Extended-interval Aminoglycoside Dosing in Patients with Cystic Fibrosis Exacerbations at The Nebraska Medical Center

The optimal dosing of aminoglycosides in patients with cystic fibrosis (CF) exacerbations has been explored in numerous studies.[1-3] Studies in CF and non-CF patients have found that extended interval aminoglycoside dosing is at least as effective as traditional dosing and may be associated with less toxicity.[1-8] The largest controlled trial in patients with CF randomized 219 patients with exacerbations into one of two study arms: tobramycin 10 mg/kg once daily, or 10 mg/kg divided three times daily.[1] All patients received ceftazidime in addition to tobramycin. There was no difference in the primary endpoint, the mean change in % predicted FEV_1 during the 14 days of treatment between the once daily (10.4%) and three times daily (10%) groups (0.4%; 95% CI -3.3 to 4.1). Furthermore, a meta-analysis that included four studies and 328 subjects found no differences in CF exacerbation clinical outcomes between once and thrice-daily dosing and found significantly less nephrotoxicity with once daily dosing in pediatric patients.[2] Based on these data, the Cystic Fibrosis consensus guidelines recommend extended interval dosing as the preferred method.[6] The recommendation for the use of extended interval dosing is based on:

1. Equivalent efficacy[1-5]
2. Potential for decreased toxicity, with specific evidence for decreased nephrotoxicity in children[1, 7, 8]
3. Increased ease of dosing, particularly where extended/continuous infusion of antimicrobials are used concomitantly or the aminoglycoside is administered in the outpatient setting

The development of aminoglycoside resistance is of particular concern for patients with cystic fibrosis as these patients are frequently colonized with multidrug-resistant pathogens such as *P. aeruginosa*. Based on pharmacokinetic/pharmacodynamic rationale, extended interval dosing may promote less resistance, given favorable peak:MIC ratios are achieved and a drug-free interval has been shown to decrease adaptive resistance.[9] However, in patients with very rapid renal elimination, a prolonged drug-free interval may occur which is longer than the duration of the aminoglycoside post-antibiotic effect. Aminoglycoside resistance development during extended interval dosing has been assessed on a limited extent basis.[10, 11] Burkhardt O, et al. examined *P. aeruginosa* resistance trends in 33 cystic fibrosis patients receiving once or thrice daily tobramycin.[10] They found an increase in tobramycin MIC after therapy in 47% (8/17) and 38% (6/16) of patients in the once and thrice-daily groups, respectively. A two-year study of tobramycin monotherapy in 44 patients found the tobramycin logarithmic geometric mean MIC increased from 13.2 mg/L to 18.4 mg/L (p=0.076) and 11.5 mg/L to 19.4 mg/L (p=0.014) in patients receiving once or thrice daily tobramycin, respectively.[11] It is difficult to draw conclusions as these studies are limited by the very small study population and the lack of isolate typing before and after therapy.

The pharmacodynamic goals of therapy with aminoglycosides relate to total exposure and pathogen MIC, frequently represented by a peak:MIC ratio of 8-12:1 for maximal clinical response.[12, 13] Most studies evaluating once daily dosing of aminoglycosides in cystic fibrosis have used daily doses of 8-10 mg/kg and have consistently resulted in tobramycin peaks of 20-30 mg/L.[1, 14-17] Based on these data, the following dosing algorithm was developed.

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Recommendation*:* All patients with CF should receive aminoglycosides per the extended-interval dosing protocol outlined below unless meeting exclusion criteria.

Exclusion: Pregnant patients or those with CrCl of <20 mL/min: dose via traditional dosing*

1. Determine dosing body weight (kg)

-Dose based on actual body weight (ABW), unless:

-If patient is >20% over ideal body weight (IBW) use dosing body weight (DBW)

IBW_{Male} = 50 + (2.3 x inches over 5 ft) IBW_{Female} = 45.5 + (2.3 x inches over 5 ft)

DBW = IBW + [0.4 (ABW - IBW)]

2. Determine initial dose

Note: If patients are unable to receive their first dose by 3pm then the dose should be held and administered at 10am the following day unless otherwise requested by the prescriber

Tobramycin: 10 mg/kg

Amikacin: 20 mg/kg

3. Obtain two serum concentrations with first dose and as indicated

Obtain two serum concentrations 1 & 5 hours after the end of the one-hour infusion.

(This typically allows for 2 half-lives to pass between levels. For patients with compromised renal function, the second serum concentration may be timed later.)

4. Determine elimination rate and half-life

$$kel = \frac{\ln(C_{1\ hr}/C_{5\ hr})}{\text{time (hr) between the two levels}}$$

$$\text{Half-life} = \frac{\ln(2)}{kel}$$

5. Determine dosing interval according to half-life

(Dosed no more frequently than every six half-lives, serum concentrations will be <1 mcg/mL for at least one half-life with this dosing)

Half-life	Dosing interval
<4 hours	Q24h
4 to 6 hours	Q36h
>6 to 8 hours	Q48h
>8 hours	Convert to traditional dosing*

*Traditional dosing goals: -tobramycin peaks of 10-12 mcg/mL & troughs <1 mcg/mL
-amikacin peaks of 15-25 mcg/mL & troughs of <5 mcg/mL

6. Determine Cmax (back-extrapolated to 30 minutes after the end of the one-hour infusion)

$$Cmax_{(30\ \text{minutes after end of infusion})} = \frac{C_{1\ hr}}{e^{-kel(t,end)}}$$

t,end = typically 0.5 h if the first level is drawn 1 h after end of infusion

Goal $Cmax_{(30\ \text{minutes after end of infusion})}$ is 20-30 mcg/mL for tobramycin & 30-45 mcg/mL for amikacin

7. If $Cmax_{(30\ minutes\ after\ end\ of\ infusion)}$ is outside goal range, increase or decrease dose by 10% and repeat steps 3-7 with next dose.

8: Inpatient monitoring:
-Pharmacist will obtain either a trough (goal <1 mcg/mL) OR two serum concentrations as described in step 3 at least every five days to verify appropriateness of dosing and make recommendations as needed.
-More frequent serum concentrations are indicated in patients with changing clinical status (changes in renal function/creatinine, clinical response, toxicity, etc.).
-Serum creatinine will be obtained on Mondays and Thursdays.

Outpatient monitoring:
-Troughs and serum creatinine drawn every four days or earlier as clinically indicated. If the trough is elevated or renal function changes then two serum concentrations will need to be obtained to determine the appropriate interval.

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