# Vancomycin Dosing in Obese Children:

# **A Growing Issue**

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# Childhood Obesity in Canada

- ↑ 2x in past 30 years
- ~ ⅓ Canadian children are overweight/obese
- Leads to
  - T2DM, HTN, depression & many other comorbidities
  - physiologic changes that complicate drug therapy

Statcan.gc.ca
Pediatrics.2007;120;S193–228
Obes Rev. 2008;9(5):474–88
Arch Dis Child. 2003;88(9):748–52

# Defining Obesity in Children

- Percentile distributions (based on age + weight)
  - OBESE: $\geq 95^{th}$ %-ile
  - OVERWEIGHT: BMI $\geq 85^{th}$ and $< 95^{th}$ %-ile

- Weight-for-Height *Z*-scores
  - OBESE: *Z*-score > 3
  - OVERWEIGHT: *Z*-score >2

Pediatrics. 2007; 120;S193-228
Int J Obesity. 2006; 30: 590-594
WHO 2008
Adv Nutr. 2011; 2: 159S-166S

# Physiological Changes in Obese Children

Body composition
- ↑ TBW, lean mass, fat mass, bone mineral content
- ↑ ECF

A
- No change*

D
- Lipophilic drugs: ↑ Vd
- Hydrophilic drugs: potentially ↓ Vd/TBW
- PPB: limited information

M
- Cl of drugs metabolized by oxidation ↑*
- Case reports: no change

E
- Limited information

*based on adult data

Pharmacotherapy. 2013;33(12):1264–72
Clin Infect Dis. 2011;52(3):e18–55
Pharmacotherapy. 2013;33(12):1278–87
J Pediatr Pharmacol Ther. 2010;15(2):94–109
Orthopedics. 2006;29(11):984–8
Int J Obes. 2006;30(10):1506–13
Applied Pharmacokinetics & Pharmacodynamics, 4th edn
Pharmacotherapy. 2007;27(8):1081–91

# Vancomycin PK & Dosing in Obese Adults

## Vd

- Vancomycin= hydrophilic = distributes into total body water
- Inconsistent & variable changes reported
- Best correlated with TBW

## Clearance

- ↑ due to ↑ blood volume, cardiac output, renal hypertrophy
- Best correlated with TBW

## Dosing

- TBW recommended for initial dosing
- Obese patients w/ normal renal function may require ↑ dosing frequency

Applied Pharmacokinetics & Pharmacodynamics, 4th edn.
Pharmacotherapy. 2007;27(8):1081–91
J Antimicrob Chemother. 2012;67(6):1305–10
Therapeutic Drug Monitoring. 1994;16:513-518
Antimicrob Agents Chemother. 1982;21(4):575–80
Clin Pharm. 1987;6(9):706–14.

# Vancomycin PK Parameters in Obese Children

| Data Source | Clearance (ml/min) | Vc (L/kg) | $V_{ss}$ (L/kg) | Kel ($h^{-1}$) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| Obese Patients | | | | | |
| Moffett et al. (2011) | - | - | 0.19- 0.55 | 0.22 - 0.28 | 2.5 – 3.2 |
| Varying Weight Groups | | | | | |
| Nassar et al. (2012) | UW 0.18 ± 0.09 L/hr/kg<br>NBH 0.2 ± 0.08 L/hr/kg<br>OW 0.16 ± 0.05 L/hr/kg | - | UW 0.97 ± 0.54<br>NBH 1 ± 0.35<br>OW 0.81 ± 0.37 | UW 0.2 ± 0.58<br>NBH 0.19 ± 0.5<br>OW 0.21 ± 0.59 | UW 3.55 ± 1.19<br>NBH 3.59 ±1.4<br>OW 3.3 ±1.17 |
| Patients with Mean BMI 21.5 (13.6-22.8), Mean weight 38 kg | | | | | |
| Camaione et al. (2013) | 62.17 ± 28.5 | 0.64 ± 0.4 | - | - | - |
| Non-Obese Patients | | | | | |
| Children (0.01-18 years) | 138.6 ± 49.3 | 0.27 ± 0.07 | 0.43 | 0.18 | 3.9 |

