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Original Article

The Use of an Antibiotic Monitoring Database to Gain Insight into Safer Prescribing of Vancomycin and Aminoglycosides

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A B S T R A C T

Background: Achieving targeted pre-dose concentrations of vancomycin and aminoglycosides is crucial for efficacy and safety. Initial doses of those antibiotics are adjusted in patients with impaired renal function but fixed dosing is used otherwise. The aim of this study is to use antibiotic monitoring data to gain insight on how prescribing can be better tailored to target the desired concentrations. **Methods:** This is a retrospective analysis of a five-year antibiotic monitoring database from a referral tertiary care hospital in Western Saudi Arabia. Multivariate logistic regression –with robust standard error as appropriate- was used to detect associations between pre-dose antibiotic concentrations being below or above targets and age, gender, and creatinine clearance, as estimated retrospectively from the database. **Results:** There were 1067 and 9394 pre-dose concentration records for aminoglycosides and vancomycin, respectively. For amikacin and gentamicin, respectively 46% and 59% of pre-dose concentrations were above 5 and 1 micrograms/ml. and for vancomycin 18% were below 10 and 30% were above 20 micrograms/ml. Regression showed estimated creatinine clearance to be an independent predictor of vancomycin and aminoglycoside plasma levels ($p<0.001$ for both). This was true with initial and subsequent level measurements and across wards (oncology, ICU and others). Gender showed significant association with vancomycin level. **Conclusion**: A substantial proportion of patients can benefit from snug tailoring of vancomycin and aminoglycoside doses based on creatinine clearance estimation. The current dataset suggests a model for vancomycin that can be validated in datasets from other populations and then may be used to guide dosing.

Key Words: Gentamycin, amikacin, vancomycin, therapeuticdrug monitoring, aminoglycosides.

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1. INTRODUCTION

With the relatively small number of new antibiotics that currently enter the market, reliance on relatively old antibiotics still continues (Moellering, 2011). The fact that bacteria fight back and develop new modes of antibiotic resistance makes the situation more complicated. Antibiotics are thus our precious weapons that we need to keep and use judiously. Sub-therapeutic doses of antibiotics may lead to therapeutic faliure and tis may invite resistance. On the other hand, higher than required concentrations may end in serious toxicities. Hence was the importance of therapeutic drug monitoring (TDM) of antibiotics. When the antibiotic concentration is desired to remain within a relatively narrow range and when factors interpaly to affect that concentration, TDM becomes an important tool (Kang and Lee, 2009). Aminoglycosides (AGs) and vancomycin are old antibiotics but they retain their important place in contemprory medical practice. Achieving targeted pre-dose concentrations of vancomycin is crucial for efficacy and safety (NHS, 2016a and NHS, 2016b). Initial dosing is usually based on estimation of renal function, which classifies patients into broad dosing categories. This however is not usually enough to guarantee attainment of the target concentration and so antibiotic monitoring is done. While lab concentration monitoring may be used on day to day basis to manage therapy of individual patients, the availability of records of the antibiotic plasma concentrations for large groups of patients can help us to look back and evaluate our practice both with initial and post-level dosing. In this study, we have tried to make use of the antibiotic monitoring database from a large referral center to evaluate the currently used guidelines for initial dosing.

The aim of this retrospective chart review study is to use antibiotic monitoring data to gain insight on how prescribing can be better tailored to target the desired concentrations.

2. MATERIALS AND METHODS

Data of five years (January, 2011-December, 2015) of antibiotic monitoring were extracted from the database of the clinical chemistry lab of a tertiary care 1000-bed, referral hospital in western Saudi Arabia. The hospital has excellence centers specialized in Neurology, Oncology, Special Surgery, and Cardiology. Patient records were included if they were 18 years or above at the time of monitoring, had available vancomycin or aminoglycoside concentrations, had available creatinine level concentrations within two days of the monitoring records, and had records of the weight and the height.

Renal function was assessed using the estimated glomerular filtration rate (eGFR) which was calculated by the Cockcroft-Gault Equation using, age in years, weight in kg and serum creatinine in mg/dl (Cockcroft and Gault, 1976):

Estimated creatinine clearance in ml/min = K X ((140-Age in years) X weight in kg) / (serum creatinine in mg/dl X 72); Where k = 1 for men and 0.85 for women.

