International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

THE CLINICAL PRACTICE OF VANCOMYCIN DOSING AND MONITORING, AND FACTORS AFFECTING LEVELS AMONGST ONCOLOGY AND CARDIOLOGY PATIENTS IN QATAR: A RETROSPECTIVE ANALYSIS

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ABSTRACT

The paper focuses on the assessment of current vancomycin (VCM) use in National Centre for Cancer Care and Research (NCCCR) and Heart Hospital (HH) (the only tertiary care specialty hospitals in Qatar) which are 2 out of 8 teaching hospitals in Hamad Medical Corporation the main and largest healthcare organization in Qatar. Primary objectives were to assess the current vancomycin use for cancer and cardiology patients among Qatar population admitted to National Centre for Cancer Care and Research (NCCCR) and Heart Hospital (HH), and to explicate the factors that affected VCM serum trough levels, secondary objective was to access the need to develop and establish a guideline, which is essential to assure the standardization of practice and meets the unique needs of our patients' population. A retrospective cross sectional study was conducted to review patients' medical record of the clinical practice of VCM use in two hospitals the NCCCR and HH. We reviewed all VCM level determinations performed during the 12-month (from January, to December, 2012) study period that met inclusion criteria. We retrospectively analyzed the trough and peak concentrations (if taken) of vancomycin in 206 hospitalized patients (between 16 to 92 years of age) with VCM treatment episodes. The relationship between dose and concentration of drug, dose and body weight/ CrCl were established by regression analysis. Statistical analyses were done using excel and statistical packages SPSS 19.0. This multicenter study shows that 71% (118/167) of patients received a total daily dose of 2000 mg/ day (1000 mg every 12 hours over 60 minutes); this dose was common among different body weights (40-145 kg) and estimated CrCl (11-139 ml/min) values, dose selections was not considered based on body weight and/ or CrCl, therefore no linear correlation were shown between VCM trough and body weight/ CrCl. Initial loading dose of VCM was not considered for any of the patients included in the study (n=167). Only 16% of trough concentrations presented therapeutic levels, therefore a high percentage of patients was found to have sub-therapeutic or supra-therapeutic concentrations, furthermore 31% of patients had no trough levels. No linear correlation was found between patients body weight and the total daily dose (r=0.037). Only 39% (65/167) had cultures done, out of which7.8% (13/167) showed various gram positive bacteria (*MRSA, MRSE, other coagulase-negative staphylococci, or Enterococcus*) were isolated. Multiple areas of improvement were identified in dosing and monitoring of VCM in NCCCR and HH, evidence based guidelines are urgently required with the direct involvement of Clinical Pharmacists and Infectious Disease department to apply the optimal VCM initial dose based on creatinine clearance (CrCl) and body weight (BW) to minimize sub-therapeutic or supra-therapeutic trough levels.

Keywords: Clinical pharmacist, *Methicillin Resistant Staphylococcus Aureus (MRSA),* pharmacokinetic, staphylococci, trough level, Vancomycin

INTRODUCTION

Vancomycin (VCM) is a glycopeptide antibiotic, first introduced in the 1950s, it has been widely used for treating various infections, and now is considered the first line treatment for infections caused by *Methicillin Resistant Staphylococcus Aureus (MRSA)* [1-3]. VCM nephrotoxicity has been a concern, especially in patients with pre-existing renal dysfunction [1–3]; therefore, VCM trough levels are recommended to be maintained appropriately in order to avoid nephrotoxicity, predict VCM efficacy, avoid therapeutic failure, and avoid development of resistance[1, 2]. Peak levels, previously used to assess toxicity, but currently they have little clinical usefulness as evidence indicating a low risk of toxicity using properly calculated doses [3]. Since VCM is mainly renally excreted [4], VCM dose should be adjusted according to renal function; a linear relationship between Creatinine Clearance (CrCl) and VCM clearance has been shown, renal function is usually estimated by creatinine clearance (CrCl), calculated by the Cockcroft–Gault equation [5-7]; Initial dosing of VCM based on body weight (BW) has been recommended then VCM dose adjustment according to CrCl should be considered [7–9]. VCM is usually prescribed as intermittent intravenous infusions with dosing regimen of 30 mg/kg per day divided into intervals of 12 hours, with adjustment for renal function. A correctly timed trough level must be drawn shortly before a dose is given and after the drug has reached steady state. Keeping VCM trough levels above 10 mcg/mL has been reported to reduce the emergence of isolates with elevated VCM minimum inhibitory concentration (MIC) [14,15]. A trough level of 15–20 mcg/mL was reported to be favored in the setting of invasive infections, including bacteremia, endocarditis, osteomyelitis, hospital-acquired pneumonia, etc. [13].

