

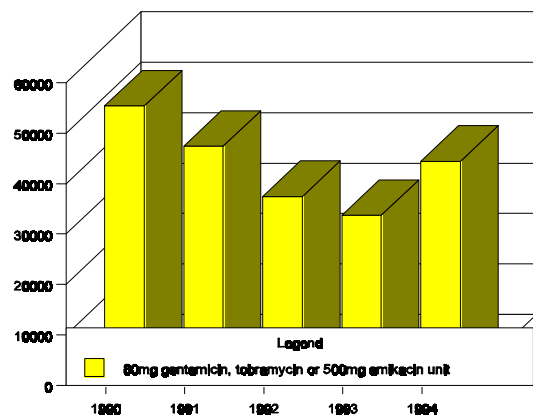
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**Modified Aminoglycoside Dosing:  
An improvement to current practice or a repeat of previous errors?**

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Despite the introduction of newer and safer antibacterial agents into our therapeutic armamentarium, aminoglycosides continue to have a role in the management of infections in the institutionalized patient. However, it is evident that the role of aminoglycosides is currently evolving into that of a "synergy drug" rather than a primary agent.



**HOW DO WE USE AMINOGLYCOSIDES AT VHSC?**

Aminoglycosides are still commonly utilized at Vancouver Hospital and Health Sciences Centre (VHSC). According to our computerized drug distribution records, over 200,000 aminoglycoside units (80mg gentamicin/tobramycin or 500mg amikacin doses) have been administered over the past five years. Utilization rates have ranged from 30,000 to 52,000 units per

year. While there was a gradual decline in utilization during the 1990 to 1993 period, 1994 data reveals an interesting reversal in this trend.

**"SINGLE DAILY DOSING" OF AMINOGLYCOSIDES - A MISNOMER**

The concept of a "single daily

dosing" (or "once daily dosing") of aminoglycosides has evolved over the last ten years.<sup>1-27</sup> Single daily dosing usually refers to a single fixed aminoglycoside dose (2mg/kg-7mg/kg) which is administered by the intravenous route every 24 hours. The term "single daily dosing" is, in fact, inaccurate, as the drug is not always administered at 24 hour intervals. The dosing interval under the single daily dosing scheme is dependent upon renal function and the subsequent ability to eliminate the drug. Patients with good renal function are given the drug every 24 hours while those with decreased renal function (i.e. an est. creatinine clearance (CrCl) < 60mL/min) are intended to receive the drug every 36 to 60 hours. As is current practice<sup>28</sup>, proponents of single daily dosing schemes continue to recommend dosing intervals which permit serum aminoglycoside concentrations to fall below 2mg/L before the next dose is administered.

In view of this misnomer, we prefer to refer to single daily dosing schemes as the "Modified Aminoglycoside Dosing (or MAD)" scheme and the current multiple daily dosing scheme as the "Traditional Aminoglycoside Dosing (or TAD)" scheme.

## **WHAT PRE-CLINICAL MAD SCHEME DATA IS AVAILABLE?**

### ***In-vitro***

The theoretical benefits of the MAD scheme is based on several pharmacodynamic properties of aminoglycosides, both in terms of efficacy

and toxicity. Aminoglycosides appear to display concentration-dependent *in vitro* bactericidal activity. This implies that the higher the serum concentration achieved, the greater the bactericidal activity against susceptible organisms.<sup>29,30</sup> Aminoglycosides also possess a postantibiotic effect (PAE), which is defined as the period of suppression of bacterial growth after cessation of exposure of the bacteria to an active antibiotic.<sup>31</sup> The PAE theoretically prevents bacterial regrowth when serum and tissue drug concentrations fall below inhibitory levels. The duration of the PAE appears to increase with prolonged exposure to the antibiotic and higher serum concentrations of aminoglycosides.<sup>30</sup> In general, maximal effects occur after 2-hour exposures to drug levels of 5 to 10 times the minimum inhibitory concentration. At these concentrations, aminoglycosides exhibit post-antibiotic effects of 2 to 6 hours against gram-positive and gram-negative organisms.<sup>30,31</sup>

### ***Animal***

The efficacy and toxicity of various dosing regimens of aminoglycosides has been studied in fifteen animal studies.<sup>32-47</sup> The experimental methodology varied markedly in these reports including factors such as the type and immune status of the animal, the infecting organism employed, the use of concomitant antibiotics, and the aminoglycoside dosing regimen tested.