Ideal body weight (IBW) was calculated for all patients according to the following equations (WHO, 2016):

IBW for men = 50 + (2.3 X (height in cm – 150)/2.5).

IBW for women = 45.5 + (2.3 X (height in cm – 150)/2.5).

The weight used in Cockcroft-Gault Equation varied as follows: (1) if the actual body weight was less than the IBW, the actual body weight was used; (2) if the actual body weight was 25% greater than the IBW, the adjusted body weight was used; and (3) the IBW was used for the remainder of patients.

Adjusted body weight = IBW + 0.3 X (Actual body weight – IBW).

For all patients over 65 years of age, if the eGFR was less than 1mg/dl it was recorded as 1mg/dL (Dowling and Comstock , 2005).

After the eGFR was estimated, it was adjusted to 1.73 m^2 of the body surface area (BSA) by multiplying the measured GFR by 1.73/BSA. The BSA was calculated by using Du Bois and Du Bois equation (Du Bois and Du Bois , 1917):

BSA = (Body weight in $kg^{0.425}$ X height in $cm^{0.725}$) X 0.007184.

Cases were excluded if they had extreme BMI (Body Mass Index) of less than 14 or more than 70 or if they had an estimated creatinine clearance above 300 ml/minute.

Cases were classified according to the BMI into: < 18.5 (Under-weight), 18.50-24.99 (Normal BMI), 25.00-29.99 (Pre-obese), and 30 or above (Obese) (WHO, 2016).

A focus was made on pre-dose concentration monitoring records which were classified into first levels or repeated levels. Files of all patients with available pre-dose concentrations were consulted to extract the dose and frequency that preceded the recorded first level. The total daily dose was calculated by multiplying the dose and the frequency and per kg doses were calculated.

1.1. Statistical method

Statistical analysis was performed on STATA version 11.0. Numeric data were presented as the mean ± the standard deviation as well as the median and quartiles. Categorical data were presented as percentages. Univariate logistic regression models were constructed to study the association of estimated creatinine clearance and high AG concentration and high and low vancomycin concentrations. Analysis was repeated stratified by various demographic factors. Antibiotic pre-dose concentration data were examined for normality of distribution and were converted to the log scale in face of right skewness. Single linear regression models were constructed to test the effect of different variables on the log transformed vancomycin concentration. Factors were then entered into a multiple regression model using a backward method with a threshold of 0.1 for factor removal from the model.

2.3 Deriving and testing a dosing model

It was attempted to use the models from multiple regression to develop a tool to tailor initial doses of AGs and vancomycin by rearranging the final equation of the model. The equation was then used to simulate calculation of initial antibiotic doses for patients with different values of estimated creatinine clearance and from both genders. Calculated doses were compared with those recommended by the guidelines and with those already given to the patients.

3. RESULTS

There were 1067 and 9394 pre-dose concentration records for AGs and vancomycin, respectively.The mean age of patients with recorded AG concentrations was 51.5±18.5 and was 57.5±12.3 for those with vancomycin levels. The median estimated creatinine clearance and quartiles were 56.6 and 30.3, 90.3 ml/min in case of AGs and 44.8 and 28.2, 75.0 ml/min in case of vancomycin. Table 1 shows other characters of studied patients. In case of AGs, equal proportions of patients were in ordinary, oncology and ICU wards, while a bigger

proportion of patients were in non-ICU-non-oncology wards in case of vancomycin. Males were slightly more than females and those above 60 years of age constituted around a third in case of AGs and a little less than a half in case of vancomycin. More than a half of the monitored patients had estimated creatinine clearance of less than 60 ml/min.

Table 2 shows pre-dose level categories. For AGs, around 27% (294) of the samples were initial samples taken after therapy initiation while 73% were repeated. Initial samples were 17% (1629) in case of vancomycin and the rest were repeated for the same patient. For amikacin and gentamicin, respectively 46% and 59% of pre-dose concentrations were above 5 and 1 micrograms/ml. and for vancomycin 18% were below 10 and 30% were above 20 micrograms/ml.

The median and quartiles of pre-dose amikacin concentrations were 4.6 and 1.7-9.1 microgram/ml. Those of gentamicin were 1.2 and 0.64-2.3 respectively and those of vancomycin were 16.3 and 11.6-21.2, respectively.