Clin Pediatr. 2011;50(5):442–6
Curr Drug Saf. 2012 Nov 1;7(5):375–81
Pharmacotherapy. 2013;33(12):1278–87
Applied Pharmacokinetics & Pharmacodynamics, 4th edn

# Vancomycin PK Parameters in Obese Children

- Limited information available
- PK parameter estimates available from small studies
- Moffet *et al*.
  - ↓ $t_{1/2}$
- Nassar *et al*.
  - PK parameter estimates similar across weight groups
- Camaione *et al*.
  - ↑ Vc and ↓ Cl

Clin Pediatr. 2011;50(5):442–6
Curr Drug Saf. 2012 Nov 1;7(5):375–81
Pharmacotherapy. 2013;33(12):1278–87
Applied Pharmacokinetics & Pharmacodynamics, 4th edn

# Vancomycin Recommendations in Children of Normal Body Habitus

- Serious MRSA infections (IDSA):
  - 15 mg/kg/dose IV every 6 hours
  - Target trough 15-20 mg/L
  - AUC/MIC values > 400
- Evidence <u>not</u> established for:

| | | |
|---|---|---|
| **target trough concentrations or AUC/MIC values** | **=** | **EFFICACY or SAFETY** |

Clin Infect Dis. 2011;52(3):e18–55

# Dosing Weight in Obese Children

- 4 possible approaches:
  - Age: does not account for PK variability
  - Allometric scaling
    - Relates physiologic function & morphology to body size
    - Impractical for clinical use
  - BSA
    - Used for chemotherapy
    - No differentiation between adipose and lean tissue
  - Weight
    - Most common
    - IBW: No standard method to calculate in children
    - DBW: Not validated in children

J Pediatr Pharmacol Ther. 2010;15(2):94–109

# Clinical Question

| | |
|---|---|
| **P** | In obese children |
| **I** | what is the most appropriate vancomycin dosing strategy |
| **C** | compared to vancomycin dosing in children of NBH |
| **O** | to achieve target trough concentrations? |

NBH= normal body habitus

# Search Strategy

| | |
|---|---|
| **Search Terms** | Vancomycin, glycopeptides, obesity, overweight, drug dose |
| **Databases** | Pubmed, Embase, IPA, Cochrane Database of Systematic Reviews, clinicaltrials.gov, Google Scholar |
| **Limits** | English, child (unspecified age) |

# Search Results

| | |
|---|---|
| **RCTs** | **None; none upcoming** |
| **Case-Control** | **Moffett *et al.***<br>**Miller *et al.***<br>**Heble *et al.***<br>Madigan *et al.* |
| **Other** | Nassar *et al.*<br>Camaione *et al.* |

# Moffett et al. (2011)

| | | | |
|---|---|---|---|
| **D** | Single-center, retrospective, matched study; 2009-2010 | | |
| **P** | n= 48, 2 -17 yrs, vancomycin IV (goal trough 15-20 mg/L)<br>(matched by age and dosing schedule)<br>Excluded: eCCl < 75 ml/min/1.73m$^2$, renal dysfunction or disease, no matched control | | |
| | **Obese** | **NBH** | ***p*** |
| n | 24 | 24 | - |
| Age (years) | 6.8 ± 4.31 | 7.2 ± 4.8 | 0.85 |
| Male (%) | 58 | 46 | 0.56 |
| Weight (kg) | 33.4 ± 21.9 | 25.1 ± 15.4 | 0.14 |
| BMI (%ile) | 97.3 ± 1.49 | 50.8 ± 13.42 | <0.01 |
| **O** | Vancomycin serum trough concentrations & PK parameters | | |

Clin Pediatr. 2011;50(5):442–6

# Moffett et al. (2011)

| | Obese (n=24) | NBH (n=24) | *p* |
|---|---|---|---|
| **Dose (mg/kg/dose) [TBW]** | 14.1 ± 1.5 | 14.9 ± 0.9 | 0.03 |
| **Interval frequency (n)** | | | |
| q6h | 1 | 1 | - |
| q8h | 21 | 21 | - |
| q12h | 2 | 2 | - |
| **Trough (mg/L)** | 6.9 ± 4.3 | 4.8 ± 3.1 | 0.052 |
| **Patients with trough level < 5mg/L (%)** | 33 | 58 | 0.15 |

