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Vancomycin Dosing in Children With Overweight or Obesity: A Systematic Review and Meta-analysis

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ABSTRACT

CONTEXT: Vancomycin is a medication with potential for significant harm with both overdosing and underdosing. Obesity may affect vancomycin pharmacokinetics and is increasingly common among children.

OBJECTIVE: We aimed to determine if children with overweight or obesity have increased vancomycin trough concentrations with total body weight (TBW) dosing compared with children with normal weight.

DATA SOURCES: We conducted a search of Medline and Medline In-Process & Other Non-Indexed Citations from 1952 (the year vancomycin was discovered) to November 2017.

STUDY SELECTION: Search terms included vancomycin, body weight, and body composition terms and were limited to children. Studies were reviewed and screened by ≥ 2 reviewers.

DATA EXTRACTION: The primary outcome was vancomycin level. Data were extracted by 2 reviewers. We performed quality assessment using the Newcastle-Ottawa quality assessment scale.

RESULTS: We identified 271 records. After abstract and full-text screening, we identified 7 studies for full review. Six of the 7 studies used a matched case-control design, although there was significant variation in study methodology. Four of the 7 studies were included in a meta-analysis, which revealed a small but significant difference in vancomycin trough levels between children with normal weight and children with overweight or obesity when dosed by using TBW ($N = 521$; mean difference 2.2 U [95% confidence interval: 1.0–3.4]).

CONCLUSIONS: High-quality data to guide vancomycin dosing in children with obesity are lacking. More studies evaluating dosing strategies in children with obesity are warranted because using TBW to dose vancomycin may lead to higher vancomycin concentrations and potential toxicity.

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Ms Azim screened studies by abstract and title and qualifying abstracts by full text, abstracted the data, designed study tables, conducted the quality analysis, and assisted in the meta-analysis and writing of the manuscript; Dr Khare reviewed the data and assisted with critical components of writing and editing the manuscript; Mr Kneese and Ms Weinstein assisted in study screening by title, abstract, and full text, as well as in editing the manuscript; Dr Rhee and Ms Haag reviewed the data and revised the manuscript; Dr Foster designed the study, screened studies by title, abstract, and full text, conducted the quality assessment and meta-analysis, and drafted the initial manuscript; and all authors approved the final manuscript as submitted.



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The prevalence of pediatric obesity has increased over the past 3 decades, reaching 17% among children 2 to 19 years in 2011–2014.^{1,2} Most medications in pediatrics use weight-based dosing, typically by using total body weight (TBW).³ For children with obesity, compared with a child with normal weight (NW), this practice results in a higher dose for a given clinical presentation. On the other hand, for some medications, providers may reach the maximum or adult dose for children with obesity earlier than a comparable child with NW, placing them at potential risk for underdosing. The altered body composition of children with obesity may affect drug pharmacokinetics, such as absorption, volume of distribution (Vd), metabolism, and clearance.^{4,5} Vd varies with obesity depending on the lipophilic characteristics of the drug, with a more lipophilic drug having a potentially greater Vd in a child with obesity. Obesity also affects clearance via effects on liver metabolism associated with hepatosteatosis and effects on renal function. High variability in practice exists regarding the most appropriate weight-based dosing strategy for children with obesity.⁶

Vancomycin is an antibiotic for the treatment of serious infections in children who are hospitalized. Vancomycin is relatively hydrophilic, and thus it may be more appropriate to use a measure such as ideal body weight to estimate Vd.⁴ For clearance, the data related to vancomycin are mixed: adults with obesity had a higher clearance, whereas the limited data in children suggest a potential decrease in clearance.⁴ The most recent Infectious Diseases Society of America (IDSA) recommendation for the target vancomycin trough concentration is 15 to 20 $\mu\text{g}/\text{mL}$ for adults and children with serious infections, although these recommendations recognize the significant data limitations in children.⁷ Some suggest targeting a lower level of 10 to 15 $\mu\text{g}/\text{mL}$ to reduce the risk of nephrotoxicity.⁹ Dosing strategies to achieve target trough concentrations in children vary widely, with no consistent recommendation. For adults with obesity, it has been recommended that vancomycin be initially dosed on the basis of TBW, with

subsequent doses adjusted on the basis of therapeutic drug monitoring, because TBW was found to have the best correlation with Vd and clearance.⁹ For children, the results are mixed, with recent studies raising concern regarding pharmacokinetic variations in children with obesity compared with children with NW.^{10–13} There are persistent concerns related to nephrotoxicity associated with vancomycin,¹⁴ particularly given the recent recommendations and possible association between trough levels $\geq 15 \mu\text{g}/\text{mL}$ and nephrotoxicity.¹⁵ There are also continued concerns related to potential underdosing and the emergent development of antibiotic resistance.^{16,17}

Our objective for this study was to conduct a systematic review of vancomycin dosing studies in children with obesity to determine if obesity is associated with elevated vancomycin concentrations as compared with children with NW. Our hypothesis, based on existing pharmacokinetic data from adults, was that children with obesity would have higher vancomycin concentrations.