Hamad Medical Corporation (HMC) is Joint Commission International (JCI) accredited premier non-profit healthcare organization and it is the main and largest healthcare organization in Qatar. National Centre for Cancer Care and Research (NCCCR) and Heart Hospital (HH) are 2 out of 8 hospitals in HMC and they are the only tertiary care oncology/ cardiology facilities in Qatar.

Problem statement: To the authors knowledge; this is the first study of its kind in Qatar, our aim is the assessment of current VCM dosing and monitoring practice amongst special patients' population of cancer and cardiovascular diseases who are predicted to have multiple comorbidities such as renal impairment, and to have special medications and therapy management (example; chemotherapy), and describing VCM prescribing practices and identifying targets for improvement at NCCCR and HH.

Primary objectives: Primary objectives of this study were to assess the current vancomycin use for cancer and cardiology patients among Qatar population admitted to National Centre for Cancer Care and Research (NCCCR) and Heart Hospital (HH), and to explicate the factors that affected VCM serum trough levels.

Secondary Objectives: Secondary objective of the study was to access the need to develop and establish a guideline, which is essential to assure the standardization of practice and meets the unique needs of our patients' population.

METHODS

Study Design: We performed a retrospective chart review analysis to assecthe clinical practice of vancomycin in two hospitals,weevaluated all vancomycin level determinations performed during the 12-month study period from January 01, 2012 to December 31, 2012, that met inclusion criteria.

Population and sampling: We retrospectively analyzed the through (Tr) and peak (Pk) concentrations (if taken) of vancomycin in 206 hospitalized patients (between 16 to 92 years of age) with VCM treatment episodes, patients included in the study were all patients to whom VCM was administered intravenously (for more than 24 hourtreatment proposes), and patietns who received oral VCM and/ or interavenous VCM for prophylaxis indications were excluded (n=167), table 1. As the study focused on the assessment of current vancomycin (VCM) use in National Centre for Cancer Care and Research (NCCCR) and Heart Hospital (HH), we would expect differences between NCCCR and HH patients' characteristics, table 2.

Data collection: Data were collected from the Pharmacy Management System (PMS) and electronic Medical Record (e-MR) viewer system, data were collected on an excel sheet to be evaluated. The relationship between dose and concentration of drug, dose and body weight/ CrCl were established by regression analysis. To conduct the pharmacokinetic characterization of vancomycin; creatinine clearance was calculated using the Cockroft-Gault equation [5] and the calculations were made for all pateints (based on inclusion criteria) which serum creatinine, age, weight and height were known (n = 167).

In our study we considered dosing regimens determined by the physician. Evaluating therapy indication and whether it was appropriate by reviewing specimens (blood, sputum, urine, pus, and others) in which various bacteria (*MRSA, MRSE, other coagulase-negative staphylococci, or Enterococcus*) were isolated. We checked if VCM trough level was measured more than once; first value should be after completing the third dose (the same approch was employed with each dose change), because it is recommended that the timing of the monitoring of troughs should be obtained just prior to the next dose at steady-state conditions.

Ethics: This study was approved by the Medical Research Centre at HMC.

Analysis: Descriptive statistics wereused to summarize all demographic and other clinical characteristics of the participants. Categorical and continuous values wereexpressed as frequency (percentage) and mean ± standrd diviation (SD). Associations between two or more qualitative or categorical variables wereassessed using chi-square test. For small cell frequencies, chi-square test with continuity correction factor was used. Correlation analys wasused to examine the relationship between two quantitative variables. Appropriate regression analysis wasused to assess factors that affect vancomycin (VCM) serum trough levels.Pearson's correlation coefficients were calculated between Total Daily Dose and VCM trough levels, total daily dose and BW, and total daily dose and CrCl. P-value < 0.05 was considered as statistically significant. All Statistical analyses were done using statistical packages SPSS 19.0.

RESULTS

Total daily doses received by patients ranged from 500 mg to 4000 mg, 71% (118/167) of patients received a total daily dose of 2000 mg/ day (1000 mg every 12 hours over 60 minutes); this dose was common among different body weight (40-145 kg) and CrCl (11-139 ml/min) values. Initial loading dose of VCM was not considered for any of the patients included in the study (n=167).

