UZ LEUVEN | LABORATORIUMGENEESKUNDE

CAT
Critically Appraised Topic

Dosisaanpassing van antibiotica, toepasbaarheid van beschikbare calculators
Dose adjustment of antibiotics, clinical use of software-based calculators

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CLINICAL BOTTOM LINE

The increasing prevalence of methicillin-resistant *S.aureus* and other penicillin-resistant Gram-positive infections led to a significant increase in vancomycin use since the 1980s. After initiation of vancomycin therapy, TDM must be performed in selected patients. Meta-analysis revealed that rational dose adjustments based on TDM leads to higher rates of clinical efficacy and decreased rates of nephrotoxicity. In this perspective, pharmacokinetic dose calculators could be very useful.

A literature search was performed and identified the following methodologies of software-based dose calculators; population analysis, linear regression, and Bayesian estimation. While there is an enormous lack of prospective and cost-effectiveness studies, the limited literature suggests that Bayesian methods have the largest potential for clinical use. During this study, an electronic survey was send to 46 Belgian laboratories. The response rate was 65% (30 participants from 30 laboratories). From the 18 labs that provide vancomycin dose suggestions based on TDM, five had experience with pharmacokinetic software tools. Dose suggestions without the use of pharmacokinetic software are provided by 16/18 laboratories. Of interest, three of them used software packages in the past but abandoned their use. Four labs did not express any interest for future implementation. However, nine other laboratories would consider using dose calculators in the future. According to the participants, software packages could lead to a significant increase in objectivity, standardization, and time-efficiency.

In conclusion, there is a need for user-friendly, cost-effective, LIS-integrated, and validated software packages that could be used by clinical laboratories for dose suggestions based on TDM results.

CLINICAL/DIAGNOSTIC SCENARIO

Vancomycin is most often used for *Staphylococcus spp*, *Streptococcus spp*, *Enterococcus spp*, and *C. difficile* infections. Initial dosages should be based on actual body weight and adjusted based on measured vancomycin serum concentrations and/or renal function. Vancomycin therapeutic drug monitoring (TDM) is warranted in patients receiving high doses, prolonged therapy, patients treated with concomitant nephro- or ototoxic agents, patients with renal impairment, and in hemodynamically unstable septic patients. Meta-analysis suggests that TDM results in significantly higher rates of clinical efficacy and decreased rates of nephrotoxicity. In a first part of the study, the current guidelines for vancomycin TDM in methicillin-resistant *S.aureus* infections were explored.

During critical illness or in specific patient populations (e.g. pediatric and obese patients), organ dysfunction might lead to changes in serum antibiotic concentrations. These changes can predispose

to clinical failure, antibiotic resistance, or toxic effects if doses are not adjusted in a rational manner. Therefore, a combination of TDM and pharmacokinetic dosing software might be useful to predict dosing needs for individual patients. Different equations, nomograms, and software algorithms have already been developed for individualized pharmacokinetic monitoring of vancomycin. In the second part, we described and evaluated the currently available dose calculators through an extensive literature search.

In the third part of the study, we evaluated the current use and/or need for software-based calculators in Belgian laboratories (incl. UZ Leuven). Data from the UZ Leuven were gathered from a query of the Laboratory Informatics System in November 2016. The effectiveness in reaching therapeutic through concentrations without the use of pharmacokinetic software was documented. In addition, an electronic survey was send to 46 Belgian laboratories to explore their interest in these software tools.

QUESTION(S)

1) *What are the current guidelines and recommendations on TDM for vancomycin therapy in S. aureus infections?*

2) *Which methods are available for individualized vancomycin dosing? Can the use of pharmacokinetic software improve clinical outcome?*

3) *How are guidelines and recommendations on vancomycin TDM implemented in Leuven and Belgium as a whole? Is there truly a need for software-driven approaches?*

SEARCH TERMS

1) *MeSH Database (PubMed): "Vancomycin[Mesh] AND (Bayes Theorem[Mesh] OR Software/therapeutic use[Mesh] OR Computer Simulation[Mesh] OR Linear Models[Mesh] OR Drug Dosage Calculations[Mesh]) AND Drug Monitoring[Mesh]) AND Humans[Mesh"].*

2) *PubMed Clinical Queries (from 1966; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi): Systematic Reviews; Clinical Queries using Research Methodology Filters (diagnosis + specific, diagnosis + sensitive, prognosis + specific)*

3) *Pubmed (Medline; from 1966), SUMSearch (http://sumsearch.uthscsa.edu/), National Guideline Clearinghouse (http://www.ngc.org/), (http://www.update-software.com/cochrane), Health Technology Assessment Database (http://www.york.ac.uk/inst/crd/htahp.htm)*

4) *UpToDate Online (2017): "Vancomycin: Parenteral dosing and serum concentration monitoring in adults".*

1) What are the current guidelines and recommendations on TDM for vancomycin therapy in S. aureus infections?

Pharmacokinetic and Pharmacodynamic properties

Vancomycin is a large cationic glycopeptide antibiotic that kills Gram-positive bacteria in a concentration-independent manner by forming a stable complex with C-teminal D-Ala–D-Ala residues of peptidoglycan precursors in the bacterial cytoplasmic membrane[1]. This prevents the use of the peptidoglycan precursor for cell wall synthesis. Steric hindrance induced by vancomycin also inhibits the glycosyltransferase and transpeptidase activities of penicillin-binding proteins (PBPs)[2]. Originally, in the 1960s and 1970s, it was classified as a second-line antibiotic due to impurities in the drug formulation leading to ototoxicity and nephrotoxicity[1].

The drug is administered intravenously with a standard infusion time ≥ 1h to minimize infusion-related adverse effects. Oral absorption is very limited. The drug is mostly excreted by glomerular filtration (> 80-90% unchanged) and has a poor tissue distribution. The volume of distribution is 0.4 – 1 L/kg[3]. Vancomycin has a half-life of 6-12 hours in patients with normal renal function[3]. Protein binding ranges from 10-50%. Only the unbound fraction diffuses into affected tissues and is microbiologically active. The pharmacokinetic profile can be characterized by a 2- or 3-comparment pharmacokinetic profile (Figure 1)[3]. It is slowly bactericidal and its activity can be affected by large bacterial inoculum sizes, changes in tissue distribution (e.g. during inflammation), and protein-binding effects. Its post-antibiotic effect is moderate (≤ 2h for *S. aureus*) and concentration-dependent[3].

