JPPT | Clinical Investigation

Vancomycin Versus Vancomycin Plus Rifampin for the Treatment of Acute Pulmonary Exacerbations of Cystic Fibrosis

Nicholas M. Fusco, PharmD; Calvin J. Meaney, PharmD; Corey Wells, PharmD; Carla A. Frederick, MD; and William A. Prescott Jr, PharmD

OBJECTIVES This study aimed to compare the change in pulmonary function in children and adolescents with cystic fibrosis (CF) who were infected with methicillin-resistant *Staphylococcus aureus* (MRSA) treated with either vancomycin (VAN) alone or vancomycin plus rifampin (VAN-RIF).

METHODS Included patients were ages 6 to 20 years; hospitalized for an acute pulmonary exacerbation (APE) of CF from May 1, 2012, to April 30, 2014; had a respiratory tract culture positive for MRSA within 1 month of index hospital admission; received at least 48 consecutive hours of VAN or VAN-RIF; and had admission and discharge pulmonary function tests. The primary end point was change in percent predicted forced expiratory volume in 1 second (FEV_1).

RESULTS A total of 39 encounters met inclusion criteria: 24 in the VAN group (mean age 15.1 years) and 15 in the VAN-RIF group (mean age 13.7 years). There were no between-group differences in mean percent change in FEV_1 (32.6% ± 28.8% vs. 21.1% ± 12.1%; p = 0.091), mean percent change in forced vital capacity (22.6% ± 25.8% vs. 14% ± 9.4%; p = 0.127), or return to baseline FEV_1 (20 [83.3%] vs. 14 [93.3%] patients; p = 0.631). Median (IQR) length of stay (13 days [11–14 days] vs. 13 days [9–14 days]; p = 0.6) and median (IQR) time to readmission (82 days [43–129 days] vs. 147 days [78–219 days]; p = 0.2) were similar between the VAN and VAN-RIF groups, respectively.

CONCLUSIONS Vancomycin monotherapy appears to be adequate when treating APEs of CF in children and adolescents with moderate lung disease and high MRSA VAN minimum inhibitory concentrations. Therefore, the addition of RIF may be unnecessary; however, larger studies are needed to confirm these findings.

ABBREVIATIONS AKI, acute kidney injury; APE, acute pulmonary exacerbation; AUC, area under the concentration–time curve; CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PFT, pulmonary function test; RIF, rifampin; VAN, vancomycin; VTCs, vancomycin trough concentrations

KEYWORDS acute pulmonary exacerbation; cystic fibrosis; pediatrics; rifampin; vancomycin

J Pediatr Pharmacol Ther 2018;23(2):125–131

DOI: 10.5863/1551-6776-23.2.125

Introduction

Selection of an antimicrobial regimen is typically driven by the suspected pathogen, institution/patient-specific culture and sensitivity results, population-based/patient-specific pharmacokinetics/pharmacodynamics, and/or evidence-based medicine. To help guide patient care, the Infectious Diseases Society of America published guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in adults and children in 2011.[1] However, because data regarding the optimal antibiotic treatment of MRSA infection in children and adolescents with cystic fibrosis (CF) acute pulmonary exacerbations (APEs) are lacking, these guidelines exclude the CF population. In line with this, the 2009 CF Pulmonary Guidelines for the treatment of APEs did not address the management of those infected with MRSA.[2] Despite the lack of a guideline recommendation, linezolid and vancomycin (VAN) are considered by many to be first-line antimicrobial choices in CF[3]; however, there are limited data supporting their use in this population,[4] and recommendations pertaining to their use are based primarily on the Infectious Diseases Society of America guidelines, which, as mentioned above, exclude individuals with CF.[1] A critical need therefore exists for studies evaluating the safety and effectiveness of antibiotic regimens targeting MRSA in the CF population.