METHODS

Study Identification

We performed a systematic literature review using Medline and the Ovid Medline In-Process & Other Non-Indexed Citations database (January 1, 1952, to November 15, 2017). Studies were limited to children only, and search items included the following: vancomycin, vancomycin administration or dosing or pharmacokinetics, body weight, and body composition or body constitution. There were no language restrictions. We identified additional studies through a pertinent hand review of article bibliographies.

Inclusion and Exclusion Criteria

We included studies containing information on vancomycin use, dosing and therapeutic monitoring (vancomycin concentrations), and body weight categorization (NW to overweight or obesity) for children aged 30 days to <18 years. We allowed for weight for length, ponderal index, or weight for age definitions in the 30-day- to 2-year-old age group. Exclusion criteria included studies on

animals only, studies on adults only, studies of neonates (aged 0–30 days) or preterm infants, and patients on extracorporeal membrane oxygenation. Because definitions of obesity and overweight have varied historically, we included all studies in which the authors used an accepted definition of obesity, regardless of the criteria used. Studies that included both children with overweight and children with obesity in the same analysis group were also included.

Study Selection

Each study was screened by title and abstract by 2 members of the research team using Covidence software (Melbourne, Australia). Next, 2 members of the research team reviewed included studies by examining the full text (Fig 1). Included studies were examined in full text by both team members and were included after consensus was reached (Fig 1).

Data Extraction

Two members of the research team independently extracted data from identified full-text articles. We extracted information, including basic study characteristics (sample size, study design, dates and location of the study, patient population, and inclusion and exclusion criteria of the studies), indication for vancomycin, vancomycin dosing in milligrams per kilogram and dosing interval, and vancomycin trough concentrations.

Quality Assessment

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting a systematic review.¹⁸ A methodologic quality assessment of individual articles was performed by using the Newcastle-Ottawa quality assessment scale; each article was evaluated independently by 2 members of the research team.¹⁹ For case-control studies, the Newcastle-Ottawa Scale is used to evaluate studies in 3 areas: selection, comparability, and exposure. For cohort studies, the scale is used to evaluate outcome assessment rather than exposure assessment but is otherwise similar. One star was awarded for each item addressed in these areas, except comparability, in