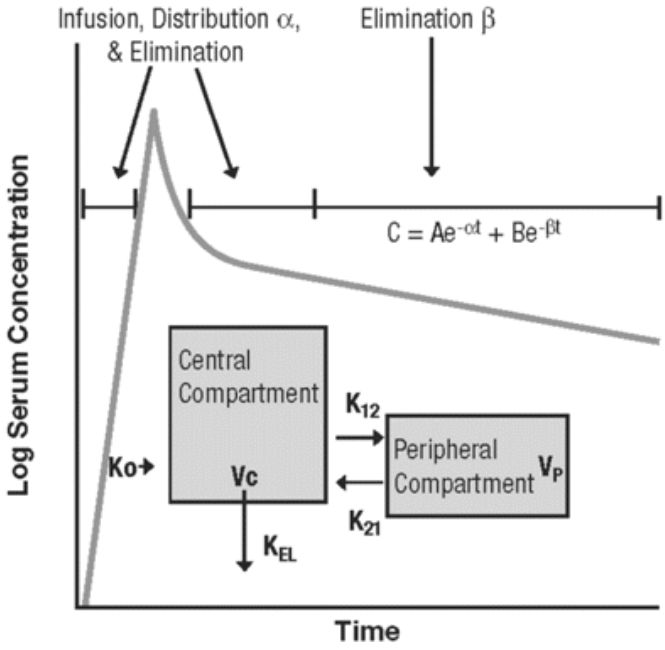

Figure 1. Schematic representation of a 2-compartment pharmacokinetic model. α and β: elimination constants; A and B: zero time intercepts for α and β; K_o: infusion rate constant; V_c: volume of the central compartment; V_P: volume of the peripheral compartment; K_{12} and K_{21}: intracompartmental rate constants; K_{EL}: elimination rate constant from the central compartment[3].

Recommended dosage regimens

Initial dosages should be based on actual body weight (ABW) and adjusted based on measured vancomycin serum concentrations and renal function[4]. An initial dose of 15 mg/kg given every 12 hours is recommended for adult patients with normal renal function when the MIC is ≤ 1 mg/L (Table 1)[5]. In children, initial doses of 10 mg/kg given on age-dependent dosing intervals are recommended (Table 2)[5]. However, in patients with normal renal function, a targeted AUC/MIC> 400 is not attainable with conventional dosing methods if the MIC ≥ 2 mg/L[4]. In such situations, use of an alternative therapeutic agent may be warranted. Due to its relatively long half-life, a loading dose of 25–30 mg/kg, rounded to the nearest 250 mg increment (max. 2000 mg), can be used in critically ill patients to rapidly achieve therapeutic concentrations. The drug should be infused over 30 minutes for each 500 mg increment (e.g. 500 mg over 30 minutes, 1000 mg over 1 hour)[4].

While vancomycin has a concentration-independent killing activity, continuous infusion (CI) has been suggested over intermittent infusion (II) to optimize serum vancomycin concentrations and improve effectiveness. A meta-analysis by Hao *et al.* found a significantly lower incidence of nephrotoxicity in patients receiving CI compared to patients receiving II (RR = 0.61 [0.47-0.80]). No significant difference in treatment failure and mortality was detected[6].

Regimen	≥ 90	89 - 60	59 - 30	29 -15	< 15	CRRT	CAPD
CI	30 mg/kg 24h	30 mg/kg 24h	20 mg/kg 24h	15 mg/kg 24h	15 mg/kg 48h	20 mg/kg 24h	15 mg/kg 48h
II	15 mg/kg q12h	15 mg/kg q12h	15 mg/kg q12-24h	15 mg/kg q24-48h	15 mg/kg q48-72h	15 mg/kg q12-24h	15 mg/kg q48-72h

Table 1. Dosage of vancomycin in adults with renal failure[5]. CAPD: Continuous ambulatory peritoneal dialysis; CI: Continuous infusion; CRRT: Continuous renal replacement therapy; II: Intermittent infusion.

Postmenstrual age	Postnatal age	Amount of drug per dose	Dosing interval	Comments
≤ 29 weeks	0 – 14 days	10 mg/kg IV	q18h	– Infusion over 60 minutes – Dose should be increased to 15 mg/kg/dose in patients with meningitis
≤ 29 weeks	> 14 days	10 mg/kg IV	q12h	
30 – 36 weeks	0 – 14 days	10 mg/kg IV	q12h	
30 – 36 weeks	> 14 days	10 mg/kg IV	q8h	
37 – 44 weeks	0 – 7 days	10 mg/kg IV	q12h	
37 – 44 weeks	> 7 days	10 mg/kg IV	q8h	
≥ 45 weeks	Any age	10 mg/kg IV	q6h	
-	Children	As in adults (Table 1)		

Table 2. Dosage in neonates and children with normal renal function[5].

Emergence of vancomycin resistance in *S. aureus*

Vancomycin is most often used for *Staphylococcus spp*, *Streptococcus spp*, *Enterococcus spp*, and *C. difficile* infections. The increasing prevalence of methicillin-resistant *S.aureus* (MRSA) and other penicillin-resistant Gram-positive infections in hospitals led to a significant increase in vancomycin use since the 1980s[1]. Few decades later, *Staphylococcus* and *Enterococcus spp* were described with reduced susceptibility to vancomycin. A timeline of the emergence of resistant strains is displayed in Figure 2.

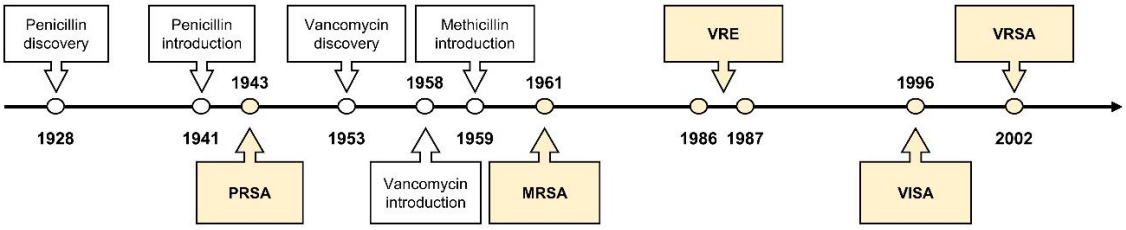

Figure 2. Timeline of the emergence of vancomycin resistant strains. Adapted from Hu et al[7]. PRSA: Penicillin resistant *S. aureus*; MRSA: Methicillin resistant *S. aureus*; VRE: Vancomycin resistant *Enterococcus spp*; VISA: Vancomycin intermediate *S. aureus*; VRSA: Vancomycin resistant *S. aureus*.

In May 1996, the first documented clinical infection with a vancomycin-intermediate *S. aureus* (VISA) strain was documented in a Japanese patient[8]. VISA strains are characterized by a vancomycin MIC of 4-8 mg/L. One year later, in 1997, the first report of an MRSA strain with heteroresistance to vancomycin (hVISA) appeared[9]. Heteroresistance is observed in MRSA strains with MICs as low as 1 mg/L[10]. Zhang *et al.* determined through a systematic review that the global pooled prevalence of hVISA and VISA was 6.05% in 99,042 MRSA strains and 3.01% in 68,792 MRSA strains, respectively[11]. VISA and hVISA exhibit common characteristics; thickened cell walls, reduced autolysis, and attenuated virulence[6]. The exact reason for emergence of these strains has not been fully elucidated but it is suggested that prolonged exposure to low serum concentrations of vancomycin leads to sequential acquisition of point mutants in key regulatory genes[12]. Therefore, it is not surprising that the majority of GISA infections occurred in patients receiving renal replacement therapy and suboptimal, prolonged, or repeated courses of vancomycin[13]. As high MIC values are associated with vancomycin treatment failure, monitoring for colonization or infection with (h)VISA strains seems warranted in patients often treated with vancomycin[14,15]. However, a consensus on the laboratory method to monitor these strains has not yet been reached and performance characteristics of the currently employed methods (e.g. E-test and Vitek2 testing) are variable[16].