At our institution, VAN plus rifampin (RIF) has been used by some prescribers for the treatment of APEs in children and adolescents with CF who are infected

with MRSA, despite a lack of evidence supporting this antibiotic combination. Historically, the use of RIF in CF has been studied as a component of MRSA eradication or decolonization protocols, which are more common outside the United States.[5] This is supported by a recent survey of Cystic Fibrosis Foundation–accredited care centers, which reported that linezolid (34%) and VAN (31%) were the most common antibiotics used for the treatment of hospitalized children with APEs of CF infected with MRSA, whereas RIF use rates were much lower (15%).[6] The role of RIF as adjunctive therapy in MRSA infections, including APEs of CF, has not been established.[1]

To our knowledge, there are no published data comparing clinical outcomes in children and adolescents with an APE of CF treated with VAN alone or with VAN plus RIF (VAN-RIF). The purpose of this study was to compare the effectiveness, clinical outcomes, and safety of VAN alone versus VAN-RIF among children and adolescents hospitalized with an APE of CF who were infected with MRSA.

Materials and Methods

Study Design and Patient Population. This retrospective cohort study was reviewed and approved by the University at Buffalo Institutional Review Board. The primary objective of this study was to compare the change in pulmonary function, as measured by forced expiratory volume in 1 second (FEV_1), in hospitalized children and adolescents with CF who were infected with MRSA and treated with either VAN alone or VAN-RIF for an APE. Secondary objectives were: to compare changes in lung function as measured by forced vital capacity (FVC) and return to baseline FEV_1; to compare hospital length of stay and time to next hospital admission; to describe VAN use characteristics; and to assess rates of adverse events from antibiotic treatment.

Patients were included if they had a diagnosis of CF, were ages 6 to 20 years, were hospitalized for an APE of CF between May 1, 2012, and April 30, 2014, had at least 1 respiratory tract culture positive for MRSA within 1 month of hospital admission, received at least 48 consecutive hours of VAN, had at least 1 appropriately measured VAN trough concentration during the study period, and had at least 2 sets of pulmonary function tests (PFTs) during the study period (within 48 hours of admission and discharge, respectively). Patients were included in the VAN-RIF group if they also received at least 48 consecutive hours of RIF in addition to VAN. Patients with multiple hospital admissions during the study period were included as separate encounters. Patients were excluded if they were treated for an APE of CF that was not attributed to MRSA; had a concomitant medical condition other than an APE of CF that indicated antibiotic therapy; had congenital malformations of the respiratory tract, chronic lung disease, or congenital heart disease; had a condition that would classify them as immunodeficient, including but not limited to hematologic/oncologic diseases; and were pregnant at the time of hospitalization.

Demographic data that were collected included: age, sex, height, weight, admission and discharge dates, and adjunctive therapies during the encounter, including chest physiotherapy, albuterol, dornase alfa, hypertonic saline, azithromycin (oral), and ivacaftor. Vancomycin dose, frequency, duration, initial and postdose adjusted (final) vancomycin trough concentrations (VTCs), and associated dosing administration times and trough concentration draw times were collected. A VTC was considered to be drawn appropriately if it was drawn within 30 minutes of the true trough. The final VTC value was considered to be the trough after which time no VAN dose adjustments were made. Concomitant antimicrobials and systemic nephrotoxic agents (e.g., aminoglycosides, contrast dye, amphotericin, colistin, and ibuprofen) administered during treatment were collected. Vancomycin clearance (L/hr) was calculated using the model by Le et al.[7] Area under the concentration–time curve (AUC) was calculated as the total daily VAN dosage (mg/day) divided by VAN clearance. The AUC/minimum inhibitory concentration (MIC) ratios were determined by 24-hour AUC divided by the MIC, where the MIC from the MRSA isolate identified closest to the hospitalization of interest was used.

Admission and discharge percent predicted FEV_1 and FVC were collected. Return to baseline lung function (based on percent predicted FEV_1) was defined as a follow-up $FEV_1 \geq 90\%$ of baseline FEV_1. Baseline FEV_1 was defined as the maximum FEV_1 recorded in the patient's medical record in the 6 months prior to the index hospitalization. Follow-up FEV_1 was defined as the highest FEV_1 value measured within 24 hours of hospital discharge up to 4 weeks after discharge. This follow-up time period was chosen to account for the variability in FEV_1 measurements and is consistent with those in other studies.[8] Sputum culture data during and within 6 months of the hospitalization were collected and included: the bacterial pathogen(s) identified, the MIC of the MRSA species, the date of the positive culture, and the qualitative description of MRSA density (reported by the microbiology laboratory as "few," "moderate," or "many"). Aspartate transaminase and alanine transaminase were recorded at baseline and throughout therapy, when available, for patients treated with RF. Serum creatinine values were recorded during hospital admission, and acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours, increase in serum creatinine to 1.5 times baseline within 7 days, or urine volume ≤0.5 mL/kg/hr for 6 hours.[9]