Clin Pediatr. 2011;50(5):442–6

# Moffett et al. (2011)

- Obesity did not *significantly* alter vancomycin trough concentrations (p= 0.052)
- Vancomycin troughs in both groups were lower than recommended target
- Suggested that overweight/obese children should receive vancomycin dosed based on TBW

Clin Pediatr. 2011;50(5):442–6

# Moffett et al. (2011)

| | |
|---|---|
| **Strengths** | • Reasonable matching parameters<br>• Dosing based on TBW<br>• Appropriate sampling of trough levels |
| **Limitations** | • Retrospective<br>• Small sample size<br>• Limited patient demographic information provided<br>• No information provided across extremes of obesity<br>• No data on clinical outcomes or adverse effect rates<br>• No information on patients < 2 years old |

Clin Pediatr. 2011;50(5):442–6

# Miller et al. (2011)

| | | | |
|---|---|---|---|
| **D** | Single-center, retrospective, matched study; 2007-2009 | | |
| **P** | n=232, 2-17 yrs, vancomycin IV (goal trough: 5-15 mg/L & 10-20 mg/L)<br>Excluded: < 3 doses, inappropriately timed trough, incomplete medical record, renal dysfunction | | |
| | **Overweight/Obese** | **NBH** | ***p*** |
| n | 70 | 162 | - |
| Age (yr) | | | |
| 2-5 | 31.4% | 46.3% | 0.035 |
| 6-11 | 41.4% | 28.4% | 0.051 |
| 12-17 | 27.1% | 25.3% | 0.77 |
| Male (%) | 62.9 | 58.6 | 0.398 |
| Weight (kg) | 43.4 ± 30.4 | 27.6 ± 16 | <0.001 |
| BMI ($kg/m^2$) | 23.3 ± 5.7 | 17.6 ± 13.0 | <0.001 |
| **O** | 1º Vancomycin serum trough concentrations<br>2º initial dose & dosing interval; nephrotoxicity; redman sydrome | | |

Am J Health Syst Pharm. 2011;68(21):2062–8

# Miller et al. (2011)

| | Overweight/Obese n= 70 | NBH n= 162 | *p* |
|---|---|---|---|
| **Dose (mg/kg/dose) [TBW]** | 16.6 ± 3.9 | 17.2 ± 4.1 | 0.295 |
| **Interval frequency (n[%])** | | | |
| q6h | 8 (11.4) | 26 (16.1) | 0.36 |
| q8h | 52 (74.3) | 131 (80.9) | 0.26 |
| q12h | 10 (14.3) | 5 (3.1) | <0.01 |
| **Trough (mg/L)** | 9.6 ± 8.9 | 7.4 ± 5.7 | 0.03 |
| **% regimens w/ trough 10-20 mg/L** | 25.7 | 20.4 | 0.367 |
| **% regimens w/ trough > 20 mg/L** | 7.1 | 3.1 | 0.16 |
| **Nephrotoxicity** | 5 (7.1) | 4 (2.4) | - |

Am J Health Syst Pharm. 2011;68(21):2062–8

# Miller et al. (2011)

- Overweight & obese children had significantly ↑ troughs compared to patients of NBH
- Across all weight categories ~ 22% of regimens achieved troughs of 10-20 mg/L
- Dosing q8h more often achieved target trough concentrations

Am J Health Syst Pharm. 2011;68(21):2062–8

# Miller et al. (2011)

| | |
|---|---|
| **Strengths** | • Reasonable matching parameters<br>• Dosing based on TBW<br>• Moderate sample size (pediatric study)<br>• Appropriate sampling of trough levels |
| **Limitations** | • Retrospective design<br>• No information provided across extremes of overweight and obesity<br>• No data on clinical outcomes<br>• Limited patient demographic information provided<br>• ↑ % of 2-5 year olds in the NBH group<br>• Unequal balance of dosing regimens used<br>• No information on patients < 2 years old |