Vancomycin-resistant *S.aureus* (VRSA) is a rare, multidrug-resistant bacterial strain of public health concern. VRSA strains are characterized by a vancomycin MIC ≥ 16 mg/L and were first described in 2002[7,17]. The mechanism for VRSA resistance is well characterized. VRSA arises when vancomycin resistance genes from VRE (e.g. the *vanA* operon located on a plasmid-born transposon) are transferred to *S. aureus*[17,18]. The *vanA*-encoded product enables VRSA to replace the D-Ala–D-Ala terminal dipeptide with D-Ala–D-Lac dipeptide, altering the binding target of vancomycin and leading to high level resistance[7]. The limited amount of VRSA cases, although possibly underestimated[19], suggests that *vanA*-mediated vancomycin resistance is significant but has not evolved or quickly spread. This could be attributed to the high fitness cost imparted by the *vanA* transposon[20].

Therapeutic drug monitoring

Table 3 summarizes the 2009 practice guidelines for vancomycin monitoring in adults with *S. aureus* infections. TDM is warranted in patients receiving high doses or prolonged therapy (> 3 days), patients treated with concomitant nephro- or ototoxic agents, patients with unstable renal function or renal replacement therapy, and in hemodynamically unstable septic patients[4]. Meta-analysis revealed that TDM resulted in significantly higher rates of clinical efficacy and decreased rates of nephrotoxicity[21]. No difference was found in the duration of vancomycin therapy[21].

Table 3. Practice guidelines for therapeutic monitoring of vancomycin treatment for *Staphylococcus aureus* infection in adult patients.

Summary	Recommendation	Evidence
Dosage	– Initial dosage calculated on the basis of actual body weight – Dosage adjustments based on actual serum concentrations – Continuous infusion is unlikely to significantly improve patient outcome compared to intermittent dosing	Level II - A
Monitoring peak vs. trough concentrations	– Through serum concentrations are the most accurate and practical – Through serum concentrations should be obtained at steady-state conditions, approximately just before the fourth dose	Level II – B
Avoidance of resistance development	– Through serum concentrations > 10 mg/L are recommended to avoid resistance development	Level III - B
Recommended through serum concentrations	– Through serum concentrations of 15-20 mg/L are recommended. – A loading dose of 25 – 30 mg/kg (ABW) can be considered. – The infusion period should be extended to 1.5 – 2 h when individual doses exceed 1 g	Level III – B Level III – B Level III – B
Vancomycin toxicity	– Vancomycin-induced nephrotoxicity = multiple high serum creatinine concentrations documented after several days of vancomycin treatment in the absence of another explanation	Level II – B
Toxicity reduction through the monitoring of serum concentrations	– Monitoring of peak serum concentrations is not recommended to decrease the incidence of nephrotoxicity – Monitoring through serum concentrations to reduce nephrotoxicity is suited for patients receiving aggressive dose targeting (15-20 mg/L) or who are at risk of toxicity – Monitoring through serum concentrations is recommended for patients with unstable renal function and for patients receiving a prolonged course of therapy (> 3 -5 days) – At least 1 steady-state through concentration (just before 4th dose) should be measured in patients receiving prolonged vancomycin treatment – Frequent monitoring (> 1 measurement) for short-course therapy (< 5 days) or lower-intensity dosing (serum through concentrations < 15 mg/L) is not recommended – The exact frequency of monitoring depends on the clinical presentation. One-weekly measurements suffice for hemodynamically stable patients, while frequent (often daily) monitoring is advised in hemodynamically unstable patients to prevent toxicity. – Monitoring through serum concentrations is not recommended to prevent ototoxicity.	Level I – A Level III – B Level II – B Level II – B Level II – B Level III – B Level III – B

Adapted from Rybak et al[4].

Monitoring of serum vancomycin concentrations is based on the need to achieve serum concentrations above a pre-determined fold-increase of the minimum inhibitory concentration (MIC) and the avoidance of potential adverse effects, including ototoxicity and nephrotoxicity. Vancomycin has a concentration-independent kill effect against *S. aureus.* The primary pharmacodynamic parameter to predict treatment success is the area under the concentration curve (AUC) divided by the MIC[22]. Moise-Broder et al. proposed a target AUC/MIC ≥ 400 for MRSA infections in adults[3,22]. A good correlation exists between the AUC and vancomycin through levels. This enables that vancomycin through levels, which are easier to obtain and measure than peak levels, can be used to predict the target AUC/MIC[4]. Through serum concentrations of 15-20 mg/L are recommended for complicated infections treated with intermittent dosing[4]. TDM Samples should be taken at pharmacokinetic steady state which should be reached right before the fourth dose[4]. In renal dysfunction, serum half-life is often prolonged and steady state may not yet be achieved after three doses[23]. For continuous dosing, a target concentration of 20-25 mg/L is needed to ensure the achievement of the same AUC as intermittent dosing[4].

Achievement of a target AUC/MIC ≥ 400 can be associated with adverse effects through large vancomycin doses (especially with *S. aureus* MIC values ≥ 1 mg/L). Nephrotoxicity rates induced by vancomycin are highly dependent on the evaluated population and range between 5% and 43%[24]. Meta-analysis revealed that high serum vancomycin concentrations (≥ 15 mg/l) are independently associated with nephrotoxicity (OR=2.67 [1.95-3.65])[24]. The probability of a nephrotoxic event increases as a function of trough concentrations, duration of therapy, and concomitant nephrotoxic agents (e.g. aminoglycosides)[3,24]. With respect to ototoxicity, more controversy exist as no clear association between (through) serum concentrations and ototoxicity has been demonstrated[25,26].

During critical illness, dysfunction of one or many organ systems might lead to changes in serum antibiotic concentrations. The range of altered pathophysiology in critically ill patients and their effects on drug concentrations are displayed in Figure 3. These changes can predispose to clinical failure, antibiotic resistance, or toxic effects if doses are not adjusted in a rational manner[27]. TDM measurement in combination with clinical dosing software, which use pharmacokinetic/ pharmacodynamic models derived from critically ill patients, can be useful to predict dosing needs for these patients[27].