Through plasma levels of VCM for patients in our study showed a clear inter-individual variability. Thirty twopercent (53/167) had no trough levels measured, measured trough levels showed wide range of variation, only 16% (27/167) were therapeutic (10-20 mg//L), 41% (68/167) of detected trough levels were < 10mg/L and 11% (18/167) were > 20mg/L. Although around 52% of patients had trough levels out of therapeutic range; only 10% (17/167) of cases had dose adjustment done, and none of them had repeated levels based on the new adjust dose. Some studies have suggested that trough serum VCM concentrations of <10 mg/L may predict therapeutic failure and the potential for the emergence of infection [18,19]. A limited number of peak values were screened (n=33), only 6% of VCM peak concentrations measured were within the target range, some patients have values even higher than 60 µg/mL; which is indicative of a very high probability that the patient presented symptoms of adverse reactions and a significant possibility for toxicity (Figure 1). When CrClwere correlated with the total dose administered no linear correlation was found (r=0.042), similarly correlation between patients' body weight and the total daily dose showed no linear correlation (r=0.037) (table 3, Figures 2,3).

Evaluating therapy indication and specimens cultures showed; 61% (102/167) of patients had no cultures ordered, 39% (65/167) had cultures done (blood, sputum, urine, pus, and others), out of which 7.8% (13/167) showed various gram positive bacteria (*MRSA, MRSE, other coagulase-negative staphylococci, or Enterococcus*) were isolated, whereas other types of bacteria (*Klebsiella pneumoniae, Citrobacter koseri, Acinetobacter Baumannii, Escherichia coli, and pseudomonas aeruginosa*) were isolated in 3.6% (6/167) of patients.

DISCUSSION

Therapeutic drug monitoring has been well established and its benefits are internationally recognized among clinicians. Drug level monitoring should always be included to monitor drugs with narrow therapeutic windows and significant inter-patient variability specially for patients with complex diseases, considering that monitoring drug levels and adjusting therapy increase the efficiency and clinical benefit of treatments, decrease risk of toxicity and play a significant role in saving costs of hospitalization.

When monitoring VCM therapy is clinically indicated; serum trough concentrations are recommended to predict VCM efficacy [12,13]. Peak levels, previously used to screened frequently to assess toxicity, however currently thought to have little clinical usefulness due to the improvement in VCM dosing practice over time as evidence indicating a low risk of toxicity if dosing standardized granted. [14, 15]

Current practice of prescribing VCM incorporates published guidelines to direct dosing and monitoring, in addition to the use of clinical pharmacists asan advisory role. Clinical pharmacists play a fundamental role in the therapeutic drug monitoring (TDM) and therapeutic dose individualization (TDI) of VCM as they are pharmacokinetic specialists.

Many literatures are recommending implementing guidelines and pharmacokinetics services by clinical pharmacists to incorporate independent dosing of VCM for patients on different medications including VCM. The obvious benefits of these expanded roles, has been published comparing this pharmacist managed dosing model [21,22]. There is an opportunity for clinical pharmacists in Qatar to assume a greater responsibility for the management of medication requiring TDM and TDI in order to provide more consistent VCM dosing and monitoring.

Currently; VCM is ordered, dosed and monitored by physicians in both NCCCR and HH, clinical pharmacists has a very limited role which is to review the case (as part of the daily therapeutic review done for all patients) and give recommendations to physicians, sometimes those recommendations are verbally accepted but not translated as orders to modify doses, request trough, or consider changing therapy based on cultures.

We clarified that only 16% (27/167) of trough levels were therapeutic (10-20 µg/mL), this was a resultof different factors; 1) no initial loading dose was used. Loading doses of VCM may be important in complicated critically ill patients and oncology patients due to diminished immunity and the high mortality rate seen among these patients. Routine loading with the recommended dose of 25–30 mg/kg of total body weight should significantly reduce the time to achieve the targeted trough concentrations [20]. Further research incorporating a loading dose seems warranted. 2) VCM adequate levels should depend mainly on proper initial dosing of the drug. Initial dosing of VCM based on body weight (BW) and dose adjustment according to CrCl should be considered [7–11]. We clarified that 71% of VCM initial doses were identical (1000 mg every 12 hours over 60 minutes) among a wide range of variable patients' BW (40 to 145 kg) and CrCl (11 to 139 mL/min), meaning that dose selections was not considered based on body weight and/ or CrCl, therefore no linear correlation were shown between VCM Dose and body weight, and the correlation between VCM dose and CrCl showed weak linear correlation (r=0.328). Therefore no linear correlation was shown between total daily dose of (VCM) and trough levels in overall patients (Figure 4) or between total daily dose of (VCM) and CrCl in overall patients (Figure 5).