The results of the studies comparing non-continuous infusion regimens were also variable. Three of the studies revealed

that shorter interval intermittent dosing regimens were more efficacious at reducing bacterial count than administering the same total daily dose at a 24-hour interval.<sup>38,43,45</sup> In contrast, three other studies identified a reverse relationship.<sup>40,41,44</sup> In the remaining studies, both regimens were found to be equivalent.<sup>42,46,47</sup> Finally, Kapusnik et al showed that relative efficacy was dependent upon the neutrophil count of the animal tested; aminoglycosides doses given at 24-hour intervals were less effective than shorter interval regimens when tested in neutropenic animals but more effective in the non-neutropenic animals.<sup>39</sup>

#### **WHAT NON-COMPARATIVE CLINICAL DATA IS AVAILABLE?**

An extensive review of the literature identified only six studies which were conducted to specifically evaluate the kinetic disposition of aminoglycosides when given under the MAD scheme.<sup>50-55</sup> These studies involved healthy volunteers and critically ill adult and pediatric patients. Two-compartment pharmacokinetic modelling techniques were employed. When directly comparing drug disposition under MAD versus TAD schemes, the investigators reported no difference in serum elimination half-life, volume of distribution and clearance parameters. When the dose per interval was tripled under the MAD scheme, the post-infusion concentration was approximately 3-fold that of the TAD scheme. Not unexpectedly, the investigators identified a significant variation in the estimated  $C_{max}$  (i.e. "peak" concentration) under each

dosing scheme, which can be attributed to significant interpatient variability in the apparent volume of distribution of the drug tested.<sup>28</sup> The median  $C_{min}$  ("trough" concentration) for both the regimens was less than 2 mg/L.

The efficacy and safety of various MAD schemes have been studied in eight non-comparative prospective studies.<sup>56-63</sup> These studies involved both non-neutropenic and neutropenic pediatric and adult patients with various types of infections including urinary tract and intra-abdominal infections, bacteremia, meningitis, osteomyelitis and otitis media. Gentamicin and amikacin were tested in dosage regimens of 2.5mg/kg and 10-20mg/kg administered every 24 hours, respectively. Various concomitant antibiotic regimens (usually beta-lactam drugs) were also used in the majority of these studies.

The reported clinical efficacy in these trials ranged from 56% (febrile neutropenia) to 100% (urinary tract infections), however the lack of a control group makes interpretation of these results difficult.<sup>6,60</sup> The definition of nephrotoxicity in these studies was variable and ranged from an increase in serum creatinine of 15% to an increase of 50% or greater. Under these definitions, the reported incidence of nephrotoxicity ranged widely from 0% to 31%.<sup>56-59,61-62</sup> Ototoxicity assessment was generally poor in these studies. Ototoxicity was often undefined or involved an assessment of clinical signs of toxicity only. The reported incidence of ototoxicity also ranged widely from 0% to 43%.<sup>57-59,61-62</sup> Vestibular toxicity was not tested in

these studies.

## WHAT COMPARATIVE CLINICAL TRIALS HAVE BEEN CONDUCTED?

There are 27 published prospective clinical trials comparing various MAD versus TAD regimen.<sup>1-27</sup> Of these 27 studies, 26 (96%) involved treatment regimen randomization,<sup>1-4,6-27</sup> while only three (11%) were conducted under double-blind study conditions.<sup>3,10,11</sup> Using the clinical efficacy success rates reported by the investigators in the control arm of each study, a power of 0.80, and an alpha of 0.05, we calculated the minimum sample size required to show a 10% and 20% difference between treatment arms for each study.<sup>64</sup> Through this process we were able to identify only four (15%) published trials which were large enough to detect a 10% difference<sup>7,8,11,26</sup> and 15 (55%) trials which involved a sample size large enough to detect a 20% difference in efficacy between the two treatment arms.<sup>5-9,11,12,14,18,19,22,24,25,27</sup> **Overall, we were able to identify only one study which involved a randomized, double-blind study design of adequate sample size.<sup>11</sup>**

Concurrent antibiotics were employed in 18 (67%) of the 27 studies reviewed. However, in seven (26%) of these 18 studies, the use of these antibiotics was uncontrolled and left to the discretion of the physician. In the majority of these studies, the mean duration of therapy was greater than seven days.