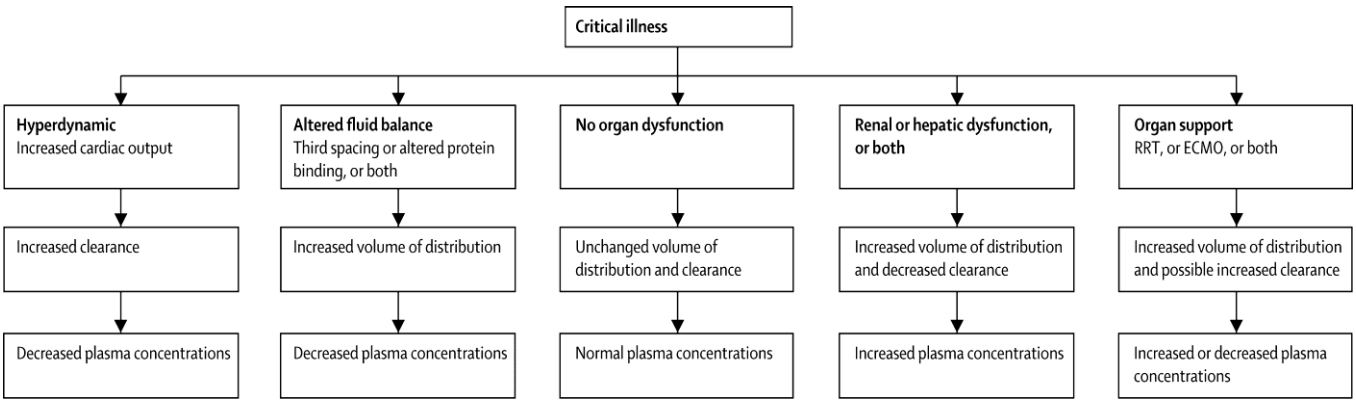

Figure 3. Changes in pathophysiology and their effect on drug concentrations in critically ill patients. Adapted from Roberts et al[27].

Changes in pharmacokinetic parameters can also be found in pediatric and obese patients. Lower vancomycin doses are used in neonates until renal function matures[5]. In infants and older children, the $t_{1/2}$ may be shorter than that of adults[28]. In obese patients, the volume of distribution is smaller and clearance of vancomycin is greater. This results in higher doses required to reach target through concentrations. Dosing using actual bodyweight is recommended and more frequent dosing may be useful[28].

Immunoassay is most widely used in clinical laboratories. At the moment, there is no date suggesting clinical superiority of any of the commercial available immunoassays[29]. However, a lack of between-method standardization and a high variability could lead to a significant bias when comparing different methods to each other[30,31]. Between-assay differences of up to 20% were documented[30,31]. A large range of results was also found during Belgian External Quality Evaluation schemes (2016/3 - CV = 9.5%) (Figure 4)[32]. Besides standardization issues, immunoassays can lack specificity. Cross-reacting substances (e.g. vancomycin degradation products) can interfere with some immunoassays[30,31]. A switch toward LC-MS/MS methodologies could prove beneficial in this aspect[33].

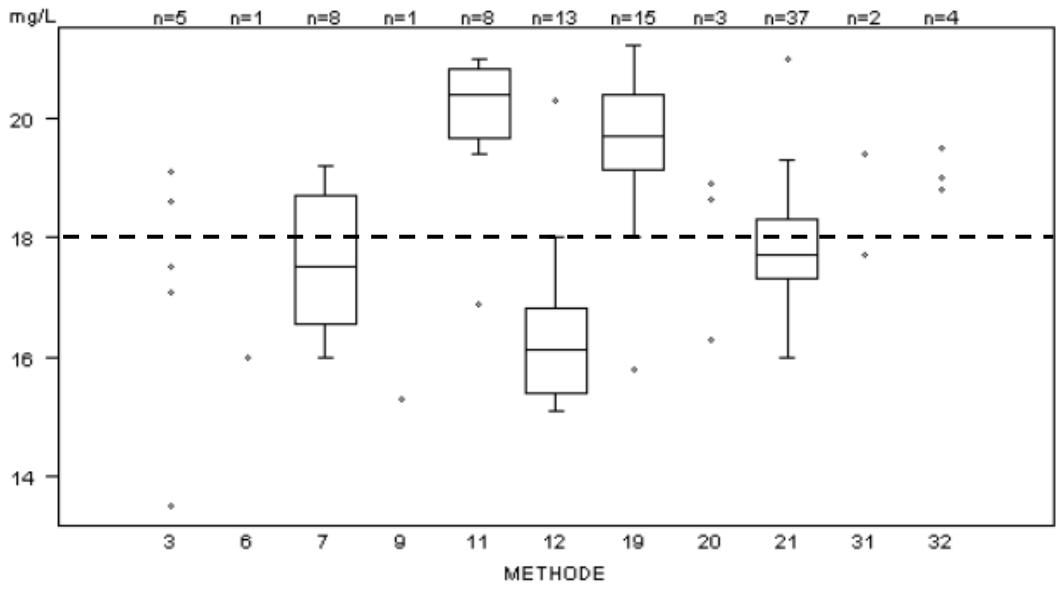

Figure 4. Belgian External Quality Evaluation scheme 2016/3: vancomycin TDM results. Different assay numbers are displayed in the x-axis. Results are presented as box-whisker plots. N= number of participating laboratories with the same assay. The median value of 18.00 mg/L is indicated by a broken line[32].

2) Which methods are available for individualized vancomycin dosing? Can the use of pharmacokinetic software improve clinical outcome?

Individualized dosing methods

Different equations, nomograms, and algorithms have been developed for individualized pharmacokinetic monitoring of vancomycin in patients. These methods can be categorized into 3 groups: population methods, linear regression analysis, and Bayesian estimation procedures[27]. Nomograms, formulas, and software screenshots can be found in Appendix 1.

Population methods

Population methods, also called *a priori* dosing methods or nomograms, determine individualized doses based on population estimates of pharmacokinetic parameters (e.g. V_d and clearance). While older nomograms target lower through concentrations, only two nomograms have been developed to obtain recommended through concentrations of 15-20 mg/L[34,35]. Initial starting doses can be increased or decreased based on patient-specific parameters (e.g. weight or Cr_{CL}) to ensure that measured steady-state serum concentration will be in the therapeutic range. These nomograms are easy to interpret, require no pharmacokinetic knowledge, and limit the use of resources (e.g. personnel and/or computers)[27]. Disadvantages are that patient parameters must remain stable (e.g. creatinine variation <20%), they are rarely designed specifically for critically ill patients, and they rely on the clinicians' experience in interpreting them[27].

Linear regression analysis

Linear regression analyses are classified as *a posteriori* drug dosing methods. They assume a 1-compartment model and calculate pharmacokinetic parameters (e.g. V_d and $T_{1/2}$) from at least two measured serum concentrations. Accurate details of dose, level, time of infusion, time of sampling, and duration of infusion are required[27]. Values of the pharmacokinetic parameters are then used in a next set of formulas to calculate individualized dosing regimens (dose and dosing interval) to achieve therapeutic drug concentrations[36]. Although being relatively simple, these methods are based on two important assumptions. First, they employ serum concentration data from a single dosing interval and discard all previous information on serum concentrations. Second, they cannot account for other factors such as changing renal function[27].