Moreover, we identified the following; 1) although VCM trough levels are recommended to be maintained appropriately in order to avoid nephrotoxicity, predict VCM efficacy and avoid therapeutic failure [1,2]; 31% of patients has no trough levels detected, and around 52% of trough levels were out of therapeutic range; only 10% (17/167) of cases had trough based dose adjustment done, and none of them had repeated levels based on the new adjust dose.2) VCM has a role in the management of gram positive infections and is considered the first line treatment for infections caused by *Methicillin resistant Staphylococcus Aureus (MRSA)* [1,2]. In 1995, the Centers for Disease Control and Prevention (CDC), Hospital Infection Control Practices Advisory Committee (HICPAC) published Recommendations for preventing the Spread of VCM Resistance indicating the need for cultures to assure efficacy and prevent resistance [23], the majority if patients (61%) had no cultures ordered, and only 7.8% (13/167) showed various gram positive bacteria senstive to VCM (MRSA, MRSE, other coagulase-negative staphylococci, or Enterococcus) were isolated, which indicats the inappropriate use of VCM which can result in increased risk of VCM resistance, delayed infection management,and increased risk of nephrotoxiciy without indication,.

Based on the results of our study and as a conclusion of study findings the identified areas for improvement were: 1) No clear protocol of VCM dosing and monitoring. 2) Initial VCM does are not properly determined based on body weight and CrCl. 3) No consistency toward trough level monitoring and culture sensitivity. 4) No proper dose adjustment. 5) Clinical pharmacists are not involved in VCM dosing and monitoring and their role is not well defined in VCM dosing. Therefore, clear guidelines are urgently required, and we suggest that there should be a complete protocol of the dosage and monitoring of VCM. Involvement of clinical pharmacy in this effort is cost effective and should be encouraged in order to provide more consistent VCM dosing and monitoring [15, 21]. Furthermore, antimicrobial stewardship program is an essential requirement to assure proper antimicrobial agents utilization and guarantee patients' safety [24].

Strengths: This is the first study of its kind in Qatar. It identified different area of improvement in the

usage of VCM which can potentially affect patients' care. This study can be conducted in other hospitals.

Limitations: Sample size was limited given the specialized population of patients included in this study. Despite this limitation, this study demonstrates use of VCM in the inpatient oncology and cardiology populations in Qatar is common. These findings emphasize the importance of development, implementation, and expansion of the same methodology in other hospitals and on different patients' populations.

Implication to practice: Establishment of pharmacokinetic service by clinical pharmacists to incorporate independent dosing of different medications including VCM can significantly impact patient care. Clinical pharmacy team should work in collaboration with Infectious Disease (ID) department to develop a protocol, based on that protocol, the clinical pharmacist should perform VCM therapy management including dosing and monitoring. Education and awareness should be considered to assure consistent and standardized VCM ordering, dosing and monitoring which will guarantee continuity of care between physicians, pharmacists, and nurses which will promote clinical outcomes and maximize patient safety.

CONCLUSION

Multiple areas of improvement were identified in dosing and monitoring of VCM in NCCCR and HH, clear guidelines are urgently required with the direct involvement of clinical pharmacists and Infectious Disease department to apply the optimal VCM initial dose based on creatinine clearance (CrCl) and body weight (BW) to promote clinical outcomes and maximize patient safety. Further studies are required to evaluate the VCM ordering, dosing and monitoring

Conflicts of interest: The author(s) declare that they have no conflicts of interests.

Acknowledgement: We would like to acknowledge Hamad Medical Corporation Medical Research Center for funding this study

Table 1. Patient characteristics

Item	Total - n (%)
Number of cases NCCCR Heart Hospital	**167** 90 (53.9%) 77 (46.1%)
Gender Male Female	 99 (59.3%) 68 (40.7%)
Age (range) [years]	49.4 ± 16.3 (16-92)
Height (range) [cm]	163.3 ± 7.9 (147-186)
Weight (range) [kg]	70.4 ± 18.1 (40-145)
BMI (range) [kg/m2]	26.3 ± 5.6 (16.1-46.8)
IBW (range)	58.0 ± 8.5 (40.6-80.4)
Serum creatinine (range) [mg/dL]	88.7 ± 73.9 (26-548) (median=69)
Considered CrCl (range) [mL/min]	73.6 ± 29.1 (9.4-138.9)
Total daily vancomycin dose (range) [mg]	1822.8 ± 509.7 (167-4000)
Duration of vancomycin dose (day)	4.6 ± 4.3 (1-34) (median=3.3)
Number of vancomycin dose	8.3 ± 8.2 (2-69) (median=6.0)
VCM trough level (range) [µg/mL]	12.1 ± 9.7 (1.7-60) (median=8.7)
Peak level (range) [µg/mL]	28.4 ± 10.4 (10.8-64.0) (median=26.1)