Am J Health Syst Pharm. 2011;68(21):2062–8

# Heble et al. (2013)

| | | | |
|---|---|---|---|
| **D** | Single-center, retrospective case-control study; 2010-2011 | | |
| **P** | n= 126, 2-18 yrs, vancomycin IV (target trough 10-20 mg/L)<br>Excluded: elevated SCr, congenital heart disease, cystic fibrosis, concomitant calcineurin inhibitor, missing data | | |
| | **Obese** | **Overweight** | **NBH** |
| n | 21 | 21 | 84 |
| Age (years) | 8.9 ± 5.1 | 9.7 ± 4.7 | 9.5 ± 4.9 |
| Male (%) | 62 | 48 | 55 |
| Weight (kg) | 44 (12-108) | 43 (11-84) | 29 (12-76) |
| BMI (%ile) | 98 (95-100) | 89 (85-94) | 49 (5-84) |
| **O** | Vancomycin serum trough concentrations | | |

Pharmacotherapy. 2013;33(12):1273–7

# Heble et al. (2013)

| | |
|---|---|
| **Dose [TBW]** | Age 2-8 years: 20 mg/kg/dose<br>Age 9-13 years: 20 mg/kg/dose<br>Age 14-18 years: 15 mg/kg/dose |
| **Dosing Interval** | 2-8 years: q6h<br>9-13 years: q8h<br>14-18 years: q8h |

Pharmacotherapy. 2013;33(12):1273–7

# Heble et al. (2013)

| | **Obese** n=21 | **Overweight** n=21 | **NBH** n=84 | ***p*** |
|---|---|---|---|---|
| **Dose (mg/kg/dose) [TBW]** | 19.7 (13.9-20.9) | 19.8 (14.1-20.7) | 19.8 (14.6-21.0) | - |
| **Mean initial trough (mg/L)** | 15.2 | 13.5 | 10.5 | Obese vs NBH: <0.001<br><br>OW vs NBH: 0.023 |
| **% regimens w/ trough 10-20 mg/L** | 71 | 57 | 46 | - |
| **% regimens w/ trough >20mg/L** | 19 | 14 | 2 | - |

Pharmacotherapy. 2013;33(12):1273–7

# Heble et al. (2013)

- Overweight & obese patients had ↑ vancomycin troughs compared to NBH patients with dosing based on TBW

- Compared to other studies which used 15 mg/kg/dose, use of median 20 mg/kg/dose resulted in:
  - ↑ trough concentrations
  - ↑ frequency of target trough attainment

Pharmacotherapy. 2013;33(12):1273–7

# Heble et al. (2013)

| | |
|---|---|
| **Strengths** | • Reasonable matching parameters<br>• Dosing based on TBW<br>• Reasonable description of baseline demographics |
| **Limitations** | • Retrospective<br>• Small sample size<br>• Data on dosing intervals utilized not provided<br>• Clinical outcomes, adverse effects, PK parameters were not assessed<br>• No information on patients < 2 years old |

Pharmacotherapy. 2013;33(12):1273–7

# Madigan et al. (2013)

| | | |
|---|---|---|
| **D** | Single-center, retrospective observational study; 2008-2012 | |
| **P** | n= 222, 1 month- 18 yrs, vancomycin IV (10-20 mg/L)<br>Excluded: received 10% above or below recommended dose, did not receive q6h dosing, renal disease | |
| | **40 mg/kg/day [TBW]** | **60 mg/kg/day [TBW]** |
| n | 78 | 144 |
| Age (years) | 5.6 | 6.8 |
| Male (%) | 61.5 | 53.5 |
| Mean Weight (kg) | 22.9 ± 17.1 | 27.1 ± 22 |
| % overweight | 30.2 | 25.8 |
| **O** | **Vancomycin serum trough concentrations, in:**<br>1º 10 mg/kg/dose q6h vs. 15 mg/kg/dose q6h<br>2º Overweight vs. NBH patients | |