The most cited nonlinear regression method is the Sawchuk-Zaske method[36]. Originally developed for intravenous gentamicin dosing regimens in burn patients, it was later adapted for several other antibiotics (incl. vancomycin) and served as input for different software-based methods. Pharmonitor, first described by Leal et al. for aminoglycoside dosing[37], implements the Sawchuk-Zaske formulas into a user-friendly software package. Ideally, measurements are performed in steady state in patients with stable renal function, patients older than one year, and patients with at least two serum TDM determinations[37]. The software was updated in 2010, with support from the Scientific Institute of Public Healthy (ISP-WIV), and freely distributed to all Belgian laboratories involved in TDM[38].

Bayesian estimation

A Bayesian approach incorporates both the population model (*a priori*) and the pharmacokinetic model (*a posteriori*). It calculates pharmacokinetic parameters and dosage adjustments based on 1 or 2 serum concentrations[27]. To put it simply, Bayesian software modifies an individual patient's *a priori* model to

derive a more individualized *a posteriori model* in response to different input parameters[27]. Bayesian methods often include analysis of sequential serum data, changes in patient pharmacokinetic parameters, and the experimental error associated with TDM measurements. In the beginning, computer software based on Bayesian statistics often lacked flexibility and were too time consuming for use in a routine TDM setting. However, several software packages that allow simple, fast, and accurate Bayesian pharmacokinetic calculations have recently been developed and have already proven their use in several clinical settings[28].

Bayesian software can calculate doses based on a single-serum concentration and predict an appropriate starting dose based on patient information. Individualized calculations of the starting dose could improve the timeliness of achieving therapeutic serum concentrations prior to steady state[28]. Disadvantages are that they often require healthcare practitioners with specialized pharmacokinetic knowledge and the input of patient parameters that, without integration into the electronic health records (EHR), are difficult and cumbersome to gather (e.g. weight, height, age, Cr_{CL}, and dose regimen information)[28].

Benchmarking of available software packages

A benchmark of TDM software was performed in 2013 by Fuchs *et al.*[39]. A thorough literature and internet search identified 12 software tools. All programs were scored on a standardized grid covering pharmacokinetic relevance, user friendliness, computing aspects, interfacing, and storage. A weighing factor was applied to account for the relative importance of each criterion. A summary of evaluated tools and their rank can be found in Table 4. The best two programs emerging from this benchmark were MwPharm (http://www.mediware.cz) and TCIWorks (http://www.tciworks.info)[39]. The other programs had good potential while being less sophisticated or user friendly. Of note, programs vary in complexity and might not fit in all healthcare settings[39].

While the benchmark by Fuchs et al. was published in 2013, several of the described software packages are not available anymore or lack further support by the company[39]. Most of these software tools still require thorough knowledge of pharmacokinetic principles for data entry and interpretation. Moreover, there is an enormous lack of prospective and cost-effectiveness studies that demonstrate the usefulness of Bayesian software tools[40]. There is an urgent need for user-friendly, cost-effective, EHR-integrated, and validated software packages. Several companies are starting to address this need and are working on solutions that will be available in next the coming years (e.g. Insight RX, DoseMe, and AutoKinetics)[40].

Besides software packages, open-access websites provide another option for individualized patient dosing. A study by Fewel compared the open-access website Vancomycin-Calculator.com to 3 similar websites that were able to calculate initial doses and did not require software downloads; GlobalRPh.com, ClinCalc.com, and SurgicalCriticalCare.net[41]. All websites calculated similar results for patients with normal body weight[41]. SurgicalCriticalCare.net calculated significantly different doses for underweight and obese patients vs. other websites. Vancomycin-calculator.com, which is based on the Bauer PK method for obese patients[42], was the only website to calculate practical doses for obese patients[41]. No evaluation of clinical efficacy was made during this study[41].

Evidence

Several studies have investigated whether software tools are beneficial for individualized vancomycin therapy. Results from these studies are summarized in Table 5.

A total of 8 studies determined the performance of these tools in predicting future serum concentrations. Correlations between observed and predicted (through) concentrations at steady state were good ($r > 0.80$)[34,37]. The mean prediction error (ME), a measure of bias, was not significantly different from zero in 2/3 studies that provided 95% CI intervals[45,47,48]. Values were smaller than 1.0 mg/L in all other studies reporting ME values. ME values were usually <0, suggesting that the software underestimates the observed serum concentration.

Only 2 prospective studies were found that investigated clinical outcome. The Kullar nomogram was able to reach through concentrations of 15-20 mg/L in 58% of the 200 evaluated patients at the first steady state measurement. Of note, 77% of patients eventually reached the through serum concentration within a median of 48 hours[35]. Pea et al. compared Bayesian forecasting software with a nomogram for dose adjustment in 2 groups of 16 patients receiving intermittent vancomycin infusions. All 16 patients in the Bayesian estimation group reached a mean through value of 5 - 10 µg/ml (= old standard) compared to 43.75% of the nomogram group[42].

Table 4. Benchmark of TDM software for vancomycin dosage regimens.

	MM-USCPack	Mw-Pharm	TCIworks	JKPD	TDM for R	Antibiotic Kinetics	APK	Kinetics	Kinetidex	TDMS 2000	Data Kinetics	RAD kinetics
General characteristics												
User interface	10	4	7	6	11	3	**1**	2	5	9	8	12
Interfacing	5	**1**	5	5	5	2	2	2	5	5	5	5
Storage	7	**1**	8	10	10	10	2	2	5	6	4	9
Report	10	**1**	7	8	12	9	2	2	6	6	4	10
Cost	4	8	3	6	6	5	**1**	**1**	12	8	10	11
Computational	3	4	**1**	2	10	5	5	5	11	9	5	12
Total	10	3	4	9	11	7	**1**	2	6	8	5	12
Pharmacokinetic aspects												
Populations	7	**1**	6	2	11	9	3	8	5	4	10	12
Models	**1**	3	2	9	10	8	7	6	4	5	11	12
Modularity	7	8	**1**	1	11	4	4	4	3	9	11	10
Plot	**1**	3	2	10	11	6	6	6	3	3	6	11
Various	9	2	7	11	11	5	5	8	4	3	**1**	11
Total	2	**1**	3	9	11	8	6	7	4	5	10	12
Authors												
Expertise	**1**	**1**	3	9	9	6	6	6	12	5	4	9
Global score	5	**1**	2	10	11	8	3	4	7	6	9	12
Software												
Bayesian analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Starting dose	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No
Cost	595$	1530$	Free	Free	Free	125$	150$	250$	1520$	600$	900$	100$
Still available	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Website	lapk.org/ software	mediware. cz	tciworks. info	pkpd.kmu.edu.tw/jpkd	pkpd.kmu.edu.tw/tdm	Rxkinetics.com			truvenhealth.com	tdms2000. com	-	Showcase.netins.net/web/radman

Adapted from Fuchs et al[39].

