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SOFTWARE-ASSISTED TDM SERVICE: A LOW-HANGING FRUIT FOR THE CLINICAL PHARMACIST

Polonca Drofenik, clinical pharmacist
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Conflict of interest

- None to declare

A single drug concentration?

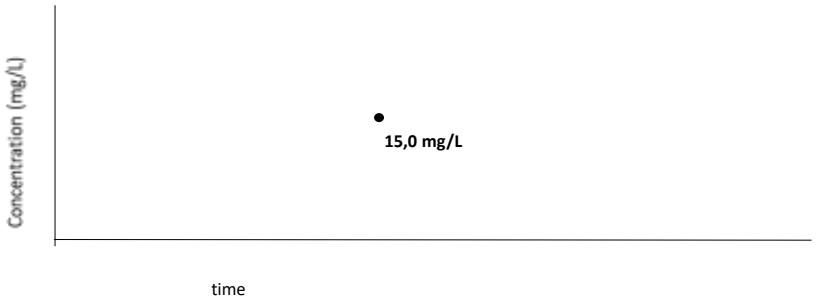
C (Vancomycin) = 15,0 mg/L

A single drug concentration?

C (Vancomycin) = 15,0 mg/L

- Patient‘s parametres
- Renal function
- Dosing history
- Kind of infection
- Pathogen‘s susceptibility

A single drug concentration?



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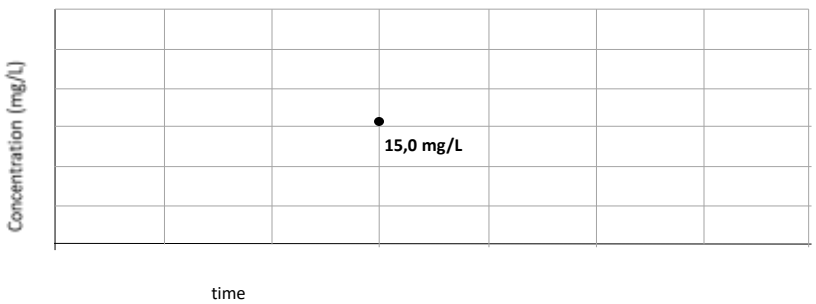
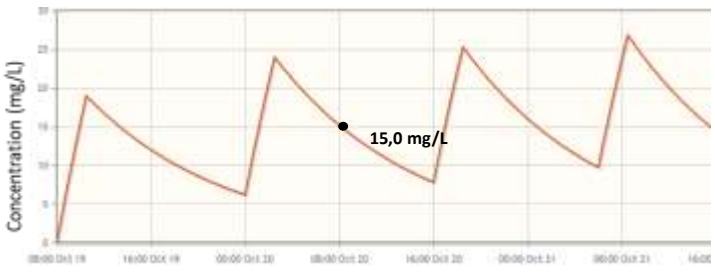


Steady state?

Is it a trough concentration?



Is a PK/PD target reached?

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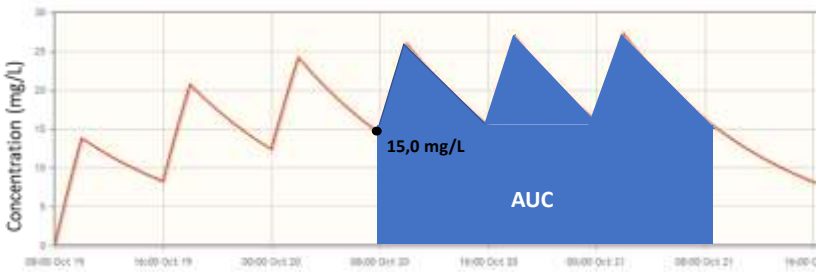
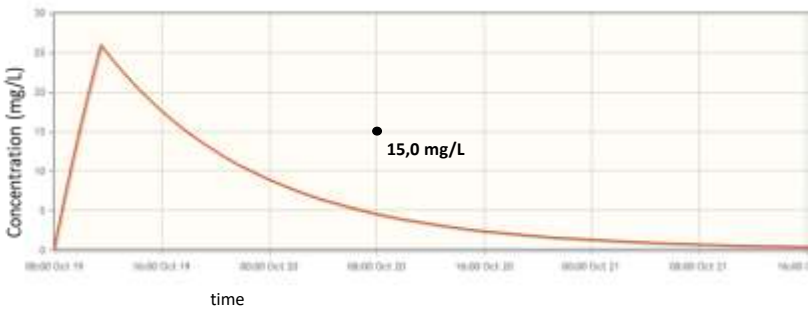


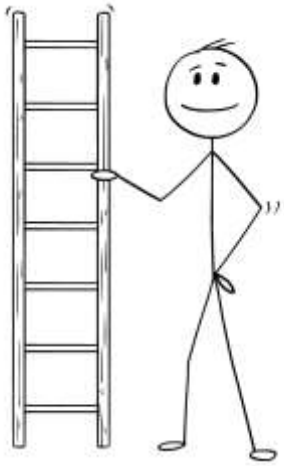
Does it make sense?



If you look at the lab result

Vancomycin (mg/L)	Ref. (mg/L)
15,0	10,0 – 20,0

Why us?



Which patients, which drugs?

