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Clinical Investigation

Evaluation of Vancomycin Dosing in Pediatric Cystic Fibrosis Patients

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OBJECTIVES: The presence of methicillin-resistant *Staphylococcus aureus* (MRSA) in cystic fibrosis (CF) patients' sputa is associated with a decline in pulmonary function and increased mortality. Vancomycin is the preferred treatment for MRSA pneumonia in children. No published studies have evaluated the vancomycin dose needed to achieve goal vancomycin trough concentrations (VTCs; 15-20 mg/L) in pediatric patients with CF. The primary objective is to determine whether a vancomycin dosage of 60 mg/kg/day achieves a goal VTC in pediatric CF patients. Secondary objectives include determining the average dosage required to reach a goal VTC and the impact of achieving a goal VTC on estimated glomerular filtration rate (eGFR) and pulmonary function.

METHODS: A retrospective review of pediatric patients with CF who received vancomycin was conducted.

RESULTS: A total of 90 vancomycin treatment courses were analyzed. Standard vancomycin dosing (60 mg/kg/day) achieved goal VTC in 11 courses (12.2%). The mean dosage required to achieve a goal VTC for all courses was 70.6 ± 16.7 mg/kg/day. Patients who achieved goal VTCs were more often older, weighed more, and had higher serum creatinine concentrations at therapy initiation. On average, a dosage of 70.6 mg/kg/day was required to achieve a goal VTC. Despite dosages up to 120 mg/kg/day, no significant changes in renal function occurred. Achieving a goal VTC had no significant impact on eGFR or pulmonary function during therapy.

CONCLUSIONS: Vancomycin dosing of 60 mg/kg/day does not reliably achieve a VTC of 15 to 20 mg/L in pediatric CF patients. Younger CF patients may require higher vancomycin doses.

INDEX TERMS: cystic fibrosis, methicillin-resistant *Staphylococcus aureus*, pediatrics, therapeutic drug monitoring, vancomycin

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by chronic airway inflammation and colonization with bacteria, resulting in chronic endobronchial infections.[1] Recently, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a common pathogen isolated from the sputum of CF patients. According to the 2013 Cystic Fibrosis Foundation Annual Registry Report, approximately 25% of CF patients were reported to have at least one MRSA-positive sputum culture, which had increased from 9.2% in 2002.[2,3]

In addition to the increased incidence of MRSA infections in children with CF, recent studies have found that MRSA in CF patients is associated with an increased rate of decline in pulmonary function.[4-6] Most notably, in 2010, a 10-year evaluation of the CF Foundation patient registry reported that persistent MRSA infections were found to result in a more rapid decline of forced expiratory volume in 1 second (FEV_1) % predicted and were an independent risk factor for death in CF patients.[7]

The preferred drug for treatment of MRSA pneumonia in the hospitalized pediatric patient is vancomycin.[8,9] Although there are currently no guidelines for the treatment of CF acute pulmonary exacerbations (APEs) caused by MRSA, guidelines for non-CF MRSA pneumonia are often applied to the CF patients with APEs caused

by MRSA in clinical practice. This is despite vancomycin's poor penetration into the lung tissue, which is, presumably, further reduced by inflammation and chronic infection in CF airways.[10,11] Thus, it is imperative that adequate doses of vancomycin be used in the CF population in order to adequately treat APEs caused by MRSA. The Infectious Diseases Society of America (IDSA) recommends maintaining a vancomycin trough concentration of 15 to 20 mg/L for treatment of MRSA pneumonia.[9,12] With no available dosing guidelines for the use of vancomycin in pediatric CF patients, there is a need to determine appropriate vancomycin dosing in this population to achieve target serum concentrations.