All data given as weighted score (rank). Rankings were given from 1 for the best classified to 12 for the worst classified.

Table 5. Individualized vancomycin dosing by software prediction methods: Clinical outcomes and predictive performances

	Method	Study	Patients	Goal	Results	
Clinical outcomes						
Kullar et al [35] 2011	Population nomogram ≈ Kullar nomogram	Prospective Multicenter	200 adults All treated Intermittent	Through concentration 15 – 20 mg/L reached at steady state (%)	– 15-20 mg/L = 58% initial – 13-22 mg/L = 80% initial	
Pea et al [43] 2002	A. Bayesian estimation ≈ Abbot PKS system* B. Population nomogram ≈ Moellering's nomogram	Randomized Prospective Multicenter	2 x 16 adults ICU Intermittent		Bayesian	Nomogram
				Mean C_{max} 20-40 µg/ml (%)	50 %	50 %
				Mean C_{min} 5-10 µg/ml (%)	100%	43,75%
Predictive performance						
Pea et al [34] 2009	Population nomogram ≈ Pea nomogram	Prospective Monocenter	63 adults Critically ill Continuous	Correlation between observed and predicted C_{ss}?	r = 0.80 (p < 0.001)	
Nunn et al [44] 2011	Bayesian estimation ≈ USC*PACK*	Prospective	All treated Non-ICU Intermittent	Comparison predicted vs. observed C_{min}	ME = -0.11 mg/L (IQR: not given) MAE = 2.8 mg/L (IQR: 1.41, 4.75)	
Hiraki et al [45] 2010	Bayesian estimation ≈ VCM-TDM version 2*	Retrospective	22 adults Stable renal Intermittent	Comparison predicted vs. observed C_{min}	ME = -0.81 µg/ml [-0.96, -0.67] MAE = 1.38 µg/ml [1.28, 1.49]	
Hurst et al [46] 1990	Bayesian estimation ≈ USC*PACK*	Retrospective	27 adults Unstable renal Intermittent	Comparison predicted vs. observed C_{min}	ME = -0.7 ± 5.3 µg/ml MAE = 3.6 ± 4.5 µg/ml	
Leal et al [37] 1991	Linear regression ≈ Pharmonitor	Prospective	52 (> 1 year) Stable renal Intermittent	Comparison predicted vs. observed C_{min} after adjustment	y = 1.05 (± 0.04) x + 0.78 (± 3.3)	
Llopis-Salvia et al [47] 2006	Bayesian estimation ≈ Abbot PKS system*	Retrospective	20 adults Critically ill Intermittent	Comparison predicted vs. observed C_{min}	ME = -0.22 mg/L [-2.83, 2.39] MAE = 3.87 mg/L [2.58, 5.16]	
Andrés et al [48] 1997	Bayesian estimation ≈ Abbot PKS system*	Retrospective	79 adults Intermittent	Comparison predicted vs. observed C_{ss}	ME = -0.54 ± 2.44 [-1.10, 0.02] MAE = 1.74 ± 1.79 [1.33, 2.15]	
Rodvold et al [49] 1994	Bayesian estimation ≈ Abbot PKS system*	Retrospective	27 adults Stable renal Intermittent	Comparison predicted vs. observed C_{min}	ME = 0.92 ± 6.41 mg/L MAE = 5.37 ± 3.46 µg/ml	

C_{ss} = Steady state plasma concentration; C_{min} = Through serum concentration; ME = Mean prediction error, a measure of bias; MAE = Mean absolute prediction error, a measure of accuracy; RMSE = Root mean squared prediction error, a measure of precision. *: Tool no longer available.

3) How are guidelines and recommendation on vancomycin TDM implemented in Leuven and Belgium as a whole? Is there truly a need for software-driven approaches?

The UZ Leuven experience: TDM results

198 patients that were started on vancomycin therapy and in whom TDM was performed between 1 and 31 November 2016 were retrospectively identified through the UZ Leuven hospital pharmacy. No patients were excluded from the study. Vancomycin serum concentrations were determined on the HITACHI/Roche COBAS c702 system. An intermittent dosing regimen of 2x1 g IV is proposed for adults with normal renal function at the UZ Leuven. For children, a dose of 4x40 mg/kg IV is suggested for most infections (- meningitis) while a higher dose of 4x60 mg/kg IV is recommended in meningitis episodes. TDM sampling is recommended right before administration of the 4th dose (steady-state).

Figure 5A displays the frequency distribution of mean through concentrations in 195 patients receiving intermittent vancomycin infusions. A total of 989 serum samples were analyzed with a median of 3 samples/patient (range: 1-30 samples). A through concentration of 15 mg/L is suggested as the optimal value for intermittent dosing at UZ Leuven, no reference interval is provided. The mean value of all 989 serum samples was 15.66 ± 6.21 mg/L. A mean through concentration of 15-20 mg/L was reached in 37.95% of the sampled patients[4]. A mean value <15 mg/L was found in a higher percentage of patients (48.72%) than >20 mg/L (13.33%). Taking into account possible variations of the assay system, 62.56% of mean values were within in an interval of 13-22 mg/L. Interestingly, 38.97% of patients never reached a through serum concentration of 15-20 mg/L during the observation period.

Figure 5B displays the frequency distribution of continuous infusion serum concentrations in 19 patients (16/19 patients also had requests for intermittent TDM during the course of their therapy). Erroneous test requests could not be excluded through this query (e.g. continuous infusion TDM incorrectly requested as intermittent infusion TDM). Therefore, it remains unclear whether this number reflects the total number of continuous infusions in our hospital. A total of 57 serum samples were analyzed with a median of 2 samples/patient (range: 1-17 samples). A reference interval of 15-25 mg/L is suggested for continuous dosing at UZ Leuven. The mean value of all 57 serum samples was 20.79 ± 7.82 mg/L. The reference interval was reached in 63.16% of patients and increased only slightly by expanding the reference interval to 13-27 mg/L (68.42%). No clear difference was found in the number of patients with a mean concentration <15 mg/L (21.05%) and >25 mg/L (15.79%). Six out of 19 patients never reached a serum concentration of 15-25 mg/L during the observation period.