Focus on:

- Infectious diseases
- Narrow therapeutic index
- Critically ill
- Special patient populations

Evaluation of Renal Drug Dosing:
Prescribing Information and Clinical Pharmacist Approaches

(Pharmacotherapy 2010;30(8):776–786)

PHARMACOTHERAPY Volume 30, Number 8, 2010

Table 6. Pharmacist Survey Item 7: Rank Order of Top 10 Drugs for Which Renal Dosage Adjustments Were Recommended by Clinical Pharmacists

Rank	Drug	No. (%) of Critical Care Pharmacists (n=149)	Drug	No. (%) of Nephrology Pharmacists (n=55)
1	Piperacillin-tazobactam	141 (94.6)	Vancomycin	42 (76.4)
2	Vancomycin	126 (84.6)	Piperacillin-tazobactam	37 (67.3)
3	Ciprofloxacin, levofloxacin	125 (83.9)	Gentamicin, tobramycin	34 (61.8)
4	Gentamicin, tobramycin	124 (83.2)	Enoxaparin	29 (52.7)
5	Imipenem, meropenem, doripenem, ertapenem[a]	115 (77.2)	Imipenem, meropemen[a]	26 (47.3)
6	Enoxaparin	95 (63.8)	Ciprofloxacin	22 (40.0)
7	Cefepime	70 (47.0)	Gabapentin	17 (30.9)
8	Famotidine	56 (37.6)	Ganciclovir, valganciclovir	16 (29.1)
9	Fluconazole, voriconazole[b]	45 (30.2)	Cefepime	14 (25.5)
10	Ampicillin-sulbactam	31 (20.8)	Levofloxacin	14 (25.5)
11	Cefazolin	31 (20.8)	Acyclovir	12 (21.8)
12	Metoclopramide	29 (19.5)	Famotidine	12 (21.8)
13	Acyclovir	26 (17.4)	Cefazolin	11 (20.0)
14	Co-trimoxazole	24 (16.1)	Fluconazole	11 (20.0)
15	Ranitidine	24 (16.1)	Ampicillin-sulbactam	10 (18.2)
16	Ceftazidime	20 (13.4)	Digoxin	10 (18.2)
17	Digoxin	19 (12.8)	Allopurinol	9 (16.4)
18	Amikacin	16 (10.7)	Ceftazidime	8 (14.5)
19	Gabapentin	14 (9.4)	Daptomycin[a]	8 (14.5)
20	Allopurinol	13 (8.7)	Co-trimoxazole	7 (12.7)

[a]Includes a new molecular entity identified in the prescribing information review.

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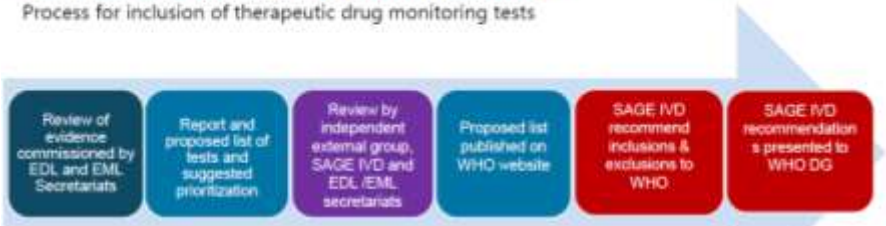
EDL secretariat
Department of Essential Medicines and Health Products
Mercedes Pérez González, Adriana Velázquez, Lucy Hattingh and William Sewell, consultants

Open Session, Second Meeting of the SAGE IVD, 18 March 2019

4. Therapeutic Drug monitoring

World Health Organization

Process for inclusion of therapeutic drug monitoring tests



Prioritization:

High (most authors consider TDM useful even for noncritically ill patients):amikacin, gentamicin, phenytoin, lithium

Moderate (TDM useful in patients with co-treatments or concomitant clinical complications [e.g., impaired renal function]): vancomycin, methotrexate, cyclosporin

Low (careful clinical assessment is enough for most cases, or there are evidences that there are no differences between patients with and without TDM): digoxin, phenobarbital, carbamazepine, valproate

19/03/2019 13

How to manage?

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

Michael J. Rybak,[1,2,3] Ben M. Lomaestro,[4] John C. Rotschafer,[5] Robert C. Moellering, Jr.,[6,7,8] William A. Craig,[9] Marianne Billeter,[10] Joseph R. Dalovisio,[11] and Donald P. Levine[12]

[1]Anti-Infective Research Laboratory, Department of Pharmacy Practice, College of Pharmacy & Health Sciences, and [2]Department of Medicine, School of Medicine, Wayne State University, and [3]Detroit Receiving Hospital & University Health Center, Detroit, Michigan; [4]Albany Medical Center, Albany, New York; [5]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis; [6]Shields Warren-Mallinckrodt Medical Research, [7]Harvard Medical School, and [8]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [9]University of Wisconsin School of Medicine and Public Health, Madison; and [10]Ochsner Medical Centers and [11]Department of Infectious Diseases, Ochsner Health System, New Orleans, Louisiana

Practice guidelines for therapeutic monitoring of vancomycin treatment for *Staphylococcus aureus* infection in adult patients were reviewed by an expert panel of the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. A literature review of existing evidence regarding vancomycin dosing and monitoring of serum concentrations, in addition to patient outcomes combined with expert opinion regarding the drug's pharmacokinetic, pharmacodynamic, and safety record, resulted in new recommendations for targeting and adjustment of vancomycin therapy.