Despite the significant

methodological shortcomings of the published clinical trials, a review of these studies is still warranted. As shown in Table 1, a total of 4631 patients have been enrolled. Infectious indications assessed include urinary tract and intra-abdominal infections, pelvic inflammatory disease, cystic fibrosis and serious infections in non-neutropenic and neutropenic patients.

Table 1. Summary of published trials comparing MAD regimen to TAD regimens for different infectious indications

Infectious indication	Use <sup>1</sup>	Number of studies	Total patients enrolled <sup>2</sup>	
Urinary Tract	T	7	664 <sup>3</sup> (480) <sup>4</sup>	
Intra-abdominal	O	1	271	
	T <sup>6</sup>	4	417 <sup>7</sup> (309) <sup>8</sup>	
Pelvic Inflammatory Disease	T	1	78	
Cystic Fibrosis	T	1	26	
Serious infection: non-neutropenic	T	9	1296 <sup>9</sup>	
			<i>Bone/Joint</i>	10
			<i>Endocarditis</i>	10
			<i>Gynecological</i>	46
			<i>Pneumonia</i>	205
			<i>Soft tissue</i> <sup>0</sup>	30
Serious infection: neutropenic	T	5	1090	
Total		27	4631	

**Footnotes:**

<sup>1</sup> T - treatment; P - prophylactic

<sup>2</sup> total number of patients enrolled in both arms

<sup>3</sup> patients in trials involving urinary tract infections only

<sup>4</sup> patients in trials involving mixed serious infections; urinary tract as the primary focus  
<sup>5</sup> including enteritis, cholangitis, cholecystitis, liver abscess, retroperitoneal abscess, abdominal wall abscess, bacterial peritonitis, and colorectal surgery  
<sup>6</sup> use of aminoglycoside in one study (reference number 33) was in both prophylaxis and treatment after colorectal surgery  
<sup>7</sup> patients in trials involving intra-abdominal infections only  
<sup>8</sup> patients in trials involving mixed serious infections; abdomen as the primary focus  
<sup>9</sup> including patients with urinary tract and intra-abdominal infections  
<sup>10</sup> including diabetes mellitus gangrene, decubitus ulcer, submandibular abscess

MAD schemes have been compared to TAD schemes in seven studies which included 664 patients with uncomplicated and complicated urinary tract infection only.<sup>1-7</sup> When considering patients with urinary tract infections who were grouped with patients with other serious infections, TAD and MAD schemes have been assessed in 1144 patients. Gentamicin, sisomicin and netilmicin have been tested in MAD schemes of 2mg/kg to 6mg/kg administered every 24 hours. The definitions for cure or improvement varied widely in these studies, and ranged from clinical resolution of signs and symptoms<sup>3,5,6</sup> to a microbiological eradication from urine.<sup>1,2,4,7</sup> Reported efficacy ranged from 40 to 100%. The MAD scheme was found to be equally effective to the TAD scheme in six studies<sup>1,3,4,5,6,7</sup> and less effective than the TAD regimen in one study.<sup>2</sup> Nephro- and ototoxicity, when defined and measured, ranged from 0% to 46% and 0% to 22%, respectively. In six of the seven studies, the reported incidence of nephrotoxicity was equivalent between the two dosing schemes.<sup>2-7</sup> However, one study reported significantly higher nephrotoxicity with the MAD scheme.<sup>1</sup> The incidence of ototoxicity was equivalent across treatment groups in all seven studies.

Four studies have been published which involved 417 patients with intra-abdominal infections.<sup>8-11</sup> When considering

patients with intra-abdominal infections who were grouped with patients with other serious infections, TAD and MAD schemes have actually been assessed in 726 patients. MAD schemes involved 4.5mg/kg to 6mg/kg of netilmicin or 15mg/kg amikacin given every 24 hours. In these studies, the MAD scheme was found to be equally effective as the TAD scheme with reported efficacy ranging from 73% to 100% and 82% to 98%, respectively. Nephrotoxicity definitions were again variable. The reported incidence of nephrotoxicity did not differ between the two regimens and ranged from 0% to 13% for the MAD scheme and 0% to 10% for the TAD scheme. Audiometric testing was carried out in one study only<sup>9</sup>, while clinical signs of auditory and vestibular dysfunction were assessed for the remaining trials.<sup>8,10,11</sup> The reported incidence of ototoxicity was less than 1% in these studies.