Table 2. Patient characteristics comparison between NCCCR and HH

Variable	NCCCR	Heart Hospital	p-value
Age (years)	45.3 ± 14.3	54.3 ± 17.1	**<0.0001**
Male	45 (50%)	54 (70.1%)	**0.008**
Height (range) [cm]	161.6 ± 7.1	165.2 ± 8.5	**0.004**
Weight (range) [kg]	66.5 ± 13.4	74.9 ± 21.5	**0.003**
BMI (range) [kg/m2]	25.5 ± 5.2	27.3 ± 6.7	0.060
IBW (range)	56.1 ± 7.7	60.2 ± 8.9	**0.002**
Serum creatinine (range) [mg/dL]	69.6 ± 46.9	111.0 ± 91.9	**0.001**
CrCl (range) [mL/min]	93.6 ± 26.0	83.4 ± 43.8	0.077
Adjusted CrCl (range) [mL/min]	72.6 ± 31.4	61.6 ± 35.7	**0.039**
Considered CrCl (range) [mL/min]	79.5 ± 25.6	66.7 ± 31.4	**0.005**
Total daily vancomycin dose (range) [mg]	1889.8 ± 402.5	1746.3 ± 603.4	0.079
Duration of vancomycin dose	3.5 ± 1.8	6.0 ± 5.8	**0.001**
Number of vancomycin dose	6.8 ± 3.7	10.1 ± 11.5	**0.024**
VCM trough level (range) [mcg/mL]	8.5 ± 5.3	16.2 ± 11.8	**<0.0001**
Peak trough level	25.2 ± 7.1	37.2 ± 13.1	**0.002**