Clinical Infectious Diseases, Volume 49, Issue 3, 1 August 2009, Pages 325–327, https://doi.org/10.1086/600877

Recommended trough serum concentrations and dosage adjustments

- On the basis of the potential to improve penetration, to increase the probability of optimal target serum concentrations, and to improve clinical outcomes of complicated infections, such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by S. aureus, trough serum vancomycin concentrations of 15–20 mg/L are recommended.
- Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of > 400 for most patients if the MIC is <1 mg/L.

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  (Level of evidence, III; grade of recommendation, B.)

Clinical Infectious Diseases, Volume 49, Issue 3, 1 August 2009, Pages 325–327, https://doi.org/10.1086/600877

Accute kidney injuries due to C 15-20 mg/L?

Systematic Review and Meta-Analysis of Vancomycin-Induced Nephrotoxicity Associated with Dosing Schedules That Maintain Troughs between 15 and 20 Milligrams per Liter

S. J. van Hal,[a,b] D. L. Paterson,[c] T. P. Lodise[d]

Department of Microbiology & Infectious Diseases, Royal Prince Alfred Hospital, Sydney, Australia[a]; Antibiotic Resistance & Mobile Elements Group, Microbiology and Infectious Diseases Unit, School of Medicine, University of Western Sydney, Australia[b]; University of Queensland Centre for Clinical Research, Brisbane, Australia[c]; Albany College of Pharmacy and Health Sciences, Albany, New York, USA[d]

In an effort to maximize outcomes, recent expert guidelines recommend more-intensive vancomycin dosing schedules to maintain vancomycin troughs between 15 and 20 mg/liter. The widespread use of these more-intensive regimens has been associated with an increase in vancomycin-induced nephrotoxicity reports. The purpose of this systematic literature review is to determine the nephrotoxicity potential of maintaining higher troughs in clinical practice. All studies pertaining to vancomycin-induced nephrotoxicity between 1996 and April 2012 were identified from PubMed, Embase, Cochrane Controlled Trial Registry, and Medline databases and analyzed according to Cochrane guidelines. Of the initial 240 studies identified, 38 were reviewed, and 15 studies met the inclusion criteria. Overall, higher troughs (≥15 mg/liter) were associated with increased odds of nephrotoxicity (odds ratio [OR], 2.67; 95% confidence interval [CI], 1.95 to 3.65) relative to lower troughs of <15 mg/liter. The relationship between a trough of ≥15 mg/liter and nephrotoxicity persisted when the analysis was restricted to studies that examined only initial trough concentrations (OR, 3.12; 95% CI, 1.81 to 5.37). The relationship between troughs of ≥15 mg/liter and nephrotoxicity persisted after adjustment for covariates known to independently increase the risk of a nephrotoxicity event. An incremental increase in nephrotoxicity was also observed with longer durations of vancomycin administration. Vancomycin-induced nephrotoxicity was reversible in the majority of cases, with short-term dialysis required only in 3% of nephrotoxic episodes. The collective literature indicates that an exposure-nephrotoxicity relationship for vancomycin exists. The probability of a nephrotoxic event increased as a function of the trough concentration and duration of therapy.

Antimicrob. Agents Chemother. 57 (Nov 1 2013) 734–744.

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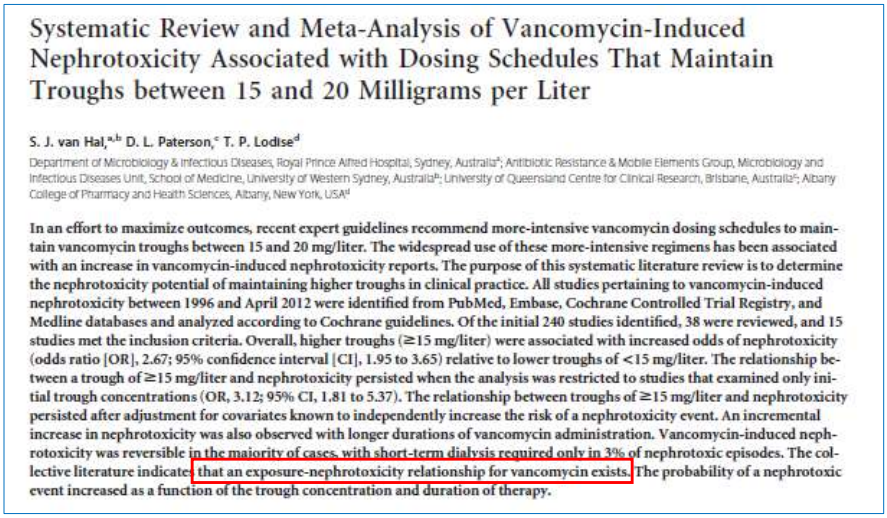

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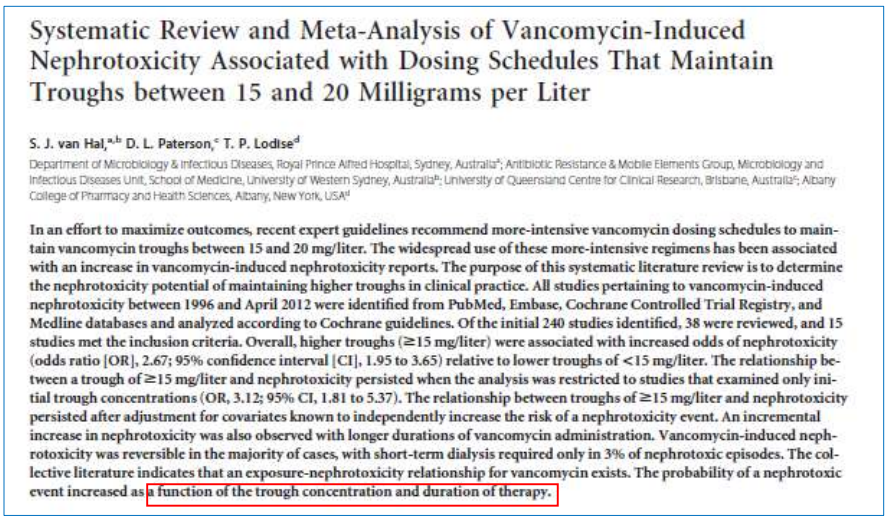