In July 2010, Texas Children's Hospital, a large teaching hospital, implemented new guidelines for vancomycin dosing in CF patients based on IDSA recommendations. This guideline increased initial dosing for CF patients from 45 mg/kg/day divided every 8 hours to 60 mg/kg/day divided every 6 hours, with the goal of achieving a therapeutic vancomycin trough concentration (VTC) of 15 to 20 mg/L. Per the guideline, doses were adjusted at the attending physician's discretion to achieve a goal VTC. The guideline did not specify a maximum mg/dose or mg/day limit.

This retrospective study was conducted to evaluate the new vancomycin dosing guidelines for CF patients. The primary objective was to determine whether a vancomycin dosage of 60 mg/kg/day divided every 6 hours achieved an initial steady-state VTC of 15 to 20 mg/L in pediatric CF patients with APEs. The secondary objectives were to: 1) determine the average daily vancomycin dosage required to achieve a VTC of 15 to 20 mg/L, 2) determine any patient characteristics associated with achieving a goal VTC, 3) determine the impact of achieving a goal VTC on serum creatinine and estimated glomerular filtration rate (eGFR), and 4) determine whether achieving a goal VTC results in improved pulmonary function (FEV_1 % predicted) from admission to discharge from the hospital.

METHODS

A retrospective chart review of all patients admitted from October 1, 2010, through September 30, 2012, was conducted. All patient information was obtained from the patient's electronic medical record.

To be included in the analysis, a patient must have had a prior diagnosis of CF, been admitted to TCH with an APE, and received vancomycin with at least one serum trough concentration obtained at steady state. A steady-state VTC was defined as one being drawn within 30 minutes of the end of the dosing interval any time after the third dose was administered. Patients receiving vancomycin were included regardless of the coadministration of other antimicrobials. Patients were excluded if they had documented renal insufficiency (eGFR <60 mL/min/1.73 m^2) at admission or prior to the first dose of vancomycin, or if they had undergone prior lung transplantation. Estimated glomerular filtration rate was calculated with the revised Schwartz equation (< 18 years) and Cockcroft-Gault equation (≥ 18 years).[13,14] Patients were excluded from pulmonary function analysis if they received less than 7 days of vancomycin therapy or did not have spirometry performed around the time of admission and discharge.

The following data were collected to complete the analysis: demographic information, anthropometric data, vancomycin dosing (mg/kg/day and dosing interval), duration of vancomycin therapy, all VTCs drawn at steady state during therapy, concurrent nephrotoxic medications (tobramycin, colistimethate, ibuprofen, tacrolimus), all serum creatinine values during therapy, FEV_1 % predicted at baseline (personal best in the previous year), admission, and discharge.

In addition to determining the percentage of patients who achieved a goal VTC with an initial dosage of 60 mg/kg/day, patient characteristics were analyzed to determine any associations with goal VTC achievement. Patients were divided into age categories for subgroup analysis of renal function. Effect of achieving a goal VTC on pulmonary function was evaluated by determining the improvement during treatment (discharge minus admission FEV_1 % predicted) and percentage of patients who returned to baseline FEV_1 between groups.

Continuous variables were evaluated using a 2-tailed *t*-test or 1-way analysis of variance, whereas nominal data were evaluated using Fisher exact test. Statistical analysis was performed using STATA version 12 (College Station, TX). A p value ≤ 0.05 was considered *a priori* as statistically significant. Baylor College of Medicine Institutional Review Board approval was obtained prior to study initiation.