Tables 3 through 5 show results of univariate logistic regression of low and high vancomycin concentrations and high AG concentration on the estimated clearance of creatinine. Association between the non-optimal antibiotic plasma concentration and creatinine clearance was examined after stratification of samples by a variety of factors. Table 3 shows that there is a highly significant association of vancomycin pre-dose concentration of greater than 20 microgram/ml with lower values of creatinine clearance, so the patients with lower clearance are more likely to have above target vancomycin concentrations. This was true for the analysis done on the total samples and was also true with all examined stratifications; for both genders, with initial and repeated vancomycin concentration determination and with both age groups and all ranges of BMI (all p values < 0.001). This was also true across wards (oncology, ICU and others) and with those with high or low creatinine clearance. Table 4 sends the same message but this time by showing highly significant associations of high creatinine clearance with lower vancomycin concentrations. Again, the association was almost equally strong and significant with all stratifications (all p values < 0.001).

Similar to the results of vancomycin, Table 5 shows a highly significant association between lower creatinine clearance levels and the probability of having pre-dose AG concentration higher than therapeutic ($p<0.001$ for total samples). With a much smaller number of patients and samples, the strength and the significance of association were a little variable among the different strata, yet mostly highly statistically significant ($p<0.001$). Subgroups like that of underweight patients failed to reach statistical significance with less than 50 observations.

Tables 6 through 8 show results of multiple linear regression of the log converted antibiotic concentrations on creatinine clearance, adjusted for all demographic factors (age, sex, BMI) and for the initial daily dose per kg. Because it was not always possible to extract the new dose given after the first antibiotic concentration determination, only concentrations following initial dosing were used for these models. The model for amikacin resulted in exclusion of all factors expect for the creatinine clearance, the dose and the BMI. The gentamicin model resulted in exclusion of all factors except for the creatinine clearance and the BMI. The dose however was included in the last two models for amikacin and gentamicin in Tables 6 and 7 because the models were intended to help with dose estimation. Table 8 shows the final model of vancomycin where all factors were excluded except for the dose and the sex. Multiple linear regression showed estimated creatinine clearance to be an independent predictor of vancomycin and aminoglycoside plasma levels ($p< 0.001$ for both).

1.1. Dose estimation equation

When it was attempted to use the models in Tables 6 through 8 to develop a tool to tailor initial doses of AGs and vancomycin, data for aminoglycosides was smaller than would give a reliable model. For vancomycin the following equation was derived:

Log concentration of vancomycin= 2.44 + (-0.006 X creatinine clearance) + 0.086 for females) + (0.014 X daily dose)

Daily dose of vancomycin = [(0.006 X creatinine clearance) - (0.086 for females) +(Log of the target concentration of vancomycin) -2.44] / 0.014

Piloting the equation to tailor a dose according to a desired trough concentration showed that values were not plausible ones when creatinine clearance was below 30 ml/min. Doses estimated for a hypothetical male patient with creatinine clearance of 59 ml/min and a target trough of 10 microgram per ml came in agreement with the recommended dose of 15 mg/kg/day. For a patient with creatinine clearance of 90 ml/min again the estimated dose was very close to the recommended one of 15 mg/kg every 12 hours. For patients with creatinine clearance between 30 and 59 ml/min, the does suggested by the model were lower than 15 mg/kg/day and for those with clearance between 60 and 90, doses ranged between the 15 and the 30 mg/kg/day. Those with estimated creatinine clearance above 90 ml/min needed doses higher than 30 mg/kg/day. Piloting dose estimation in females gave a lot of implausible results especially for those with lower creatinine clearance values.

The equation was used to estimate doses that would result in a pre-dose concentration of 10 microgram/ml in all males with estimated creatinine clearance of 30 ml/min or greater. Estimated doses were compared with

those actually given, categorized by vancomycin concentration. Of those with vancomycin concentration > 20 microgram/ml, 76% had received an initial dose that was > 2 mg/kg/day bigger than the estimated one and 35% of those with trough concentrations lower than 10 microgram/ml had received doses that were less than those estimated, by at least 2 mg/kg/day.