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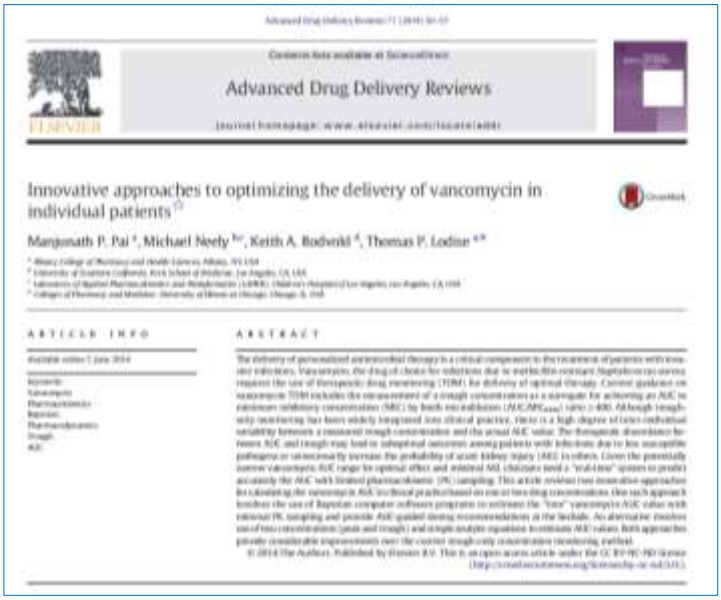


Advanced Drug Delivery Reviews

Innovative approaches to optimizing the delivery of vancomycin in individual patients ☆

Manjunath P. Pai [a], Michael Neely [b,c], Keith A. Rodvold [d], Thomas P. Lodise [e,*]

Advanced Drug Delivery Reviews 77 (2014) 50–57

Poor C_{trough} and AUC correlation!

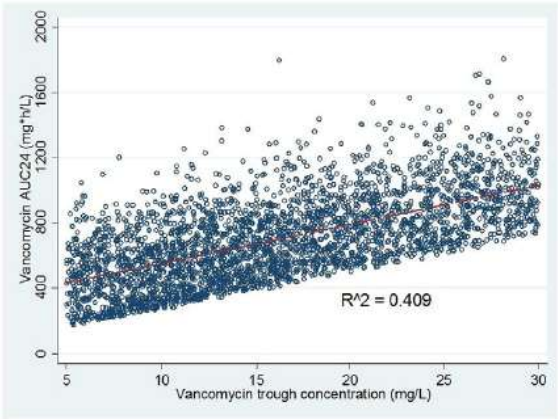


Fig. 2. Scatter and linear fit plot of vancomycin area under the curve over 24 h (AUC24) versus trough vancomycin concentration from 5000 subject Monte Carlo simulation.

Advanced Drug Delivery Reviews 77 (2014) 50–57

How to manage AUC-guided dosing?

Option 1

BAYESIAN APPROACH (Bayesian dose optimising software)

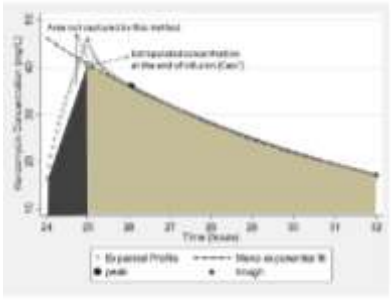
- Population data (Bayesian prior)
- Measured drug concentration
- Revised probability distribution of a given patient‘s PK parameter values after dosing and concentration taken into account (Bayesian posterior)