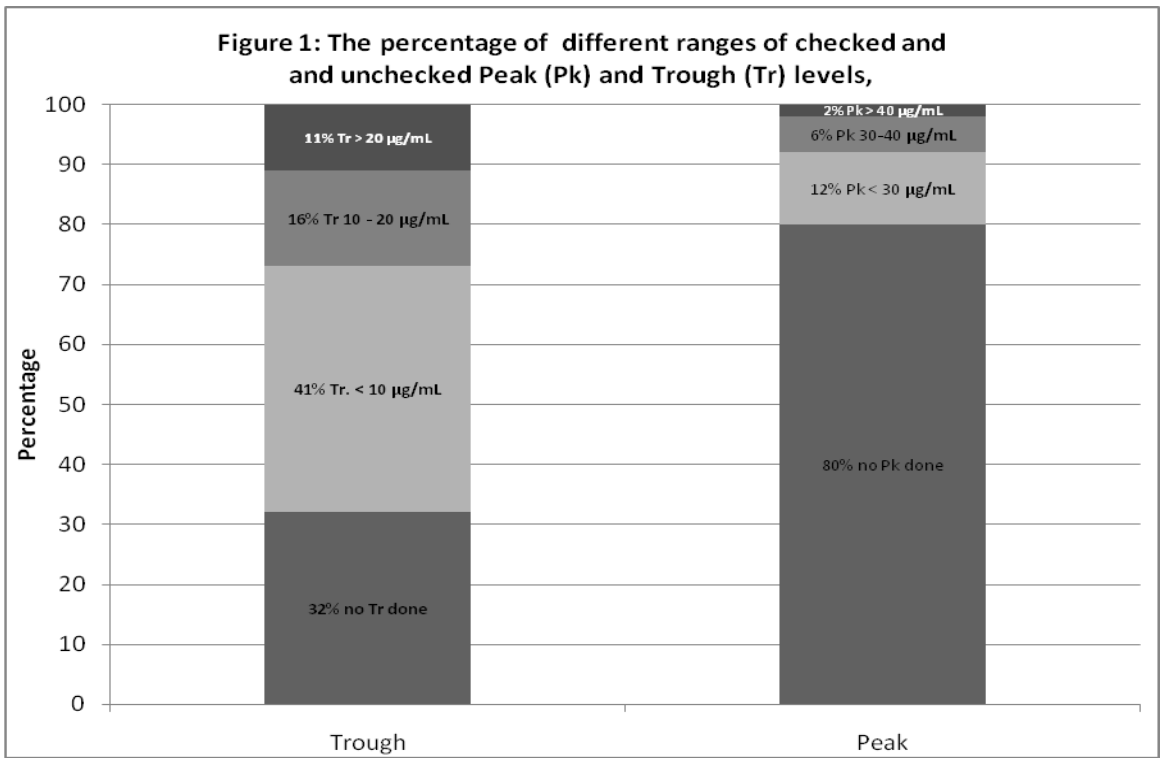


Table 3: Correlations

		Age	Weigh	Height	BMI	Serum	Conside	Dose
Age	Pearson Correlation	1	.148	-.212**	.254**	.267**	-.665**	-.088
	Sig. (2-tailed)		.056	.006	.001	.000	.000	.260
	N	167	167	167	167	167	167	165
Weight_Kg	Pearson Correlation	.148	1	.409**	.923**	.136	.006	.037
	Sig. (2-tailed)	.056		.000	.000	.080	.935	.641
	N	167	167	167	167	167	167	165
Height_cm	Pearson Correlation	-.212**	.409**	1	.039	-.035	.485**	.138
	Sig. (2-tailed)	.006	.000		.617	.652	.000	.078
	N	167	167	167	167	167	167	165
Serum Creatinin	Pearson Correlation	.267**	.136	-.035	.167*	1	-.619**	-.474**
	Sig. (2-tailed)	.000	.080	.652	.031		.000	.000
	N	167	167	167	167	167	167	165
Considered CrCl	Pearson Correlation	-.665**	.006	.485**	-.203**	-.619**	1	.328**
	Sig. (2-tailed)	.000	.935	.000	.008	.000		.000
	N	167	167	167	167	167	167	165
Total Daily Dose	Pearson Correlation	-.088	.037	.138	-.022	-.474**	.328**	1
	Sig. (2-tailed)	.260	.641	.078	.776	.000	.000	
	N	165	165	165	165	165	165	165
Trough Level	Pearson Correlation	.303**	.042	-.108	.074	.231*	-.462**	.005
	Sig. (2-tailed)	.001	.652	.249	.430	.013	.000	.956
	N	115	115	115	115	115	115	115
Peak Level	Pearson Correlation	.059	.123	-.021	.111	.206	-.106	-.065
	Sig. (2-tailed)	.743	.496	.908	.538	.251	.558	.720
	N	33	33	33	33	33	33	33

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 2. Scatter plots showing the relationship between Total Daily Dose of vancomycin (VCM) and patients body weight (BW) in overall patients. (r=0.037)