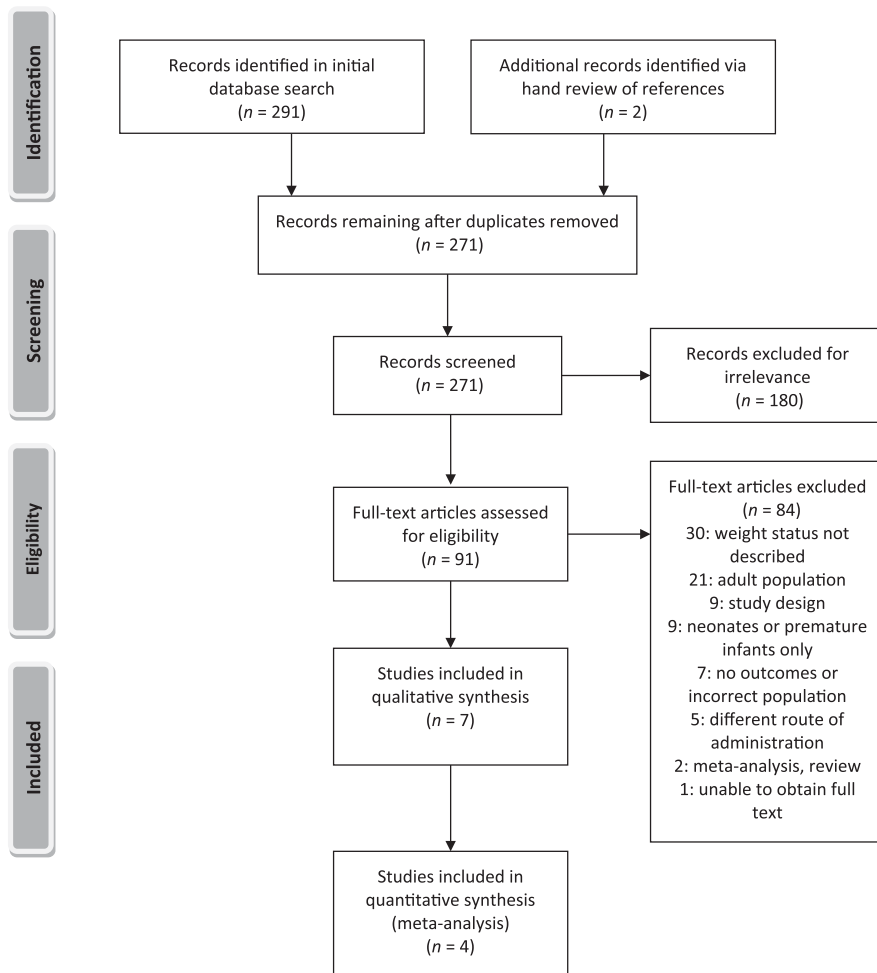


FIGURE 1 Flow diagram adapted from PRISMA showing results of search strategy and exclusions at different stages of review

which 2 stars were awarded if studies were matched for age and sex and matched for dosing regimen. The Newcastle-Ottawa assessment was adapted for our systematic review in 2 ways: (1) 1 star was awarded for studies that used hospital controls because this was appropriate for our systematic review, and (2) the item in the Newcastle assessment regarding follow-up and response rate was not applicable to any of the included studies and was thus excluded. Case-control studies with ≥ 7 stars were considered high quality, 5 to 6 stars were considered intermediate quality, and < 5 stars were considered poor quality.

Statistical Analysis

We conducted a meta-analysis comparing the vancomycin trough level achieved in

children with NW compared with children with overweight and children with obesity. For this analysis, we used Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to generate forest plots and used the calculated mean difference between combined overweight and obesity groups and the NW group using a random-effects model, given the design heterogeneity.

RESULTS

Search Strategy Results

We identified 271 unique publications, of which 180 were excluded on the basis of title and abstract (Fig 1). We then assessed 91 full-text articles and identified 7 that met the inclusion criteria. The primary

reasons for exclusion of full-text articles were lack of weight status description (30 articles) and adult population (21 articles) (Fig 1).

Study Characteristics

The included studies were conducted within the United States, with the exception of 1 from Israel (Table 1). The majority used the Centers for Disease Control and Prevention definition of obesity as ≥ 95 th BMI percentile and overweight as ≥ 85 th BMI percentile, using age- and sex-appropriate cutoffs.²⁰ The exceptions to this were 1 study that used > 95 th BMI percentile for the definition of obesity,²¹ another study that used > 85 th BMI percentile for the definition of overweight,²² and 1 study that included children < 2 years of age in the analysis, using their weight, not BMI, at ≥ 85 th or ≥ 95 th percentile.²³

Of the 7 studies included in this review, 6 used a matched case-control study design, and 1 study was designed as a cohort study (Table 1).^{13,21–26} The case-control studies matched NW controls with patients with overweight or obesity by age and sex most commonly. Two case-control studies also used dosing regimen as a matching variable,^{13,21} and 1 stratified the analysis by dosing regimen.²² Indications for therapy with vancomycin were similar across studies, although 1 study²¹ did not include any patients with central nervous system infections.

Study Quality and Risk-of-Bias Assessment

Of the 6 included case-control studies, 3 were high quality,^{13,21,26} and 3 were intermediate quality.^{22,23,25} (Table 1) The study by Nassar et al²⁴ was a cohort study that was graded by using the Newcastle-Ottawa Scale for cohort studies. The areas included in this assessment are selection, comparability, and outcomes, with 9 stars possible. The study was awarded 8 of 9 stars.