Nine studies have been published which involved a comparative assessment of MAD and TAD schemes in 1296 non-neutropenic patients with various serious infections.<sup>14-22</sup> Infectious indications included urinary tract, intra-abdominal, lower respiratory tract, skin/soft tissue infections, prostatitis and bacteremia. Reported experience with endocarditis has been limited to ten patients only.<sup>16,20</sup> An assessment of MAD schemes has also been published for only ten osteomyelitis/septic arthritis patients<sup>16</sup> and 26 cystic fibrosis patients.<sup>13</sup> There is even less experience with MAD schemes in the treatment of meningitis, neonates, infections associated with pregnancy and hemodialysis, surgical prophylaxis, bone marrow and solid organ

transplant patients.<sup>8,12</sup>

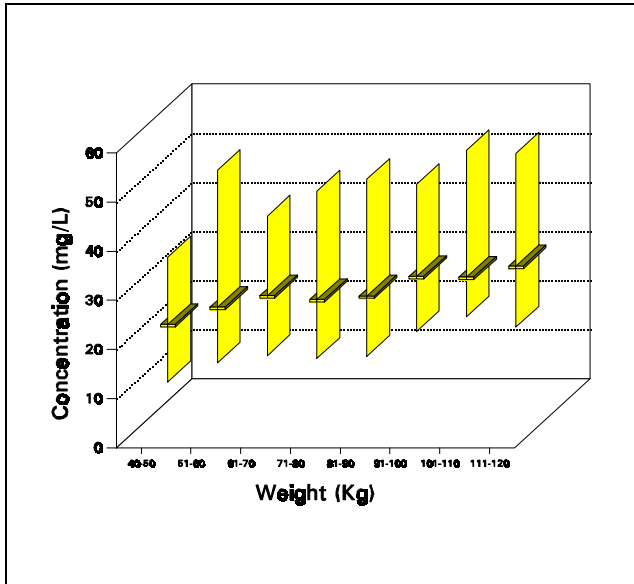
In these nine studies, MAD schemes involved gentamicin and netilmicin in regimens of 3.9mg/kg to 5mg/kg or amikacin in regimens of 15mg/kg to 20mg/kg given every 24 hours. MAD schemes were found to be equivalent to TAD schemes in eight of these studies,<sup>14-16,18-22</sup> and more effective than the TAD scheme in the remaining study.<sup>17</sup> Under variable definitions, the reported incidence of nephrotoxicity ranged from 0% to 34% for the MAD scheme and 0% to 32% for the TAD scheme. In eight of the nine studies, there was no difference across dosing schemes.<sup>14-19,21,22</sup> In the remaining study, the TAD scheme resulted in a higher incidence of nephrotoxicity than the MAD scheme.<sup>20</sup> Ototoxicity was reported in 0% to 25% of patients receiving the MAD scheme and 0% to 27% of patients receiving the TAD scheme. In all nine studies there was no difference in ototoxicity between the two treatment arms.

Experience with 1296 neutropenic patients has also been published.<sup>23-27</sup> MAD schemes were found to be equivalent to TAD schemes in all of these studies with reported efficacy rates ranging from 23% to 71% for the MAD arm versus 35% to 74% for the TAD arm. Nephrotoxicity was also considered equivalent between the dosing schemes with the incidence ranging from 0% to 7%. The incidence of ototoxicity was also equivalent and ranged from 0% to 9%.

## WHAT AMINOGLYCOSIDE DISPOSITION CHARACTERISTICS CAN WE EXPECT UNDER A MAD SCHEME?

We assessed the predicted disposition of gentamicin and tobramycin under MAD guidelines using prospective pharmacokinetic data collected for 415 VHHSC inpatients.<sup>65</sup> This data was used to create the empiric TAD guidelines that are currently promoted in this hospital. Under a MAD scheme of 7mg/kg (total body weight) as promoted by Nicolau et al<sup>66</sup>, a mean steady-state  $C_{maxss}$  of 26.4mg/L (range 8.5-55.6mg/L) can be expected. Figure 1 represents the mean and range of  $C_{maxss}$  across patients stratified into eight 10-kg increment weight groups as was undertaken in our previous study. The mean  $C_{maxss}$  tended to increase with increasing body weight and variability in  $C_{maxss}$  remained through all eight weight groups. As identified by previous investigators, the variability in  $C_{maxss}$  is related to the interpatient variation in the volume of distribution of the drug.