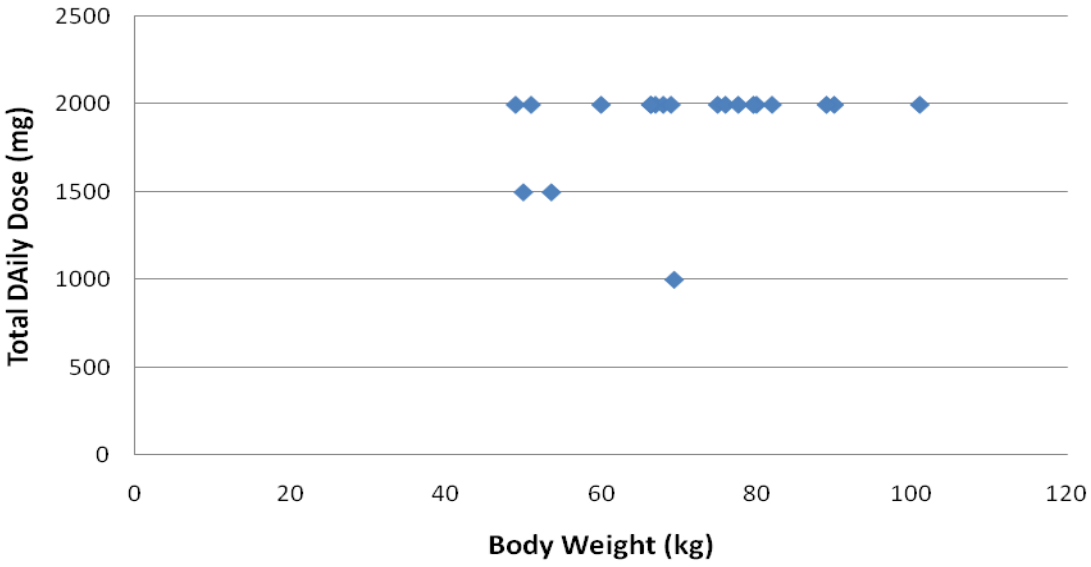
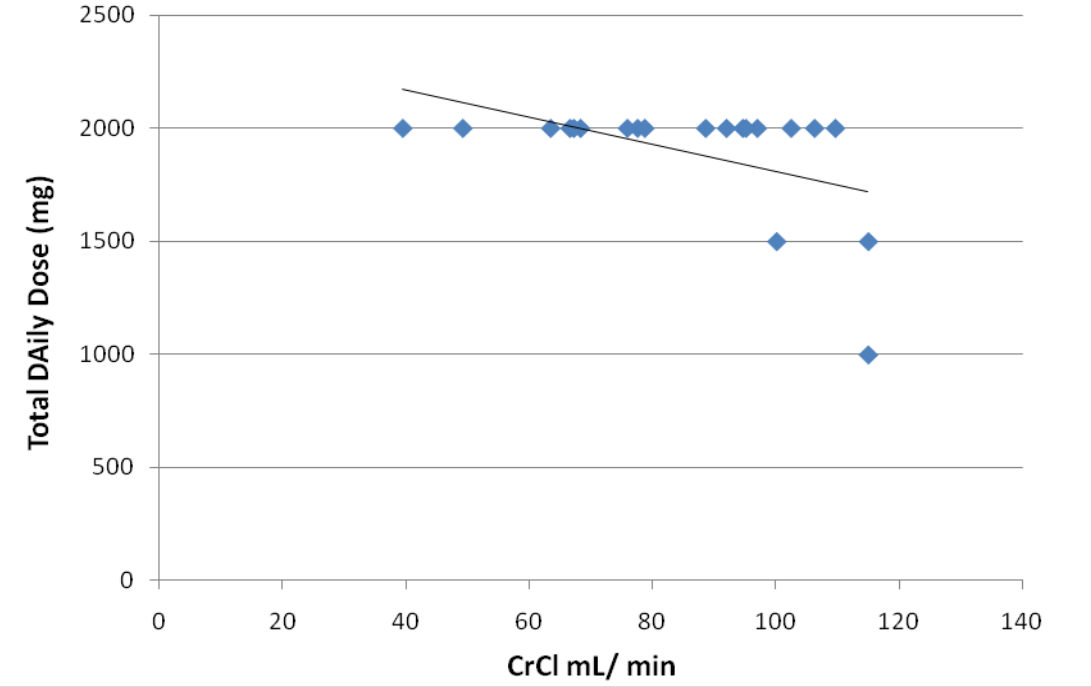


Figure 3. Scatter plots showing the relationship between Total Daily Dose of vancomycin (VCM) and Creatinine Clearance (CrCl) in overall patients. (r=0.328)