Advanced Drug Delivery Reviews 77 (2014) 50–57

Option 2

EQUATION-BASED APPROACH

$$AUC_{t0-t2} = \frac{t' \times (Ceoi' + Ct)}{2} + \frac{Ceoi' - Ct}{Ke}$$



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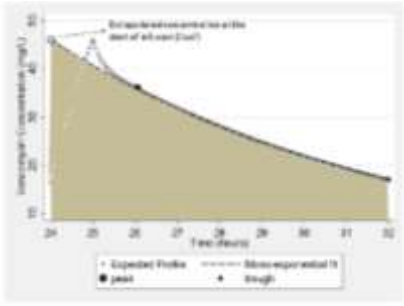
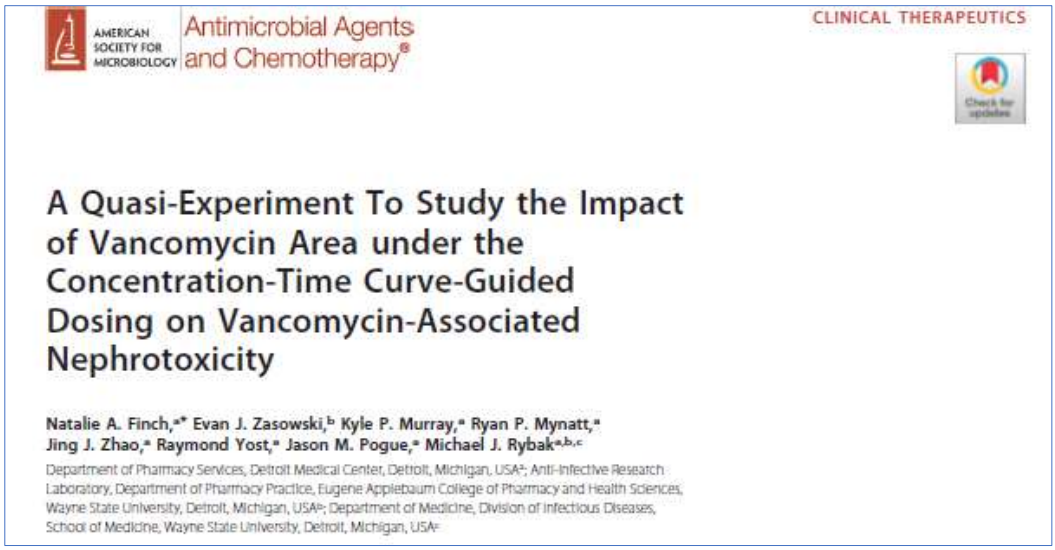


Advanced Drug Delivery Reviews 77 (2014) 50–57

Advantages of Bayesian approach

- Requires 1 concentration (trough-only), 97% (93%-102%) accurate AUC!
- Allows loading doses or irregular dosing patterns
- Allows non-steady state concentrations
- Allows any-time concentratios
- Allows including covariates (e.g. serum creatinine changes)

AUC-based dosing efficacy & safety



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CLINICAL THERAPEUTICS

A Quasi-Experiment To Study the Impact of Vancomycin Area under the Concentration-Time Curve-Guided Dosing on Vancomycin-Associated Nephrotoxicity

Natalie A. Finch,[a]* Evan J. Zasowski,[b] Kyle P. Murray,[a] Ryan P. Mynatt,[a] Jing J. Zhao,[a] Raymond Yost,[a] Jason M. Pogue,[a] Michael J. Rybak[a,b,c]

Department of Pharmacy Services, Detroit Medical Center, Detroit, Michigan, USA[a]; Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA[b]; Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, Michigan, USA[c]

2018. Antimicrob Agents Chemother 61:e01293-17.

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Department of Pharmacy Services, Detroit Medical Center, Detroit, Michigan, USA[a]; Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State Univer[illegible] School of Medicine,

tional hazards regression (hazard ratio, 0.53; 95% CI, 0.35 to 0.78; $P = 0.002$). AUC-guided dosing was associated with lower total daily vancomycin doses, AUC values, and trough concentrations. Vancomycin AUC-guided dosing was associated with reduced nephrotoxicity, which appeared to be a result of reduced vancomycin exposure.

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CLINICAL THERAPEUTICS

Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing

Michael N. Neely,[a,b] Lauren Kato,[c] Gilmer Youn,[a] Lironn Kraler,[a] David Bayard,[b] Michael van Guilder,[b] Alan Schumitzky,[b] Walter Yamada,[b] Brenda Jones,[a] Emi Minejima[c]

[a]University of Southern California, Keck School of Medicine, Los Angeles, California, USA
[b]Laboratory of Applied Pharmacokinetics and Bioinformatics (LAPKB), Saban Research Institute, and Division of Infectious Diseases, Children's Hospital of Los Angeles, Los Angeles, California, USA
[c]University of Southern California School of Pharmacy, Los Angeles, California, USA

2018. Antimicrob Agents Chemother 62:e02042-17.

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[a]University of Southern California, Keck School of Medicine, Los Angeles, California, USA
[b]Laboratory of Applied Pharmacokinetics and Bioinformatics (LAPKB), Saban Research Institute, and Division of

Compared to trough concentration targets, AUC-guided, Bayesian estimation-assisted vancomycin dosing was associated with decreased nephrotoxicity, reduced per-patient blood sampling, and shorter length of therapy, without compromising efficacy. These benefits have the potential for substantial cost savings. (This study has been registered at ClinicalTrials.gov under registration no. NCT01932034.)

TDM: acitve role of the pharmacist

pharmacy

MDPI

Article

Bridging the Gap between Theory and Practice; the Active Role of Inpatient Pharmacists in Therapeutic Drug Monitoring

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Figure 1. Patient's enrollment.

Table 1. Baseline characteristics.

	Pre-Phase (n = 75)	Post-Phase (n = 75)	*p*-Value [a]
	n (%) or Median; IQR		
Age (years)	66 (49–79)	63 (51–77)	0.7607
Sex (male)	38 (51%)	38 (51%)	1
Body Mass Index (kg/m^2)	24.8 (20.6–30.8)	25.3 (21–31.2)	0.3904
Patients on dialysis	7 (9.33%)	13 (17.33%)	0.150
Prescribed antibiotic			
Vancomycin	71/75 (95%)	71/75 (95%)	1
Gentamicin	4/75 (5%)	3/75 (4%)	1
Amikacin	0/75 (0%)	1/75 (1.3%)	1
Baseline lab values at the time of initiation of antibiotic			
CrCl (mL/min) [b]	67.9 (37.3–106.5)	60 (30–94)	0.3082
WBCs ($\times 10^9$ cells/L)	10.9 (7.6–16.1)	11 (7.7–16)	0.7042
Wards at which antibiotics were initiated			
Emergency	36 (48%)	35 (46.6%)	0.87
Medical	23 (30.7%)	32 (42.6%)	0.127
Surgical	16 (21.3%)	8 (10.6%)	0.075
Indications			
Skin and Soft Tissue	5 (6.6%)	5 (6.6%)	1
Bacteremia	24 (32%)	35 (46.6%)	0.066
Osteomyelitis	6 (8%)	3 (4%)	0.494
Pneumonia	20 (26.6%)	16 (21.3%)	0.472
Endocarditis	0 (0%)	1 (1.3%)	1
Meningitis	8 (10.6%)	4 (5.3%)	0.367
Urinary Tract Infection	8 (10.6%)	7 (9.3%)	0.785
Intra-abdominal infection	1 (1.3%)	4 (5.3%)	0.367
Other [c]	3 (4%)	0 (0%)	0.367