Table 1: Characters of patients for which concentration monitoring was done

Character	N %	
	AG	Vancomycin
Facility in which the patient was admitted		
Ordinary ward	101 (34.4)	803 (49.3)
Oncology	86 (29.3)	279 (17.1)
ICU	107 (36.4)	547 (33.6)
Age		
18-60 years	186 (63.6)	877 (53.8)
Above 60 years	107 (36.4)	752 (46.2)
Sex		
Male	175 (59.5)	950 (58.3)
Female	119 (40.5)	679 (41.7)
BMI category		
Under weight	25 (8.5)	113 (6.9)
Normal weight	106 (36.1)	541 (33.2)
Over weight	82 (27.9)	475 (29.2)
Obese	80 (27.2)	496 (30.4)
Creatinine clearance category		
Below 60 ml/min	160 (54.4)	1072 (65.8)
60 ml/min or above	134 (45.6)	557 (34.2)

N = number; AG = aminoglycosides

Table 2: Results of plasma concentration with regards to the required therapeutic level

	N%		
	Total	1st level	Repeated level
Amikacin> 5	359 (47.6)	76 (37.1)	283 (51.5)
Gentamicin >1	183 (58.5)	46 (51.7)	137 (61.2)
Vancomycin below therapeutic	1644 (17.5)	601 (36.9)	1043 (13.4)
Vancomycin above therapeutic	2835 (30.2)	264 (16.2)	2571 (33.1)

Table 3: Results of univariate logistic regression for the association of creatinine clearance with high vancomycin concentration stratified by different factors

Factor	Number of observations	OR	95%CI	P value
All samples	9394	0.986	0.984 - 0.988	<0.001*
First or repeated level				
First level	1629	0.988	0.984 - 0.993	<0.001*
Repeated levels	7765	0.986	0.984 - 0.988	<0.001*
Gender				
Male	5795	0.987	0.985 - 0.990	<0.001*
Female	3599	0.985	0.981 - 0.988	<0.001*
Age				
< 60 years	5007	0.986	0.983 - 0.988	<0.001*
60 years and above	4387	0.983	0.978 - 0.988	<0.001*
BMI				
Underweight	687	0.987	0.983 - 0.991	<0.001*
Normal	3241	0.987	0.984 - 0.990	<0.001*
Pre-obese	2528	0.982	0.978 - 0.987	<0.001*
obese	2915	0.980	0.973 - 0.987	<0.001*
Facility				
General ward	4477	0.987	0.984 - 0.990	<0.001*
Oncology ward	1004	0.075	0.969 - 0.982	<0.001*
ICU	3913	0.990	0.987 - 0.994	<0.001*
Creatinine clearance category				
<60 ml/min	6412	0.979	0.975 - 0.983	<0.001*
60 ml/min or above	2982	0.987	0.983 - 0.991	<0.001*

* = Statistically significant association

Table 4: Results of univariate logistic regression for the association of creatinine clearance with low vancomycin concentration stratified by different factors

Factor	Number of observations	OR	95%CI	P value
All samples	9394	1.016	1.013 – 1.018	<0.001*
First or repeated level				
First level	1629	1.013	1.010 – 1.016	<0.001*
Repeated levels	7765	1.017	1.015 – 1.020	<0.001*
Gender				
Male	5795	1.015	1.012 – 1.018	<0.001*
Female	3599	1.016	1.013 – 1.019	<0.001*
Age				
< 60 years	5007	1.015	1.013 – 1.017	<0.001*
60 years and above	4387	1.012	1.005 – 1.019	<0.001*
BMI				
Underweight	687	1.012	1.007 – 1.018	<0.001*
Normal	3241	1.017	1.014 – 1.020	<0.001*
Pre-obese	2528	1.021	1.016 – 1.025	<0.001*
obese	2915	1.022	1.017 – 1.028	<0.001*
Facility				
General ward	4477	1.014	1.011 – 1.017	<0.001*
Oncology ward	1004	1.018	1.014 – 1.022	<0.001*
ICU	3913	1.012	1.008 – 1.016	<0.001*
Creatinine clearance category				
<60 ml/min	6412	1.023	1.016 – 1.030	<0.001
60 ml/min or above	2982	1.013	1.010 – 1.017	<0.001

* = Statistically significant association

Table 5: Results of univariate logistic regression for the association of creatinine clearance with high aminoglycoside concentration stratified by different factors

