Pediatric Assessment of Vancomycin Empiric Dosing (PAVED)

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Background

- At BC Children's Hospital (BCCH), vancomycin and a third-generation cephalosporin are used for empiric treatment of severe infections including sepsis, meningitis, and severe pneumonia.
- This strategy is used to prevent treatment failure due to third-generation cephalosporin resistant *Streptococcus pneumoniae* and/or methicillin resistant *Staphylococcus aureus*.
- High target trough serum concentrations of 15-20 mg/L are recommended for severe infections.
- The empiric dosing regimen (60 mg/kg/day divided q6h or q8h) is used to target trough concentrations of 10-15 mg/L and 15-20 mg/L; the regimen is modified as needed using patient specific pharmacokinetics (PK).
- Studies and anecdotal experience suggest that the current empiric dosing regimen does not reach therapeutic targets.

Objectives

- **Primary:**
  - Describe proportions of patients achieving initial vancomycin concentrations of 10-15 or 15-20 mg/L.
  - Describe PK parameters within each age group.
- **Secondary:**
  - Describe differences between q6h and q8h in achieving trough concentrations of 10-15 or 15-20 mg/L.
  - Compare patient-specific and population estimated AUC:MIC values using initial dosing regimen.
  - Describe changes of individual PK parameters within patients with multiple sets of peak and trough vancomycin concentrations.

Methods

- **Design:** Retrospective review
- Institutional ethics board approval
- **Population:** Patients who received IV vancomycin at BCCH and had peak and trough serum concentrations measured between Jan 2011 and July 2012
- **Inclusion:** > 1 month post-natal age, two evaluable vancomycin serum concentrations
- **Exclusion:** Extracorporeal life support, renal replacement therapy, dialysis, cystic fibrosis
- **Statistics:** X^2; Fishers exact; Wilcoxon rank sum and signed rank; $p < 0.05$ deemed statistically significant
- **Sample size:** Based on 50% reaching indication target, absolute precision of 7%, 95% confidence interval = 196 patients

Results

Table 1. Patient demographics.

		Group 1 1 mo - 1 y	Group 2 1 - 6 y	Group 3 6 - 13 y	Group 4 13 - 18 y	Total
n		50	50	50	50	200
Age (years)†		0.5 (0.41)	3.1 (2.20)	9.2 (3.61)	15.6 (1.78)	6.0 (11.9)
Sex (% male)		58	58	60	62	60
Weight (kg)†		7.3 (2.3)	13.7 (5.7)	29.2 (12.7)	54.0 (18.4)	20.0 (30.4)
Initial S_{cr} (μmol/L)†		22 (8.8)	25 (8)	39 (13.5)	59 (22)	32 (26)
Vancomycin dose (mg/kg/day)†		60.0 (1.7)	60.0 (1.2)	59.8 (6.2)	58.7 (14.5)	60.0 (2.9)
Dosing interval‡	q6h	28 (56)	26 (52)	17 (34)	16 (32)	87 (44)
	q8h	22 (44)	24 (48)	32 (64)	30 (60)	108 (52)
	q12h	0	0	1 (2)	4 (8)	5 (3)
Goal trough Concentration‡	10-15 mg/L	9 (18)	11 (22)	16 (32)	16 (32)	52 (26)
	15-20 mg/L	41 (88)	39 (78)	34 (68)	34 (68)	148 (74)

† median (IQR); ‡ n (%)