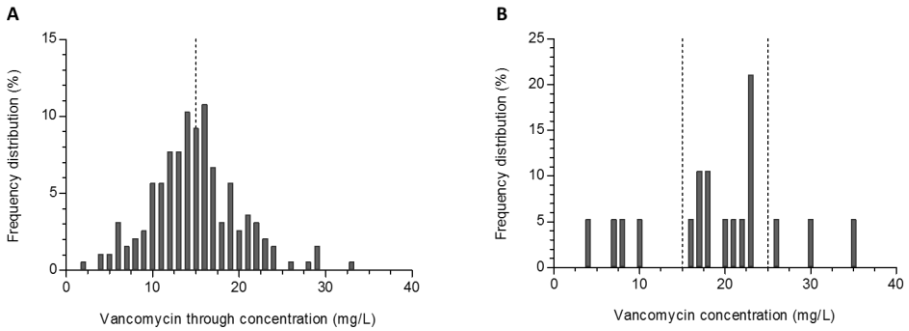

Figure 5A. Frequency distribution of mean through concentrations in November 2016 in 195 patients (989 serum samples) receiving intermittent dosing. **5B.** Frequency distribution of mean serum concentrations in 19 patients (57 serum samples) receiving continuous infusion. The UZ Leuven reference values of ± 15 mg/L and 15-25 mg/L are indicated by broken lines.

Dosage suggestions were provided for 458/1046 (43.8%) TDM samples. No specific calculators or software packages were used. The percentage of samples was determined in which the clinician followed the laboratories advice and adjusted the vancomycin dose in the next 48 hours. The dose was adjusted based on our dose suggestions in 32.6% of the evaluated 458 samples. Vancomycin therapy was stopped in 13.6% of samples after the TDM measurement. Clinicians made dose adjustments based on their clinical judgment in the remaining 53.8%. The exact reason for the low percentage of followed dose suggestions is unclear. The turn-around-time (TAT) was investigated as a possible contributing factor. The median total TAT (from sample receipt to dose suggestion) was 5h6min (IQR: 2h56min-8h27min). The median TAT for TDM results was 37min (IQR: 34min-46min) while the median TAT for interpretation of TDM results and dosage suggestion was significantly longer (4h24min, IQR: 2h5min-7h48min). As the next dose is often given 12h later (except in patients in whom vancomycin is given three or four times a day), it remains undetermined if this long TAT impacts the clinical decision making.

The Belgian experience: Electronic survey results

To assess the current situation on vancomycin TDM in Belgium, an electronic survey was send to 49 clinical biologists from 46 different Belgian hospital laboratories on 7 February 2017. The response rate was 65% (30 participants from 30 laboratories). Questions are displayed in Figure 6.

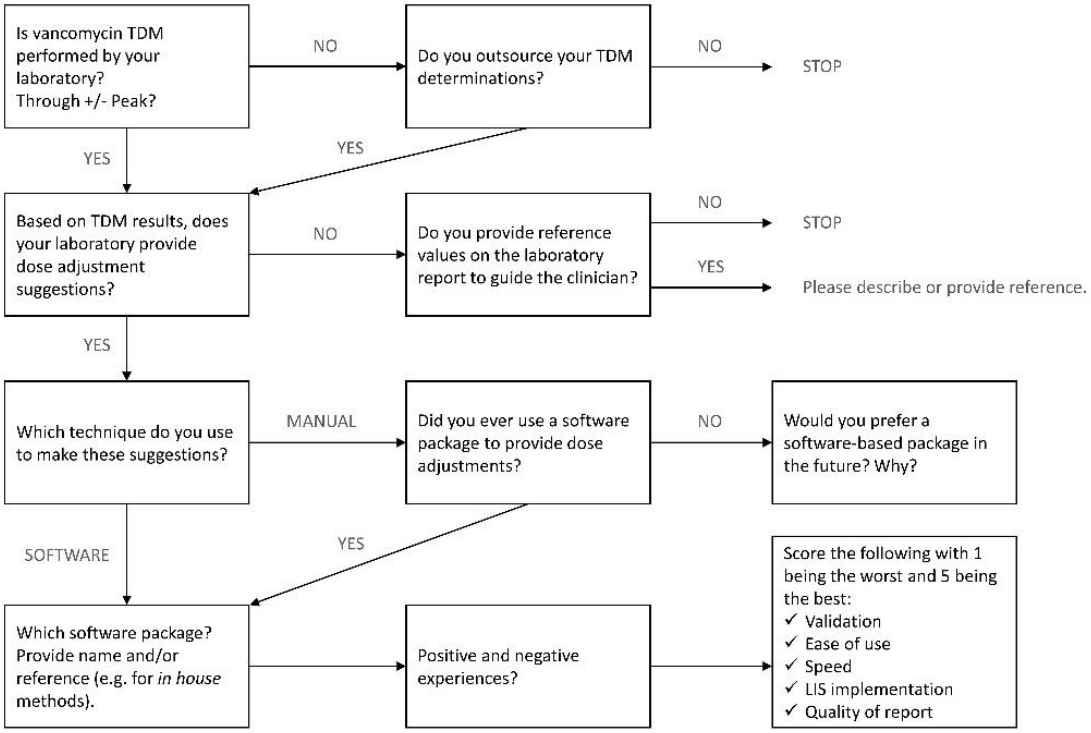

Figure 6. Survey questions on vancomycin dose suggestions in Belgian laboratories

TDM vancomycin measurements were performed in 28/30 laboratories. Most laboratories measured both peak and through concentrations (16/28), whereas 11/28 measured only through concentrations. One laboratory did not measure peak and through but determined concentrations solely for continuous infusions. Seven other labs also performed TDM for continuous infusions (total 8/28). Dose

suggestions were provided for all TDM samples by 18/28 laboratories. Most labs (16/18) are currently not using specific software tools for dose suggestions. Others provide dose suggestions in collaboration with other hospital departments (5/28) or when asked by the clinician (3/28).

Reference ranges for through concentrations were provided by 21 labs (range: 5-35 mg/L). Five laboratories reported reference values from the Sanford guide (15-25 mg/L and 25-35 mg/L for uncomplicated and complicated infections, respectively)[5]. Eleven laboratories follow the Rybak 2009 guidelines (10-15 mg/L and 15-20 mg/L for uncomplicated and complicated infections, respectively)[4]. Nine laboratories provided reference ranges for peak concentrations (range: 20-50 mg/L). There was no clear consensus; the mostly used reference intervals were 20-40 mg/L (2x) and 20-50 mg/L (2x). Reference ranges for continuous infusion were given by 21 laboratories. The Sanford guide was referenced in 3/21 laboratories (20-25 mg/L and 25-35 mg/L for most and complicated infections, respectively)[5] . The mostly used reference interval was 20-35 mg/L (11x).

From the 18 laboratories that provide dose suggestions, five of them had previous experience with pharmacokinetic software tools. Two laboratories are currently using the Pharmonitor software while three others labs have used it in the past. Two laboratories have stopped using it due to malfunctioning software (1x) and a switch from intermittent to continuous infusion (1x). One laboratory switched to an Excel based formula that was validated using Pharmonitor. Users have praised the quality of the Pharmonitor reports, its user-friendliness and its validation in literature. The following disadvantages were reported: only usable with 2 concentrations in the same dosing interval, difficulties in LIS implementation, and its predictive performance is highly dependent on the accuracy of sampling and the provided sample information. No other software package were used by the participating laboratories.