Factor	Number of observations	OR	95%CI	P value
All samples	672	0.979	0.971 – 0.987	<0.001*
First or repeated level				
First level	165	0.970	0.957 – 0.984	<0.001*
Repeated levels	507	0.983	0.974 – 0.993	0.001*
Gender				
Male	380	0.976	0.964 – 0.989	<0.001*
Female	292	0.979	0.969 – 0.990	<0.001*
Age				
< 60 years	424	0.980	0.970 – 0.990	<0.001*
60 year sand above	248	0.961	0.932 – 0.990	0.009*
BMI				
Underweight	47	0.988	0.970 – 1.006	0.195
Normal	201	0.966	0.952 – 0.981	<0.001*
Pre-obese	173	0.985	0.972 – 0.999	0.031*
obese	250	0.982	0.964 – 1.000	0.048*
Facility				
General ward	202	0.978	0.966 – 0.989	<0.001*
Oncology ward	32	0.970	0.945 – 0.996	0.025*
ICU	438	0.986	0.973 – 0.999	0.042*
Creatinine clearance category				
<60 ml/min	518	0.971	0.948 – 0.996	0.022*
60 ml/min or above	154	0.983	0.970 – 0.997	0.015*

*** = Statistically significant association**

Table 6: Results of multiple regression analysis for factors affecting the log plasma level of amikacin (n= 204)

Variables in the equation	Beta coefficient	95% CI of the beta coefficient	p value
Constant	3.313	2.595-4.032	<0.001*
Creatinine clearance in ml/min/1.7m^2	(-0.013)	(-0.016) – (-0.011)	< 0.001*
BMI (kg/m^2)	(-0.032)	(-0.051) – (-0.012)	0.011*
Daily dose in mg/kg	(-0.021)	(-0.042) – 0.001	0.057

* = Statistically significant association; CI = confidence interval

Table 7: Results of multiple regression analysis for factors affecting the log plasma level of gentamicin

Variables in the equation	Beta coefficient	95% CI of the beta coefficient	p value
Constant	1.600	0.268-2.931	0.019*
Creatinine clearance in ml/min/1.7m^2	(-0.014)	(-0.019) – (-0.009)	< 0.001*
BMI (kg/m^2)	(-0.031)	(-0.069) – (-0.007)	0.104*
Daily dose in mg/kg	(-0.003)	(-0.176) – 0.169	0.969

*** = Statistically significant association; CI = confidence interval**

Table 8: Results of multiple regression analysis for factors affecting the log plasma level of vancomycin

Variables in the equation	Beta coefficient	95% CI of the beta coefficient	p value
Constant	2.440	0.268-2.740	< 0.001*
Creatinine clearance in ml/min/1.7m^2	(-0.006)	(-0.007) – (-0.005)	< 0.001*
Female gender	0.086	0.023 – 0.150	0.008*
Daily dose in mg/kg	0.014	0.010 – 0.017	< 0.001*

*** = Statistically significant association; CI = confidence interval**

4. DISCUSSION

Accurate antibiotic dosing and meticulous dosage adjustment are crucial for effectiveness of therapy and minimization of toxicity. This study involved the analysis of the antibiotic monitoring database from a large referral center and it shows that a substantial proportion of concentrations fall outside the targeted ranges. This was true for initial as well as for repeated levels. The institution from which data was obtained is a tertiary care, 1000-bed hospital with a number of clinical excellence centers, an international accreditation and an established clinical pharmacy service. The results in the current study thus are likely to reflect the outcome of a fairly high level of care. Some previous studies in other areas of the world also reported high rates of trough concentrations outside the therapeutic range (Islahudin and Ong, 2014).

AGs and vancomycin are well known for the dependence of their clearance on the kidney and thus its relation to that of creatinine. Thus there are very clear dosing guidelines based on categorizing patients into levels of renal function according to their estimated creatinine clearance. Univaraiate regression models in this study however display a highly significant association between the non-optimum antibiotic concentrations obtained and the retrospectively estimated creatinine clearance for patients in the database. This clearly indicates that whatever adjustment was made was not sufficient to achieve targeted concentrations and that there is a big room for improvement. Although estimation of creatinine clearance is more or less a routine step before prescribing in institutions with a clinical pharmacy service, yet there may be variations among pharmacists in the way it is estimated. Variations may arise when deciding which body weight to use for

calculation, when old individuals with little muscle mass have very low creatinine levels, or when creatinine values are rapidly changing (Johnston et al., 2014). Even with ensuring standardization of such issues, the fact remains that patients within broad creatinine clearance categories are prescribed the same per kg dose.