Statistical Analysis. Data were summarized using descriptive and inferential statistics. Continuous data were described with mean ± standard deviation if normally distributed and median (IQR) if not normally distributed.

Frequency and percentages were used to describe discrete variables. Data were assessed for normality by visual inspection of histograms and through the Kolmogorov-Smirnov test. Non–normally distributed data were transformed with log or reciprocal functions. Changes in lung function parameters from admission to discharge were analyzed with paired *t*-tests. General linear models were developed for dependent parameters, including change in FEV_1, change in FVC, length of stay, and time to readmission. Multivariate models were developed to assess the influence of independent variables, including RIF exposure, on dependent variables, including lung function. The regression selected for each variable represents a parsimonious and statistically significant model. Variables tested included VAN troughs (continuous and bins), duration of VAN, VAN AUC, AUC/MIC, age, baseline lung function parameters, aminoglycoside use, and presence of *Pseudomonas aeruginosa*. Model fit was assessed through diagnostic plots and r^2 value. All tests were 2-tailed with α set at 0.05. Statistical analysis was completed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 243 patient encounters were identified through the pharmacy database query, of which 204 did not meet the inclusion criteria and were excluded. Of the excluded patients, 170 did not have a diagnosis of CF, 11 did not receive at least 48 hours of either VAN alone or VAN-RIF, 10 were age 21 years or older, 5 did not have a respiratory culture positive for MRSA within 1 month of hospitalization, 5 lacked PFT data at the time of admission or discharge, 2 had admissions for reasons other than an APE of CF, and 1 had an incomplete electronic medical record. Demographic characteristics for the 39 patients encounters that met the inclusion criteria are summarized in Table 1. No patients received ivacaftor during the study period and all patients received standard chest physiotherapy treatment 4 times daily.

Vancomycin use characteristics and pharmacokinetic variables are summarized in Table 2. A total of 19 patients (79.2%) in the VAN group and 10 patients (66.7%) in the VAN-RIF group required a VAN dose adjustment prior to achieving the final VTC (p = 0.384). For patients treated with RIF, the RIF oral dosing regimens were: 600 mg every 24 hours (8 patients [53.3%]); 300 mg every 12 hours (5 patients [33.3%]); 300 mg every 24 hours (1 [6.7%]); and 300 mg every 12 hours (1 [6.7%]). The mean ± SD duration of RIF was 11 ± 5.26 days.

The admission and discharge PFT data are summarized in Table 3. All patients in the study experienced improvement in the percent predicted FEV_1 and FVC from admission to discharge, and all were successfully discharged from the hospital. There were no between-group differences in the mean percent change in FEV_1 from admission (32.6% ± 28.8% vs. 21.1% ± 12.1%; p = 0.091). A total of 20 patients (83.3%) in the VAN group returned to baseline FEV_1 compared with 14 patients (93.3%) in the VAN-RIF group (p = 0.631). Results of the multivariable linear regression for pulmonary function outcomes are displayed in Table 4. Variables not listed in Table 4 had a p value >0.05 on bivariate analysis. A positive response was considered an improvement in the lung function variable from admission to discharge. Among the dependent variables, younger age and lower admission lung function were significant predictors for a positive response. For percent change in FVC, a shorter duration of VAN was also a significant predictor for a positive response. Use of RIF was not a significant predictor for lung function response variables.