Vancomycin Dose, Schedules, and Therapeutic Monitoring Variation

Significant heterogeneity existed in the vancomycin dosage and dosing schedules

TABLE 1 Assessment of Bias for Included Studies by Using the Newcastle-Ottawa Quality Assessment Scale

	Selection			Comparability		Exposure		Total Score	
	Case Definition Adequate or Representativeness of Exposed Cohort	Representativeness or Selection of the Nonexposed Cohort	Selection of Controls or Ascertainment of Exposure	Definition of Controls or Outcome Not Present at Start of Study	Controls for Age and Sex	Controls for Dosing Regimen	Ascertainment of Exposure or Assessment of Outcome		Consistent Method of Ascertainment or Follow-up Length
Case-control studies									
Moffett et al ²¹	Yes	Yes	Yes	Yes	No (age only)	Yes	Yes	Yes	N/A
Eiland and Sonawane ²⁵	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A
Heble et al ¹³	Yes	Yes	Yes	Yes	No (age only)	Yes	Yes	Yes	N/A
Madigan et al ²²	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A
Miller et al ²⁶	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A
Le et al ²³	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A
Cohort study									
Nassar et al ²⁴	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	N/A

N/A, not applicable.

across studies (Table 2). Most studies used every-6-to-8-hours dosing, although Nassar et al²⁴ used twice-daily dosing. The empirical daily dose was between 40 and 60 mg/kg across studies, with the exception of children 2 to 8 years of age in the study by Heble et al,¹³ who received 80 mg/kg per day. Four of the 7 studies had a mean or median dose of 45 mg/kg per day.^{21,23,25,26}

Trough vancomycin concentrations were reported in all 7 studies, although Le et al²³ used the trough concentrations to estimate pharmacokinetic parameters and did not report a direct comparison between weight-based groups. Of the 6 studies that directly compared vancomycin trough concentrations between children with NW and children with overweight or obesity, 5 identified no significant differences.^{21,22,24–26} In contrast, Heble et al¹³ found higher median trough concentrations in patients with overweight and obesity compared with controls, matched by the initial dosing amount. This study also identified that children with overweight or obesity were more likely to experience a trough level >20 µg/mL.¹³ One notable characteristic distinguishing the Heble et al¹³ study is the higher dosage of vancomycin administered to all children regardless of body weight, with a regimen of 80 mg/kg per day used for 2- to 8-year-old children, 60 mg/kg per day used for 9- to 13-year-old children, and 45 mg/kg per day for 14- to 18-year-old children. Nineteen of 42 (45%) children in the overweight and obesity categories in this study were in the 2- to 8-year-old age range (see also Table 2). Le et al²³ reported a lower clearance in children with overweight and obesity in their pharmacokinetic model.

Target trough concentrations differed in each of the included studies according to the respective institution, with target ranges of 10 to 15, 10 to 20, and 15 to 20 µg/mL all used. Some institutions stratified target ranges on the basis of severity of infection. Most of the patients included in these studies did not attain the IDSA-recommended vancomycin trough concentrations for serious infections of 15 to 20 µg/mL. In Eiland and Sonawane²⁵,

84% of the patients with overweight or obesity did not achieve their target vancomycin trough concentrations (10–20 $\mu\text{g}/\text{mL}$). Heble et al¹³ found that 51% of children with NW, 29% of children with overweight, and 10% of children with obesity had trough vancomycin concentrations that fell below their target range. Miller et al²⁶ found that 22% of patients achieved their target trough concentration of 10 to 20 $\mu\text{g}/\text{mL}$. The likelihood of achieving serum target vancomycin concentrations varied by dosing frequency. The least frequent dosing schedule was in the study by Nassar et al²⁴, which used every-12-hours dosing and in which only 3% of patients (3% of those with NW, none of the overweight group) achieved that institution's target vancomycin trough concentration of 10 to 20 $\mu\text{g}/\text{mL}$ (Table 3).

Clinical outcome data outside of vancomycin trough concentrations (eg, clinical treatment failure or persistent fever) were not systematically reported in the included studies, with the exception of Nassar et al²⁴. Additionally, only 3 of the included studies revealed data on nephrotoxicity between weight-based groups (Miller et al²⁶, Madigan et al²², and Eiland and Sonawane²⁵). No differences in nephrotoxicity by weight status were noted in these 3 studies, although this outcome was uncommon.