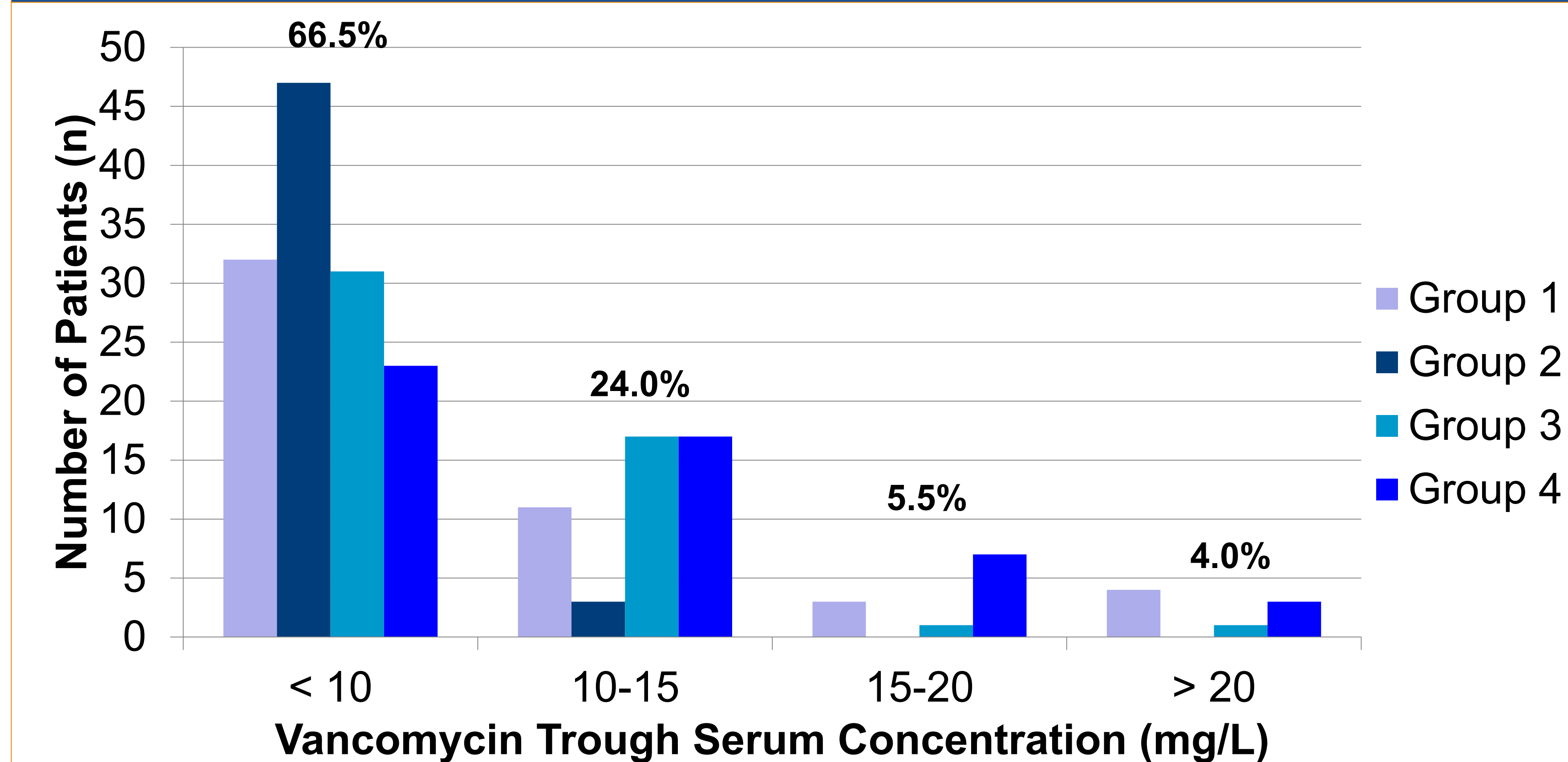### Figure 1. Rates of targets achieved using empiric dosing regimen.

Table 2. Description of the pharmacokinetic parameters within and between each group. Median (IQR)

	Group 1 Set 1	Group 1 Set 2	Group 2 Set 1	Group 2 Set 2	Group 3 Set 1	Group 3 Set 2	Group 4 Set 1	Group 4 Set 2
n	50	15	50	20	50	14	50	13
k_e (h^{-1})	0.25 (0.09)	0.25 (0.08)	0.29 (0.07)	0.29 (0.07)	0.24 (0.10)	0.23 (0.15)	0.22 (0.07)	0.23 (0.08)
$t_{1/2}$ (h)	2.8 (1.1)	2.8 (1.2)	2.37 (0.5)	2.8 (0.5)	2.9 (1.1)	3.0 (1.6)	3.2 (1.0)	3.0 (1.0)
V_d (L/kg)	0.55 (0.20)	0.61 (0.20)	0.60 (0.23)	0.61 (0.35)	0.45 (0.23)	0.52 (0.27)	0.45 (0.18)	0.44 (0.23)

- Between groups: Wilcoxon rank sum; $p < 0.05$. Except k_e and $t_{1/2}$ (group 1 vs. 3) and V_d (groups 1 and 2 vs. 3 and 4), $p > 0.05$.
- Within group sets: Wilcoxon signed rank; $p > 0.05$.