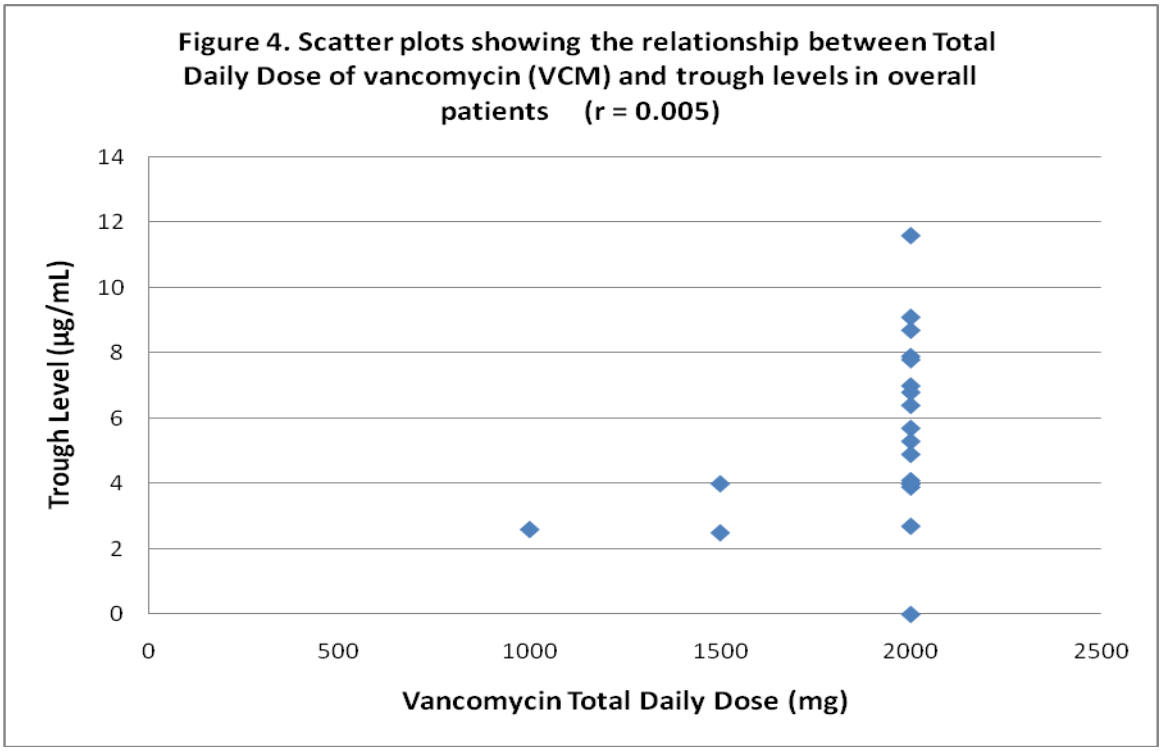
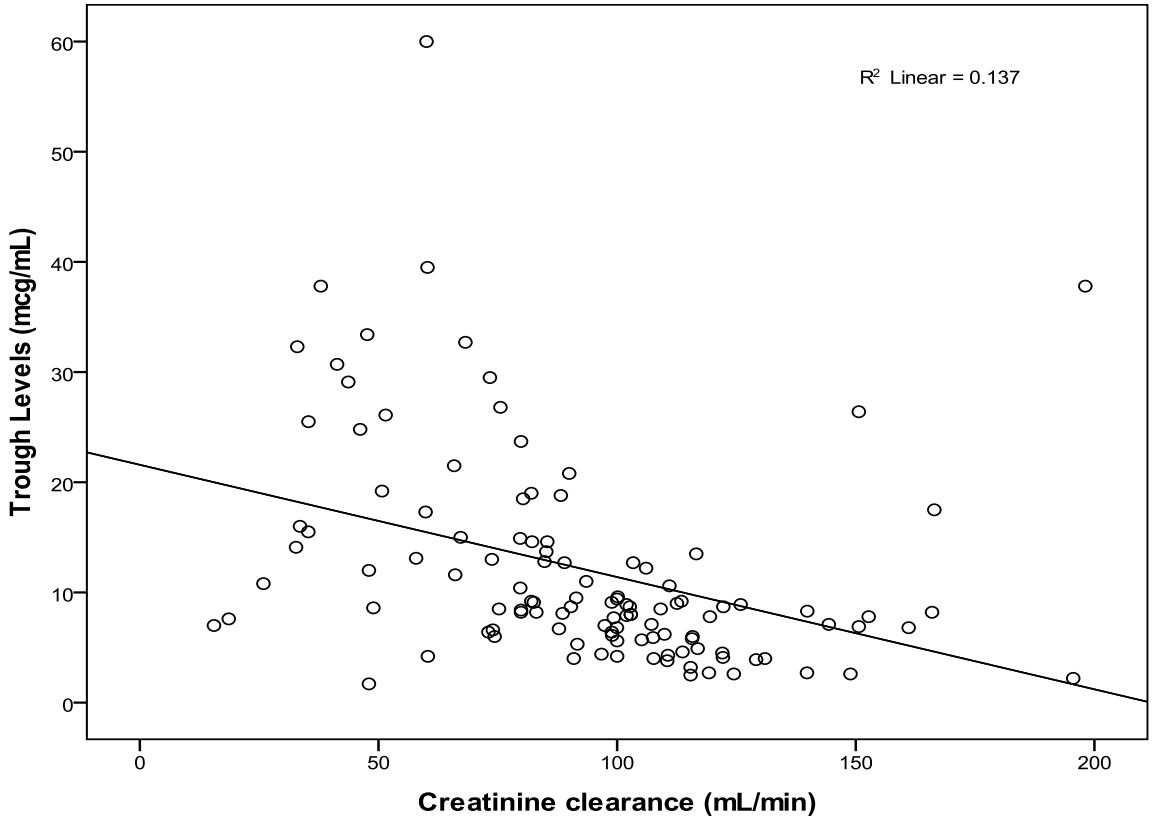


Figure 5. Scatter plots showing the relationship between creatinine clearance (CrCl) and vancomycin (VCM) trough levels in overall patients



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