Median (IQR) hospital length of stay was similar between groups: 13 days (11–14 days) in the VAN group and 13 days (9–14 days) in the VAN-RIF group (p = 0.716). There was no difference in median (IQR) time to next hospital admission between the VAN group (79 days [38–133 days]) and the VAN-RIF group (147 days [78–219 days]; p = 0.16). For length of hospital stay, only lower lung function, as determined by FVC, was a significant predictor for a positive response. Use of RIF was not a significant predictor for length of hospital stay (Table 4). No cases of AKI and no elevations of liver enzymes were identified during hospital admission.

Discussion

This is the first study to compare clinical outcomes in children and adolescents with an APE of CF treated with VAN alone or VAN-RIF. Most of the patients in the present study realized improvement in FEV_1, FVC, and a return to baseline FEV_1 such that all patients in the study were successfully discharged from the hospital. There was no between-group difference in change in pulmonary function, as measured by change in FEV_1, FVC, and return to baseline FEV_1 in patients treated with VAN alone versus VAN-RIF. Additionally, there was no difference in hospital length of stay or in time to next hospital admission between treatment groups. Although this data set is limited by a small sample size, these data suggest that in addition to standard pulmonary-directed therapy, VAN and VAN-RIF are both effective regimens for the treatment of APEs of CF, and the addition of RIF may be unnecessary.

The optimal treatment of MRSA infections in children and adolescents with CF is not well defined, and there is a need for additional research.[3,4,6] In the United States, RIF is suggested as an alternative therapy in patients that have an allergy or contraindication to widely accepted first-line antimicrobial choices of VAN or linezolid.[3] However, the adjunctive role of RIF for treatment of MRSA infections in patients with CF has not been established.[1] RIF is a potent cytochrome P450 3A4 inducer and may affect the metabolism of several drugs used by individuals with CF, including azole antifungals, ivacaftor, and ivacaftor/lumicaftor.[10]

Table 1. Demographic Characteristics of the Study Population (n = 39)

Variable	VAN (n = 24)	VAN-RIF (n = 15)	p value
Age, yr, mean ± SD	15.1 ± 3.6	13.7 ± 4.5	0.243
6 to 12 yr, n (%)	5 (20.8)	5 (33.3)	0.463
13 to <21 yr, n (%)	19 (79.2)	10 (66.7)	
Sex, n (%)			
Male	11 (45.8)	6 (40.0)	0.721
Female	13 (54.2)	9 (60.0)	
Height, cm, mean ± SD	151.9 ± 13.7	149.2 ± 17.5	0.598
Weight, kg, mean ± SD*	45.9 ± 11.6	44.1 ± 15.3	0.662
Underweight, n (%)	3 (12.5)	1 (6.7)	0.389
Healthy weight, n (%)	18 (75)	14 (93.3)	
Overweight, n (%)	3 (12.5)	0 (0.0)	
Preadmission anti-MRSA antibiotics, n (%)	10 (41.7)	8 (53.3)	0.477
Admission MRSA sputum density, n (%)			
Few	8 (33.3)	7 (46.7)	0.305
Moderate	14 (58.3)	5 (33.3)	
Many	2 (8.3)	3 (20)	
Admission MRSA VAN MIC, median (IQR)	2 (1.5–2)	2 (1.5–2)	0.642
1, n (%)	0 (0.0)	1 (6.7)	0.631
1.5, n (%)	8 (33.3)	5 (33.3)	
2, n (%)	16 (66.7)	9 (60)	
Pseudomonas sputum culture positive, n (%)†	5 (20.8)	6 (40)	0.277
Concurrent IV aminoglycoside, n (%)	9 (37.5)	6 (40)	0.876
Adjunctive therapies, n (%)			
Albuterol	22 (91.7)	15 (100)	0.318
Dornase alfa	24 (100)	15 (100)	
Hypertonic saline	24 (100)	15 (100)	
Inhaled antibiotics	1 (4.2)	3 (20)	
Azithromycin (oral)	2 (8.3)	5 (33.3)	
Baseline SCr, mg/dL, mean ± SD	0.81 ± 0.26	0.61 ± 0.08	0.001
Baseline AST, U/L, mean ± SD	ND	24.4 ± 8.2	
Baseline ALT, U/L, mean ± SD	ND	27.9 ± 12.7	
Baseline percent predicted FEV_1, mean ± SD	84.1 ± 12.3	89.8 ± 14.2	0.242

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; IV, intravenous; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus*; ND, not done; RIF, rifampin; SCr, serum creatinine; VAN, vancomycin; —,*

* Underweight (BMI <5th percentile), healthy weight (BMI 5th–85th percentile), and overweight (BMI >85th percentile).