Meta-analysis

A meta-analysis using the data from all studies in which vancomycin trough concentrations were reported is presented in Fig 2. The meta-analysis was conducted on 4 of the 7 identified studies. Three of these 4 studies (Heble et al¹³, Madigan et al²², and Miller et al²⁶) grouped patients with overweight and obesity together, and 1 study (Moffett et al²¹) did not include patients with overweight in the analyses. Nassar et al²⁴ used a markedly different dosing regimen (every-12-hours dosing across all patients) and a different design, and their study was excluded from the meta-analysis. Eiland and Sonawane²⁵ and Le et al²³ did not report vancomycin trough concentrations and could therefore not be included in the meta-analysis. The mean difference in vancomycin trough concentrations from the 4 studies included

($N = 521$ children) was 2.2 (95% confidence interval: 1.0–3.4) units higher in children with overweight or obesity compared with children with NW, with statistical heterogeneity by I^2 of 39%.

DISCUSSION

In this systematic review, we found evidence supporting differences in pharmacokinetics related to vancomycin for children with overweight or obesity compared with children with NW. The meta-analysis, although limited to 4 studies by virtue of study design heterogeneity, revealed higher vancomycin concentrations among children with overweight or obesity.

These findings have some support from pharmacokinetic data and physiology, although data from adults and children vary. Le et al²³ compared 7 different measures of body size descriptors and their influences on vancomycin Vd and clearance in children with overweight or obesity by population-based pharmacokinetic studies that incorporated Bayesian estimation, showing a lower clearance in children with obesity, a potential mechanism underlying the higher trough concentrations observed here. That study also revealed that Vd is strongly correlated with TBW and that clearance is correlated with allometric weight and body surface area.²³ In contrast, studies in adults with obesity revealed significantly higher clearance of vancomycin compared with studies in adults without obesity, suggesting the need to shorten dosing intervals for weight-based dosing to avoid high peak concentrations.^{5,27} Pharmacokinetic studies in adults with obesity also reveal a correlation between Vd and clearance with TBW.^{28,29} For adults with obesity, the most recent recommendation is to use TBW for dosing rather than ideal or adjusted body weight.³⁰

For children, it is still unclear if alterations in metabolism (absorption, Vd, and clearance) are different in children with overweight compared with children with obesity because most studies grouped these children into 1 group. We also do not know at what point in weight gain these pharmacokinetic parameters start to shift from what is expected. Some of the effects of excess adiposity probably only have a

meaningful impact at the extremes of obesity at which hepatic steatosis and renal dysfunction occurs, whereas Vd may well be affected in children with overweight.

In 2011, the IDSA released a guideline for the treatment of invasive methicillin-resistant *Staphylococcus aureus* infections in children and recommended dosing vancomycin at 15 mg/kg per dose every 6 hours.³¹ The IDSA also recommended the vancomycin area under the curve (AUC)/minimum inhibitory concentration (MIC) ratio should be ≥ 400 , which corresponds to the target trough serum concentration of 15 to 20 $\mu\text{g}/\text{mL}$ in adults. The recommendation for children was also a target trough concentration of 15 to 20 $\mu\text{g}/\text{mL}$ for complicated infections (bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and skin structure infections), with an acknowledgment that data were limited in pediatrics and additional studies were needed. These recommendations were based on moderate evidence from clinical experience, opinions, descriptive studies, or reports of expert committees. The majority of studies across different institutions reported in this review revealed that most patients were not achieving the IDSA target vancomycin trough levels by using dosing according to TBW. However, researchers of many of the included studies did not follow that recommended vancomycin dosing regimen of 15 mg/kg per dose every 6 hours. The authors of only 2 of the studies^{13,22} identified in this review reported on patients receiving an approximation of the most recent IDSA-recommended dosing regimen. The proposed new IDSA guidelines (unpublished and open for public comment³²) propose similar AUC and MIC targets, and further examination of children with overweight and obesity receiving these higher doses will be needed.

Alternative dosing strategies have also been examined recently. Some authors have suggested that a dosing maintenance regimen of 60 mg/kg per day by TBW and the use of Bayesian-based methods of dosing resulted in the highest achievement of an AUC/MIC ratio of ≥ 400 in children with