Pharmacotherapy. 2013;33(12):1264-72

# Madigan et al. (2013)

Table 2. Mean Initial Vancomycin Trough Concentrations (µg/ml) by Age and Weight in Patients with Detectable Trough Concentrations (≥ 5 µg/ml) at the Mayo Clinic Children's Hospital from January 2008–February 2012

| | 40 mg/kg/day (µg/ml) ± SD (no.) | 60 mg/kg/day (µg/ml) ± SD (no.) | p Value[a] |
|---|---|---|---|
| All patients with trough concentrations ≥ 5 µg/ml | 7.4 ± 2.3 (n=55) | 10.7 ± 5.2 (n=125) | <0.001 |
| 1–23 mo | 7.5 ± 2.3 (n=18) | 9.5 ± 3.7 (n=31) | 0.03 |
| 2–5 yrs | 6.7 ± 2.0 (n=9) | 7.5 ± 2.3 (n=28) | 0.33 |
| 6–12 yrs | 7.4 ± 2.5 (n=23) | 10.7 ± 4.2 (n=39) | <0.001 |
| 13–18 yrs | 7.8 ± 1.6 (n=5) | 15.3 ± 6.8 (n=27) | <0.001 |
| ≤ 25 kg | 7.3 ± 2.5 (n=34) | 8.7 ± 3.7 (n=70) | 0.02 |
| 25–50 kg | 7.4 ± 1.9 (n=15) | 10.6 ± 3.3 (n=33) | <0.001 |
| > 50 kg | 7.6 ± 1.5 (n=6) | 17.1 ± 6.5 (n=22) | <0.001 |
| Normal weight[b] | 7.1 ± 2.4 (n=20) | 10.4 ± 4.6 (n=59) | <0.001 |
| Overweight[b] | 7.7 ± 2.1 (n=11) | 13.8 ± 7.1 (n=25) | <0.001 |

[a]For comparison of 40 mg/kg versus 60 mg/kg group.
[b]Includes only patients 2 years of age and older for whom body mass index (BMI) percentiles could be calculated. Normal weight was defined as BMI < 85th percentile and overweight as BMI ≥ 85th percentile.

Pharmacotherapy. 2013;33(12):1264-72

# Madigan et al. (2013)

- ↑ vancomycin daily dose from 40 to 60mg/kg led to ↑ vancomycin trough concentrations, in all patients except in 2-5 yo

- Troughs were ↑ in overweight patients vs. NBH patients when dosed 60mg/kg/day

- Suggested that vancomycin dosing strategies should consider age and weight

Pharmacotherapy. 2013;33(12):1264-72

# Madigan et al. (2013)

| | |
|---|---|
| **Strengths** | • Reasonable description of baseline characteristics<br>• Dosing based on TBW<br>• Reported trough concentrations based on age and weight<br>• Moderate sample size (pediatric study)<br>• Appropriate sampling of trough levels |
| **Limitations** | • Retrospective<br>• Subgroup analysis of weight based differences<br>• Limited number of overweight patients (~25%)<br>• Clinical outcomes not assessed<br>• No differentiation between overweight & obese |

Pharmacotherapy. 2013;33(12):1264-72

# Summary

| Study | Obesity impact on trough [] |
|---|---|
| Moffett *et al.* *2011* | ↑ |
| Miller *et al.* 2011 | ↑ |
| Heble *et al.* 2013 | ↑ |
| Madigan *et al.* 2013 | ←→ 40mg/kg/day<br>↑ 60mg/kg/day |

# Conclusion

- TBW based dosing = ↑ trough for obese patients
- Mean trough concentrations in pediatric patients of all weight categories is often below recommended target
- ↑ dose & ↑ dosing frequency may be appropriate in ***all*** pediatric patients to achieve target concentrations
- TDM of trough concentration required to guide therapy
- Future prospective PK/PD and clinical outcome studies are required to optimize vancomycin therapy in pediatric patients

# Conclusion

In obese pediatric patients what is the most appropriate approach to

dose vancomycin?

# TBW