Sixteen laboratories are currently providing dose suggestions without the use of pharmacokinetic software tools. Three laboratories did use software in the past but abandoned their use (reasons were described earlier). Four labs did not express any interest for future implementation. Nine laboratories expressed their interest and would consider using them under the following conditions: presence of an easy to use interface, compatible with the LIS, practically usable dosage suggestions, uniformity for different disease states, validated in literature, and compatibility with different patient groups. The following advantages were suggested for software implementation: objectivity, standardization, and a possible time-benefit.

Table 6. Results of the electronic survey on vancomycin TDM in Belgium.

	Laboratories n = 30
TDM performed by laboratory	28
– Through only	11
– Peak and through	16
– Continuous infusion separately	8
Reference values	
– Through reference values – Sanford edition 2010[5] – Rybak et al. 2009[4]	21 5 11
– Peak reference values	9
– Continuous reference values – Sanford edition 2010[5] – 20-30 mg/L	21 3 11
Dose suggestions proposed	
– Yes	18
– Manual	16
– Software-based in the past	3
– Software-based currently	2
– No	4
– When asked by clinician	3
– In collaboration with other departments (e.g. hospital pharmacy)	5

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COMMENTS

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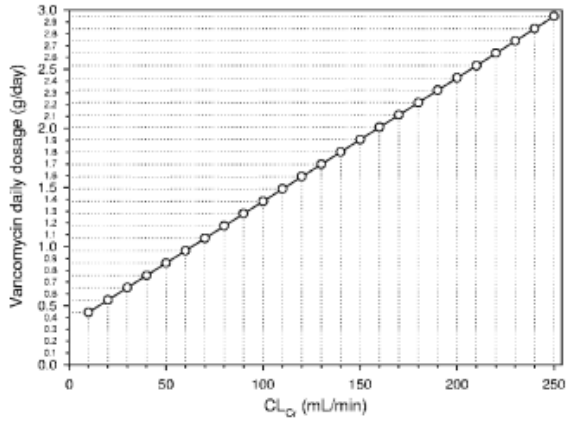
TO DO/ACTIONS

1) The time between start of the therapy and achievement of therapeutic through concentrations (± 15 µg/ml) will be determined in all patients started on vancomycin therapy in November 2016 at the UZ Leuven. The number of through serum concentrations obtained at steady-state conditions (= after the 3rd dose, right before administration of the 4th dose) will also evaluated. Age, gender, renal function, vancomycin through serum concentrations, and dose suggestions of all patients will be extracted from the Laboratory Informatics System for investigation of confounding factors. At the time of writing, queries are in process.

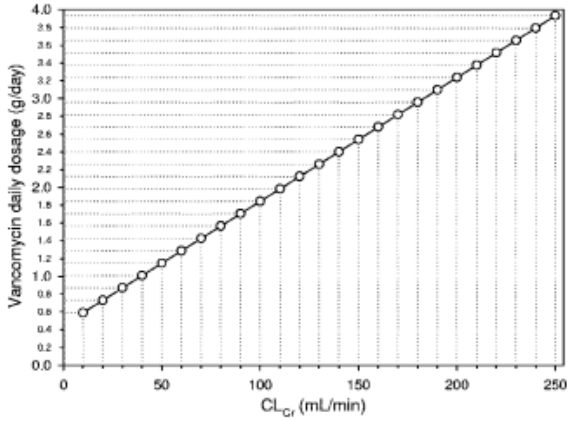
ATTACHMENTS

Pea nomogram[34]

Nomogram based on Cl_{CR} estimates for calculation of the vancomycin daily dosage administered by continuous infusion which is needed for achievement of the target through serum concentration of 15 mg/L in critically ill patients.



Nomogram based on Cl_{CR} estimates for calculation of the vancomycin daily dosage administered by continuous infusion which is needed for achievement of the target through serum concentration of 20 mg/L in critically ill patients.



Kullar nomogram[35]

Doses ≥ 2 g should be infused over 2 hours; doses of 1.5 g should be infused over 90 minutes. Weight refers to total weight. Creatinine clearance was calculated by usin th Cockcroft-Gault equation.

		Creatinine Clearance (ml/minute)						
		40–49	50–59	60–69	70–79	80–89	90–99	≥ 100
Weight (kg)	50–54	500 mg q12h	750 mg q12h	1000 mg q12h	750 mg q8h	1000 mg q8h	1000 mg q8h	1250 mg q8h
	55–59	750 mg q12h	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1000 mg q8h	1250 mg q8h
	60–64	750 mg q12h	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h
	65–69	750 mg q12h	1000 mg q12h	1250 mg q12h	1000 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h
	70–74	750 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1500 mg q8h
	75–79	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h
	80–84	1000 mg q12h	1250 mg q12h	1000 mg q8h	1250 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h
	85–89	1000 mg q12h	1250 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
	90–94	1000 mg q12h	1500 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
	95–99	1250 mg q12h	1500 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
	100–104	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2000 mg q8h
	105–109	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2250 mg q8h
	≥ 110	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2250 mg q8h

Sawchuk-Zaske formulas[36]

1. Calculation of PK parameters

$$t_{1/2} = \frac{\ln(2)}{k_e}$$

$$Vd = \frac{K}{k_e} \times \frac{(1 - e^{-k_e \times t_{inf}})}{(C_{max} - C_0 \times e^{-k_e \times t_{inf}})}$$

$$CL = Vd \times k_e$$

$t_{1/2}$ = Elimination half-life (h)
K_e = Elimination rate constant (h^{-1})
Vd = Volume of distribution (L)
K = Infusion rate (mg/h)
T_{inf} = infusion duration (h)
C_{max} = Maximal concentration extrapolated at the end of infusion (mg/L)
C_0 = Minimal concentration obtained from the previous dosage regimen (mg/L)
CL = Total boday clearance (L/h)

2. Calculation of the optimal theoretical dose and interval

$$\tau = \frac{-1}{k_e} \times \ln\left(\frac{C_{min\,target}}{C_{max\,target}}\right) + t_{inf}$$

$$Dose = t_{inf} \times C_{max\,target} \times Vd \times k_e \times \frac{(1 - e^{-k_e \times \tau})}{(1 - e^{-k_e \times t_{inf}})}$$

τ = Interval of administration (h)
$C_{min\ target}$ = Target minimal concentration (mg/L)
$C_{max\ target}$ = Target maximal concentration (mg/L)
Dose is expressed in mg

3. Calculation of predicted peak and through concentrations corresponding to the calculated dosage regimen

$$C_{max} = \frac{K_{desired}}{Vd \times K_e} \times \frac{(1 - e^{-k_e \times t_{inf}})}{(1 - e^{-k_e \times \tau_{desired}})}$$

$$C_{min} = C_{max} \times e^{-k_e \times (\tau_{desired} - t_{inf})}$$

$K_{desired}$ and $\tau_{desired}$ = Desired infusion rate (mg/h) and interval of administration (h)

Pharmonitor screenshot[37,38]