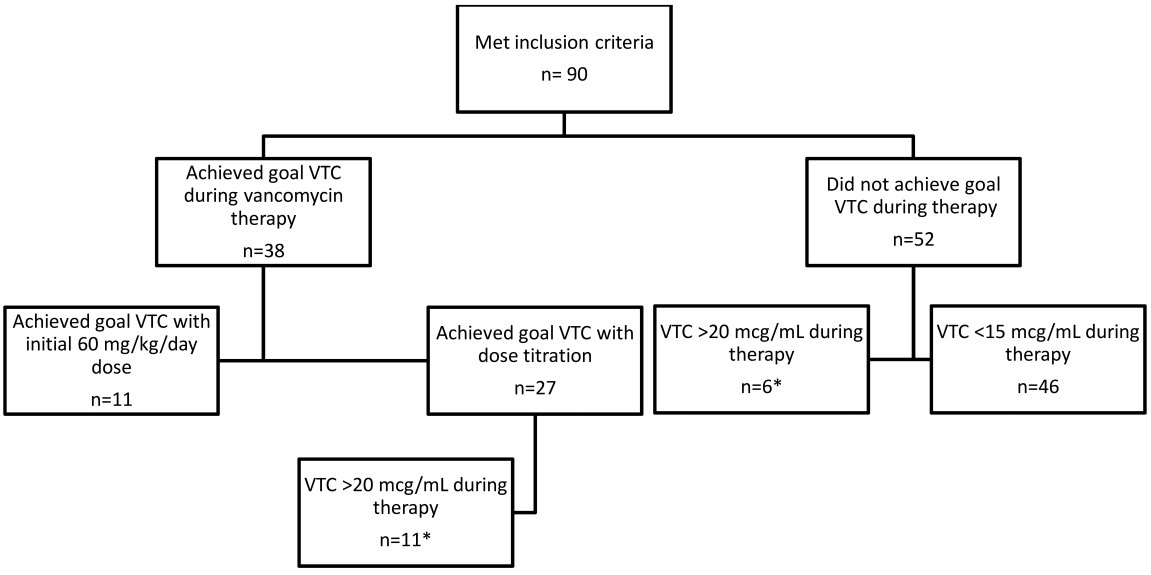

Figure 1. Flow diagram of the study population.
*Five patients had a vancomycin trough concentration (VTC) > 20 mg/L with the initial dosage of 60 mg/kg/day; after titration, 3 of these patients achieved a goal VTC.

RESULTS

A total of 90 vancomycin treatment courses from 58 unique CF patients were eligible for inclusion; of those, 49 treatment courses (33 patients) were eligible for pulmonary function evaluation. A total of 11 treatment courses (12.2%) achieved a therapeutic VTC with an initial vancomycin dosage of 60 mg/kg/day. An additional 27 treatment courses (30.0%) achieved a VTC after dose escalation (Figure 1). The mean dosage required to achieve a VTC of 15 to 20 mg/L for all treatment courses was 70.6 ± 16.7 mg/kg/day (median 66 mg/kg/day; range, 60-120 mg/kg/day). Included patients' ages ranged from 11 months to 20 years.

A total of 52 treatment courses (57.8%) never achieved a goal VTC. The average vancomycin dosage in those who never achieved a VTC of 15 to 20 mg/L was 72.9 ± 19 mg/kg/day, which was not significantly different from those who did achieve a goal VTC (p = 0.56). Supratherapeutic VTCs (>20 mg/L) were detected during 17 treatment courses (18.9%), including 5 with the initial dosage of 60 mg/kg/day. The average supratherapeutic VTC for all 17 courses was 23.9 ± 2.3 mg/L (median 21 mg/L; range, 20.1-38 mg/L). Patients who achieved a goal VTC with a dosage of 60 mg/kg/day were older, male, and weighed more (Table 1). Figure 2 demonstrates the difference in VTC achieved with initial 60 mg/kg/day dose by age. There was no difference in the change in eGFR during therapy between patients who did and those who did not achieve a goal VTC (Table 2). There was no difference in improvement of FEV_1 % predicted between treatment courses that did and did not achieve a goal VTC (Table 3).

To ensure that dose escalation in pursuit of a goal VTC did not result in renal dysfunction, change in eGFR during therapy was compared between those who did and those who did not achieve a goal VTC at any point in therapy (renal function subgroup analysis by age group). There was no difference found in the change in eGFR during therapy for any age group between those who did and those who did not achieve a goal VTC.