Table 2. Primary and secondary outcomes.

Outcome	Pre-Phase	Post-Phase	Mean Difference (95% Confidence Interval)	*p*-Value
Optimal initial dosing	60 % (45/75)	91% (68/75)	0.31 (0.18–0.44)	<0.0001
Optimal dose adjustments	55 % (61/111)	65% (52/80)	0.1 (−0.05–0.26)	0.2113
Optimal drug level requests	55 % (153/279)	58% (171/293)	0.03 (−0.13–0.19)	0.7110

Research Report

Evaluation of a Pharmacist-Directed Vancomycin Dosing and Monitoring Pilot Program at a Tertiary Academic Medical Center

Annals of Pharmacotherapy
2015, Vol. 49(9) 1009–1014

DOI: 10.1177/1060028015587900
aop.sagepub.com
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Kathleen A. Marquis, PharmD, PhD[1], Jeremy R. DeGrado, PharmD[1], Stephanie Labonville, PharmD[1], David W. Kubiak, PharmD[1], and Paul M. Szumita, PharmD[1,2]

Annals of Pharmacotherapy 2015, Vol. 49(9) 1009–1014.

Table 1. Baseline Demographics.

	Preimplementation (n = 161)	Postimplementation (n = 158)	*P* Value
Age (years)[a]	49 ± 15.6	49 ± 13.5	0.99
Gender, female[b]	64 (40)	84 (53)	0.02
Height (inches)[a]	66.4 ± 4.4	67.1 ± 3.9	0.13
Weight (kg)[a]	75.2 ± 17.7	77 ± 16.6	0.35
Past medical history[b]			
DM	46 (28.6)	40 (25.3)	0.23
Asthma/COPD	35 (24.2)	30 (19.0)	0.26
Hypertension	89 (55.3)	23 (14.6)	0.88
CHF	10 (6.2)	13 (8.2)	0.28
Cancer	23 (14.3)	13 (8.2)	0.49
Liver disease	7 (4.3)	9 (5.6)	0.58
Laboratory values at vancomycin initiation[c]			
Scr (mg/dL)	0.72 ± 0.23	0.76 ± 0.24	0.13
BUN (mg/dL)	13.2 ± 5.3	12.4 ± 6.3	0.22
CL_{CR} (mL/min)	94 ± 22	92 ± 22.2	0.42
WBC ($\times 10^3$ cells/L)[a]	11.5 ± 4.5	11.1 ± 7.1	0.55
Indication[b]			
Pneumonia	69 (42.9)	73 (46.2)	0.57
Bacteremia	36 (22.4)	36 (22.8)	0.99
Skin and soft tissue	22 (13.7)	27 (17.1)	0.44
Endocarditis	7 (4.3)	6 (3.8)	0.97
Catheter related	7 (4.3)	7 (4.4)	0.98
Osteomyletis	5 (3.1)	5 (3.2)	0.92
Meningitis	5 (3.1)	4 (2.5)	0.89
Urinary tract	7 (4.3)	9 (5.7)	0.62
Intrasbdominal	0	3 (1.9)	0.12

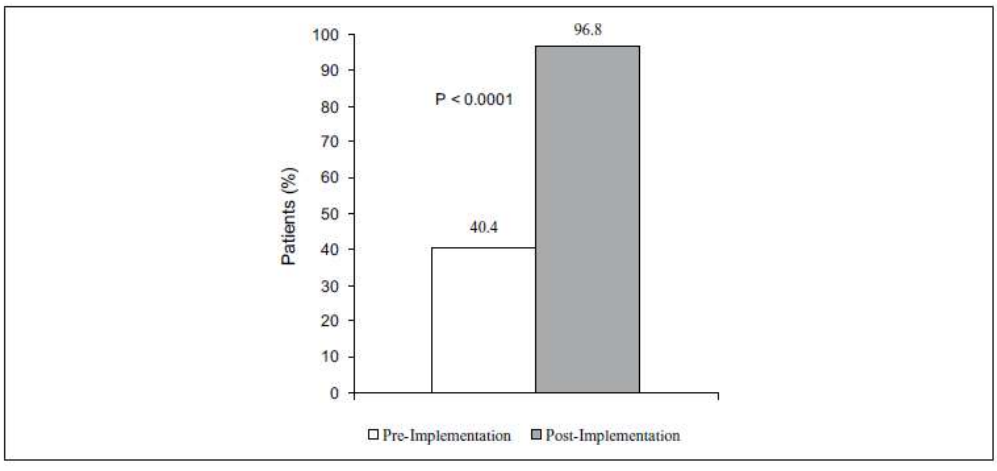

Figure 2. The percentage of patients who received optimal vancomycin dosing within 24 hours of therapy pre- and postimplementation of pharmacist-directed vancomycin dosing guideline.