TABLE 3 Outcome Data from Included Studies

Study	Dosing	Outcome Data (Vancomycin Level)	Conclusion
Moffett et al ²¹	Initial dosing in institution: 15 mg/kg per dose q 8 h; children with obesity: 14.1 (SD 1.5) mg/kg per dose; controls: 14.9 (SD 0.9) mg/kg per dose ($P = .03$); 21 of 24 in each group dosed q 8 h	Obesity trough level: 6.9 (SD 4.3) $\mu\text{g/mL}$; control trough level: 4.8 (SD 3.1) $\mu\text{g/mL}$ ($P = .052$)	No statistically significant difference was found between dose groups. Dosing in both groups were, in general, subtherapeutic compared to the IDSA goal of 15–20 $\mu\text{g/mL}$.
Eiland and Sonawane ²⁵	Healthy wt: 48.86 (SD 10.5) mg/kg per d; overweight and obesity: 44.4 (SD 14.1) mg/kg per d ($P = .08$); dosing that produced target trough serum concentrations: 51.6 mg/kg per d in healthy wt versus 53.63 mg/kg per d in overweight and obesity	Ten of 48 (21%) in the healthy wt group and 13 of 50 (26%) in the overweight and obesity group achieved a 10–20 mg/L trough level. One patient in the healthy wt group was in the supratherapeutic range, with a vancomycin trough level >20 mg/L. Three patients in the overweight and obesity group had a supratherapeutic vancomycin range	No statistically significant difference in dosing was found between patients with healthy wt and patients with overweight and obesity.
Heble et al ¹³	Based on patient age and body wt; age 2–8 y: received vancomycin at 20 mg/kg per dose q 6 h; age 9–13 y: received 20 mg/kg per dose q 8 h; 14–18 y of age: received 15 mg/kg per dose q 8 h; median dose: 19.8 mg/kg per dose (range 14.6–21.0) for NW, 19.8 mg/kg per dose (range 14.1–20.7) for overweight ($P = .6$ [pairwise]), and 19.7 mg/kg per dose (13.9–20.9) for obesity ($P = .8$ [pairwise with NW])	Overweight and obesity initial median trough level of 14.4 $\mu\text{g/mL}$ versus 10.5 $\mu\text{g/mL}$ for NW ($P < .001$); also, overweight and obesity significantly more likely to have trough level >20 $\mu\text{g/mL}$ (14% overweight and 19% obesity versus 2% NW; $P = .01$)	Patients with overweight and obesity had significantly higher vancomycin trough levels and were significantly more likely to have a supratherapeutic trough level.
Madigan et al ²²	40 mg/kg d before protocol change at Mayo Clinic in 2010; 60 mg/kg per d thereafter	NW: 7.1 $\mu\text{g/mL}$ with 40 mg/kg dosing, 10.4 $\mu\text{g/mL}$ with 60 mg/kg dosing; overweight: 7.7 $\mu\text{g/mL}$ with 40 mg/kg dosing, 13.8 $\mu\text{g/mL}$ with 60 mg/kg dosing; only statistically significant difference when stratified by <50 kg or >50 kg (17.1 vs 9.3; $P < .0001$)	No statistically significant differences in trough levels were found when patients were stratified by NW and overweight, only when patients were grouped by absolute wt of >50 kg or <50 kg.
Miller et al ²⁶	Mean initial dose: 17.2 mg/kg for patients with NW versus 16.6 mg/kg for patients with overweight and obesity ($P = .295$); median dose among those who achieved 5–15 $\mu\text{g/mL}$ serum concentration: 17.3 (SD 4.2) for patients with NW and 17.3 (SD 4.3) for patients with overweight and obesity ($P = .989$)	7.4 (SD 5.7) $\mu\text{g/mL}$ for patients with NW, 9.6 (SD 8.9) for patients with overweight and obesity; 22% of patients achieved goal trough concentration of 10–20 $\mu\text{g/mL}$; no difference among wt classes	No statistically significant difference was found between dose groups.
Nassar et al ²⁴	20 mg/kg per dose twice daily	Overall trough level of 3.36 ± 2.58 ; only 3% fell in therapeutic range (>10 mg/L); underweight: trough level of 4.16 ± 3.55 ; NW: trough level of 3.53 ± 2.53 ; overweight: trough level of 3.06 ± 1.86 ; 8% of the underweight group, 3% of the NW group, and 0% of the overweight group had trough levels >10 $\mu\text{g/mL}$	No statistically significant difference was found between dose groups.
Le et al ²³	40 mg/kg per d to 100 mg/kg per d; median initial dose: 44 mg/kg per d	Clearance: 0.12 L/kg per h in NW and 0.11 L/kg per h ($P = .003$) in overweight and obesity; Vd: 0.56 in NW and 0.56 in overweight and obesity ($P = .3$)	There was a statistically significant difference in clearance of vancomycin between NW and overweight and obesity groups.