DISCUSSION

This retrospective study in pediatric CF patients is the first, to our knowledge, to evaluate whether a dosage of 60 mg/kg/day reliably achieves a VTC of 15 to 20 mg/L in accordance with IDSA recommendations for the treatment of MRSA pneumonia in children.[8,9,12] This study is also the first in CF patients to determine the average dosage of vancomycin needed to achieve a goal VTC (15-20 mg/L). It was found that it is

Table 1. Variables Associated with the Attainment of Goal Vancomycin Trough Concentrations

Variables	Following Initial Dosage	
	Goal VTC Achieved (n = 11)	No Goal VTC (n = 79)
Age, yr*	15.6 ± 3.3	12.5 ± 3.9
Males†	5 (45.5%)	24 (30.3%)
Weight, kg*	51.4 ± 9.2	37.2 ± 13.7‡
Body mass index, mg/kg^2*	19.8 ± 1.5	18.7 ± 2.6
Serum creatinine at initiation, mg/dL*	0.53 ± 0.14	0.43 ± 0.13
eGFR at initiation of therapy, mL/min/1.73 m^2*	114.0 ± 38.3	138.8 ± 32.6
Change in serum creatinine during therapy, mg/dL*	0.1 ± 0.1	0.06 ± 0.1
Change in eGFR during therapy, mL/min/1.73 m^2*	−17.8 ± 26.2	−16.1 ± 21.5
Concurrent nephrotoxic medications†	8 (72.7%)	37 (46.8%)
Aminoglycoside, No.	6	34
Colistimethate, No.	0	3
NSAID, No.	4	3
Tacrolimus, No.	1	0
Pseudomonas aeruginosa coinfection†	2 (18.2%)	26 (32.9%)
Doses administered prior to VTC, median (range)	5 (3-32)	4 (3-49)
VTC > 20 mg/L, No.	0	5
Average supratherapeutic VTC, mg/L*	n/a	21.8 ± 2.3

eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; n/a, not applicable; NSAID, non-steroidal anti-inflammatory drug; VTC, vancomycin trough concentration
* mean ± SD
† n (%)
‡ *p < 0.05*
§ *Change from baseline*
¶ *Change from admission*

difficult to obtain a goal VTC with 60 mg/kg/day of vancomycin in pediatric CF patients, similar to the results of other studies evaluating vancomycin dosing in non-CF pediatric patients.[15,16] In this study, only 12.2% of vancomycin treatment courses in pediatric CF patients achieved a VTC of 15 to 20 mg/L using an initial dosage of 60 mg/kg/day. Despite escalating dosages up to 120 mg/kg/day, only 42% of vancomycin treatment courses achieved the goal VTC during vancomycin therapy. On average, patients required 70.6 ± 16.7 mg/kg/day to achieve a goal VTC. Patients were more likely to achieve a goal VTC with 60 mg/kg/day dosing if they were older, had a higher weight (but not higher body mass index), or had a higher (but within normal range) serum creatinine concentration at initiation of vancomycin. This raises the question of whether the starting dose for vancomycin in CF patients should be increased from 15 mg/kg/dose every 6 hours (60 mg/kg/day) to 17.5 mg/kg/dose every 6 hours (70 mg/kg/day). However, given that fewer than half of the vancomycin treatment courses in this study achieved a goal VTC, further research is needed to determine the appropriate starting dose of vancomycin to achieve a goal VTC.

In addition, in our population, escalating vancomycin doses in an attempt to achieve a goal VTC was not associated with increased risk of rising serum creatinine concentrations, regardless of the use of concurrent nephrotoxic medications, most often intravenous tobramycin or intravenous colistin. Furthermore, this study was not able to detect any differences in FEV_1 between patients who did and those who did not achieve a goal VTC. This was not surprising, because improvement in FEV_1 during the treatment of a CF APE is dependent on multiple factors. For example, administration of other antimicrobials and weight gain during vancomycin treatment