Now that automated calculations and hand held applications have become a characteristic feature of our lives, more snug fitting of initial doses can be achieved for AGs and vancomycin based on individual patient characters, most importantly creatinine clearance. In the current study, it was not possible to derive a reliable model for dose tailoring of AGs due to the small number of samples. For vancomycin a model was derived that shows promise only in male patients with estimated creatinine clearance above 30 ml/min. Models like this one can be helpful in guiding initial doses based on creatinine clearance within the broad categories suggested by current guidelines. Benefit is particularly anticipated in patients with values of estimated clearance exceeding 100 ml/min.

Although vancomycin and AGs are among the oldest antibiotics, yet room for improving dose estimation for them still exists. Also reliance on creatinine clearance is very sensitive to the method of its estimation as indicated by Glatard et al. (2015) who found that using different methods of creatinine clearance estimation would result in different dose calculations for vancomycin (Charhon et al., 2012). The need for more meticulous estimation of vancomycin and AG dosing has been recognized by several authors and several attempts have been made for more customized individual dosing than is currently practiced. DeCock et al., (2014) for example, tried to study the impact of maturation of glomerular filtration on dosing of vancomycin and AGs from neonates to adulthood. Adane et al., (2105) studied extremely obese patients, Le et al., (2013) studied vancomycin dosing in children, Delattre et al., (2010) studied AGs in septic patients, and Lim et al., (2014) studied patients with MRSA infection. The current study included only adults but did not focus on a special group. Yet, splitting analysis by various patient categories showed more or less the same magnitude and direction of association of antibiotic concentrations and creatinine clearance and multiple regression eliminated almost all variables except for creatinine clearance as a determinant of the concentration. The results however point out that different calculation approaches should be used in females and also in those with creatinine clearance below 30 ml/min. It was attempted to use the data from the current study to construct a model to predict accurate estimates of vancomycin doses. The equation was applied to predict doses retrospectively in patients already on the database. It was found that those who would benefit from applying the equation were those with creatinine clearance around 30 ml/min or above 90 ml/min. Most of the former were given a dose bigger than that estimated and it resulted in a high vancomycin concentration. The opposite happened with those with creatinine clearance greater than 90, where smaller than estimated doses were given and the result was a low vancomycin concentration.

The general direction of the results is that vancomycin-treated patients with clearance less than 30 ml/min would require smaller doses than what's usually prescribed and those with clearance more than 90 require higher ones. In between those boundaries patients should be treated individually with finer dosing adjustments.

Some authors like Haesekeret al., (2016) argue that estimated creatinine clearance is not adequate to predict trough vancomycin levels and they advocate TDM instead. TDM however comes in after initial dosing and after results of steady state samples are available. Proper dose tailoring with initial dosing is still needed to guarantee the best therapeutic outcome.

Like other retrospective studies, this one has the limitation of possible data inaccuracies. The results however depend on only a few clinical parameters and since lab parameters of creatinine and antibiotic concentration are routinely and automatically electronically reported and stored, we can fairly trust their accuracy. Another problem is the possible variation in the timing of pre-dose concentration determination but as a general hospital policy they are strictly taken within half an hour from the next dose. Definitely a part of the difference between the observed antibiotic plasma levels and the optimum ones can be eliminated by more consistency in the creatinine clearance estimation practice, yet we assume that there would still be a big room for more accurate individualized dosing than what is currently practiced. The equations derived by this study represent only results from a single institution and are also a function of the constellation of characters of included patients. Patients with AG levels were also relatively few. This calls for prospective studies on a wider scale in parallel with attempting validation of the findings reported in the current study.

5. CONCLUSION

A substantial proportion of patients can benefit from snug tailoring of vancomycin and aminoglycoside doses based on creatinine clearance estimation. In addition to recommending more meticulous creatinine clearance estimation for all patients. The dataset in the current study suggests a model that can be validated in datasets from other populations and then may be used to guide dosing.

6. REFERENCES

Adane, E.D., Herald, M., Koura, F., 2015. Pharmacokinetics of vancomycin in extremely obese patients with suspected or confirmed Staphylococcus aureus infections.Pharmacotherapy. 35(2), 127-139.