RESEARCH ARTICLE

Effects of pharmacist intervention in Vancomycin treatment for patients with bacteremia due to Methicillin-resistant *Staphylococcus aureus*

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Endpoints

Absence of failure

- Death within 30 days from the start of VCM therapy
- Positive blood culture 7 days after the start of VCM therapy
- Change of VCM to another anti-MRSA agent
- Development of nephrotoxicity

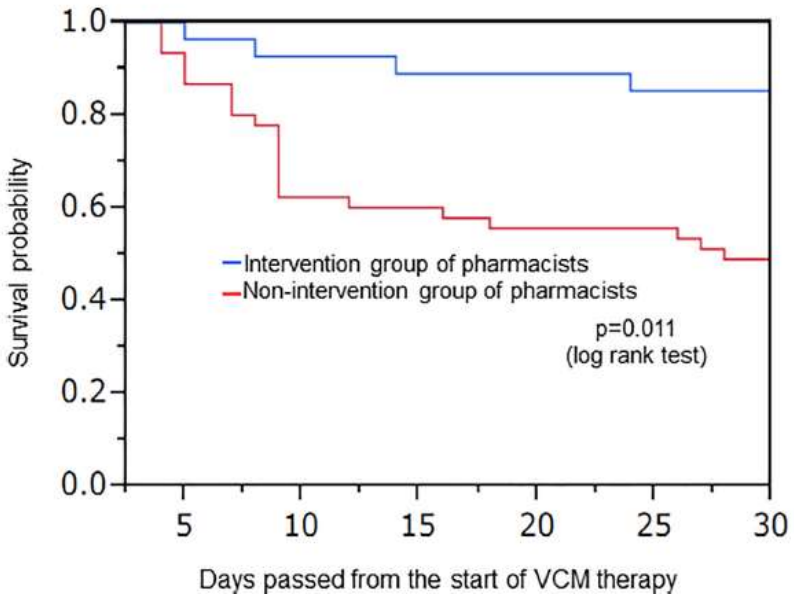
Table 1. Baseline characteristics of patients.

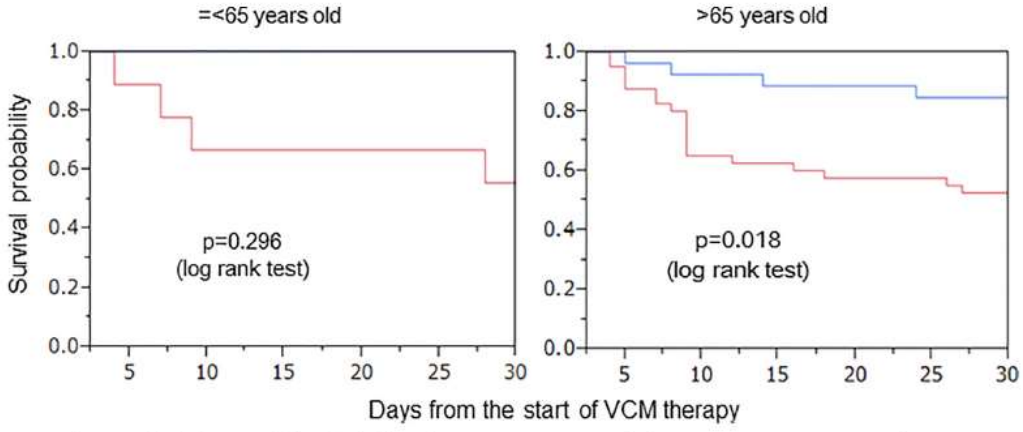
	Non-intervention group	Intervention group	p value
Number of patients	49	28	-
Age[a]	74.7 ± 1.72	79.8 ± 2.22	0.074
Sex (male %)	31 (68.9%)	13 (48.2%)	0.081
Weight[a] (kg)	50.9 ± 1.48	51.5 ± 1.91	0.798
CCI[a,b]	2 [0, 3]	3 [2, 5]	0.101
PBS[a,b]	2 [1, 4]	1 [0, 3]	0.019
Trough Levels[a]	17.6 ± 10.2	11.2 ± 3.25	0.002
Percent that hit target on first trough	40.8 (20/49)	64.3 (18/28)	0.048
mg/kg dose[a]	29.1 ± 12.5	21.1 ± 9.41	0.004
VCM MIC* (<2mg/liter %)	44 (89.8%)	26 (92.9%)	0.653

*CCI: Charlson Comorbidity Index, PBS: Pitt Bacteremia score, VCM MIC: Vancomycin MIC.

[a] Data shown as mean ±standard deviation.

[b] Data shown as median [interquartile range].





International Journal of Clinical Pharmacy
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COMMENTARY

Optimising antimicrobial therapy through the use of Bayesian dosing programs

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Abstract
The optimisation of antibiotic dosing therapy with therapeutic drug monitoring is widely recommended. The aim of therapeutic drug monitoring is to help the clinician to achieve target pharmacokinetic/pharmacodynamic parameters, maximising efficacy and minimising toxicity. Computerised programs, utilising the Bayesian estimation procedures, are able to achieve target concentrations in a greater percentage of patients earlier in the course of therapy compared to linear regression analysis and population methods. This article summarises various methods for dose optimisation of antibiotics with a focus on Bayesian programs.