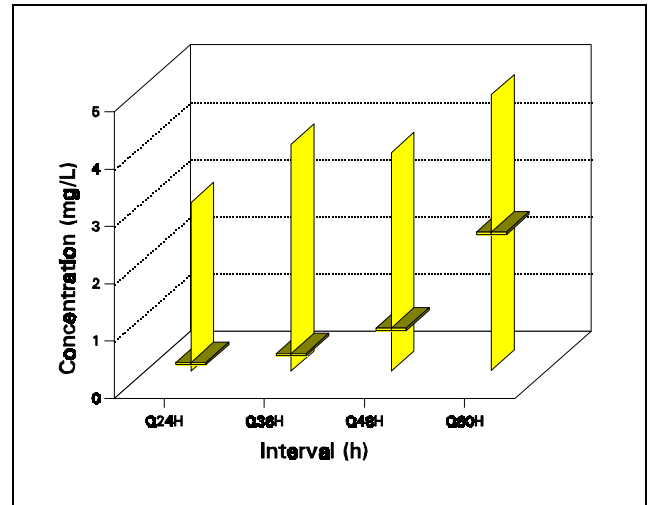
Figure 1: Gentamicin/Tobramycin  $C_{maxss}$  under a MAD scheme



To determine the predicted  $C_{minss}$  associated with the MAD scheme, an empiric dosing interval was also determined using the published guidelines (Figure 2). For each patient, an estimated CrCl was calculated. According to Nicolau and Quintiliani, patients with an estimated CrCl of 60mL/min or greater should receive doses as 24-hour intervals, those with CrCl of 40 to 59mL/min should receive doses at intervals of 36 hours, those with CrCl of 20 to 39mL/min should receive doses at intervals of 48 hours and those with a CrCl of less than 20mL/min should receive doses every 60 hours.<sup>66</sup> Under this dosing scheme, the predicted  $C_{minss}$  was greater than 2mg/L in 2% of patients receiving an empiric dose every 24 hours (n= 329), 3% of patients on a 36 hour regimen (n= 63), 10% of patients on a 48 hour regimen (n= 21) and 50% of patients on a 60 hour regimen (n= 2). The incidence of patients

with aminoglycoside concentrations less than or equal to 0.5mg/L at the dosing interval midpoint was 23% for the 24 hour interval, 13% for the 36 hour interval, and 10% for the 48 hour interval.

Figure 2: Gentamicin/Tobramycin  $C_{minss}$  under a MAD scheme



In summary, wide variations in  $C_{maxss}$  can be expected if a fixed mg/Kg MAD scheme is employed. In addition, some patients will require dosing interval extensions beyond those predicted by the published dosing nomogram. Finally, the MAD scheme may result in low aminoglycoside concentrations for a period of time beyond the anticipated post antibiotic effect. For these reasons, serum level monitoring would still be warranted under a MAD scheme to ensure subtherapeutic or excessive drug concentrations are not obtained with the empiric dosing regimens.

**WHAT ARE THE POTENTIAL COST**

## IMPLICATIONS OF A MAD SCHEME?

Using current VHHSC daily cost estimates for the acquisition, preparation and administration of aminoglycosides, a MAD regimen of 7mg/Kg for gentamicin and tobramycin given every 24 hours (70kg patient) will cost \$19.45 and \$39.54, respectively. In comparison, the cost of a TAD regimen of 1.5mg/kg for the same patient is \$24.15 and \$37.68, respectively. Thus, the MAD regimen is approximately \$4.70 per day less expensive for gentamicin and \$1.86 per day more expensive for tobramycin. Cost comparisons involving lower dose MAD schemes (e.g. 6mg/kg) will obviously alter the magnitude of these differences. When a MAD regimen is compared with non-weight-based regimens (e.g. 80mg Q8H) commonly prescribed when aminoglycosides are employed for prophylactic purposes, the cost of the former is significantly higher. Thus, potential cost savings associated with MAD schemes appear to be minimal.

## WHAT IS THE CURRENT POSITION OF THE ANTIBIOTIC USE SUBCOMMITTEE AND THE DRUG AND THERAPEUTICS COMMITTEE ?

It is the position of the Committees that the current published clinical literature does not permit a definitive assessment of the relative benefits and risks of MAD schemes. Despite these flaws, the current evidence would suggest that MAD schemes are no more effective, no less toxic and no cheaper than the current TAD scheme.

Accordingly, the Drugs and Therapeutics committee does not currently endorse the promotion of MAD schemes at this hospital.

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