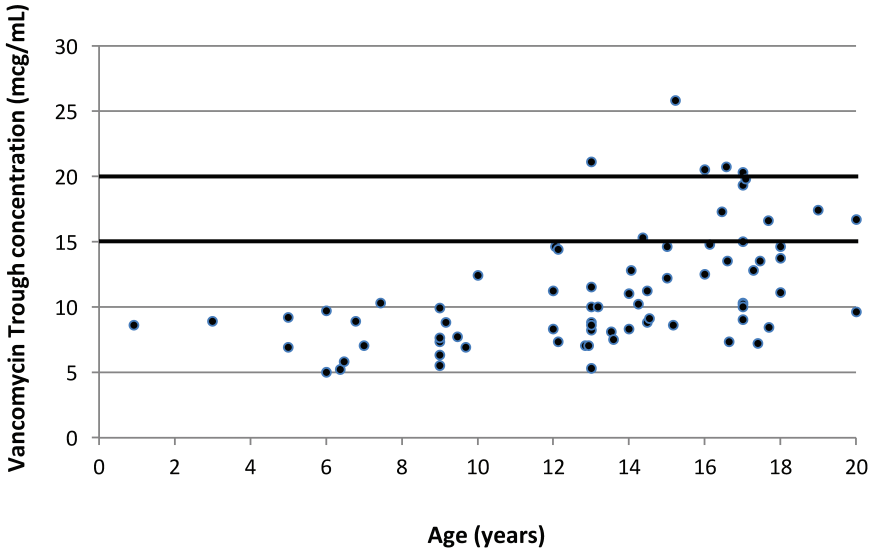

Figure 2. Graph of patient age versus vancomycin trough concentration achieved with initial dosage (60 mg/kg/day).

were not controlled for in this retrospective study.

Our patients who achieved a goal VTC were more likely to be older and weigh more than those who did not achieve a goal VTC. These findings can best be explained because younger patients, who typically weigh less, frequently require higher doses of water-soluble drugs because of their larger volume of distribution and a faster clearance compared with older children. This has been found during evaluations of vancomycin and other water-soluble medications, such as gentamicin.[17,18] Having a higher serum creatinine concentration at initiation of vancomycin therapy resulted in greater likelihood of reaching a goal VTC with initial dosing and could correlate with slower vancomycin clearance, more drug accumulation, and greater likelihood of achieving a goal VTC. However, this finding may be more related to normal changes in serum creatinine with age because there was no difference found in initial eGFR between those who did and those who did not achieve a goal VTC when divided into age groups. One result that was interesting was that body mass index was not found to be different in patients who achieved a goal VTC with the initial dose, but weight was. We attribute this discrepancy to the small number of patients who actually achieved a goal VTC with initial dosing (11 of 90 courses).

Our study had several limitations. First, it was a retrospective chart review of vancomycin prescribing practices in a single hospital with a limited number of patients. Second, there was no protocol in place for dose escalation; therefore, all dosage adjustments were made at the discretion of the prescribing physician with input from the clinical pharmacist. Although many patients did not achieve a goal VTC in this study, this could be due to prescriber apprehension to escalate doses beyond his or her specific comfort level. Third, the goal VTC of 15 to 20 mg/L for pediatric CF patients at TCH, at the time of study initiation in 2010, was based on adult guidelines for non-

Table 2. Pulmonary Function and Attainment of Goal Vancomycin Trough Concentrations

Pulmonary Function Assessment	Goal VTC at Any Point in Therapy	
	Yes (n = 4)	No (n = 45)
Baseline FEV_1 % predicted†	82.5 (16.8)	78.1 (24.4)
Change in FEV_1 % predicted at admission*§	–23.1 (13.1)	–21 (15.8)
Change in FEV_1 % predicted during therapy†¶	14.5 (12.6)	13.4 (12.6)
Returned to baseline FEV_1†	1 (25)	7 (15.6)

FEV_1, forced expiratory volume in 1 second; VTC, vancomycin trough concentration
* mean ± SD
† n (%)
‡ $p < 0.05$
§ *Change from baseline*
¶ *Change from admission*