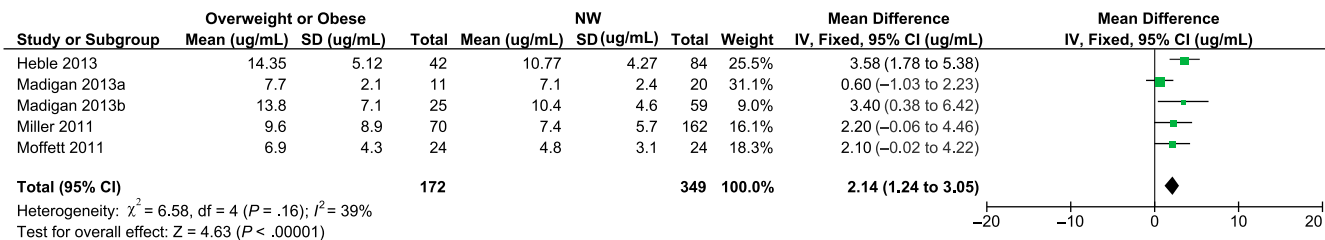


FIGURE 2 Forest plot of meta-analysis comparing vancomycin trough concentrations of children with over weight or obesity to children at a normal weight. CI, confidence interval; df, degrees of freedom; IV, inverse variance.

obesity.^{35,34} Continuous dosing regimens have also recently been examined in infants, with promising results,³⁵ and this is also an area for further work in children with overweight and obesity.

There were limited data from studies identified in this review examining nephrotoxicity associated with these higher trough concentrations, with the authors of only 3 studies reporting this outcome and those being incomplete. However, other studies have revealed that greater exposure to vancomycin, as assessed via higher trough concentrations, results in an increased risk of nephrotoxicity,^{8,36} and thus there may be some increased risk of nephrotoxicity in children with overweight or obesity, although this requires further examination.

Given the limitations of the data included in this review, we cannot recommend a systematic change in practice for dosing vancomycin in children with overweight or obesity. In light of the continuing obesity epidemic and the lack of clear empirical data, physicians and other providers should continue to consider how obesity affects pharmacokinetic parameters in children and take those parameters into account when adjusting a treatment plan.

Future Research

Further pharmacokinetic studies are warranted to aid decision-making support given the increasing prevalence of obesity. There is also a need to understand the variability in current clinical practice and to identify possible clinical measures to assess the association between obesity and pharmacokinetics in children. Additional and more intense pharmacokinetic studies

in which researchers look at vancomycin Vd, AUC, and clearance of the drug should be conducted in children with obesity to guide appropriate dosing strategies to optimize therapeutic dosing and avoid toxic effects. Future vancomycin pharmacokinetic studies should also be focused strictly on children with obesity who have severe infections, such as those with bacteremia, infective endocarditis, hospital-acquired pneumonia, meningitis, osteomyelitis, or confirmed methicillin-resistant *S aureus* infections. This would assist clinicians in determining the appropriate guidelines on dosing alterations on patient outcomes in children with obesity.

Limitations

The studies available for inclusion in this systematic review have several limitations. The studies assessed were of varying methodologic quality, with the majority of data derived from small observational studies. The number of children with obesity included in these studies was generally small. Most studies involved only a single center and reflected highly variable local vancomycin dosing practices, which precludes extrapolation to other patient populations and institutions. Furthermore, clinical efficacy was not assessed, and the primary study end point was the attainment of the target trough concentration in most studies, which lacks definitive prospective evidence to support its use as a surrogate marker for clinical outcome. The studies were not powered to adequately assess nephrotoxicity and other adverse effects associated with supratherapeutic doses in children with obesity. Finally, there was some heterogeneity in the definitions of

overweight and obesity across studies, although any misclassification resulting from the differences in definitions is likely to be minor.

CONCLUSIONS

In this review and meta-analysis, we found higher vancomycin trough concentrations in children with overweight or obesity compared with children with NW, although the clinical significance is uncertain given the small magnitude of the difference. Additionally, the published studies have relatively small sample sizes, heterogeneous populations, and dosing practices that vary between studies and from published guidelines. This heterogeneity in published studies makes it difficult to draw definitive conclusions related to altering dosing in children with overweight and obesity.

Clinicians should still be aware of potential altered pharmacokinetics in children with overweight and obesity. Authors of future studies need to examine alternate vancomycin dosing strategies in children with overweight and obesity and examine how children's weight status affects parameters, such as Vd and clearance, to maximize efficacy, minimize toxicity, and provide antimicrobial cost savings.

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