Table 3. Number of patients achieving target concentrations.

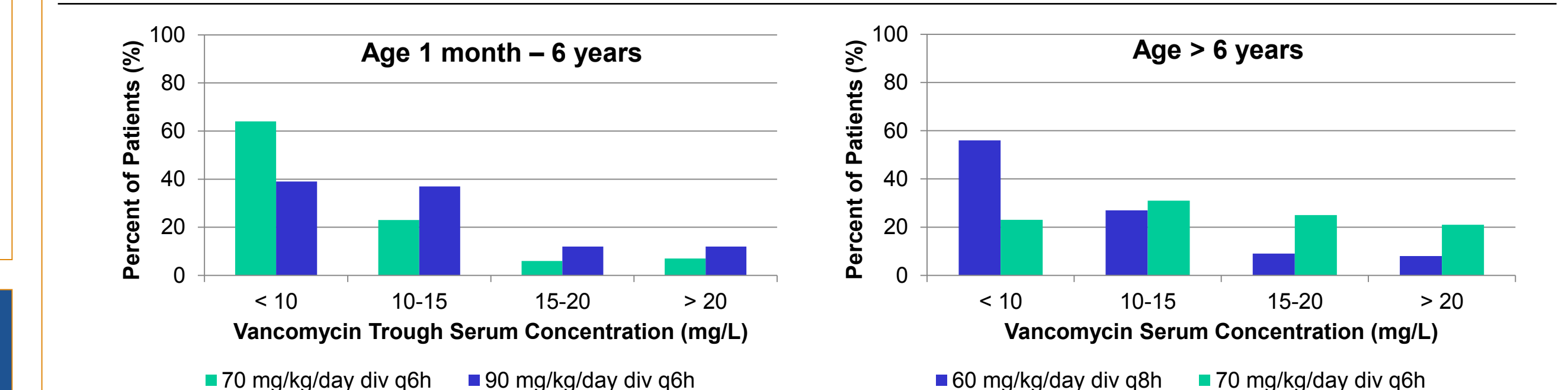|	Vancomycin serum concentration (mg/L)			
Dosage (mg/kg)	< 10	10-15	15-20	> 20
15 q6h (n, %)	55 (63)	25 (29)	2 (2)	5 (6)
20 q8h (n, %)	74 (69)	22 (20)	9 (8)	3 (3)

- Fishers exact test; $p > 0.05$.

Table 4. Description of patient-specific AUC:MIC compared to population estimated AUC:MIC. Values median (IQR)

	Group 1 Patient AUC	Group 1 Pop. AUC	Group 2 Patient AUC	Group 2 Pop. AUC	Group 3 Patient AUC	Group 3 Pop. AUC	Group 4 Patient AUC	Group 4 Pop. AUC
n	50	22	50	15	50	13	50	17
Median (IQR)	465 (178)	428 (79)	338 (132)	837 (320)	501 (197)	1560 (659)	519 (211)	2886 (472)

	AUC:MIC							
MIC 0.5	931	855	676	1674	1003	3120	1038	5771
MIC 1.0	465	428	338	837	501	1560	519	2886
MIC 2.0	233	214	169	419	251	780	259	1443

- Wilcoxon signed rank; $p < 0.05$ (groups 2, 3 and 4); $p > 0.05$ (group 1).

Recommendations: New Empiric Dosing

	Target Trough Concentration (mg/L) 10 – 15	Target Trough Concentration (mg/L) 15 – 20
Age 1 month – 6 years	70 mg/kg/day div q6h	90 mg/kg/day div q6h
Age > 6 years	60 mg/kg/day div q8h	70 mg/kg/day div q6h

Conclusions

- New initial empiric dosing regimen is required to reach target vancomycin serum concentrations.
- No significant difference overall between q6h and q8h dosing intervals compared with published study data
- No significant difference in PK parameters in patients who had second concentrations measured
- Patient-specific AUC:MIC was significantly lower than population estimated in all populations except infants (group 1)
- Next steps: Validation of new dosing recommendations through retrospective pharmacokinetic analysis and/or prospective implementation