† Upon admission or within 1 month of admission.

Table 2. Vancomycin (VAN) Dosing and Pharmacokinetic Characteristics (n = 39)

Characteristic	VAN (n = 24)	VAN-RIF (n = 15)	p value
Final VAN dose, mg, mean ± SD	662.3 ± 227.8	566.7 ± 162.4	0.103
Final VAN dose, mg/kg, mean ± SD	14.9 ± 4.87	13.5 ± 2.96	0.296
Final VAN daily dosage, mg/kg/day, mean ± SD	57.4 ± 20.8	49.76 ± 11.8	0.152
Final VAN dosing interval, hr, median (IQR)	6 (6–6)	6 (6–6)	0.796
Every 6 hr, n (%)	20 (83.3)	12 (80)	1
Every 8 hr, n (%)	3 (12.5)	2 (13.3)	
Every 12 hr, n (%)	1 (4.2)	1 (6.7)	
Duration of VAN, days, mean ± SD	11.7 ± 3.3	12.8 ± 4.7	0.422
Final VAN trough concentration, mg/L, mean ± SD	12.1 ± 2.2	13.5 ± 4.9	0.698
5 to <10 mg/L, n (%)	3 (12.5)	1 (6.7)	0.49
10 to <15 mg/L, n (%)	19 (79.2)	13 (86.7)	
15 to <20 mg/L, n (%)	2 (8.3)	0 (0.0)	
≥20 mg/L, n (%)	0 (0.0)	1 (6.7)	
VAN AUC (0–24 hr), mean ± SD, mg × hr/L	640.9 ± 219.4	549.4 ± 139.18	0.158
VAN AUC/MIC, mean ± SD	359.7 ± 143.6	317.4 ± 116.8	0.345
AUC/MIC ≥400, n (%)	9 (37.5)	2 (13.3)	0.15

AUC, area under the concentration–time curve; MIC, minimum inhibitory concentration; RIF, rifampin

This effect could not be assessed in the present study because no patients received ivacaftor during the study period. Given the lack of benefit observed in this study, and the potential for serious drug-drug interactions, RIF use should be discouraged for the treatment of APEs of CF in children and adolescents in whom first-line therapies may be used.

Most of the patients in this study were treated with VAN doses that yielded VTCs of 10 to 15 mg/L. There is an increased risk of treatment failure when VAN MICs approach or exceed 2 mg/L because of an inability to achieve an AUC/MIC ≥400, the desired pharmacodynamic parameter associated with positive outcomes in serious MRSA infections.[11] At the time of admission, a high proportion of patients in this study had VAN MICs of 2 mg/L, most of whom did not achieve an AUC/MIC ≥400. Despite this, most patients achieved a return to baseline FEV_1, and all were successfully discharged from the hospital. Additional data are needed to determine what the optimal VAN targets are in the treatment of APEs of CF in children and adolescents. Our data did not reveal any difference in lung function improvements when RIF was added in a population of children and adolescents that may be considered at risk for treatment failure with VAN when traditional VAN pharmacodynamics targets are applied.

There were no cases of AKI and no cases of elevations in liver enzymes during this study. The risk of AKI with VAN is known, and risk factors that increase the rate of AKI in patients receiving VAN include higher VAN doses, longer durations of VAN treatment, higher VAN troughs (≥15 mg/L), pediatric intensive care unit

Table 3. Pulmonary Function Tests

Pulmonary Function Test	VAN (n = 24)	VAN-RIF (n = 15)	p value
Admission percent predicted FEV_1, mean ± SD	62.2 ± 14.7	71.4 ± 18.5	0.094
Discharge percent predicted FEV_1, mean ± SD	79.5 ± 13.9	85.1 ± 18.2	0.282
Relative percent change in FEV_1, mean ± SD	32.6 ± 28.8	21.1 ± 12.1	0.091
Admission percent predicted FVC, mean ± SD	75.8 ± 14.5	85.2 ± 15.1	0.059
Discharge percent predicted FVC, mean ± SD	89.9 ± 11.3	96.3 ± 14.5	0.133
Relative percent change in FVC, mean ± SD	22.6 ± 25.8	14.0 ± 9.4	0.147
Return to baseline FEV_1, n (%)	20 (83.3)	14 (93.3)	0.631