Charhon, N., Neely, M.N., Bourguignon, L., Maire, P., Jelliffe, R.W., Goutelle, S., 2012. Comparison of four renal function estimation equations for pharmacokinetic modeling of gentamicin in geriatric patients.Antimicrob Agents Chemother. 56 (4), 1862-1869.

Cockcroft, D.W., Gault, M.H., 1976. Prediction of creatinine clearance from serum creatinine.Nephron 16 (1), 31-41.

De Cock, R.F., Allegaert, K., Brussee, J.M., Sherwin, C.M., Mulla, H., de Hoog, M., van den Anker, J.N., Danhof, M., Knibbe, C.A., 2014. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. Pharm Res. 31(10), 2643-2654.

Delattre, I.K., Musuamba, F.T., Nyberg, J., Taccone, F.S., Laterre, P.F., Verbeeck, R.K., Jacobs, F., Wallemacq, P.E., 2010. Population pharmacokinetic modeling and optimal sampling strategy for Bayesian estimation of amikacin exposure in critically ill septic patients. Ther Drug Monit. 32(6), 749-756.

Dowling, T.C., Comstock, T.J., 2005. QUANTIFICATION OF RENAL FUNCTION. In: DiPiro, J.T., Talbert, R. L. Pharmacotherapy: A Pathophysiologic Approach, Sixth Edition. MCGRAW-HILL Medical Publishing Division, the USA. pp. 774.

Du Bois, D., Du Bois, E.F., 1917. A formula to estimate the approximate surface area if height and weight are known. Arch Intern Med 17, 863–871.

Glatard, A., Bourguignon, L., Jelliffe, R.W., Maire, P., Neely, M.N., Goutelle, S., 2015. Influence of renal function estimation on pharmacokinetic modeling of vancomycin in elderly patients.Antimicrob Agents Chemother. 59(6), 2986-2994.

Haeseker, M., Croes, S., Neef, C., Bruggeman, C., Stolk, L., Verbon, A., 2016. Evaluation of Vancomycin Prediction Methods Based on Estimated Creatinine Clearance or Trough Levels. Ther Drug Monit. 38(1), 120-126.

Islahudin, F., Ong, H.Y., 2014. Appropriate vancomycin use in a Malaysian tertiary hospital based on current HICPAC recommendations. J Infect Dev Ctries. 15;8(10), 1267-1271.

Johnston, C., Hilmer, S.N., McLachlan, A.J., Matthews, S.T., Carroll, P.R., Kirkpatrick, C.M., 2014. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J ClinPharmacol. 70(5), 549-555.

Kang, J.S., Lee, M.H., 2009. Overview of therapeutic drug monitoring. Korean J Intern Med. 24(1), 1-10.

Le, J., Bradley, J.S., Murray, W., Romanowski, G.L., Tran, T.T., Nguyen, N., Cho, S., Natale, S., Bui, I., Tran, T.M., Capparelli, E.V., 2013. Improved vancomycin dosing in children using area under the curve exposure. Pediatr Infect Dis J. 32(4), e155-163.

Lim, H.S., Chong, Y.P., Noh, Y.H., Jung, J.A., Kim, Y.S., 2014. Exploration of optimal dosing regimens of vancomycin in patients infected with methicillin-resistant Staphylococcus aureus by modeling and simulation. J Clin Pharm Ther. 39(2), 196-203.

Moellering, R.C. Jr., 2011. Discovering new antimicrobial agents. Int J Antimicrob Agents. 37(1), 2-9.

NHS, 2016a. Guidelines for the Dosing and Monitoring of Gentamicin, Vancomycin and Teicoplanin from the NHS. http://www.ruh.nhs.uk/For_Clinicians/departments_ruh/Pathology/documents/haematology/Dosing_of_Gentamicin_Vancomycin_and_Teicoplanin.pdf. Accessed on 10th of Nov, 2016.

NHS, 2016b. Therapeutic Drug Monitoring from the NHS.https://www.surreyandsussex.nhs.uk/wp-content/uploads/2013/04/Gentamicin-Therapeutic-drug-monitoring.pdf. Accessed on 22 Nov, 2016.

WHO, 2016. World Health Organization. Global database on body mass index. (Updated 2016 May 21). http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed May 21, 2016.