infused faster than 1g/hour (ideally 10 mg/minute) to minimise the risk of red man syndrome.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au