Table 3. Renal Function and Attainment of Goal Vancomycin Trough Concentrations

Renal Function Subgroup Analysis	Group 1: ≤ 9 yr (n = 18)		Group 2: 0-16 yr (n = 50)		Group 3: > 16 yr (n = 22)	
	Goal VTC	No Goal VTC	Goal VTC	No Goal VTC	Goal VTC	No Goal VTC
eGFR at initiation of therapy, mL/min/1.73 m^2	n/a	167.8 (44.3)	111.2 (36.2)	130.9 (22.3)	116.3 (43.2)	128.2 (23.2)
Change in serum creatinine during therapy, mg/L	n/a	0.07 (0.09)	0.09 (0.12)	0.04 (0.10)	0.04 (0.04)	0.08 (0.1)
eGFR change during therapy, mL/min/1.73 m^2	n/a	−31.3 (37.5)	−15.1 (20.4)	−8.8 (13.8)	−20.5 (33.2)	−18.7 (21.4)

eGFR, estimated glomerular filtration rate; n/a, not applicable; VTC, vancomycin trough concentration

CF patients. Although pediatric guidelines have been published since then, these guidelines are based mainly on expert opinion and do not address the pediatric CF population.[8,9]

Also, data support monitoring area under the curve to minimum inhibitory concentration (AUC:MIC) ratio over traditional VTC monitoring.[19] However, this method is less practical, and therefore VTC monitoring is used as a surrogate marker for AUC:MIC and remains common practice. According to adult IDSA recommendations, maintaining a VTC of 15 to 20 mg/L correlates to an AUC:MIC ratio ≥ 400 for MRSA isolates with MICs ≤ 1 mg/L.[12] However, Frymoyer and colleagues[15] found that in most non-CF pediatric patients, a VTC of 7 to 10 mg/L results in an AUC:MIC ratio ≥ 400.[15] The only currently published data evaluating the pharmacokinetics of vancomycin in pediatric CF patients were recently reported by Stockman and colleagues.[18] They found that, on average, the VTC achieved was 10.3 mg/mL and the mean daily AUC was 282.6 mg/hr/L.[18] These findings indicate that a trough concentration of approximately 10 mg/L in a pediatric CF patient may be appropriate for a MRSA isolate with an MIC ≤ 0.7 mg/L (resulting in an AUC:MIC ratio > 400) but would not be appropriate for an isolate with an MIC > 0.7 mg/L (resulting in an AUC:MIC ratio < 400). These findings suggest that higher VTCs (15-20 mg/L) may be needed for pediatric CF patients, especially at institutions where MRSA vancomycin MICs are increasing.

The ability of this study to detect a difference in FEV_1 % predicted was limited by the small number of treatment courses that achieved a goal VTC during the study period. In addition, given its retrospective design, this study did not control for other antimicrobials used, which could also affect pulmonary function outcomes. Further research is necessary to determine whether achieving a VTC of 15 to 20 mg/L has an impact on pulmonary function.

CONCLUSIONS

In conclusion, a vancomycin dosage of 60 mg/kg/day divided every 6 hours did not reliably achieve a therapeutic VTC of 15 to 20 mg/L in pediatric CF patients. The clear increase in the prevalence of MRSA in the CF population, and the association between MRSA and an increased mortality in the CF patients make these findings of great concern. Investigation of higher initial dosages may be warranted, especially in young children with CF and those with low body weight. Although additional studies are warranted, the use of aggressive vancomycin dosing to achieve a VTC of 15 to 20 mg/L does not appear to result in significantly increased serum creatinine concentrations.

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Abbreviations APE, acute pulmonary exacerbation; AUC, area under the curve; CF, cystic fibrosis; eGFR, estimated glomerular filtration rate; IDSA, Infectious Diseases Society of America; FEV_1, forced expiratory volume in 1 second; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; TCH, Texas Children's Hospital; VTC, vancomycin trough concentration

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