Keywords Antibiotics · Bayesian statistics · Pharmacodynamics · Pharmacokinetics · Software

- **Summary**

The ideal method for monitoring antibiotics is one that predicts an accurate, clinically appropriate dose, requires minimal resources and is easy to use.

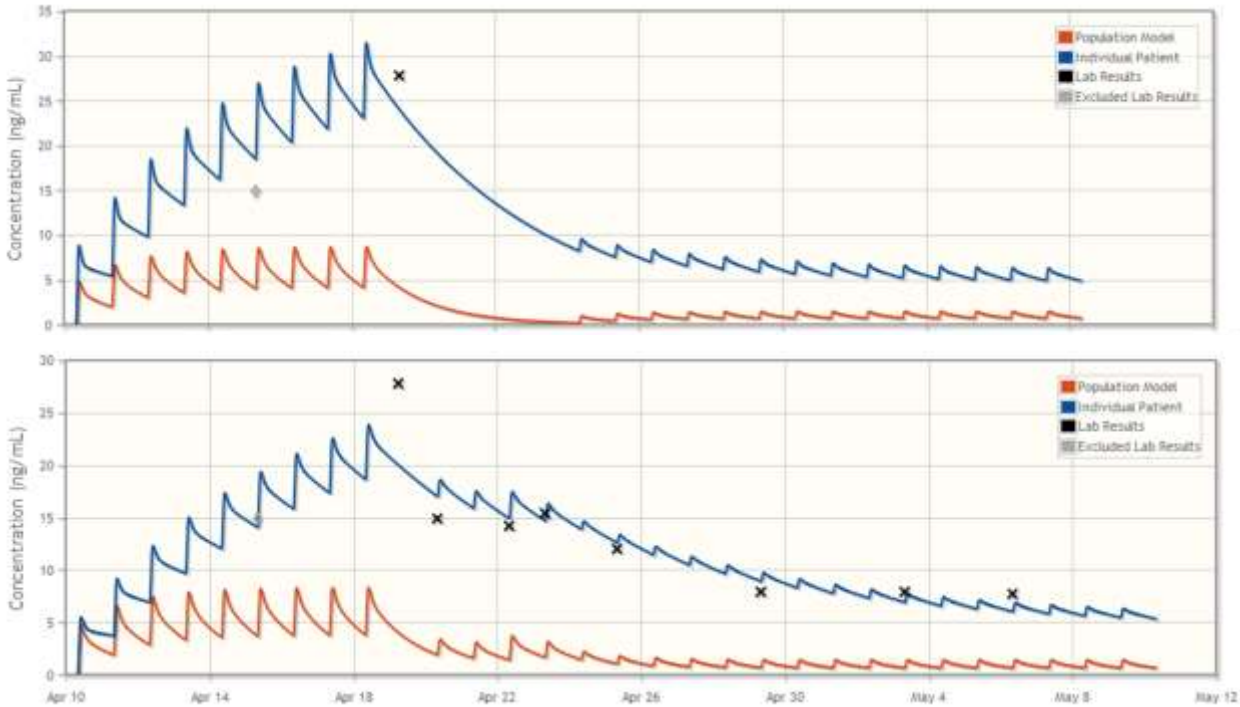
The advantage of the nomograms are that they require only one serum concentration, are easy to interpret and require no specialised pharmacokinetic knowledge. Nevertheless, concerns have been raised about their reliability given the large interpatient variability in antibiotic pharmacokinetics and are no longer recommended by published guidelines.

The linear regression methods, i.e. Sawchuk–Zaske and ALADDIN, require two serum concentrations after an antibiotic dose and do not utilise population data to assist in calculating the patients pharmacokinetic/ pharmacodynamic indices.

Utilising population data the Bayesian estimation procedures can calculate doses based on one serum concentration. They are **currently the closest to an ideal solution for clinical use** which can achieve a greater percentage of patients attaining target concentrations as compared to other methodologies.

But...

- the Bayesian estimation procedures are decision support programs - not diagnostic tools!
- They allow the end user the flexibility to choose appropriate target parameters to tailor the recommendations to a patient
- they require skilled personnel, usually clinical pharmacists and or clinical pharmacologists, with an understanding of pharmacokinetics and pharmacodynamics to use and interpret the information
- the software is only as good as the data entered!



PHARMACOTHERAPY
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ORIGINAL RESEARCH ARTICLES

Review and Validation of Bayesian Dose-Optimizing Software and Equations for Calculation of the Vancomycin Area Under the Curve in Critically Ill Patients

R. Brigg Turner,[1,2,*] Kyle Kojiro,[2] Emily A. Shephard,[1] Regina Won,[3] Eric Chang,[3] Dominic Chan,[2] and Fawzy Elbarbry[1,2]

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AVSTRIJA
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- 1.300 hospital beds
- 52.000 hospital admissions/y
- 400.000 outpatients/y
- av. length of stay: 7 days
- 3.000 employees
- 5 clinics (>30 wards)
- 7 independent wards

TDM team in 2012

Our TDM service

- 24/7
- Bayesian software
- All pharmacist included

	2015	2016	2017	2018
VANCOMYCIN	845	962	1153	1714
GENTAMICIN	206	289	360	530
AMIKACIN	72	46	218	146
OTHER			102	17
Σ	1245	1354	1885	2420

TDM team in 2019

Nobody is perfect, but a team can be!

100th Anniversary of the Maribor Hospital Pharmacy, October 2019