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; RIF, rifampin; VAN, vancomycin

Table 4. Multivariate Linear Regression Model Results (n = 39)*

Variable	Regression Estimate	p value	Model Fit
% △ in FEV_1			
Admission FEV_1 (%)	−1.332	<0.001	r^2 53.2% Intercept: 147.1
Age (yr)	−2.37	0.0122	
Aminoglycoside use	+8.61	0.1844	
RIF use	−3.13	0.6053	
% △ in FVC			
Admission FVC (%)	−1.50	<0.001	r^2 67.0% Intercept: 187.0
Age (yr)	−2.33	0.0019	
Duration of VAN (days)	−1.198	0.0389	
RIF use	+4.14	0.3868	
Length of stay			
Admission FVC (%)	−0.160	0.0007	r^2 30.7% Intercept: 28.1
Age	−0.205	0.2093	
RIF use	+1.211	0.2506	
Time to readmission	No significant predictors		

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RIF, rifampin; VAN, vancomycin

* Example regression equation from table: Percent change in FEV_1 = 147 − 1.332(admission FEV_1) − 2.37(age) + 8.61 if on aminoglycoside, −3.13 if on RIF.

admission, and administration of concurrent nephrotoxic medications.[12–14] These risk factors are common among patients with CF, particularly repeated exposure to nephrotoxic medications, such as aminoglycoside antibiotics. Careful monitoring of kidney function during VAN therapy is warranted. Although hepatotoxicity with RIF is rare, other issues, including the development of resistance, is of concern.[4] Given the above-cited concerns and the lack of additional efficacy found in this study, until further data are published supporting the use of RIF for the acute treatment of APEs of CF, its use should be avoided.

There are several limitations to this study. This was a non-randomized, retrospective medical chart review with a small number of patients from a single CF center, which introduces the risk of type II error. A major assumption made during the study was that MRSA was the primary cause of the APE of CF. Individuals with CF may be colonized or infected with other bacteria, such as *P aeruginosa*, which may contribute to an APE. To mitigate this limitation, we excluded patients who did not have MRSA isolated from their sputum upon admission or within 1 month of admission. However, we are unable to fully separate the effect that other coinfections (e.g., *P aeruginosa*) or antibiotics (e.g., antipseudomonal β-lactams) had on lung function response. Another major limitation was that RIF MICs were not available. During the study period, a specific antibiotic susceptibility panel for sputum cultures from individuals with CF existed and did not include RIF testing. We were therefore unable to assess the susceptibility profile of MRSA isolates to RIF. A review of the institution's antibiogram for the medical floor where patients with CF were treated revealed that 100% of MRSA isolates were susceptible to RIF. However, given that individuals with CF have altered susceptibility patterns, it would be inappropriate to apply this antibiogram data to the patients in our study.

The addition of RIF to VAN for the treatment of an APE in children and adolescents with moderate lung disease and high MRSA VAN MICs had no significant impact on pulmonary function or length of stay in this small, single-center study. Until further data are published regarding the role of combination VAN and RIF for treatment of an APE of CF, data from this study suggest VAN monotherapy is adequate and the addition of RIF is unnecessary.

ARTICLE INFORMATION

Affiliations Department of Pharmacy Practice (NMF, CJM, CW, WAP) University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, and Pulmonary and Critical Care Medicine, Department of Medicine (CAF), Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York

Correspondence Nicholas M. Fusco, PharmD; nmfusco@buffalo.edu

Disclosures The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript including grants, equipment, medications, employment, gifts or honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgment Results of this study were presented at the 26th Pediatric Pharmacy Advocacy Group (PPAG) Annual Meeting; May 5, 2017; Charlotte, North Carolina.

Accepted October 9, 2017

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